Republic of Zambia
MINISTRY OF HEALTH

NATIONAL TUBERCULOSIS AND LEPROSY PROGRAMME

CONSOLIDATED TUBERCULOSIS GUIDELINES

First Edition 2022

Foreword

Tuberculosis continues to be a public health threat in our country and globally. TB continues to cause ill-health and deaths in Zambia, across all circles, women and children inclusive. TB is the leading cause of death by an infectious disease ranking above HIV/AIDS. Every year in Zambia, we lose not less than 4000 lives to a cause attributed to TB. The burden of TB in Zambia remains high with an estimated incidence of 319/100,000 translating into 59,000 new infections every year. Of concern is that at least 30% of the estimated new cases are not detected therefore are not linked to care. It is these missed cases of TB that continue to drive the TB epidemic in our country. Through the National Tuberculosis and Leprosy Programme, Zambia has steadily reduced the TB incidence and mortality rates in the last two decades. Notwithstanding this progress, the incidence and mortality rates in Zambia remain high. According to the 2021 World Health Organization Global TB Report, the TB incidence rate in 2020 was 319/100,000 population, a 58% decrease compared to rates from the year 2000. The total TB mortality rate in 2020 was 81/100,000 population down from 223/100,00 in 2000. Of concern is the TB mortality rate among HIV negative persons that has oscillated around 30/100,000 and started to increase in the last two years.

Over the past three years (since 2018), the World Health Organization (WHO) has revised normative guidance on TB prevention, diagnosis, and treatment. With this background, these guidelines have incorporated the current WHO guidance, including the approved rapid diagnostic tools and sensitive TB screening and diagnostic algorithms. A departure from the traditional approach of publishing standalone guidelines for drug-sensitive (DS-TB), drug-resistant (DR-TB) and childhood TB guidelines, we have combined all these components in the new consolidated guidelines, again in line with the WHO, which is now publishing its guidelines by module. These consolidated guidelines are cognizant of the urgent actions needed to accelerate the TB response and efforts towards TB elimination by 2030. Combined guidelines for DS-TB and DR-TB for children, adolescents and adults have several benefits because drug-resistant TB is mainly due to poorly managed drug-susceptible TB, and the source of TB infection in most children are untreated cases of adult TB.

The approaches and practices in these guidelines have considered the effect of the COVID-19 pandemic on TB services that have brought to light the need for effective and inclusive multilateralism and coordinated actions at all levels of health service delivery. In addition, the guidelines harness the lessons from this pandemic and build on our best practices demonstrated by increasing TB case notifications and TB Preventive initiations amidst COVID 19. The guidelines provide rich and simplified guidance on how to continue providing TB services at health facility and community levels in times of emergencies and outbreaks like the COVID-19 Pandemic.

These consolidated guidelines place a premium on differentiated services across all levels of health care with a focus on primary health care and the community. Embedding quality improvement in TB prevention, diagnosis, and treatment activities such as TB case finding has been prioritized.

The guidelines were developed in collaboration with all stakeholders, including cooperating and implementing partners, representatives of civil society organisations, and community-based organisations. These guidelines supersede previous DS-TB, DR-TB, and childhood TB guidelines. I, therefore, encourage all health care workers in public and private health facilities at all levels of the health sector to use these guidelines as they implement various TB curative and preventive services.

Honourable Sylvia T. Masebo, MP

Minister of Health

Acknowledgements

These Consolidated Tuberculosis Guidelines represent a pivotal milestone in translating policy to evidence-based tuberculosis prevention, diagnosis, and treatment services as we aim to eliminate tuberculosis by 2030.

I wish to take this opportunity to thank the Director of Public Health and Research, the Manager of the National Tuberculosis and Leprosy Programme, and NTLP staff, and all advisors seconded to the NTLP with support from co-operating partners whose immense support, coordination and guidance steered the development of these guidelines. I am also thankful to all writing team members for their dedication, extensive knowledge, and expertise that was invested in developing this document.

Special gratitude goes to our all-weather partners: The United States Agency for International Development (USAID) and its implementing partners (Eradicate TB Project and TB LON managed by PATH and Centre for Infectious Disease Research in Zambia, CIDRZ respectively), the World Health Organization (WHO), Centres for Disease Control and Prevention (CDC) Churches Association of Zambia (CHAZ), representatives of civil society and community-based organizations and all health care workers from all tiers of our healthcare structures which contributed to the development of these guidelines right through to their logical conclusion. I would also like to highlight the input from our physicians, paediatricians, pharmacists, and nurses from the teaching hospitals for their contribution to ensure these guidelines translate evidence-based information and practice. The multi-sectoral and consultative approach assured a final product that incorporated ideas from experts and practitioners across the health care continuum. These guidelines also had special input from community structures, an ever so vital piece towards holistic health care in the Zambian context.

The Ministry of Health is grateful for the generous support from USAID and the Global Fund, which enabled the writing, editing, and printing of these guidelines which I envisage will be implemented even in the remotest parts of Zambia

Prof Lackson Kasonka
Permanent Secretary - Technical Services
Ministry of Health

Contents

List of tables

List of figures

Abbreviations

AFB	acid-fast bacilli
AHD	advanced HIV disease
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ART	antiretroviral therapy
AST	aspartate aminotransferase
ATT	anti-TB treatment
BCG	bacillus Calmette-Guérin
CAD	computer-aided diagnosis
CEC	Clinical Expert Committee
CKD	chronic kidney disease
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CPT	cotrimoxazole preventive therapy
CRP	C-reactive protein
CSF	cerebrospinal fluid
CT	computed tomography
CXR	chest x-ray
DHO	district health officer
DM	diabetes mellitus
DNA	deoxyribonucleic acid
DOT	directly observed therapy
DR-TB	drug-resistant tuberculosis
DST	drug susceptibility testing
DS-TB	drug-susceptible tuberculosis
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EPTB	extrapulmonary tuberculosis
FEV_1	forced expiratory volume
FFP	filtering face piece
FL-LPA	first-line line probe assay
FNAC	fine needle aspirate cytology
FQ	fluoroquinolone
HIV	human immunodeficiency virus
HMIS	health management information system
IGRA	interferon-gamma release assay
IPC	infection prevention and control
IRIS	Immune Reconstitution Inflammatory Syndrome
LAM	lipoarabinomannan
LAMP	loop-mediated isothermal amplification
LF-LAM	lateral flow urine lipoarabinomannan assay
LPA	line probe assay
M&E	monitoring and evaluation
MDR-TB	multidrug-resistant tuberculosis

MEMS	medication event monitoring system
MERS	Middle East respiratory syndrome
mRD	molecular rapid diagnostic
MRI	magnetic resonance imaging
MTB	*Mycobacterium tuberculosis*
MTBC	*Mycobacterium tuberculosis* complex
MUAC	mid-upper arm circumference
NTLP	National Tuberculosis and Leprosy Programme
PCR	polymerase chain reaction
pDST	phenotypic drug susceptibility testing
PEF	peak expiratory flow
PEPFAR	US President's Emergency Plan for AIDS Relief
PLHIV	people living with HIV
PPD	purified protein derivative
PTB	pulmonary tuberculosis
RH	rifampicin/isoniazid
RHZE	rifampicin/isoniazid/pyrazinamide/ethambutol
RR-TB	rifampicin-resistant tuberculosis
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SL-LPA	second-line line probe assay
SMS	Short Message Service
TB	tuberculosis
TB/HIV	tuberculosis and HIV co-infection
TPT	tuberculosis preventive treatment
TSS	technical supportive supervision
TST	tuberculin skin test
VOT	video observed therapy
WHO	World Health Organization

1. Tuberculosis case and treatment outcome definitions

The purpose of establishing case definitions is to correctly classify and notify cases, register patients, and allocate cases to standardized treatment. Bacteriologically confirmed or clinically diagnosed cases of tuberculosis (TB) are classified according to anatomical site of TB disease, history of previous treatment, drug resistance, and HIV status.

1.1 TB case definitions

The table below includes TB case definitions based on classification.

Table 1. Tuberculosis case definitions.

Classification	Case	Definition
Case definition based on bacteriological status	Bacteriologically confirmed tuberculosis (TB) case	Biological specimen is positive by smear microscopy, culture, or World Health Organization–approved rapid diagnostic test, such as Cepheid's GeneXpert® MTB/RIF or Ultra, Truenat™ by Molbio Diagnostics, line probe assay, lateral flow urine lipoarabinomannan assay, and TB loop-mediated isothermal amplification (LAMP).
	Clinically diagnosed TB case	Does not fulfil the criteria for bacteriological confirmation but has been diagnosed with TB by a qualified practitioner who has decided to give the patient a full course of TB treatment. This definition includes cases diagnosed based on x-ray abnormalities or suggestive histology and extrapulmonary cases without laboratory confirmation. **Note:** Clinically diagnosed cases should be reclassified to bacteriologically confirmed once laboratory results confirm the presence of TB by any microbiological means (e.g., GeneXpert, microscopy, LAMP).
Classification based on anatomical site of disease	Pulmonary tuberculosis (PTB)	TB involving the lung parenchyma or the trachea-bronchial tree. Miliary TB is classified as PTB because there are lesions in the lungs.
	Extrapulmonary tuberculosis (EPTB)	TB involving organs other than the lungs (e.g., pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges). A patient with both PTB and EPTB should be classified as a case of PTB.
Classification based on history of previous TB treatment (patient registration group)	New TB patients	Patients who have never been treated for TB or have taken anti-TB drugs for less than 1 month.
	Previously treated TB patients: patients who received 1 month or more of anti-TB drugs in the past	
	Relapsed TB patients	Patients previously treated for TB and declared cured, or who have completed their most recent course of treatment and are diagnosed with an episode of TB that is either a true relapse or a new episode caused by reinfection.
	Treatment after failure patients	Patients previously treated for TB and their most recently completed course of treatment failed.
	Treatment after loss to follow-up patients	Patients previously treated for TB and declared "lost to follow-up" at the end of their most recent course of treatment.
	Other previously treated patients	Patients previously treated for TB but whose outcome after their most recent course of treatment is unknown or undocumented.

Classification	Case	Definition
Classification based on HIV status	HIV-positive TB patient	Any diagnosed case of TB who has a positive HIV result at the time of TB diagnosis/during treatment, or other documented evidence of enrolment in HIV care.
	HIV-negative TB patient	Any diagnosed case of TB who has a negative HIV result from testing conducted at the time of TB diagnosis or during TB treatment.
	HIV status unknown TB patient	Any case of TB who has no result of HIV testing or other documented evidence of enrolment in HIV care.
Classification based on drug resistance	Mono-resistant	Resistance to one first-line anti-TB drug only.
	Rifampicin resistant	Resistance to rifampicin.
	Isoniazid resistant	Resistance to isoniazid.
	Polydrug-resistant	Resistance to more than one first-line anti-TB drug (other than both isoniazid and rifampicin).
	Multidrug-resistant tuberculosis (MDR-TB)	Resistance to both isoniazid and rifampicin, in combination with other drugs or not.
	Pre extensively drug-resistant tuberculosis	TB caused by *Mycobacterium tuberculosis* strains that fulfils the definition of MDR-TB and rifampicin-resistant tuberculosis (RR-TB) and that is resistant to any fluoroquinolone.
	Extensively drug-resistant tuberculosis (XDR-TB)	TB caused by *Mycobacterium tuberculosis* strains that fulfils the definition of MDR/RR-TB and that is resistant to any fluoroquinolone and at least one additional Group A drug. (Group A drugs are the most potent drugs in the ranking of second-line medicines for the treatment of drug-resistant forms of TB.
Other definitions/ classifications	Miliary TB	Blood-borne dissemination of TB from either a primary infection or erosion of a secondary tuberculous lesion into a blood vessel (TB bacteraemia) and classified as PTB.
	Contact tracing and investigation	A systematic process of identifying and investigating undiagnosed cases of TB among the contacts of an index TB case. The goal includes evaluating for active TB disease and testing for latent tuberculosis infection to identify possible candidates for preventive treatment.
	Presumptive TB	A patient who presents with symptoms or signs or chest x-ray findings suggestive of TB.
	Index case	The initially identified case of TB in a specific household or other comparable setting in which others may have been exposed.
	Contact	Any person who has been exposed to an index case (as defined above).
	Household contact	A person who shared the same enclosed living space with the index case 3 months before commencement of the current treatment episode.
	Close contact	A person who is not in the household but shared an enclosed space, such as a social gathering place, workplace, or facility, for extended periods during the day with the index case 3 months before commencement of the current treatment episode.
	Incident TB cases	Sum of new and relapse cases of TB.

Classification	Case	Definition
	Fast-track services	Dedicated TB services in which patients being evaluated for TB can be seen early, ahead of other patients.

Key messages

- Bacteriologically confirmed cases include those for which the sputum or any histopathology specimen examined and is positive for TB.
- A positive Lateral flow urine lipoarabinomannan assay (LAM) should be classified as bacteriologically confirmed (pulmonary and/or extrapulmonary).
- The classification of TB patients as pulmonary or extra pulmonary in patients diagnosed by Urine LAM should be based on clinical features and organs

1.2 Treatment outcome definitions

The following treatment outcome definitions apply to both drug-resistant tuberculosis and drug-susceptible tuberculosis.

Table 2. Treatment outcomes for both drug-resistant and drug-susceptible tuberculosis.

TB treatment outcome	Definition
Cured	A PTB patient with bacteriologically confirmed TB who completed treatment as recommended by the national policy, with evidence of bacteriological response[a] and no evidence of failure.
Treatment completed	A patient who completed treatment as recommended by the national policy, whose outcome does not meet the definition for cured or treatment failure.
Treatment failed	A patient whose treatment regimen needed to be terminated or permanently changed[b] to a new regimen or treatment strategy.
Died	A patient who died[c] before starting treatment or during treatment.
Lost to follow-up	**6-month regimen** A patient diagnosed with TB who did not start treatment or whose treatment was interrupted for 2 consecutive months or more.
Not evaluated	A patient for whom no treatment outcome was assigned.[d]
Treatment success	The sum of cured and treatment completed.
An optional definition proposed for use in operational research only	
Sustained treatment success	An individual assessed at 6 months (for DR-TB and DS-TB) and at 12 months (for DR-TB only) after successful TB treatment, who is alive and free of TB.

Abbreviations: DR-TB, drug-resistant tuberculosis; DS-TB, drug-susceptible tuberculosis; PTB, pulmonary tuberculosis; TB, tuberculosis.

a. "Bacteriological response" refers to bacteriological conversion with no reversion.
   - "Bacteriological conversion" describes a situation in which a patient with bacteriologically confirmed TB has at least two consecutive cultures (for DR-TB

and DS-TB) or smears (for DS-TB only), taken on different occasions at least 7 days apart, and the results are negative.

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

b. Reasons for the change include:
   - no clinical response and/or no bacteriological response (see note a);
   - adverse drug reactions; or
   - evidence of additional drug resistance to medicines in the regimen.

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

2. Tuberculosis case detection and management in adults

This chapter discusses tuberculosis (TB) case detection and describes activities to be undertaken to improve detection in Zambia. TB case detection in the country is estimated to be 68% for drug-susceptible tuberculosis (DS-TB); 32% of TB cases are missed[1] Undiagnosed cases of TB continue to be the source of infection and fuel the epidemic through unabated transmission in the community, health facilities and congregate settings. All health care providers including community care providers should be involved in TB case detection; a health care worker should initiate TB screening in all patients they see irrespective of the patient's presenting complaint.

2.1 Strategies to reduce missed TB cases

Causes of missed TB cases

- Health systems barriers
- Individual barriers
- Low index of suspicion for TB
- Use of low-sensitivity diagnostic tools
- Suboptimal (poor-quality) samples
- Under-notification and under-reporting

- Health systems barriers:
  - Fast-track TB screening services should be created, which is also one of the infection control measures.
  - TB screening should be done at all service points, including the outpatient department, the antiretroviral therapy (ART) clinic, maternal and child health, nutrition unit and the inpatient ward.
  - Districts should ensure that TB services are available at all facilities and in the community.
- Individual barriers:
  - Bring the TB diagnostic services as close to patients as possible (i.e., targeted community screening for high-risk groups and those with access barriers to the facilities).
  - Conduct education/sensitization activities to increase patient awareness of TB (demand creation).
  - Raise TB awareness
- Low index of suspicion among health care workers:
  - Provide orientations on TB; job aids; information, education, and communication materials; and technical supportive supervision.
- Increasing access to highly sensitive diagnostic tools like Cepheid's GeneXpert®.
  - Adoption of sensitive TB screening and diagnostic algorithms.
  - Strengthen the courier system to GeneXpert sites.
- Poor-quality samples:
  - Ensure correct instructions are given to the patient before they produce sputum samples.
- Under-notification and under-reporting:

[1] WHO (2021) Global Tuberculosis Report. https://worldhealthorg.shinyapps.io/tb_profiles/?_inputs_&entity_type=%22country%22&lan=%22EN%22&iso2=%22ZM%22

- Strengthen notification and reporting by ensuring that:
  - Each department reconciles the records in their presumptive registers and inpatient registers with the TB treatment register weekly.
  - Each department in-charge ensures TB patients are notified as soon as they are diagnosed or start treatment.
  - Each facility assigns a staff to update the records from all departments daily, including weekends and holidays.
- Expand use of electronic health record systems.

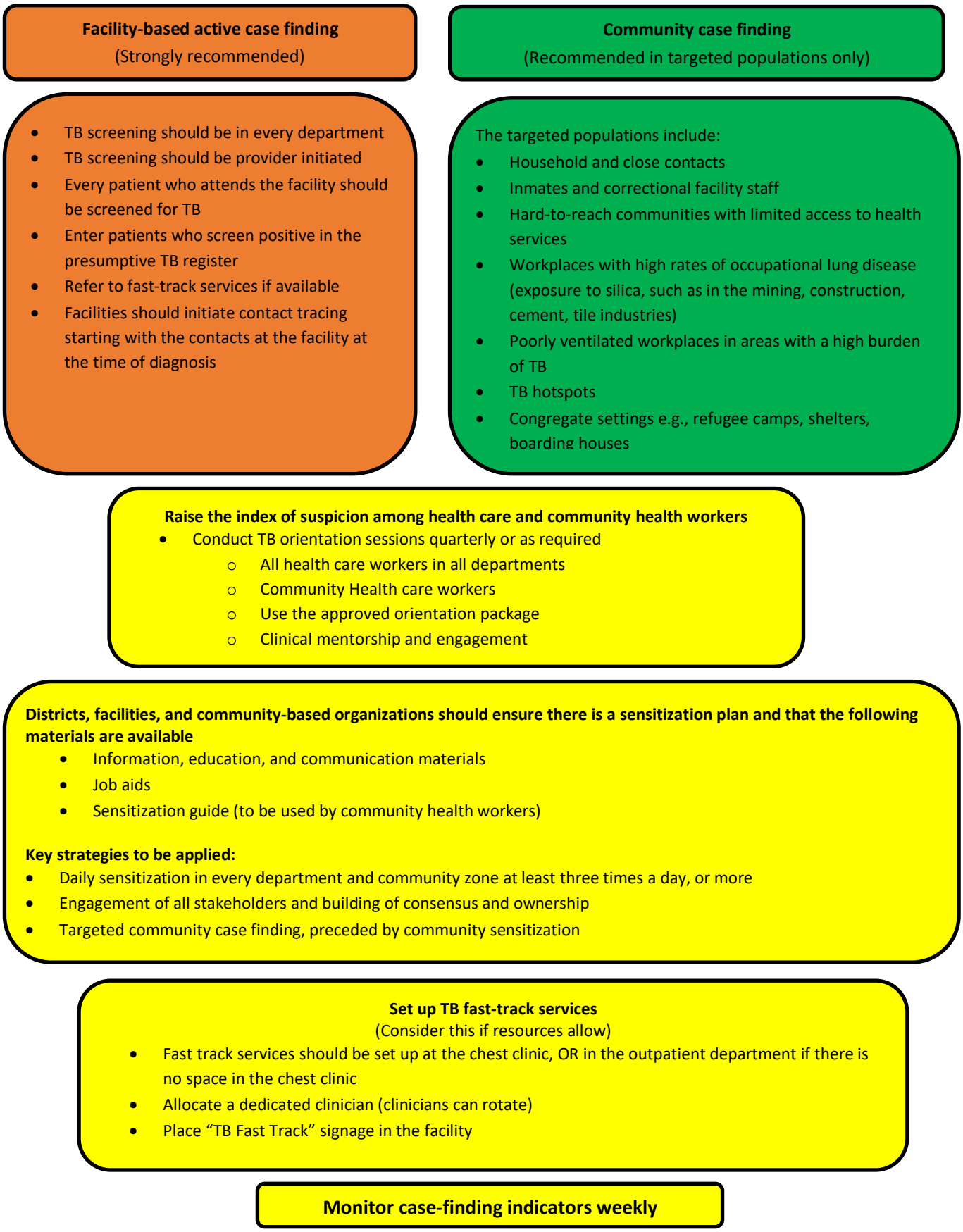
2.1.1 Types of case finding

There are two types of case finding: passive and active.

Passive TB case finding, also known as the patient-initiated pathway to TB diagnosis, happens when a person with TB disease who experiences symptoms recognized as serious and seeks health care for their symptoms. Relying on passive case finding alone can perpetuate delays in accessing TB diagnosis and treatment, so this approach should be implemented concurrently with active case finding.

Active case finding or intensive case finding is recommended to increase TB case detection. In this approach, the provider initiates TB screening in every patient in contact with the health system, irrespective of their presenting complaint. Routine contact investigation in household and close contacts of TB patients is an integral part of the active case finding.

Figure 1. Case finding recommendations.



2.2 Screening and diagnosis of TB

Screening aims to identify patients with a high likelihood of active TB disease. Screening must be followed by a confirmatory TB diagnostic test.

2.2.1 Symptom screening

Symptom screening requires asking the following questions:

- Do you have a cough?
  - Is it productive?
  - If productive, are there streaks of blood?
- Do you have fever?
- Have you lost weight?
- Do you have night sweats?
- Do you have chest pains?

A patient who says yes to any of these questions should be considered a presumptive TB patient (screen positive for TB).

In HIV-positive adolescents and adults, a cough of any duration. In HIV-negative adolescents and adults, a cough of 2 weeks or more should be carefully evaluated for TB.

Additional questions should always be asked regarding the following co-morbid conditions and lifestyle habits that can predispose a patient to TB:

- HIV
- Smoking
- Alcohol and substance abuse
- Diabetes
- Undernutrition

- Always take a comprehensive history including history of contact. This is cardinal, as it is very useful when the patient knows about the index patient's history. If there is a known contact, ask about the form of TB the index patient had and what the outcome of treatment was.
- Within the context of COVID-19 screening, risk should be stratified using duration of symptoms and risk factors for TB for the identification of presumptive TB cases.

2.2.2 Chest x-ray screening

Chest x-ray (CXR) has been shown to have high sensitivity when used as a screening tool and can identify lung abnormalities before the onset of symptoms (WHO, Chest Radiology in TB detection, 2016). Where available, patients should be screened for TB using both CXR and symptom screening. When used as a screening tool, CXR may be scored as "Any abnormality" or "Abnormality suggestive of TB" or "Normal". Patients with either abnormal score should be considered TB screen positive and followed up with confirmatory testing.

Abnormalities suggestive of TB

- Cavitation
- Consolidations in the upper zones
- Pleural and pericardial effusion
- Pleural reaction
- Pneumothorax
- Hilar lymphadenopathy
- Miliary infiltrates
- Nodules and fibrotic changes
- Lower zone infiltrates in people living with HIV, who can have atypical presentation, such as infiltrates in the lower lobes

Note: CXR has value in identifying patients with subclinical TB (i.e., before onset of symptoms, but lung changes are evident).

Chest x-ray for triaging

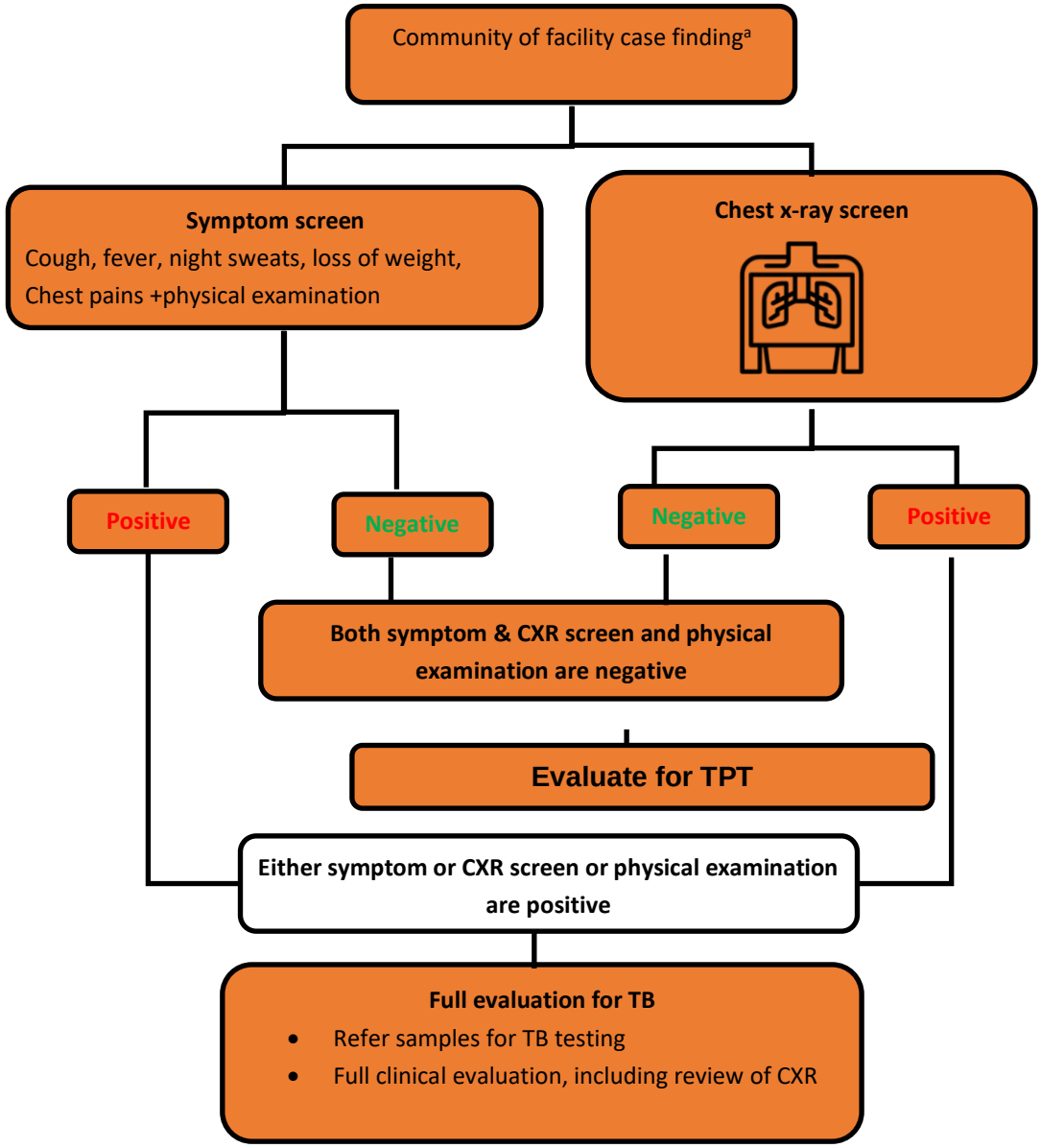
CXR is used in triaging patients with symptoms or physical findings suggestive of TB. The purpose of triaging is to reduce the number of people who need to be tested. This is required where there is limited access to confirmatory testing reagents. Please see Figure 2 below for the algorithm.

Computer-aided diagnosis

Digital CXR machines may have artificial intelligence software often referred to as "computer-aided diagnosis", or CAD. CAD analyses CXR images and generates a continuous score from 0 to 100 (this score is not a percentage). CXR images are scored as normal or abnormal based on a set and agreed-upon thresholds. All patients with an abnormal score are presumptive TB patients (screen positive).

- A high CAD score does not necessarily mean that the changes on the CXR are due to TB but indicates the level of abnormality and the likelihood of it being TB. An experienced clinician or radiologist should read and interpret the image to diagnose TB.
- All patients with CXR suggestive of TB must submit sputum for evaluation of TB before beginning treatment.

Figure 2. Screening algorithm: Symptom screening and chest x-ray screening.



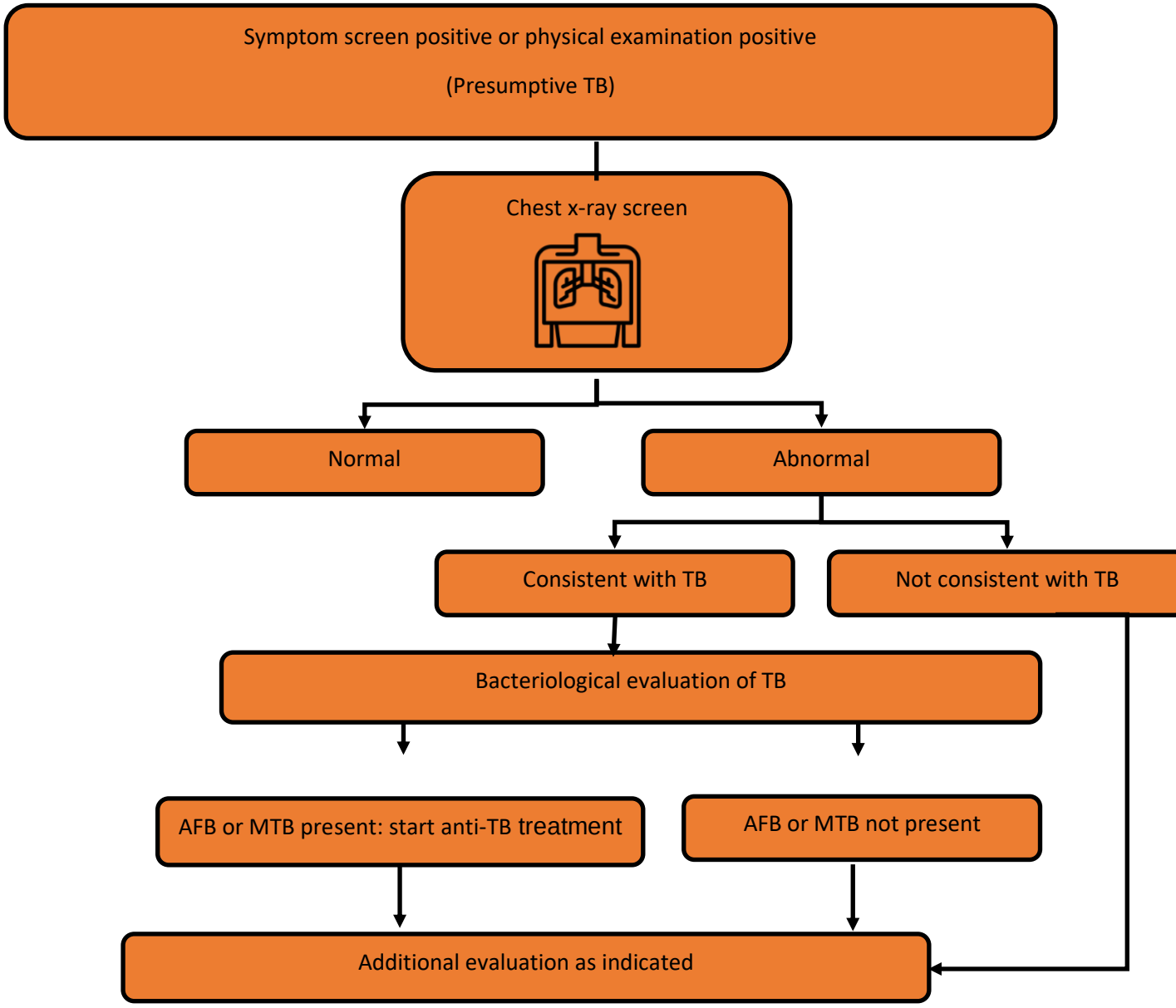
Abbreviations: CXR, chest x-ray; TB, tuberculosis; TPT, tuberculosis preventive treatment.

a. Where available, CXR can be used for screening. Patients with any abnormality showing in the CXR, regardless of symptoms, must be considered as presumptive TB and submit samples for evaluation.

- Chest x-ray should be done without relegating good clinical practice. A good history and head to toe examination

The following algorithm should only be followed where CXR and expertise are available to interpret the results. CXR may be scored by a human reader or by CAD.

Figure 3. Triaging algorithm.



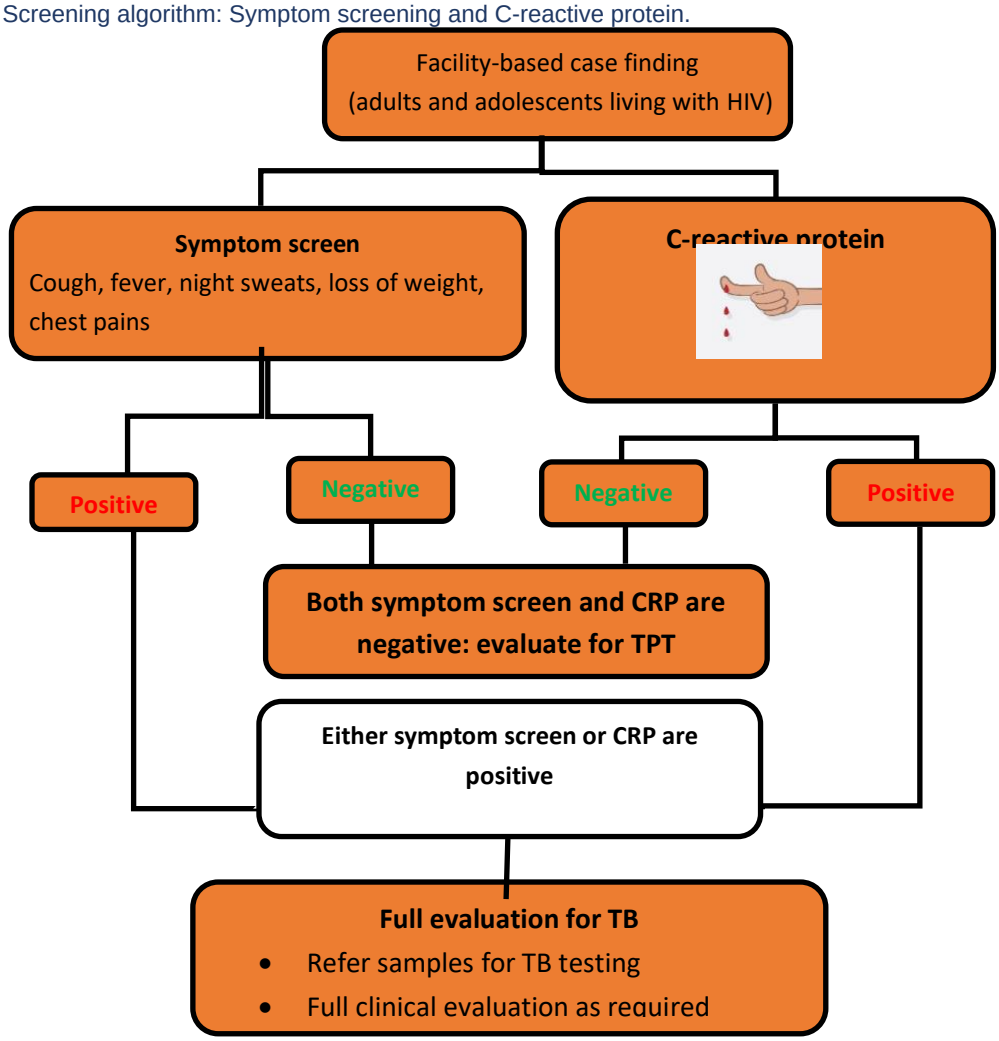
Abbreviations: AFB, acid-fast bacilli; MTB, *Mycobacterium tuberculosis*; TB, tuberculosis.

2.2.3 C-reactive protein

C-reactive protein (CRP) is an acute-phase protein and a biomarker of conditions associated with inflammation. This tool should only be used for TB screening among adults and adolescents living with HIV in combination with symptom screening. If either is positive, a person should be considered a presumptive TB patient.

The turnaround time from testing to result with many point-of-care CRP test kits is 3 to 5 minutes, allowing a quick clinical decision to refer a patient for diagnostic evaluation for TB disease or initiation of tuberculosis preventive treatment (TPT). An additional benefit of CRP is that it can alert clinicians to the presence of other diseases, such as bacterial pneumonia, bronchitis, or other infectious or non-infectious conditions (e.g., lymphoma).

Figure 4. Screening algorithm: Symptom screening and C-reactive protein.



Abbreviations: CRP, C-reactive protein; TB, tuberculosis; TPT, tuberculosis preventive treatment.

NOTE:

- CRP above the upper limit has a sensitivity of 98% and specificity of 59% in diagnosing TB.
- A very low CRP concentration < 1.5mg/l has a 100% negative predictive value.
- A concentration of CRP > 400 mg/l has a 100% positive predictive value for TB.

2.3 TB diagnosis

A diagnosis of TB can be made based on either bacteriological confirmation or clinical presentation. All presumptive TB patients should be subjected to laboratory investigations for TB using the appropriate recommended diagnostics. If a negative result is obtained but a clinician suspects TB, radiological and clinical evaluation can be used to guide diagnosis.

Bacteriological confirmation of TB

- Every effort must be made to confirm diagnosis of TB bacteriologically
- Ensure that good-quality sputum samples are given
- Where extrapulmonary tuberculosis is suspected, extrapulmonary samples should be sent for diagnostic testing
- The recommended first-line diagnostic tests are GeneXpert MTB/RIF or Ultra, Truenat, and TB LAMP

2.3.1 Laboratory investigation for TB

The tools and tests that are used for TB diagnosis provide either a definitive diagnosis (bacteriological confirmation of TB) or supportive information to aid in diagnosis of TB. Recommended diagnostic tools in Zambia include:

- GeneXpert® MTB/RIF or Ultra (Cepheid)
- Truenat™ (Molbio Diagnostics)
- TB loop-mediated isothermal amplification (LAMP)
- Smear microscopy
- Lateral flow urine lipoarabinomannan assay (LF-LAM)
- Line probe assay (LPA)
- Solid and liquid culture
- Whole Genome sequencing

This section describes recommendations for use of molecular rapid diagnostics, microscopy, and lateral flow urine lipoarabinomannan assay (LF-LAM) in the initial laboratory investigation for TB.

Molecular rapid diagnostics

Use of molecular rapid diagnostics (mRDs) is recommended for the initial detection of *Mycobacterium tuberculosis* complex (MTBC) and rifampicin resistance in all presumptive TB patients (Table 3 below)[2]. These tools include GeneXpert MTB/RIF or Ultra, Truenat, and TB LAMP. Xpert MTB/RIF or Ultra and Truenat detect both MTBC and rifampicin resistance, and TB LAMP detects only MTBC.

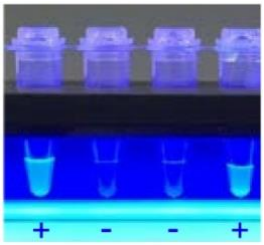
[2] WHO (2021) Consolidate guidelines on tuberculosis Module 3. https://www.who.int/publications/i/item/9789240029415

Key messages

- Molecular rapid diagnostics should only be used for diagnosis, not for monitoring treatment response.
- HIV-positive patients with signs and symptoms of disseminated TB who test GeneXpert negative should have specimens sent for culture or whole genome sequencing (WGS).

GeneXpert MTB/RIF

Truenat



LAMP

mRD tools should be used following the algorithm in Figure 5, where molecular diagnostic testing can be conducted on-site or accessed through a reliable sample referral system with short turnaround times.

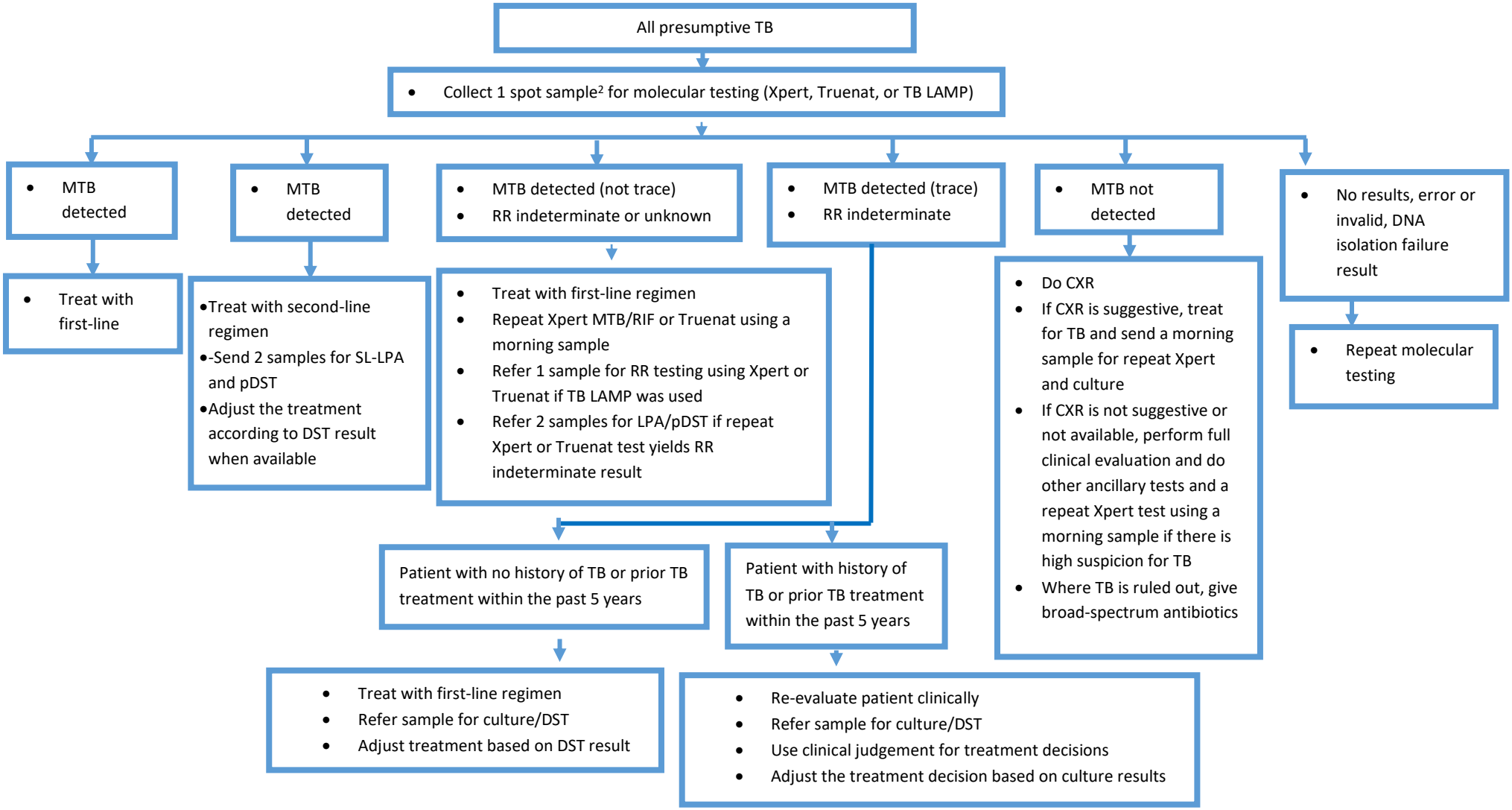
Table 3. Recommendations for use of molecular rapid diagnostic tests for initial detection of *Mycobacterium tuberculosis* complex and rifampicin resistance.

Patient category	Recommended molecular test(s)	Recommended specimens
All presumptive TB cases with signs and symptoms of PTB	• GeneXpert MTB/RIF or Ultra • Truenat • LAMP	• Sputum • Stool • Gastric lavage • Nasopharyngeal • Sputum
All presumptive TB cases with signs and symptoms of EPTB	• GeneXpert MTB/RIF or Ultra • •	• Sputum • CSF • Lymph node aspirate • Lymph node biopsy • Pleural fluid • Peritoneal fluid • Pericardial fluid • Synovial fluid • Urine • Pus
All HIV-positive presumptive TB cases with signs and symptoms of disseminated TB	• GeneXpert MTB/RIF or Ultrap	• Sputum • Blood • CSF • Lymph node aspirate

		• Lymph node biopsy • Pleural fluid • Peritoneal fluid • Pericardial fluid • Synovial fluid • Urine • Pus

Abbreviations: CSF, cerebrospinal fluid; EPTB, extrapulmonary tuberculosis; LAMP, loop-mediated isothermal amplification; PTB, pulmonary tuberculosis; TB, tuberculosis.

Figure 5. Algorithm for use of molecular rapid diagnostic testing as initial testing for detection of *Mycobacterium tuberculosis* complex and rifampicin resistance.



Abbreviations: CXR, chest x-ray; LAMP, loop-mediated isothermal amplification; MTB, *Mycobacterium tuberculosis*; pDST, phenotypic drug susceptibility testing; RR, rifampicin resistance; SL-LPA, second-line line probe assay; TB, tuberculosis.

- MTB detected includes high, medium, low, and very low, and does not include trace.
- Full clinical evaluation for TB may include CXR; additional clinical assessments; use of ancillary tests such as CRP, repeat Xpert, Truenat, or TB LAMP testing; culture or clinical response following treatment with broad-spectrum antimicrobial agents.
- In people living with HIV, under-5 malnourished children, and chronic kidney disease patients, irrespective of HIV status, an LF-LAM assay may also be used if available (refer to urine LAM algorithm).
- Samples can include sputum, cerebrospinal fluid, stool, gastric aspirates, etc. (Refer to table 3 for recommended specimen types.)
- For patients with RR not detected, a sample should be sent for first-line line probe assay and culture/phenotypic DST if there is a risk of drug-resistant tuberculosis, such as in previously treated TB patients, loss to follow-up, relapse, failure, DR-TB contacts, or smear positive at month 2 or any other month of first-line treatment.
- For patients with MTB detected (not trace), RR indeterminate, or unknown results, if the repeat Xpert or Truenat is negative, continue the first-line TB treatment and await LF-LPA and pDST.
- Recent history of TB treatment (within the past 5 years) may generate a false-positive result; hence, patients with MTB detected trace results must be investigated for recent history of TB.
- Even with a GeneXpert result of no RR detected, patients not responding to treatment should have a sample sent for culture and DST.

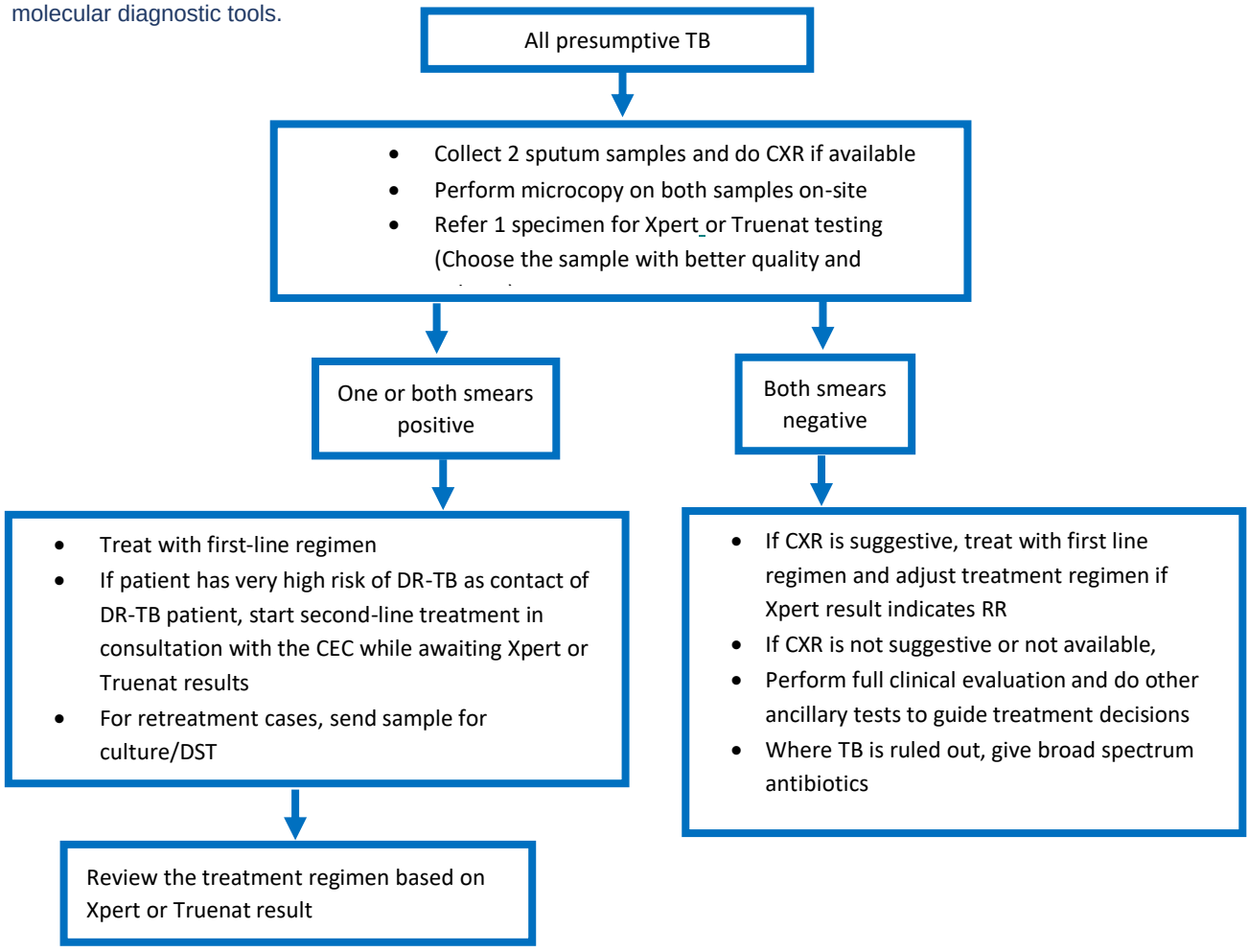
Care must be taken when interpreting CXRs of patients with a prior history of TB when confirmatory tests are negative for TB:

- CXR changes due to prior TB maybe difficult to distinguish from those of active TB.
- Patients with a prior history of TB may present with symptoms suggestive of TB due to post-TB lung disease (e.g, bronchochiectasis).
- Careful evaluation must be considered for this group of patients to avoid over-diagnosis of TB.

Smear microscopy

Smear microscopy remains useful and should be used for initial detection of acid-fast bacilli in facilities where mRD tools are not available on-site and cannot be accessed through a reliable sample referral system with short turnaround times. The algorithm for smear microscopy is shown in this figure.

Figure 6. Algorithm for use of microscopy for initial diagnosis of tuberculosis where there is no access to molecular diagnostic tools.



Abbreviations: CEC, Clinical Expert Committee; CXR, chest x-ray; DR-TB, drug-resistant tuberculosis; DST, drug susceptibility testing; RR, rifampicin resistant; TB, tuberculosis.

- Each sputum sample should be accompanied by one form to be used to report the microscopy results and a second form to be sent with the sample for GeneXpert or Truenat testing.
- Microscopy is not recommended for extrapulmonary specimens. These samples should be referred for Xpert testing.

Key message

- Sputum smear microscopy should only be used for initial diagnosis where there is no access to rapid molecular tests.
- Sputum smear microscopy should be used for monitoring treatment response for both DS-TB and DR-TB

Urine LAM assay

The lipoarabinomannan (LAM) assay is an immunocapture assay based on detection of the mycobacterial LAM antigen in urine. The detection of mycobacterial LAM antigen in urine does not provide any information on drug resistance.

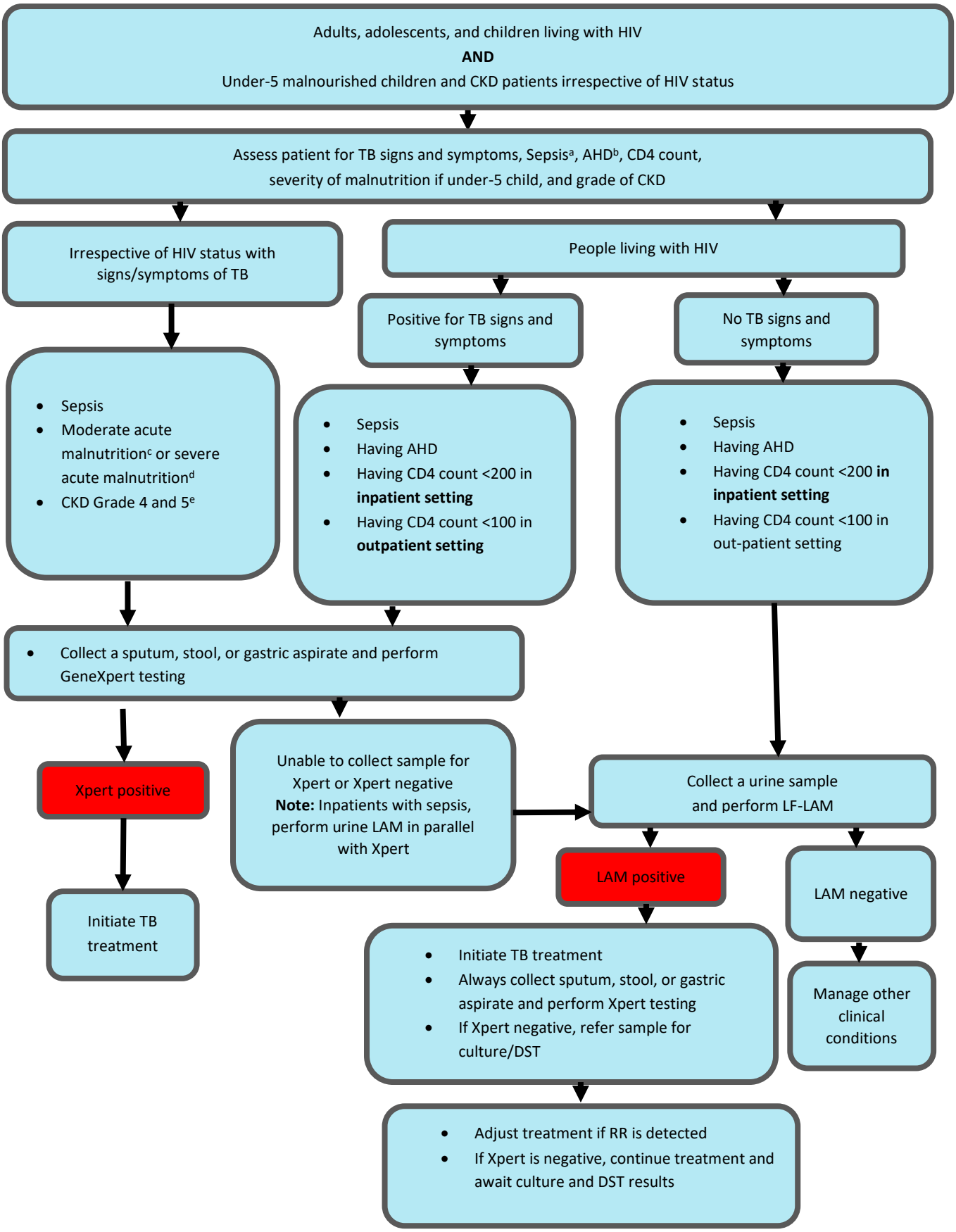
LF-LAM should be used as an initial/add-on test for bacteriological investigation of TB following the algorithm in Figure 7 below.

Key messages

- LAM is not a replacement for mRD tests.
- LAM should be used for diagnosis in recommended patient groups (fig 7).
- LAM should be used for diagnosis only and not for treatment monitoring.

Figure 7. Algorithm for use of LF-LAM to aid in the diagnosis of tuberculosis.

Note: In patients with signs and symptoms of TB, use LAM if patient is unable to provide sputum immediately OR sputum result is negative but patient history is highly suggestive of TB.



Abbreviations: AHD, advanced HIV disease; CKD, chronic kidney disease; DST, drug susceptibility testing; TB, tuberculosis.
Notes:

a. For adults, sepsis is defined by a respiratory rate of more than 30/minute, temperature of more than 39°C, heart rate of more than 120/minute, blood pressure >100/60, unable to walk unaided, and probable or suspected infection. In children, sepsis is a diagnosis of exclusion, defined as presence of acute fever (>39°C) and severe illness when no other cause is found.
b. For adults, adolescents, and children aged 5 years or more, "advanced HIV disease" is defined as a CD4 cell count of less than 200 cells/mm³ or a World Health Organization (WHO) clinical stage 3 or 4 event at presentation for care. **All children with HIV aged under 5 years should be considered as having advanced disease at presentation.**
c. Moderate acute malnutrition is defined as moderately low weight-for-age or weight-for-length (between –3 and –2 z-scores of the WHO Child Growth Standards median) and/or a mid-upper arm circumference (MUAC) 11.5 cm or greater and less than 12.5 cm.
d. Severe acute malnutrition is defined by a very low weight-for-age or weight-for-length (less than –3 z-scores of the median WHO growth standards) or MUAC <11.5 cm, by visible severe wasting, or by the presence of nutritional edema.
e. Grade 4 chronic kidney disease (CKD) is defined by an estimated glomerular filtration rate (eGFR) of 29 to 15 mL/minute/1.73m^2. Grade 5 CKD is defined by an eGFR of >15 mL/minute/1.73m^2.

2.3.2 Collection of a good-quality sputum sample

A good-quality sputum specimen is required for accurate diagnosis of TB in the laboratory—described as ≥2.5 mL in volume and mucoid/mucopurulent in appearance. Efforts should be made to avoid sending salivary samples to the laboratory.

Definition of good-quality sample

- Volume ≥2.5 mL
- Appearance/Consistency—mucoid/mucopurulent

Give clear instructions to the patient

- Sputum, not saliva, is required for laboratory testing
- Salivary samples are not good-quality specimens for TB diagnosis
- The sample should come from the chest and not from the mouth
- Show the patient the level sample should reach
- Instruct the patient to tightly close the container after serving the specimen

What to do if patient cannot expectorate spontaneously (simple respiratory physio-maneuvers)
May result in cough spasm with aerosol production. Must be done in a well-ventilated area. The health care or community health worker must stand behind the patient when giving instructions and wear an N95 mask every time they support a patient with this procedure.

- Explain the procedure to the patient
- Instruct the patient to take a deep breath and hold for a few seconds, then breathe out slowly three times
- On the third breath, ask the patient to forcibly cough out
- Check the quality of the collected sample before submission to the laboratory
- If salivary specimen is submitted, ask the patient to try again

Sputum induction

Recommended only for general and higher-level hospitals. Saline inhalation may cause bronchoconstriction, thus careful safety measures should be taken. Lung function must be determined before this procedure. Use of salbutamol is required before the procedure. Must be done in a well-ventilated area, and staff must wear an N95 mask.

- Sputum induction should be done by trained medical staff
- Explain the procedure to the patient
- Oxygen saturation must be >92%
- Respiratory rate must be less than 20 breaths/minute
- Set nebuliser (output ~1 mL/minute); fill it with sterile saline solution
- Measure baseline forced expiratory volume (FEV_1) (or peak expiratory flow [PEF])
- Premedicate patient with inhaled salbutamol (200 µg) and repeat FEV_1 (or PEF) after 10 minutes
- Start nebulization and ask the patient to perform tidal breathing (15 to 20 minutes)
- Ask the patient to perform inhalation for 5-minute intervals, followed by coughing and expectoration
- After each 5-minute interval, carry out FEV_1 (or PEV); if FEV_1 (or PEV) falls >20% from post salbutamol value, stop the procedure

2.3.3 Laboratory investigation for drug resistance

Patients who have rifampicin-resistant tuberculosis (RR-TB) detected by rapid molecular testing and patients in whom drug-resistant tuberculosis (DR-TB) is suspected must have samples sent for a full investigation of drug resistance. Recommended diagnostic tools for drug susceptibility testing (DST) include molecular and culture-based phenotypic DST (pDST).

High-risk groups for DR-TB

- Previously treated for TB
- DR-TB contacts
- Smear positive after 2 months of treatment
- Health care workers

Molecular-based DST

Currently available molecular DST methods in-country include LPAs, namely GenoType MTBDR*plus* and GenoType MTBDRsl.

Recommendations for use of LPAs for DST

LPAs are recommended for rapid detection of resistance to rifampicin, isoniazid, fluoroquinolones, and aminoglycosides.

First-line LPAs (FL-LPAs), such as the GenoType MTBDR*plus*, detect both isoniazid and rifampicin resistance and are key in confirming a diagnosis of mono-isoniazid or rifampicin resistance and multidrug-resistant tuberculosis (MDR-TB). FL-LPA should be performed for all patients at high risk for DR-TB.

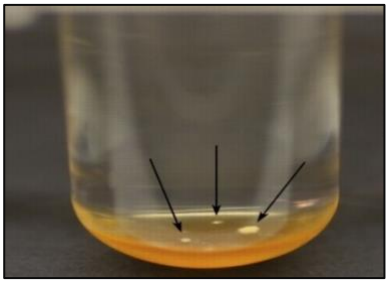
Second-line LPAs (SL-LPAs), such as the GenoType MTBDRsl test, allow for the detection of resistance to fluoroquinolones and aminoglycosides. SL-LPA should be performed in patients with confirmed MDR/RR-TB.

Recommendations for use of Whole Genome Sequencing for DST

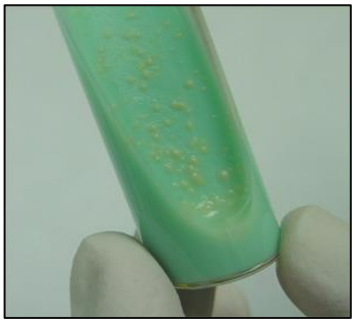
Whole Genome Sequencing (WGS) is a method for rapid detection of mutations associated with drug resistance for many anti-TB drugs. WGS is particularly useful for drugs for which phenotypic DST is unreliable. WGS is indicated on culture isolates for all DR TB patients with a positive culture result at any time point during treatment and for DR TB patients with unsuccessful pDST results.

Recommendations for use of culture-based DST (pDST)

Culture-based pDST methods are currently the gold standard for drug resistance detection[3]. Two culture methods are available: solid culture (LJ) and liquid culture (MGIT) systems.



Positive liquid culture



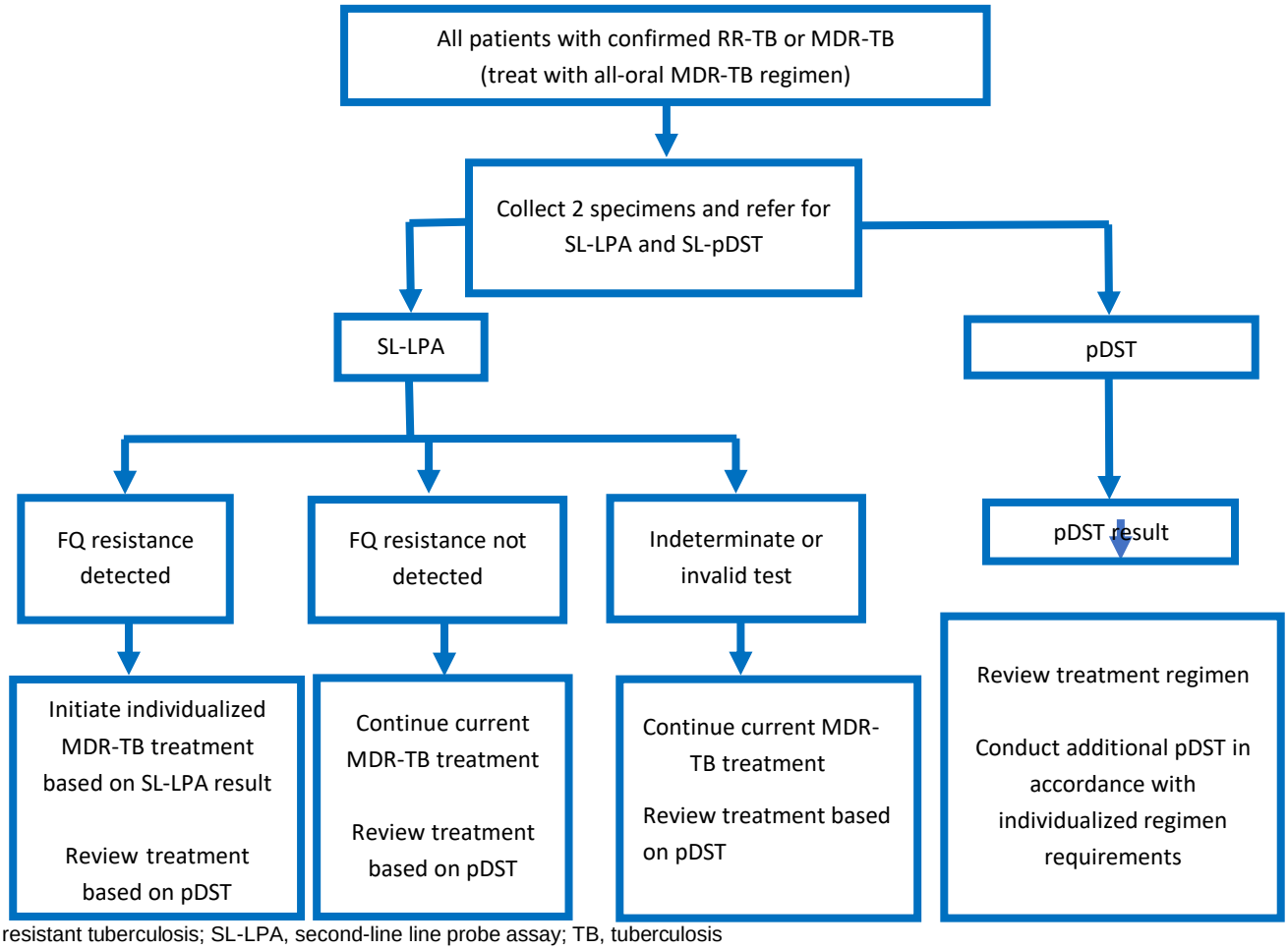
Positive solid culture

First-line pDST is recommended for detecting resistance to RIF, INH, EMB, and STR and is recommended for investigation of drug resistance in patients at high risk of DR-TB.

Second-line pDST is recommended for detecting resistance to second-line drugs and is recommended for investigation of drug resistance in patients with confirmed MDR/RR-TB. Second-line drugs for which the critical concentration has been determined and can currently be used for DST include LEV, MOX, AMK, BDQ, LZD, CFZ, DLM, ETO, and PTO. Drugs for which critical concentrations have not been determined and cannot be used for pDST currently include CS, TZD, IMP/CLN MPM, and PAS. All patients with confirmed MDR/RR-TB should be subjected to second-line DST following the algorithm below.

[3] WHO (2018) Technical manual for drug susceptibility testing of medicines used in the treatment of tuberculosis. https://apps.who.int/iris/bitstream/handle/10665/275469/9789241514842-eng.pdf

Figure 8. Algorithm for testing for second-line drug resistance among MDR/RR-TB patients.



Abbreviations: MDR-TB, multidrug-resistant tuberculosis; pDST, phenotypic drug susceptibility testing; RR-TB, rifampicin-resistant tuberculosis; SL-LPA, second-line line probe assay; TB, tuberculosis

- For any positive culture recovered during treatment monitoring that is suggestive of treatment failure, perform second-line pDST.
- Review the treatment regimen based on the current pDST result.
- If access to LPA is available in the province, one sample should be sent to the provincial laboratory for LPA and two samples should be sent for pDST at the culture laboratory.
- If there is discordancy in the LPA and pDST results, treat the patient based on the positive results
- If there is discordancy in the LPA and pDST results, management treat the patient based on the result with the highest level of resistance detected and await WGS results.
- Review treatment decisions based on WGS results.

NOTE: Facilities should alert the culture laboratory about the need for WGS for patients with discordant DST results.

2.3.4 Laboratory investigation for monitoring treatment

Recommended tests for treatment monitoring are smear microscopy and culture.

Recommendations for use of smear microscopy for treatment monitoring are described in section 2.11 for drug-susceptible tuberculosis (DS-TB) and section 2.21.6 for DR-TB.

Culture is recommended to monitor treatment for DR-TB. All patients on treatment for DR-TB should have specimens examined for viable bacilli monthly using culture.

Table 4. Specimen collection, storage considerations, and turnaround time.

Method	Specimen type	Storage conditions	Volume/amount required	Number of specimens	Turnaround time
Microscopy	Sputum	2°C to 8°C for 7 days Up to 48 hours at room temperature	3 to 5 mL	2 spot specimens (2nd specimen to be collected one hour post the submission of the 1st specimen) 1 spot specimen for follow-up smears	24 hours
Culture	Sputum	2°C to 8°C for 7 days	3 to 5 mL	2 spot specimens	4 to 6 weeks
	Pleural effusions	2°C to 8°C for 24 hours	20 to 50 mL	1	
	Bronchial secretions	2°C to 8°C for 24 hours	5 to 10 mL	1	
	Gastric lavage	2°C to 8°C for 24 hours	5 to 10 mL	1	
	CSF	2°C to 8°C for 24 hours	3 mL	1	
Molecular tests (Xpert, TB LAMP, Truenat)	Sputum	2°C to 8°C for 10 days Up to 72 hours at room temperature (maximum 35°C)	3 to 4 mL	1	24 hours
	Pleural effusions	2°C to 8°C for a maximum of 7 days	20 to 50 mL	1	
	Bronchial lavage	2°C to 8°C for a maximum of 7 days	2 to 4 mL	1	
	Gastric lavage	2°C to 8°C for a maximum of 7 days	5 to 10 mL	1	
	CSF	2°C to 8°C for a maximum of 7 days	3 mL	1	
	Stool	2°C to 8°C for 72 hours Up to 8 hours at room temperature	2 to 5 grams (equivalent to 2 to 5 scoops)	1	
Urine LAM	Urine	2°C to 8°C for 72 hours Up to 8 hours at room temperature	2 to 5 mL	1	2 hours
LPA	Sputum	2°C to 8°C for 7 days	2 to 5 mL	1	2 to 5 days for culture laboratories
					2 to 3 days for provincial laboratories

Abbreviations: CSF, cerebrospinal fluid; LAM, lipoarabinomannan; LAMP, loop-mediated isothermal amplification; LPA, line probe assay; TB, tuberculosis.

Notes:

- All efforts should be made to collect the required volume of specimen. If a specimen does not meet the volume requirements, the specimen should still be submitted to the laboratory and the laboratory should follow steps to avoid unnecessary rejections**.**
- Where possible, such as in inpatient settings, collection of early morning sputum samples is encouraged.

2.4 Interpretation of results

2.4.1 Rapid diagnostics

The results shown in the table below should be reported immediately after performing rapid diagnostic tests.

Table 5. Rapid diagnostic test results and their interpretation.

Method	Result	Interpretation
GeneXpert MTB/RIF, GeneXpert Ultra, Truenat	MTB not detected	Specimen is negative for MTB.
	MTB detected; rifampicin resistance not detected	Patient is positive for rifampicin-sensitive MTB; and therefore, has bacteriologically confirmed TB.
	MTB detected; rifampicin resistance detected	Patient is positive for rifampicin-resistant MTB; and therefore, has bacteriologically confirmed DR-TB.
	MTB detected; rifampicin resistance indeterminate	Patient is positive for MTB and therefore the patient has bacteriologically confirmed TB. However, the result is inconclusive for RIF resistance
	Inconclusive results (error, invalid, no result)	Successful test could not be performed on the submitted specimen. Test should be repeated.
	MTB detected, trace/rifampicin result indeterminate	Patient is positive with trace amounts of MTBC DNA and inconclusive results for RIF resistance. In patients with no history of TB in the past 5 years, this result implies the patient has bacteriologically confirmed TB.
TB LAMP	Positive	MTB was detected from the specimen therefore the patient has bacteriologically confirmed TB.
	Negative	MTB was not detected from the specimen.
	Indeterminate	The result is not conclusive. Test should be repeated.
Urine LAM	Positive	MTB was detected from the specimen therefore the patient has bacteriologically confirmed TB.
	Negative	MTB was not detected from the specimen.
	Invalid/Indeterminate	The result is not conclusive. Test should be repeated.

Abbreviations: DR-TB, drug-resistant tuberculosis; LAM, lipoarabinomannan; LAMP, loop-mediated isothermal amplification; MTB, *Mycobacterium tuberculosis*; MTBC, *Mycobacterium tuberculosis* complex; TB, tuberculosis.

2.4.2 Smear microscopy

The number of acid-fast bacilli (AFB) seen in a smear reflects the patient's infectivity. The laboratory records the number of bacilli seen as shown in Tables 6 and 7.

Table 6. Reporting for fluorescence microscopy results (x400).

Number of AFB found (x400)	Record as (laboratory register)	Report as (requisition/report form)	Interpretation
No AFB in one length	No AFB seen	No AFB seen	Negative
1–2 AFB in one length	Report actual number[a]	Low yield positive	Positive
3–24 AFB in one length	Scanty positive	Low yield positive	Positive
1–6 AFB in one field	1+	1+	Positive
7–60 AFB in one field	2+	2+	Positive
>60 AFB in one field	3+	3+	Positive

Abbreviation: AFB, acid-fast bacilli.

Confirmation is required by another technician. Preparation and examination of a second smear is required if a second reader is not available Report as positive (actual number only if the result is confirmed by a second reader or a repeat smear also shows an actual grading).

Table 7. Reporting of Ziehl–Neelsen results.

Number of bacilli seen in smear	Record as (laboratory register)	Report as (requisition/report form)	Interpretation
No AFB in 100 fields	No AFB seen	No AFB seen	Negative
1–9 AFB in 100 fields	Record exact number of bacilli	Low yield positive	Positive
10–99 AFB in 100 fields	1+	1+	Positive
1–10 AFB per fields; check 50 fields	2+	2+	Positive
>10 AFB per field; check 20 fields	3+	3+	Positive

Abbreviation: AFB, acid-fast bacilli.

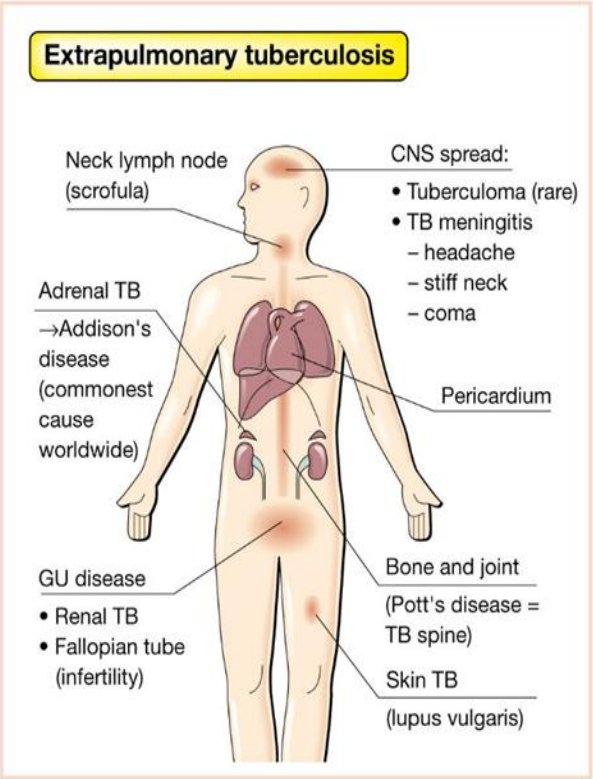
Notes:

- A patient with at least one smear-positive sputum is considered a positive case of TB.
- A patient with two negative sputum smear results must be further evaluated clinically by qualified clinician. Chest x-ray and other forms of medical imagining, and patient examination, are key for clinical evaluation and to decide whether to treat for TB.

2.5 Extrapulmonary tuberculosis

Clinical findings of extrapulmonary tuberculosis (EPTB) depend on the organ that is affected.

- Nonspecific symptoms such as fever, night sweats, and weight loss may be present.
- Cold abscess could be due to TB.
- Symptoms specific to the organ involved.
- Diagnosis is usually through a combination of clinical examination and laboratory and radiological evaluation.



Source: Medicine at a glance (www.ataganceseries.com).

Key messages

- All forms of EPTB can have pulmonary involvement; therefore, send sputum samples for GeneXpert MTB/RIF or Ultra, smear, or culture. Where sputum cannot be collected, send a stool sample.
- EPTB samples (e.g., cerebrospinal fluid, plural fluid, lymph node aspirate/biopsy, etc.), depending on the site, should also be sent for Xpert testing.

2.5.1 Clinical Findings of EPTB

The clinical presentation of EPTB depends on the affected site.

Table 8. Clinical findings of extrapulmonary tuberculosis.

Site	Typical presentation	Examination findings	Investigations	Management
Lymph nodes (TB adenitis)	Painless swelling in the neck (but also axillae, inguinal can be affected).	• Asymmetrical enlarged lymph nodes (can be matted). • Discharging sinus, cold abscess.	**Needle aspiration** • If the node is fluctuant, send sample for Xpert MTB/RIF and culture. • Fine needle aspirate cytology (FNAC) if not fluctuant. Sample referred to cytology. • If FNAC is negative, do an excision biopsy for histopathology. **Chest x-ray** • Nodes in chest (mediastinum enlargement). **Abdominal ultrasound** • Intra-abdominal lymph nodes. **CT scan** of abdomen and chest.	• Start TB treatment • In the absence of bacteriological diagnosis and poor clinical response consider differential diagnosis
Pleura (pleural TB)	Initially asymptomatic, then chest pain (usually unilateral). Shortness of breath.	• Reduced breath sounds and dullness on percussion.	**Chest x-ray:** • Obliteration of costo-phrenic angle if massive homogeneous opacity with fluid level. **Pleural tap:** • If pleural tap is done, send sample for GeneXpert MTB/RIF, smear, and culture though have low positivity rate: AFB <5%, culture <15%. • Elevated adenosine deaminase is suggestive of TB.	• Start TB treatment. • Massive pleural effusion: do drainage, • If pus in pleural tap, consider empyema and refer to higher level for drainage. • If haemorrhagic refer to higher level to exclude malignancy.

Site	Typical presentation	Examination findings	Investigations	Management
Spine (Pott's disease)	Localized pain in the spine followed by deformation (Gibbus) and destruction (dorsal or lumbar). If neurological compromise: numbness, tingling and weakness in the lower limbs may be present.	• Spinal deformation. • If neurological compromise: signs of paralysis, sensory loss, and/or incontinence.	• X-ray of the spine: Wedge shaped collapse of the vertebra. • CT scan/MRI.	• Treat TB for 12 months. • Refer to physiotherapy and consult with orthopaedic surgeon.
Joint (TB arthritis)	Chronic swelling usually involving a hip, knee or elbow.	• Chronic monoarthritic, limitation of the movements, unilateral effusion in the affected joints	• X-ray of the joint: destruction of affected joint. • CT scan/MRI. • Needle aspiration of synovial fluid. • Synovial biopsy. • Specimens can be sent for Xpert MTB/RIF and culture; note low positivity rate.	• Start TB treatment. • Refer to a specialist.
Abdomen (abdominal TB)	Nonspecific symptoms: abdominal pain, abdominal distention, chronic diarrhoea, bloody stools, abdominal mass.	• Evidence of ascites or abdominal mass.	• Abdominal ultrasound: para-aortic nodes, loculated ascites, abdominal mass. • Ascitic tap: send specimen for Xpert MTB/RIF and culture (low positivity rate). • Albumin-SAAG ratio serum-ascitic albumin gradient <1.1 g/dl is consistent with TB. Elevated adenosine deaminase is suggestive of TB. • Elevated adenine deaminase. • Endoscopic examination.	• Start TB treatment. • Ascitic drainage if there is discomfort.
Meninges (TB meningitis)	Headache, fever, confusion, vomiting, stiff neck, lethargy, photophobia.	• Fever, nuchal rigidity and altered mental state, loss of consciousness, cranial nerve palsies.	• Lumbar puncture, send sample of CSF for smear, Xpert MTB/RIF, and culture. Protein increased, glucose decreased and elevated lymphocyte count (in early PMN, then lymph). • Brain CT scan or MRI.	• Start TB treatment. • Give steroids. • Treat TB for 12 months • Add corticosteroids.

Site	Typical presentation	Examination findings	Investigations	Management
Genitourinary tract (Genitourinary TB)	Renal asymptomatic for a time with slow development of dysuria, back flank pain, blood in urine. Male: swelling and pain of testes. Female: main complaint is **infertility** (nonspecific symptoms abdominal pain).	• Nonspecific: renal angle tenderness. • Genital TB, male: scrotal swelling, epididymitis.	• Urine Xpert MTB/RIF or Ultra. • Urine LAM. • Urinalysis: low PH, haematuria, leucocytes, or bacteria on microscopy with a negative urine culture. • **Ultrasound:** renal, scrotum, ovary, gynaecological. • Fluid collection with loculation, fibrinous strands. • **Cystoscopy:** urethral strictures. • Biopsy/Needle aspiration.	• Start TB treatment. • Consult urologist or gynaecologists as needed.
Skin (cutaneous TB)	Chronic, painless, non-pathognomonic lesions.	• Typically: undermined edges of an ulcer, erythema or large tuberculomas	• Punch biopsy: send specimen for smear, culture, and pathology.	• Start TB treatment.
Eyes (Ocular TB)	Pain in the eyes, loss of or reduced vision, swelling or mass with foreign body sensation.	• Nonspecific findings (granulomatous uveitis, endophthalmitis, retinal detachment, retrobulbar mass, disc oedema).	• Diagnosis is usually presumptive.	• Start TB treatment in consultation/collaboration with ophthalmologists.

Adapted from: Medicine at a glance (www.ataganceseries.com).

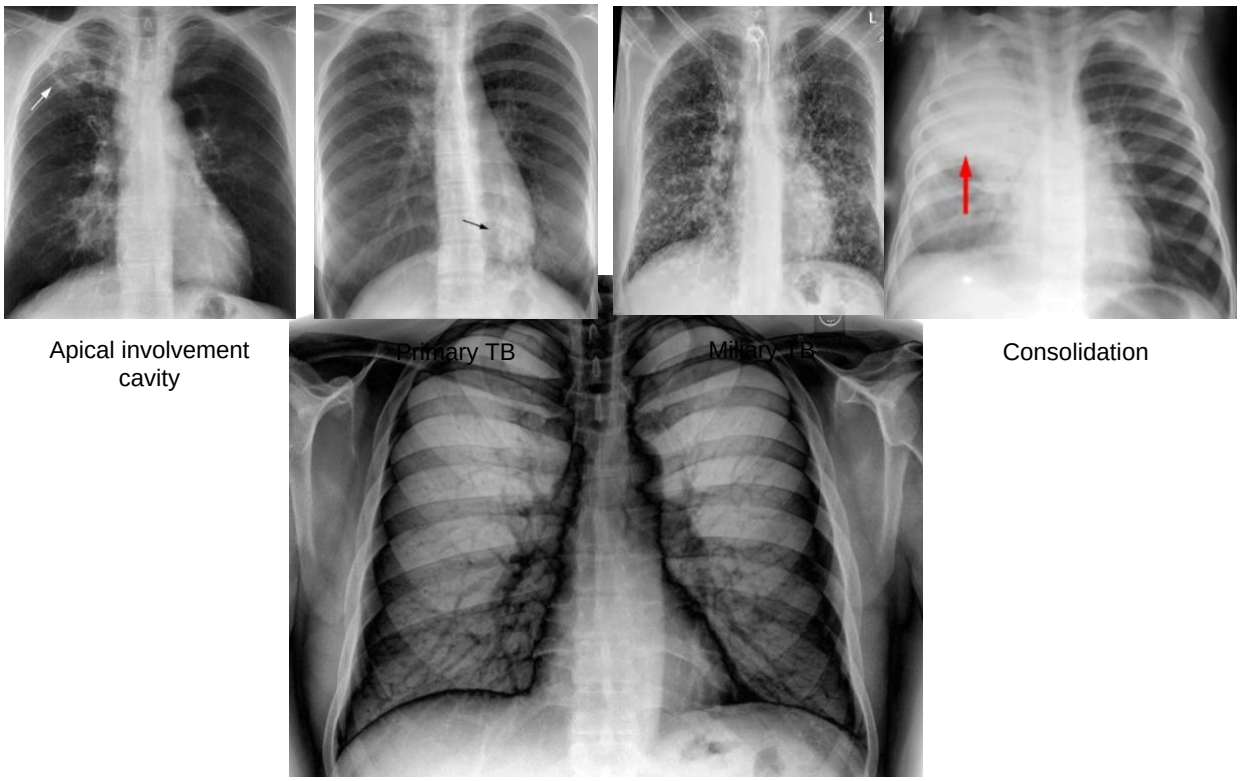
2.6 Radiology and imaging

2.6.1 Chest radiography

Chest x-ray is an important TB diagnostic aid. Care must be exercised in interpreting CXR and should always be supported by clinical findings and bacteriological diagnostic test[4]. In addition, where a CXR is not suggestive of TB, a computed tomography (CT) scan or magnetic resonance image scan can be requested, where available.

- A CXR can be done prior to sputum examination. Where it is suggestive of TB, treatment can be started. However, sputum must be collected from the patient and treatment adjusted if rifampicin resistance is detected and patient classified as bacteriologically confirmed.
- Where the bacteriological tests are negative, but a clinician suspects TB based on history and examination findings, a CXR should be used as a diagnostic aid to make a clinical diagnosis of TB.
- CXR can also diagnose complications of TB, such as pneumothorax, bronchiectasis, and fibrosis.
- A CAD value above threshold is not equivalent to TB. The CAD score should always be complemented by a human reader and clinical correlation should always be considered.

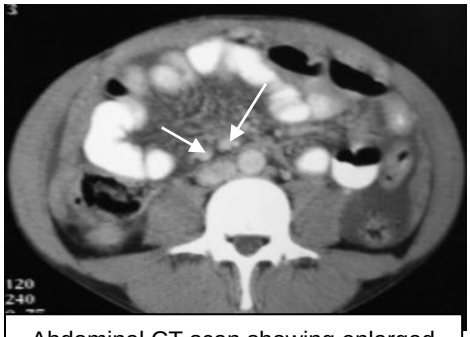
Figure 9. Abnormalities on chest x-ray suggestive of tuberculosis.



[4] WHO (2016) Radio in Tuberculosis detection https://www.who.int/tb/publications/Radiography_TB_factsheet.pdf

2.6.2 Ultrasound

- Ultrasound is specifically useful in aiding diagnosis of EPTB of the abdomen or TB affecting the pericardium and pleura. Para-aortic lymph nodes, septation and fibrinous stranding are key features of ultrasound imaging.
- Useful in diagnosing pulmonary consolidation.



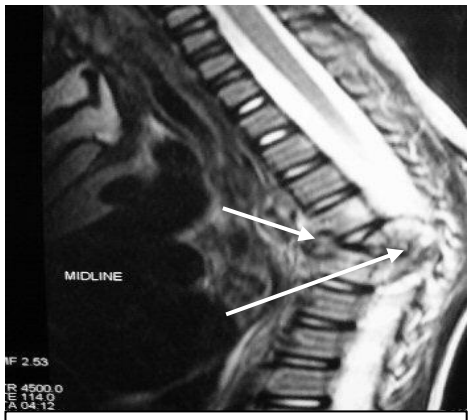
Abdominal CT scan showing enlarged lymph nodes

2.6.3 Computed tomography scan

- High-resolution imaging.
- CT scan aids in diagnosis especially when TB affects parts of the body that cannot easily be seen on standard radiography.

2.6.4 Magnetic resonance imaging

- High-resolution imaging.
- Useful in diagnosis, especially TB affecting the spine or the brain.



Collapsing disks with caseation

Where there are challenges in making a clinical diagnosis of TB, please consult by calling this toll-free number: 7040.

2.7 Tuberculosis treatment and management

2.7.1 Treatment of new and previously treated TB patients

Recommendations for treatment of new and previously treated TB patients.

Recommendations
• All drug-susceptible TB patients should be treated with first-line TB drugs. • Provide adherence support and counselling to all patients starting treatment. • As part of treatment response monitoring, **all** patients should submit sputum at month 2. • Pulmonary bacteriologically confirmed TB cases should also submit sputum at months 5 and 6 months.
Previously treated patients: • Send sample for Xpert test (if diagnosis was made using other tests). • Send samples for LPA and culture and DST. • Start first-line treatment while waiting for the full DST results.
Patients failing first-line treatment (Smear positive after 2 months of treatment) • Send samples for expedited Xpert MTB/RIF, first-line LPA, and culture, and perform full clinical evaluation of the patient. Continue with intensive phase until results of the above tests are negative. At the same time, consult with experts to guide on the management of the patient. • Provide patient with intensive adherence support.

Abbreviations: DST, drug susceptibility testing; LPA, line probe assay; TB, tuberculosis.

Principles of TB treatment

- TB treatment involves use of correct doses of multiple drugs to ensure effectiveness of therapy.
- There is no role for adding a single drug to a failing regimen.
- At no time should monotherapy (use of a single anti-TB drug) be employed as treatment for active TB disease.
- TB drugs should be taken daily for a specified period depending on the severity of the disease and clinician expert opinion.

Standard TB medicines and recommended regimens

Table 9. Standard TB medicines and recommended regimens.

TB disease category	Recommended regimen	
Treatment phase	**Intensive phase**	**Continuation phase**
All forms of TB (nonsevere)	2RHZE	4RH
Miliary TB	2RHZE	4 RH (when the meninges are affected then treatment should be for 12 months).
TB meningitis, tuberculoma, osteoarticular, ocular, and spinal TB	2RHZE	10RH

Abbreviations: RHZE, rifampicin/isoniazid/pyrazinamide/ethambutol; TB, tuberculosis.

The total duration of treatment is 12 months for TB meningitis and tuberculomas because of serious risk of disability; and mortality and osteoarticular/spinal TB and ocular TB because of difficulties of assessing response to treatment.

Weight bands for dosing of anti-tuberculous drugs

Table 10. Weight bands for dosing of anti-TB drugs.

Body weight (kg)	Intensive phase (RHZE 150/75/400/275)	Continuation phase (RH 150/75)
25–37	2	2
38–54	3	3
55–70	4	4
71 and above	5	5

Abbreviation: RHZE, rifampicin/isoniazid/pyrazinamide/ethambutol.

Indications for steroids in the treatment of tuberculosis

The most common indications for use of steroids are:

- TB meningitis
- TB pericarditis
- TB Immune Reconstitution Inflammatory Syndrome
- Massive pleural effusion
- Massive lymphadenopathy with pressure effects
- Severe hypersensitivity reactions to anti-TB drugs

More rarely:

- Hypoadrenalism
- Renal tract TB (to prevent ureteric scarring)
- TB laryngitis with life-threatening airway obstruction

Note: Steroids doses must be tapered, not be stopped abruptly.

Key message

Steroids are immunosuppressant and may theoretically increase the risk of developing opportunistic infections in TB/HIV patients. However, used as indicated above, the overall benefit of steroid use outweighs the potential risk.

Recommended doses of adjuvant steroid therapy

Table 11. Recommended doses of adjuvant steroid therapy (drug of choice is prednisolone).

Indication	Prednisolone (dosage)
TB meningitis	1–2 mg/kg (max 60 mg) for 4 weeks, then taper off over several weeks
TB pericarditis	1–2 mg (max 60 mg) for 4 weeks, then half for 4 weeks (max 30 mg/day), then taper off over several weeks
TB pleural effusion (severe)/or IRIS and others	0.5 to 1 mg (max 30 mg) for 1–2 weeks, then taper off over several weeks

Abbreviations: IRIS, Immune Reconstitution Inflammatory Syndrome; TB, tuberculosis.

What to do before starting anti-TB treatment (ATT):

- Explain to the patient their responsibilities in their treatment and the health care worker's responsibilities in their treatment.
- Provide adherence counselling
- Discuss with family members about TB and treatment of TB including a need for supporting the patients to adhere to treatment.
- Provide nutritional counselling.
- Baseline complete blood count, renal function tests, and liver function tests should be performed where available. **However, this should not cause delay of treatment start.**

2.8 Management of TB in special conditions

2.8.1 Pregnancy and breastfeeding mothers

TB and pregnancy

- All first-line anti-TB drugs (RHZE) are safe in pregnancy.
- Pregnant women diagnosed with TB should start anti-TB treatment (ATT) immediately.
- Women who become pregnant during treatment should continue with their treatment.
- Women on TB treatment should be encouraged to consult with their clinician if they intend to get pregnant.
- Women using oral contraceptives and taking rifampicin should use alternative methods of contraception, such as condoms, because rifampicin lowers blood concentration of the contraceptive drug, thereby increasing the risk of unplanned pregnancy.

2.8.2 TB and breastfeeding mothers

- **Breastfeeding should not be stopped** when the mother is on TB treatment.
- If a mother is sputum positive, she should be encouraged to spend less time with the child.
- She should also be advised to be in a place with good ventilation and wear a mask when breastfeeding, as possible.
- Children born to mothers with TB should be vaccinated with BCG at birth. TPT should be given if the child is well and has no signs and symptoms suggestive of congenital TB. After completion of TPT, the child should be revaccinated if they do not have the BCG scar.
    - If a mother develops TB during breastfeeding, give TPT to the child if they screen negative for TB. Revaccinate the child if they do not have the BCG scar.
    - HIV-positive or HIV-exposed infants should be given BCG at birth; and when active TB is excluded, they should be initiated on TPT. At the end of the TPT course, the child should be revaccinated if they do not have the BCG scar.

2.8.3 Patients with kidney disease or liver disease

Kidney disease

- Isoniazid and rifampicin are eliminated by biliary excretion, so no change in dosing is necessary.
- There is significant renal excretion of ethambutol and metabolites of pyrazinamide, and doses should therefore be adjusted:
    - Give a half-dose of ethambutol daily.
    - Pyrazinamide dosage should be adjusted as per creatinine clearance.
    - Dosing of pyrazinamide at 25 mg/kg and ethambutol at 15 mg/kg is recommended if creatinine clearance is less than 30 mL/minute.
    - While receiving isoniazid, patients with severe renal insufficiency or failure should also be given pyridoxine to prevent peripheral neuropathy.

Liver disease

- Most anti-TB drugs can cause liver injury; and therefore, care is needed in treating TB patients with underlying liver disease.
- Caution should be exercised in prescribing pyrazinamide, as it is the most hepatotoxic anti-TB drug.
- Rifampicin and isoniazid plus one or two non-hepatotoxic drugs such as streptomycin or ethambutol can be used, for a total treatment **duration of 6 months or 12 months, depending on the regimen used**.
- If the patient has severe liver damage (two times the upper limit of normal if symptomatic and three times the upper limit of normal if asymptomatic), an alternative regimen is streptomycin plus isoniazid, rifampicin, and ethambutol in the initial phase, followed by either rifampicin and isoniazid for 4 months **or** isoniazid and ethambutol in the continuous phase, for a total of 12 months.

Alternative regimen in liver disease

- Streptomycin, isoniazid, and ethambutol in the intensive phase; isoniazid and ethambutol in the continuation phase (2S(RHE)/4(RH) or 2S(EH/10(EH).
- Pyrazinamide should not be used in patients with liver disease.

2.9 TB and nutrition

Health care workers should educate patients on TB treatment on the importance of a balanced diet and how to have a balanced diet using locally available foods.

All patients should have a nutritional assessment (body mass index at a minimum) at the start of treatment.

Undernourished patients may benefit from micronutrient supplementation with vitamin D, zinc, thiamine, vitamin B complex, or multivitamins, depending on the clinical evaluation and the existence of other conditions, like alcoholism. Encourage patients to consume indigenous food and fruits.

2.10 Side effects of first-line TB drugs

Side effects can be grouped into minor, major and life threating categories (refer to Table 12).

In general, a patient with minor side effects should:

- Continue the TB treatment.
- Receive symptomatic treatment.

If a patient develops major side effects, the TB treatment should be temporarily withdrawn, and the patient referred to a higher level of care.

2.10.1 Risk factors for developing side effects

- Concomitant use of herbs (hepatotoxic and nephrotoxic).
- Concurrent regular alcohol use.
- Concurrent use of hepatotoxic medication or drugs (e.g., fluconazole, nevirapine, protease inhibitors).
- Concurrent liver disease (viral hepatitis, chronic liver disease).
- History of peripheral neuropathy.
- Diabetes.
- Alcoholism.
- Pregnancy and immediate postpartum period.
- Malnutrition (low albumin, low body mass index).

Table 12. Summary of side effects of anti-TB drugs and their management.

Side effects	Drug(s) probably responsible	Management
Minor		**Continue anti-TB drugs, review drug doses**
Anorexia, nausea, abdominal pain	Pyrazinamide Rifampicin	Give drugs with small meals or last thing at night.
Joint pain	Pyrazinamide	Non-steroidal anti-inflammatory drugs (aspirin, ibuprofen, diclofenac).
Burning sensation in the feet (peripheral neuropathy)	Isoniazid	• Pyridoxine 25 mg as prophylaxis. • In case of peripheral neuropathy, the dose can be increased to 50–75 mg (up to 200 mg). • Once the symptoms of peripheral neuropathy subside, revert to 25 mg. • Other options for treatment of peripheral neuropathy in those who do not respond to pyridoxine include pregabalin, carbamazepine, gabapentin, and amitriptyline.
Orange/red urine	Rifampicin	Reassure the patient that it is expected after taking the drug.
Itching	Isoniazid Pyrazinamide Rifampicin	Antihistamines and emollients; observe.
Major		
Severe skin rash with mucosal involvement (Steven-Johnson Syndrome)	Isoniazid Pyrazinamide Rifampicin	• Stop anti-TB drugs (see below reintroduction of TB drugs). • Stop all other possible offending drugs, like sulphur-containing drugs (e.g., cotrimoxazole). • Isolate patient to avoid secondary infection. • Start prednisolone 1 mg/kg. • Add anti- histaminic (e.g., promethazine). • Keep the patient warm. • Give adequate hydration (using intravenous fluids). • Consider a broad-spectrum antibiotic (for prevention of secondary infection).
Shock, purpura rash, acute renal failure, thrombocytopenia	Rifampicin (very rare, extensively exclude other causes of shock)	Stop TB treatment and institute appropriate management of shock, then refer to the next level of management.[a]
Jaundice (exclude other causes) Hepatitis	Isoniazid Pyrazinamide Rifampicin	**Stop anti-TB drugs** • When jaundice is severe or worsening. • >5x rise in ALT if asymptomatic and >3x rise if symptomatic. • Raised International Normalization Ratio (normal is <1.1). • Exclude other causes.
Psychosis, convulsions	Isoniazid	Stop TB treatment, refer for psychiatric evaluation.[a]

Side effects	Drug(s) probably responsible	Management
Visual impairment (exclude other causes)	Ethambutol	Stop TB treatment and refer to an ophthalmologist.

Abbreviations: ALT, alanine aminotransferase; TB, tuberculosis.

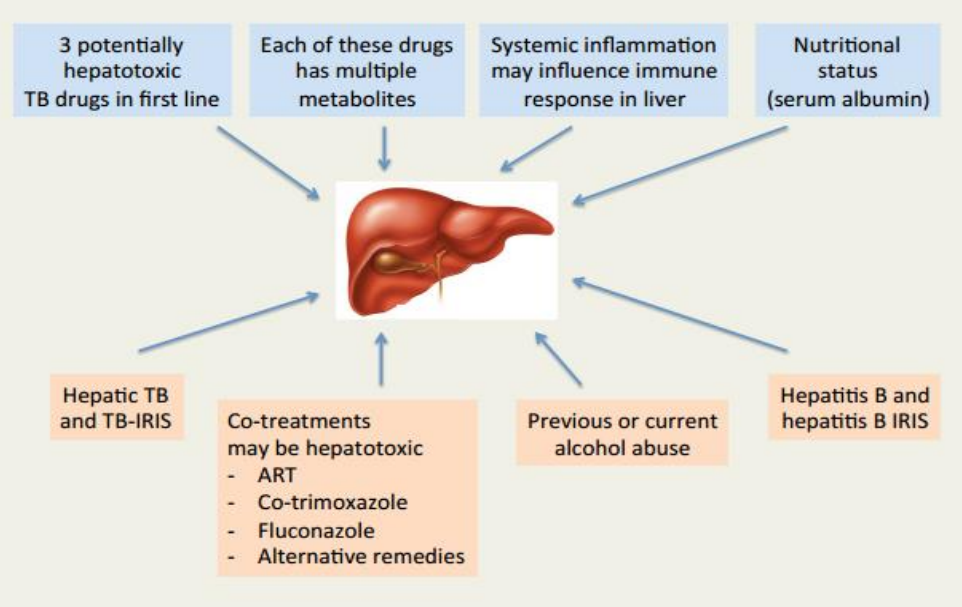
a. Fill out an adverse drug reaction form and send the report to the necessary authority within 24 hours.

Key message

Patients with Steven-Johnson Syndrome/toxic epidermal necrolysis should be referred to a level 2 or 3 hospital for appropriate management.

2.10.2 Drug-induced hepatitis

Figure 10. Etiology of drug-induced hepatitis.



Source: *A practical approach to the management of TB drug-induced liver injury*. University of Cape Town, Imperial College London (2013). www.idm.uct.ac.za.

Reintroducing ATT in TB patients' drug induced liver injury

Before reintroducing ATT, ensure the following:

- In the absence of laboratory indicators (alanine aminotransferase [ALT] and bilirubin), wait for jaundice to subside.
- There is no hepatic encephalopathy.
- ALT less than 100 IU/l (<2 times and bilirubin levels normal).
- There is no alcohol abuse.

If the patient develops drug-induced hepatitis again, refer the patient to a physician.

- Monitor ALT weekly for a month; if it remains normal after a month of close monitoring, repeat when clinically necessary.
- Monitor clinically for recurrence of jaundice at each weekly visit.
- If the condition reoccurs, refer the patient to a higher-level hospital or specialist.

Options for ATT reintroduction

The reintroduction of ATT may be undertaken using two approaches:

- Resume TB treatment at once (RHZE) if in the intensive phase or RH if in the continuation phase, gradually.
- Sequential incremental introduction from the least hepatotoxic to the most hepatotoxic single-step daily dose escalation.

Where the risk of recurrence of hepatic injury is low, option 1 is preferred. Where the risk is high, option 2 is preferred. Patients who need rechallenging with ATT should be referred to the next higher level.

Table 13. Re-challenging with anti-TB drugs following drug-induced hepatitis.

Day	Drug and dose (RHZE)	Clinical parameter to monitor laboratory tests prior to dose adjustment
1	1 tablet	Alanine aminotransferase/aspartate aminotransferase
2	2 tablets	
3	Full dose*	Alanine aminotransferase/aspartate aminotransferase
4	Full dose	
5	Full dose	Alanine aminotransferase/aspartate aminotransferase
After day 5, review liver function tests weekly for the first 1 month, twice weekly for the next 1 month, and then every 3 months.		

Abbreviation: RHZE, rifampicin/isoniazid/pyrazinamide/ethambutol.

Table 14. Option 2 : Re-challenging with Anti-TB drugs following drug-induced hepatitis[5]

Day	Drug and dose (H→R→Z) Or (R→H→Z)	Clinical parameter to monitor
1-3	E Full dose plus INH 50mg	Day 0 and Day 3 ALT/AST
4-7	E plus INH 300mg	Day 6 ALT/AST
7-9	E plus INH 300mg plus Rif 75mg	Day 9 ALT/AST
10-12	Increase Rif to 300ng	Day 12 ALT/AST
13-15	Normal dose RHE plus Z (15mg/kg)	Day 15 ALT/AST
16 onwards	Increase dose of Z to max (30-40mg/kg)	
After day 15, review liver function tests weekly for the first 1 month, twice weekly for the next 1 month, and then every 3 months.		

2.11 TB patient monitoring and follow-up

All TB patients must be seen at least once monthly by a health care provider, where the following should be done:

- Clinical review
- Assessment of side effects
- Dose adjustment according to weight
- Assessment of adherence and continue counselling

Patients who are very sick should be seen more frequently, depending on the clinician's assessment.

Frequency of clinical review can be adjusted during disease outbreaks to protect both patients and health care workers.

[5] Surendra K. et al (2010). Safety of 3 different reintroduction regimens of antituberculosis drugs after the development of antituberculosis treatment-induced hepatotoxicity. Clinical Infectious Diseases, Volume 50, Issue 6, Pages 833–839, https://doi.org/10.1086/650576

- All patients should have one sputum specimen (morning) taken for AFB smear at month 2, regardless of the type of TB and treatment regimen. Further follow-up sputum samples are required, at months 5 and 6, for patients on a 6-month regimen. Sputum monitoring during treatment should be done as shown in Table 14.

Key messages

- If a patient is found to have a drug-resistant strain of TB at any time during therapy, treatment should be declared as failed and the patient referred for DR-TB treatment and re-register as such.
- For previously treated TB patients, specimens for GeneXpert MTB/RIF, LPA, culture, and phenotypic DST should be sent before starting treatment (DST should be performed for at least rifampicin and isoniazid).

- Should sputum smear be positive at month 2, extend the intensive phase for 1 month and send samples for expedited GeneXpert, culture, and DST. Review treatment when DST results are available.

Table 14. Summary of sputum monitoring by smear during first-line treatment.

Treatment phase	Months of treatment	Sputum smear exam
Continuation phase	2[a]	• If smear positive, send sample for GeneXpert MTB/RIF, culture, and DST. • Provide intensive adherence counselling. • Do full clinical evaluation. • Extend intensive phase of treatment for 1 month.
	3	• If smear was positive at month 2, repeat smear at month 3; ensure that samples for culture and DST arrive at the laboratory. • If smear negative at month 2, do not repeat smear at month 3.
	5[a]	• If smear positive, obtain samples for Xpert MTB/RIF, culture, and DST. • Declare this patient a treatment failure; treat patient as per the DST results.
	6 or 12[a]	• If smear negative, assign appropriate treatment outcome; if positive, obtain samples for Xpert MTB/RIF, culture, and DST.

Abbreviation: DST, drug susceptibility testing.

a. Sputum smear testing should be done at these time points regardless of smear result in the preceding month.

2.12 Adherence

Recommendations

- All TB patients should receive adherence sessions at the beginning of treatment and throughout the course treatment.
- The treatment supporter (relative and community) should receive similar information as the TB patient.
- Some TB patients should receive intensive adherence counselling depending on their psychosocial needs.

Adherence to treatment refers to taking the correct doses, at the correct time, in the correct way for as long as prescribed. It is a key factor in TB treatment success.

Adherence to care refers to keeping all clinic appointments and following other instructions given by health facility staff.

2.12.1 Importance of adherence

The following are the benefits of good adherence:

- Reduces treatment failure.
- Prevents development of drug resistance.
- Decreases morbidity and mortality.
- Prevents further transmission of TB.
- Improves quality of life.

2.12.2 Adherence strategies

Adherence counselling takes a patient-centered approach:

- Establish patient social and psychological needs, taking consideration the barriers and enablers to adherence (see Table 15).
- Health care workers should encourage patients to identify a treatment buddy with whom they are comfortable.
- If a patient has a treatment buddy, encourage the treatment buddy to attend the counselling sessions and clinic visits, as possible.
- Before the start of treatment, structured adherence sessions must be given to all patients.
- Clearly outline the treatment plan prior to TB treatment initiation.
- Adherence support must be provided at each follow-up visit. Where needed, this can be done outside the standard visits.
- When a patient is not improving clinically or might not be adhering to treatment, intensive adherence counselling must be provided.
- Offer patients all the directly observed therapy (DOT) options so that they can choose what they are most comfortable with.

Recommendations for a patient who is smear positive at month 2

- Reassess the current DOT plan.
- Discuss alternatives for daily DOT as convenient for the patient, until smear-negative/DST results are available.
- Provide adherence support and counselling once a week until the patient becomes smear negative. Intensive adherence support/enhanced adherence counselling can be provided by either health care or community health workers.
- First visit must be in person to build rapport as barriers to adherence are being identified, but subsequent visits can he held virtually.
- When an in-person adherence counselling session is done, it should be documented in the patients file or records.
- Where possible, guided patient support groups should be set up as they reduce stigma and provide psychosocial support.
- Completion certificates, home visits.

Table 15. Barriers to adherence.

Patient barriers	Health system barriers
• Inadequate knowledge on the length of treatment • Inadequate knowledge of TB/HIV services • Self-stigma (denial) • Side effects due to TB/HIV medications • Language • Other comorbidities • Depression, other psychiatric problems • Difficult life conditions • Unstable living conditions (high mobility) • Patient attitudes and beliefs	• Inadequate DOT supporters • Time, cost, and distance to DOT facility • Failure of service providers to give adequate information on TB/HIV • Medication stockouts • Shortage of human resources for TB/HIV • Failure to monitor and evaluate patients • Long results turnaround times • Poor health worker attitudes

Abbreviations: DOT, directly observed therapy; TB/HIV, tuberculosis and HIV co-infection.

2.12.3 Dealing with non-adherent patients

- Be non-judgmental—develop a trusting/caring relationship.
- Make every effort to obtain the patient's voluntary adherence.
- Discuss the benefits of treatment with the patient, family, and community.
- Discuss the risks of inadequate treatment for the patient and others.
- Discuss reasons for poor adherence and try to address the barriers. A patient-led and patient-centered approach should be used in devising solutions to the barriers.
- In case of difficult patients, consult/refer for help (family, respected community members, social workers, church elders, etc.).

Should all options fail, and the patient is infectious, involuntary isolation would be the last option. The Public Health Act authorizes any registered medical practitioner to order the

involuntary admission of any person at risk of spreading disease. The patient should be hospitalised until free from infection or can be discharged without danger to the public.

2.13 Directly observed therapy

TB treatment should always be taken under direct observation. An “observer” acceptable to the patient and the health system observes the patient taking every dose of their medication, and records this for the health system to monitor.

There are three types of DOTs:

- DOT plan C: Clinic
- DOT plan V: Volunteers
- DOT plan R: Relatives

During outbreaks, Plan C and Plan V are not feasible and Plan R is recommended, coupled with regular telephone calls from the health facility staff. Emerging evidence from the mortality study shows that patients supported by family members had better outcomes of TB treatment.

2.13.1 How to conduct DOT

- Drugs should be administered under supervision of a designated trained observer; this may be a health care worker or community volunteer.
- Drug intake should be monitored every time a patient swallows a TB drug and recorded on patient’s identification card/treatment card.
- If TB treatment is supervised by someone other than the health care worker, the patient must be involved in selecting the person to supervise them.

Key messages

- Good adherence leads to better outcomes, prevents the development of drug resistance, and reduces morbidity and mortality.
- Inadequate adherence can lead to morbidity or mortality, new cases of TB, and drug resistance.

- The patient and his relatives should be made aware of the importance of daily intake of drugs for the sake of the patient’s own health and to reduce transmission to others.

2.14 Digital monitoring technologies

Different types of digital technology platforms that have some evidence of use and impact have been identified, including Short Messaging Service (SMS), medication event monitoring systems (MEMS), and video observed therapy (VOT)[6].

2.14.1 Short Message Service

Recommendation: Where available, SMS systems can be used to support adherence. SMS systems can be used in a unidirectional or bidirectional way to communicate with patients. Unidirectional communication is used to send reminders to patients about taking medication or educational information. Bidirectional is a more interactive format of communication between the patient and the health care provider.

2.14.2 Medicine Event Monitoring Systems

Recommendations: Where available, MEMS can be used for adherence monitoring[7]. Requires customized pill boxes, phone, mobile network, and internet services. The use of MEMS does not preclude the provision of patient-centered care with the support of treatment buddies.

2.14.3 Video observed therapy

VOT is a derivation of DOT whereby the observation of dose taking is achieved with real-time video and/or video recording. The technology eliminates the need for health care workers and patients to be in the same physical space and allows for virtual observation at times convenient for the patient's schedule, reducing some of the costs and barriers associated with treatment adherence. In addition to creating a detailed dosing history, the transmission of videos has the potential to generate real-time data on a patient's well-being (e.g., medication side effects, etc.).

Various apps, including WhatsApp and Google Duo, can be used for VOT.

2.15 Patient education

TB education should begin at the patient's initial visit and continue at each visit. Health staff should educate TB patients and their relatives about TB. Education is essential for obtaining the patient's cooperation over the required treatment. It is important to keep in mind that patient education is a dialogue essential to attain a high cure rate and good adherence.

Education messages should include:

- What TB is and how it is transmitted.
- Duration of treatment and outcomes.
- Importance of adherence.

---

[6] WHO (2017) Handbook for the Use of Digital Technologies to Support Tuberculosis Medication Adherence. http://apps.who.int/iris/bitstream/handle/10665/259832/9789241513456-eng.pdf?sequence=1&isAllowed=y

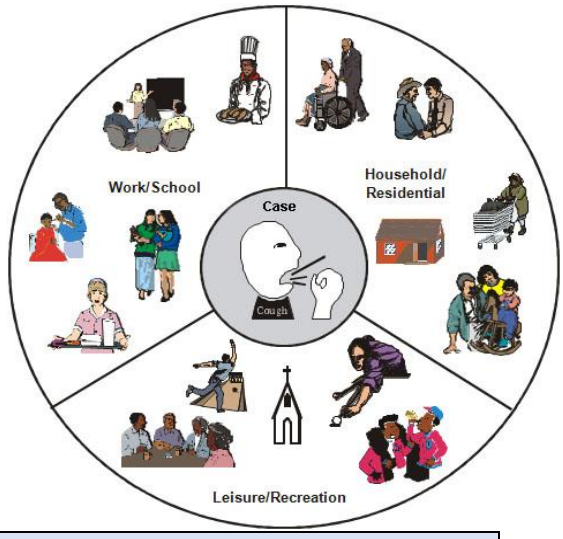
[7] WHO (2017) 6

- How to deal with circumstances such as travel and loss of tablets.
- Possible side effects.
- Importance of keeping appointments.
- Importance of eating a balanced diet and timing of the meals (taking drugs 30 minutes before eating).
- Prevention and infection control, which includes cough etiquette (coughing into a handkerchief or tissue paper, covering the mouth when coughing, using the inner elbow, and spitting into a container).
- Discourage use of concomitant remedies (herbs) due to the increased risk of toxicities and drug-to-drug interactions.
- Stigma.

2.16 Contact investigation

Contact investigation is a systematic process to identify persons (contacts) who were exposed to someone with infectious TB. The goal of TB contact investigation is to successfully stop TB transmission and prevent future cases. Contact investigation should:

- Evaluate contacts for active TB disease.
- Provide TB negative contacts with treatment for latent TB infection or TB disease (refer to the consolidated TPT guidelines).
- Educate contacts about the risk of TB and TB infection control.



Index patient who needs contact investigation

- All TB patients bacteriologically confirmed and clinically diagnosed pulmonary TB, irrespective of age.
- Priority should be given to bacteriologically confirmed TB cases and under-5 contacts of TB cases.

2.16.1 Rationale for contact investigation

People recently infected with *M. tuberculosis* are at increased risk for the development of active TB within 1 to 2 years after acquisition of the infection. This period is even shorter in children. It is assumed that people exposed to a person with infectious TB might recently have been infected and are thus at increased risk for currently having TB or for development of the disease soon. A contact investigation is required for household and close contacts of all confirmed infectious cases of TB disease. If a patient is younger than 5 years of age, a

source case investigation is recommended (reverse contact investigation). Given that some household and close contacts of index TB patients may not show any symptoms of TB at the time of TB diagnosis, contact investigation should be repeated at a time an index case completes treatment.

Recommendations

TB contacts investigation is critical in finding the cases early

- TB contact investigation saves as the entry point for TB preventive therapy for the close contacts
- Contacts investigation includes symptom screening, physical examination, radiography, and microbiological examinations of specimens
- morbidity and mortality.
- Adverse drug reactions to anti-TB medications are more common in HIV-infected patients.
- TB increases HIV viral replication, immune activation, and risk of progression to AIDS in individuals co-infected with HIV.
- Higher rates of mortality are seen in patients with MDR-TB and **HIV.**

2.16.2 Systematic approach to TB contact investigation

The TB contact investigation process should start as soon as an infectious TB patient is confirmed using a systematic process that includes the following steps. **The actual sequence and timing of contact investigation steps and activities may vary from one investigation to another.**

Figure 11. Systematic approach to TB contact investigation.

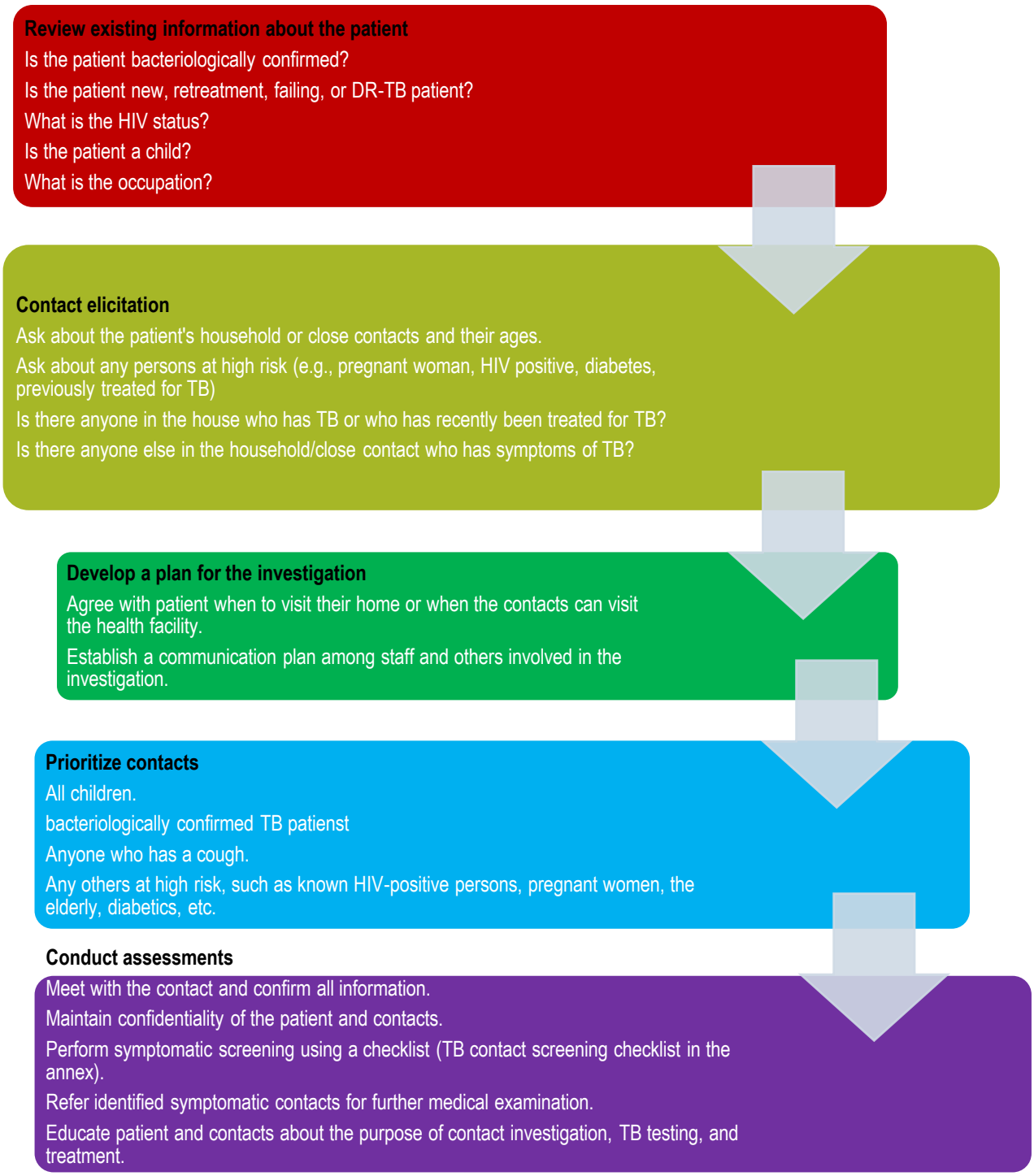
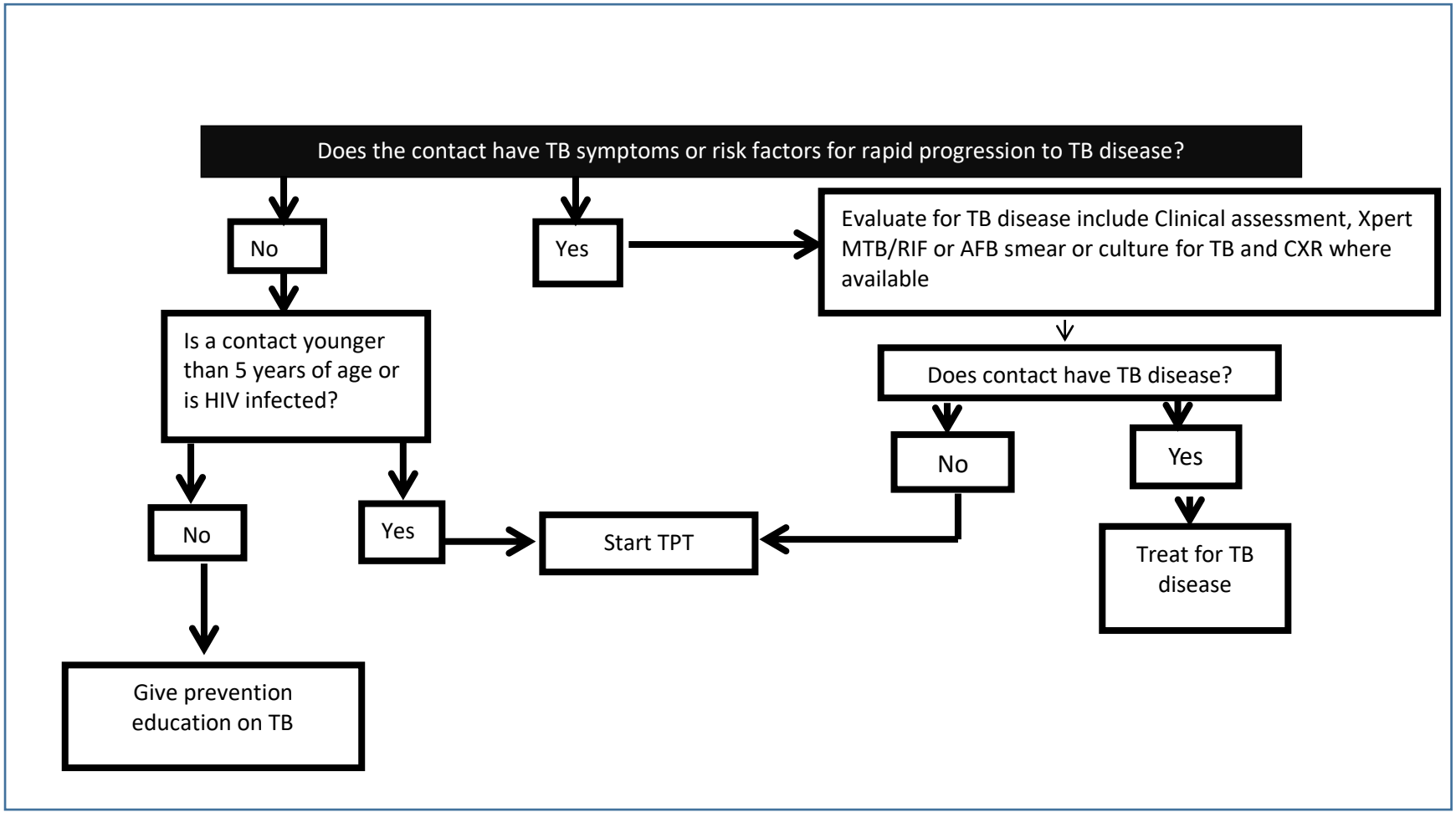


Figure 12. Contact investigation flowchart.



Abbreviations: CXR, chest x-ray; TB, tuberculosis; TPT, tuberculosis preventive treatment.

The TB team at health facility level must work collaboratively with the maternal and child health and nutrition unit teams to ensure that under-5 contacts are screened for TB at all time and points of interaction with the health system.

2.17 TB and HIV

The burden of TB among people living with HIV remains high. TB alone is responsible for at least 40% of the deaths in PLHIV. Its diagnosis among PLHIV may be challenging due to severe immunosuppression that may occur especially among patients with advanced HIV disease, also known as AIDS. Patients may not exhibit the classical symptoms of TB, as they have weak immune systems that are unable to mount adequate immune reaction. In some instances, the patients will be asymptomatic for TB and only diagnosed as an incidental finding. This is also evident among children living with HIV, as they too may not exhibit typical symptoms, compounded by diagnostic challenges associated with specimen collection. Furthermore, PLHIV have a high risk for disseminated TB, which may be subtle on presentation and thus a high index of suspicion by clinicians is needed to identify these patients. Diagnosis in such patients is cardinal before ART initiation to avoid IRIS and increased risk of mortality.

Key messages

- A high index of suspicion of TB is critical in evaluating PLHIV
- PLHIV have higher risk of progression to TB disease: an annual risk of 10% compared to HIV non-infected individuals, who have 5% to 10% lifetime risk.
- PLHIV have a higher risk of TB relapse.
- HIV-infected TB patients may present more frequently with EPTB and smear-negative TB.
- Children living with HIV may present with atypical symptoms of TB and have high risk of morbidity and mortality.
- Adverse drug reactions to anti-TB medications are more common in HIV-infected patients.
- TB increases HIV viral replication, immune activation, and risk of progression to AIDS in individuals co-infected with HIV.
- Higher rates of mortality are seen in patients with MDR-TB and **HIV.**

2.17.1 Diagnosis of co-infected TB and HIV patients

- Diagnosis of TB includes clinical, bacteriological, and radiological testing, as discussed under the diagnosis section.
- LF-LAM can be used for patients with CD4 counts of less than 100 cells/mL in outpatients or hospitalized AHD patients.

When making a diagnosis of TB in PLHIV, keep in mind that:

- A good number of PLHIV will have smear-negative results due to paucibacillary disease.
- The patients may have atypical presentations of pulmonary tuberculosis and more frequently EPTB.
- Radiological findings may be normal or atypical.
- Concomitant HIV/associated illnesses are common. The presence of one diagnosis does not exclude other causes.

Other infectious and neoplastic complications of HIV can present, like TB in HIV infection:

- Bacterial pneumonia
- Fungal pneumonia
- Pneumocystis jirovecii pneumonia
- Viral pneumonias such as COVID-19, herpes simplex, or Cytomegalovirus pneumonitis
- Nontuberculous Mycobacterium
- Pulmonary Kaposi's sarcoma
- Lymphoma
- In HIV-infected children, lymphoid interstitial pneumonitis
- Castleman disease

2.17.2 Management of TB/HIV co-infected patients

- All TB patients with HIV should start ART regardless of CD4 count. TB treatment should be initiated first, followed by ART as soon as the patient can tolerate ART, preferably within the first 2 weeks of TB treatment.
- HIV-positive patients with profound immunosuppression should receive ART within the first 2 weeks of initiating TB treatment. There should be adequate treatment preparation to minimize loss to follow-up.
- Modifications to the ARV regimen should be made to avoid overlapping toxicities and drug-drug interactions between ART and TB medications (refer to ART guidelines).
- Drug interactions occur between rifampicin and integrase strand transfer inhibitors, non-nucleoside reverse transferase inhibitors, and protease inhibitors. Co-infected patients have an increased risk of drug toxicity and TB Immune Reconstitution Inflammatory Syndrome. For ART regimens in TB patients, refer to the latest ART guidelines.

2.17.3 Identifying and managing Immune Reconstitution Inflammatory Syndrome

Patients with TB/HIV co-infection may experience a temporary exacerbation of symptoms or radiographic manifestations after initiation of ART. This phenomenon is called Immune Reconstitution Inflammatory Syndrome (IRIS). There are two types of IRIS: paradoxical and unmasking:

- This paradoxical reaction in HIV-infected patients with TB is a result of immune reconstitution. This occurs because of the initiation of ART in a patient with a known TB diagnosis and already on anti-TB drugs. An exacerbation of TB symptoms occurs following ART initiation.

- Unmasking IRIS occurs in patients who have undiagnosed TB disease, with symptoms emerging after initiating ART.

Symptoms and signs may include:

- Fever, worsening respiratory symptoms
- Worsening constitutional symptoms, such as weight loss and night sweats
- Lymphadenopathy
- Worsening of CXR findings
- Expanding central nervous system lesions on CT scan

Management of TB IRIS

- Do a thorough clinical evaluation to exclude other causes, particularly DR-TB and other opportunistic infections.
- Patients should continue TB treatment without change unless MDR-TB is diagnosed, or drug-drug interactions are suspected.
- If MDR-TB is diagnosed, switch to second-line ATT.
- When unmasking IRIS is diagnosed, initiate TB treatment.
- Temporal interruption of ART may be recommended if life-threatening complications of IRIS develop, but it should be restarted when the patient is stabilized.
- Administer prednisone (0.5–1.0 mg/kg/day) for moderate to severe cases.

Side effects shared by anti-TB and antiretroviral drugs

The table below highlights some of the side effects that can be caused by ATTs and ARVs.

Table 16. Side effects shared by anti TB and antiretroviral drugs.

Side effects	Antiretroviral treatment	TB treatment
Nausea and vomiting	AZT, protease inhibitors	PZ, ethionamide, PAS
Hepatitis	NVP, EFV, LPV/r, DRV/r	RH, INH, PZ
Neuropsychiatric	EFV, DTG	INH, ethionamide, quinolones, cycloscerine
Renal	TDF, DRV/r, LPV/r	Aminoglycosides, capreomycin, RH
Rash	NVP, EFV, ABC, DTG	RH, INH, PZ, EH, S

Abbreviations: ABC, abacavir; AZT, zidovudine; DRV/r, darunavir/ritonavir; DTG, dolutegravir; EFV, efavirenz; EH, ethambutol/isoniazid; INH, isoniazid; LPV/r, lopinavir/ritonavir; NVP, nevirapine; PZ, pyrazinamide; RH, rifampicin/isoniazid; S, streptomycin; TB, tuberculosis.

2.17.4 Key management considerations in TB/HIV co-infection

- TB/HIV co-infection increases the chance of drug-drug interactions, which may reduce treatment options, especially in treatment-experienced HIV patients.
- TB/HIV co-infection increases patients' pill burden, which may reduce their treatment adherence. This may lead to the development of drug resistance for both TB and HIV.
- The presence of drug-resistant TB and/or HIV causes therapeutic challenges as treatment options are reduced and there is the employment of molecules that

may have unfavorable side effect profiles. There is usually an increase in pill burden and increase in treatment duration (DR-TB), which further complicates the management of these patients.

- Undiagnosed TB infection at HIV diagnosis, before initiation of ART, poses a high risk of mortality from TB IRIS.
- TB meningitis in HIV increases the risk of mortality, especially when the diagnosis is delayed with consequent treatment delay.
- Health care workers should heighten index of suspicion to identity EPTB to avoid diagnosis and treatment delay.

Table 17. First- and second-line ART regimens in TB/HIV co-infection.

Specific conditions	Recommended ART regimens	Alternative ART regimens
HIV on first-line ART and TB co-infection	TDF + XTC + DTG (plus DTG 50 mg BD)	TDF + XTC + EFV or TDF + XTC + LPV/r (double the dose of LPV/r if on rifampicin regimen) or switch rifampicin to rifabutin (avoid in pregnancy or breastfeeding mothers) or ABC + 3TC + DTG (plus DTG 50 mg BD) or ABC + 3TC + EFV ABC + 3TC + LPV/r Double dose LPV/r (LPV/r 800 mg/200 mg twice daily)
HIV on second-line ART and TB co-infection	AZT + 3TC + DTG (50 mg twice daily) If DTG is not available: Double-dose LPV/r (LPV/r 800 mg/200 mg twice daily)	AZT + XTC + LPV/r Double-dose LPV/r (LPV/r 800 mg/200 mg twice daily) Increase LPV/r from 2 tablets twice daily to 3 tablets twice daily for 2 weeks and then 4 tablets twice daily for the remainder of the TB treatment.
• If rifabutin is available, use the same protease inhibitor or DTG-based regimens as recommended for adults and adolescents. • LPV/r and BDQ co-administration should be avoided. • Use LPV/r in first- or second-line ART if DTG not available or contraindicated.		

Table 18. TB/HIV co-infection case scenarios and recommended management for susceptible TB.

Clinical scenario	TB management	Recommended ART
Pregnant and breastfeeding women on ART and develops TB	Start ATT immediately	• If on EFV-based regimen, continue the same regimen; if on DTG based, give DTG 50 mg twice daily.
Pregnant and breastfeeding women on ATT and diagnosed with HIV	Continue ATT	• Start ART immediately: TDF + XTC + DTG* (DTG 50 mg twice daily).
Children 3 months to <3 years with TB/HIV co-infection	Start ATT (RHZE) immediately	• ABC+ 3TC + EFV. • If DTG 10 mg is available, use it in place of EFV at a twice-daily dose.

Clinical scenario	TB management	Recommended ART
An adult diagnosed with TB/HIV co-infection TB retreatment case and HIV co-infection	ATT immediately	• Start ART within 2 weeks of ATT initiation regardless of CD4 count or WHO clinical staging; delay ART by up to 8 weeks in TB meningitis. • Preferred ART: TDF + XTC + DTG* (DTG 50 mg twice daily). • Alternatively: TDF + XTC + EFV.
PLHIV on ART develops TB	Start ATT immediately	• Continue ART: TDF + XTC + DTG* (DTG 50 mg twice daily). • Alternatively: TDF + XTC + EFV. • If on ATV/r, switch to DTG 50 mg twice daily. • If DTG single tablets are not available, give a double dose of LPV/r.
ATT and diagnosed with HIV	Continue on ATT	• Start ART within 2 weeks of ATT initiation regardless of CD4 count or WHO clinical staging. • Preferred ART: TDF + XTC + DTG* (DTG 50 mg twice daily). • Alternatively: TDF + XTC + EFV.
Second-line ART on LPV/r and develops TB	ATT as per guidelines immediately	• Switch LPV/r to DTG 50 mg 12-hourly. • If DTG single tablet not available, increase LPV/r from 2 tablets twice daily to 3 tablets twice daily for 2 weeks and then 4 tablets twice daily for the remainder of the TB treatment. If available, replace rifampicin with rifabutin (150 mg Monday/Wednesday/Friday).
Second-line ART on LPV/r (failed DTG based regimen) and develops TB	ATT as per guidelines immediately	• Increase LPV/r from 2 tablets twice daily to 3 tablets twice daily for 2 weeks and then 4 tablets twice daily for the remainder of the TB treatment. If available, replace rifampicin with rifabutin (150 mg Monday, Wednesday, and Friday).

Abbreviations: ART, antiretroviral therapy; ATT, anti-TB treatment; PLHIV, people living with HIV; TB, tuberculosis.

Key messages

- Patients on TB treatment should be initiated on TDF + XTC + DTG. Take note that 50 mg DTG tablets should be given 12 hours apart from the TLD.
- REMEMBER to switch back to DTG 50 mg once daily and LPV/r 2 tablets twice daily after completion of TB treatment.
- Patients on TAF-based ART who develop TB should be switched to ABC if renal dysfunction still exists, or TDF if eligible.
- HIV-positive TB patients with profound immunosuppression should receive ART within the first 2 weeks of initiating TB treatment.
- TB meningitis patients with a new HIV diagnosis should have ART initiation delayed until after the first 8 weeks of ATT are completed, regardless of CD4 count.

2.17.5 Drug-drug interactions between antiretrovirals and ATT

The most important drug-drug interactions in the treatment of HIV-related TB are those between rifampicin and non-nucleoside reverse transferase inhibitors, protease inhibitors, and integrase strand transfer inhibitors. Rifampicin is the only rifamycin available in most of the world, and initial antiretroviral or first-line regimens in areas with high rates of TB consist of efavirenz and dolutegravir. Several therapeutic changes need to be made when administering both ARVs and ATT.

Knowledge of the mechanisms of drug interactions can help predict the likelihood of interaction if that specific combination of drugs has not been formally evaluated. The rifamycin class upregulates (induces) the synthesis of several classes of drug-transporting and drug-metabolizing enzymes. With increased synthesis, there is increased total activity of the enzyme (or enzyme system), thereby decreasing the serum half-life and serum concentrations of drugs that are metabolized by that system. The rifamycin vary in their potential as CYP450 inducers, with rifampin being most potent, rifapentine intermediate, and rifabutin being much less active.

Table 19. Major antiretroviral and anti-TB drug-drug interactions.

ARVs that interact with rifampicin	Rifampicin	Recommendation	Other comments
Efavirenz (EFV)	Rifampicin leads to a modest reduction in efavirenz concentrations.	No dose adjustments or therapeutic changes required.	
Lopinavir/ritonavir (LPV/r)	Rifampicin causes large decreases in lopinavir concentrations.	Double-dose LPV/r (LPV/r 800 mg/200 mg twice daily). If rifabutin is available, use the same LPV/r dose as recommended for adults and adolescents.	Co-administration can lead to a higher risk of liver and gastrointestinal toxicity.
Atazanavir/ritonavir (ATV/r)	Rifampicin causes a significant reduction in ATV/r concentrations.	Do not co-administer. If rifabutin is available, use the same dose of atazanavir.	Alternatively use a double dose of LPV/r.
Darunavir/ritonavir (DRV/r)	Rifampicin causes a significant reduction in DRV/r concentrations.	If rifabutin is available, use the same DRV/r dose as recommended for adults and adolescents.	
Dolutegravir (DTG)	Rifampicin causes a significant reduction in DTG concentrations.	If rifabutin available, no dose adjustments to DTG. Alternatively, DTG 50 mg 12-hourly.	
Raltegravir (RAL)	Rifampicin causes a significant reduction in RAL concentrations.	Double dosing is required.	

Tenofovir alafenamide (TAF)	Rifampicin causes a significant reduction in TAF concentrations.	Do not co-administer.	If renal impairment (CrCl <30 mL/minute) exists, administer ABC. If no renal impairment exists, give TDF. Give TAF if CrCl >30 mL/minute.

2.18 DR-TB/HIV co-infection

- DR-TB/HIV co-infection poses treatment challenges associated with potential drug-drug interactions, side effects, and pill burden, which reduces treatment adherence.
- Both longstanding TB and HIV increase the risk of renal disease, which is further worsened by the high number of nephrotoxic drugs. Therefore, concomitant use of nephrotoxic drugs, for example, tenofovir dixoproxil fumarate (TDF) and aminoglycosides, is discouraged, especially in patients with increased risk of renal disease. Replace TDF with TAF in such a situation.
- Dolutegravir does not interact with the second-line anti-TB drugs and its use is encouraged among DR-TB patients. Therefore, the preferred first-line ART, TDF (or Taf) + XTC + DTG, is recommended for use among DR-TB patients.
- Efavirenz co-administration with bedaquiline is discouraged, as bedaquiline activity is significantly reduced.
- Bedaquiline and LPV/r should not be co-administered. Use an alternative ARV in such a situation.
- AZT and linezolid both cause bone marrow suppression and concomitant use should be avoided.
- Protease inhibitors have significant interactions with second-line anti-TB drugs. When faced with such a scenario, consult the National Clinical Expert Committee (CEC).

2.18.1 TB and HIV integration and collaborative activities

- TB/HIV integration means both TB and HIV services are provided by the same provider at the same visit, a “one-stop shop.”
- TB/HIV collaboration means cross-referral of patients between TB and HIV services.

TB services in the HIV clinic

- All PLHIV attending ART/prevention of mother-to-child transmission of HIV clinics should be screened for TB at every visit.
- Presumptive TB patients should be further investigated and registered in a presumptive TB register.
- All PLHIV diagnosed with TB should be commenced on TB treatment.
- TPT should be provided to PLHIV without active TB.
- TB infection control measures should be implemented in all facilities.

HIV services in the TB clinic

- All TB patients should be offered HIV counseling and testing.

- All those found HIV positive should be initiated on ART, cotrimoxazole prevention therapy, and offered TB prevention interventions.
- All patients that were already on ART need CD4 and viral load to rule out ART failure.

Key messages

- Screen for TB in all patients diagnosed with HIV before initiating ART to reduce risk of IRIS, which has high mortality.
- In newly diagnosed TB/HIV co-infection, initiate ATT first then ART within 2 weeks.
- In the case of TB meningitis, ART should be delayed until after 8 weeks on TB therapy.
- When a PLHIV on ART is diagnosed with TB, ATT should be initiated, and ART continued.
- All PLHIV who screen negative for active TB should be offered TPT to treat latent infection TB every 3 years.
- LF-LAM can be used in PLHIV with CD4 <100 cells/mL (inpatients, hospitalized AHD patients).
- When a DTG-based ART regimen is used with rifampicin, give DTG twice daily and revert to the usual dose after completion of ATT.
- TAF should not be given concomitantly with rifampicin. It should be replaced with TDF in the absence of renal impairment or ABC if there is renal impairment.
- When rifabutin is available, replace the rifampicin and do not make any dose adjustments to the ARVs.
- Protease inhibitors and second-line ATT have significant drug interactions. Consult the

2.19 Drug-resistant tuberculosis

Recommendations

- A thorough history and clinical evaluation is critical in the management of DR-TB.
- All MDR/RR-TB patients should be put on full MDR-TB treatment.
- All patients with DR-TB/HIV co-infection must be on ART and should be supported to achieve viral suppression.
- Sputum samples for patients started on MDR/RR-TB treatment should be sent for second-line DST (LPA, culture) at baseline and monthly during treatment.
- All DR-TB must be assessed clinically monthly in addition to sputum cultures.
- Incorporate active TB drug safety monitoring and management for all patients on TB treatment.
- Contact tracing and investigation must be done for all DR-TB index cases and TPT provided to those who screen negative.
- All patients must have a nutritional assessment; those determined to have undernutrition must be recommended for nutritional supplements or therapy.
- All DR-TB patients must be followed up for 24 months post discharge.
- All provinces must have a functional CEC at district and provincial levels.

DR-TB is a growing problem in Zambia, caused by TB organism that is resistant to one or more anti-TB medicines. DR-TB is spread in similar fashion as DS-TB, through the air from one person to another. Resistance to anti-TB drugs can be primary or secondary.

Primary resistance

- This occurs in a patient with no history of taking first-line anti-TB drugs or those who have a history of taking first-line drugs for less than 1 month.
- The main mechanism is the transmission of drug-resistant strains from an existing DR-TB patient to a close contact.
- Primary resistance implies ongoing transmission within the community.
- Contact with a patient with DR-TB is the main risk factor for primary DR-TB.

Secondary resistance

- Also called acquired drug resistance.
- Occurs in patients with a history of exposure to first-line drugs or can develop during treatment.
- The main mechanism of drug resistance is usually mismanagement of drug-susceptible cases; for example, when health care providers prescribe the wrong treatment or dose of first-line drugs.
- Other reasons include shortages of first-line drugs and poor-quality drugs.

Risk factors for development of secondary DR-TB

- Poor adherence to treatment by patients.
- Use of anti-TB drugs of unproven quality (sale of such medications over the counter and on the black market).

- Incorrect management of individual cases by clinician.
- Suboptimal dosage.
- Poor drug absorption.
- Prolonged shortages of anti-TB drugs.

2.19.1 DR-TB case detection

In principle, case detection approaches for DR-TB are the same as for drug-susceptible TB. The basis for identification of DR-TB patients is bacteriological examination, which includes Xpert MTB/RIF or Ultra, Truenat, LPA, culture, pDST and WGS. The DR-TB case detection approach involves identification of individuals at risk of DR-TB.

Groups of people at risk for DR-TB

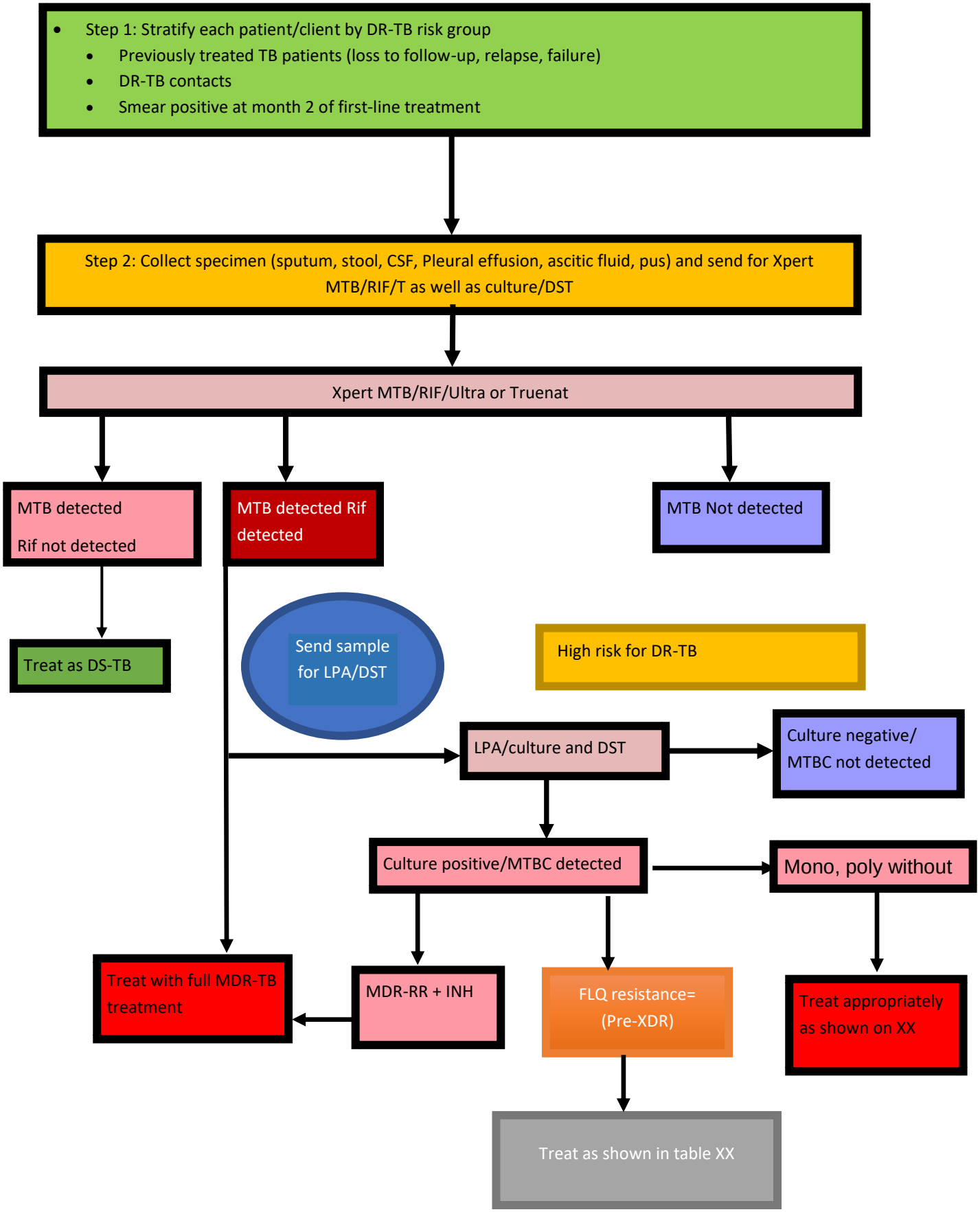
- Households and close contacts (including children) of DR-TB patients.
- Patients previously treated for TB (treatment failures, relapses, treatment after loss to follow-up).
- Patients who are smear positive after 2 months of first-line TB treatment.
- Health care workers.

2.19.2 Laboratory diagnosis of drug-resistant TB

The important tools for DR-TB laboratory diagnosis include:

- GeneXpert MTB/RIF and Ultra
- Truenat MTB/RIF
- LPA
- Culture (solid and liquid) and DST
- WGS

Figure 13. Evaluation of presumptive DR-TB patients.



For all patients with rifampicin resistance detected on Xpert MTB/RIF/Truenat, samples should be sent for FL-LPA, SL-LPA, smear/culture, and pDST.

2.19.3 Approach to discordant drug susceptibility testing results

Discordance in DST results may happen, usually when comparing culture-based results (pDST) with molecular results (genotypic DST). Each individual case of discordant results will need to be investigated in collaboration with laboratory personnel, and treatment regimen decisions should be discussed with the DR-TB CEC. As a rule, the patient should be treated according to the positive result and highest resistance pattern. DNA sequencing of the TB genome can solve the dilemma.

Table 20. Potential patterns of discordant results.

Discordant results	Treatment decision(s)
Xpert MTB/RIF MTB detected; culture negative	Treat the patient according to the Xpert MTB/RIF detected result. Submit another sample for culture.
Xpert MTB/RIF MTB not detected; culture positive	Treat the patient based on the positive culture result.
Xpert MTB/RIF MTB detected; rifampicin resistance detected; rifampicin susceptible by pDST	Treat the patient according to the rt MTB/RIF resistant result and repeat culture and pDST using solid media.
Xpert MTB/RIF MTB detected; rifampicin resistance not detected (susceptible); rifampicin resistance by pDST	Treatment decisions should be based on the culture pDST rifampicin resistant result.
Xpert MTB/RIF MTB detected; rifampicin not detected (susceptible); FL-LPA rifampicin detected (resistant)	Treat the patient based on FL-LPA (rifampicin resistant). Apply the same approach in the case of discordance with WGS

Abbreviations: DST, drug susceptibility testing; FL-LPA, first-line line probe assay.

2.19.4 Clinical diagnosis of DR-TB

The clinical features of a patient with DR-TB are not different from those of DS-TB patients (both PTB and EPTB).

In a few patients for which bacteriological confirmation is difficult, a clinical diagnosis of DR-TB can be made. These patients include:

- Children
- Close contacts of known DR-TB patients with symptoms consistent with TB
- HIV-positive patients not improving on first-line therapy
- EPTB patient who is a contact of a DR-TB patient or one who is not improving on first line treatment.

- A chest x-ray should be obtained when evaluating for possible clinical diagnosis of DR-TB.
- Clinical diagnosis of DR-TB should **always** be discussed with the clinical expert committee (facility, district, provincial, and national).

2.20 Management of DR-TB patients

To improve DR-TB treatment outcomes and quality of life for DR-TB patients, early detection and initiation of appropriate treatment is cardinal, therefore, health care workers need to heighten index of suspicion for DR-TB and ensure there is quality of care.

The major goals of treatment for DR-TB disease are to:

- Cure DR-TB disease and prevent relapse in individual patients.
- Minimize the risk of death and disability
- Reduce infectiousness and transmission of DR-TB strains to other people

2.20.1 Principles of DR-TB treatment

- Detect DR-TB patients as early as possible.
- Promptly initiate appropriate therapy for patients with DR-TB.
- Select medicines and regimens for the treatment of DR-TB in a manner that prevents emergence of further resistance
- Improve quality of life of DR-TB patients

Steps to initiating a patient on DR-TB treatment

1. Provide information about DR-TB and the plan of care to the patient and next of kin or guardian (treatment duration, reviews, and monthly sputum submission). Patient education should include potential side effects of drugs, adherence counseling, choosing a treatment supporter (DOT plan), and inviting family members to support the patient on treatment.
2. Classify and register patient (patient details, address/phone, and contacts of next of kin).
3. Perform a clinical evaluation by taking a history and conducting a physical examination using both a paper-based and an electronic baseline assessment tool.
4. Collect baseline samples for LPA, culture, and DST if you have not already done so. Conduct baseline laboratory investigations: biochemistries, full blood count, pregnancy test, HIV testing and counselling (if newly diagnosed, request CD4 count); if on ART, request for/review viral load and CD4 to evaluate for treatment failure. Do any other relevant tests as indicated by the clinical assessment.
5. Conduct radiological investigations (chest x-ray, CT scan), electrocardiogram, and if on amikacin or will be prescribed amikacin, do audiometry.
6. Start treatment with second-line drugs with the most effective regimen.
7. List all contacts and start contact tracing and investigation.
8. Link patient to nutritional and psychosocial support and other support.
9. Ensure ALL HIV-positive patients are linked to HIV care

2.20.2 Models of DR-TB patient care

Patients with DR-TB may need both inpatient and outpatient care at different times during treatment. It is not required to hospitalize patients to initiate DR-TB treatment if they are stable and have uncomplicated disease.

Ambulatory (outpatient) model of care: Zambia has adopted a patient-centered approach to DR-TB care that includes ambulatory care in decentralized settings to treat DR-TB patients that do not have acute medical conditions. The following ambulatory treatment options are considered.

Ambulatory care throughout DR-TB treatment: Treatment is initiated on an ambulatory patient on the following basis:

- A non-acute medical condition.
- Infection prevention is assured at home and patient's business place.
- Monthly clinical reviews and tests are carried out for the patients.

Ambulatory care after stabilization: Seriously ill patients are hospitalized to initiate DR-TB treatment and/or address comorbidities and complications, and then they are discharged to ambulatory care once their clinical condition has stabilized, and major symptoms have been controlled.

Inpatient model of care: Hospitalization of patients starting treatment (or at any time on treatment) should be considered for the following indications or reasons:

- The patient is too ill (clinically or psychologically) to commence DR-TB treatment on an ambulatory basis.
- DOT and adherence support are not guaranteed.
- The patient experiences a severe adverse drug reaction.
- Implementation of adequate infection control measures is not feasible at home or the place of employment.

Note: Hospitalization should not be for the entire course of treatment; after stabilization and management of the adverse drug reaction, or in certain cases sputum conversion, the patient should be discharged and managed on an ambulatory basis. Patients must be engaged in deciding the care plan.

Decentralization of patient care

- All provinces must decentralise DR-TB care services; each district must have at least one DR-TB treatment initiation site.
- All provinces must have functional a CEC at the provincial, district, and facility levels
- Provincial CEC meetings should be held at least quarterly, and district CEC meetings can be held monthly. Facilities are encouraged to hold CEC meetings monthly and consult one another whenever a new case of DR-TB is detected, especially a complicated case.
- A mentorship and outreach model in which a trained and experienced multidisciplinary team routinely provides technical support to all facilities treating DR-TB is recommended.
- The team should consist of a medical doctor who can be a trainer of trainers, a trained DR-TB nurse, clinical officer and a pharmacist, laboratory staff, nutritionist, and M&E (DHIO).
- Outreach programs can be done monthly or quarterly and should coincide with patient reviews.

- The district TB coordinator should be part of the team.

2.20.3 Grouping of second-line drugs

Second line drugs are grouped as shown in Table 21**.**

Table 21. World Health Organization grouping of medicines recommended for second-line treatment.

Group A Select 3 if there are no contraindications	Levofloxacin (Lfx)/Moxifloxacin (Mfx) Bedaquiline (Bdq) Linezolid (Lzd)
Group B Select 1 if 3 drugs from group A can be safely used OR select 2 if only 2 can be used from group A	Clofazimine (Cfz) Cycloserine (Cs)/Terizidone (Trd)
Group C Add to complete the regimen and when medicines from Groups A and B cannot be used	Ethambutol € Delamanid (Dlm) Pyrazinamide(Z) Imipenem-cilastatin (Ipm-Cln)/ Meropenem (Mpm) Amikacin (Am)/Streptomycin (S) Ethionamide (Eto)/Prothionamide (Pto) p-aminosalicylic acid (PAS)

2.21 DR-TB treatment regimens

There are two main treatment regimens currently recommended for use in Zambia; both are oral-based regimens. The drugs used are the same. The only difference between the two regimens is the treatment duration. Patient characteristics inform the choice of the regimen. Figure 15 outlines the steps and characteristics for choosing a regimen.

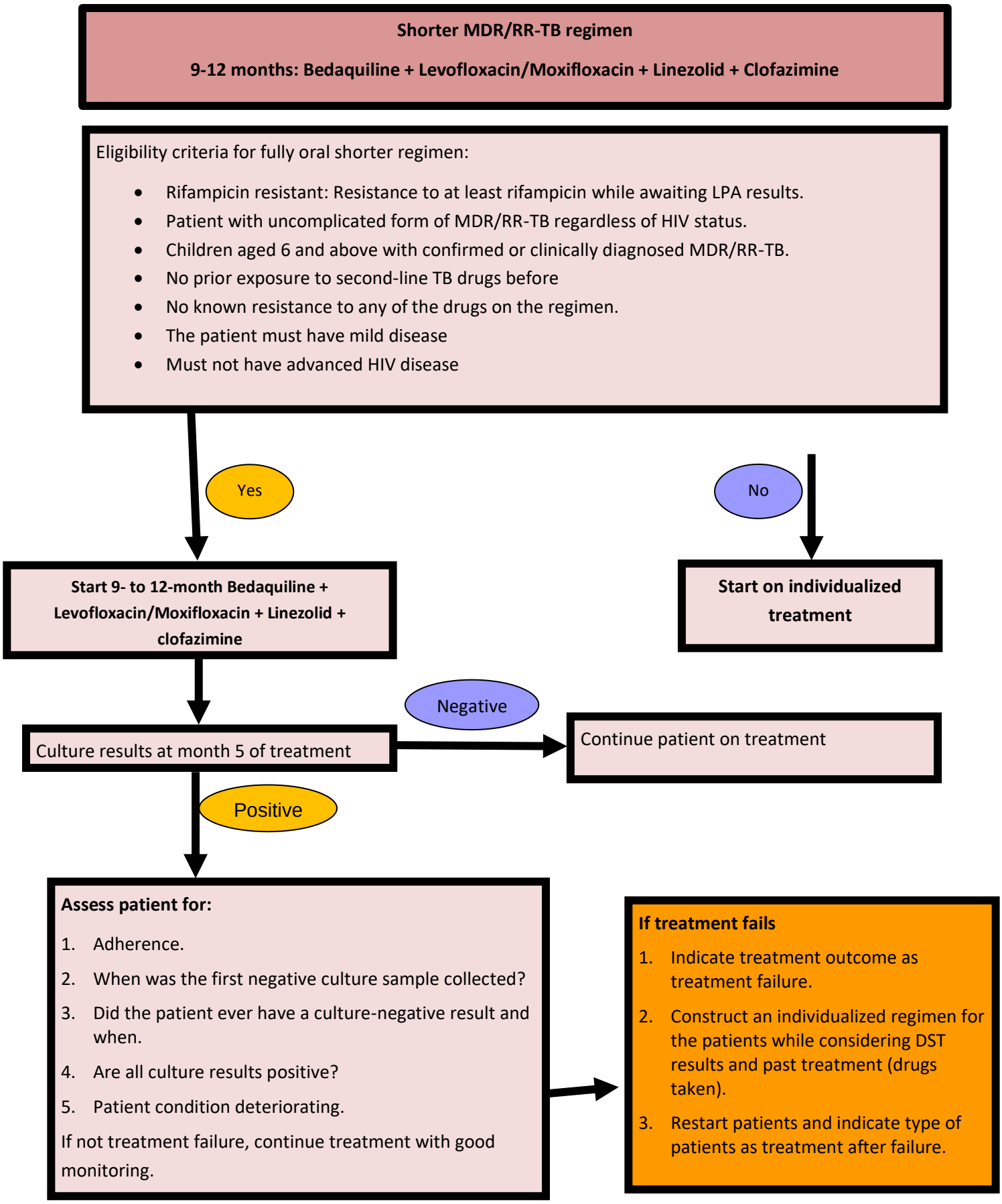
- All oral shorter regimen
- All oral longer regimen

Use of the second-line injectable regimen is currently not recommended unless under specific circumstances after discussion with the National DR-TB CEC.

2.21.1 Shorter regimen for MDR/RR-TB

The regimen is bedaquiline + levofloxacin/moxifloxacin + linezolid + clofazimine given for 9 to 12 months.

Figure 14. Steps of the shorter treatment regimen for MDR/RR-TB.



Indications for continuations of the shorter regimen:

- The patient remains culture negative post 4 months of treatment.
- The patient remains asymptomatic from month 5.

Indications for transitioning from shorter to longer regimen:

- Failure to culture convert by month 5.
- Remains symptomatic by month 5.
- Deterioration of the radiological picture.
- Unsuppressed viral load in the case of the TB/HIV co-infection

2.21.2 All oral longer treatment regimen

Patients who do not qualify for all oral shorter regimen receive 18-20 months all oral longer regimen

The all-oral longer regimen is bedaquiline + levofloxacin/moxifloxacin + linezolid + clofazimine given for 6 months/levofloxacin/moxifloxacin + linezolid + clofazimine given for 12 months.

(6 Bdq-Levo-Lzd-Cfz/12Levo-Lzd-Cfz) given for a total treatment duration of 18 months.

The following patients should be started on all oral longer regimen:

- Any previous exposure to second-line treatment (more than 1 month) regardless of treatment outcome or pattern of resistance (e.g., MDR-TB, pre-XDR-TB, or XDR-TB).
- MDR/RR-TB in persons with presumed resistance to second-line drugs, even if susceptibility is demonstrated on DST.
- Persons with complicated EPTB: MDR/RR-TB meningitis, osteoarticular disease, abdominal, pericardial effusion, or miliary/disseminated.
- Persons with extensive disease (i.e., bilateral, cavitary disease with significant fibrosis, or scarring/cavities in three or more lung zones).
    - Any other situation in which the clinician, in consultation with the provincial or national CEC, is uncertain of the patient's eligibility for the STR.

2.21.3 DR-TB treatment in special populations

All these patient categories MUST be discussed at provincial and/or national DR-TB CEC meetings.

Table 22: DR TB treatment in special populations

Condition	Preferred regimen	Alternative regimen
Liver Disease	9-12 BDQ Mfx Lzd CFZ Cs can be used as well	6 BDQ+MFx+Lzd+Cfz / 12 Mfx+Cfz+Lzd Cs can be used as well
FQ resistance(Pre-XDR) or as a relative contraindication in pregnancy	**6 Bedaquiline + Linezolid + Clofazimine + Cycloserine / 12 Linezolid+ Clofazimine+ Cycloserine**	
Pregnancy and Breast feeding	**CFZ + CS +INH^{HD}(if sensitive or low level resistance) + ethambutal + PZ**	**Introduced FLQ, BDQ and DLM after delivery**
Kidney Failure	**6 Bdq + Lfx+ Lzd+Cfz/ 12 Lfx+Lzd+Cfz** **Or substitute Mfx for Lfx or Cs for Cz**	Lfx should be given at 750-1,000 mg/dose 3 times a week Cs 250 mg once daily or 500 mg/dose 3 times per week No need to adjust dose of the other drugs
Diabetes mellitus	**9-12 BDQ Mfx Lzd CFZ**	Use ethionamide sparingly
Pre-existing heart disease	**LZD+LFX +CS+CFZ (PZ+E and INH^{HD} if sensitive or low level resistance)**	Avoid BDQ and DLM; use of these drugs should be in consultation with CEC
Seizure disorder		Avoid Cs and INH
Peripheral neuropathy, severe anemia, and optic neuritis	**6 bedaquiline + levofloxacin/moxifloxacin + clofazimine + cycloserine / 12 levofloxacin/moxifloxacin + clofazimine + cycloserine**	

For patients who are not eligible for all oral standard longer or shorter regimens, an individualized treatment regimen should be designed in consultation with the CEC. These patients include pre-XDR-TB and XDR-TB patients.

Note: The individualized regimen should usually be designed to include at least five medicines considered to be effective.

- Patients need to be on four oral agents at the start.
- Bedaquiline may be used beyond 6 months up to 12 months.
- The regimen needs to have at least three effective agents after BDQ is stopped.
- If BDQ cannot be used due to toxicities, that medicine should be replaced with group B agents.
- If Clofazimine and Cycloserine are already included, a choice from group C will be determined in the order they are ranked in the medicines grouping table.

2.21.4 Treating mono- and poly-drug-resistant TB

Treatment for mono- and poly-drug-resistant TB should never rely solely on DST results.

It is also important to assess the history of previous TB treatment, contact history, risk of amplification of resistance, extension of disease, and the patient's condition. If a patient has mono- or poly-resistant TB on laboratory results, further resistance should be suspected, and it is essential to follow up on the second-line LPA and culture/DST.

Table 23: Suggested treatment for mono and poly-resistant DR-TB

Drug resistance pattern	Suggested regimen	Comments
RIF mono- or poly-drug-resistance	Full MDR-TB regimen	The patient should be started on the appropriate MDR-TB regimen.
INH poly-drug resistance susceptible to RIF (e.g., INH+EMB and/or pyrazinamide)	Full MDR-TB regimen	Treat as MDR-TB. Rationale is that many patients with DST results suggesting poly-drug resistance have MDR-TB. Determine the patient's treatment history. If any doubt, consult with the clinical expert committee.
INH mono-resistance (Hr-TB) **Note:** Should be diagnosed by full pDST, if available, not only by FL-LPA.	6 REZ-Lfx (6 months of rifampicin, ethambutol, pyrazinamide, levofloxacin) HREZ as a fixed-dose combination can be used where this is the only option available instead of REZ	Patient with no previous treatment of TB, no risk of amplification of resistance, and no risk of unfavorable outcome: Consider treatment with levofloxacin + REZ for 6 months.
		Patient with a history of previous TB treatment, risk of amplification of resistance, or risk of unfavorable outcome (extensive disease), treated with an individualized treatment regimen.

Abbreviations: FL-LPA, first-line line probe assay; MDR-TB, multidrug-resistant tuberculosis

Key messages

- Review all stable DR-TB patients monthly. Patients who are unstable should be reviewed frequently.
- Evaluate patient's adherence to treatment at every visit.
- Link all patients to a treatment supporter.
- Keep both paper and electronic registers.
- A comprehensive baseline assessment should be done on all patients.
- Perform follow-up monthly smears, cultures, and biochemistry tests.
- Perform audiometry at baseline when using amikacin and do monthly audiometry for 6 months.
- Conduct active monitoring and reporting of any adverse effects.
- DR-TB CEC should review **all** complicated cases and patients who are failing treatment.
- Report interim and final outcomes to the National TB and Leprosy Programme.
- Follow up all DR-TB patients for at least 2 years post treatment, initially every 3 months in the

2.21.5 Dosage and administration

Table 24. Weight-based drug-resistant tuberculosis drugs in adults ≥30 kg.

Drugs	Daily dose	30–35 kg	36–45 kg	46–55 kg	56–70 kg	>70 kg
Isoniazid high dose (H^h)	10 mg/kg maximum 600 mg/day	300 mg	400 mg	500 mg	600 mg	600 mg
Pyrazinamide (Z)	20–30 mg/kg once daily	800 mg	1,000 mg	1200 mg	1600 mg	2,000 mg
Ethambutol I	15–25 mg/kg once daily	600 mg	800 mg	1000 mg	1200 mg	1,200 mg
Amikacin (Am)	15–20 mg/kg once daily	500 mg	625 mg	750 mg	825 mg	1,000 mg
Levofloxacin (Lfx)	750–1,000 mg once daily	750 mg	750 mg	1000 mg	1000 mg	1,000 mg
Moxifloxacin (Mfx)	400 mg once daily	400 mg	600 mg	<50kg=600 mg >50kg=800 mg	800 mg	800 mg[3]
Prothionamide (Pto)/ Ethionamide (Eto)	500–750 mg/day in 2 divided doses	500 mg	500 mg	750 mg	750 mg	1,000 mg
Cycloserine (Cs)/	500–750 mg/day in 2 divided doses	500 mg	500 mg	500 mg	750 mg	750 mg
p-aminosalicylic acid (PAS)	8 g/day in 2 divided doses	8 g	8 g	8 g	8 g	8–12 g
Bedaquiline (Bdq)	400 mg once daily for 2 weeks then 200 mg 3 times per week					
Delamanid (Dlm)	100 mg twice daily (total daily dose = 200 mg)					
Clofazimine (Cfz)	100 mg twice daily for 2 first months, then reduce to 100 mg daily					
Linezolid (Lzd)	600 mg once daily	600 mg	600 mg	600 mg	600 mg	600 mg
Amoxicillin/clavulanate (Amx/clv) 7/1	80 mg/kg/day in 2 divided doses	2,600 mg	2,600 mg	2,600 mg	2,600 mg	2,600 mg
Amoxicillin/clavulanate (Amx-clv) 8/1	80 mg/kg/day in 2 divided doses	3,000 mg	3,000 mg	3,000 mg	3,000 mg	3,000 mg
Imipenem/Cilastatin (Imp/cln)	1,000 mg imipenem/1,000 mg cilastatin twice daily					
Meropenem (Mpm)	1,000 mg three times daily (alternative dosing is 2,000 mg twice daily)					

2.21.6 Treatment monitoring for MDR/RR-TB patients on therapy

Patient monitoring

Clinical monitoring:

- All patients should be assessed clinically for symptoms of new or ongoing adverse reactions as well as signs of treatment failure.
- Weight monitoring monthly. Poor weight gain may be a sign of treatment failure.
- Psychosocial assessment at every visit.
- ECG weekly for the first 2 weeks, then monthly for patients on Bdq and/or Dlm.
- Chest x-ray monitoring as indicated (individualized).
- PLHIV failing on ART should be followed up more closely and early action taken.
- HIV-negative patients and those with unknown HIV status should be advised to test for HIV according to national HIV guidelines.
- Women of child-bearing age (15–49 years) should be assessed for pregnancy at every visit.

Laboratory monitoring (see schedule):

- Monthly sputum for culture/DST is the best mode of monitoring. Smears can be used in addition to culture/DST.
- For PLHIV, CD4 and viral load testing according to the consolidated HIV guidelines.
- Serum creatinine, potassium, and TSH whenever possible.
- ALT/AST and albumin.
- FBC weekly for the first 2 weeks then monthly after starting the patient on Lzd If low Hb discuss with CEC prior to discontinuing Lzd.

Table 25: DR-TB treatment monitoring schedule for conventional DR-TB regimen

Parameters	Month of treatment																				
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Clinical evaluation	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Sputum-smear	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
DST		If culture is positive																			
FBC/DC	V						✓						V						✓		✓
LFTs	✓			✓			✓			✓			✓			✓			✓		✓
Na^{2+} , K^{2+}, u , Creatine	✓	✓	✓	✓	✓	✓	✓			✓	I	I	I	I	I	I	I	I	I	I	I
TSH/free T-4	✓			✓			✓			✓			✓			✓			✓		✓
Pregnancy test	✓																				
HIV test	✓			✓			✓			✓			✓			✓			✓		
Audiometry	✓	✓	✓	✓	✓	✓	✓														
CXR	✓						✓						✓								✓
ECG	✓	✓	✓	✓	✓	✓	✓	I	I	I	I	I	I								
Albumin	✓			✓			✓			✓			✓			✓			✓		

KEY: 0=Required, O=Optional, P=If culture is positive, I=If indicated.

2.22 Indication for adjuvant therapy during DR-TB treatment

Table 26: Indication for adjuvant therapy during DR-TB treatment

Patient group	Drug and dose	Rationale
All patient on INH, LZD, and cycloserine	Pyridoxine (vitamin B6) at 50–150 mg/day or Neurobion forte for patients with history of pellagra or those that develop pellagra.	To minimize peripheral neuropathy, neurologic side effects and myelosuppression.
TB meningitis, TB pericarditis, and IRIS	Prednisolone 1 mg/kg decreasing by 10 mg per week when a long course is indicated. Dexamethasone at 4–8 mg bd is preferred for TB meningitis. For TB pericarditis, steroids should be given for 2 months and 1 month for TB meningitis.	Minimizes inflammation.
All patients	Vitamin D 50,000–60,000 units (one capsule per week).	

Abbreviations: IRIS, Immune Reconstitution Inflammatory Syndrome; TB, tuberculosis.

2.23 Role of surgery in the management of DR-TB

The most common operative procedure in patients with pulmonary DR-TB is resection surgery. At least 2 months of therapy should be given prior to resection surgery to decrease the bacterial load in the surrounding lung tissue. Even with successful resection, an additional 12 to 24 months of DR-TB treatment should be given. Refer all patients who need surgery to a cardiothoracic surgeon (tertiary hospital).

Elective partial lung resection (lobectomy or wedge resection) may be used alongside a recommended DR-TB regimen. The following should be considered for surgical intervention:

- Patients who remain smear positive while on fully monitored treatment for more than 6 months.
- Have resistance to many medicines.
- Gave localized pulmonary disease.

2.24 DR-TB treatment and Psychiatric disorders

- All facilities treating DR-TB should set up an organised system for psychiatric emergencies (e.g., psychosis or suicidal tendencies).
- Patients with a history of overt psychiatric illness should be evaluated by a psychiatrist at the start of DR-TB treatment and at any point if severe symptoms re-appear.
- There is a high baseline incidence of depression and anxiety in patients with DR-TB, often related to the chronicity of the condition and socioeconomic stress factors associated with the disease.

- Medical treatment, individual counselling, and/or group therapy may be necessary to manage the patient suffering from a psychiatric condition or an adverse psychiatric event caused by DR-TB medication.
- Group therapy provides a supportive environment for DR-TB patients and should be provided for all patients, including those without psychiatric conditions. Every facility that treats DR-TB patients is encouraged to conduct regular support group sessions for patients.
- Psychiatric adverse events from cycloserine or high dose isoniazid may be more prevalent in the psychiatric patient; close monitoring is recommended if either drug is used in patients with psychiatric disorders.
- Atypical antipsychotics should not be used for DR-TB patients on multiple QT prolonging DR-TB drugs as haloperidol significantly prolongs the QTc interval and has been associated with torsades de pointes.
- Avoid using serotonin reuptake inhibitors and tricyclic antidepressants alongside linezolid, as there is a risk of serotonin syndrome.

2.25 DR-TB treatment and substance abuse

- Patients with substance dependence disorders, including alcohol dependence, should be offered treatment for their addiction; consultation with a social worker, psychiatrist, and/or drug rehabilitation centre is encouraged to formulate the treatment plan.
- Complete abstinence from alcohol or other substances should be strongly encouraged, although active consumption is not a contraindication to DR-TB treatment and moderation should be emphasized.
- If DR-TB treatment is repeatedly interrupted because of the patient's dependence to alcohol or psychoactive substances, the treatment may be suspended until measures to increase adherence support have been established.
- Directly observed therapy gives the patient an opportunity to interact with and get support from health care providers, which often allows treatment completion even in patients with substance dependence (DOT should be provided by health care worker).
- Cycloserine will have a higher incidence of adverse effects in patients who are dependent on alcohol or other substances and predisposes to seizures; however, if cycloserine is considered essential to the regimen, it should be used, and the patient closely observed for adverse events.

2.26 Adverse events

Table 27: Severity grading scale of adverse events

Severity grading scale of adverse events	
Grade	Description
GRADE 1: Mild	Mild or transient discomfort without limitation of normal daily activities*. No medical intervention or corrective treatment required.
GRADE 2: Moderate	Moderate limitation of normal daily activities*. Minimal medical intervention or corrective treatment required.

GRADE 3: Severe	Marked limitation of normal daily activities*. Medical intervention, therapy, stop or reduction of the offending drug is required. Possible hospitalization.
GRADE 4: Life-threatening or permanently disabling	Severe limitation of normal daily activities*. Medical intervention and corrective treatment required almost always in a hospital setting.

*The term 'activity' covers basic self-care functions such as bathing, dressing, toileting, transfer/movement, continence and feeding, as well as usual social and functional activities or adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, or pursuing a hobby.

3. Tuberculosis case detection and management in children

Tuberculosis (TB) is a major cause of morbidity and mortality among children, particularly those under the age of 5 years. TB in children is associated with faster disease progression, severe complicated forms, and a greater risk of death when compared to adults. The proportion of children among total TB patients notified annually has been less than 10% in the past ten years which is below the expected standards of at least 10% to 15%[8]. The difference can be attributed to under-diagnosis and under-reporting of TB in children within the health system. Local autopsy studies have shown that TB is the frequent cause of death in children with respiratory illness and is not often detected at the time of death[9].

Children most at risk of TB:

- Those living with HIV, regardless of antiretroviral therapy (ART) status.
- Those in contact with bacteriologically confirmed TB patients.
- Undernourished children from any cause.

3.1 Presentation of TB in children

- The clinical spectrum of TB in children is usually wider than in adults.
- Although pulmonary tuberculosis (PTB) is the most common type of TB, extrapulmonary forms occur more frequently in children.
- The most common clinical presentation of PTB is persistent respiratory symptoms and poor weight gain.
- Most children present with typical signs and symptoms of TB.
- Younger children (usually under 5 years) present with atypical clinical signs and symptoms.
- All samples collected from children must be subjected to more sensitive diagnostic testing, like culture and Cepheid's GeneXpert® MTB/RIF tests.
- Bacteriological confirmation is often challenging in children due to the paucibacillary nature of the disease and inability to collect a suitable specimen for laboratory analysis.

Typical presentation of TB in children

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

[8] MOH (2021). National TB Programme Annual Report

9 Bates, M. et al. (2016). Burden of respiratory tract infections at post mortem in Zambian children. BMC Medicine (2016) 14:99 DOI 10.1186/s12916-016-0645-z.
https://bmcmedicine.biomedcentral.com/track/pdf/10.1186/s12916-016-0645-z.pdf

Atypical presentation of TB in children

Acute severe pneumonia:

- Fast breathing and chest in-drawing; often occurs in infants and HIV-infected children.
- Failure to respond to appropriate antibiotic therapy.

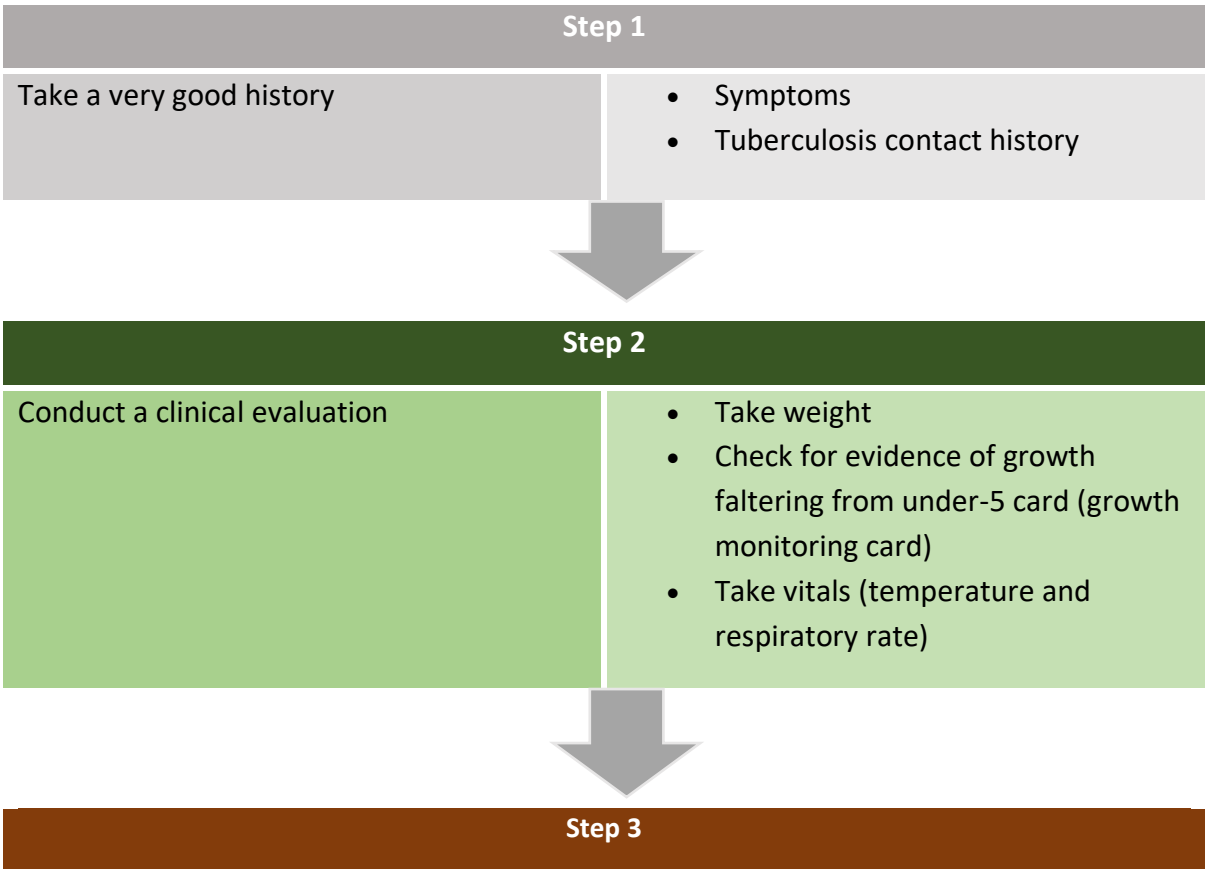
Wheeze:

- Asymmetrical and persistent wheeze, caused by airway compression due to enlarged TB hilar lymph nodes.
    - PTB should be presumed when wheeze is asymmetrical; persistent; not responsive to bronchodilator therapy; and associated with other typical features of TB, such as malnutrition. **Note: Asthma is rare in malnourished children.**

3.2 Evaluation of TB in children

The steps of evaluating TB in children are shown in the following figure.

Figure 15. Systematic evaluation of childhood tuberculosis.



Collect specimens and order a chest x-ray	• Gastric aspirate/lavage for children younger than 8 years • Stool for children where gastric lavage/sputum is not feasible • Sputum if able to expectorate children older than 8 years • Urine for lipoarabinomannan

Note: Check the z-score for every child being evaluated for TB (a z score of –2 or –3 is indicative of undernutrition).

Table 28. Diagnostic tools for childhood tuberculosis.

Tool	Features indicative of TB
Radiography (chest x-ray, computed tomography)	Chest x-ray is an important tool for diagnosis of TB in children who are sputum smear negative or who cannot produce sputum. The following abnormalities on imaging are suggestive of TB: • Enlarged hilar lymph nodes • Opacification in the lung tissue • Miliary mottling in lung tissue • Cavitations (tends to occur in older children) • Pleural or pericardial effusion (forms of EPTB seen on chest x-ray; tends to occur in older children)
Molecular methods (GeneXpert MTB/RIF and Ultra, Molbio Diagnostics' Truenat™)	Sensitive tools for TB diagnosis, these methods provide results on rifampicin resistance: • Sputum • Gastric aspirate • Stool • Lymph node aspirate • Ascitic/pleural fluid • Cerebrospinal fluid
Culture and DST	• Request culture for relapse and retreatment cases, and those with negative GeneXpert test results who are presumptive TB patients/contacts of DR-TB patients. • For every gastric aspirate, submit a sample for culture and DST.
Sputum microscopy	• Request microscopy for diagnosis where there is not GeneXpert. • For monthly monitoring in patients that can submit sputum during treatment.
Urine LAM	• Request urine LAM in children with HIV and those presenting with sepsis or malnutrition. • Urine LAM is most useful in children with severe immune suppression or advanced HIV disease.
TST/IGRA	• The two tests help to confirm exposure to TB. • They tell us about latent TB infection.

Tool	Features indicative of TB
	• They do not distinguish between active and latent TB. • Where available, request test to support clinical evaluation. • A positive test means the patient with TB symptoms has a high likelihood of having active TB disease.

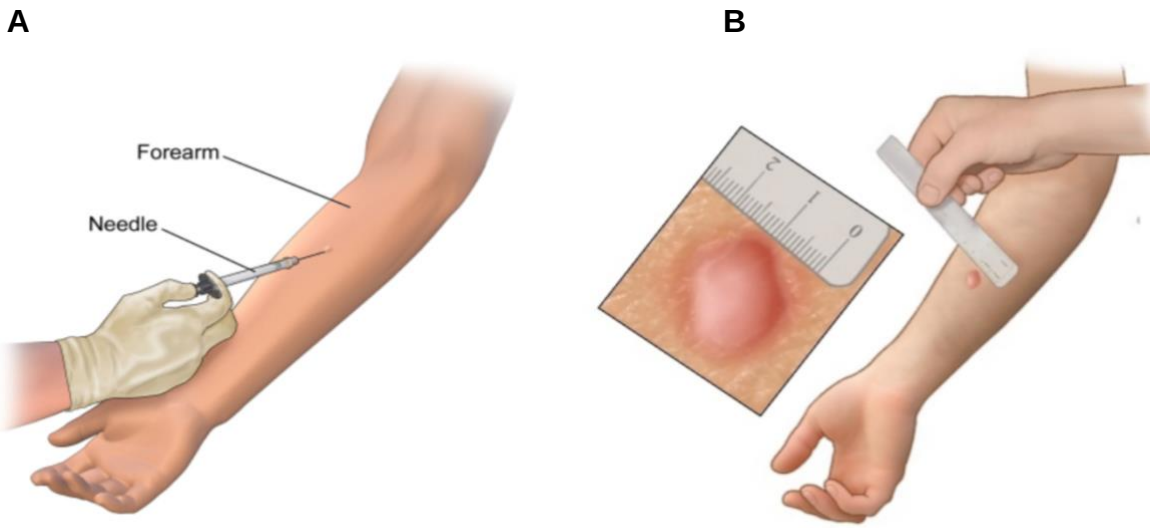
Abbreviations: DR-TB, drug-resistant tuberculosis; DST, drug susceptibility testing; EPTB, extrapulmonary tuberculosis; IGRA, interferon-gamma release assay; LAM, lipoarabinomannan; TST, tuberculin skin test.

3.2.1 Tuberculin skin test

The following steps are required to conduct a tuberculin skin test (TST), as illustrated in Figure 18:

- Bring the purified protein derivative (PPD) reagent to room temperature.
- Disinfect the site of injection and allow to dry.
- Draw up just more than 0.1 mL of PPD using a 1 mL syringe. If necessary, remove excess PPD to ensure exactly 0.1 mL and remove air from the syringe if present.
- Using a 27-gauge needle, inject the PPD intradermally to make the deposition wheel, at a diameter of 6 mm to 8 mm, which will rise to the point of needle.
- Mark the area of injection with an indicator.
- Read the result after 48 to 72 hours for induration.

Figure 16. Tuberculin skin test procedure.



Interpretation of TST results is as follows:

- Induration ≥5 mm in diameter is considered positive in:
  - HIV-positive children

- Severely malnourished children (with clinical evidence of marasmus or kwashiorkor)
- Induration of ≥10 mm in diameter is considered positive in:
- All other children (whether they received a bacillus Calmette-Guérin [BCG] vaccination).

Causes of a false-negative TST result

- Incorrect administration of the test.
- Incorrect interpretation of the test results.
- HIV infection.
- Improper storage of tuberculin.
- Viral infection (e.g., measles, varicella).
- Malnutrition.
- Bacterial infection (e.g., typhoid, pertussis).
- Immunosuppressive medications (e.g., corticosteroids).
- Neonatal patient.
- Diseases of the lymphoid tissue (e.g., Hodgkins disease, lymphoma, leukemia, sarcoidosis).
- Severe TB.

Causes of a false-positive TST result

- Incorrect interpretation of the test.
- Within two years post BCG vaccination.

Non-tuberculous mycobacteria.

3.2.2 Interferon-gamma release assay

The interferon-gamma release assay (IGRA) test is laboratory based. Steps to conduct the test are as follows:

- Collect 4 mL of blood in a heparin bottle (green top bottle).
- Submit the collected sample to the laboratory immediately.
- Maintain the sample at room temperature; do not refrigerate.

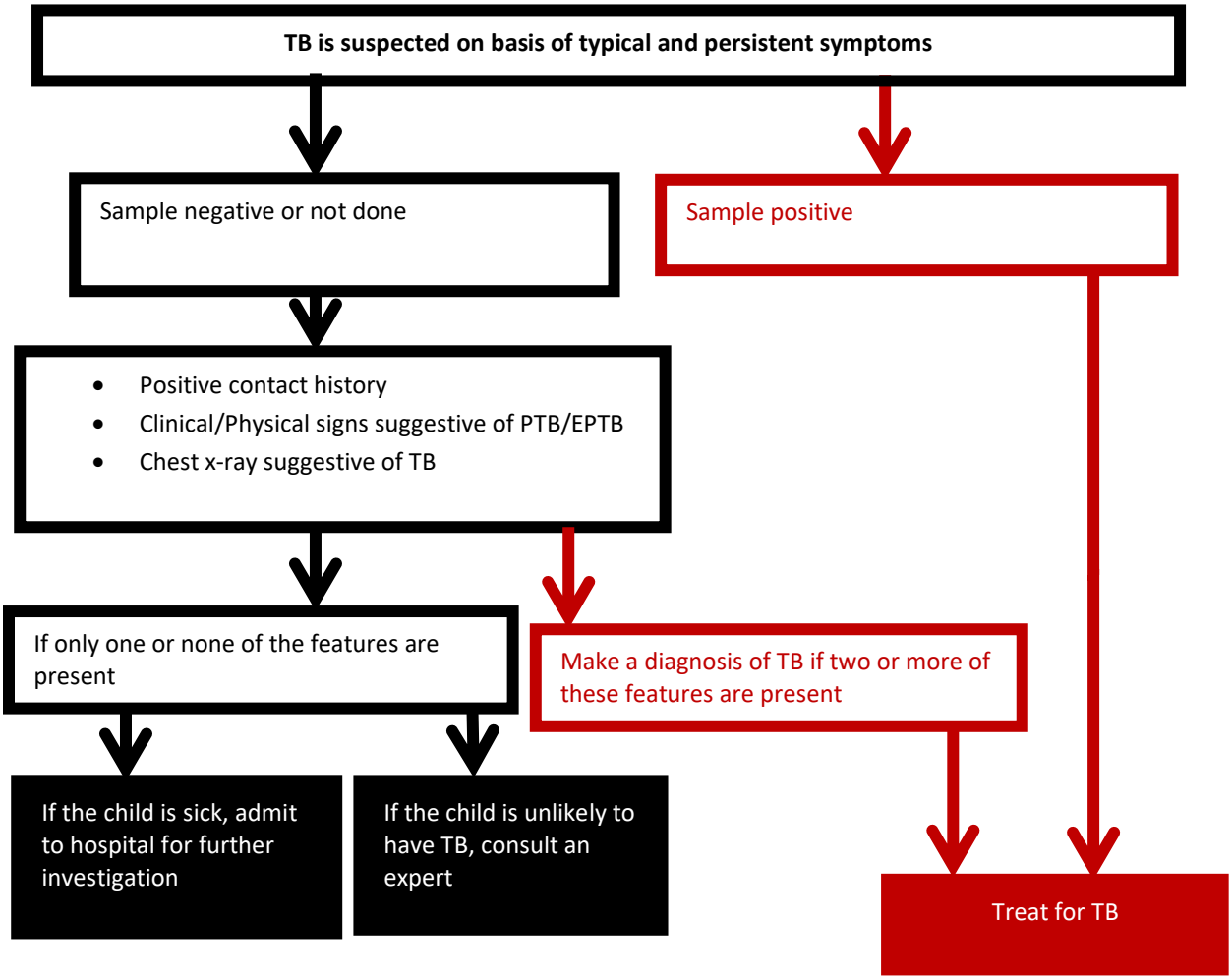
Interpretation of IGRA results is as follows:

- **Negative:** Does not have latent tuberculosis infection.
- **Positive:** Has latent tuberculosis infection or active TB.
- **Indeterminate:** Requires a repeat test; collect a new sample.

3.3 Diagnosis of TB in children

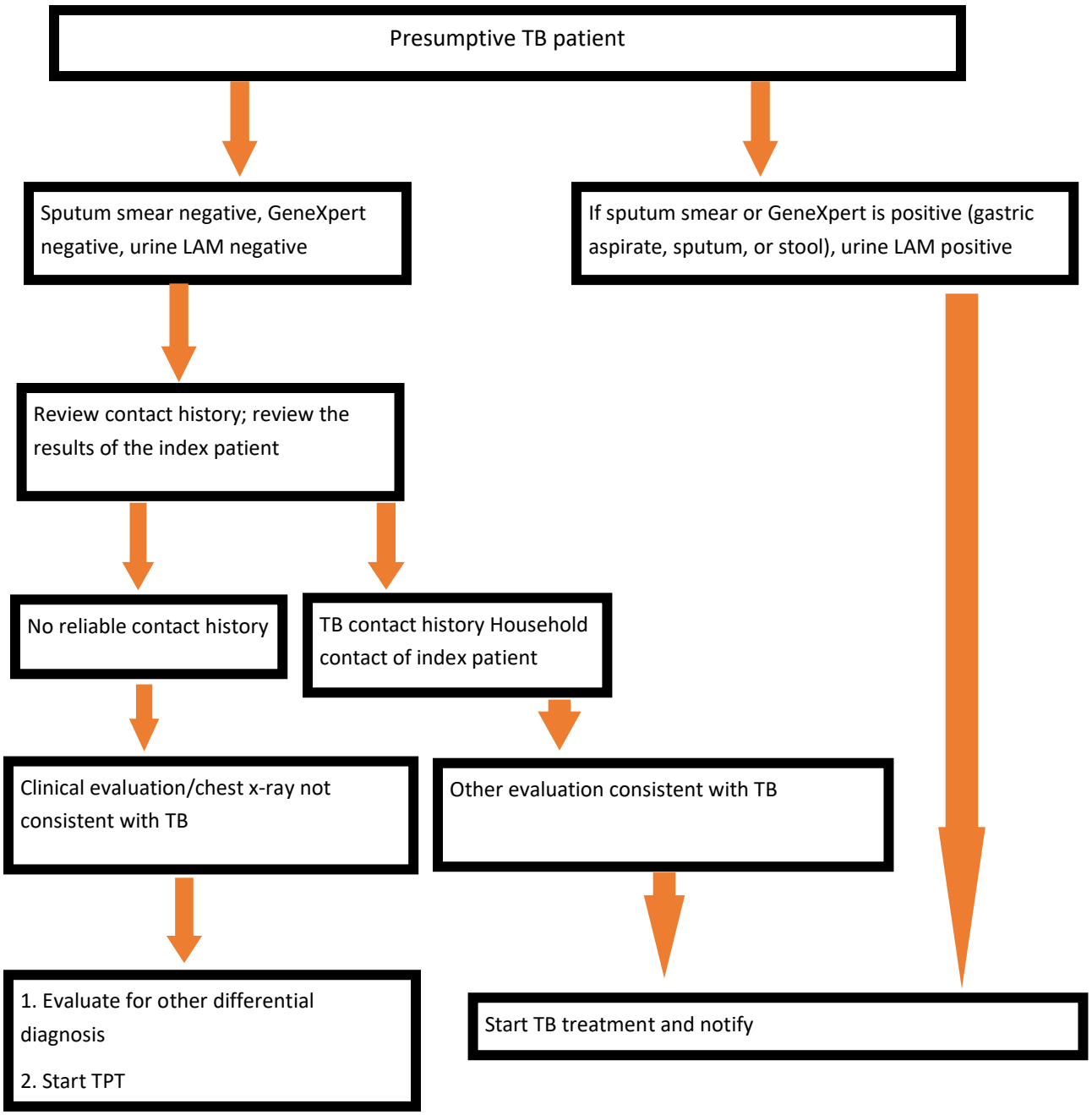
3.3.1 Diagnostic algorithms

Figure 17. Algorithm for tuberculosis diagnosis in HIV negative children.



Abbreviations: EPTB, extrapulmonary tuberculosis; PTB, pulmonary tuberculosis; TB, tuberculosis.

Figure 18. Algorithm for tuberculosis diagnosis in HIV-infected children.



Abbreviations: LAM, lipoarabinomannan; TB, tuberculosis; TPT, tuberculosis preventive treatment.

Where TB diagnostic tools are not available, refer specimens to a TB diagnostic facility.

If TB has been excluded by the above steps and the child is not improving, please consider other differentials or refer to the next level of care or consult experts.

Table 29. Features of extrapulmonary forms of tuberculosis to watch for.

Site of EPTB	Typical clinical presentation	Investigation	Management
TB adenitis	Asymmetrical, painless, nontender lymph node enlargement for more than 1 month +/- discharging sinus, most commonly in neck	• Fine-needle aspiration when possible for GeneXpert MTB/RIF or Ultra, culture, AFB microscopy, and histology • Lymph node biopsy	• Start TB treatment • If axillary node enlargement on same side as BCG scar, consider BCG disease if HIV-infected infant and consult
Pleural TB	Dullness on percussion and reduced breath sounds +/- chest pain	• Chest x-ray • Pleural tap[a] (for GeneXpert or culture, smear)	• Start TB treatment • If pus in pleural tap, consider empyema and refer to the next level of care
Usually young (<5 years) with disseminated disease and severely ill			
TB meningitis	Headache, irritability/abnormal behavior, vomiting (without diarrhea), lethargic/reduced level of consciousness, convulsions, neck stiffness, bulging fontanelle, cranial nerve palsies	• Lumbar puncture, obtain CSF for GeneXpert culture, smear, LAM • Biochemistry (high protein, low glucose) • Brain CT scan or MRI	• Hospitalize for TB treatment • Start TB treatment • Add steroids (corticosteroids; see page 63 for detail)
Miliary TB	Nonspecific, lethargic, persistent fever, wasted	• Chest x-ray • Lumbar puncture to exclude concomitant TB meningitis	• Start TB treatment or refer
Usually 5 years and older			
Abdominal TB	Abdominal swelling with ascites or abdominal masses	• Ascitic tap for GeneXpert/smear • Abdominal ultrasound	• Start TB treatment or refer
Spinal TB	Deformity of spine; may have lower limb weakness/paralysis or be unable to walk	• Chest x-ray of spine • CT scan/MRI of the spine • Biopsy	• Start TB treatment • Refer to orthopedic surgeon
Pericardial TB	Cardiac failure, distant heart sounds, apex beat difficult to palpate	• Chest x-ray • Pericardial tap for GeneXpert, culture, smear • Echocardiogram	• Start TB treatment • Refer to the next level of care • Add steroids page 63 for details)
TB of the bone and joint	Swelling in the end of long bones, with limitation of movement; unilateral effusion of usually knee or hip	• Chest x-ray of bone/joint • Joint tap for GeneXpert culture, smear	• Start TB treatment or refer to orthopaedic surgeon

Abbreviations: AFB, acid-fast bacilli; BCG, bacillus Calmette-Guérin; CSF, cerebrospinal fluid; CT, computed tomography; LAM, lipoarabinomannan; MRI, magnetic resonance imaging; TB, tuberculosis.

a. Typical findings: Straw-colored fluid, exudate with high protein, white blood cells predominantly lymphocytes on microscopy. Note that pleural aspirate GeneXpert MTB/RIF and culture are most often negative. Referral may be necessary for investigation procedure and laboratory support, as well as clinical care. **If all options for referral have been explored and referral is not possible, start TB treatment. Start TB treatment immediately if TB meningitis is suspected.**

3.4 Treatment of TB in children

3.4.1 Recommended medication regimens

Table 30. Recommended dosages according to weight.

Drug	Daily dosage in mg per kg (range)	Maximum dose
Isoniazid (H)	10 mg/kg (7–15 mg)	300 mg/day
Rifampicin €	15 mg/kg (10–20 mg)	600 mg/day
Pyrazinamide (Z)	35 mg/kg (30–40 mg)	1500 mg/day
Ethambutol €	20 mg/kg (15–25 mg)	1200 mg/day

Table 31. Tuberculosis treatment categories and recommended regimens.

TB disease category	Recommended regimen	
	Intensive phase	Continuation phase
All no severe forms of PTB and EPTB	2 (RHZE)	4 (RH)
Severe forms: TB meningitis; osteo-articular, spinal, and military TB; other	2 (RHZE)	10 (RH)

Abbreviations: EPTB, extrapulmonary tuberculosis; PTB, pulmonary tuberculosis; TB, tuberculosis.

Use the child friendly formulations RHZ 75/50/150 mg and RH 57/50 mg to treat childhood TB as shown in the table below. RHZ is dispersible/easily dissolved in water and palatable (child-friendly flavor).

Table 32. Dosing by weight band for children using the RHZ (75/50/150 mg) and RH (75/50 mg) formulations.

Weight band	Intensive phase		Continuation phase
	RHZ (75/50/150 mg)	E[a] (100 mg)	RH (75/50 mg)
	Number of tablets		
4–7 kg	1	1	1
8–11kg	2	2	2
12–15 kg	3	3	3
16–24 kg	4	4	4
>25 kg	Use adult dosages and formulations (RHZE 150/75/400/275, 2 tablets)		

a. Ethambutol is provided as a separate 100 mg tablet.

3.4.2 Other management issues

Corticosteroids are indicated in the management of some complicated forms of TB, such as:

- TB meningitis
- Complications of airway obstruction by TB lymph glands
- Pericardial TB

Prednisolone is recommended at a dose of **2 mg/kg daily**, increased to 4 mg/kg daily in the case of the most seriously ill children, with a maximum dosage of 60 mg/day for **4 weeks**. The dose should then be gradually tapered over 1 to 2 weeks before stopping.

Pyridoxine supplementation (5–10 mg/day) should be given to all children on anti-TB treatment. Isoniazid may cause symptomatic pyridoxine deficiency, which presents as neuropathy, particularly in severely malnourished and HIV-positive children on ART.

Nutritional support

- Assess the nutritional status of all children with TB.
- Refer children with TB and severe malnutrition for a therapeutic feeding program.
- Breastfeeding infants and children should continue to breastfeed while receiving TB treatment.
- Additional energy is particularly important during the intensive phase of treatment and is best given through additional household foods provided as part of a balanced varied diet.

2.4.2 Monitoring response to treatment

- Review children with TB every 2 weeks during the intensive phase and monthly during the continuation phase, at a health facility.
- At every visit, evaluate for resolution of symptoms.
- Children not improving while on treatment must be re-evaluated for drug-resistant tuberculosis (DR-TB) and noncompliance to treatment.
- Weigh and monitor weight at every visit.
- Look for adverse reactions to treatment at every visit: yellow eyes, abdominal pain, skin rash.
- Younger children diagnosed by gastric lavage do not need to have it repeated to monitor response to therapy. Instead, use a clinical evaluation.
- When treatment failure is suspected, collect a specimen for molecular testing and culture/drug susceptibility testing (DST) to assess for rifampicin resistance.
- Older children with bacteriological-confirmed TB should be monitored similarly to adults; use a sputum smear examination at months 2, 5, and 6.
- Use chest x-ray for children who are deteriorating on treatment or when clinically indicated. For children who are co-infected with HIV, monitor response to ART as well, using viral load (use the standards under the national HIV guidelines).

Key messages

- The principles of treatment of TB in children are the same as for adults.
- A caregiver should be identified as a directly observed therapy provider for all ages, including older children.
- Once treatment starts, it must be completed; “trial of treatment “should not be used as a diagnostic approach.
- Record weight at each visit on the under-5 and treatment cards.
- Always calculate drug dosages by body weight.
- Pyridoxine supplementation should be provided to all children on anti-TB treatment.
- Nutritional support should be provided for malnourished children.
    - All children diagnosed with TB should be recorded in the Facility TB Register and on the treatment card and issued a TB identification card.

Key messages

- Children respond better to treatment when started early.
- Directly observed therapy is critical for successful treatment.
- Take a family approach to treatment.
- Closely monitor response to therapy.
- Optimize ART for children co-infected with HIV.
    - Monitor for and manage adverse reactions.

3.5 Drug-resistant TB in children

The clinical presentation of DR-TB is like drug-susceptible tuberculosis (DS-TB) in children. Bacteriological confirmation is not always possible; therefore, the diagnosis is often made on clinical and radiological grounds. Contact history is an important factor in evaluation for DR-TB. Patient evaluation is the same as for DS-TB patients.

When to presume DR-TB in children

- Close contact with a person known to have DR-TB, including household and school contacts.
- Close contact with a patient who died from TB, failed, or is not adherent to TB treatment.
- History of previous TB treatment (in the past 6 to 12 months).
- Not improving after 2 to 3 months of first-line TB treatment, including persistence of positive smear or culture, persistence of symptoms, and failure to gain weight (radiological improvement is frequently delayed).
- A child who develops active TB while on isoniazid prophylaxis.

3.5.1 Bacteriologic confirmation

- Use GeneXpert MTB/RIF or Ultra as the primary diagnostic test in all children with signs and symptoms of TB, where available.
- Where Xpert MTB/RIF is not available, send samples to the nearest facility where the test is available, especially for individuals with presumed DR-TB.
- Send all gastric aspirate and sputum for culture and line probe assay (LPA) for DST for both first- and second-line drugs.
- Patients who require TB retreatment based on history should undergo DST with rapid molecular testing (Xpert MTB/RIF or Ultra, first- and second-line LPA) to inform the choice of treatment.
- For all patients with rifampicin resistance detected on GeneXpert, samples should be sent for first- and second-line LPA, culture, and phenotypic DST.
- Complete laboratory request forms completely and clearly.

3.5.2 DR-TB treatment regimens

The duration of the of treatment for children on the longer all oral regimen is 18 to 20 months and 9-12 months for children over the age of 6 years on the shorter oral regimen, like in adults. The duration of Bedaquiline or Delanamind is dependent on the clinical indication. Conversion between months 6 and 8:

- Use the clinical response to treatment to guide the decision to progress to the continuation phase, since repeat sputum is not feasible in children.
  - Screen family members for TB, if there is a high risk of re-infection of the child and treatment is likely to fail.
  - Provide tuberculosis preventive treatment (TPT) to other children in the household who test negative for TB, using isoniazid or, preferably, rifampicin/isoniazid (3HR).
  - DR-TB and multidrug-resistant tuberculosis treatment regimens for children are summarized in the tables below.

Table 33. Drug-resistant tuberculosis treatment regimens.

Age	Intensive phase (6–8 months)	Continuation phase (12 months)	Notes
0 to <3 years	Lfx-Lzd-Cfz-Cs	LFx-Lzd-Cfz	If fluoroquinolone resistant, replace Lfx with Dlm, PAS, Eto
3 to 6 years	Lfx-Lzd-Cfz-Cs-Dlm	LFx-Lzd-Cfz	If fluroquinolone resistant, drop Lfx in the intensive phase and replace it with Dlm in continuation
>6 years	Bdq-Lfx-Lzd-Cfz-Cs	Lfx-Lzd-Cfz	If flouroquinolone resistant, use the guidelines for management of adult patients with fluroquinolone resistance

Abbreviations: Bdq, bedaquiline; Cfz, clofazimine; Cs, cycloserine; Dlm, delamanid; Eto, ethionamide; LFx, levofloxacin; Lzd, linezolid; PAS, para-aminosalicylic acid.

Table 34. Medicines used in the treatment of multidrug-resistant tuberculosis in children younger than 15 years.

Group	Medicine	Weight-based daily dose[b]	Formulation	Weight bands among patients not yet 15 years old[a]							Usual upper daily dose[b]	Comments
				5–6 kg	7–9 kg	10–15 kg	16–23 kg	24–30 kg	31–34 kg	>34 kg		
A	*Fluoroquinolones*											
	Levofloxacin	15–20 mg/kg	100 mg dt	1	1.5	2 or 3	3 or 4	(>14 y)	(>14 y)	(>14 y)	1.5 g	
			250 mg tab	0.5	0.5	1 or 1.5	1.5 or 2	2	3	(>14 y)	1.5 g	
	Moxifloxacin	10–15 mg/kg	100 mg dt[c]	0.8	1.5	2	3	4	(>14 y)	(>14 y)	400 mg	
			400 mg tab[c]	2 ml[c]	3 ml[c]	5 ml[c]	0.5 or 0.75	1	(>14 y)	(>14 y)	400 mg	Use 10 mg/kg in <6 months
	Bedaquiline	–	100 mg tab	–	–	-	2 tabs od for two weeks; then 1 tab od M/W/F for 22 weeks		4 tabs od for 2 weeks; then 2 tabs od M/W/F for 22 weeks		–	Only in patients >5 years old (lower dose from 15–29 kg; higher dose from >29 kg)
	Linezolid	15 mg/kg od in <16 kg 10–12 mg/kg od in >15 kg	20 mg /ml susp	4 ml	6 ml	8 ml	11 ml	14 ml	15 ml	20 ml[d]	600 mg	
			600 mg tab[c]	0.25	0.25	0.25	0.5	0.5	0.5	0.75[d]		
B	Clofazimine	2–5 mg/kg	50 mg cap or tab	1 alt days	1 alt days	1 alt days	1	2	2	(>14 y)	100 mg	Give on alternate days if dose in mg/kg/day is too high
			100 mg cap or tab	M/W/F	M/W/F	1 alt days	1 alt days	1	(>14 y)	(>14 y)	100 mg	
	Cycloserine or terizidone	15–20 mg/kg	125 mg mini capsule (cycloserine)[c]	1	1	2	3	4	(>14 y)	(>14 y)	1 g	
			250 mg cap[c]	4–5 ml[c]	5–6 ml[c]	7–10 ml[c]	2	2	2	(>14 y)	1 g	
C	Ethambutol	15–25 mg/kg	100 mg dt	1	2	3	4	-	-	(>14 y)	–	
			400 mg tab[c]	3 ml[c]	4 ml[c]	6 ml[c]	1	1 or 1.5	2	(>14 y)		

Key messages

- Confirmation of DR-TB may not be feasible in children.
- Contact history is cardinal in evaluation for DR-TB.
- Use the age bands when choosing the regimen for reach patient.
- Directly observed therapy is critical in the management of DR-TB.

3.6 TB and HIV co-infection in children

HIV-infected children are at an increased risk of developing TB, both because they are likely to be exposed to TB from a parent/guardian and because HIV infection weakens their immunity to TB. HIV-infected children may develop multiple episodes of TB: a previous TB episode does not exclude future TB. Diagnosis and treatment of TB are similar for both HIV-infected and uninfected children. The diagnosis of PTB can be particularly challenging in HIV-infected children because of clinical overlap with other HIV-related diseases.

A comprehensive approach to TB and HIV management

- Integration of HIV into TB clinics
- Screening all HIV-positive children for TB at every visit
- Diagnosis and treatment of TB
- Cotrimoxazole preventive therapy and combination ART for HIV-positive children
- Nutritional support for children with TB/HIV, as needed

The management of children with TB and HIV should be integrated and all households counseled and tested for HIV and screened for TB. Children with TB/HIV co-infection may not have a caregiver to ensure treatment adherence. A treatment supporter/community health worker should then be identified.

When to start ART in TB/HIV co-infected children:

- ART should be started in all HIV-infected children with TB regardless of their CD4 count.
- TB treatment should be initiated first, followed by ART within the first 8 weeks of treatment.
- In children with confounding immunosuppression, ART should be commenced within the first 2 weeks of initiating TB treatment.

Table 35. Recommended anti-tuberculosis and antiretroviral therapy regimens in TB/HIV co-infected children.

Specific population	Recommended anti-TB treatment	Preferred ART regimen	Alternative ART regimen
<20 kg	All DS-TB: 2 months of RHZE, then 4 months of RH TB forms such as meningitis, osteoarthritis, pericardial, spinal: 2 months of RHZE, then 10 months of RH	ABC+3TC+RAL (double dose of RAL) or ABC+3TC+AZT When DTG 10 mg is available, use it in place of RAL and increase frequency to twice daily 12 hours apart	AZT+3TC+EFV (if older than 3 months)
20–29.9 kg		ABC+3TC+DTG (DTG 50 mg twice daily)	ABC+3TC+LPV/r (LPV/r double dose)

≥30 kg		TDF+3TC+DTG (DTG 50 mg twice daily)	or ABC+3TC+EFV or ABC+3TC+RAL

Abbreviations: 3TC, lamivudine; ABC, abacavir; ART, antiretroviral therapy; AZT, zidovudine; DS-TB, drug-susceptible tuberculosis; DTG, dolutegravir; EFV, efavirenz; RHZE, rifampicin/isoniazid/pyrazinamide/ethambutol; LPV/r, lopinavir/ritonavir; RAL, raltegravir; TDF, tenofovir disoproxil fumarate.

Key messages

- All children with TB should be tested for HIV.
- All children with HIV should be screened for TB at each clinic visit.

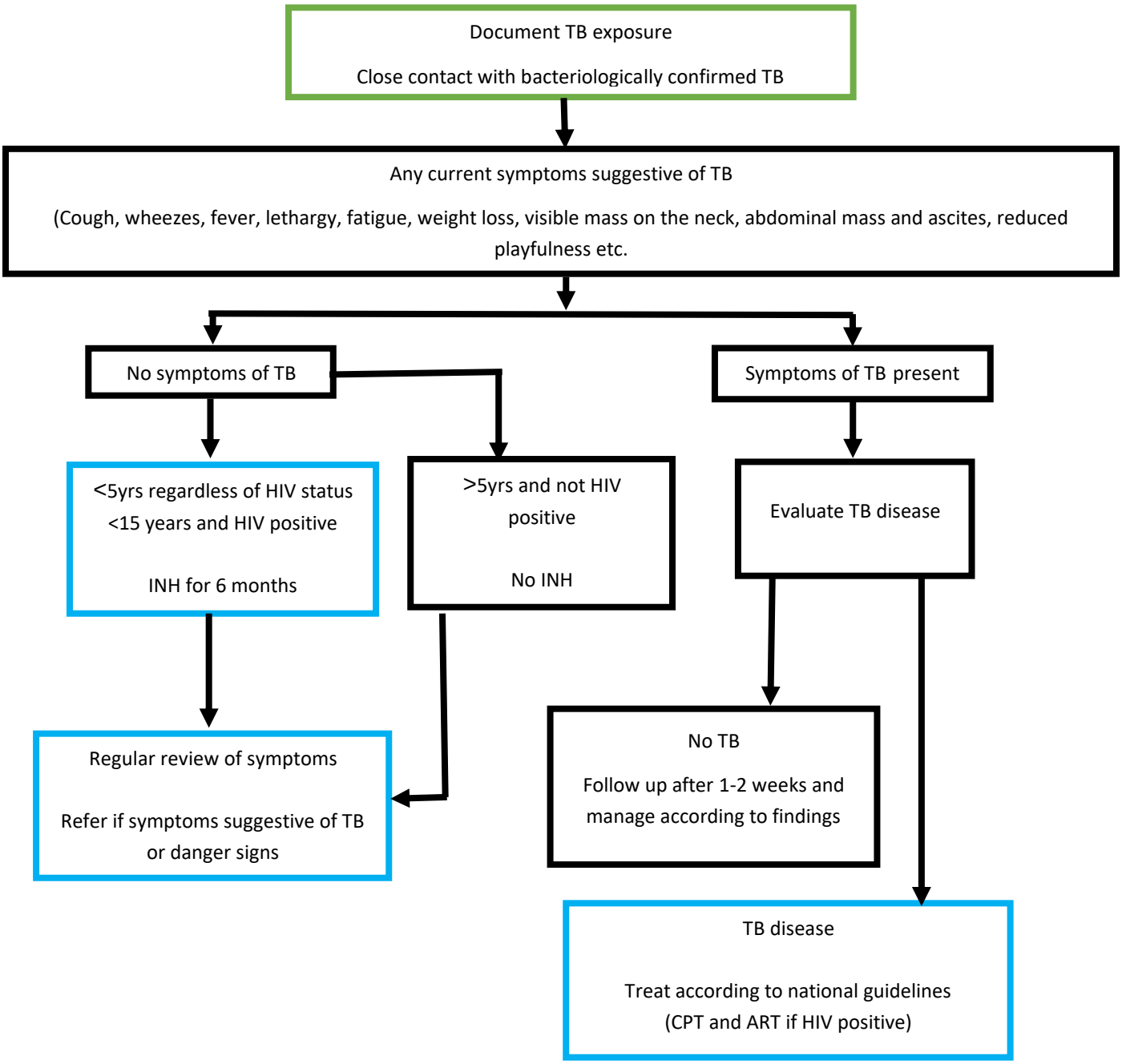
3.7 Contact screening and management for children living with an infectious TB patient

- It is recommended that all children who are household contacts of bacteriologically confirmed TB patients be screened for TB.
- Children who are under 5 and have no symptoms of TB should be started on TPT.
- Any child contact with symptoms should be carefully assessed for TB.
- Clinical assessment alone is sufficient to decide whether the contact is well or symptomatic.
- Routine screening of exposed contacts does not always require chest x-ray or a TST.
- Symptom-based screening should be used to screen child contacts for TB.
- Available TPT includes isoniazid administered at a recommended dose of 10 mg/kg for a full 6 months to be effective or isoniazid and rifampicin for 3 months or weekly rifapentine and isoniazid for 3 months. Eligible children include:
  - Infants (aged <12 months) living with HIV who are in contact with a case of TB.
  - Children (aged ≥12 months) living with HIV who are unlikely to have TB disease on symptomatic screening with or without a history of TB contact.

- Follow-up should be carried out at least every 2 months until treatment is complete. If TB is suspected at initial assessment or a subsequent follow-up, the child should be treated for TB. Referral to a district or tertiary hospital may be necessary when there are uncertainties of diagnosis.

The algorithm for conducting contact tracing is shown in the figure below.

Figure 19. Algorithm for contact tracing.



Abbreviations: ART, antiretroviral therapy; CPT, cotrimoxazole preventive therapy; INH, isoniazid; TB, tuberculosis.

Key messages

- Source case investigations should be conducted on other members of the household whenever a child is diagnosed with TB.
- TPT is indicated for all children younger than 5 years who are household contacts of a case of bacteriologically confirmed TB and do not have any evidence of active TB.

4. Tuberculosis and COVID-19

4.1 General guidance

Tuberculosis (TB) patients are at increased risk of contracting COVID-19; and conversely, people who have had COVID-19 are at increased risk of re-activating from latent to active TB. COVID-19 infection and the high dose of corticosteroid therapy used as part of the treatment contributes to this. Thus, bidirectional TB and COVID-19 screening is warranted.

To support TB patients during the COVID-19 pandemic, it is critical both to patients and the health care system to minimize visits to health facilities. This guidance prioritizes how to provide uninterrupted TB treatment during the COVID-19 outbreak. In addition to outlining recommended service delivery approaches for drug-susceptible and drug-resistant tuberculosis (DS- and DR-TB) patients, guidance on additional areas is provided, including patient support, contact tracing, infection prevention, differentiating TB from COVID-19, and differentiated service delivery models for both tuberculosis preventive treatment (TPT) and anti-TB treatment (like telephonic monitoring).

Table 36. Comparisons between tuberculosis (left) and COVID-19 (right).

How it is spread	Airborne	Droplet spread
Symptoms	Fever, cough, weight loss, poor appetite, drenching night sweats, chest pains	Difficulty breathing, cough, fever, sore throat
How it is diagnosed	Sputum tests for those with cough; other samples depending on symptoms	Nasal swabs and/or sputum tests
Pathogen	*Mycobacterium tuberculosis*	Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
Infectiousness	Ranges from less than one to up to four people infected per one person with TB	Current average: 2.2 people infected per one person with COVID-19
Prevention	Prevention measures include TPT for those with known contacts with TB and good respiratory hygiene measures	Social distancing, good respiratory hygiene measures, and handwashing with soap for at least 20 seconds
Treatment	Antibiotics (ATT)	Supportive care

Abbreviations: TB, tuberculosis; TPT, tuberculosis preventive treatment.

Note: Obtaining a contact history is very important in the case of both diseases. However, in most cases, there may be no positive contact history.

Table 37. Radiological features of COVID-19 versus tuberculosis.

COVID-19	Tuberculosis
Bilateral lower-zone infiltrates (consolidation), likely to be peripheral	May be unilateral, typically apical in HIV-negative patients
Has not been observed in Covid-19	Miliary infiltrates in immunocompromised
No effusion	Effusion is a common feature
No evidence of cavitation	Cavitation in immunocompetent patients
Ground glass on computed tomography scan	Not a typical feature
No lymphadenopathy	Hilar lymphadenopathy is typical
Chest x-ray may be normal	Chest x-ray may be normal
Rapid progression (within hours or days)	Slow progression (weeks to months)

4.1.1 Bidirectional TB screening

Bidirectional screening will be carried out in two settings: the chest clinic and the post-acute COVID-19 clinic.

Figure 20.1. Algorithm for COVID-19 screening in a tuberculosis clinic.

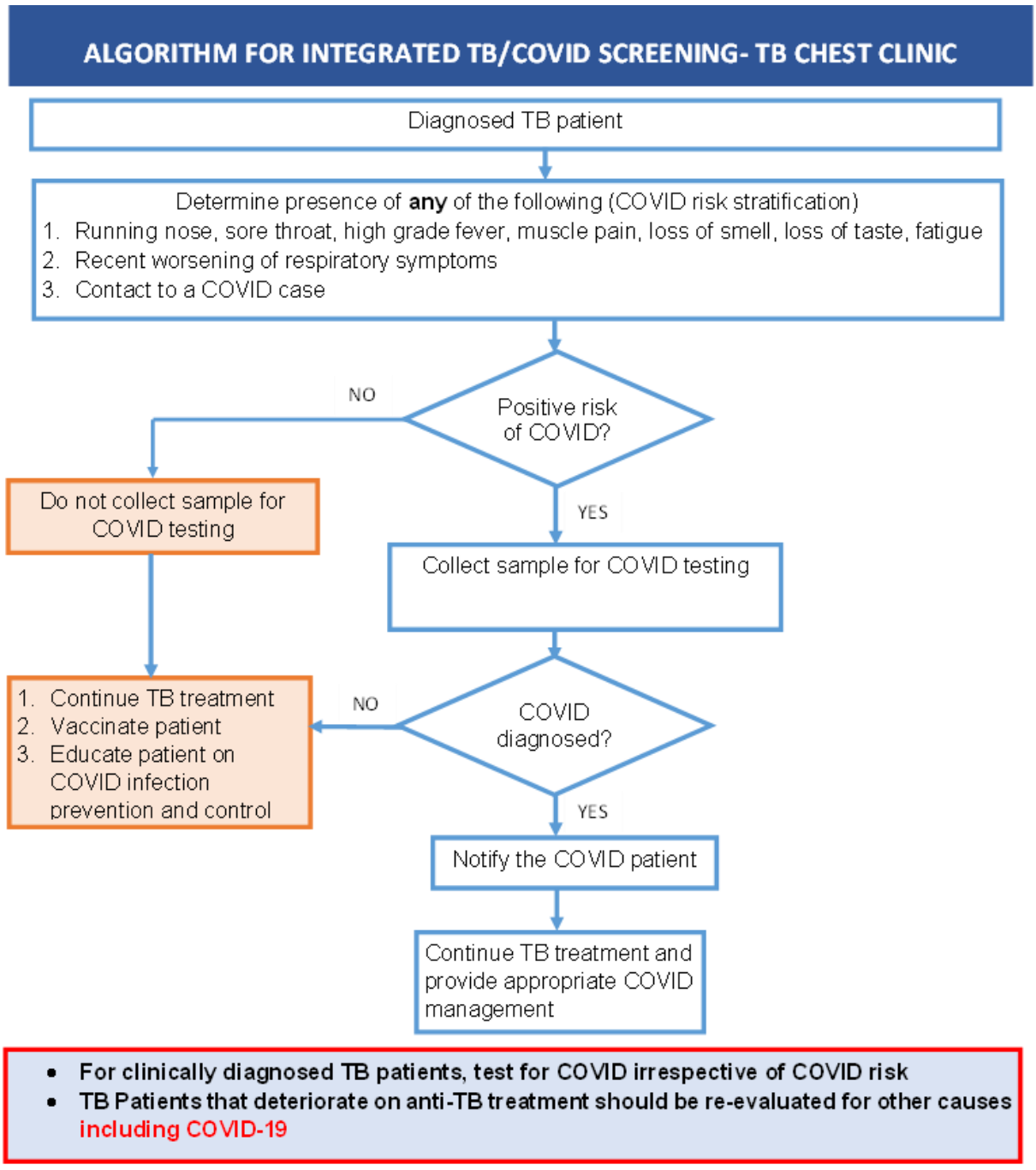


Figure 21.2. Algorithm for COVID-19 screening at COVID 19 Screening.

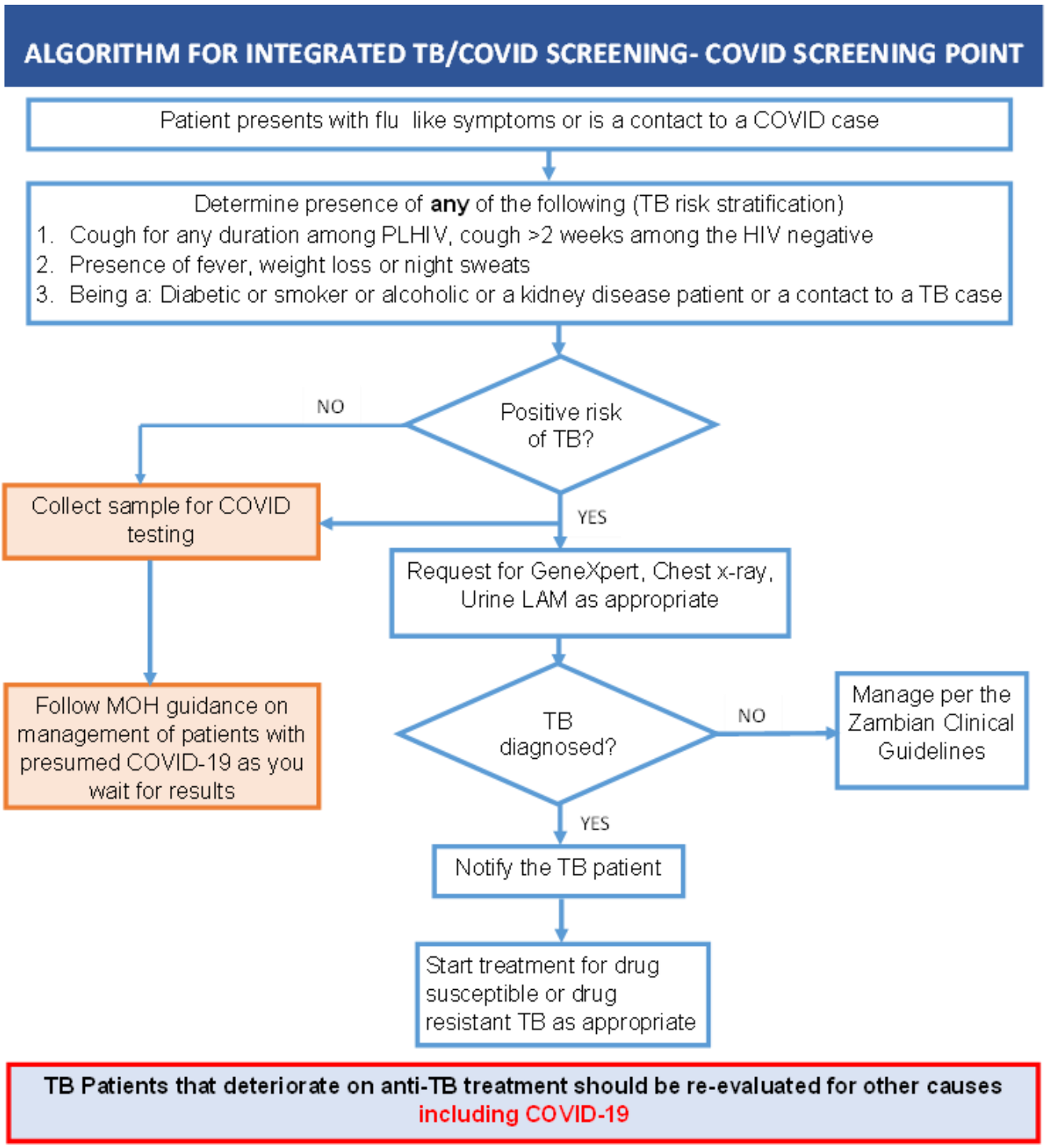
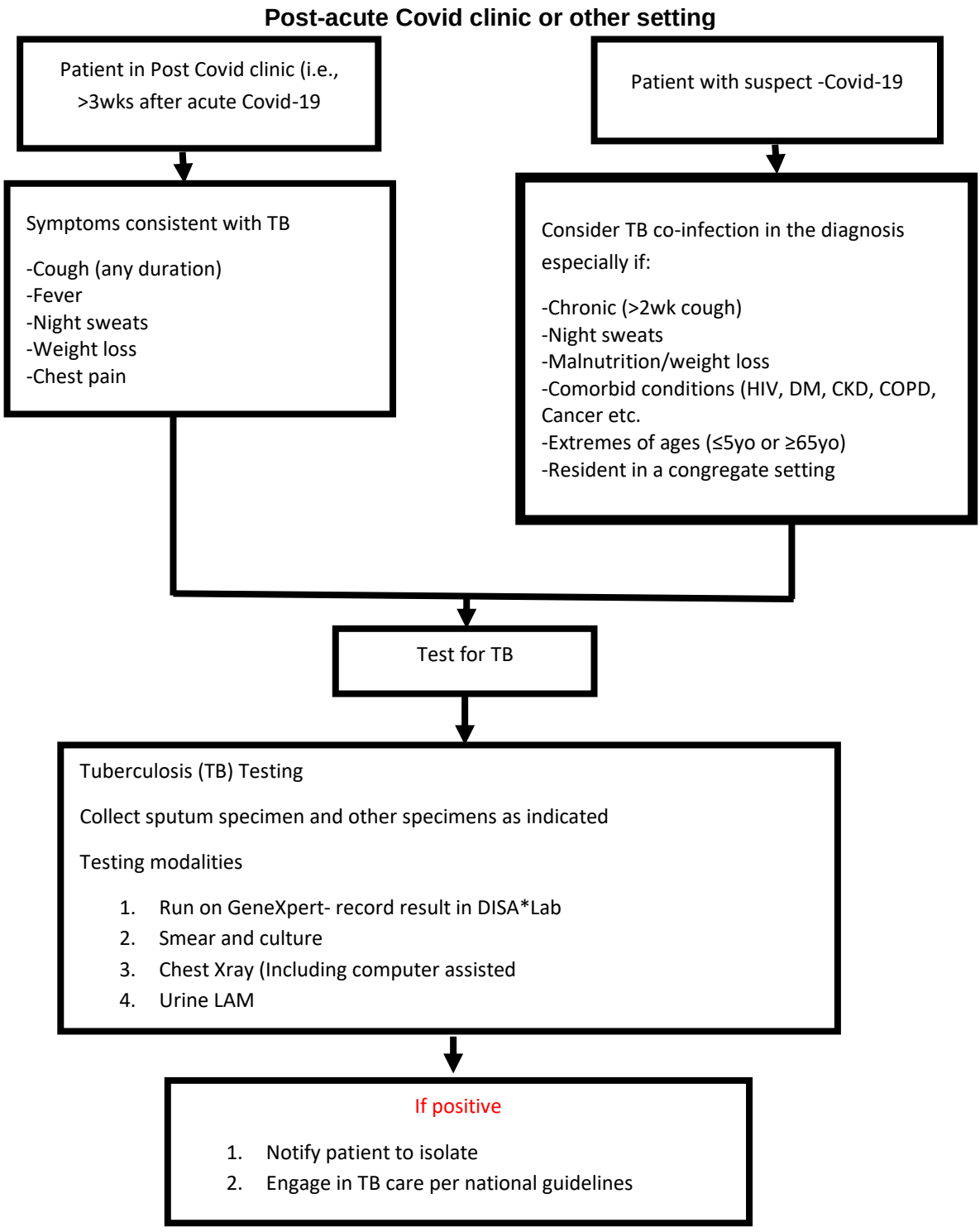


Figure 22. Algorithm for tuberculosis and Covid 19 screening



Abbreviations: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; LAM, lipoarabinomannan; TB, tuberculosis.

4.2 Specific guidance for management of TB patients during COVID-19

4.2.1 Drug-susceptible TB patients

Primary recommendation

Provide 2 months of intensive-phase TB treatment to align with a scheduled return to the health facility for a clinical assessment 8 weeks include follow ups sputum examination after TB treatment start. The If smear negative at this visit, provide 2 months of continuation-phase treatment. At month 5, patient should have a clinical visit and sputum submission for examination, then provided with 2 months treatment to continue continuation phase. At 6 months (completion of treatment), return for an exit clinical consultation.

.

Operational details for specific populations

Patients already on DS-TB treatment

For those in the intensive phase:

- At the next scheduled health facility visit, provide sufficient intensive-phase TB treatment to last until the 8-week visit. Schedule the return appointment to the health facility for the week 8 follow-up.
    - If the smear was positive at diagnosis, also provide two labeled TB sputum jars and instructions to produce two sputum samples at home at the 7-week mark (give date reminder). The patient should drop off the samples at the health facility as soon as possible after producing them (no need to wait for consultation). Return for clinical assessment at 8 weeks.
- At the 8-week clinical assessment:
    - If the week 7 sample is smear negative and there is no clinically significant deterioration: Provide a continuation-phase TB treatment refill for the remaining 4 months of treatment and schedule a return appointment to the health facility for an exit clinical consultation at the completion of 6 months of treatment.
        - If the smear was positive at diagnosis, again provide two labeled TB sputum jars with similar instructions to produce and drop sputum samples at month 5 and return for an exit clinical consultation at month 6.
    - If the week 7 sample is smear positive or the patient is clinically deteriorating: Request culture and drug susceptibility testing (DST) on the second sample from week 7 (if available) or send an additional sample for smear, culture, and DST. Provide a refill of intensive-phase TB treatment for an additional 4 weeks and schedule a return appointment to the health facility at week 12. Again, provide two labeled TB sputum jars with similar instructions to produce and drop off sputum samples at the health facility 3 weeks later and return for further clinical assessment in 4 weeks. Clinicians should

follow up on culture and DST results and recall the patient immediately if drug resistance is detected.

- If the smear result is not available at the 8-week clinical assessment:
  - If the patient did not return a sputum sample at week 7: Take sputum at the 8-week clinical assessment visit and provide further intensive-phase TB treatment for an additional week and schedule a return to the health facility for a clinical assessment at 9 weeks.
  - If the laboratory result is not yet available for the week 7 sputum: Provide a refill for intensive-phase TB treatment for an additional week and schedule an appointment for a return to the health facility for clinical assessment at 9 weeks.

For those in the continuation phase:

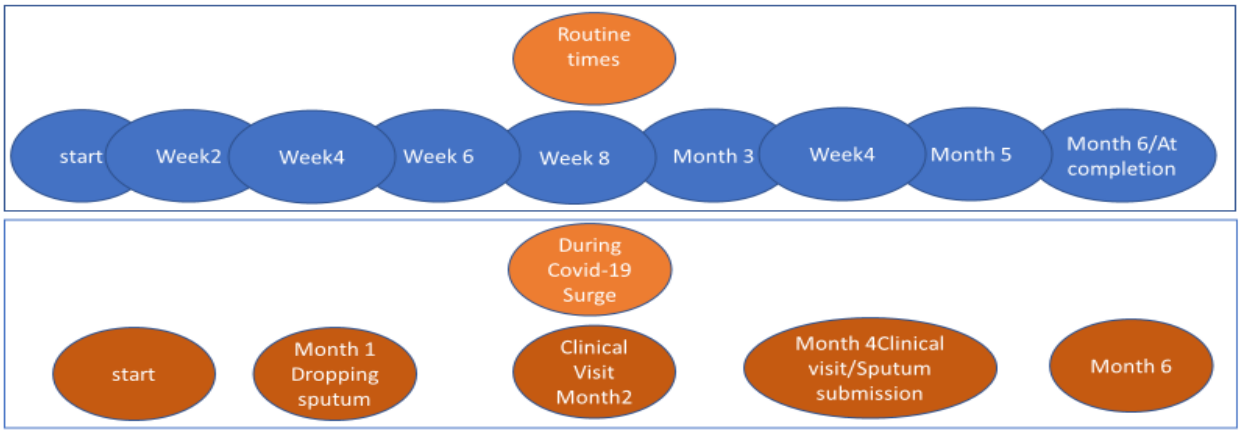
- At the next scheduled facility visit, provide a continuation-phase TB treatment refill to last until completion at 6 months. Have the patient return at 6 months for an exit clinical consultation.
  - If the smear was positive at diagnosis, also provide two labelled TB sputum jars and instructions to produce and drop samples at the end of month 5 and return for an exit clinical consultation at month 6.

<u>Patients starting DS-TB treatment</u>

- At the TB treatment start visit, provided the patient is well, provide the full 2 months of intensive-phase TB treatment and schedule a return appointment to the health facility for a week 8 follow-up.
  - If the smear was positive at diagnosis, provide two labelled sputum jars and instructions to produce and drop two sputum samples at the 7-week mark (see details above), and to return for a clinical assessment at 8 weeks.
- If the TB patient is co-infected with HIV and not on antiretroviral therapy (ART), arrange to start ART 2 weeks later, and thereafter align ART refills with TB treatment (i.e., 2 months of intensive-phase TB treatment and a 2-month ART refill).
- Counselling remains important. Ideally, the first session should be provided telephonically to reduce the time spent at the health facility on the TB treatment start date. If this is not possible, it should be provided at or near the health facility with existing TB infection control measures in place.
- Thereafter, follow the approach for TB patients already on treatment outlined above.

Schedules for clinic visits for DS-TB patients are illustrated in the following figure.

Figure 23. Drug-susceptible tuberculosis clinic review schedules: Routine and during COVID-19 surges.



4.2.2 Drug-resistant TB patients

Primary recommendation

Provide DR-TB treatment refills to align with a health facility visit schedule for clinical assessment at 2 weeks, 4 weeks, 8 weeks, and 2 monthly thereafter.

Operational details for specific populations

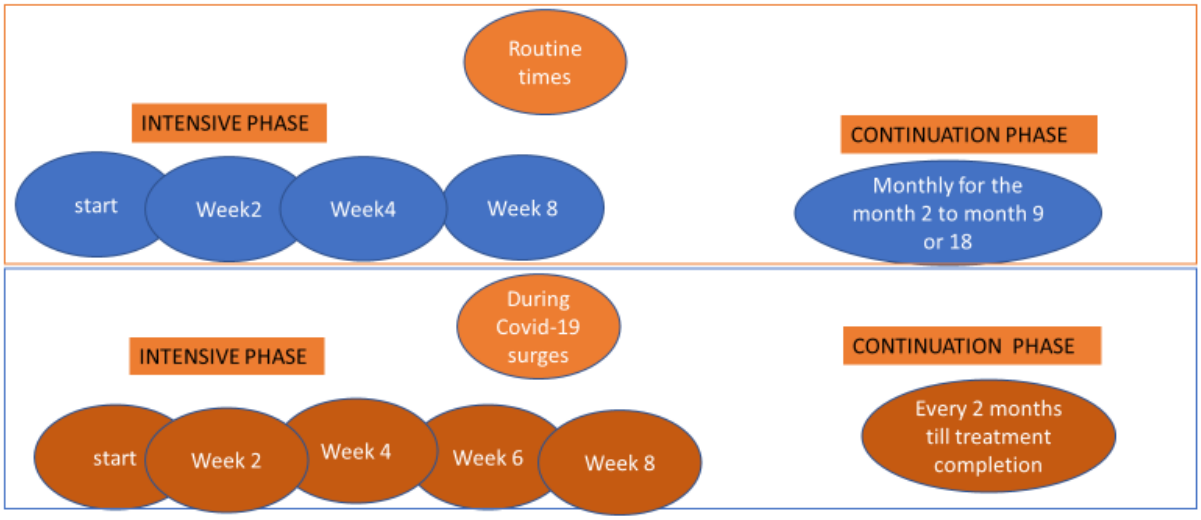
Patients already on or starting an oral DR-TB regimen

- Whether on the short, standardized regimen or one of the longer oral regimens, DR-TB patients on linezolid require more intensive monitoring in the first 2 months due to the risk of a rapid drop in hemoglobin levels. DR-TB patients require a hemoglobin check (finger prick, or full blood count if possible) at weeks 2, 4, and 8 and should be given DR-TB treatment refills to align with returning for clinical assessment at these time points. Clinicians should follow up full blood count results and attempt to manage dose adjustments by telephone when feasible; otherwise, patient must be recalled for clinical assessment.
- Thereafter, irrespective of DR-TB regimen (including patients on longer regimens which continue linezolid beyond 2 months), provide 2 monthly DR-TB treatment refills aligned with clinical consultations at the health facility.
- Electrocardiogram and hemoglobin should be assessed at each clinical visit together with other monitoring parameters set out in local guidelines. The 2-, 4-, and 6-month clinical consultations are particularly important to assess treatment effectiveness, follow up on sputum culture results, make treatment modifications, and monitor ECGs for patients receiving QT-prolonging drugs.

- If the doctor is concerned about a patient's hemoglobin (<10 g/dL) or QT prolongation (>470 ms) beyond 2 months of treatment, the clinician should review monthly (refer to local management guidelines).
- It is important for treatment monitoring and decision-making that patients on DR-TB treatment give sputum samples every month until confirmed sputum culture conversion. Thereafter 2-monthly is sufficient. At each 2-monthly visit, patients should be given labelled sputum jars with instructions to produce and drop sputum samples between the 2-monthly clinical assessment visits.
- Counselling remains critical. Follow the guidance set out for patients with DS-TB at treatment start, above.

Schedules for clinic visits for DR-TB patients are illustrated in the following figure.

Figure 24. Drug-resistant tuberculosis clinic review schedules: Routine and during COVID-19 surges.



4.2.3 Unwell TB patients

- Advise all TB patients who become unwell at home to first contact the health facility by telephone to advise on whether it is necessary to come into the health facility. When it is necessary, ensure understanding of procedures upon arrival.
- Ensure an appropriate triage system is implemented upon arrival, including screening of TB patients for COVID-19. TB patients who test negative for COVID-19 should be triaged directly to TB services. TB patients who test positive for COVID-19 should be provided a surgical mask and separated from other patients in a COVID-19 investigative area (or at least 1.5 m from another COVID-19-positive person under investigation) and TB services informed.

- Visit frequency and treatment refill length should be determined at the discretion of the clinician. Patients positive for COVID-19 should not make unnecessary repeat in-person health facility visits during the duration of their illness.

4.2.4 Additional areas of consideration

- Pregnant and breastfeeding women: Management of TB should be the same as detailed above. All attempts should be made to communicate and consolidate the number of clinical visits to different health care facilities for various indications (e.g., antenatal and TB and HIV follow-up appointments).
- Childhood TB: Children with TB require regular dose adjustment due to rapid weight gain while on treatment. Maintain monthly clinical visits for the purpose of adjusting dosages. When weight monitoring is assured from home, the above guidance should apply.
- Patient support during COVID-19:
    - MDR-TB community nurses should continue to provide daily directly observed therapy and psychosocial support to patients and their families.
    - All TB patients who have not identified a TB supporter in the home should be encouraged to do so for the period of treatment. Home support is critical during times of less frequent interactions with health care workers and COVID-19 surges.
    - Where resources allow, clinical follow-up and counseling can be provided by telephone at the same frequency as the health facility visits mandated in existing national guidelines. For example, if a TB patient is required to return for a clinical check-up and/or to receive further counseling sessions at weeks 2 and 4, these can be conducted by telephone at the same time points.
- Contact tracing:
    - Identification of contacts of TB patients (names, ages, contact details) should continue to be conducted at the diagnosis/treatment start visit.
    - Patients should be advised to inform all identified contacts of their TB diagnosis and on the importance of informing a health care worker of their contact with a known TB case should they present at a health facility unwell during the COVID-19 pandemic. This will support appropriate triage. Where possible, the TB clinician can provide the patient with contact notification slips for TB contacts to present to a health facility if they feel unwell.
    - At the exit clinical assessment review at 6 months, the clinician should review whether the patient informed their contacts; and if the COVID-19 pandemic is over, initiate appropriate contact management procedures.
- TB preventive therapy:
    - This is a high-impact intervention and should continue.

- Patients already started on TPT should be given enough supplies of TPT commodities (isoniazid plus rifapentine, isoniazid plus rifampicin, isoniazid, and B6) to complete the three to 6 months of therapy.
- For people living with HIV, TPT refills should coincide with ART medication pick-up.
- Patients on TPT should be counseled on possible adverse effects and be advised to inform the care provider either by phone or report to the facility.
- Facilities should quantify the stocks of TPT commodities they need and ensure all commodities are available.
- Facilities and districts should review their initiations and stocks weekly/monthly.

- TB/COVID-19 infection prevention:
    - Administrative controls: Triage presumptive TB clients by ensuring they are directed to separate waiting area or an isolation room, if available, and attended to quickly.
  - Environmental controls: Always ensure adequate ventilation when reviewing patients with all forms of TB. In addition, ensure adequate cleaning and disinfection protocols are adhered to.
  - Patient use of personal protective equipment:
    - Where possible, provide presumed TB patients with a medical mask during triage.
    - Ensure TB inpatients **always** use a mask.
  - Health care worker use of personal protective equipment:
    - Health care workers should **always** use a medical mask.
    - Use eye protection (goggles) when providing care in close contact with a patient with respiratory symptoms (e.g., coughing or sneezing).

4.2.5 Infection prevention in TB laboratories: Core biosafety requirements

- Laboratory in-charges need to review biosafety practices with all laboratory staff and ensure everyone observes and adheres to laboratory safety standards.
- Ensure adequate preparation and use of recommended disinfectants, such as 70% alcohol and 1% bleach, to disinfect surfaces. Note that these disinfectants are active against enveloped viruses such as coronavirus.
- Pay deliberate attention to employ pipetting and smear preparation skills that minimize the generation of aerosols and droplets.
- Increase the frequency of wiping laboratory work benches and handwashing.
- Where available, line up paper towels soaked in disinfectant on the sputum processing work bench and discard upon completion of sample processing. Where paper towels are not available, wipe the work bench thoroughly after sample processing.

- Do not store food, drinks, or personal items such as clothing and bags in the laboratory. Activities such as eating, drinking, smoking, and/or applying cosmetics should be performed outside the laboratory.
- Do not put materials such as pens, pencils, or gum in the mouth while inside the laboratory.
- Protect registers and other written documents from contamination by adequately separating areas for documentation from those used for sample processing.
- Refrain from using mobile electronic devices such as phones, tablets, or laptops within sample processing areas.
- Use appropriate personal protective equipment, including gloves and coats, and avoid contact of gloved hands with the face. N95 masks and goggles are recommended for use.

5. Tuberculosis infection prevention and control

Recommendations

- All health facilities should implement tuberculosis infection control measures.
- Each unit or department of a health facility must ensure the core components of infection prevention and control are in place.
- Resources should be made available to execute activities in the infection control plan.
- Each room should be adapted to have at least 12 air changes per hour to prevent airborne infection, as recommended by the World Health Organization.
- Health facilities should maximize natural ventilation before considering other ventilation systems.
- Each facility using respirators must have a respirator program in place.
- Health care workers and relatives visiting tuberculosis wards must put on N95 respirators or their equivalent.
- Patients and presumptive patients must wear surgical masks when in the public and the wards.
- Quality assurance and improvement should be incorporated into all infection control activities.

Tuberculosis (TB) infection prevention and control (IPC) focuses primarily on decreasing the risk of transmission in health care facilities. Guidelines emphasize the importance of implementing IPC measures in a systematic and objective way that prioritizes consideration of the hierarchy of IPC measures. These interventions should not be implemented individually or in a way that dissociates them from other administrative and environmental controls or personal protection; rather, they must be considered as an integrated package of IPC interventions to prevent *Mycobacterium tuberculosis* transmission.

5.1 Infection control assessment at the health facility level

- The risk of TB transmission and other infectious diseases, such as COVID-19, should be evaluated for the facility and for the areas within the facility where patients might receive care. These areas include examination rooms, the laboratory and pharmacy, waiting areas, the outpatient department, medical wards, and the radiology department.
- An assessment of the risk of transmission of infection should be conducted as the first step in improving IPC because not all areas within the facility pose the same risk.

5.2 Guiding principles

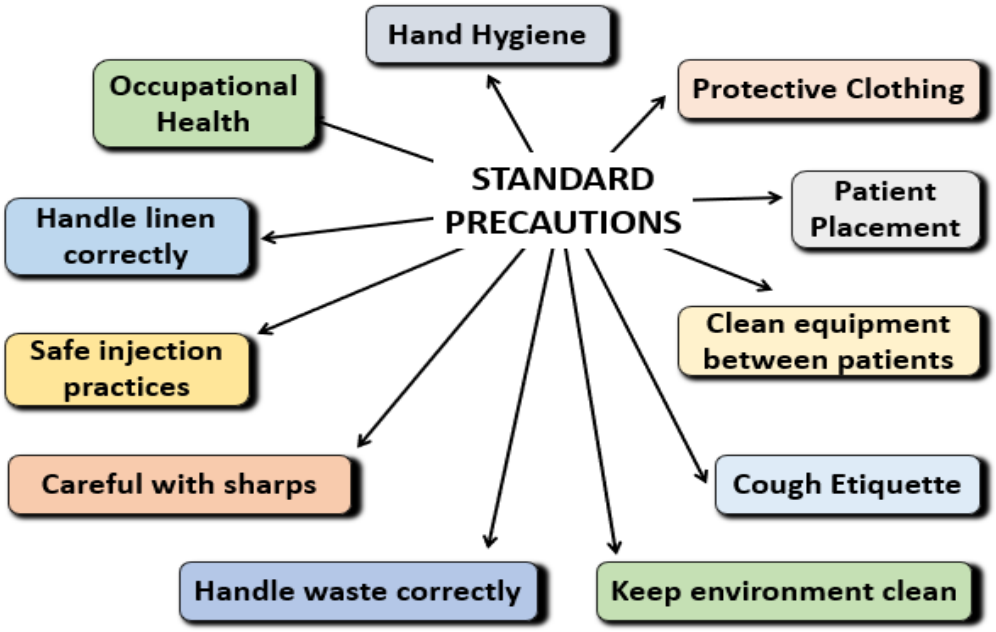
- Effective IPC measures are a critical part of high-quality, people-centered approaches to health service delivery.
- Implementing IPC guidelines requires an understanding of the interdependence of the three-level hierarchy of IPC, giving priority to the implementation of administrative controls as the basis for reducing the risk of transmission of TB.

- Implementation of the recommendations needs to be accompanied by efforts to promote and protect the human rights of all patients, their communities, and care providers.

5.3 Tenets of infection prevention and control

Universal Standard Precautions are the minimum infection prevention practices that apply to all patient care, regardless of presumed or confirmed infection status, in any setting where health care is delivered. These practices protect health care workers and prevent transmission of infection from these workers or through the environment to other patients. The figure below illustrates the primary elements of IPC.

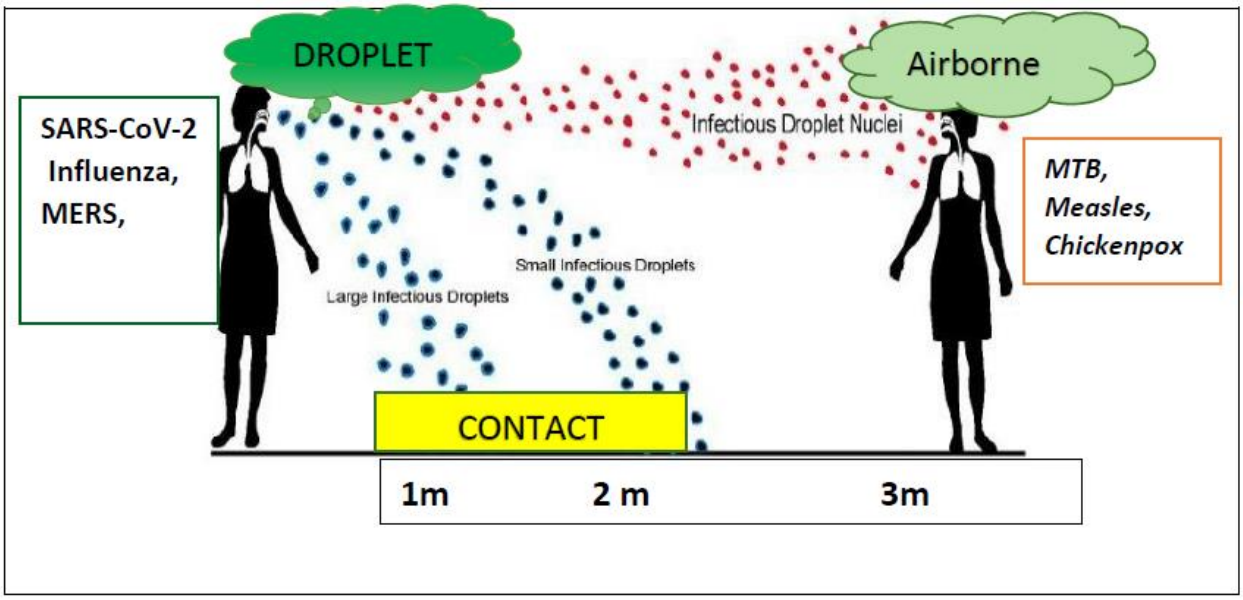
Figure 25. Primary elements of infection prevention and control.



Additional precautions may be added to the standard control measures, depending on the transmission mode of the pathogen. It is good to have an idea of how different diseases are transmitted, to determine the extent of precaution that needs to be taken.

Figure 21 on the following page illustrates the transmission patterns of infectious droplets—information crucial to determining effective IPC procedures to ensure the safety of health care workers and patients.

Figure 26. Transmission of infectious droplets after aerosol generation through coughing or sneezing.



Abbreviations: MERS, Middle East respiratory syndrome; MTB, *Mycobacterium tuberculosis*; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

5.4 Core components of TB infection prevention and control

District health offices and health facilities have primary responsibility for preventing and controlling TB. Health facilities should be able to carry out the following core activities—the backbone of IPC. No other control measures will work effectively in their absence.

- Develop easy to follow, evidence-based plans and standard operating procedures that include requirements for implementation of TB IPC at all levels.
- Conduct IPC education, training, and mentorship.
- Conduct health care–associated infection surveillance.
- Address TB IPC awareness, including actively engaging civil society organizations.
- Monitor and evaluate IPC measures.
- Make available built environment, materials, and equipment for carrying out IPC.

5.4.1 Administrative controls

Administrative controls are the most important components of any IPC strategy. They are designed to reduce staff, patient, and visitor exposure to—and thus, transmission of—TB in health care settings. These key measures comprise specific interventions, including:

- Systems to triage and separate patients (i.e., management of patient flows to promptly identify and separate presumptive TB cases).
- Prompt initiation of effective treatment and respiratory hygiene.

Health facilities should:

- Promptly implement triage through identification and separation of “coughers” from others, to reduce time-lag (time to diagnosis and time to treatment following diagnosis).
- Educate patients about cough etiquette and respiratory hygiene.
- Provide a package of care for health care workers, including annual TB screening.

To complement administrative measures, health facilities should ensure:

- Early and rapid diagnosis of TB.
- Use of rapid diagnostic tests.
- Timely turnaround of laboratory results.
- Prompt initiation of appropriate treatment.

5.4.2 Environmental controls

Implementation of environmental controls is the second line defense in preventing the spread of TB in health care, community, and congregate settings and helps to reduce the concentration of droplet nuclei in the air.

Environmental control measures include the following:

- Ventilation systems (natural, mixed-mode, mechanical, and recirculated air through high-efficiency particulate air filters).
- Germicidal ultraviolet light (a special ultraviolet light lamp that kills *M. tuberculosis* bacteria contained in droplets).

5.4.3 Personal protective equipment

- Use of personal protective equipment is critical in IPC. Particulate respirators should be used in conjunction with administrative and environmental measures.
- A respiratory protective device with a capacity to filter 0.3 to 0.4 micrometer particles is needed. They are manufactured with at least 95% filter efficiency.
- Filtering face piece (FFP) respirators are manufactured as US Centers for Disease Control and Prevention/National Institute for Occupational Safety and Health–certified N95 (or greater) and European Committee for Standardization–certified FFP2 (or greater) pieces.

A comparison of surgical masks and N95 respirators is provided in the figure below.

Figure 27. Important differences between surgical masks and N95 respirators.

Features	SURGICAL MASK 	N95 RESPIRATOR 
DISPOSABLE	Yes	Yes
DESIGN	Standard Earloop Mask	Molded Cup Style
TESTING/APPROVAL	U.S. Food & Drug Administration (FDA)	National Institute for Occupational Safety & Health (NIOSH)
PROTECTION	Droplets, sprays & splashes that may contain germs	Airborne particles, viruses & bacteria. (Non-Oil)
FACE FIT	Loose-fitting	Tight-fitting
FILTRATION	Does not filter very small particles	At least 95% of airborne particles both large & small
LIMITATION OF USE	One time use	Discard when contaminated, damaged or deformed

- Particulate respirators (e.g., N95, FFP2 masks) should be used in conjunction with other administrative and environmental control measures in specific high-risk areas. It is generally the third line of defense against nosocomial *M. tuberculosis* infection.
- Particulate respirators must only be used by health care workers and relatives visiting TB patients.

Key messages

- Ventilation is a vital environmental control measure. It is important to recognize that if work practices or administrative controls are inadequate, environmental controls will not eliminate the risk.
- Procure equipment (e.g., vanometers, ventilation smoke tube kits (incense/mosquito coils are a less-expensive alternative), measuring tape, and if applicable anemometers) to measure the effectiveness of different ventilation systems.
- Locate health care workers (or other patients) near the clean air source.
- Locate patients who may be infectious near a place where the air is exhausted away.
- In existing health care facilities with natural ventilation, the use of natural ventilation should be maximized before considering other ventilation systems.
- Administrative measures are a first-line measure because they block the first step in the pathway of TB transmission.
- A surgical or procedure mask worn by health care workers does not adequately protect them from inhalation of air contaminated with *M. tuberculosis*.
- Each facility using respirators must have a respirator program in place.
- Due to the high cost, it is most appropriate to use respirators in high-risk areas such as drug-resistant TB wards or rooms where sputum induction is performed.

6. Monitoring and Evaluation

Recommendations

- Tuberculosis presumptive registers must be placed and used in each facility service area.
- All confirmed tuberculosis patients (bacteriologically and clinically diagnosed) must be notified as soon as they are diagnosed or started on treatment.
- Facilities must put in place measures to notify patients over the weekend and on public holidays.
- Health facilities/districts and provinces are required to report key performance indicators on a weekly basis to track progress in performance and give an opportunity for timely intervention.
- All tuberculosis deaths must be recorded and reported (notified) to the national level through the outlined reporting structures.
- Tuberculosis deaths that occur before commencement of treatment must be notified and outcome indicated.
- Community contribution must be accounted for at the district level and reported to the national level.
- Public-sector contributions must be recorded and reported at all levels (district, provincial, and national).

The essential element of TB elimination in Zambia is the establishment and maintenance of a system to monitor case detection and treatment outcomes. Zambia NTLP has a well-established recording and reporting system. This system is hybrid (paper-based and electronic using DHIS2, SmartCare and DISA for laboratory information).

6.1 Sources of information

The Zambia NTLP uses the following data sources:

- **Routine information:**
  - patient TB cards, Treatment TB registers and DHIS2, DISA, Smartcare
  - monthly, quarterly, and annual reports
- **Periodic surveys:** e.g. Drug resistance surveillance (DRS), National Prevalence Survey
- Periodic programme technical assistance reports:
  - Mid-term reviews
  - End term reviews
  - Mission reports such as the Green Light Committee (GLC) and Global Drug Facility (GDF)

6.2 Recording & Reporting

The NTLP utilizes various recording and reporting tools that are listed in annex D.1.

6.3 Data collection

Data recording and reporting tools are critical determinants of data quality. To ensure that data that are collected and reported are precise, reliable, and valid, the NTLP at all levels must ensure the following is done:

- The NTLP Central Unit develop or revise, disseminate and distributed data recording and reporting tools to ensure they capture all data on the indicators required to allow for comprehensive TB surveillance and monitoring and evaluation system.
- The program at all levels should ensure that data collected and reported can be disaggregated by age, geographical area, gender, and HIV status e.t.c.
- Training, orienting, and mentoring of various carder of health care workers in the operational definitions of indicators, appropriate data collection, reporting, and management responsibilities

6.4 Data reporting

To ensure the timeliness, completeness, and accuracy of submitted data, systematic processes should be followed to:

- Remind reporting entities at all levels to submit data on time.
- Check on submitted data at all levels for completeness, accuracy, and timeliness.
- Deal with errors in submitted data.
- Manage the transfer of paper-based data to the computer database, including post entry verification.
- Back up data, including in off-site storage.
- Store paper and electronic records.
- Periodically check to verify that backup data can be retrieved.
- Ensure data management and quality.

6.5 Activities after data reporting

After reporting, the following activities are essential:

- Monthly M&E visits to district health facilities and quarterly by national- and provincial-level staff to conduct data verification and auditing.
- Biannual data review meetings and quality assessment to ensure data quality.
- These activities should be done to determine that data received from the health facilities, districts, and provinces are accurately recorded and aggregated as documented in reports submitted to the NTLP. The data audits will also be used to understand factors that promote or hinder accurate reporting so that appropriate action can be taken.

- All levels must be accountable for the data under their jurisdiction. For this reason, data quality assessments must be conducted by all levels per the schedules in table below

Table 38: Reporting timelines

Level	Type of report	Deadline	Dissemination strategy
Health facility	Quarterly TB facility report	Within 1 week after the close of the quarter	Send to the district
District	Quarterly TB facility report	Within week 2 after the close of the quarter	Send to the province
	Semi-annual progress report		
	Annual progress report		
Province	Quarterly TB facility report	Within week 2 after the close of the quarter	Send to the NTLP central level
	Semi-annual progress report		
	Annual progress report		
National	Quarterly TB facility report	Within week 3 after the close of the quarter	Annual report disseminated to partners
	Semi-annual progress report		
	Annual progress report		

Abbreviations: NTLP, National Tuberculosis and Leprosy Programme; TB, tuberculosis.

6.6 Data flow

Data flow is from the health facility to the district, then to the province through to the national level when using a paper-based system submitted by email using an excel sheet. Through DHIS2, data from the health facility to the district is paper based. Any person with rights can view aggregated data entered DHS2 at the district level. In health facilities with activated SmartCare, information is entered right at the health facilities and is accessible at the district, provincial and national levels. Please see annex D.2 for the well-illustrated data flow.

6.7 Treatment outcomes reporting.

Examples of schedule for patient outcome, evaluation & reporting for DS-TB. To the national level:

Registration quarter	Assessment period	Report due date
1st quarter 2020	1st Quarter 2021	30 April 2021
2nd quarter 2020	2nd quarter 2021	31 July, 2021
3rd quarter 2020	3rd Quarter 2021	31st October, 2021

4th quarter 2020	4th Quarter 2021	31 January 2022

6.8 Data Management

- Data is of vital importance to the NTLP because it guides decision-making.
- Data that is inaccurate or incomplete will result in poor public health policy design.
- All the patient data should be recorded and reported through approved recording and recording platforms (paper-based or electronic).
- The data should be checked for accuracy before entering it in the system to minimize errors.
- The NTLP utilizes DHIS2 for aggregated data which is entered and reported every month.
- DHIS2 will be linked to smart care
- Also, data management within the programme has been enhanced by rolling out DISA for all diagnosed TB patients through Xpert MTB/RIF and other diagnostic platforms.

Supervision is an extension of training, to maintain high quality TB services an effective supervion at all levels should be conducted regularly. The table below summarizes the levels of supervision that must be used by the NTLP.

Table 39. Supervisory levels under the National Tuberculosis and Leprosy Programme.

Level	Mechanism	Frequency	Responsible officer
Within the health facility	Supervision, mentorship, and data audits	Weekly	Facility in-charge/facility TB focal point person
District to the health facility	Data review visits and overall TSS	Monthly	District TB coordinator
Province to the district	Quarterly data review meetings and overall TSS	Quarterly	Provincial TB focal person
National level	Data review meetings and TSS	Biannual and quarterly respectively	M&E officer

Abbreviations: M&E, monitoring and evaluation; TB, tuberculosis; TSS, technical supportive supervision.

Annex A. Adverse events

Table A1. Severity grading scale of adverse events.

Grade	Description
Grade 1: Mild	Mild or transient discomfort without limitation of normal daily activities.[a] No medical intervention or corrective treatment required.
Grade 2: Moderate	Moderate limitation of normal daily activities.[a] Minimal medical intervention or corrective treatment required.
Grade 3: Severe	Marked limitation of normal daily activities.[a] Medical intervention, therapy, discontinuation, or reduction of the offending drug is required. Possible hospitalization.
Grade 4: Life-threatening or permanently disabling	Severe limitation of normal daily activities.[a] Medical intervention and corrective treatment required, almost always in a hospital setting.

a. The term "activity" covers basic self-care functions such as bathing, dressing, toileting, transfer/movement, continence, and feeding, as well as usual social and functional activities or adaptive tasks and desirable activities, such as going to work, shopping, cooking, using transportation, or pursuing a hobby.

Table A2. Severity grading scale of the primary laboratory parameters.

	Hb (g/dL)	Platelets (/mm^3)	Neutrophils (/mm^3)	AST (UI/L)	ALT (UI/L)	Creatinine (µmol/L)	K+ (mEq/L) / (mmol/L)
Normal values	>12	>150,000	>1,500	*	*	*	3.5-5.0
Grade 1	10-11.9	100,000-149,999	1,000-1,500	1.5-2.5 x ULN	1.5-2.5 x ULN	1.1-1.5 x ULN	3.2-3.4
Grade 2	8-9.9	50,000-99,999	750-999	2.6-5.0 x ULN	2.6-5.0 x ULN	1.6-3 x ULN	2.8-3.1
Grade 3	6-8	20,000-49,999	500-749	5.1-10 x ULN	5.1-10 x ULN	3-6 x ULN	2.5-2.7
Grade 4	<6	<20,000	<500	>10 x ULN	>10 x ULN	>6 x ULN	<2.5

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; Hb, hemoglobin; ULN, upper limit of normal.

*Normal values vary from laboratory to laboratory and might be slightly different in men, women, and children (check normal parameters for local laboratory).

Table A3. Management of adverse events associated with drug-resistant tuberculosis treatment.

Prolonged QT interval **Possible DR-TB drug causes: Bdq, Dlm, Mxf, Cfz**				
Normal values (msecs)	**Grade 1** **Mild**	**Grade 2** **Moderate**	**Grade 3** **Severe**	**Grade 4** **Potentially life-threatening**
Male: ≤430 Female: ≤450	Borderline: Male: 430-450 Female: 450-470	Prolonged: Male: >450-<500 Female: >470-< 500	Pathological: >500 *or* ≥60 above baseline	Life-threatening consequences: QTcF ≥500 or >60 ms change from baseline and torsade de pointes or other associated serious ventricular dysrhythmia.
Action	Monitor ECG frequently	Monitor more closely, at least weekly ECG, until QTcF has returned to grade 1 or less. Check electrolytes and replete as necessary.	Confirm with two additional 12-lead ECG (15-30 minutes apart). Stop the suspected causative drug. Hospitalize and replete electrolytes as necessary. Check TSH.	Stop suspected causative drug. Hospitalize and replete electrolytes as necessary. Check TSH.
Hypokalemia **Possible DR-TB drug causes: Am, Km, Cm, S**				
Normal value (mmol/L)	**Grade 1** **Mild**	**Grade 2** **Moderate**	**Grade 3** **Severe**	**Grade 4** **Potentially life-threatening**
3.5-5.0	3.4-3.2	3.1-2.8	2.7-2.5	<2.5
Action	Continue injectable. Start oral potassium. Slow K* 600 mg = 8 mEq: 1 tab twice daily. Monitor K monthly.	Continue injectable. Start oral potassium. Slow K* 600 mg = 8 mEq: 2 tabs twice daily. Oral magnesium gluconate: 1,000 mg twice daily. Monitor K every 2 weeks and adjust the slow K dose accordingly.	Continue injectable. Oral potassium: Slow K* 600 mg = 8 mEq: 2 tabs thrice daily. Oral magnesium gluconate: 1,000 mg twice daily. Monitor K every 1-2 days and adjust dose accordingly.	Stop injectable temporarily. Hospitalization. Start IV potassium in addition to oral. Replace magnesium and other electrolytes. Monitor K 1 hour after replacement and repeat until K is >2.8 mmol/L.

Nephrotoxicity **Possible DR-TB drug causes: Am, Km, Cm, S**				
	Grade 1 **Mild**	**Grade 2** **Moderate**	**Grade 3** **Severe**	**Grade 4** **Life-threatening**
Creatinine	1.1-1.5 x ULN	1.6-3.0 x ULN	3.1-6 x ULN	>6 x ULN or dialysis required
Creatinine clearance* **Normal value** **Cr Cl grading [13]** **Male: 97-137 mL/min** **Female: 88-128 mL/min**	>90 mL/min	60-89 mL/min	30-59 mL/min	15-29 mL/min **Note:** <15 mL/min is grade 5 and requires dialysis
Action	Continue monitoring	Reduce injectable to 3 times a week, dosing at 12-15 mg/kg.**	Reduce injectable to 2 times a week, dosing at 12 mg/kg.**	Stop injectable.** Monitor creatinine and electrolytes weekly until creatinine returns to normal. Adjust other drug dosages (Annex 4).
Hearing loss (ANRS scale) **Possible DR-TB drug causes: Am, Km, Cm, S**				
Normal values	**Grade 1** **Mild**	**Grade 2** **Moderate**	**Grade 3** **Severe**	**Grade 4** **Profound**
0-20 dB	21-40 dB Speech perceived if voice is normal, difficulties arise if voice is low pitched or distant from the subject. Most daily life noises are perceived.	41-70 dB Speech is perceived if the voice is loud. Subject understands better what is being said if they can see their interlocutor.	71-90 dB Speech is perceived if the voice is loud and close to the ear. Loud noises are perceived.	>90 dB Speech is not perceived at all. Only very loud noises are perceived.

Hepatotoxicity **Possible DR-TB drug causes: Z, H, Pto, Lzd, Cfz, Bdq, Mfx**				
	Grade 1 **Mild**	**Grade 2** **Moderate**	**Grade 3** **Severe**	**Grade 4** **Life-threatening**
ALT (SGPT)	1.25-2.5 x ULN	2.6-5.0 x ULN	5.1-10.0 x ULN	>10.0 x ULN
AST (SGOT)	1.25-2.5 x ULN	2.6-5.0 x ULN	5.1-10.0 x ULN	>10.0 x ULN
Action	Continue treatment. Patients should be followed until resolution (return to baseline) or stabilization of AST/ALT elevation.	Continue treatment. Patients should be followed until resolution (return to baseline). If JAUNDICE: stop all anti-TB drugs until resolution.	Stop all drugs, including anti-TB drugs; measure LFTs weekly. Treatment may be reintroduced after toxicity is resolved.	Stop all drugs, including anti-TB drugs; measure LFTs weekly. Treatment may be reintroduced after toxicity is resolved.
Peripheral neuropathy **Possible DR-TB drug causes: Lzd, Cs, H, S, Km, Cm, H, FQ, Pto/Eto, E** **Possible other causes: Diabetes mellitus, alcohol, HIV infection, vitamin B deficiency, hypothyroidism, and other drugs**				
	Grade 1 **Mild**	**Grade 2** **Moderate**	**Grade 3** **Severe**	**Grade 4** **Life-threatening**
Neurosensory alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social and functional activities.	Sensory alteration or paresthesia causing greater than minimal interference with usual social and functional activities.	Sensory alteration or paresthesia causing inability to perform usual social and functional activities.	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions.
Action	Stop offending drugs (Lzd, high-dose INH). If symptoms improve after 2 weeks, consider restarting Lzd at a lower dose (300 mg).	Stop Lzd. Do not reintroduce Lzd.	Stop Lzd. Do not reintroduce Lzd.	Stop Lzd. Do not reintroduce Lzd.
Myelosuppression (anemia, thrombocytopenia, or neutropenia) **Possible anti-TB drug causes: Lzd[1]** **Possible other causes: AZT, cotrimoxazole, HIV Infection, chemotherapy**				
	Grade 1 **Mild**	**Grade 2** **Moderate**	**Grade 3** **Severe[2]**	**Grade 4** **Life-threatening[2]**
Absolute neutrophil count	1,000-1,300 /mm^3	750-999/ mm^3	500-749 /mm^3	<500/ mm^3
Hemoglobin	8.5-10.0 g/dl	7.5-8.4 g/dl	6.5-7.4 g/dl	<6.5 g/dl
Platelets, decreased	100,000-124,999 /mm^3	50,000-99,999 /mm^3	25,000-49,999 /mm^3	<25,000 /mm^3
WBC, decreased	2,000-2,500 /mm^3	1,500-1,999 /mm^3	1,000-1,499 /mm^3	<1,000 /mm^3
Action	Monitor carefully, and consider reduction of dose of Lzd to 300 mg daily.	Monitor carefully and consider reduction of Lzd to 300 mg daily; in case of Grade 2 neutropenia, stop Lzd immediately. Restart at reduced dose (300 mg) once toxicity decreases to Grade 1.	Stop Lzd immediately. If Hb ≤7 g/dl, transfuse. Restart at reduced dose (300 mg) once toxicity has decreased to Grade 1.	Stop Lzd immediately. Give transfusion and erythropoietin if available. Restart at reduced dose (300 mg) once toxicity has decreased to Grade 1.

Optic neuritis **Possible anti-TB drug causes: Lzd, E** **Possible other causes: Multiple sclerosis, quinine, herpes, syphilis, sarcoidosis, cytomegalovirus (HIV)** The first sign of optic neuritis is usually the loss of red-green color distinction. This is best tested using the Ishihara test. Other symptoms include central scotoma (loss of central vision or blind spot).				
	Grade 1 **Mild**	**Grade 2** **Moderate**	**Grade 3** **Severe**	**Grade 4** **Life-threatening**
Optic neuritis is inflammation of the optic nerve resulting in permanent vision loss.	Visual changes causing minimal or no interference with usual social and functional activities.	Visual changes causing greater than minimal interference with usual social and functional activities.	Visual or changes causing inability to perform usual social and functional activities.	Disabling visual loss.
Action	Stop Lzd or E immediately if there are any suspicions of optic neuritis. Do not restart.	Stop Lzd or E immediately if there are any suspicions of optic neuritis. Do not restart.	Stop Lzd or E immediately if there are any suspicions of optic neuritis. Do not restart.	Stop Lzd or E immediately if there are any suspicions of optic neuritis. Do not restart.
Lactic acidosis **Possible anti-TB drug causes: Lzd** **Possible other causes: AZT, 3TC**				
	Grade 1 **Mild**	**Grade 2** **Moderate**	**Grade 3** **Severe**	**Grade 4** **Life-threatening**
Lactate and pH	<2.0 x ULN without acidosis	≥2.0 x ULN without acidosis.	Increased lactate with pH <7.3 without life-threatening consequences.	Increased lactate with pH <7.3 with life-threatening consequences.
Action	Continue treatment regimen. Patients should be followed until resolution (return to baseline).	Stop Lzd immediately. Do not restart it.	Stop Lzd immediately. Do not restart it.	Stop Lzd immediately. Do not restart it.
Pancreatitis **Possible DR-TB drug causes: Bdq, Lzd** **Other causes: Gallstones, heavy and long-term alcohol use, high triglycerides**				
	Grade 1 Mild	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Life-threatening**
Pancreatitis	Not applicable.	Symptomatic and Hospitalization not indicated	Symptomatic and Hospitalization indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)
Lipase	1.1-1.5 x ULN	1.6 – 3.0 x ULN	3.1 – 5.0 x ULN	> 5.0 x ULN
Amylase	1.1-1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.1 x ULN
Action	Continue treatment regimen. Patients should be followed until resolution (return to baseline).	Stop Lzd immediately. Do not restart it.	Stop Lzd immediately. Do not restart it.	Stop Lzd immediately. Do not restart it.

Gastrointestinal (nausea and vomiting) **Possible DR-TB drugs: Eto/Pto, PAS, Bdq** (less common: H, E, Z, Amx/Clv, Cfz, Dlm)			
Grade 1 **Mild**	**Grade 2** **Moderate**	**Grade 3** **Severe**	**Grade 4** **Life-threatening**
1 episode in 24 hours.	2-5 episodes in 24 hours.	>6 episodes in 24 hours or needing IV fluids.	Physiologic consequences requiring hospitalization or requiring parenteral nutrition.

Gastritis
Possible DR-TB drug causes: Eto, Pto, PAS, Cfz, FQs, H, E, Z

If symptoms are associated consistent with gastritis (epigastric burning or discomfort, a sour taste in mouth associated with reflux), initiate medical therapy (prolonged duration):

- Omeprazole 20 mg once daily (proton-pump inhibitors). Give 2 hours before or 3 hours after the TB medication.
- Ranitidine 150 mg twice daily or 300 mg once daily (H2 blockers).

Avoid use of antacids, as they decrease absorption of fluoroquinolones.

Stop any nonsteroidal anti-inflammatory drugs the patient may be taking.

Diagnose and treat for *Helicobacter pylori* infections.

Abdominal pain
Possible DR-TB drugs: Eto, Pto, Cfz, Lzd

Diarrhea
Possible DR-TB drugs: PAS, Eto/Pto

Grade 1 **Mild**	**Grade 2** **Moderate**	**Grade 3** **Severe**	**Grade 4** **Life-threatening**
Mild or transient; 3-4 loose stools/day or mild diarrhea lasting <1 week.	Moderate or persistent; 5-7 loose stools/day or diarrhea lasting >1 week.	>7 loose stools/day or bloody diarrhea; or orthostatic hypotension or electrolyte imbalance or >2L IV fluids required	Hypotensive shock or physiologic consequences requiring hospitalization

Rash, allergic reaction and anaphylaxis
Possible DR-TB drug causes: Any drug

Grade 1 **Mild**	**Grade 2** **Moderate**	**Grade 3** **Severe**	**Grade 4** **Life-threatening**
Erythema; moderate pruritus.	Extended maculopapular eruption (with or without pruritus).	Extensive papulovesicular eruption, palpable purpura cut., mist desquamation, or ulcerations.	Exfoliative dermatitis, mucous membrane involvement or erythema multiforme or suspected Stevens-Johnson or cutaneous necrosis requiring surgery.

Arthralgia/Arthritis
Possible DR-TB drug causes: Z (less frequent: FQ, Bdq)

	Grade 1 **Mild**	**Grade 2** **Moderate**	**Grade 3** **Severe**	**Grade 4** **Life-threatening**
Arthralgia (joint pain)	Mild pain not interfering with function.	Moderate pain, analgesics and/or pain interfering with function but not with activities of daily life.	Severe pain; pain and/or analgesics interfering with activities of daily life.	Disabling pain.
Arthritis (inflammation involving a joint)	Mild pain with inflammation, erythema, or joint swelling, but not interfering with function.	Moderate pain with inflammation, erythema or joint swelling; interfering with function, but not with activities of daily life.	Severe pain with inflammation, erythema, or joint swelling, and interfering with activities of daily life.	Permanent and/or disabling joint destruction.

Psychosis
Possible DR-TB drug causes: Cs, H, FQ, Eto/Pto

Grade 1 **Mild**	**Grade 2** **Moderate**	**Grade 3** **Severe**	**Grade 4** **Life-threatening**
Mild psychotic symptoms.	Moderate psychotic symptoms (e.g., disorganized speech; impaired reality testing).	Severe psychotic symptoms (e.g., paranoia, extreme disorganization); hospitalization not indicated.	Acute psychosis (suicidal ideation, maniac status, hallucinations). Life-threatening consequences; threats of harm to self or others; hospitalization indicated.

Depression **Possible DR-TB drug causes: Cs, FQ, H, Eto/Pto** **Other causes:** Psychological and socioeconomic circumstances, chronic disease.			
Grade 1 **Mild**	**Grade 2** **Moderate**	**Grade 3** **Severe**	**Grade 4** **Life-threatening**
Mild depressive symptoms; and/or PHQ9 depression score 1-9.	Moderate depressive symptoms; limiting instrumental activities of daily life; and/or PHQ9 depression score 10-14.	Severe depressive symptoms; limiting self-care activities of daily life; hospitalization not indicated; and/or PHQ9 depression score 15-19.	Life-threatening consequences, threats of harm to self or others; PHQ9 depression score 20-27; and/or hospitalization indicated.
Seizures **Possible DR-TB drug causes: Cs, H, FQ, Imp/Clan**			
Hypothyroidism **Possible DR-TB drug causes: Eto/Pto/PAS**			
Grade 1 **Mild**	**Grade 2** **Moderate**	**Grade 3** **Severe**	**Grade 4** **Life-threatening**
Subclinical hypothyroidism (TSH 6-10mIU/L, T4 free normal).	Simple hypothyroidism without complications. Treatment required (TSH >10 mU/L).	Severe hypothyroidism with clinical symptoms. Urgent treatment.	Myxedematous coma.

Annex B. Managing discordant results

Discordant results	Treatment decision(s)
Cepheid's GeneXpert® MTB/RIF MTB detected, culture negative	Treat the patient according to the Xpert MTB/RIF detected result. Submit another sample for culture.
Xpert MTB/RIF MTB not detected; culture positive	Treat the patient based on the positive culture result.
Xpert MTB/RIF MTB detected; rifampicin resistance detected; rifampicin susceptible by phenotypic DST	Treat the patient according to the Xpert MTB/RIF resistant result and repeat culture and phenotypic DST using solid media.
Xpert MTB/RIF MTB detected; rifampicin resistance not detected (susceptible); rifampicin resistance by phenotypic DST	Treatment decisions should be based on the culture phenotypic DST rifampicin resistant result.
Xpert MTB/RIF MTB detected; rifampicin not detected (susceptible); FL LPA rifampicin detected (resistant)	Treat the patient based on FL LPA (rifampicin resistant).

Annex C. Admission and discharge criteria for tuberculosis patients

REPUBLIC OF ZAMBIA

MINISTRY OF HEALTH

DR-TB Discharge Summary

Province: _____ District: _____

Name of health facility: _____

Department/Ward: _____ Facility phone number: _____

Full names of patient: _____Sex: M / F (circle) DOB/Age:_____

Physical address: _____

TB patient #: _____Patient contact number: _____

NRC: _____

DATE of ADMISSION:

D	D	M	M	Y	Y	Y	Y

***DATE of DISCHARGE*:**

D	D	M	M	Y	Y	Y	Y

REASON(s) for ADMISSION:

TB microbiology data from CURRENT hospitalization:

Ordered	N	Y	Date RESULTED	RESULT				
Xpert #1			D D M M Y Y Y Y	TB det: ☐	No TB ☐	RR+ ☐	RR- ☐	Lab #_____
Smear #1			D D M M Y Y Y Y	3+ ☐	2+ ☐	1+ ☐	Sc ☐	Lab #_____
Smear #2			D D M M Y Y Y Y	3+ ☐	2+ ☐	1+ ☐	Sc ☐	Lab #_____
Smear #3			D D M M Y Y Y Y	3+ ☐	2+ ☐	1+ ☐	Sc ☐	Lab #_____
LPA(FL)			D D M M Y Y Y Y	INH S ☐	INH R ☐	RIF S ☐	RIF R ☐	Lab #_____
LPA(SL)			D D M M Y Y Y Y	FLQ S ☐	FLQ R ☐	Km S ☐	Km R ☐	Cs S ☐ Cs R ☐
Culture #1			D D M M Y Y Y Y	TB ☐	No TB ☐	Lab #_____		
Culture #2			D D M M Y Y Y Y	TB ☐	No TB ☐	Lab #_____		
Culture #3			D D M M Y Y Y Y	TB ☐	No TB ☐	Lab #_____		
Culture DST#1	INH S ☐	INH R ☐	RIF ☐	RIF ☐	STR S ☐	STR R ☐	ETH ☐	ETH ☐ Lab #_____
Culture DST#2	INH S ☐	INH R ☐	RIF ☐	RIF ☐	STR S ☐	STR R ☐	ETH ☐	ETH ☐ Lab #_____
Culture DST#3	INH S ☐	INH R ☐	RIF ☐	RIF ☐	STR S ☐	STR R ☐	ETH ☐	ETH ☐ Lab #_____

Key for drugs: *INH- Isoniazid, RIF- Rifampicin, FLQ-Fluroquinolone, Km- Kanamycin, Cs- Cycloserine, STR- Streptomycin ETH - Ethambutol*

HIV Laboratory Data from CURRENT hospitalization:

Test	***Results***	***Date (DD-MMM-YYYY)***
HIV Rapid test (tick one)	☐ R ☐ NR ☐ ND	D D M M Y Y Y Y
CD4 (cells/mm^3)		D D M M Y Y Y Y
VL (c/mL)		D D M M Y Y Y Y
Genotype		D D M M Y Y Y Y

Hospital Course (treatments rendered, pertinent diagnostic imaging and pathology findings, etc.)

1. Discharge Diagnosis/ Diagnoses: (*Tick one*)

RR-TB ☐ MDR-TB ☐ pre-XDR-TB ☐ XDR-TB ☐ DS-TB ☐ Mono ☐ Poly ☐

2. **Regimen** (tick one): D D M M Y Y Y Y All oral Longer ☐ Shorter ☐
3. Modified Shorter ☐ Individualized ☐
4. **DR-TB Treat Start Date**:

Discharge TB Medication(s):

	Drug	Dosage	Frequency	Duration
1.				
2.				
3.				
4.				
5.				
6.				
7.				

ART Regimen (tick one)		***Other Non-ARV, Non-ATT Medications (tick and list)***	
	TLE		
	TLD		
	NVP + 3TC + TDF		
	DTG (high-dose) + 3TC + AZT		
	DTG (high-dose) + 3TC + TDF + AZT		
	AZT + 3TC + LPV/r		
	Other (specify): _____		

Discharge Instructions (specific instructions to patient/ family about activity, medication, diet, and follow-up)

Multi-Disciplinary Discharge Checklist (*review with Nurse, Pharmacist, and Social Worker***)**

Tick when complete	***Task***
☐	Patient's clinical status has improved to the extent that s/he can be managed on an ambulatory basis.
☐	Contact tracing and investigation has been completed
☐	Patient has been on appropriate therapy with at least 4 active drugs for 14-21 days or more.
☐	Patient has negative sputum smears or a negative culture result (tick appropriate box) ☐ *Negative smear* ☐ *Negative culture* Comment (*other specify*):_____
☐	Accurate locator information has been obtained and confirmed with the patient and their family/ caregivers.

☐	Measures to ensure full implementation of DOT and adherence support have been put into place (e.g. peer treatment supporter assigned, DR-TB nurses assigned, etc.)
☐	The inpatient medical team has educated the patient, family or relatives on DOT options, adherence support, and infection control measures in the home/community
··	Patient has a DR-TB follow-up visit scheduled. D D M M Y Y Y Y Date of follow up visit: Indicate where follow-up will take place: Facility Name _____Department _____ District _____
☐	If not same hospital, the receiving facility has been contacted by phone or in person by the inpatient team and oriented on the patient's management Name of receiving facility:_____ Name of contact person at receiving facility: _____ Phone number of contact person at receiving facility: _____
☐	A transport plan has been developed with the patient, family, and receiving health worker team to ensure the patient will be able to attend their follow-up visit
☐	1-month supply of DR-TB medications given if returning to same hospital. *If going to outside facility, at least a 3-month supply of DR-TB medications (and preferably the entire course of treatment) have been sent to and confirmed collected by the receiving facility.*
☐	_____Supply of ARVs given as per ART plan(indicate duration of supply)
☐	Co-morbidities reviewed and continuity of care plan made (for NCDs like DM, nutrition support for malnutrition, psychiatric care, etc.) Comments: _____

SIGNATURE: _____ PRINT: _____ Cell No.: _____

Annex D. National Tuberculosis and Leprosy Programme routine data collection, analysis, and reporting

Zambia's health management information system (HMIS) is an integrated data collection, collation, aggregation, storage, and reporting system used by the Ministry of Health, National Tuberculosis and Leprosy Programme, development partners, and stakeholders to gather and manage relevant and functional information on a routine and nonroutine basis.

The health sector information generated through the HMIS is used for planning, decision-making, and monitoring and evaluation of the health care delivery system, as prescribed in the National Health Strategic Plan, National Development Plans, and other health programs.

TB program data are collected from paper-based tools at the health facility level. Flow of data is outlined in illustrated in the figure below. Case notification and treatment outcome data flow upward from health facilities through the district and provincial levels, thus allowing for aggregation of data at all levels. The outcomes of TB treatment for individual patients are tracked and reported and the aggregated data at the district, provincial, and national levels are used to measure the quality of the program through the quarterly cohort analysis.

Annex D.1 Recording & Reporting tools

The NTLP utilises different recording and reporting tool that are listed below.

Drug Susceptible TB:

1. Laboratory sample request form
2. Presumptive register
3. Tuberculosis Laboratory Register
4. Facility Tuberculosis Treatment Register
5. Tuberculosis Treatment Card
6. Patient Tuberculosis Card (Appointment and DOT Card)
7. Tuberculosis Contact Screening Form
8. Transfer of a Patient form
9. District Tuberculosis Register
10. Community TB Care Treatment Supporter Card
11. Monthly and quarterly reporting form
12. Mentoring Support and Supervisory Visit Tool
13. Annual cohort analysis of Treatment Outcome

Drug Resistant TB

1. DR-TB Treatment Card
2. DR-TB Register
3. DR-TB Contact Examination Form
4. Annual Report of Treatment Outcomes of MDR-TB Patients
5. aDSM form (GDF)

D2: Data flow

There are four traditional data collation points that the NTLP follows:

1. **Facility/Community Level.** Data collected from paper-based recording and reporting tools is compiled by the TB Facility Focal Point Person at the service points on a weekly, monthly, quarterly, and annual basis. The In-charge then reviews the data and approves it before being sent to the district, for the purpose of creating a sense of ownership. All diagnostic facilities will eventually be using SmartCare (e-first or e-last) to capture primary patient data.
2. **District Level.** The district TB Coordinator receives and consolidates facility level data into a district report depending on the prescribed reporting period, which could be weekly, monthly, quarterly, or annually. The District Health Director should, thereafter, review and approve the district report before it sent to the next level
3. **Provincial Level.** In the same manner, the Provincial TB Coordinator receives and compiles the district data into a Provincial report, which is equally reviewed and approved by the Public Health Specialist. The provincial report should then be sent to the National Level.

4. **National Level.** The NTLP M&E Unit through the Head of the unit receives the provincial data for review, analysis and interpretation based on the annual data

> The NTLP is quickly transitioning to an electronic data collection, reporting and management system by introducing TB module in SmartCare, which captures patient level data.
>
> SmartCare will supplement the traditional DHIS2 as a data management platform once countrywide coverage with SmartCare is achieved**.**
>
> Data analysis and validation must be done at all levels.
>
> When national wide coverage with Smartcard is achieved the paper-based system will be phased out

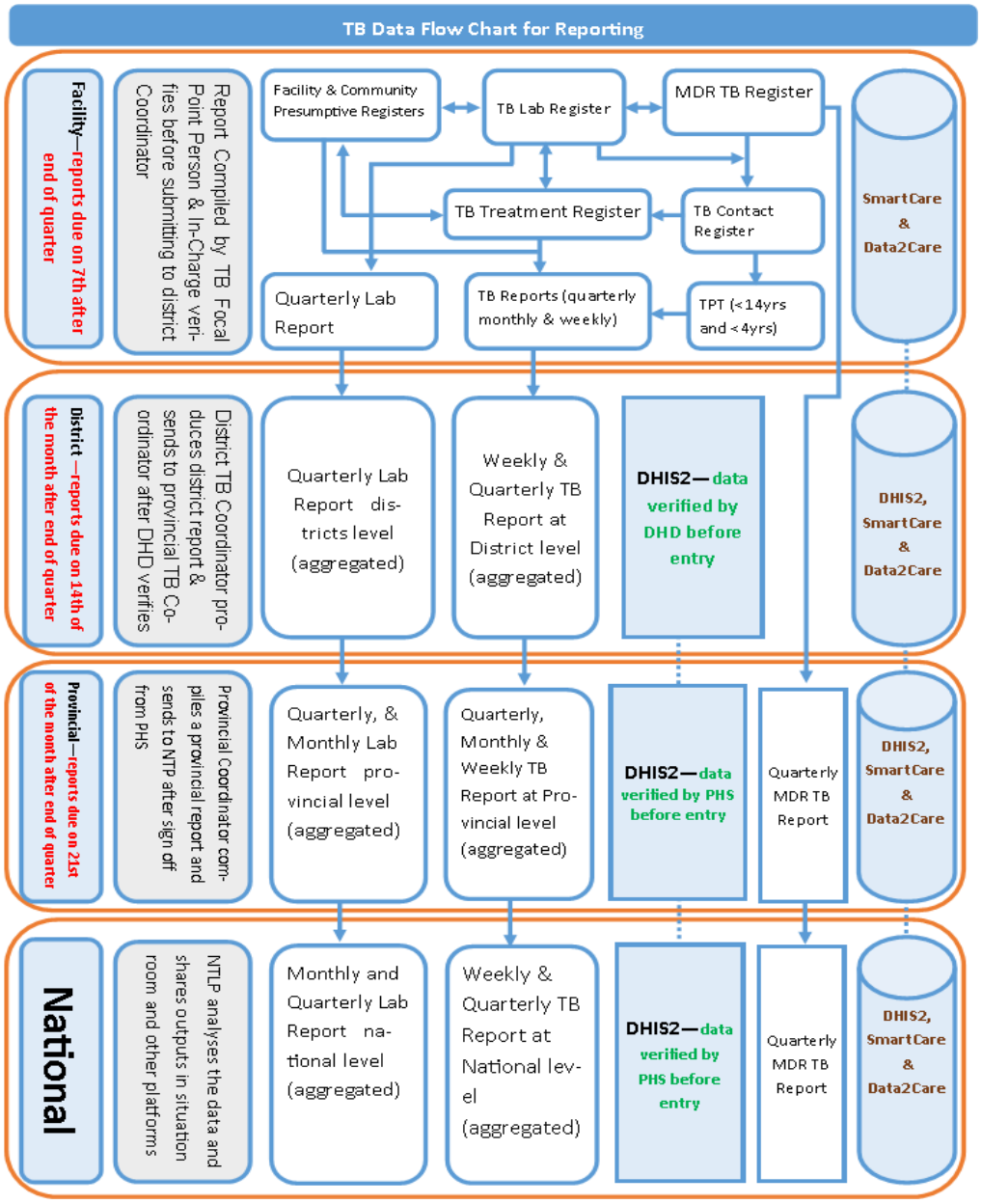
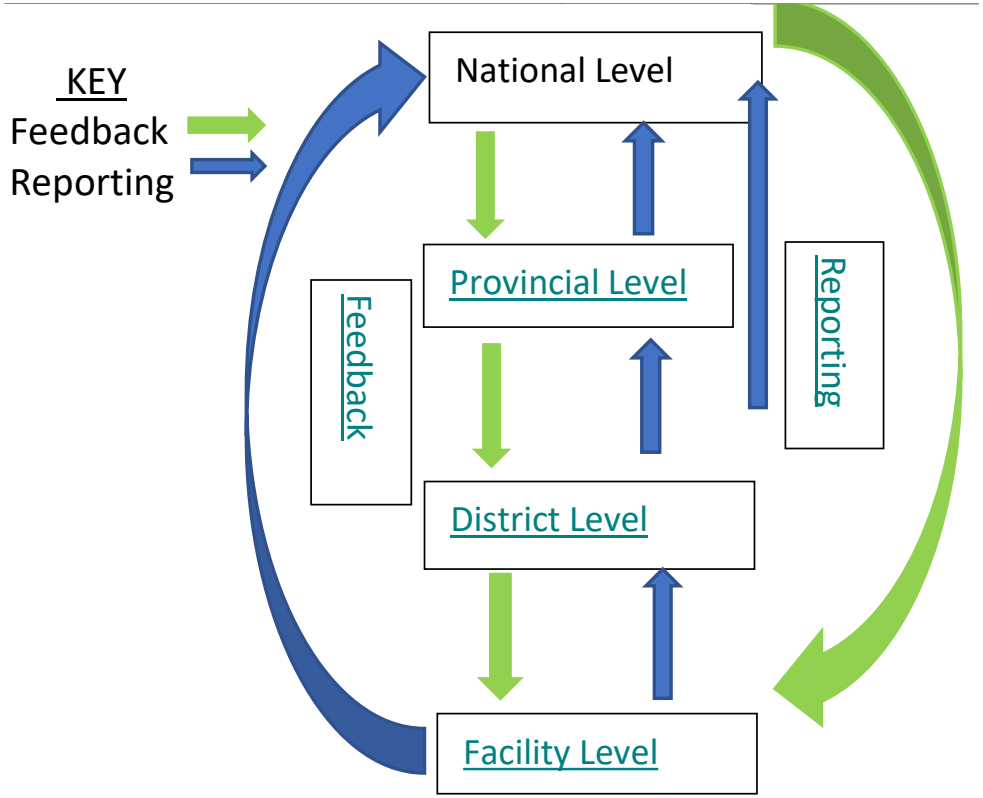

TB Data Flow Chart for Reporting
Facility—reports due on 7th after end of quarter
Report Compiled by TB Focal Point Person & In-Charge verifies before submitting to district Coordinator
Facility & Community Presumptive Registers
TB Lab Register
MDR TB Register
TB Treatment Register
TB Contact Register
TPT (<14yrs and <4yrs)
TB Reports (quarterly monthly & weekly)
Quarterly Lab Report
SmartCare & Data2Care
District—reports due on 14th of the month after end of quarter
District TB Coordinator produces district report & sends to provincial TB Coordinator after DHD verifies
Quarterly Lab Report districts level (aggregated)
Weekly & Quarterly TB Report at District level (aggregated)
DHIS2—data verified by DHD before entry
DHIS2, SmartCare & Data2Care
Provincial—reports due on 21st of the month after end of quarter
Provincial Coordinator compiles a provincial report and sends to NTP after sign off from PHS
Quarterly, & Monthly Lab Report provincial level (aggregated)
Quarterly, Monthly & Weekly TB Report at Provincial level (aggregated)
DHIS2—data verified by PHS before entry
Quarterly MDR TB Report
DHIS2, SmartCare & Data2Care
National
NTLP analyses the data and shares outputs in situation room and other platforms
Monthly and Quarterly Lab Report national level (aggregated)
Weekly & Quarterly TB Report at National level (aggregated)
DHIS2—data verified by PHS before entry
Quarterly MDR TB Report
DHIS2, SmartCare & Data2Care

Figure D1. Data flowchart.



D3: Training, mentoring, technical support & supervision

The NTLP undertakes TB Case Management Training and Mentoring, technical support supervision visits in all provinces, districts and facilities to improve programme quality of care and performance. The following are some of the critical training and mentorship that the NTLP should conduct.

1. **TB Case Management Training:** This is a 5-day intensive training targeting clinicians, nurses, laboratory staff, radiology, pharmacy personnel. The training content covers the basic epidemiology, diagnosis, management, monitoring and evaluation of TB patients. Trainees are equipped with knowledge and skills to manage TB patients in line with national TB guidelines properly. **Districts must ensure that all HCWs caring for TB patients are well trained.**

2. **Advanced Clinical management of TB patients training:**

3. **Mentorship:** Onsite mentorship is an extension of training, and it is the preferred capacity building method. It involves:

-
    a. following those trained or not trained in workplace settings to ensure that new knowledge and skills are imparted into practice.
        i. Mentorship works by building relationships and identifying which areas require improvement, coaching and modelling of best practices.
        ii. Other important aspects of mentoring are advocacy for an environment conducive to quality TB care and demonstrating data collection and reporting practices.
        iii. Mentors spend time working with programme implementers using a mentoring tool.

4. **Technical support supervision (TSS):**
    - The NTLP central unit and partners staff should visit all provinces and districts quarterly to:
        - assess the programme performance
        - provide technical support, and guide implementers in the identified areas of improvement
    - The provincial teams and district teams should visit the districts and health facilities quarterly and monthly, respectively.
    - These visits should also be geared towards building HCW capacity and commitment to achieve the highest standards of care.
    - The technical support visits also address administrative and system issues and strengthens the district and health management team in supervising TB Programme implementation in their districts.
    - Before undertaking TSS the level undertaking TSS should adequately for this task

- Always remember to pay courtesy call to the head of the of the institution, for examples Provincial Health Director, Senior Medical Superintendent, District Director of Health
- At the end of technical support visits feedback should be provided to heads of the institution and staff at the end of each visit.

D4 Review Meetings

The NTLP organizes meetings with provinces, districts, partner organizations and other stakeholders to help review programme achievements and challenges. Province, districts, and partners should hold detailed discussions about DS-TB, DR-TB case detection, treatment outcomes, TB/HIV collaboration, including TB preventive therapy, community TB care, ACSM e.t.c

The following meetings must happen regularly:

- Weekly TB Situation Room
- Weekly meeting on marching towards achieving annual targets
- Bi-annual data review meeting: national level
- Quarterly provincial data review meeting: provincial and district level
- Bi-monthly MDR-TB clinical meeting
- Annual TB-HIV conference
- Monthly Technical Working group
- Quarterly National and provincial DR-TB Clinical Expert Committee meeting

Table 40. Monitoring and evaluation performance indicators, measures, and tools.

Performance indicator	Type	Definition and unit of measure	Data source	Method or tool	Frequency of collection/ reporting	Use of information
TB mortality rate	Impact	This indicator refers to the estimated number of deaths due to TB within a specified period. Disaggregated by province, age, and sex.	TB treatment register	Monthly TB report	Monthly	The information helps the TB program measure the effect of strategies designed for early diagnosis and prompt treatment initiation and adherence. This is an impact indicator. It reflects on the program's ability to detect, diagnose, and treat patients for TB to prevent transmission.
Rate of presumptive TB patients identified	Outcome	Number of presumptive identified/health facility attendees 10 years and above x100.	HMIS records	Presumptive register	Monthly	To identify TB notifications.
Rate of presumptive patients tested for TB in the laboratory	Outcome	This indicator measures the number of presumptive TB patients examined for TB in the laboratory by either GeneXpert® or microscopy from facilities in the ten NTLP intervention provinces. Number of presumptive TB patients examined/number of presumptive TB cases identified X 100. Disaggregated by province, district, sex, and age.	Laboratory register, HMIS records	NTLP monthly data collection tool, NTLP monthly reports	Monthly	This information helps the TB program calculate the proportion of presumptive TB patients examined in the laboratory. It also helps the TB program determine the positivity yield.
Rate of presumptive TB patients bacteriologically confirmed	Outcome	Number of bacteriologically confirmed/number of presumptive TB cases examined x100.	HMIS records, presumptive TB register, laboratory register		Monthly	
Number of new and relapse TB cases (all forms) notified	Outcome	This indicator measures the number of new and relapse TB patients (bacteriologically confirmed and clinically diagnosed) reported within the national surveillance system, and then on to WHO. Disaggregated by province, district, sex, age, type of TB, and type of patient.	Facility TB treatment register	NTLP monthly data collection tool, NTLP monthly reports	Monthly	This is an output indicator. It provides the proxy measurement of incident cases of TB.

Performance indicator	Type	Definition and unit of measure	Data source	Method or tool	Frequency of collection/ reporting	Use of information
TB case notification rate (new and relapse, all forms per 100,000 population)		**Numerator:** Number of notified new and relapse TB cases (all forms). **Denominator:** Estimated population/100,000.				This is an outcome indicator. It provides the proxy measurement of incident cases of TB within a given population.
Number of individuals notified with TB	Outcome	This indicator measures the number of individuals diagnosed with TB reported within the national surveillance system, and then on to WHO. **Numerator:** Number of notified new and relapse TB cases (all forms). **Denominator:** Estimated population/100,000. Disaggregated by province, district, sex, age, type of TB, and type of patient.	Facility TB treatment register	NTLP monthly data collection tool, NTLP monthly report	Monthly	This is an outcome indicator. It provides the proxy measurement of incident cases of TB within a given population. This indictor measures the number of documented TB notifications within a given period. Detailed analysis also shows provincial trends, and distribution of TB notification by province and trends.
Treatment success rate	Outcome	**Numerator:** Number of new and relapse TB cases (all forms) registered in a specified period that were cured or completed treatment. **Denominator:** Total number of new and relapse TB cases (all forms) registered in the same period.	Facility TB treatment register	NTLP quarterly report	Quarterly	This is an outcome indicator. It is key to reducing the spread of new TB infections and mortality attributed to TB.
Percentage of patients cured of TB	Outcome	This indicator measures the proportion of patients cured of TB. These are TB patients bacteriologically confirmed at the beginning of treatment who were smear- or culture-negative in the last month of treatment and on at least one other occasion during the course of treatment. **Numerator:** Total number of TB patients (new cases, bacteriologically confirmed) that were cured of TB in the ten NTLP-targeted provinces. **Denominator:** Total number of TB patients (new cases, bacteriologically confirmed) that initiated TB treatment 12 months earlier. (Cohort analysis is done at 12 months after treatment initiation to allow completion of patient evaluation and documentation process.) Disaggregated by province, district, sex, and age.	TB treatment register	NTLP monthly data collection tool	Monthly	This indicator informs the TB program of the effectiveness of the treatment support strategies; includes treatment adherence and monitoring.

Performance indicator	Type	Definition and unit of measure	Data source	Method or tool	Frequency of collection/ reporting	Use of information
Percentage of TB/HIV co-infected patients on HIV treatment	Outcome	This indicator measures the proportion of TB/HIV patients on ART (both newly initiated and continuing). This treatment should be in line with NTLP treatment guidelines and TB is the entry point. This is a PEPFAR indicator. **Numerator:** Total number of TB/HIV patients on ART (new and continuing) during the reporting period. **Denominator:** Total number of TB/HIV patients during the reporting period. Disaggregated by province, district, age, and sex.	TB treatment register, ART register	NTLP monthly data collection tool	Monthly	To inform the TB program on the promptness of ART initiation in co-infected patients to abate mortality due to TB in this special group.
Number of patients diagnosed with DR-TB	Outcome	This indicator measures the number of individuals diagnosed with DR-TB by culture or molecular method. Disaggregated by province, district, facility, age, and sex.	Second-line TB treatment register, laboratory register	NTLP monthly data collection tool, DR-TB database	Monthly	To inform the TB program on the efforts and strategies aimed at early detection of DR-TB cases.
Number and percentage of DR-TB patients initiated on second-line treatment	Output	This indicator measures the number of individuals diagnosed with DR-TB initiated on treatment. It also measures the proportion of total DR-TB patients initiated on treatment. According to Zambian guidelines, individuals detected with rifampicin resistance are to be started on second-line treatment immediately, as drug susceptibility testing is being processed. **Numerator:** Number of RR-TB patients initiated on second-line TB treatment. **Denominator:** Number of RR-TB patients detected. Disaggregated by province, district, age, and sex.	DR-TB treatment register	NTLP monthly data collection tool, DR-TB database	Monthly	To inform the TB program on the promptness of second-line initiation and devise strategies to enhance early second-line initiation.

Performance indicator	Type	Definition and unit of measure	Data source	Method or tool	Frequency of collection/ reporting	Use of information
Treatment success rate among registered DR-TB patients in the ten NTLP provinces	Outcome	This indicator measures the sum of patients cured and those who completed treatment out of the total notified within the specified period of time. **Numerator:** Number of registered TB patients successfully treated (cured and completed treatment) x100. Number of DR-TB patients cured during the reporting period plus the number of DR-TB patients who completed second-line TB treatment during the reporting period. **Denominator:** Number of registered TB patients. Number of individuals who were due to complete second-line TB treatment during the reporting period. Disaggregated by province, district, age, and sex. **"Cured":** Treatment completed as recommended by the national policy without evidence of failure, AND three or more consecutive cultures taken at least 30 days apart were negative after the intensive phase. **"Treatment completed":** Treatment completed as recommended by the national policy without evidence of failure, AND no record that three or more consecutive cultures taken at least 30 days apart were negative after the intensive phase.	DR-TB treatment register	DR-TB database	Quarterly	The indicator informs the TB program on the effectiveness of the treatment support strategies, which includes treatment adherence and monitoring.
Number of children notified with TB	Outcome	This indicator measures the number of children (0 to 14 years of age) diagnosed with TB. Disaggregated by province, district, sex, and age.	Laboratory register, TB treatment register, x-ray records	Monthly reports	Monthly	To help the TB program calculate the proportion of TB in children, thereby assessing the extent to which NTLP-supported provinces are meeting the set targets.

Abbreviations: ART, antiretroviral therapy; DR-TB, drug-resistant tuberculosis; HMIS, health management information system; NTLP, National Tuberculosis and Leprosy Program; PEPFAR, US President's Emergency Plan for AIDS Relief; RR-TB, rifampicin-resistant tuberculosis; TB, tuberculosis; WHO, World Health Organization.