REPUBLIC OF ZAMBIA

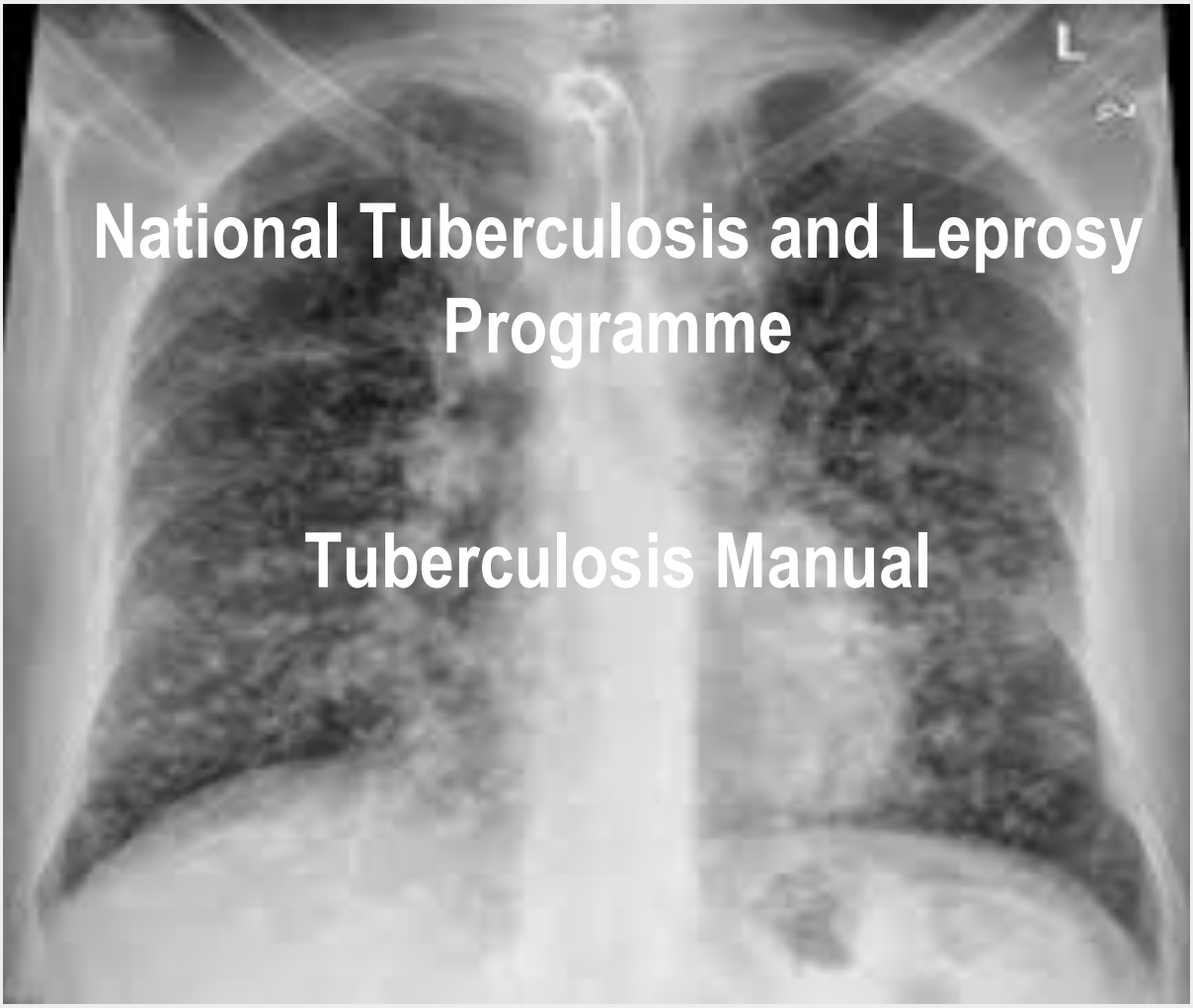
THE NATIONAL TUBERCULOSIS AND LEPROSY CONTROL PROGRAM

TB MANUAL

UNITE TO END TB

FIFTH EDITION - 2017

Republic of Zambia
Ministry of Health



National Tuberculosis and Leprosy Programme

Tuberculosis Manual

Fifth Edition
2017

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Foreword

The Ministry of Health through the National Tuberculosis and Leprosy Program (NTLP) has launched an ambitious National Strategic Plan (NSP) 2017-2021 for TB Prevention, Care and elimination in Zambia with the theme "Towards TB Elimination." The publication of the fifth edition of the TB manual compliments the NSP 2017-2021. This manual provides the latest guidance for TB screening, diagnosis, treatment and prevention and is in line with international standards. In addition, the manual sets the pace in achieving all the TB National Strategic Plan targets, developed in line with the Global End TB Strategy, and the Sustainable Development Goals (SDGs). Since 2015 several important developments in the diagnosis and treatment of TB have occurred. These changes justify the revision of the preceding TB manual.

Tuberculosis continues to be a major public health problem in Zambia. Currently, a third of TB cases in the country go undetected, thus this manual provides step by step approaches in finding these missing TB cases in health facilities and the communities. In this new edition, latest international guidelines have been adapted including making Xpert/MTB-RIF the initial diagnostic tool for all cases requiring a TB test and use of Urine Lateral Flow TB lipoarabinomannan (LAM), making screening and diagnosis of TB in very sick patients easier. The manual has also prioritized the use of digital-X-ray (where available) as a critical tool for TB screening and changes in the treatment of TB patients have also been highlighted. The regimen for treating patients with previous episodes of TB will no longer be used. This means that all patients previously treated for TB should have their sputum collected for drug susceptibility testing (DST) to help make decision whether they will be treated with first or second line drugs.

This manual, therefore, comes at the most opportune time when the Ministry of Health has prioritized delivering high quality and people-centred TB care and prevention services with a focus on the primary health care (PHC) level of the health services and the community, thus the manual is for use by all health care workers at all levels including those working at community level.

I encourage all healthcare workers at all levels to use these guidelines as we move towards elimination of TB in Zambia.

HON. DR. CHITALU CHILUFYA, MP
MINISTER OF HEALTH

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PERMANENT SECRETARY-TECHNICAL SERVICES

Abbreviations

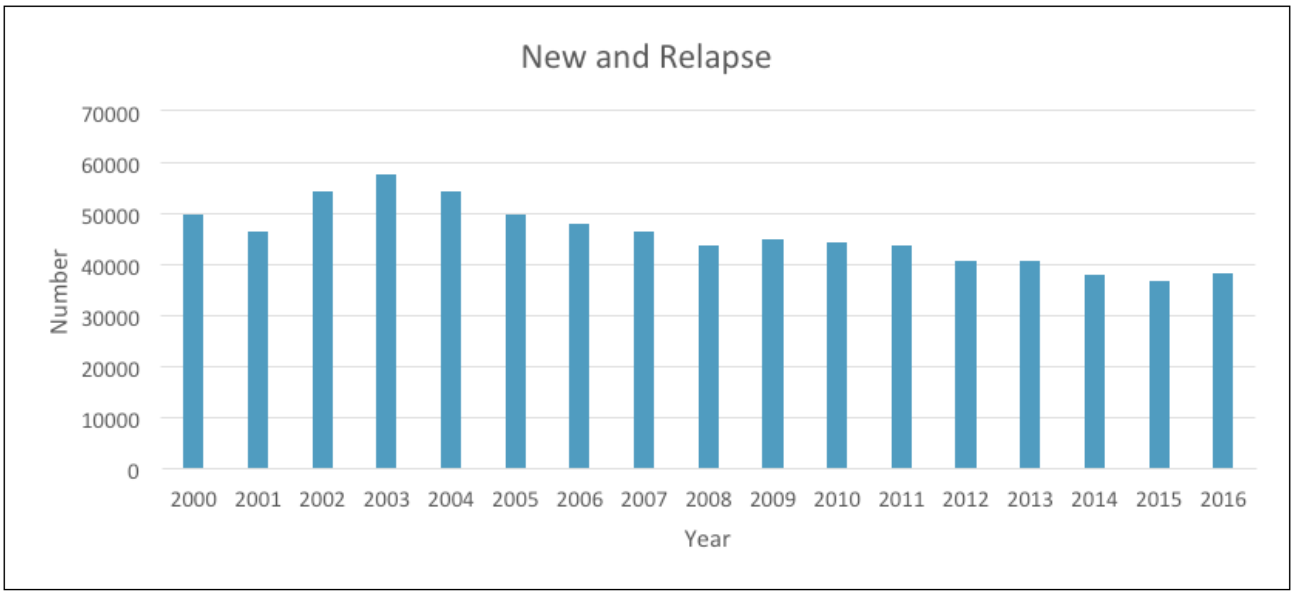
ACSM	advocacy, communication, and social mobilization
ADR	adverse drug reaction
AFB	acid-fast bacilli
ALT	alanine amino-transferase
ART	antiretroviral therapy
ATT	anti-tuberculosis treatment
Bdq	bedaquiline
cART	combined antiretroviral therapy
CHW	community health worker
Cfz	clofazimine
Cm	capreomycin
CPT	cotrimoxazole preventive therapy
Cs	cycloserine
CSF	cerebrospinal fluid
CT	computerized tomography
CXR	chest x-ray
DIH	drug-induced hepatitis
Dlm	delamanid
DOT	directly observed treatment
DRS	drug-resistance survey
DR-TB	drug-resistant tuberculosis
DST	drug-susceptibility testing
E	ethambutol
EPTB	extrapulmonary tuberculosis
FDC	fixed-dose combination
FLD	first-line drug
FQ	fluoroquinolone
H	isoniazid
HHD	isoniazid high dose
HCW	health care worker
IEC	information, education, and communication
Imp/Cln	imipenem/cilastatin
IPT	isoniazid preventive therapy
IRIS	immune reconstitution inflammatory syndrome
Km	kanamycin
Lfx	levofloxacin

LF-LAM	lateral flow urine lipoarabinomannan assay
LPA	line probe assay
Lzd	linezolid
M&E	monitoring and evaluation
MDR-TB	multidrug-resistant tuberculosis
Mfx	moxifloxacin
MGIT	Mycobacteria Growth Indicator Tube
MOTT	mycobacteria other than M. tuberculosis
Mpm	meropenem
MRI	magnetic resonance imaging
NRL	National TB Reference Laboratory
NTLP	National Tuberculosis and Leprosy Programme
NTM	nontuberculous mycobacteria
Ofx	ofloxacin
PAS	para-aminosalicylic acid
PLHIV	people living with HIV
PMDT	programmatic management of drug-resistant tuberculosis
PMTCT	prevention of mother-to-child transmission of HIV
PSM	procurement and supply chain management
Pto	prothionamide
R	rifampicin
RR	rifampicin resistance
RR-TB	rifampicin-resistant tuberculosis
R&R	recording and reporting
S	streptomycin
SLD	second-line drug
SLI	second-line injectable
SL-LPA	second-line line probe assay
TB	tuberculosis
TBM	tuberculosis meningitis
TST	tuberculin skin test
VL	viral load
WHO	World Health Organization
XDR-TB	extensively drug-resistant tuberculosis
Z	pyrazinamide

Chapter 1 Background

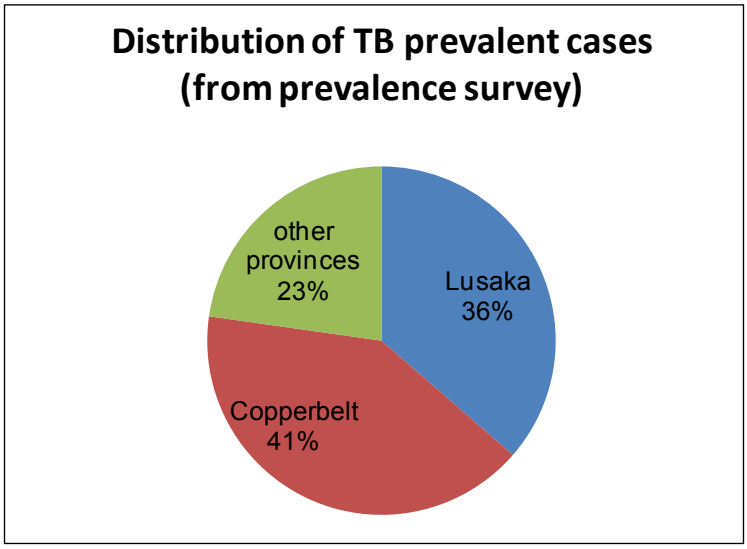
Tuberculosis continues to be a major public health problem in Zambia. With an incidence of 376 per 100,000 population, Zambia is ranked among the 30 countries with the highest per capita burden of TB in the world [1]. The notification rate and absolute numbers of TB have been declining over the last decade (see Figure 1). However, this is not a true decline. According to the TB prevalence survey conducted in 2013–2014, the burden of TB varied across provinces. Copperbelt Province had the highest prevalence of TB, followed by Lusaka Province (see Figure 2). Concerted efforts are required to find the missing cases of TB to meet the milestones and targets in the National TB Strategic Plan (2017–2021), which was developed in line with the National Health Strategic Plan (2017-2021), the Global End TB Strategy, and the Sustainable Development Goals. The main driver of the TB epidemic in Zambia is human immunodeficiency virus (HIV) [2, 3, 4]. HIV has been shown to be the highest risk factor for the development of active TB from latent and new infection. Following exposure and infection, the lifetime risk of an HIV-negative person developing TB is 10%, whilst in an HIV-positive person the risk is 10% per year [5, 6]. Other risk factors for TB are poverty, overcrowded living conditions, silica dust, and other causes of immune suppression such as diabetes, cancer treatment, and exposure to dust (e.g. among miners with damage to lungs [silicosis]). TB prevention and elimination agenda thus address the main risk factors of TB to meet the set targets for elimination of TB in Zambia. Every undiagnosed case of TB contributes to ongoing transmission; therefore, early TB detection and treatment is a key component of TB elimination. Every level of the health service–including the community–should be aware of the high burden of TB and should use every opportunity to screen clients and patients for TB at every entry point into care and the community. Infection prevention is also key in preventing infections, especially nosocomial spread of TB (see infection control section).

Figure 1: TB case notification trends in Zambia



Source: National Tuberculosis and Leprosy Programme (NTLP) data reports

Figure 2: Distribution of prevalent TB cases



Source: Evaluation of TB surveillance and TB epidemiological analysis in Zambia Mission report June 6-17, 2016

Chapter 2 Tuberculosis Case and Treatment Outcome Definitions

The purpose for making case definitions is to correctly classify and notify cases, as well as to register patients and allocate cases to standardized treatment. Bacteriologically confirmed or clinically diagnosed cases of tuberculosis are classified according to anatomical site of TB disease, history of previous treatment, drug resistance, and HIV status [7].

Tuberculosis Case Definitions

Table 1: Tuberculosis case definitions

Classification	Case	Definition
Case definition based on bacteriological status	Bacteriologically confirmed TB case	Biological specimen is positive by smear microscopy, culture, or World Health Organization (WHO)-approved rapid diagnostics such as Xpert MTB/RIF, line probe assay (LPA), and lateral flow urine lipoarabinomannan (LF-LAM) assay.
	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 extra-pulmonary cases without laboratory confirmation. (Clinically diagnosed cases should be reclassified to bacteriologically confirmed once laboratory results confirming presence of acid-fast bacilli [AFB] become available.)
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.
	Extra-pulmonary tuberculosis (EPTB)	TB involving organs other than the lungs (e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges, etc.). 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 who have taken anti-TB drugs for less than 1 month.
	Previously treated TB patients	Patients who have received 1 month or more of anti-TB drugs in the past.
	Relapse TB patients	Patients who have previously been treated for TB and were declared cured or treatment completed at the end of their most recent course of treatment, who are now diagnosed with a recurrent episode of TB (either a true relapse or a new episode of TB caused by reinfection).
	Treatment after failure patients	Patients who have previously been treated for TB and whose treatment failed at the end of their most recent course of treatment.
	Treatment after loss to follow-up patients	Patients who have previously been treated for TB and were declared lost to follow-up at the end of their most recent course of treatment.
	Other previously treated patients	Patients who have previously been treated for TB but whose outcome after their most recent course of treatment is unknown or undocumented.

Classification based on HIV status	HIV-positive TB patient	Any diagnosed case of TB who has a positive HIV test result at the time of TB diagnosis (or during TB 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-resistance	Resistance to only one first-line anti-TB drug.
	Poly-drug resistance	Resistance to more than one first-line anti-TB drug (other than both isoniazid and rifampicin).
	Multidrug resistance (MDR)	Resistance to both isoniazid and rifampicin whether or not in combination with other drugs.
	Pre XDR-TB	MDR-TB isolates with resistance to either a fluoroquinolone or any of the injectable agents (i.e. one drug away from developing XDR-TB).
	Extensive drug resistance (XDR)	Resistance to any fluoroquinolone and to at least one of three second-line injectable drugs (capreomycin, kanamycin, and amikacin), in addition to multidrug resistance.
	Rifampicin resistance (RR)	Resistance to rifampicin.
Other definitions and classifications	Miliary TB	Blood-borne dissemination of tuberculosis from either a primary infection or erosion of a secondary tuberculous lesion into a blood vessel (TB bacteraemia). Miliary TB is classified as pulmonary TB.
	Contact investigation	A systematic process to identify previously undiagnosed cases of TB among the contacts of an index case. In some settings, the goal also includes testing for latent TB infection (LTBI) to identify possible candidates for preventive treatment.
	Contact identification and prioritization	A systematic process to identify contacts with or at increased risk for development of TB.
	Contact clinical evaluation	A systematic process for the diagnosis or exclusion of active TB among contacts.
	Presumptive TB	A patient who presents with symptoms or signs suggestive of TB (previously known as a TB suspect). In addition, in our context, close contacts, people living with HIV [PLHIV] newly in enrolled in care, and inmates are also presumed TB cases with or without symptoms.
	Index case	The initially identified case of bacteriologically confirmed 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.

Key Messages

- Clinically diagnosed patients subsequently found to be bacteriologically positive should be reclassified as bacteriologically confirmed.
- Tuberculous intra-thoracic lymphadenopathy (mediastinal and/or hilar) or tuberculous pleural effusion, without radiographic abnormalities in the lungs, constitutes a case of extra-pulmonary tuberculosis (EPTB).
- A patient with both PTB and EPTB should be classified as a case of PTB.
- Miliary TB is classified as PTB because there are also lesions in the lungs.
- New and relapse cases of TB are incident TB cases.

Treatment Outcome Definitions

The treatment outcome definitions described here make a clear distinction between two types of patients: patients treated with first-line drugs (Table 2) and patients treated with second-line drugs (Table 3)

Table 2: Treatment outcomes for drug-susceptible tuberculosis (patients treated with first-line drugs)

TB treatment outcome	Definition
Cured	A TB patient with bacteriologically confirmed TB at the beginning of treatment who was smear- or culture-negative in the last month of treatment and on at least one previous occasion.
Treatment completed	A TB patient who completed treatment without evidence of failure BUT with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or because results are unavailable.
Treatment failed	A TB patient whose sputum smear or culture is positive at month 5 or later during treatment.
Died	A TB patient who dies for any reason before starting or during the course of treatment.
Lost to follow-up	A TB patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more.
Not evaluated	A TB patient for whom no treatment outcome is assigned. This includes cases "transferred out" to another treatment unit as well as cases for whom the treatment outcome is unknown to the reporting unit.
Treatment success	The sum of cured and treatment completed patients.

Table 3: Treatment outcomes for rifampicin-resistant (RR), multidrug-resistant (MDR), and extensively drug-resistant (XDR) tuberculosis cases (patients treated with second-line drugs)

TB treatment outcome	Definition
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 are negative after the intensive phase.
Treatment completed	Treatment completed as recommended by the national policy without evidence of failure BUT no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.
Treatment failed	Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of: lack of conversion by the end of the intensive phase, or bacteriological reversion in the continuation phase after conversion to negative, or evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs, or adverse drug reactions (ADRs).
Died	A patient who dies for any reason during the course of treatment.
Lost to follow-up	A patient whose treatment was interrupted for 2 consecutive months or more.
Not evaluated	A patient for whom no treatment outcome is assigned. (This includes cases "transferred out" to another treatment unit and whose treatment outcome is unknown.)
Treatment success	The sum of cured and treatment completed patients.

The terms "conversion" and "reversion" of culture as used here are defined as follows:

Conversion (to negative): Culture is considered to have converted to negative when two consecutive cultures, taken at least 30 days apart, are found to be negative. In such a case, the specimen collection date of the first negative culture is used as the date of conversion.

Reversion (to positive): Culture is considered to have reverted to positive when, after an initial conversion, two consecutive cultures, taken at least 30 days apart, are found to be positive. For the purpose of defining treatment failed, reversion is considered only when it occurs in the continuation phase.

Chapter 3 Tuberculosis Case Detection

This chapter discusses TB case detection and describes activities to be undertaken to improve TB case detection in Zambia. In 2015, TB case detection in Zambia was estimated to be 58% for drug-sensitive TB; thus, 42% of TB cases were missed. Undiagnosed cases of TB continue to be the source of transmission and fuel the epidemic. All health care providers should be involved in TB case detection; TB case detection activities are not the preserve of community health care workers only.

Missed TB Cases

Causes of missed TB cases include:

- Health system barriers
- Individual barriers
- Low index of suspicion for TB among health care workers
- Use of low-sensitivity TB screening and diagnostic tools
- Poor-quality samples

Strategies to reduce missed TB cases include:

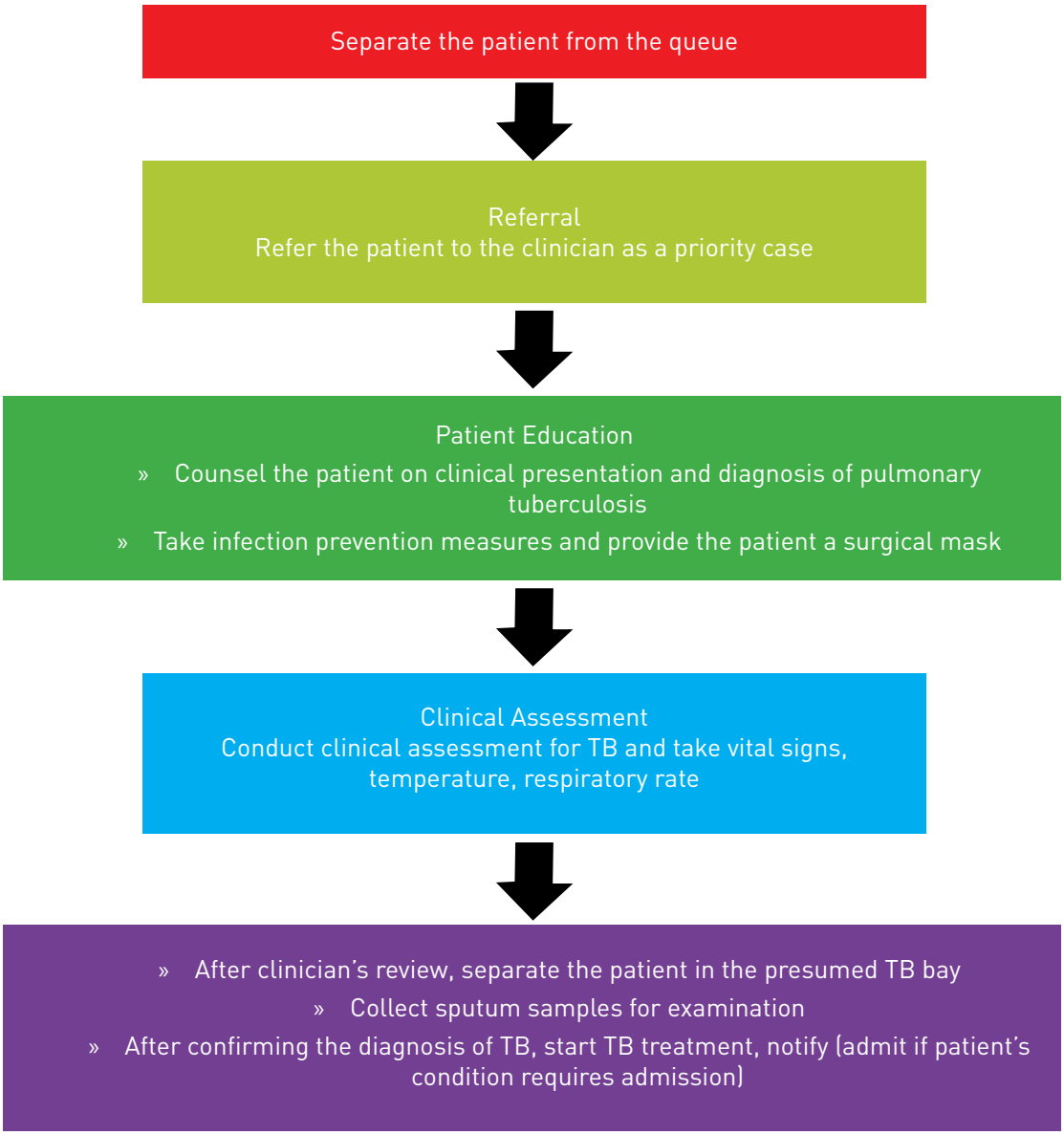
- Health system barriers: Create fast-track services of TB screening (also acts as an infection control measure). Introduce routine TB screening in high-risk areas (outpatient departments, antiretroviral therapy(ART) clinics, and maternal and child health care).
- Individual barriers: Take the diagnostic process as close to the patient as possible (e.g. door-to-door screening, community sputum collection points). Conduct education/sensitization activities to increase patient awareness of TB.
- Low index of suspicion among health care workers (HCWs): Provide orientation and on-site mentorship on TB; job aids; and information, education, and communication (IEC) materials to HCWs.
- Poor quality samples: Ensure correct instructions are given to the patient.

Table 4: Facility-level TB case detection indicators

Indicator	Definition	Output	Frequency	Source
Rate of presumptive TB cases identified	Number of presumptive TB cases identified / Number of health facility (HF) attendees 10 years and older X 100	10%	Quarterly	HF records, health information systems(HMIS) records
Rate of presumptive TB cases examined	Number of presumptive TB cases examined / Number of presumptive TB cases identified X 100	100%	Quarterly	HF records, HMIS records, presumptive TB register
Rate of presumptive TB cases bacteriologically confirmed (Bacteriologically confirmed TB rate)	Number of bacteriologically confirmed TB cases / Number of presumptive TB cases examined X 100	10%	Quarterly	HF records, HMIS records, presumptive TB register, laboratory register

Triaging of Patient with Presumed Pulmonary Tuberculosis

1. **Screen for symptoms**
   - » Do you have a cough?
   - » Is the cough productive?
   - » If yes, are there streaks of blood?
   - » Do you have chest pains?
   - » Do you have a fever?
   - » Have you lost weight?
   - » How is your appetite?
   - » Do you have night sweats?
2. **If YES to one or more questions, take the following steps.**



Chapter 4 Diagnosis of Tuberculosis

This chapter describes TB diagnostic tools and the diagnostic process for TB. Important tools for diagnosis of TB include:

- Detailed history taking including presenting symptoms and contact history
- Physical examination including general and systemic
- Laboratory testing: sputum for Xpert MTB/RIF, microscopy, or culture; urine for lateral flow urine lipoarabinomannan (LF-LAM) assay
- Radiological examination: chest x-ray, ultrasound, computerized tomography (CT) scan, and magnetic resonance imaging (MRI) scan

Clinical Presentation and Diagnosis of Pulmonary Tuberculosis

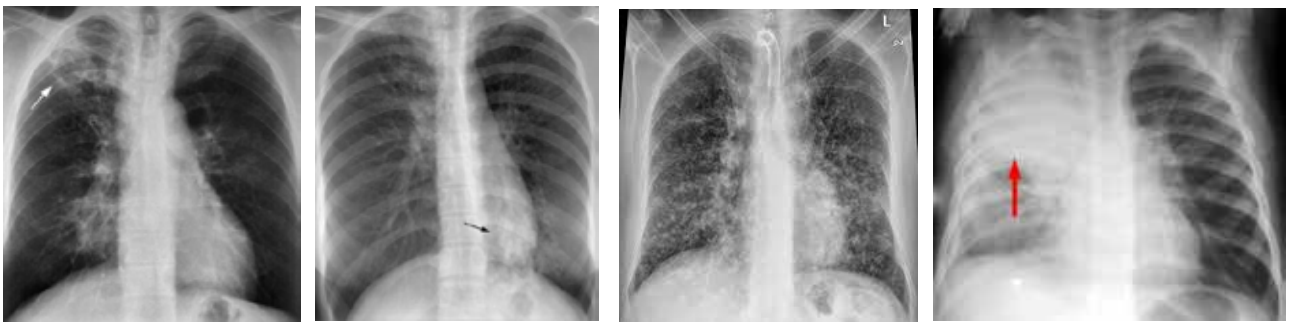
- Pulmonary TB is presumed in any individual presenting with some or all of the following symptoms:
- Dry or productive cough (2 or more weeks, any duration in people living with HIV [PLHIV])
- Haemoptysis (coughing up blood)
- Chest pain
- Shortness of breath (dyspnoea)
- Loss of weight
- Fever
- Drenching night sweats
- Other nonspecific symptoms like loss of appetite, general malaise, and weakness

Chest Examination

Pulmonary TB may present with many abnormalities on chest examination, but the most common are:

- **Signs of consolidation**: Decreased air entry, dullness to percussion
- **Signs of cavity**: Increased vocal resonance and bronchial breathing
- **Signs of inflammation**: Crepitations

Figure 3: Abnormalities on chest x-ray that are suggestive of TB



Apical involvement - cavity ***Primary TB*** ***Miliary TB*** ***Consolidation***

Clinical Presentation of Extrapulmonary Tuberculosis

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

» Diagnosis of EPTB

» Extrapulmonary TB is difficult to diagnose bacteriologically.

» Nonspecific symptoms such as fever, night sweats, and weight loss may be present.

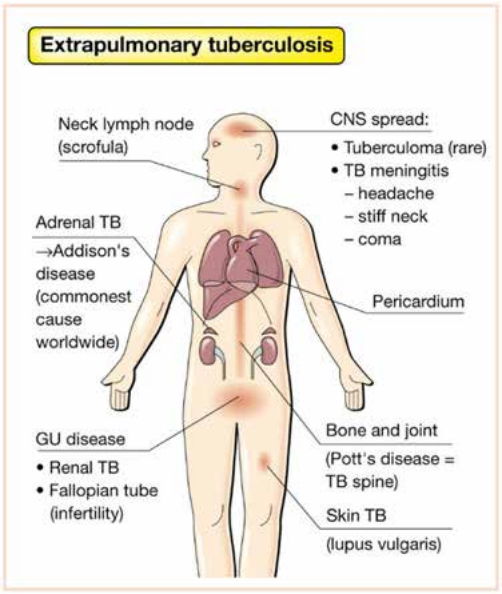
» Symptoms are specific to the organ involved.

» Diagnosis is usually through a combination of clinical examination and laboratory and radiological evaluations.

Key Message

All forms of EPTB can also have pulmonary involvement; therefore, send sputum samples for smear, Xpert MTB/RIF, or culture.

Figure 4: Parts of the body that can also be attached by TB



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

Clinical Findings of EPTB

The clinical presentation of EPTB depends on the affected site.

Table 5: Clinical findings of extrapulmonary tuberculosis (EPTB)

Site	Typical presentation	Examination findings	Investigations	Management
TB adenitis (lymph nodes TB)	Painless swelling in the neck, axillae, and inguinal	Asymmetrical enlarged lymph nodes (often matted) Discharging sinus, cold abscess	Needle aspiration If node is fluctuant, aspirate content and send sample for Xpert MTB RIF and culture If not fluctuant use Fine needle aspiration to obtain a specimen and send for cytology (FNAC) Chest x-ray mediastinal lymph node enlargement) Abdominal ultrasound Intra-abdominal lymph nodes CT scan of abdomen and chest which may reveal paraortic lymph nodes.	In the absence of bacteriological diagnosis and poor clinical response to treatment, consider differential diagnosis

Site	Typical presentation	Examination findings	Investigations	Management
Pleural effusion (pleural TB)	Initially asymptomatic, can present with chest pain .usually unilateral and may present with 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 smear, Xpert MTB/RIF, and culture, although these have low positivity rate: acid-fast bacilli (AFB) <5%, culture <15%. An elevated adenosine deaminase (ADA) is suggestive of TB	Massive pleural effusion: do drainage If there is pus in the pleural tap, refer the patient to a higher level hospital for drainage If haemorrhagic, refer to higher level to exclude malignancy
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 there is neurological compromise: signs of paralysis, sensory loss, and/or incontinence	X-ray of the spine: wedge-shaped collapse of the vertebra CT scan or MRI	Treat TB for 12 months Refer to physiotherapy and consult with orthopaedic surgeon
Joint (TB arthritis)	Chronic swelling usually involving the hip, knee, or elbow	Chronic monoarthritis, limitation of movement, unilateral effusion in the affected joints	X-ray of the joint: destruction of the affected joint CT scan or MRI Needle aspiration of synovial fluid Synovial biopsy Specimens can be sent for Xpert MTB/RIF and culture, but note the low positivity rate	Refer to specialist
Abdominal TB	Nonspecific symptoms: abdominal pain, abdominal distention, chronic diarrhea, abdominal mass	Evidence of ascites or abdominal mass	Abdominal ultrasound: para-aortic nodes, 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 ADA	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 cerebrospinal fluid (CSF) for smear, Xpert MTB/RIF, and culture; protein increased, glucose decreased, and elevated lymphocytes count (in early polymorphonuclear(PMN), then lymph) Brain CT scan or MRI	Treat TB for 12 months Add corticosteroids

Site	Typical presentation	Examination findings	Investigations	Management
Genitourinary TB	Renal asymptomatic for a time with slow development of dysuria, back flank pain, blood in urine Male: swelling and painful testes Female: complaint is infertility (usually nonspecific symptoms such as abdominal pain)	Nonspecific: renal angle tenderness Genital TB: Male: testicular swelling, epididymitis	Ultrasound: renal, testes, gynecological Cystoscopy: urethral strictures	
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	

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

Diagnostic Tools and Tests for TB

Tools and tests used for TB diagnosis provide either a definitive diagnosis (bacteriological confirmation of TB) or supportive information to aid diagnosis of tuberculosis.

Key Messages

- Xpert MTB/RIF is recommended as initial diagnostic test in all presumptive TB patients.
- Smear microscopy continues being initial test where Xpert MTB/RIF is not yet available.
- Smear microscopy should be used for treatment monitoring.
- All TB retreatment patients should have samples sent for first-line (FL) line-probe assay (LPA), culture, and drug-susceptibility testing (DST).
- All rifampicin-resistant (RR)-TB patients should be commenced on second-line drugs (SLDs) and specimen sent for second-line DST (LPA, culture, and DST.
- A negative laboratory test: smear, Xpert MTB/RIF, LPA, and culture doesn't mean that the patient does not have TB; patient should be clinically evaluated.
- Patients with strong clinical evidence of TB (especially people living with HIV, children, extrapulmonary TB) should start TB treatment even if bacteriological tests are negative or not available (clinically diagnosed TB).

Xpert MTB/RIF

The Xpert MTB/RIF assay is a fully automated, real-time, polymerase chain reaction (PCR) (molecular), disposable, cartridge-based nucleic acid amplification test.

» It is highly sensitive and specific: 40 times more sensitive than smear microscopy.

» It provides rapid and simultaneous detection of TB and rifampicin resistance (a reliable proxy for MDR-TB).

» It does not detect resistance to isoniazid.

» Results are available within 2 hours.

» Xpert MTB/RIF should not be used for follow-up testing as the result may remain positive even after treatment kills the bacteria because the assay detects DNA; instead use smear microscopy.

» Only one spot specimen (3–5 ml) is needed.

» Submit specimen as soon as possible. Samples must be stored at 2°C to 8°C for maximum of 5 days or at room temperature for a maximum of 3 days if testing cannot be done on the same day.

» Xpert MTB/RIF is recommended as the first diagnostic test in all adults and children with signs and symptoms of TB where available (Algorithm 1).

» If Xpert MTB/RIF is not available, samples from priority patients (e.g. PLHIV, children, EPTB, risk of DR-TB, HCWs, miners, and inmates) should be referred to facilities with GeneXpert machines.

Figure 5: Four module geneXpert machine and cartridge

Xpert MTB/RIF Cartridge

Reporting Xpert MTB/RIF Results

Xpert positive results reporting must include the rifampicin resistance results:
- MTB detected, RR+ve (MTB detected with rifampicin resistance detected)
- MTB detected, RR-ve (MTB detected with no rifampicin resistance detected)
- MTB detected, RRI (MTB detected with rifampicin resistance indeterminate)

Xpert negative results must be reported:
- MTB not detected

In rare cases, where the only result that is available for Xpert MTB/RIF is error, invalid, or no result, this result should be captured as:
- Err, Inv, No result

Note: Operational problems associated with this test include: the shelf-life of the cartridges is only 18 months, a very stable electricity supply is required, the machine needs to be calibrated annually, and the temperature ceiling is critical.

Key Message

- Xpert MTB/RIF should not be used for follow-up testing as the result may remain positive even after anti-TB treatment has killed the bacteria because the assay detects DNA; use smear microscopy instead.

Smear microscopy

Sputum smear microscopy is the first-line diagnostic test in facilities where Xpert MTB/RIF is not available. (In these facilities, high-priority patients such as PLHIV, children, health care workers, prisoners and miners should have samples referred for Xpert MTB/RIF testing.)

Evaluating anti-TB treatment response should be monitored using smear microscopy.

» Two spot specimens should be collected for smear microscopy at the time of request (at least 15 to 30 minutes apart).

» The results of positive sputum examination should be recorded in red ink in registers for easy identification.

» Sputum results must be reported within 24 hours.

Key Message

Smear microscopy should be used for diagnosis only where Xpert MTB/RIF is not available.

Limitations

Smear microscopy is usually negative in samples from PLHIV, children, and EPTB patients and cannot detect rifampicin resistance. The following World Health Organization (WHO)-recommended method for reporting smear microscopy results should be used [6].

Table 6: Reporting for fluorescence microscopy (FM) results (x400)

Number of acid-fast bacilli (AFB) found	Results	Report as
No AFB in at least 100 fields	0	No AFB seen
1–19 AFB in 100 fields	Actual AFB counts	Actual AFB counts
20–199 AFB in 100 fields	1+	1+
5–50 AFB per field in at least 50 fields	2+	2+
>50 AFB per field in at least 20 fields	3+	3+

Fig 6: LED microscope

Fig 7: Acid-fast bacilli on auramine staining

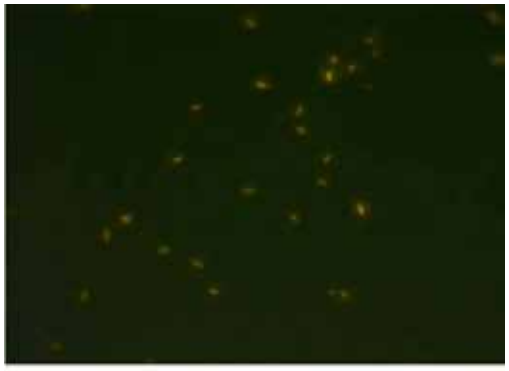


Table 7: Reporting of Ziehl–Neelsen (ZN) results

Number of acid-fast bacilli (AFB) seen in smear	Results	Result reported
No AFB in 100 fields	Negative	No AFB seen
1–9 AFB in 100 fields	Positive	Record exact number of bacilli
10–99 AFB in 100 fields	Positive	1+
1–10 AFB per field, check 50 fields	Positive	2+
>10 AFB per field, check 20 fields	Positive	3+

Line probe assay (LPA)

» LPAs are based on polymerase chain reaction (PCR) and DNA strip technology.

» LPA does not eliminate the need for conventional culture and phenotypic drug-susceptibility testing.

» LPA is available in Zambia at referral mycobacterial culture laboratories.

» LPA can be performed directly using a processed sputum sample (smear positive) or indirectly using DNA isolated and amplified from a culture of Mycobacterium (M.) tuberculosis.

» First-line LPA is recommended for the rapid detection of resistance to rifampicin and isoniazid in sputum specimens and cultures of M. tuberculosis.

» Second-line LPA is recommended for patients with confirmed rifampicin resistance (RR-TB) or multidrug-resistant tuberculosis (MDR-TB).

Table 8: Interpretation of results for line probe assay (LPA)

Result	Interpretation
Mycobacterium tuberculosis (MTB) complex detected	MTB was isolated from the specimen; therefore, the patient has bacteriologically confirmed TB
MTB complex not detected	MTB was not isolated from the specimen
Rifampicin and isoniazid susceptible	Patient has drug-susceptible TB
Rifampicin and isoniazid resistant	Patient has multidrug-resistant TB (MDR-TB)
Rifampicin resistant and isoniazid susceptible*	Patient has rifampicin-resistant TB (RR-TB)
Rifampicin susceptible and isoniazid resistant	Patient has isoniazid-resistant TB

Mycobacterial culture

Mycobacterial culture is the gold standard for TB diagnosis [5].

- Highly sensitive and specific method.
- There are two culture methods available: solid and liquid. Liquid culture is +10% more sensitive than Löwenstein-Jensen solid culture.
- Refrigerate culture specimens at 2°C to 8°C until ready for transport to the laboratory.
- If a refrigerator is not available, specimens must be held in coolers with ice packs.
- Specimens must be delivered as soon as possible but no later than 48 hours from time of collection.
- Limitations of culture include long turnaround time of the results (42 to 60 days to inform a negative result).

Priority Groups for Mycobacterial Culture

- All previously treated TB patients (lost to follow-up, relapse, failure)
- Smear-positive after 2 months of first-line treatment
- Contacts of drug-resistant TB patients
- Rifampicin-resistant (RR)-TB patients by Xpert MTB/RIF
- Patients who develop active pulmonary TB during or after isoniazid preventive therapy (IPT)
- Health care workers, miners, prisoners
- Extrapulmonary specimens
- Children
- Diagnostic uncertainty

Table 9: Interpretation of results for culture

Result	Meaning
Mycobacterium tuberculosis isolated	Positive
Mycobacterium tuberculosis not isolated	Negative
Contaminated	Specimen not properly handled (repeat specimen collection)
Not done	Test not performed due to reasons such as leaked specimen, mismatched information on the sample and request form, insufficient specimen, etc.
Mycobacteria other than Mycobacterium tuberculosis isolated (MOTT)	Non-tuberculous mycobacterium (NTM)

Notes: Practical descriptions of the procedures for sputum smear microscopy, culture, drug-susceptibility testing (DST), and Xpert MTB/RIF are detailed in the relevant TB laboratory manuals.

Fig 8: Mycobacterium TB group on Liguid and Solid culture

Discordant Laboratory Results

Discordant results are rare but may occur when comparing culture-based results with molecular results. Each discordant result will need to be investigated on a case-by-case basis. General considerations

include:

1. **Xpert MTB/RIF: MTB detected, rifampicin resistance not detected (susceptible); phenotypic DST: rifampicin resistance detected**
   - » Treatment decisions should be based on the culture phenotypic DST (rifampicin-resistant) result.
   - » Repeat phenotypic DST if still rifampicin resistance not detected; continue treatment. F
   - » False rifampicin-susceptible Xpert MTB/RIF results are rare but have been observed in 1% to 5% of TB cases according to some studies.
2. **Xpert MTB/RIF: MTB detected, rifampicin resistance not detected (susceptible); FL LPA: rifampicin resistance detected**

   Treatment decisions should be based on FL LPA (rifampicin-resistant) result.
   - » This discordance is rare but occurs due to hetero-resistant strains. Different populations of bacteria are coexisting with varying susceptibility to TB drugs (some are resistant and some sensitive). Depending on the treatment and "fitness" of the bacteria, different DST results from different samples may occur (especially if an interval has elapsed). Hetero-resistance to rifampicin can be detected by FL LPA (can detect absence of wild type and mutations) but not always by Xpert MTB/RIF (detects resistance by absence of wild type and single copy target of rpoB).

3. **Xpert MTB/RIF: MTB detected;**
   culture: negative

   Treatment decisions should be based on the Xpert MTB/RIF result.

   » Submit another sample for culture.

   Possible reasons for negative cultures in persons with pulmonary TB

   » Patient is already being treated for TB

   » Transport or processing problems that inactivated the tubercle bacilli

   » Inadequate testing volume

   » Laboratory or clerical error

4. **Xpert MTB/RIF: MTB not detected;**
   culture: positive

   Treatment decisions should be based on the culture result.

   » The culture-positive result should be considered as bacteriological confirmation of TB (culture is more sensitive).

   » Using a sputum specimen, Xpert MTB/RIF has a pooled sensitivity of 89% for detecting MTB compared to culture.

   » Xpert MTB/RIF sensitivity is lower in PLHIV, children, and other specimen types such as cerebrospinal fluid (CSF).

   » False positive cultures are very rare (but may occur due to laboratory errors such as cross contamination and sample labelling problems).

5. **Xpert** MTB/RIF: MTB detected, rifampicin resistance detected;
   phenotypic DST: rifampicin susceptible

   Treatment decisions should be based on the Xpert MTB/RIF resistant result.

   » Repeat culture and phenotypic DST using solid media.

   » Certain mutations are known to generate this discordant result, particularly in the BACTEC™ MGIT system (i.e. a false rifampicin-susceptible phenotypic result).

   » In some low DR-TB prevalence settings, silent mutations have been observed that generate a false rifampicin-resistant MTB/RIF result, but this tends to be very rare.

Phenotypic drug-susceptibility testing (DST)

Phenotypic culture methods are based on assessment of the ability of M. tuberculosis to grow in culture media (solid or liquid) containing a critical concentration of specific anti-TB agents (which indicates resistance) or, conversely, its inability to grow in the same media (which indicates susceptibility).

» Phenotypic DST for first-line agents (isoniazid, rifampicin, ethambutol, and streptomycin) and selected second-line anti-TB drugs (kanamycin, amikacin, ofloxacin, levofloxacin) is generally reliable and reproducible.

» Other anti-TB agents such as the later generation fluoroquinolones (moxifloxacin and gatifloxacin), capreomycin, cycloserine, and pyrazinamide are becoming increasingly important in the treatment of DR-TB and there is a need for their critical concentrations to be re-evaluated.

» For new and repurposed drugs for the treatment of MDR-TB, such as bedaquiline, delamanid, linezolid, and clofazimine, DST is currently not available.

Lateral flow urine lipoarabinomannan (LF-LAM)

These tests are based on the detection of LAM antigen in urine. LAM antigen is released from metabolically active or degenerating bacteria.

» A positive LF-LAM result is diagnostic of active TB disease.

» A negative LF-LAM result does not rule out TB.

» Urine is easy to collect; the test can be performed at bedside and lacks the infection control risks associated with sputum collection.

» LF-LAM is recommended for persons with HIV infection with low CD4 (<100 cell/ul) counts or who are seriously ill without a known CD4 count [7].

» LF-LAM can be used as an additional test in a critically ill patient with sputum negative.

Figure 9: TB LAM strip

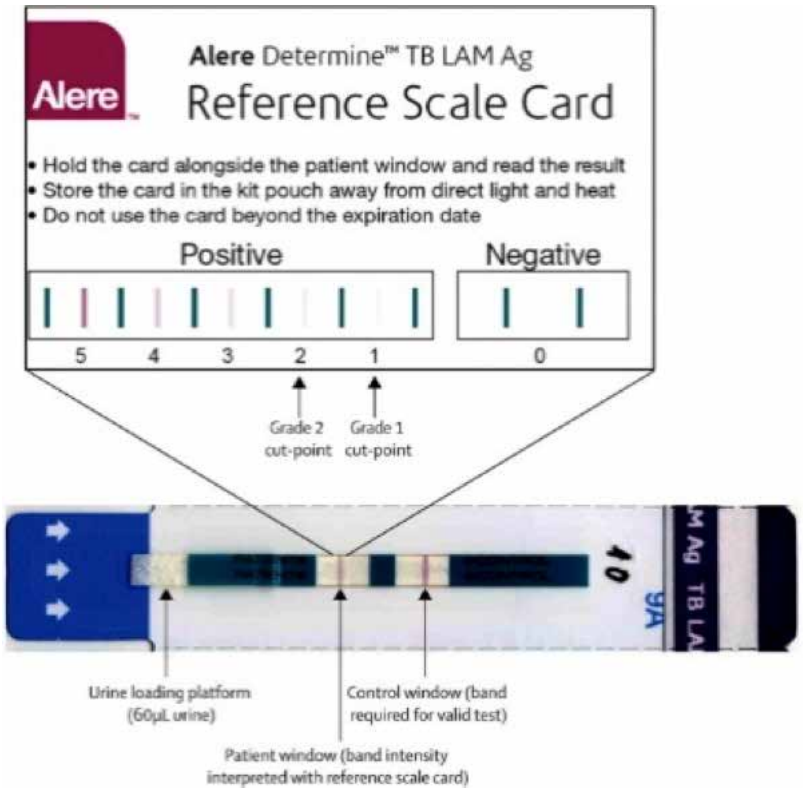
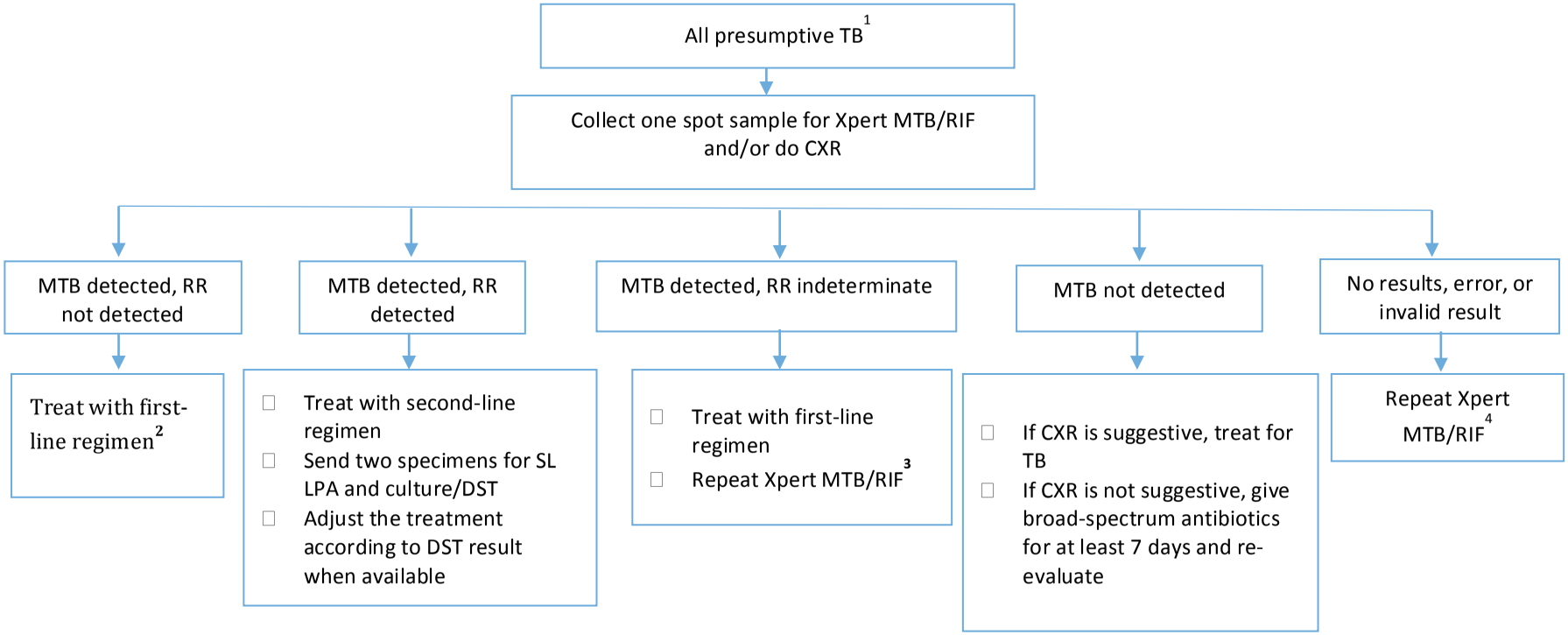


Figure 10: Xpert MTB/RIF algorithm



1For PLHIV who have CD4 counts ≤100 cells/µl or are seriously ill with one or more danger signs, a urine LF-LAM assay may also be used if available.

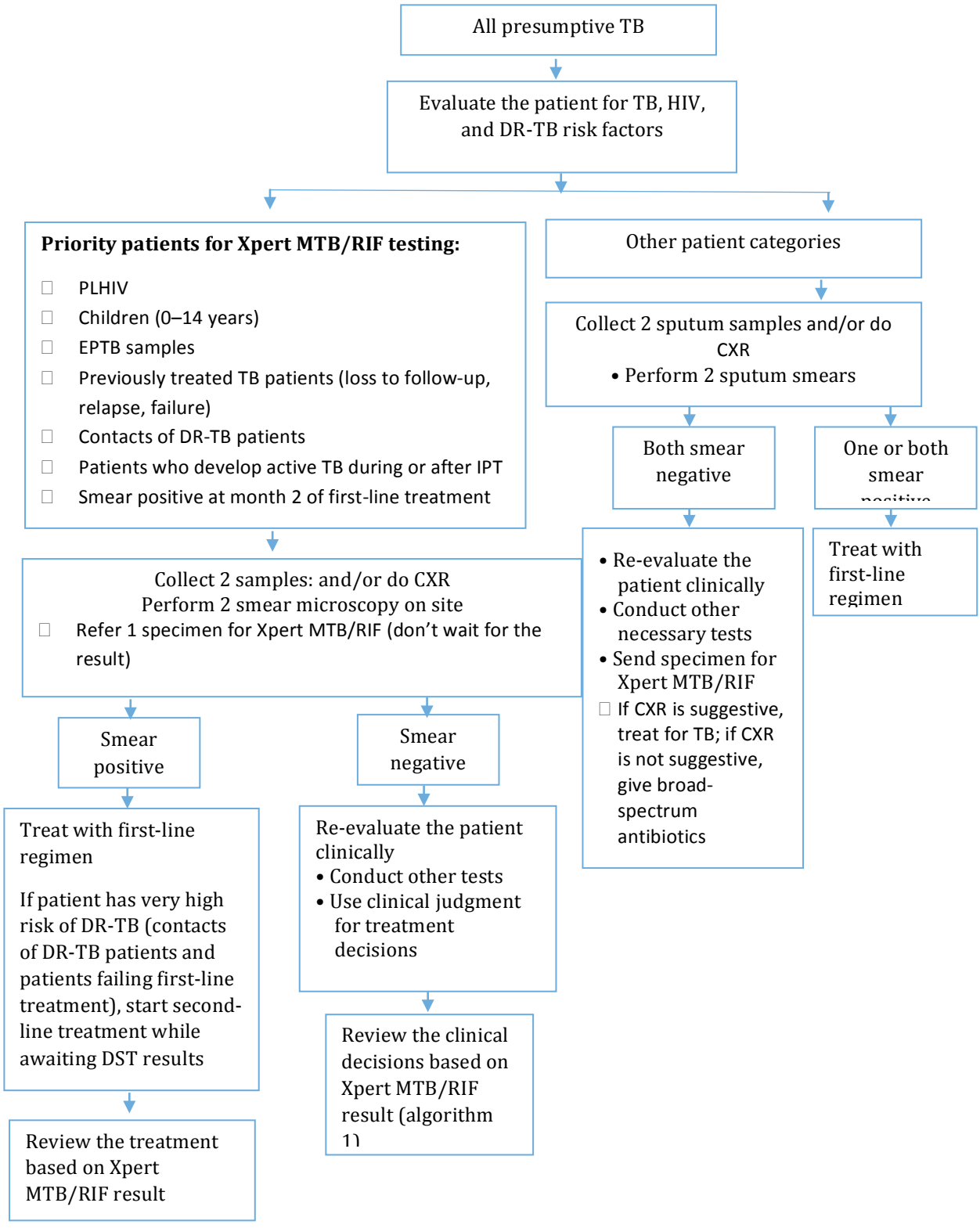
2 Patients should be initiated on a first-line regimen. A sample may be sent for FL LPA and culture/phenotypic DST if there is a risk of DR-TB: 1) previously treated TB patients, 2) loss to follow-up, 3) relapsed, 4) failure; 5) DR-TB, 6) DR-TB contacts, 7) smear positive at month 2 of first-line treatment, 8) health care workers, 9) miners, and 10) prisoners. If patient has a very high risk of DR-TB (e.g. contacts of DR-TB patients and patients failing first-line treatment), start second-line treatment while awaiting DST results.

3Treat the patient according to the result of the repeat test. If the second Xpert MTB/RIF is negative, continue the first-line TB treatment and send specimen for FL LPA, culture, and phenotypic DST.

4Treat the patient according to result of the repeat test.

Abbreviations: CXR, chest x-ray; DR-TB, drug-resistant tuberculosis; DST, drug-susceptibility testing; FL LPA, first-line line probe assay; LF-LAM, lateral flow urine lipoarabinomannan; MTB, Mycobacterium tuberculosis; PLHIV, people living with HIV; RR, rifampicin resistant; SL LPA, second-line line probe assay.

Figure11: Algorithm of sputum smear plus priority patients for Xpert MTB/RIF testing (for facilities without Xpert MTB/RIF)



Note: TB treatment should not be stopped once started.

Abbreviations: CXR, chest x-ray; DR-TB, drug-resistant tuberculosis; DST, drug-susceptibility testing; FL LPA, first-line line probe assay; IPT, isoniazid preventive therapy; LF-LAM, lateral flow urine lipoarabinomannan; MTB, Mycobacterium tuberculosis; PLHIV, people living with HIV; RR, rifampicin resistant; SL LPA, second-line line probe assay.

Radiology and Imaging

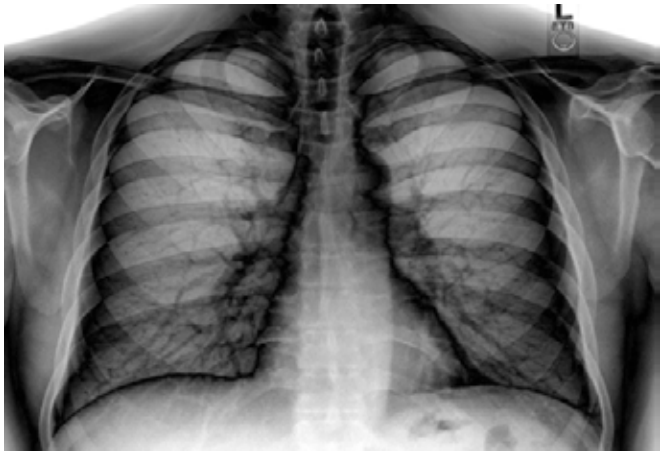
Chest radiography (CXR)

- CXR is an important TB screening and diagnostic tool [8-12]. Care must be exercised in interpreting CXR and should always be supported by clinical findings.
- CXR should be used as a supplementary diagnostic aid, although specificity is low.
- An abnormal CXR is an indication for full diagnostic evaluation.
- CXR is useful in aiding diagnosis of pulmonary and extrapulmonary TB in combination with history and bacteriological testing.
- CXR can also diagnose complications of TB such as pneumothorax, bronchiectasis, and fibrosis.
- Digital CXR is now available; it is easier and cheaper to use than film. Can be used with computer-aided diagnosis (CAD) to automatically score CXR images as normal or abnormal.
- Remember always to send samples for Xpert MTB/RIF and/or smear for acid-fast bacilli (AFB) before or at the time CXR is being requested.
- For TB screening, CXR and further clinical assessment can be used to triage who should get tested with Xpert MTB/RIF to reduce the number of individuals tested.

The following abnormalities of CXR are suggestive of TB:

- Cavitation.
- Consolidations in the upper zones.
- Pleural and pericardial effusion.
- Hilar lymphadenopathy.
- Miliary infiltrates.
- Nodules and fibrotic changes.
- Persons living with HIV can have atypical presentation as infiltrate in lower lobes.

Figure 12: Digital chest x-ray (posterior), inverted and enhanced



Ultrasound

- Ultrasound is specifically useful in aiding diagnosis of extrapulmonary TB of the abdomen or TB affecting the pericardium and pleura.
- Ultrasound is also useful to diagnose pulmonary consolidation.

Computerized tomography (CT) scan

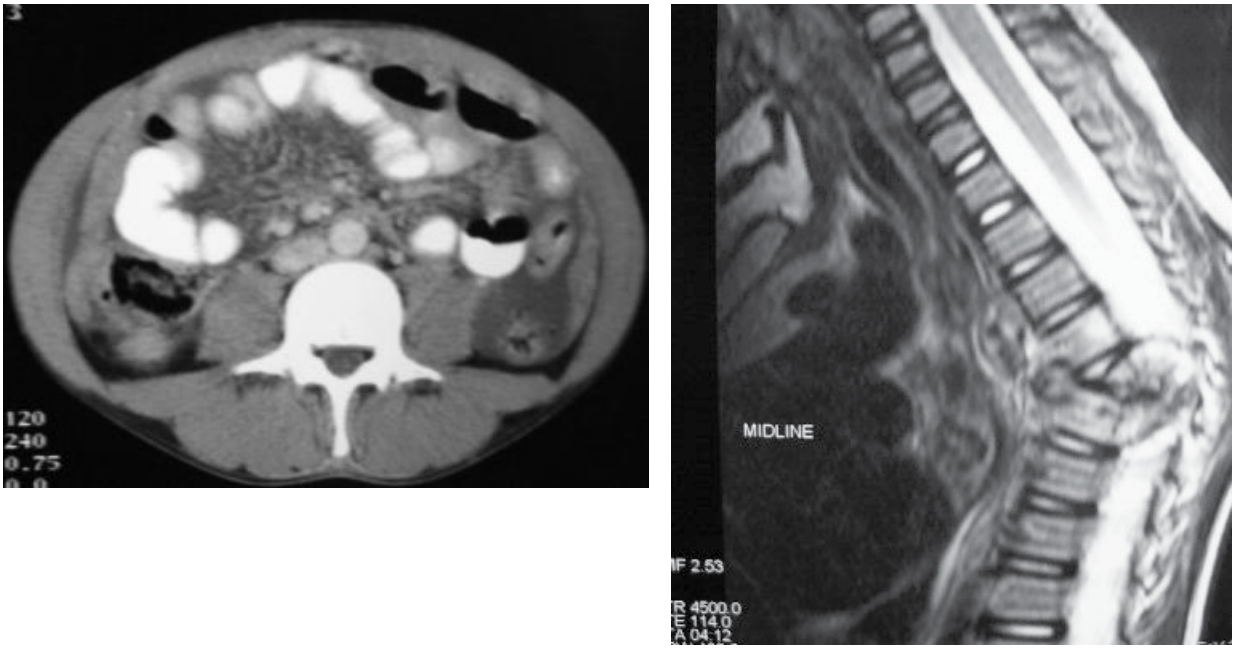
High-resolution imaging.

CT scan is useful to aid diagnosis especially when TB affects parts of the body that cannot easily be seen on standard radiography.

Magnetic resonance imaging (MRI)

- High-resolution imaging.
- MRI is useful to aid diagnosis especially for TB affecting the spine or the brain.

Figure 13: Abdominal CT scan showing enlarged lymph nodes (left) and MRI showing collapsing disc with caseation (right)



Chapter 5 Tuberculosis Treatment and Management

Aims and Principles of TB Treatment

Early case finding and adequate treatment of tuberculosis using directly observed treatment (DOT) is the cornerstone of TB elimination.

The aims of treatment are:

- To cure patients and restore their quality of life and productivity.
- To prevent further transmission of TB in the communities.
- To prevent relapse.
- To prevent death from active TB or its late effects and complications.
- To prevent the development of drug resistance—including MDR-TB and XDR-TB.

The principles of TB treatment are:

- 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.
- TB drugs should be taken daily for a specified period depending on the severity of the disease.

Essential Anti-TB Medicines

The recommended essential first-line anti-TB medicines are rifampicin (R), isoniazid (H), ethambutol (E), pyrazinamide (Z), and streptomycin (S). Only fixed-dose combination (FDC) treatment should be used, not single drug formulation. The fixed-dose combinations in use are 4FDC (RHZE), 3FDC (RHZ), and 2FDC (RH).

Properties of Anti-TB Drugs

Table 10: Properties of first-line anti-TB drugs

Drug	Drug property	Target bacilli	Site of action
Rifampicin	Bactericidal within 1 hour High potency Most effective sterilizing drug	All populations including dormant bacilli	Intracellular and extracellular
Isoniazid	Bactericidal after 24 hours High potency: kills >90% of bacilli in the first few days of treatment	Rapid and intermediate growing bacilli	Intracellular and extracellular
Ethambutol	Bacteriostatic, with low potency Minimizes the emergence of drug resistance	All bacterial populations	Intracellular and extracellular
Pyrazinamide	Bactericidal, with low potency Achieves its sterilizing action within 2–3 months	Slowly growing bacilli	Intracellular bacilli in macrophages
Streptomycin	Bactericidal, with low potency	Rapidly growing bacilli	Extracellular

Standardized First-Line Treatment: The standardized treatment regimen comprises 4FDC (RHZE) and 2FDC (RH) for a period of 6 to 12 months depending on the severity of the disease.

Intensive Phase of TB Treatment

- Designed for the rapid killing of actively growing and semi-dormant bacilli.
- Achieves a shorter duration of infectiousness.
- Duration of the intensive phase is 2 months.

Continuation Phase of TB Treatment

- Eliminates bacilli that are still multiplying and reduces the risk of failure and relapse.
- Duration of the continuation phase is 4 months.
- If the patient has TB meningitis or osteoarticular/spinal TB, the duration is 10* months.

*The total duration of treatment is 12 months for TB meningitis because of serious risk of disability and mortality and for osteoarticular/spinal TB because of the difficulty of assessing response to treatment.

The recommended treatment regimens are shown in Table 11 and the weight bands for dosing are shown in Table 12.

Table 11: Recommended treatment regimens

TB disease category	Recommended regimen	
Treatment phase	Intensive phase	Continuation phase
All forms of TB (non-severe)	2 months of RHZE	4 months of RH
TB meningitis, osteoarticular/spinal TB (and other severe forms)	2 months of RHZE	10 months of RH

Table 12: Weight bands for dosing anti-TB drugs

Body weight (kg)	Intensive phase (RHZE 150/75/400/275) Number of Pills/tablets	Continuation phase (RH 150/75) Number of Pills/tablets
25–37	2	2
38–54	3	3
55–70	4	4
Above 71	5	5

Key Message

Dosing for all patients should be based on weight; adjust according to weight changes.

TB Treatment of New and Previously Treated Patients

- All drug-susceptible TB patients should be treated with first-line TB drugs.
- In previously treated patients, send samples for Xpert MTB/RIF, first-line LPA, culture, and phenotypic DST. Start first-line treatment while waiting for the results.
- For patients failing the first-line regimen, send samples for Xpert MTB/RIF, first-line LPA, and culture and refer patient immediately to the DR-TB Clinical Expert Committee.

Key Messages

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

Indications for Steroids in the Treatment of Tuberculosis

The most common indications for steroids are:

- TB meningitis
- TB pericarditis
- TB immune reconstitution inflammatory syndrome (IRIS)
- Massive pleural effusion
- Massive lymphadenopathy with pressure effects
- Severe hypersensitivity reactions to anti-TB drugs

Rarer indications for steroids include:

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

The drug of choice for adjuvant steroid therapy is prednisolone. Recommended doses are shown in Table 13.

Table 13: Recommended doses for adjuvant steroid therapy

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/kg (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), TB immune reconstitution inflammatory syndrome (IRIS), and others	0.5–1 mg/kg (max 30 mg) for 1–2 weeks, then taper off over several weeks

Note: Steroid doses must not be stopped abruptly; they must be tapered.

Key Messages

Steroids are immunosuppressant and may 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.

Adherence

Adherence is the extent to which a patient's behavior coincides with the prescribed health care regimen as agreed upon through a shared decision-making process between the patient and health care provider.

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 other instructions given by health facility staff.

Importance of adherence

The following are the effects of good adherence:

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

The aim should be achieved 100% adherence. Adherence strategies include:

- Health care workers should encourage patients to identify treatment supporters with whom they are comfortable—preferably not relatives because they may feel sympathetic to see a relative taking many tablets.
- Structured adherence sessions must be given to all patients and their treatment supporters prior to treatment and reinforced to patients at every visit for successful TB treatment and care.
- Encourage treatment supporters to attend counseling sessions and clinic visits.
- Structured treatment preparation prior to TB treatment initiation should be conducted.

Barriers to adherence

Patient barriers to adherence include:

- Inadequate knowledge about the length of treatment
- Inadequate knowledge of TB/HIV services
- Self-stigma (denial)
- Side effects due to TB/HIV medications
- Language barriers
- Other co-morbidities
- Depression or other psychiatric problems
- Difficult life conditions
- Unstable living conditions (high mobility)
- Patient attitudes and beliefs
- Pill burden

Health care system barriers to adherence include:

- Inadequate DOT supporters
- Time, cost, and distance to DOT facility
- Failure to give adequate information on TB/HIV co-infection by service providers
- Medication stockouts
- Shortage of human resources for TB/HIV care
- Failure to monitor and evaluate patients

» Slow turnaround time for results
» Non-integrated TB/HIV clinics for TB/HIV co-infected patients

Barriers to adherence in children:

» Poor supervision of medication by caregiver
» Unreliable or multiple caregivers
» Lack of understanding of the disease by caregivers and by the children themselves
» No caregiver in case of street children

Dealing with nonadherent patients

» Be nonjudgmental—develop a trusting/caring relationship with the patient
» Make every effort to obtain the patient's voluntary adherence
» Discuss with the patient the benefits of the treatment to patient, the family, and the community
» Discuss with the patient the risks of inadequate treatment to the patient and others
» Show empathy

In case of difficult patients, consult/refer for help (family, respected community members, social worker, church elder, etc.).

When dealing with nonadherence in children, try the following approaches:

» Identify the primary caregiver
» Identify the reasons for the nonadherence
» Conduct adherence sessions for all involved caregivers, as it is insufficient to counsel only the child or adolescent
» Disclosure of the condition to the child or adolescent is important
» Offer verbal praise for adherence efforts
» Develop a supportive and continuous relationship with the child or adolescent

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

Key Points

- 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 and to new cases of TB and drug resistance.

Direct Observed Treatment (DOT)

- DOT ensures that the TB patient takes the right medicines, in the right doses, at the right intervals.
- Drugs should be administered under supervision of a designated trained observer, who 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 the patient's ID card/treatment card.
- If TB treatment is supervised by someone other than a health care worker, the patient must be involved in selecting the person to supervise her/him (preferably not a relative).
- The patient and his/her 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.

Patient Education

TB education should begin at the patient's initial visit and continue at each visit. Health staff and community supporters should educate TB patients and their relatives about their disease. 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 and is essential to attain a high cure rate and good adherence.

Patient education messages should include:

- What TB is and how it is transmitted
- Duration of treatment and outcomes
- Importance of adherence
- How to deal with circumstances such as travel and loss of tablets, among other things
- Possible side effects
- Importance of keeping appointments
- Importance of eating a varied diet
- Taking drugs 30 minutes before eating
- Prevention and infection control, which includes cough etiquette (coughing into handkerchief or tissue papers, covering the mouth when coughing using inner elbow, and spitting into a container)
- Discourage use of concomitant remedies (such as traditional medicines or herbs)

Side Effects of First-Line TB Drugs

Side effects can be grouped into minor and major categories. In general, a patient with minor side effects should continue the TB treatment and seek symptomatic treatment at primary health facility level.

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

Risk factors for developing side effects include:

- 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 (e.g. diabetes, alcoholism, malnutrition)
- Pregnancy and immediate post-partum period
- Malnutrition (low albumin)

Table 14: Summary of side effects of anti-TB drugs and their management

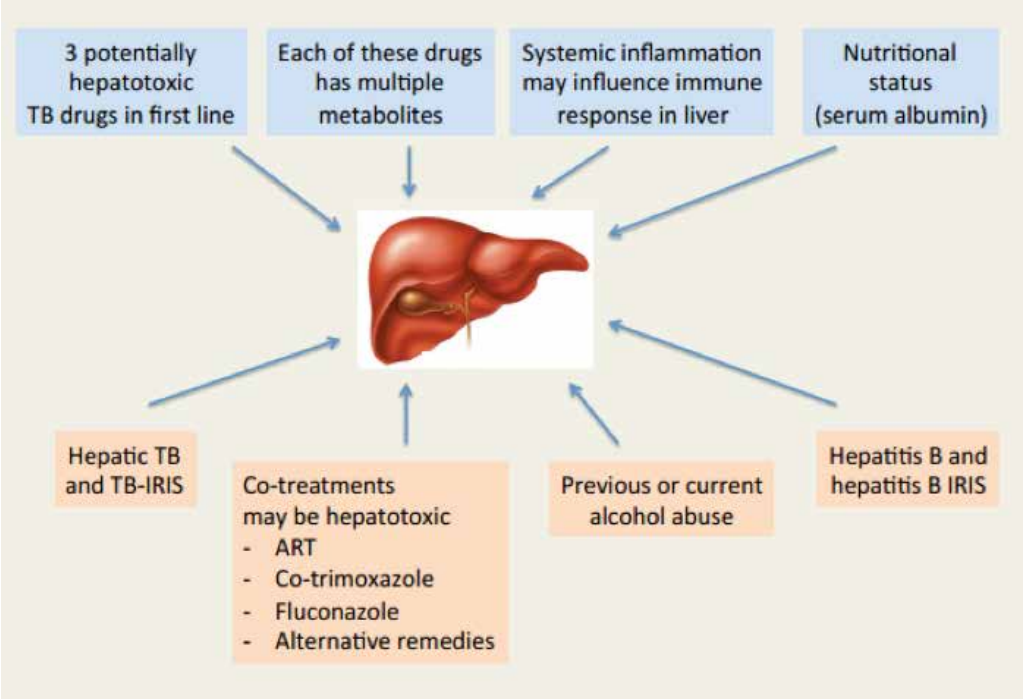
Side effects	Drug(s) probably responsible	Management
Minor	Continue anti-TB drugs but review drug doses	
Anorexia, nausea, abdominal pain	Pyrazinamide Rifampicin	Give drugs with small meals or last thing at night
Joint pain	Pyrazinamide	Nonsteroidal anti-inflammatory drugs (aspirin, ibuprofen, diclofenac)
Burning sensation in the feet	Isoniazid	Pyridoxine (vitamin B6)
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 mucosa involvement	Isoniazid Pyrazinamide Rifampicin	Stop anti-TB drugs (see below re-introduction of TB drugs)
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 next level of management
Jaundice (exclude other causes) or hepatitis	Isoniazid Pyrazinamide Rifampicin	Stop anti-TB drugs Exclude other causes
Psychosis, convulsions	Isoniazid	Stop TB treatment and refer* for psychiatric evaluation
Visual impairment (exclude other causes)	Ethambutol	Stop TB treatment and refer to ophthalmologist

*Note: Referral may be within the facility or to another higher level medical facility.

Drug-induced hepatitis

- Hepatotoxicity during administration of first-line anti-TB medications (i.e. isoniazid, rifampicin, and pyrazinamide) is common and may limit their use.
- It can occur at any time during the course of TB treatment.
- Drug-induced hepatitis (DIH) is ultimately a diagnosis of exclusion. Other causes of liver injury, such as acute viral hepatitis and disseminated TB, should be methodically sought; their absence makes the diagnosis plausible.
- It is important to factor in that the etiology of DIH is complex and multi-factorial.
- An increase in serum alanine amino-transferase (ALT) is more specific for hepatocellular injury than an increase in aspartate amino-transferase (AST).
- Discontinuation of the medication leading to a fall in ALT is the strongest confirmation of the diagnosis. DIH can be life-threatening if not managed.
- One measure to stop further deterioration of the hepatic function is to temporarily discontinue all the anti-tuberculous drugs (RHEZ or RH).

Figure 14: 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. Available at:www.idm.uct.ac.za

Abbreviations: ART, antiretroviral therapy; IRIS, immune reconstitution inflammatory syndrome.

When to stop anti-TB treatment in a patient with drug-induced hepatitis

- Severe and worsening jaundice.
- Development of hepatic encephalopathy (confusion, flapping tremors, convulsions, coma).
- Greater than 5 times rise in ALT if asymptomatic and greater than 3 times if symptomatic.
- Raised international normalized ratio (INR); a normal INR is less than 1.1

Key Message

Refer to a higher-level hospital for severe forms of drug-induced hepatitis and in the event you are unable to monitor the patient.

Re-introducing anti-TB treatment

Before re-introducing anti-TB treatment, ensure the following:

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

Re-introduction of anti-TB treatment

- Resume the TB treatment at once (RHZE) if in the intensive phase or RH if in the continuation phase), but gradually.
- Monitor the ALT weekly for a month; if it remains normal after a month of close monitoring, then repeat when clinically necessary.
- Monitor clinically for recurrence of jaundice at each weekly visit.
- If the DIH re-occurs, refer the patient to a higher-level hospital or specialist.

Table 15: Re-challenging of TB drugs following drug-induced hepatitis

Day	Drug and dose (RHZE)
1	1 tablet
2	2 tablets
3	Full dose*
4	Full dose
5	Full dose (do Liver function tests) and if acceptable, proceed)

A full dose is the patient's normal dose based on weight.

Stevens-Johnson Syndrome (SJS)

Anti-TB treatment–induced SJS is a severe skin reaction and is considered a medical emergency. It is called SJS when the rash involves 10% of the body surface and toxic epidermal necrolysis (TENS) when the rash involves more than 30% of the body surface.

Management of SJS includes:

- Stop all anti-TB drugs.
- Stop all other possible offending drugs such as co-trimoxazole and nevirapine.
- Isolate the patient to avoid secondary infections.
- Start prednisolone (1 mg/kg).
- Add an antihistamine such as promethazine.
- Keep the patient warm.
- Give adequate hydration (using intravenous fluids).
- Consider a broad-spectrum antibiotic (for prevention of secondary infection).
- After the rash has subsided, reintroduce anti-TB drugs by sequential dose escalation (known as desensitisation).

Key Message

Patients with Stevens-Johnson Syndrome (SJS) or toxic epidermal necrolysis (TENS) should be referred to level 2 or 3 hospitals for management.

Peripheral neuropathy

Patients with isoniazid-induced peripheral neuropathy usually present with numbness, tingling, and burning sensations of the hands or feet. There is increased risk of peripheral neuropathy in people with:

- HIV infection
- Alcohol dependency
- Pregnancy
- Malnutrition
- Diabetes
- Chronic kidney disease

The prophylactic treatment for peripheral neuropathy is pyridoxine (25 mg).

- The dose can be increased to 50–75 mg in case of peripheral neuropathy (up to 200 mg).
- Once the symptoms of peripheral neuropathy, subside revert to 25 mg.

Key Message

All patients on anti-TB treatment should be on 25 mg of pyridoxine (as prophylaxis for peripheral neuropathy) for the duration of the treatment.

TB Patient Monitoring and Follow-Up

- All TB patients must be seen at least once a month by a health care provider for clinical review, assessment of side effects, and dose adjustment according to weight.
- All patients should have one sputum specimen (morning) taken for AFB smear at 2, 5, and 6 months regardless of the smear result in the preceding month.
- Sputum monitoring during treatment should be done as shown in Table 15.

Table 16: Summary of sputum monitoring by smear in first-line treatment

Treatment phase	Months of treatment	Sputum smear exam
Continuation phase	2*	If smear positive, send sample for Xpert MTB/RIF, culture, and DST.
	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*	If smear positive, send samples for Xpert MTB/RIF, culture, and DST.
	6 or 12*	If smear negative, assign appropriate treatment outcome, but if positive, send samples for Xpert MTB/RIF, culture, and DST.

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

Key Message

Most TB patients complete their treatment without any significant drug side effects, but some patients do develop side effects. Clinical monitoring of all TB patients for side effects is important during TB treatment.

Management of TB in Special Conditions

Pregnancy and breastfeeding mothers

All first-line anti-TB drugs (HRZE) are safe in pregnancy. Pregnant women diagnosed with tuberculosis should start anti-TB treatment immediately. Women who become pregnant during treatment should continue with their treatment. Women on TB treatment should 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.

Breastfeeding should not be stopped when the mother is on TB treatment. However:

- 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 where possible.
- If the baby does not have active TB, give the baby INH prophylaxis for 6 months, followed by BCG vaccination (refer to guidelines for the management of TB in children).

Patients with renal failure

- 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. Three times per week administration of these two drugs at the following doses is recommended if creatinine clearance is less than 30 ml/minute: pyrazinamide (25 mg/kg) and ethambutol (15 mg/kg).
- While receiving isoniazid, patients with severe renal insufficiency or failure should also be given pyridoxine to prevent peripheral neuropathy.

Patients with liver disease

- Most anti-TB drugs can cause liver injury and, therefore, care is needed in treating TB patients. If a patient has liver disease, do not give pyrazinamide, because this is the most hepatotoxic anti-TB drug. Isoniazid or rifampicin plus one or two non-hepatotoxic drugs such as streptomycin or ethambutol can be used for total treatment duration of 8 months.
- If the patient has severe liver damage, an alternative regimen is streptomycin plus isoniazid, rifampicin, and ethambutol in the initial phase followed by isoniazid and ethambutol in the continuous phase, with a total of 12 months.
- Recommended regimen is 2 S (RHE)/4 (RH) or 2 S (EH)/10 (EH).

Alternative Regimen for TB Patients with Liver Disease

- Streptomycin, isoniazid, and ethambutol in intensive phase; isoniazid and ethambutol in continuation phase: (2S(HE)/4(RH) or two months of streptomycin, Ethambutol and Isoniazid in the intensive phase and 10 months of Ethambutol and Isoniazid in the Continuation phases (2S(EH/10(EH).
- Pyrazinamide should not be used.

Chapter 6 Drug-Resistant Tuberculosis

Multidrug-resistant (MDR)-TB is a growing problem in Zambia. The WHO estimated that in 2015 there were 1,500 MDR-TB cases among notified pulmonary TB cases, but only 196 and 99 cases of MDR/RR-TB were detected and put on treatment respectively [1]. Drug-resistant TB case detection is low, as less than 10% of previously treated TB cases are accessing culture and DST testing; and second-line DST is rarely being done. This clearly shows that there is a wide gap between the estimated number of MDR-TB patients in the country and those the program is detecting. The most recent drug resistance survey (DRS), carried out in 2008, showed that in new TB cases with no history of prior treatment with anti-TB drugs, the prevalence of any drug resistance was 9.8% and that of multidrug resistance was 1.2% [13]. According to the WHO 2016 Global Tuberculosis Report, the estimated MDR/rifampicin resistant (RR)-TB prevalence among new and previously treated TB patients was 1.1% and 18% respectively [1].

Causes of DR-TB

- Transmission from a patient with drug-resistant 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 clinicians
- Suboptimal dosage
- Poor drug absorption
- Prolonged shortages of anti-TB drugs

Groups at Risk of DR-TB

- Contacts 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
- TB patients who are close contacts of DR-TB cases
- Health care workers
- Prisoners from facilities with high rates of DR-TB

Management of Presumptive DR-TB Patients

If a patient is presumed to have DR-TB, the following should be done:

- Collect sputum specimens for Xpert MTB RIF, first-line LPA, culture, and phenotypic DST.
- Do not admit patient to a general ward (especially in high HIV settings as HIV-positive individuals can easily get infected).

If hospital admission is necessary, the patient should be admitted to a special ward that has good ventilation. At home, advise the patient to sleep in a well-ventilated room that is separate from others (if possible). If DR-TB is confirmed by the laboratory, the patient should be referred for treatment at a designated treatment facility under strict supervision.

Detection of Drug-Resistant (DR)-TB patients

Case detection for DR-TB is like that for TB in general. The basis for identification of DR-TB patient is bacteriological examination, which includes Xpert MTB/RIF, line probe assay (LPA), culture, and phenotypic drug-susceptibility testing (DST).

Treatment Regimens for RR-TB and MDR-TB Patients

Shorter regimen and individualized regimens containing new drugs

To improve treatment outcomes, adherence, and the quality of life for RR/MDR-TB patients, the NTLP has adopted the WHO-recommended shorter regimen in patients without additional resistance or intolerance to key second-line drugs (SLDs)—i.e. fluoroquinolones (FQs) and second-line injectables (SLIs). For ineligible patients, an individualized regimen is recommended that may include the new drugs bedaquiline (Bdq) and delamanid (Dlm).

Eligibility criteria

All patients with DR-TB are eligible to start DR-TB treatment without delay. The patient should be evaluated to assess the risk of resistance or intolerance to FQs and/or SLIs and the eligibility criteria. If there is no risk of intolerance and/or resistance for FQs and/or SLIs, the patient will start with the shorter regimen. If there is risk of intolerance/resistance to FQs and/or SLIs and/or bacterial confirmation of drug resistance or other risk factors for poor treatment outcome (such as severe TB disease), the patient should start with an individualized treatment regimen. Before starting treatment, two sputum samples must be sent for second-line line probe assay (SL-LPA) and for culture, as well as first-line and second-line drug susceptibility tests (phenotypic FL/SL DST). Once the results are available, the initial regimen may then be adjusted if necessary.

Standardized shorter regimen for RR/MDR-TB patients (9–11 months regimen)

Standard duration of the intensive phase is at least 4 months of Km (Am, Cm), Mfx (Gfx), Cfz, Z, E, HHD*, PTO (Eto) given daily. If smear conversion is not achieved at month 4, the intensive phase shall be extended to a maximum of 6 months until sputum smear conversion. The Km (Am or Cm) will be given three times weekly from the fourth month onwards. The continuation phase consists of Mfx (Gfx), Cfz, E, Z for a fixed duration of 5 months. If the patient remains smear positive and/or is still culture positive at 6 months, the patient will be declared as a failure. Failure declaration and a switch to an individualized treatment will be considered earlier in patients

*HD – High Dose

Shorter Regimen for RR/MDR-TB Patients
Intensive phase: 4–6 months Km, Mfx, Cfz, Z, E, Eto, H^{HD}
Continuation phase: 5 months Mfx, Cfz, E, Z
Add vitamin B6 100 mg

[11]KM=Kanamycin, AM=Amikacyn, CM=Capreomycin, Mfx=Moxifloxacin, Gfx=Gatifloxacin, Z=Pyrazinamide, E=Ethambutoal, HHD=high dose Isoniazid, PTO=Prothionamide, Eto=Ethionamide

Individualized DR-TB regimens

Patients who are not eligible for the shorter DR-TB regimen should be initiated on an individualized DR-TB regimen, including patients with MDR-TB treatment failure, pre-XDR-TB, and XDR-TB. The design of the individualized regimen will include new and repurposed drugs such as Bdq, Dlm, linezolid (Lzd), and clofazimine (Cfz) with few exceptions such as pregnancy.

Key Message

It is strongly recommended that individualized regimens should be designed by the DR clinical expert committee.

Principles for designing individualized DR-TB treatment regimens

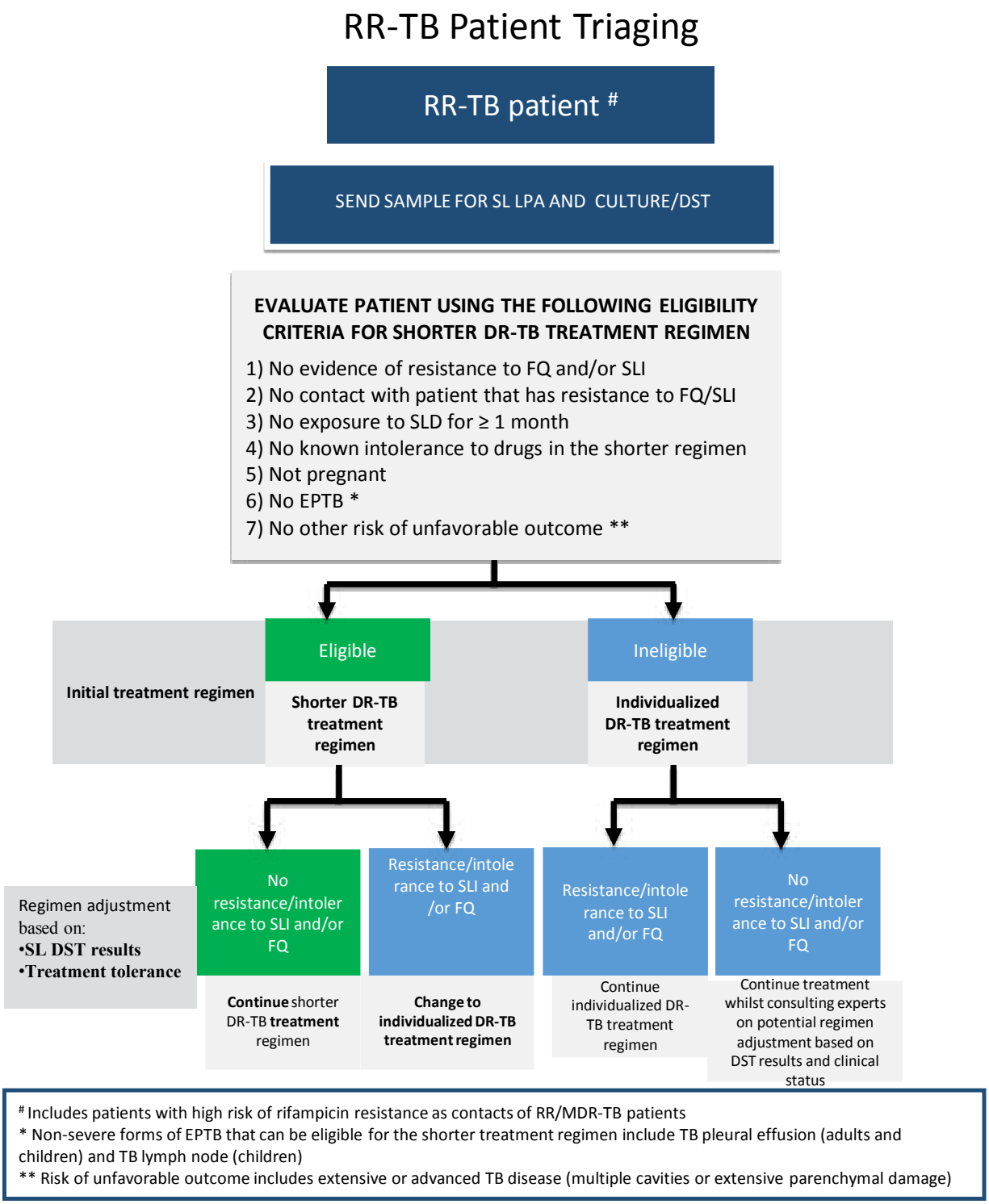
- The standard duration of the intensive phase should be at least 8 months and duration of the continuation phase should be at least 12 months.
- The regimen should be designed based on the patient's most recent DST results and history of previous drug use and/or exposure.
- The regimen should consist of at least five drugs in the intensive phase with confirmed or high likelihood of susceptibility, including four core second-line drugs plus pyrazinamide. In the continuation phase, at least three effective drugs should remain.
- For a patient with limited treatment options (MDR treatment failure, pre-XDR, and XDR-TB), a regimen combining Bdq and Dlm should be designed and approved by the DR-TB clinical expert committee. Ensure close monitoring of the QT interval by performing an ECG at baseline, at 2 weeks, and monthly until the end of treatment with Bdq or Dlm.
- Bdq or Dlm should be initially given for 6 months; the use of Bdq or Dlm can be extended in consultation with the MDR-TB Clinical Expert Committee in cases with highly resistant forms of DR-TB where the remaining regimen is insufficient (fewer than three effective drugs) without Bdq or Dlm and the drug is well tolerated.

Table 17: Regimen design steps for RR-TB patients who are not eligible for the shorter DR-TB regimen and require an individualized regimen

Step 1: Choose either Bdq or Dlm (Group D2). Patients with shorter regimen treatment failure, intolerance to one or more drugs in the shorter regimen, pre-XDR, or XDR-TB should have either Bdq, Dlm, or both in their regimen. The choice of which drug (or potentially both drugs) is outlined in 'additional considerations' below.
Step 2: Choose a fluoroquinolone (Group A – Mfx or Lfx). If only ofloxacin resistance from DST is known, Mfx or Lfx high dose (Lfx is preferred due to less QT prolongation than Mfx) can still be added to the regimen, but it should not be counted as one of the effective drugs. Treatment with a later generation FQ (Mfx or Lfx) significantly improves RR-TB or MDR-TB treatment outcomes; they should therefore always be included unless there is an absolute contra-indication for their use.
Step 3: Choose an injectable (Group B – Km, Cm, Am). If clinical history or DST suggests resistance to all SLI drugs, or in case of a serious adverse event (hearing loss, nephrotoxicity), the injectable should not be used or should be promptly discontinued. If the patient's strain is still susceptible to one of the injectable drugs, it can be included in the regimen only if consistent monitoring for adverse events is assured. In children with mild forms of DR-TB disease, the harms associated with an injectable may outweigh potential benefits and therefore injectable agents may be excluded in this group.
Step 4: Choose at least two or more Group C drugs (Lzd, Cfz, Eto, Cs) thought to be effective as additional core second-line drugs to Bdq/Dlm, FQs, and SLI drugs. If efficacy is uncertain, the drug can be added to the regimen, but it should not be counted as an effective drug.
Step 5: Choose Group D1 drugs (PZA, HHD EMB) as add-on agents. PZA is routinely added to most regimens. High-dose INH may further strengthen the regimen if DST shows INH sensitivity (e.g. inhA mutation alone) or if INH resistance is unknown. Do not use INH if the katG mutation is present. D1 drugs are usually added to the core second-line drugs, unless the risks from confirmed resistance, pill burden, and intolerance or drug-drug interaction outweigh potential benefits.
Step 6: Only choose Group D3 drugs if there are no other treatment options available due to highly resistant forms of DR-TB or multiple intolerances to other DR-TB drugs.
The final individualized DR-TB regimen will consist of at least five drugs with confirmed or high likelihood of susceptibility from the following list: Bdq or Dlm, Lfx or Mfx, Km (Am, Cm), Eto, Lzd, Cfz, Cs, Z, High dose Isoniazid , E.

Abbreviations: Bdq, bedaquiline; Cfz, clofazimine; Cm, capreomycin; Cs, cycloserine; Dlm, delamanid, DR-TB, drug-resistant tuberculosis; DST, drug-susceptibility testing; E, ethambutol; Eto, ethionamide; FQ, fluoroquinolone; H, isoniazid; HHD, isoniazid high dose; Km, kanamycin; Lfx, levofloxacin; Lzd, linezolid; Mfx, moxifloxacin; MDR-TB, multidrug-resistant tuberculosis; RR-TB, rifampicin-resistant tuberculosis; SLI, second-line injectable; Z, pyrazinamide.

Figure 15: Rifampicin-resistant/drug-resistant (RR/DR) TB patient triage flow chart



Abbreviations: DR-TB, drug-resistant tuberculosis; EPTB, extrapulmonary tuberculosis; FQ, fluoroquinolone; RR-TB, rifampicin-resistant tuberculosis; SLD, second-line drug; SLI, second-line injectable; SL DST, second-line drug susceptibility test.

Table 18: Weight-based DR-TB drugs in adults

DRUGS	DAILY DOSE	30–35 KG	36–45 KG	46–55 KG	56–70 KG	>70 KG
Isoniazid	4–6 mg/kg once daily	150 mg	200 mg	300 mg	300 mg	300 mg
Rifampicin	8–12 mg/kg once daily	300 mg	450 mg	450 mg	600 mg	600 mg
Pyrazinamide	20–30 mg/kg once daily	800 mg	1000 mg	1200 mg	1600 mg	2000 mg
Ethambutol	15–25 mg/kg once daily	600 mg	800 mg	1000 mg	1200 mg	1200 mg
Rifabutin	5–10 mg/kg once daily	300 mg	300 mg	300 mg	300 mg	300 mg
Levofloxacin	750–1000 mg once daily	750 mg	750 mg	1000 mg	1000 mg	1000 mg
Moxifloxacin	400 mg once daily	400 mg	400 mg	400 mg	400 mg	400 mg
Ethionamide	500–750 mg/day in 2 divided doses	500 mg	500 mg	750 mg	750 mg	1000 mg
Prothionamide	500–750 mg/day in 2 divided doses	500 mg	500 mg	750 mg	750 mg	1000 mg
Cycloserine	500–750 mg/day in 2 divided doses	500 mg	500 mg	500 mg	750 mg	750 mg
***p*-aminosalicylic acid**[a]	8 g/day in 2 divided doses	8 g	8 g	8 g	8 g	8–12 g
Bedaquiline	400 mg once daily for 2 weeks then 200 mg 3 times per week					
Delamanid	100 mg twice daily (total daily dose = 200 mg)					
Clofazimine	200–300 mg daily (2 first months) then reduce to 100 mg daily (alternative dosing 100 mg daily)					
Linezolid	600 mg once daily	600 mg	600 mg	600 mg	600 mg	600 mg

Notes: High-dose isoniazid is 10–15 mg/kg daily, maximum 600 mg daily

High-dose levofloxacin is 1000–1500 mg once daily

Clofazimine in the shorter regimen is given 100 mg daily from the start of treatment

Linezolid can be reduced to 300 mg daily in the event of toxicity at 600 mg daily

Meropenem dosing is 1000 mg three times daily (alternative dosing is 2000 mg twice daily)

Imipenem/cilastatin dosing is 1000 mg imipenem/1000 mg cilastatin twice daily

Treatment monitoring for MDR/RR-TB patients on therapy

Adverse effects may occur with MDR-TB drugs and are dose dependent, although adverse effects can occur at normal doses. Patients should be monitored for adverse effects at each contact with a health care provider.

Patients should be monitored closely for signs of treatment failure and adverse drug reactions (compare baseline and follow-up examinations).

- Treatment can be monitored through clinical history; physical examination; psychosocial assessment; chest radiography; audiometry, bacteriological testing (smear and culture); laboratory monitoring (haematology-full blood count (FBC), creatinine, potassium, liver function test, Thyroid stimulating hormone (TSH)); pregnancy testing; hepatitis B and C testing; and HIV testing (if positive, then CD4 and VL every 6 months) should be included when doing the baseline investigations.
- Weight should be monitored monthly and drug dosages should be adjusted accordingly.
- Patients in individualized regimens require additional monitoring: ECG (Dlm, Bdq), serum albumin (Dlm), and for linezolid: vision test charts, serum amylase/lipase, and monthly hematology-FBC.

For details on adverse effects monitoring and management, refer to the DR-TB guidelines (3rd Edition).

Table 19: Treatment monitoring schedule for conventional DR-TB regimen

Prompt action on abnormal clinical or laboratory findings is essential Instructions: Circle each test completed												
Patient name: DR-TB registration number: Age: Sex: Height:												
Month/Year												
Examination	Baseline	1	2	3	4	5	6	7	8	9	10	11
Clinical exam	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X
Psychosocial, functional status	X	X	X	X	X	X	X	X	X	X	X	X
Weight/body mass index (wt/ht2) (monthly in children)	X	X	X	X	X	X	X	X	X	X	X	X
Xpert MTB/RIF	X											
Second-line line probe assay (SL LPA)	X	Repeat if smear or culture positive or suspect failure										
Smear	X	X	X	X	X	X	X	X	X	X	X	X
Culture	X	X	X	X	X	X	X	X	X	X	X	X
Phenotypic drug-susceptibility test (DST)	X	Repeat if smear or culture positive or suspect failure										
X-ray	X						X					X
Full blood count (FBC)[1]	X						X					
Creatinine, potassium[2]	X	X	X	X	X	X	X	X				
Liver function tests (ALT/AST)	X			X			X			X		
Thyroid-stimulating hormone (TSH)	X			X			X					
Fasting blood sugar	X											
Vision test charts[3]	X											
Audiometry	X	X	X	X	X	X	X					
HIV test[4]	X			X								
Hepatitis B (HBsAg)	X											
Pregnancy test[5]	X											
CD4 count (HIV-positive patients)	X						X					
Viral load (HIV-positive patients)	X						X					

1. Repeat FBC as necessary if HIV infected (especially in patients taking AZT) or if basal result is low.
2. Creatinine, potassium, and audiometry should be done monthly while on injectables.
3. Repeat vision testing there is if any change/complaint in acuity or colour vision.
4. If HIV negative at baseline, HIV testing should be repeated at month 3 and then every 6 months.
5. Pregnancy test: at baseline, then offer use of effective contraceptives (Depo-Provera or intrauterine device [IUD]).

Chapter 7 Tuberculosis in Children

Tuberculosis 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 higher chances of death when compared to adults. The proportion of children among reported TB patients has been decreasing, from 8.8% in 2011 to 6.2% in 2015. It is estimated that in high TB burden countries such as Zambia, TB in children should account for at least 10% to 15% of all cases that are notified [14]. The current low number is 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 deaths in children with respiratory illness that is not often detected at the time of death [15].

Guidance on Diagnosis of TB in Children

- Careful history (including history of TB contact and symptoms consistent with TB)
- Clinical examination (including growth assessment)
- Bacteriological confirmation with Xpert MTB/RIF or culture or smear microscopy
- Chest x-ray
- HIV testing
- Tuberculin skin testing
- Investigations relevant for suspected extrapulmonary TB

Diagnosis of TB in Children

The presentation of TB in children is usually different from that of adults. Although pulmonary TB is the commonest type of TB, extrapulmonary forms occur more frequently in children. Bacteriological confirmation is often not possible in children due to the paucibacillary nature of the disease and inability to collect a suitable specimen for laboratory analysis. Therefore, all specimen samples collected from children must be subjected to more sensitive diagnostic tools such as culture and Xpert MTB/RIF tests. For this reason, most children with TB are diagnosed based on clinical grounds. The diagnosis of TB can be made with confidence in most children using careful clinical assessment.

Pulmonary TB (PTB): The most common clinical presentation of pulmonary TB is persistent respiratory symptoms and poor weight gain. Note that in at-risk groups such as infants or HIV-infected individuals, pulmonary TB can also present as acute pneumonia. The approach to diagnosis of TB in an HIV-infected child is like that for an HIV-uninfected child. Most children will present with typical signs and symptoms of TB. However, the clinical presentation in younger children (under 5 years) has a wide spectrum of clinical signs and symptoms (atypical). History taking is an important part of the diagnostic work-up of TB in children.

Presentation of TB in Children

Typical symptoms

The following list show typical symptoms of TB in children, especially if such symptoms persist for more than 2 to 3 weeks without improvement following other appropriate therapies (e.g. broad-spectrum antibiotics for cough; antimalarial treatment for fever; or nutritional rehabilitation for malnutrition).

- 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

History of contact with TB source

- Close contact, such as with a person with TB living in the same household. Or the source may be someone with TB from outside the household (e.g. neighbour, relative) with whom the child has had frequent contact.
- A source case with sputum smear-positive PTB is more likely to infect contacts than cases with sputum smear-negative PTB.

» If no source case is identified, always ask about anyone in the household with a chronic cough. If so, request assessment of that person for possible TB.

» In older children, the contact with a TB source case may be outside the household (e.g. school).

» Timing of contact: most children develop TB within 2 years after exposure (90% within the first year).

A typical Clinical Presentations of PTB

Acute severe pneumonia

» Severe pneumonia presents with fast breathing and chest in-drawing This occurs especially in infants and HIV-infected children; PTB should be presumed if there is poor response to antibiotic therapy.

» If the child is HIV infected, then also suspect other HIV-related lung diseases, such as pneumocystis jiroveci pneumonia (PCP/ PJP) or lymphocytic interstitial pneumonia (LIP).

Wheeze

» Asymmetrical and persistent wheeze can be caused by airway compression due to enlarged tuberculous hilar lymph nodes.

» PTB should be presumed when wheeze is asymmetrical, persistent, and not responsive to bronchodilator therapy and associated with other typical features of TB such as malnutrition (asthma is rare in malnourished children).

Note that wheeze due to asthma is usually recurrent and variable rather than persistent, is responsive to inhaled bronchodilator, and is not associated with other typical features of TB such as poor weight gain and persistent fever.

Clinical examination

» Weigh child accurately and compare to previous weights.

» Look for weight loss or poor weight gain.

» Check for evidence of growth faltering.

» Look for fever and increased respiratory rate (record vital signs).

Respiratory system

» May have signs of respiratory distress.

» Auscultation and percussion: usually normal but may reveal lung disease (e.g. crackles, bronchial breathing) or pleural effusion (dullness and reduced breath sounds).

Clinical features that might suggest other causes of chronic lung disease

» Generalised lymphadenopathy, oral thrush, or parotid enlargement suggests HIV infection.

» Finger clubbing suggests LIP or bronchiectasis

» Recurrent cough and/or wheeze responsive to bronchodilators suggests asthma.

Differential diagnosis of chronic respiratory symptoms

Asthma

» HIV-associated chronic lung disease

» Lymphocytic interstitial pneumonia (LIP)

- Aspirated foreign body
- Bronchiectasis
- Pertussis (whooping cough)
- Cardiac disease
- Severe gastro-oesophageal reflux
- Severe cerebral palsy
- Cystic fibrosis

Specimen collection

- In children of all ages with presumed pulmonary TB, sputum should be collected for bacteriological examination.
- Specimens may be collected by means of sputum expectoration and gastric lavage.
- Other methods include sputum induction and nasopharyngeal aspiration.
- All samples obtained from children should be sent for Xpert MTB/RIF and/or culture.
- Where Xpert MTB/RIF and culture services are not available or inaccessible, perform smear microscopy.
- Usually children older than 5 years can be encouraged to cough and produce sputum. Gastric aspirate, nasopharyngeal aspirate, or induced sputum is usually performed in children unable to provide sputum by coughing.

Key Message

Negative Xpert MTB/RIF, culture, or smear results do not exclude TB disease in a child.

Other investigations

Chest x-ray (CXR)

CXR remains an important tool for diagnosis of TB in children who are sputum smear negative or who cannot produce sputum. The following abnormalities on CXR 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 (although seen on CXR) are forms of extrapulmonary TB that tend to occur in older children.

*It can be difficult to clearly define what is "suggestive of PTB" on clinical or radiological findings in HIV-infected children because of clinical overlap between PTB and other forms of HIV-related lung disease.

HIV test

A positive HIV test also indicates the need for HIV-related care for the child and possibly other family members.

Key Message

Any child with presumptive/diagnosed TB should have an HIV test done.

Tuberculin skin test (TST)

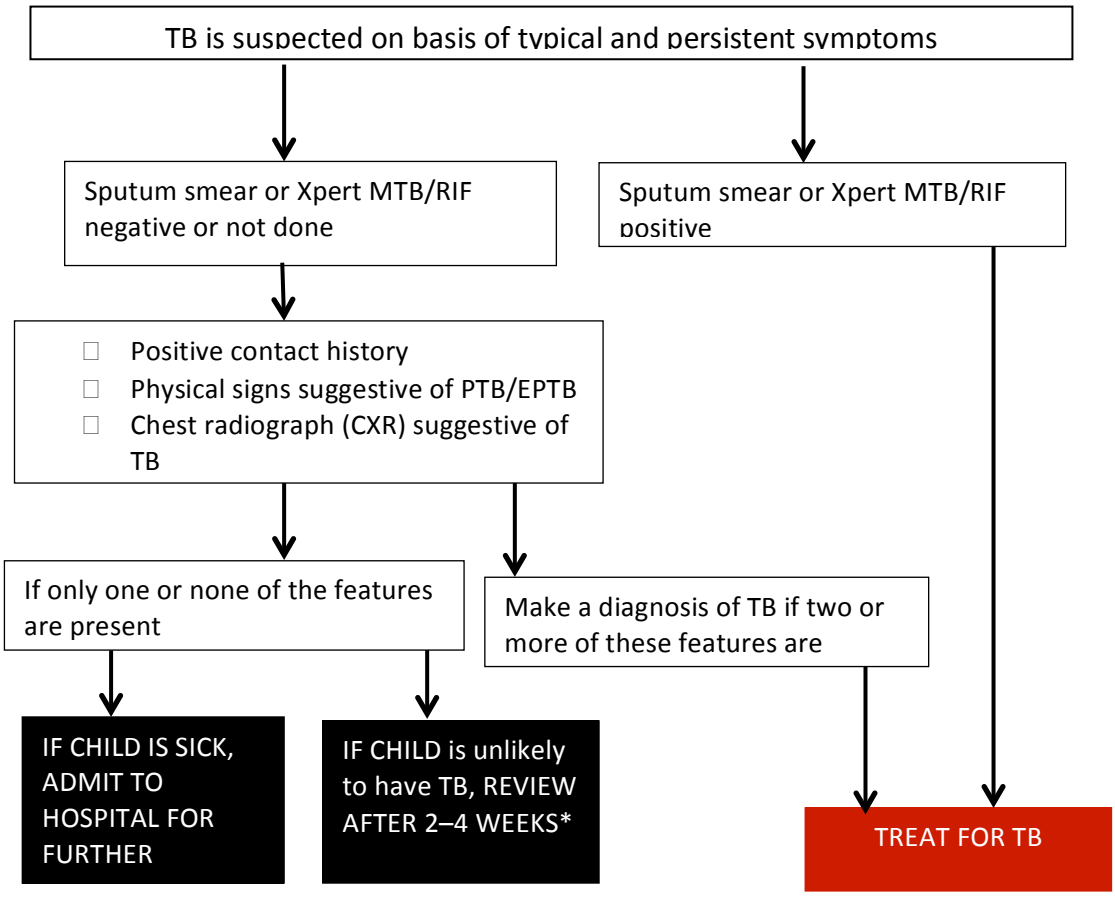
TST is useful to support a diagnosis of TB in children with suggestive clinical features who are bacteriologically negative or who cannot produce sputum. A positive TST indicates infection and not active TB disease.

- A TST ≥ 10 mm is considered positive in any child, regardless of BCG immunization status.
- A TST ≥ 5 mm is considered positive in an HIV-infected or severely malnourished child.
- A positive TST is particularly useful to indicate TB infection when there is no known TB exposure on clinical assessment (i.e. no positive contact history).
- A positive TST can occur after recent BCG immunization.
- A negative TST may occur in the presence of TB if there is HIV infection, malnutrition, and severe disseminated TB.

Caution

- A positive tuberculin skin test (TST) does not distinguish between TB infection and active disease.
- A negative TST does not exclude TB disease.

Figure 16: Approach to TB diagnosis in HIV-uninfected child algorithm



*If a child is not improving after a course of antibiotics, consider starting TB treatment.

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

Extrapulmonary Tuberculosis (EPTB)

EPTB is common in children, and presentation varies with age and site of infection. Clinical assessment in all cases should consider: history of contact (see above) for time lapse from exposure to disease; presentation can be quite variable—shorter for young children with disseminated disease, longer for other forms that present in school-aged children; sputum for bacteriological examination with Xpert MTB/RIF; and HIV test. An attempt should be made to obtain the relevant specimen for bacteriological confirmation with Xpert/smear or culture. Possible specimens include lymph node aspirates, ascetic fluid, CSF, and pericardial/pleural/joint effusions. For other relevant investigations see Table 20.

Table 20: Investigating extrapulmonary TB in children

Site of EPTB	Typical clinical presentation	Investigation	Management
TB adenitis	Asymmetrical, painless, non-tender lymph node enlargement for more than one month +/- discharging sinus. Most commonly seen in neck.	• Fine needle aspiration when possible for Xpert MTB/RIF, culture, acid-fast bacilli (AFB) microscopy and histology • Lymph node biopsy	Start TB treatment If axillary node enlargement is on same side as BCG, consider BCG disease and refer
Pleural TB	Dullness on percussion and reduced breath sounds +/- chest pain.	• Chest x-ray (CXR) • Pleural tap* (for Xpert MTB/RIF, culture, smear)	Start TB treatment If pus in pleural tap, consider empyema and refer
Usually young (< 5 years) with disseminated disease and severely ill			
TB meningitis	Headache, irritability/ abnormal behavior, vomiting (without diarrhoea), lethargic/reduced level of consciousness, convulsions, neck stiffness, bulging fontanelle, cranial nerve palsies.	• Lumbar puncture, obtain CSF for Xpert MTB/RIF, culture, smear • Biochemistry (high protein, low glucose) • Brain CT scan or MRI	Hospitalize for TB treatment Add steroids
Miliary TB	Nonspecific, lethargic, persistent fever, wasting.	• CXR • 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 Xpert MTB/RIF, smear • Abdominal ultrasound	Start TB treatment or refer
Spinal TB	Deformity of spine; may have lower limb weakness or paralysis or be unable to walk.	• X-ray of the spine • CT scan or MRI of the spine	Start TB treatment Refer for othopedic surgeon
Pericardial TB	Cardiac failure; distant heart sounds; apex beat difficult to palpate.	• CXR • Pericardial tap for Xpert MTB/RIF, culture, smear • Echocardiogram	Start TB treatment Refer Add steroids
TB of bone and joint	Swelling end of long bones with limitation of movement; unilateral effusion, usually of knee or hip.	• X-ray of bone/joint • Joint tap for Xpert MTB/RIF, culture, smear	Start TB treatment or refer

*Typical pleural tap findings: straw-coloured fluid, exudate with high protein, white blood cells predominantly lymphocytes on microscopy. Note that pleural aspirate XpertMTB/RIF and culture are mostly 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.

Key Message

- The principles of treatment of TB in children are the same as for adults.
- A caregiver should be identified as a directly observed treatment (DOT) 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.
- Drug dosages are calculated by body weight.
- Streptomycin should no longer be used for treatment of any form of TB in children.
- Record weight at each visit on the under-five and treatment cards.
- Pyridoxine is recommended in children with the following conditions: severely malnourished, HIV infected, pregnant adolescents, children with diabetes mellitus, and children with renal failure.
- Nutritional support should be provided for malnourished children.
- All children diagnosed with TB should be recorded in the facility TB register, treatment card and issued with a TB ID card.

Treatment of TB in children

Table 21: Recommended dosages for children 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 (R)	15 mg/kg (10–20 mg)	600 mg/day
Pyrazinamide (Z)	35 mg/kg (30–40 mg)	
Ethambutol (E)	20 mg/kg (15–25 mg)	

Table 22: TB disease category and recommended treatment regimens for children

TB disease category	Recommended regimen	
	Intensive phase	Continuation phase
All non-severe forms of pulmonary TB and extrapulmonary TB	2 months (HRZE)	4 months (HR)
Severe forms: TB meningitis, osteo-articular TB, spinal TB, miliary TB, other severe forms of TB	2 months (HRZE)	10 months (HR)

RHZ 60/30/150 mg and RH 60/30 mg has been phased out and replaced with RHZ 75/50/150 mg and RH 75/50 mg, which is dosed as shown in Table 23 below.

The RHZ 75/50/150mg has the following advantages

- » It is dispersible/easily dissolved in water
- » Palatable and child friendly flavour
- » High ratios of R and H for appropriate dosing

Table 23: TB dosing by weight band for children using the RHZ (75/50/150 mg) and RH (75/50 mg) formulations

Weight bands	Number of tablets		
	Intensive phase	Continuation phase	
	RHZ (75/50/150 mg)	E* (100 mg)	RH (75/50 mg)
4–7 kg	1	1	1
8–11 kg	2	2	2
12–15 kg	3	3	3
16–24 kg	4	4	4
25 kg and above	Use adult dosages and formulations		

*Ethambutol is provided as a separate 100 mg tablet.

Abbreviations: E, ethambutol; H, isoniazid; R, rifampicin; Z, pyrazinamide.

Monitoring response to treatment

- Children should be reviewed every 2 weeks in the first month and monthly thereafter.
- Children responding to treatment should experience improvement or resolution of symptoms by the end of intensive phase. The following should be assessed:
  - Presence of symptoms.
  - Weight: monitor weight at each visit and adjust medication dosages accordingly
  - Risk factors for poor adherence and possible solutions
  - Adverse side effects (yellow eyes, abdominal pains, skin rash).
- Younger children diagnosed by gastric lavage do not need to have it repeated.
- Older children with bacteriologically confirmed TB should be monitored similarly to adults; repeat sputum smear examination at 2, 5, and 6 months of treatment if able to expectorate.
- Chest x-ray is a poor indicator of response to treatment as mediastinal and hilar lymph glands can enlarge because of the improvement in the child's immunity and can also persist for more than a year after successful treatment.
- Chest x-ray should not be routinely used for monitoring of TB treatment, but it should be considered for children who are deteriorating on treatment or when clinically indicated.
- Xpert MTB/RIF test should not be used to monitor treatment response.
- If there is poor response to therapy (no weight gain, persistent symptoms after 2–3 months of treatment), then investigate and take appropriate action. TB drugs are very well tolerated in almost all children. Adverse events (side effects) are uncommon, but the most important is hepatotoxicity.

Key Message

The most important adverse effect is hepatitis, which usually presents with jaundice, nausea, and vomiting. There may be abdominal pain and a tender, enlarged liver. If hepatitis is considered a possibility, stop the TB drugs immediately and refer to hospital.

Other Management Issues

Corticosteroids

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 1–2 weeks before stopping.

Pyridoxine supplementation

Isoniazid may cause symptomatic pyridoxine deficiency, which presents as neuropathy, particularly in severely malnourished children and HIV-positive children on antiretroviral therapy (ART). Supplemental pyridoxine (5–10 mg/day) is recommended in HIV-positive or malnourished children being treated for TB.

Nutritional support

TB in children can trigger malnutrition or can occur because of malnutrition. All children diagnosed with TB require nutritional assessment and support. 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 and varied diet. Children diagnosed with TB and severe malnutrition should be referred to a therapeutic feeding programme.

DR-TB in children

The clinical presentation of DR-TB is similar to drug-susceptible 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. DR-TB should be considered in any child who has the following:

- Persistent non-remitting cough or fever
- Weight loss
- Focal findings that are suggestive of TB

When DR-TB is presumed, it is important to try as best as possible to get samples for bacteriological confirmation by Xpert MTB/RIF and culture. If there is a known contact with DR-TB, it is also important to know which drugs the index case is resistant to. All children suspected or with confirmed DR-TB should be referred to the nearest DR-TB treatment site for further management. For further details on DR-TB treatment, refer to the 3rd Edition Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis in Zambia (Chapters 4 and 7.)

When to Presume Drug-Resistant TB in Children

- Close contact with a person known to have DR-TB including household and school contacts.
- Close contact with a patient that died from TB, failed, or is not adherent to TB treatment.
- History of previous TB treatment (in the past 6–12 months).
- Not improving after 2–3 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 (INH) prophylaxis.

TB and HIV coinfection 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 is similar for both HIV-infected and HIV-uninfected children. The diagnosis of PTB can be particularly challenging in a HIV-infected child because of clinical overlap with another HIV-related lung disease.

Key Message

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

The management of children with TB/HIV co-infection should be integrated, and all household members should be counselled and tested for HIV and screened for TB. Children with TB/HIV co-infection may not have a caregiver to ensure compliance and adherence to treatment. A treatment supporter such as a community health worker (CHW) should then be identified.

Comprehensive Approach to TB and HIV Management

- Integrate HIV care in TB clinic.
- All children who are HIV positive should receive cotrimoxazole preventive therapy (CPT) and antiretroviral therapy (ART).
- Nutritional support is often needed for children with TB/HIV co-infection.
- Integrate TB care in HIV clinic.
- Screen all HIV-positive children for TB at every visit.
- Diagnose and treat TB.

When to start antiretroviral therapy in TB/HIV co-infected children

Antiretroviral therapy (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. For details of the ART, refer to "**Zambia Consolidated Guidelines for Treatment and Prevention of HIV Infection."**

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 should be screened for TB. Children who are under 5 and have no symptoms of TB should be started on INH prophylaxis. 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.

Key Message

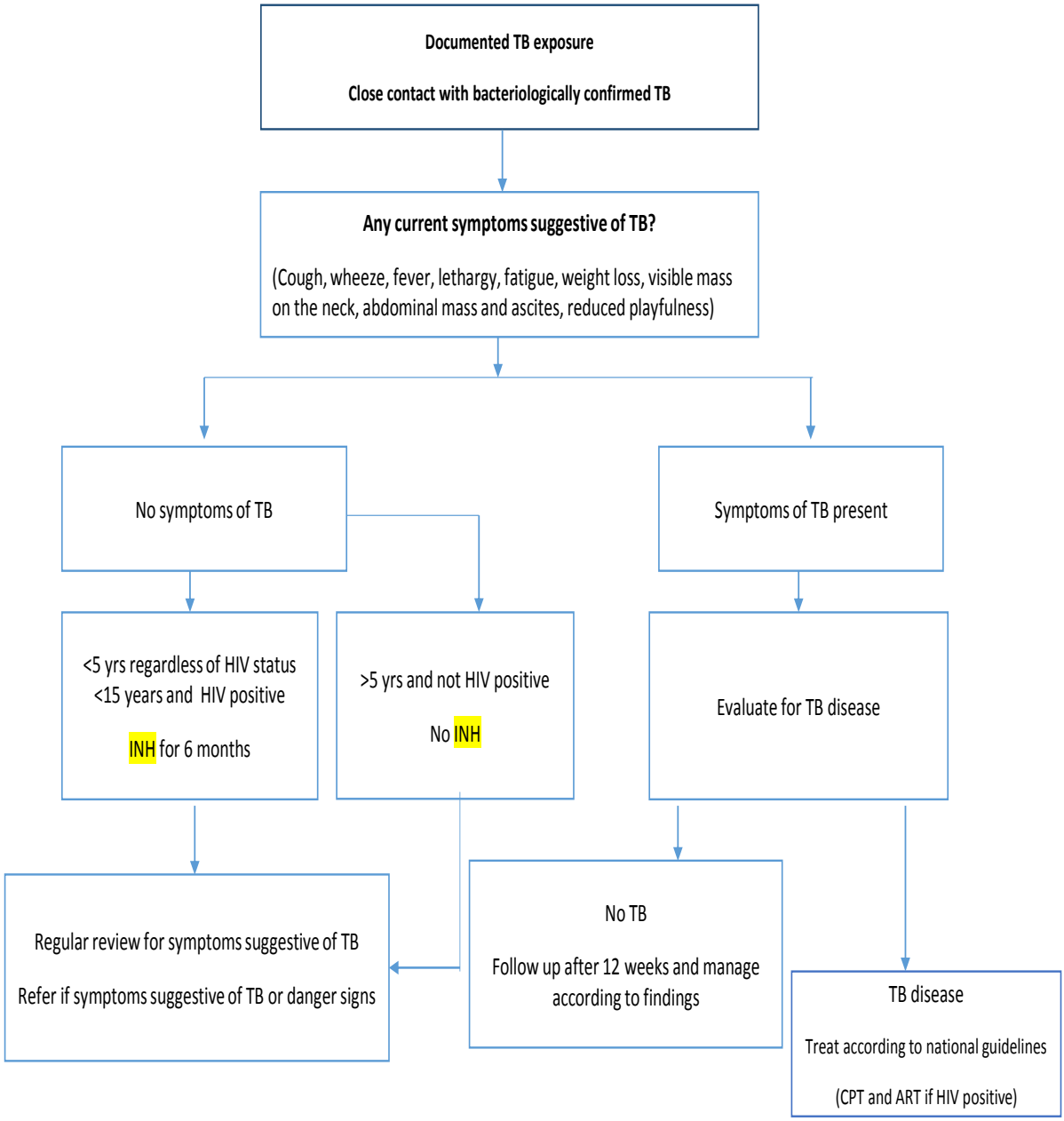
INH prophylaxis is indicated for all young children aged below 5 years that are household contacts of a case of bacteriologically confirmed TB and do not have any evidence of active TB.

- » Routine screening of exposed contacts does not always require CXR or TST. Symptom-based screening should be used to screen child contacts for TB.
- » INH should be administered at a recommended dose of 10 mg/kg for a full 6 months to be effective.
- » Follow-up should be carried out at least every 2 months until treatment is complete. If TB is suspected at initial assessment or at 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.

Key Message

Source case investigations should be conducted on other members of the household whenever a child is diagnosed with TB.

Figure 17: Contact tracing algorithm for children with exposure to TB patient



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

Chapter 8 Tuberculosis and HIV

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 people living with HIV (PLHIV) attending a clinic for antiretroviral therapy (ART) or prevention of mother-to-child transmission of HIV (PMTCT) should be screened for TB at every visit.
- Presumptive TB patients should be further investigated and registered in presumptive TB register.
- All PLHIV diagnosed with TB should be started on TB treatment.
- Isoniazid preventive therapy (IPT) 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 counselling and testing.
- All those found HIV positive should be initiated on ART and cotrimoxazole preventive therapy (CPT).
- All TB patients should be offered HIV prevention interventions.
- All patients that were already on ART should have CD4 and viral load (VL) testing to rule out ART failure.

Diagnosis and management of co-infected TB and HIV patients

- Diagnosis of TB includes clinical, bacteriological, and radiological testing to diagnose active TB.
- Bacteriological tests include smear microscopy, Xpert MTB/RIF, line probe assay (LPA), and culture.
- Lateral flow urine lipoarabinomannan assay (LF-LAM) can be used for patients with CD4 counts of less than 100 cells/ml or in critically ill PLHIV with unknown CD4 status.

TB diagnosis in HIV-positive patients can be challenging

- TB is more difficult to confirm bacteriologically in PLHIV due to paucibacillary disease.
- PLHIV may have atypical presentations of PTB and more frequently have EPTB.
- Radiological findings for PLHIV can be normal or atypical.
- Concomitants HIV/oportunitsic infections 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. For example:

- Nontuberculous mycobacteria (NTM) infection
- Pneumocystis jiroveci pneumonia (PCP/PJP)
- Pulmonary Kaposi's sarcoma
- Lymphoma
- Fungal pneumonia
- Suppurative pneumonia
- Herpes simplex or cytomegalovirus (CMV) pneumonitis
- In HIV-infected children: lymphoid interstitial pneumonitis (LIP)

Management of TB/HIV co-infected patients

All TB patients with HIV should start ART regardless of the CD4 count. TB treatment should be initiated first, followed by ART as soon as the patient is able to tolerate anti-TB treatment—preferably within the first 2–3 weeks of TB treatment.

HIV-positive patients with profound immune suppression should receive ART within the first 2 weeks of initiating TB treatment. Modifications to the antiretroviral 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 NNRTIs (non-nucleoside reverse-transcriptase inhibitors) and protease inhibitors. Co-infected patients have increased risk of drug toxicity and TB IRIS. For ART regimens in TB patients, refer to the latest ART guidelines.

Key Messages

- Tuberculosis is the most common cause of morbidity and mortality in people living with HIV (PLHIV).
- PLHIV with latent TB infection have a considerably higher risk of rapid progression to TB disease.
- PLHIV have a 10% annual risk of developing TB disease compared to HIV non-infected individuals, who have a 5% to 10% lifetime risk.
- PLHIV have a higher risk of TB relapse.
- HIV-infected TB patients may present more frequently with extrapulmonary TB and smear-negative TB.
- Adverse drug reactions to anti-TB medications are more common in HIV-infected patients.
- TB increases HIV viral replication, leading to higher risk of progression to AIDS in individuals co-infected with HIV.
- Higher rates of mortality are seen in patients with multidrug-resistant tuberculosis (MDR-TB) and HIV.

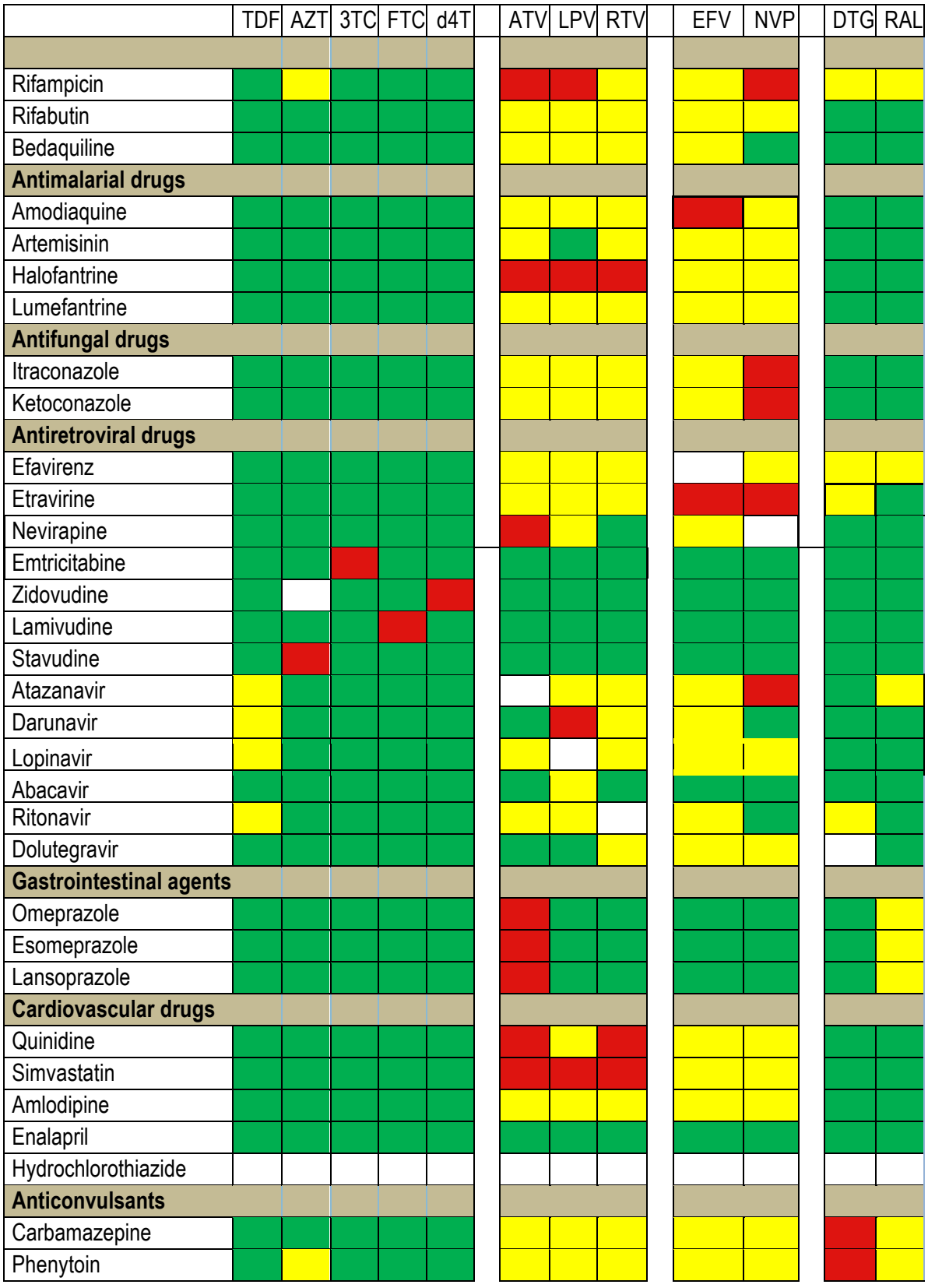
Table 24: TB/HIV co-infection case scenarios and recommended management for susceptible TB

Scenario	TB management	Recommended combined antiretroviral therapy (cART)
Pregnant, on cART, and develops TB	Start ATT immediately	Continue EFV-based cART Evaluate for failure and consider switching to second-line cART in consultation with next level
Pregnant, on ATT, and diagnosed with HIV	Continue ATT	Start cART immediately TDF + XTC + EFV If renal insufficiency, ABC + 3TC + EFV
Children 3 months to <3 years old with TB-HIV co-infection	Start ATT immediately	ABC + 3TC + EFV
Newly diagnosed TB and HIV co-infection TB retreatment case and HIV co-infection	Start ATT immediately	Start cART as soon as ATT is tolerated (usually within 2–3 weeks) regardless of CD4 count or WHO clinical stage TDF + XTC + EFV If renal insufficiency, ABC + 3TC + EFV
On cART and develops TB	Start ATT immediately	If NVP-based regimen, switch NVP to EFV and continue cART If on ATV-r, switch to LPV-r and double the dose; if on LPV-r, double the dose of LPV-r Evaluate for failure and consider switching to second-line cART, in consultation with next level
On ATT and diagnosed with HIV	Continue ATT	Start cART as soon as ATT is tolerated (usually within 2–3 weeks*), regardless of CD4 count or WHO clinical stage TDF + XTC + EFV If renal insufficiency, ABC + 3TC + EFV

On second-line cART with LPV-r and develops TB	Start ATT per guidelines immediately	Increase LPV-r from 2 tabs BD to 3 tabs BD for 2 weeks and then to 4 tabs BD for the remainder of TB treatment If can't tolerate LPV-r, then give rifabutin (in place of rifampicin), starting at 150 mg once daily
Patients on TB treatment should be initiated on EFV. Patients on cART on DTG who develop TB should be switched to EFV, while those on TAF should be switched to TDF. HIV-positive TB patients with profound immunosuppression (e.g. CD4 counts less than 50 cells/μL) should receive cART within the first 2 weeks of initiating TB treatment.		

Abbreviations: 3TC, lamivudine; ABC, abacavir; ATV-r, atazanavir/ritonavir; ATT, anti-tuberculosis treatment; BD, twice daily; cART, combined antiretroviral therapy; DTG, dolutegravir; EFV, efavirenz; LPV-r, lopinavir/ritonavir; NVP, nevirapine; TAF,tenofovir alafenamide]; TDF, tenofovir; WHO, World Health Organization; XTC, lamivudine or emtricitabine.

Table 25: Key drug–drug interactions for antiretroviral drugs



Abbreviations: 3TC, lamivudine; ATV, atazanavir; AZT, azidothymidine; d4T, stavudine; DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; LPV, lopinavir; NVP, nevirapine; RAL, raltegravir; RTV, ritonavir; TDF, tenofovir.

Identifying and managing immune reconstitution inflammatory syndrome (IRIS)

Patients with HIV-related TB may experience a temporary exacerbation of symptoms or radiographic manifestations of TB after beginning ART. The two types of IRIS associated with TB are paradoxical and unmasking.

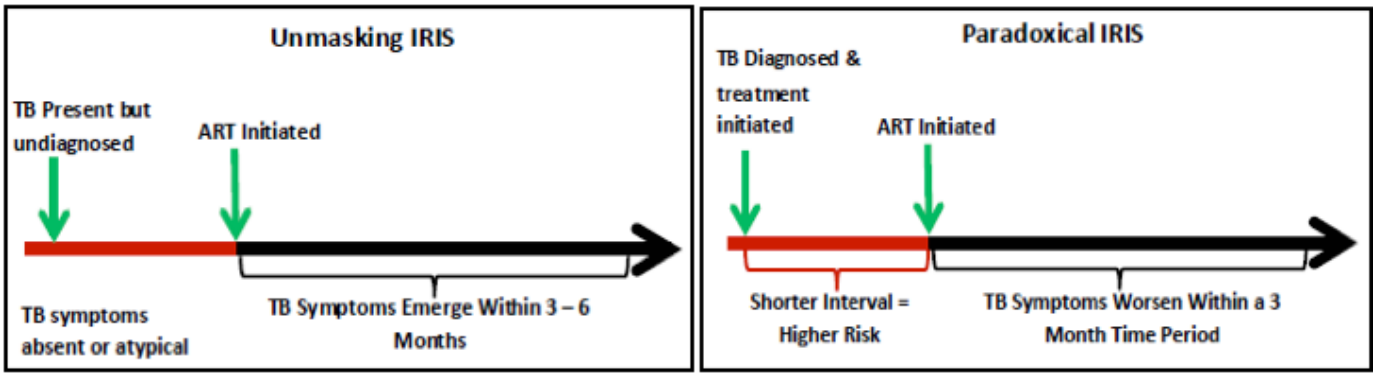
- » Paradoxical IRIS in HIV-infected patients with TB is thought to be a result of immune reconstitution. This occurs as a result of initiation of ART in a patient already on anti-TB drugs.
- » Unmasking IRIS occurs in patients that have undiagnosed TB disease, whose TB symptoms emerge after initiating ART.

Symptoms and signs of IRIS may include:

- » High fever
- » Lymphadenopathy
- » Expanding central nervous system lesions
- » Worsening of CXR findings

A thorough evaluation is necessary to exclude other causes, particularly DR-TB patients should continue TB treatment without change unless MDR-TB is diagnosed or drug-drug interactions are suspected. For unmasking IRIS, initiate TB treatment. Temporary interruption of ART may be recommended if life-threatening complications of IRIS develop. Administer prednisone (1–2 mg/kg) in patients with life threatening forms of TB like TB meningitis, or upper airway obstruction by TB lymph nodes, severe pleural effusion, or TB pericarditis.

Figure 18. Two types of immune reconstitution inflammatory syndrome (IRIS) associated with TB



Side effects shared by antiretroviral and anti-TB drugs

Table 26: Side effects shared by antiretroviral and anti-TB drugs

Side effects	Antiretroviral treatment	TB treatment
Nausea and vomiting	AZT, PIs	PZ, ethionamide, PAS
Hepatitis	NVP, EFV, PIs	RH, INH, PZ
Neuropsychiatric	EFV, DTG, RAL	INH, ethionamide, quinolones, cycloserine
Renal	TDF, RAL	Aminoglycosides, capreomycin, RH
Rash	NVP, EFV, ABC, RAL	RH, INH, PZ, EH, S

Abbreviations: ABC, abacavir; AZT, azidothymidine; DTG, dolutegravir; EFV, efavirenz; EH, [def]; FTC, emtricitabine; INH, isoniazid; LPV, lopinavir; NVP, nevirapine; PAS, para-aminosalicylic acid; PIs, [def]; PZ, [def]; RAL, raltegravir; RH, [def]; RTV, ritonavir; S, streptomycin; TDF, tenofovir.

Chapter 9 Contact Investigation

Contact investigation is a systematic process to identify persons (contacts) who were exposed to someone with infectious TB. Contact tracing aims to:

- Assess contacts for infection with M. tuberculosis and TB disease
- Provide contacts with treatment for latent TB infection or TB disease

Conducting contact investigations is a priority for the TB programme. It is important to remember that every TB patienth has a TB contact. The goal of TB contact investigation is to successfully stop TB transmission and prevent future cases.

Rationale for Contact Investigation

People who were 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. It is assumed that people exposed to a person with infectious TB might have been infected and are thus at increased risk for currently having TB or for development of the disease in the near future. 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).

Index Case Who Needs Contact Investigation

- Bacteriologically confirmed pulmonary tuberculosis
- Rifampicin-resistant (RR), multidrug-resistant (MDR), or extremely drug-resistant (XDR) TB proven or presumed
- Child less than 5 years of age (reverse contact investigation)

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 steps shown in the following figure. The actual sequence and timing of contact investigation steps and activities may vary from one investigation to another.

Figure 19: Systematic approach to TB contact investigation

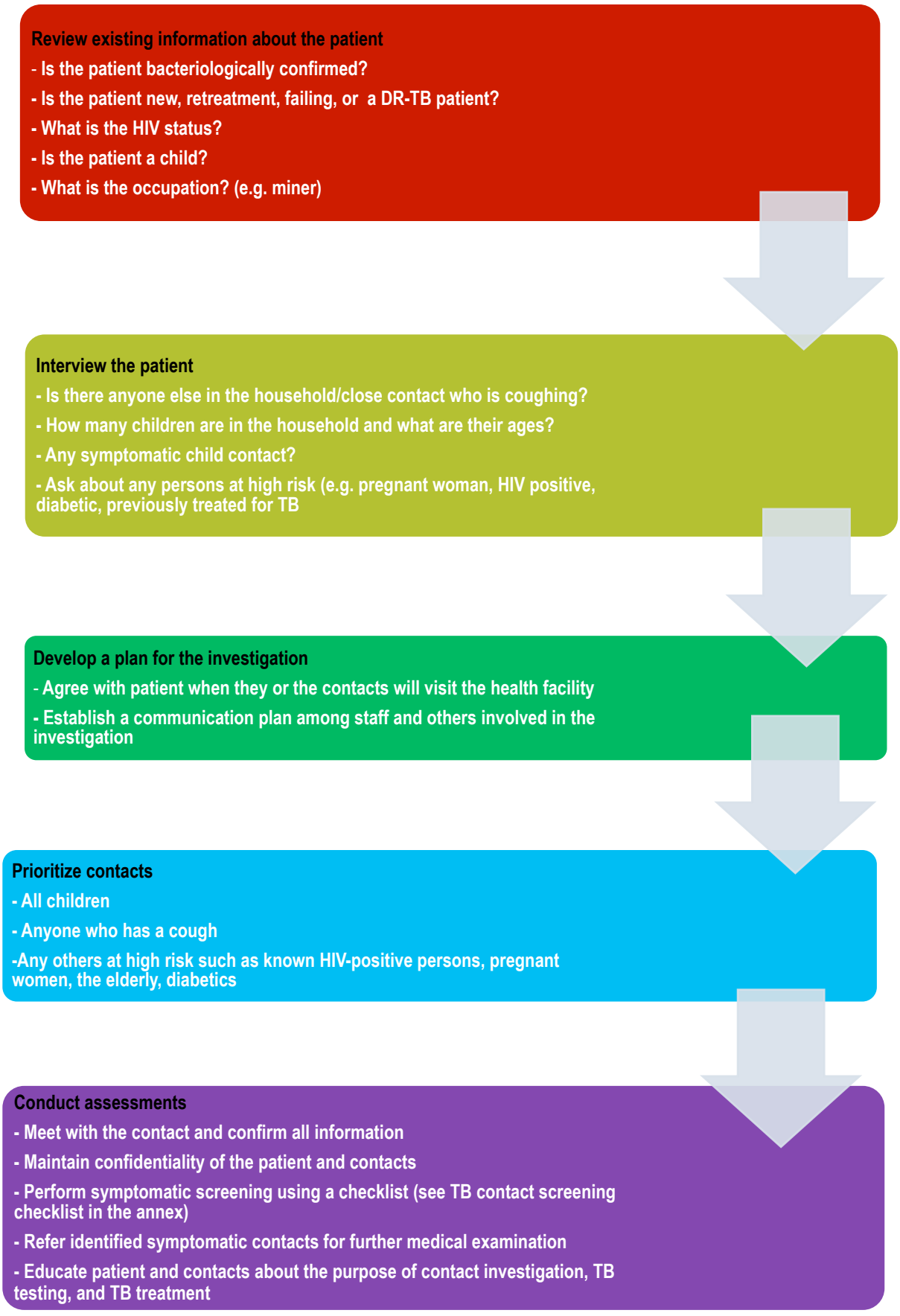
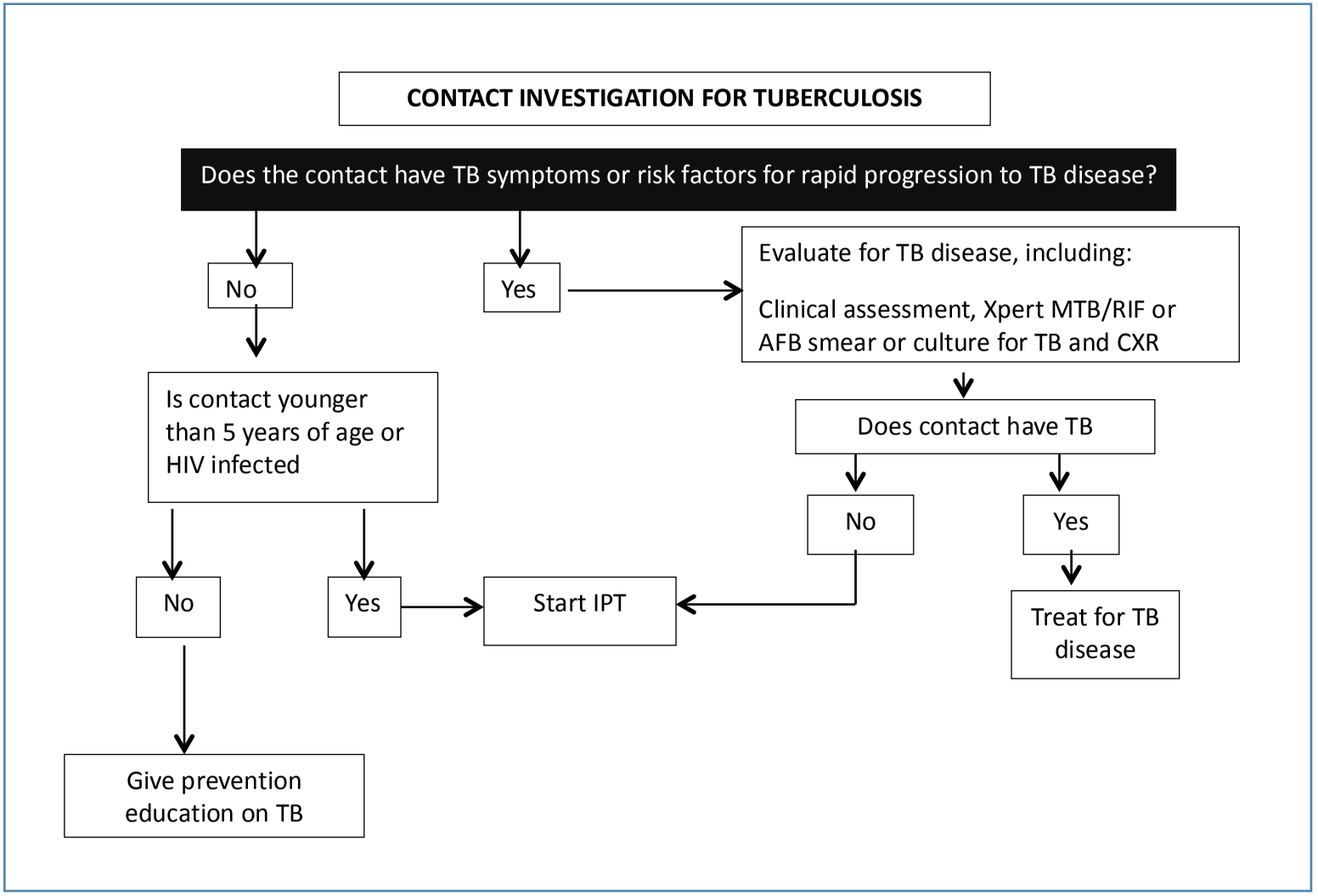


Figure 20: TB patient contact tracing flow chart



Abbreviations: AFB, acid-fast bacilli; CXR, chest x-ray; IPT, isoniazid preventive therapy.

Chapter 10 TB Infection Control Introduction

Introduction

Persons with undiagnosed TB are often seen in clinical care settings, including HIV care settings. The risk of patients and health care workers (HCWs) acquiring TB could be significantly reduced if governments, health authorities, and HCWs themselves would make infection control a high priority. TB infection control (TB IC) looks at how the transmission of tuberculosis can be prevented from one person to another. There are four levels of TB infection control:

- Managerial control measures
- Administrative control measures
- Environmental control measures
- Personal protective equipment (respiratory protection)

Managerial and Administrative control measures are the initial measures to consider when implementing TB IC, because environmental control measures and personal protective equipment (respiratory protection) will not work effectively in the absence of solid managerial and administrative control measures. Each level operates at a different point in the transmission process.

Managerial Control Measures

Managerial control measures are those that are used by program managers to support and facilitate the implementation, operation, maintenance, and evaluation of TB IC at the different levels which include the national, subnational, and facility levels. These measures aim to:

- Identify focal person
- Strengthen coordinating body
- Develop infection control plan (national, provincial, district, or facility)
- Assess facility, rethinking use of available spaces where necessary
- Conduct surveillance of TB disease among health workers
- Address advocacy, communication, and social mobilization (ACSM) for health workers, patients, and visitors
- Monitor and evaluate set of TB IC measures

Infection Control Plan

Each facility should have a written TB IC plan that will include outlining a protocol for the prompt recognition, separation, provision of services, investigation for TB, and referral of patients with presumed or confirmed TB disease. The TB IC focal person is responsible for ensuring the infection control procedures are implemented and should be a member of the health facility's infection control committee. Regardless of the size of the health facility, assessment of health care workers' risk of M. tuberculosis infection and assessment of the facility should be conducted as the first step in improving TB infection control.

Administrative Control Measures

Administrative controls serve as the first line of defense for preventing the spread of TB in health care settings, reducing the exposure of staff and patients to M. tuberculosis. It is important to have prompt recognition by triaging coughers as they enter the facility, separating coughers from others, fast-tracking them for care and the initiation of treatment, and referring individuals with potentially infectious TB disease. There are five components to good work practice and administrative controls:

- Promptly identify patients with TB symptoms by triage (triage means prioritizing patients to receive health services quickly in the facility).

» Separate TB patients from other patients where possible.
» Teach cough etiquette to all patients.
» In all departments, minimize time spent in the health facility.
» Provide a package of prevention and care for health workers, including HIV prevention and treatment.

Environmental Control Measures

When employed in conjunction with administrative control measures (e.g. prompt triage, separation, cough etiquette, diagnosis, and treatment of infectious TB patients), environmental control measures can be used effectively to reduce the concentration of infectious droplet nuclei to which HCWs, patients, or visitors may be exposed. Environmental control measures include the following:

» Ventilation (natural and mechanical)
» Filtration
» Ultraviolet germicidal irradiation (special ultraviolet light lamp that kills M. tuberculosis bacteria contained in droplets)

If feasible, it is advisable to maximize the use of natural ventilation before considering the other types of environmental controls. Ventilation for patient areas includes the following:

» Open all doors and windows to increase natural ventilation.
» Arrange for patient waiting areas with maximum natural ventilation and sunlight.
» Ensure that sitting arrangements in consultation rooms take advantage of natural airflow and thus minimize the exposure of HCWs (the wind should blow through the room from the HCW to the patient or across the HCW and patient in parallel).
» Ask patients to provide sputum specimens outside or in well-ventilated spaces away from others.

Key Message

Immunocompromised health care providers should be given opportunities to work in areas with a lower risk of exposure to TB.

» For new construction or any renovations, design for proper natural ventilation with the help of your works and supply department and environmental health officers.

Personal Protective Equipment (Respiratory Protection)

Respiratory protection (respirators) is generally the third line of defense for HCWs against nosocomial M. tuberculosis infection. Without appropriate administrative and environmental control measures, respirators alone will NOT adequately protect the HCWs from infection.

Respirators

» Respirators are a special type of mask that provide a high level of filtration and are closely fitted to the face to prevent leakage around the edges.
» Respirators are the preferred device to reduce the concentration of M. tuberculosis bacilli inhaled.
» Respirators are manufactured with at least 95% filter efficiency for particles of 0.3–0.4 micrometre in diameter.
» Respirators are recommended for use by HCWs, community health care workers, and close relatives of TB patients.
» Respirators are disposable but can be re-used for one month if they are properly stored. If the respirator is breached it must be disposed of.

Surgical or procedure masks

Surgical or procedure masks (cloth or paper) are a less-effective form of protective equipment and should be worn by potentially infectious TB patients.

- Masks prevent the spread of microorganisms from the wearer (potentially infectious TB patients) to others by capturing the large wet particles near the nose and mouth and limiting the distance aerosols are expelled when coughing, sneezing, and talking.
- Masks may be used to reduce aerosols generated from potentially infectious TB patients.
- Masks should be considered for presumptive and known infectious TB patients leaving isolation rooms for medically essential procedures or when a presumptive or known patient with TB disease is unable to use cough etiquette to protect others.

Key Message

A surgical or procedure mask worn by health care workers does not adequately protect them from inhalation of air contaminated with M. tuberculosis.

Chapter 11 Community Engagement in TB Care

Community members play an important role in addressing TB due to the fact that they are the ones who experience the lived reality of being affected by TB. Thus, community-based organizations, families, and networks have a vital role to play in the development of integrated and community-driven approaches to delivering health. Community services include the meaningful engagement of current and former TB patients as partners in care. Communities can help with TB awareness, case finding, supervising TB treatment, contact tracing and investigation, and monitoring and evaluation if provided with education, encouragement, and capacity-building activities.

Case Finding

Below are some ways that communities can be engaged in case-finding activities:

- Raise awareness on TB to generate demand for services through patient education and community sensitization through campaigns or house-to-house visits.
- Identify and refer presumptive TB patients.
- Help with contact-tracing of persons with infectious TB in their families and communities.
- Help with sputum collection and transportation of samples to testing facilities.
- Identify and participate in relevant TB/HIV operational research with guidance from the health centre and district levels.

TB Case Management

Communities can support case management through the following activities:

- Provide TB treatment adherence support, including establishment and empowerment of treatment support groups.
- Provide HIV counselling for TB patients.
- Conduct directly observe treatment (DOT).
- Inform the health worker in case of any problem.
- Provide health education to patients and networking with other patients and community members.
- Provide support to improve the health care delivery system (e.g. human resources, infrastructure, supply, TB infection control).
- Promote and use the Patients' Charter for Tuberculosis Care.
- Make sure that the patient goes for follow-up sputum examination as scheduled.
- Follow up with TB patients who miss doses.

Building Capacity

Community capacity-building activities include:

- Identify community members to be trained.
- Identify community-based TB areas which need capacity-building.
- Train community members.

Monitoring and Evaluation

Engagement of civil society organizations (CSOs) in delivery of community-based TB activities should be routinely monitored to inform their contribution to TB control and to ensure quality and effectiveness of their involvement.

- CSOs should ensure that planned activities are implemented in line with guidelines.
- CSOs should use existing standardized TB recording and reporting tools.
- CSOs should hold monthly TB/HIV meetings.
- CSOs should compile and submit reports on TB/HIV-related activities within the community to the health centre.
- CSOs should conduct joint supervision and training with NTLP.

Advocacy, Communication and Social Mobilization (ACSM) in TB Prevention, Care, and Support

Advocacy

Advocacy for TB is a broad set of coordinated interventions, designed to place TB high on the political and development agenda, foster political will, and increase and sustain financial and other resources.

Activities for advocacy include:

- Lobby for support from politicians and community and religious leaders
- Conduct press conferences and appear on radio and TV talk shows
- Publish articles in the newspapers
- Hold summits, conferences and symposia, and partnership meetings
- Use celebrity, high-level champions, and TB survivors as spokespersons
- Meet with government ministries and departments, CSOs, patient groups, and health care providers

Communication

The goal of communication is to create and improve awareness among the public about TB and the 'end TB' services available and to improve interpersonal communication between patients and HCWs. It also helps to reduce stigma around the disease.

Activities for communication include:

- Mass media campaigns—use of radio, TV, and print and online media as a distance-learning tool
- Interpersonal communication—peer education, traditional folk media, and nonconventional media in communities and schools and among HCWs
- Information, education, and communication (IEC) materials for mass distribution
- Target audiences include the general public, school-going youth, teachers, HCWs, and journalists

Social mobilization

This is the process of bringing together allies to raise awareness of and demand for TB control, to assist in the mobilization and delivery of resources and services, and to empower communities to participate and be self-reliant in TB control.

Refer to the community TB treatment supporters' manual for more details of community engagement.

Chapter 12 Monitoring and Evaluation

Introduction

Monitoring and evaluating the performance of the NTLP involves assessing activities, monitoring costs and expenditure, determining the extent of programme coverage, evaluating treatment outcomes, and determining the impact of the programme on the epidemiology of the disease in Zambia.

Definitions

Monitoring is the careful observation of programme activities to ascertain whether these activities are being accomplished as planned.

Evaluation is the periodic use of data collected in a systematic manner to assess process, outcome, and impact of the programme.

Purpose of monitoring and evaluation of the NTP:

- Ensure that training, supervision, logistics, and communication activities are being carried out effectively at each level—from the national level to the primary health-care level
- Ensure that data needed to assess case notification rates and treatment outcomes are collected, analysed, and sent to the central unit by all health facilities
- Help identify technical and operational problems and determine the reasons for the problems, which will enable management to take the necessary corrective actions
- Provide evidence which enables staff to improve standards of practice in patient care and support

Programme monitoring involves:

- Keeping good records in the "monitoring tools"
- Reviewing and updating the records regularly
- Compiling data and analysing key indicators related to TB case detection, treatment, and other activities of the TB programme
- Carrying out supportive supervision

The tools used to record and report data in the NTP are:

- Request for bacteriological examination for TB form
- Request and reporting form for TB culture and DST
- TB laboratory register
- TB treatment card
- TB ID card
- TB treatment register
- Presumptive TB register
- TB referral/transfer form (health facility and community)
- Quarterly reporting forms
- Facility report and request for drugs (FRRD)
- Contact investigation register
- Isoniazid preventive therapy (IPT) register
- Death review forms
- Community presumptive / contact tracing TB register
- Drug resistant (DR) TB register
- DR treatment cards

Recording and reporting (R&R)

The data used for monitoring and evaluation (M&E) of the NTP comes from the routine recording and reporting from all levels of the health service. R&R of TB cases is an essential part of the End TB strategy. TB is a notifiable disease according to the Public Health Act. The purpose of recording and reporting is to:

- Provide relevant information for the planning, management, policy formulation, and assessment of overall program performance.
- Maintain accurate records for each patient.
- Update registers and produce regular reports of data to the central unit. This is essential for the proper management of the TB program at all levels.

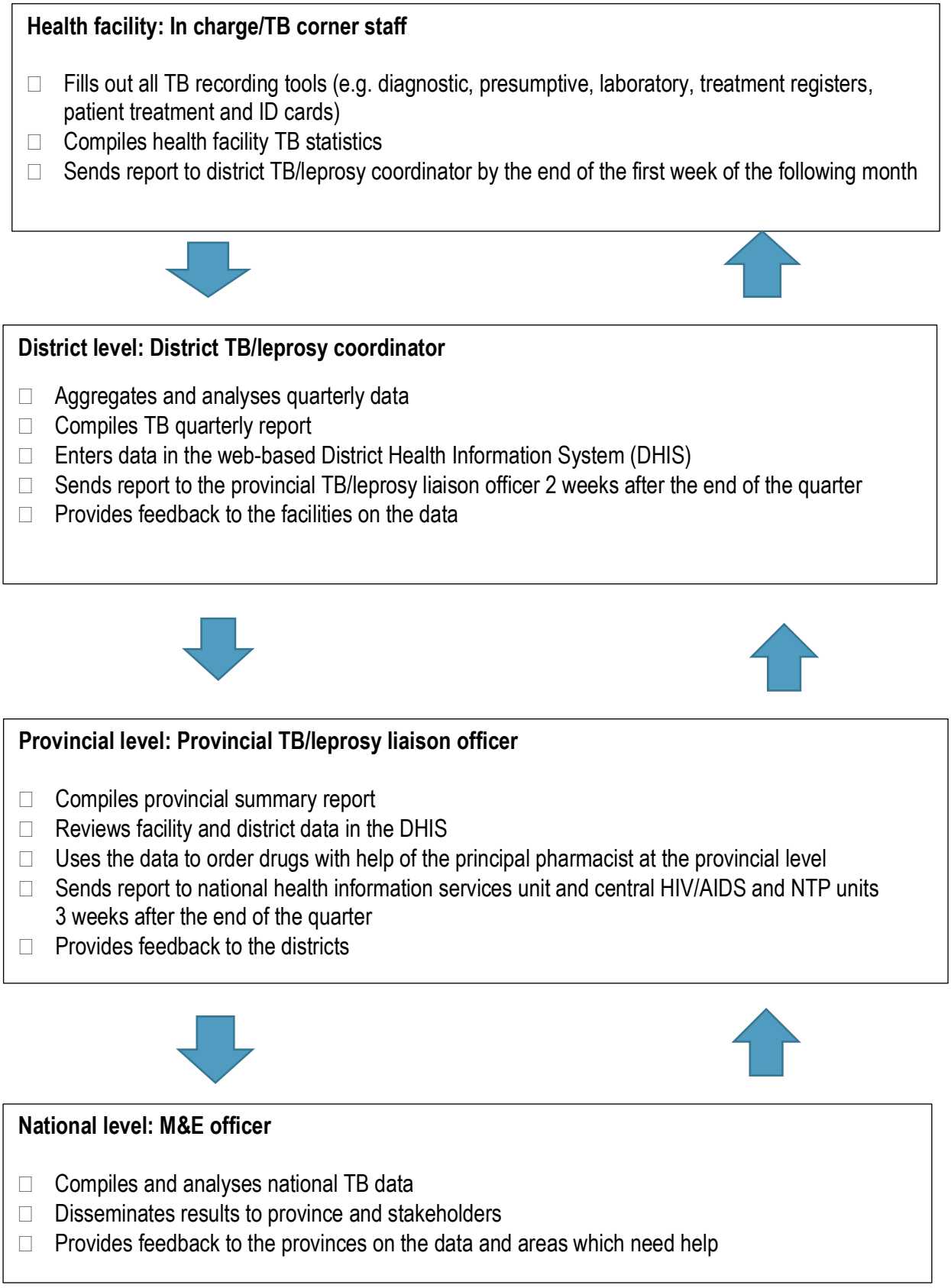
Table 27: The use of NTP data at each level of the health care system in Zambia

Health facility	The data should be used for evaluation of case detection and case management. The data are used to calculate the case detection rate and compare to the set targets for the facility. The data should also be used to rapidly assess programme performance at the facility. Individual patients who are not doing well (e.g. those interrupting treatment, whose sputum is not converted to negative after 2 months of intensive phase, or who have poor weight gain) should be identified and helped to make satisfactory progress.
District	The data are used for planning and distribution of resources, comparisons between health facilities, early detection of problematic areas, provision of feedback, and remedying problems in the district.
Provincial	The data are used for comparisons between districts, allocation of resources to districts, early detection of problem districts, and the provision of feedback and help to improve performance.
National	The data are used for resource mobilization, international reporting requirements, general TB policy formulation, and advocacy for political commitment to the program.

Data flow and transmission

Data are generated from the health facilities, transmitted to district, provincial, and national levels, and then disseminated downwards and internationally according to agreed timelines.

Figure 21: TB Data flow (from the source to the national level) and reporting periods



Analysis of treatment outcomes

A cohort is a group of patients diagnosed and registered for treatment during a specific time period.

- » Analysis allows the identification of problems, so that appropriate action is taken to overcome them and improve programme performance.
- » Analysis also involves comparing results achieved from one quarter to another.
- » Each health facility TB focal point needs to analyse its own TB data and utilise it at local level. Evaluation of treatment outcome in bacteriologically confirmed patients is a major indicator of programme quality.
- » Treatment outcome in other patients (clinically diagnosed, extra pulmonary TB) should be analysed in separate cohorts.
- » Evaluation of the results of treatment and trends must be done at peripheral, district, provincial, and national levels.
- » The district TB coordinator should analyse notification and treatment outcome indicators regularly (every 3 months and at the end of every year).
- » The district health director, the public health specialist, and the provincial TB liaison officer should verify that the compiled district reports are correct and complete before submitting the data to the next level.

Indicators measured to monitor TB programme performance

1. Input indicators: human resources, equipment, finances, and other material resources.
2. Process indicators: training of staff, procurement of equipment, and production of reports.
3. Output indicators: availability of services (such as laboratory services to perform microscopy, culture, and drug sensitivity testing).
4. Outcome indicators: case detection rates, treatment outcome rates, etc.
5. Impact indicators: prevalence and incidence.

Table 28: Main national TB programme (NTP) indicators

Outcome and impact indicators for global reporting	Key outcome indicators for national reporting
1. TB case detection rate (CDR) 2. Prevalence 3. Incidence 4. Treatment success 5. HIV sero-prevalence among TB patients	» Proportion of TB cases who are identified through contact investigation among all the notified TB cases » Proportion of patients with presumptive TB who are assessed for TB through care providers practicing within the NTP network » Proportion of patients with presumptive TB who are assessed for TB through care providers practicing outside the NTP network » Number of presumptive TB patients whose sputum was examined » Number of presumptive TB patients examined who were bacteriologically confirmed » Number of TB patients notified (drug-susceptible and drug-resistant TB) » Proportion of notified TB cases who were detected through care providers practicing within the NTP network » Proportion of notified TB cases who were detected through care providers practicing outside the NTP network » Number of TB patients who were bacteriologically confirmed » Number of TB patients tested for HIV, those HIV positive, and those commenced on antiretroviral therapy (ART) and cotrimoxazole preventive therapy (CPT) » Proportion of bacteriologically confirmed TB patients who were cured, completed treatment, died, treatment failure, lost to follow-up, and not evaluated » New pulmonary TB cases with no laboratory result » Retreatment cases » Number of bacteriologically confirmed, clinically diagnosed, or extra pulmonary TB that: » Were cured » Completed treatment » Were lost to follow-up » Died » Were not evaluated » Had treatment failure » Sputum conversion rate at the end of the initial phase of treatment

Chapter 13 Mycobacteria Other Than Tuberculosis

Mycobacteria other than those comprising the M. tuberculosis complex are called nontuberculous mycobacteria (NTM) or mycobacteria other than tuberculosis (MOTT).

The organisms are commonly referred to as MOTT and the laboratories use this term when reporting them from culture results. These ubiquitous environmental organisms, usually found in water and soil, have emerged as important opportunistic pathogens of human beings in recent years. They may cause human disease, but they do not cause tuberculosis and are not transmitted from one person to another.

These mycobacteria may cause pulmonary disease resembling TB and most commonly affect people with an underlying lung disease, such as chronic obstructive pulmonary disease (COPD), bronchiectasis, cystic fibrosis, primary ciliary dyskinesia, and alpha-1-antitrypsin disease, but individuals with no prior history of lung disease can also be affected. MOTT can also affect other organs.

It is important to note that infection with MOTT also may produce AFB-positive sputum smear results and positive Mantoux skin test readings mimicking M. tuberculosis. Culture and Xpert MTB/RIF tests can distinguish between M. tuberculosis and MOTT.

Diagnosis of MOTT

If a laboratory result reports MOTT for a patient, a second sample should be collected and sent for culture. A patient is said to have MOTT when two consecutive cultures are reported as MOTT. Once confirmed, a third sample should be collected for speciation. LPA (Hain Life science company) – has two kits for identification of MOTT, which are GenoType Mycobacterium CM (common mycobacterium) and GenoType Mycobacterium AS (additional species of mycobacterium). GenoType Mycobacterium CM identifies 15 common MOTTs and GenoType Mycobacterium AS identifies 16 additional species of MOTT.

Treatment of MOTT

The most common MOTTs that may require treatment are M. avium complex, M. kansasii, M. abscessus, M. chelonae, M. fortuitum, M. terrae, M. xenopi, and M. simiae.

Treatment of MOTT is complex. Disease due to MOTT is usually unresponsive to first-line anti-TB drugs; a few species respond to some second-line drugs.

There is a common misperception that MOTT are a type of MDR-TB. This is clearly not the case, as the organisms causing MOTT are from a different species and require different treatment regimens from those used for MDR-TB. Treatment for MOTT is empirical and based on information from studies. Therefore, all patients with confirmed MOTT should be referred to physicians.

Table 29: Major clinical syndromes associated with nontuberculous mycobacteria infections

Syndrome	Common causes	Less common causes
Pulmonary disease (especially in adults)	Mycobacterium avium-intracellulare, M. kansasii, M. abscessus	Uncommon: M. fortuitum, M. malmoense, M. szulgai, M. scrofulaceum, M. smegmatis, M. simiae, M. xenopi Rare: M. celatum, M. asiaticum, M. shimodei
Cervical and lymphadenitis (especially children)	M. avium-intracellulare	M. scrofulaceum, M. malmoense, M. abscessus, M. fortuitum
Skin and soft tissue disease	M. fortuitum, M. chelonae, M. abscessus, M. marinum	M. haemophilum, M. kansasii, M. smegmatis, M. ulcerans
Skeletal (bones, joints, tendons) disease	M. marinum, M. avium complex, M. kansasii, M. fortuitum group, M. abscessus, M. chelonae	M. haemophilum, M. scrofulaceum, M. smegmatis, M. terrae-nonchromogenicum complex
Catheter-related infections	M. fortuitum, M. abscessus, M. chelonae	M. mucogenicum
Disseminated infection	HIV-seropositive host: M. avium, M. kansasii	M. haemophilum, M. genavense, M. xenopi, M. marinum, M. simiae, M. intracellulare, M. scrofulaceum, M. fortuitum
HIV-seronegative host	M. abscessus, M. chelonae	M. marinum, M. kansasii, M. haemophilum, M. fortuitum

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Annexes

Annex 1: Collection of sputum specimens from presumptive TB patients

Before collecting any sputum	• Explain to the patient the reason for sputum collection and technique. • Fill the laboratory request form as completely as possible, including traceable address and telephone number. • Write the patient's name on the side and not on the lid of the sputum container. • One specimen should be collected and sent for Xpert MTB/RIF. • If Xpert MTB/RIF is not available, two specimens should be collected and sent for direct microscopy. • Spot specimen is collected from the patient at the time of request (if two specimens, collect at least 15 minutes apart).
Technique for collecting sputum	General rules • A specimen collected under the supervision of a member of the health staff is likely to be better than a specimen collected without supervision. • Sputum collection should take place in a well-ventilated area or outside the room. • Explain to the patient that saliva is not the same as sputum and that it is sputum which is needed. • Patients who have had some food shortly before sputum collection should rinse their mouths with water first.
How to collect a sputum specimen	• Ask the patient to cough deeply (demonstration is usually more effective than words). • Simple deep breathing techniques (at least three deep slow breaths in and out) or walking around/exercising can improve sputum production. • Avoid contaminating the outside of the sputum container with sputum. If the outside is contaminated, discard the container and repeat the collection with a fresh container. • If the specimen is not suitable (e.g. if the quantity is insufficient or if it contains saliva), ask the patient to repeat the coughing until a sufficient amount of sputum has been obtained (3 to 5 ml).
After collecting the sputum specimen	• The health worker should check the quality and adequacy of the sputum. • Ensure that the lid on the container is closed firmly. • Ensure that the patient's details are clearly written on the container (NOT on the lid), and then wash your hands with soap and water. • Store the sputum specimens in a cool and dark place, such as a cupboard or refrigerator, that can be locked and which is used solely for this purpose. • Send the specimens to the laboratory as soon as possible (within 48 hours after collection). • Accompany each specimen with a properly completed laboratory request form.

Annex 2: Other procedures for specimen collection

Gastric lavage	• Gastric lavage is indicated in children younger than 5 years or in older children if unable to produce sputum. • Ensure that the child has been fasting for at least 3–4 hours. • Explain the procedure to the patient or caregiver. • Prepare an NG tube, completely fill in laboratory forms, and completely label specimen container. • Get KY jelly or water. • Measure the distance of the tubing from the tip of the nose to the ear lobe to the xiphoid process (mouth of the stomach). • Mark the distance on the tube with strapping. • Place the patient in a head-down, left side-lying position to reduce the risk of aspiration if the patient vomits. • Apply a water-soluble lubricant (KY jelly) or water to the first 4 inches of the distal end of the tube. • Insert the tube in one of the nostrils. • Slowly push in the NG tube while blocking the entry of free air until you reach the designated mark/strapping. • Use a syringe to aspirate the specimen (specimen should be fluid). Collect a minimum of 2 ml of the specimen. • Put it in the specimen containers. • Send specimen to laboratory for examination. • Note: Ensure that the tube is in the stomach and not the trachea. Signs of being in the trachea include coughing, bleeding (blood during aspiration), and suffocating.
Induced sputum Intubation	• Examine children in advance to ensure they are well enough to undergo the procedure. • Children with the following characteristics should not undergo sputum induction: • Inadequate fasting: If a child has not been fasting for at least 3 hours, postpone the procedure until the appropriate time. • Severe respiratory distress (including rapid breathing, wheezing, hypoxia). • Bleeding: Low platelet count, bleeding tendency, severe nosebleeds (symptomatic or platelet count <50/ml blood). • Reduced level of consciousness. • History of significant asthma (diagnosed and treated by a clinician).

	Procedure 1. Administer a bronchodilator (e.g. salbutamol) to reduce the risk of wheezing. 2. Administer nebulized hypertonic saline (3% NaCl) for 15 minutes or until 5 ml of solution have been fully administered. Terminate the nebulization if the patient develops any side effects or if no sputum is produced after 20 minutes of nebulization. 3. Carry out chest physiotherapy if necessary; this is useful to mobilize secretions. 4. For older children who are able to expectorate, follow procedures as described under sputum collection. 5. For children who are unable to expectorate (e.g. young children), carry out suction of the nasal passages to remove nasal secretions or nasopharyngeal aspiration to collect a suitable specimen. Any equipment that will be reused must be disinfected and sterilized before use for a subsequent patient. Remember: • Label the containers (not the lids) before collecting the sputum samples. • Collect sputum in a well-ventilated area, preferably outdoors. • Check whether the sample contains sufficient sputum, not just saliva. If not, ask the presumptive TB patient to add more. • After collecting the sputum, be sure that the lid is closed tightly. • Wash your hands thoroughly with soap and water.
Nasopharyngeal aspiration	• The child's nose is cleaned with saline drops and cotton wool. If old enough, the child can be asked to blow the nose into a tissue. If the nasal mucus is too thick to be removed with the measures above, it can be suctioned prior to nasopharyngeal aspiration (NPA). A soft catheter size F6/7 is used for suctioning and is discarded immediately afterwards. • One drop of oxymetazoline may be instilled into each nostril to prevent nose bleeds. • Two drops of sterile saline are instilled into each nostril. • The length of the cannula used for aspirating the NPA sample is measured as the distance from the nostril to the tragus of the ear; then the posterior nasopharynx is suctioned using a soft plastic cannula connected to a mucus trap. • Suctioning is activated only when the tip of the cannula is in the posterior nasopharynx. When the cannula is passed through the nostrils (during introduction and extraction), the suction is de-activated. • Transfer full volume of sample into a sterile container. • Clean the exterior of container with alcohol swabs. • Label sample: sample type and number, date, time, total sample volume. • Place specimen in sample bag, seal, and put into a cold box for transport to the laboratory.
Bronchoscopy	• Bronchoscopy is an endoscopic procedure that allows visualisation of the inside of the airways for diagnostic or therapeutic purposes. • Specimens can be collected during bronchoscopy, bronchioalveolar lavage (BAL), and/or biopsy. • Bronchoscopy should be done only by qualified personnel in level 2/3 facilities. • Bronchoscopy should be done in well-ventilated rooms. • Personal protective equipment (N95 respirators) should be used by all attending staff.

Annex 3: Transport of sputum specimens

- Sputum specimens must be suitably packed and sent by any means available to the microscopy/ Xpert MTB/RIF centre together with the request form for sputum examination.
- Every staff member in every health unit should be responsible for seeing that specimens are sent to the laboratory as soon as possible.
- This is particularly important for specimens for culture since viability suffers rapidly if transit time is prolonged (preferably send within 48 hours).
- Samples must be stored at 2°C to 8°C for maximum of 5 days or at room temperature for a maximum of 3 days if testing cannot be done on the same day.
- The results of sputum testing can be improved by collecting a quality sample.
- Clear saliva is not suitable, though if a better specimen cannot be produced, it should be sent anyway and the lab personnel should not reject the sample but should document the quality of it.

Key Message

- The results of sputum testing can be improved by collecting a quality sample.
- Clear saliva is not suitable, though if a better specimen cannot be produced, it should be sent anyway and the lab personnel should not reject the sample but should document the quality of it.

Disclaimer

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