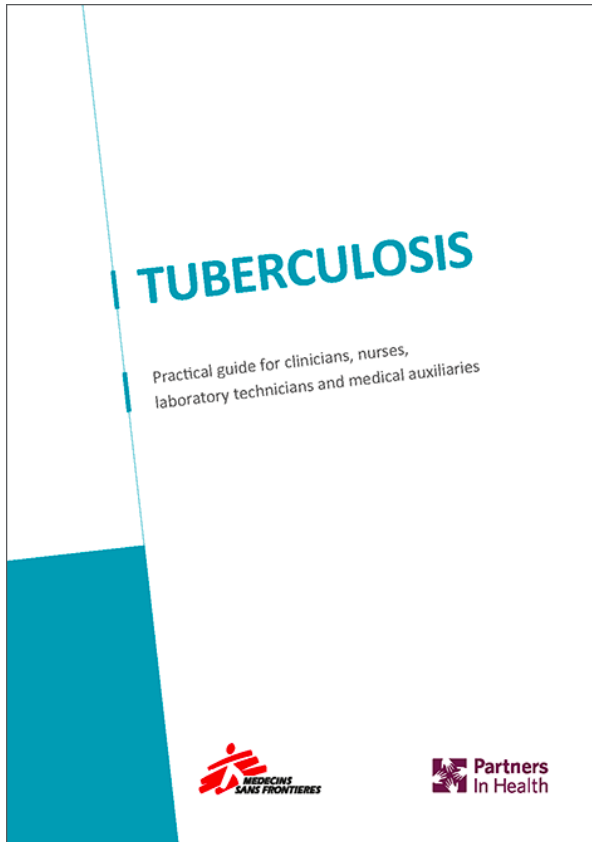


# Tuberculosis

Practical guide for clinicians, nurses, laboratory technicians and medical auxiliaries



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# Table of contents

[Authors/Contributors](#)

[Introduction](#)

[Abbreviations and acronyms](#)

[Chapter 1: Introduction and epidemiology](#)

[Chapter 2: Clinical presentation](#)

[Chapter 3: Diagnosis and follow-up investigations](#)

[Chapter 4: Diagnosis of active tuberculosis in children](#)

[Chapter 5: Diagnostic algorithms for pulmonary tuberculosis \(PTB\) in adults and adolescents](#)

[Chapter 6: Screening for active tuberculosis](#)

[Chapter 7: Case definitions for registration](#)

[Chapter 8: Tuberculosis drugs and treatment regimens](#)

[Chapter 9: Treatment of drug-susceptible tuberculosis](#)

[Chapter 10: Treatment of multidrug-resistant and rifampicin-resistant tuberculosis](#)

[Chapter 11: Treatment of rifampicin-susceptible and isoniazid-resistant tuberculosis](#)

[Chapter 12: Tuberculosis and HIV co-infection](#)

[Chapter 13: Adherence to tuberculosis treatment](#)

[Chapter 14: Infection prevention and control](#)

[Chapter 15: Follow-up of staff exposed to tuberculosis](#)

[Chapter 16: Treatment of latent tuberculosis infection](#)

[Chapter 17: Monitoring and evaluation](#)

[Appendices](#)

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# Introduction

Update: January 2014

Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis*. Tuberculosis typically attacks the lungs, but can also affect other parts of the body. The disease has become rare in high income countries, but is still a major public health problem in low- and middle-income countries.

It is estimated that between the years 2000 and 2010, eight to nine million new cases emerged each year. Approximately 1.5 million people die from the disease each year. In adults, tuberculosis is the second leading cause of death due to an infectious disease (after AIDS), with 95% of deaths occurring in low-income countries. Tuberculosis is a major problem of children in poor countries where it kills over 100,000 children each year.

The treatment of tuberculosis remains a constraint for patients and a heavy burden for the healthcare system. Drug-susceptible tuberculosis requires at least six months of therapy under close supervision. A treatment for multidrug-resistant tuberculosis requires nearly two years of treatment with poorly tolerated and less effective drugs. In most places the diagnosis still relies mainly on direct microscopy that is unable to detect a large proportion of patients. The BCG vaccine, developed almost a century ago, confers only partial protection.

After 40 years of minimal progress in the tools to fight tuberculosis there are some reasons for hope. A few new drugs are reaching the final phase of development; a new molecular test that can be decentralized to some extent and allows the rapid diagnosis of tuberculosis and of resistance to rifampicin has been introduced. Though this is undeniable progress, much will be needed to bring the new tools and drugs to the patients in need. Furthermore, a true “point of care” diagnostic test still does not exist and little progress has been made in research for a more effective vaccine.

Case management of patients does not necessarily have to involve a major, vertical programme. It should be incorporated into the framework of other medical activities in order to offer comprehensive and integrated treatment even if the number of patients being treated is relatively small.

This guide has been developed jointly by Médecins Sans Frontières and Partners In Health. It aims at providing useful information to the clinicians and health staff for the comprehensive management of tuberculosis. Forms of susceptible and resistant tuberculosis, tuberculosis in children, and HIV co-infection are all fully addressed.

As treatment protocols are constantly changing, medical staff are encouraged to check this website for [updates](#).

# Abbreviations and acronyms

Update: February 2024

ACH	air change per hour
AFB	acid-fast bacilli
ALT	alanine aminotransferase
Am	amikacin
Amx/Civ	amoxicillin/clavulanic acid
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
BCG	bacillus Calmette-Guérin
Bdq	bedaquiline
BPNS	brief peripheral neuropathy screen
BSC	biosafety cabinet
CDC	Centers for Disease Control and Prevention
Cfz	clofazimine
CMX	cotrimoxazole
CNS	central nervous system
CPC	cetylpyridinium chloride
CPT	cotrimoxazole preventive therapy
CrCl	creatinine clearance
Cs	cycloserine
CSF	cerebrospinal fluid
CXR	chest x-ray
Dim	delamanid
DOT	directly observed therapy
DR	drug resistance
DR-TB	drug-resistant tuberculosis
DS-TB	drug-susceptible tuberculosis
DST	drug susceptibility test
E	ethambutol
ECG	electrocardiogram
e.g.	for example
EPTB	extrapulmonary tuberculosis

Eto	ethionamide
FDC	fixed-dose combination
FNA	fine needle aspiration
FQ(s)	fluoroquinolone(s)
gDST	genotypic drug susceptibility test
GUV	germicide ultraviolet
H	isoniazid (standard dose)
HbA1c	glycated haemoglobin
HEPA	high efficiency particulate air
H <sup>h</sup>	isoniazid (high dose)
HIV	human immunodeficiency virus
HPF	high-power field
Hr	isoniazid resistance
Hr-TB	isoniazid resistant tuberculosis
i.e.	that is
IGRA	interferon gamma release assay
IM	intramuscular
Imp/Cln	imipenem/cilastatin
INH	isoniazid
INI	integrase inhibitor
IPC	infection prevention and control
IRIS	immune reconstitution inflammatory syndrome
IV	intravenous
LF-LAM	lateral flow urine lipoarabinomannan assay
LFT	liver function test
Lfx	levofloxacin
LPA	line probe assay
LTBI	latent tuberculosis infection
LTR	long treatment regimen
Lzd	linezolid
MDR	multidrug resistance
MDR-TB	multidrug-resistant tuberculosis

Mfx	moxifloxacin (standard dose)
Mfx <sup>h</sup>	moxifloxacin (high dose)
Mpm	meropenem
MSF	Médecins Sans Frontières
MTB	<i>Mycobacterium tuberculosis</i>
NAAT	nucleic acid amplification test
NGS	next generation sequencing
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
P	rifapentine
Pa	pretomanid
PAS	para-aminosalicylic acid
PCP	pneumocystosis
PCR	polymerase chain reaction
pDST	phenotypic drug susceptibility test
PI	protease inhibitor
PIH	Partners In Health
PO	orally (per os)
PTB	pulmonary tuberculosis
Pto	prothionamide
R	rifampicin
Rfb	rifabutin
RIF (or Rif)	rifampicin
RMT	rapid molecular test
RR	rifampicin resistance
S	streptomycin
SAT	self-administered treatment
STR	short treatment regimen
TB	tuberculosis
tNGS	targeted next generation sequencing
Trd	terizidone
TSH	thyroid-stimulating hormone



TST	tuberculin skin test
ULN	upper limit of normal
VOT	video-observed therapy
VVS	ventilated workstation
WGS	whole genome sequencing
WHO	World Health Organization
XDR	extensive drug resistance
XDR-TB	extensively drug-resistant tuberculosis
Z	pyrazinamide

# Chapter 1: Introduction and epidemiology

[1.1 Characteristics of Mycobacterium tuberculosis bacillus](#)

[1.2 Transmission](#)

[1.3 Evolution of tuberculosis infection and disease in humans](#)

[1.4 Prognosis](#)

[1.5 Factors modifying tuberculosis epidemiology](#)

[1.6 Epidemiological indicators](#)

[1.7 Global burden of tuberculosis](#)

Update: January 2024

# 1.1 Characteristics of *Mycobacterium tuberculosis* bacillus

*Mycobacterium tuberculosis* (variant tuberculosis), along with other variants (e.g. bovis, africanum, microti), make up the *Mycobacterium tuberculosis* complex, a group of bacteria that cause clinical tuberculosis (TB) in humans<sup>[1]</sup>.

Most TB cases are caused by *M. tuberculosis* variant tuberculosis. Cases due to other variants are less prevalent.

*M. tuberculosis* is a small, rod-shaped, strictly aerobic, acid-fast bacillus<sup>a</sup>. Like other mycobacteria, it is slow growing, resulting in a slower development of disease when compared with other bacterial infections.

## Footnotes

(a) Acid-fast bacilli are bacilli, which once stained, resist discoloration by acid and alcohol.

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# 1.2 Transmission

*M. tuberculosis* is mainly transmitted from human-to-human and spread is mainly airborne. The source of infection is usually a person with pulmonary TB (PTB) or laryngeal TB. During coughing, speaking, or sneezing, the person produces tiny infectious droplets. These particles, called droplet nuclei, are about 1 to 5 microns in diameter. They can remain suspended in the air for several hours.

Transmission may occur when these infectious droplets are inhaled. UV light (sunshine or artificial sources) and ventilation reduce the risk of transmission ([Chapter 14](#)).

Other modes of transmission are far less common. Inoculation of cutaneous or mucous membranes rarely occurs, although such cases have been observed in laboratory personnel. Congenital infection (by transplacental transmission or via aspiration or swallowing of infected amniotic fluid at birth) has been reported, but is very rare. Transmission through breast milk does not occur.

The infectiousness of a person is associated with the quantity of bacilli contained in their sputum. Patients with smear-positive sputum on microscopy are by far the most infectious. Those with smear-negative/culture-positive results are less infectious, but still contribute to TB transmission due to more frequent delays in diagnosis.

Persons infected with *M. tuberculosis*, but who have not developed active TB (i.e. persons with latent tuberculosis infection), are not infectious. Persons with extrapulmonary TB (EPTB) are only infectious in exceptional circumstances.

Children are generally less infectious than adults. This may be due to weaker cough mechanics, less sputum production and lower bacillary load.

Not everyone who is exposed to an infectious TB patient becomes infected with *M. tuberculosis*. The probability that TB will be transmitted depends on several factors:

#### **Infectiousness of the source** (the most important factor)

- Bacteriological status: smear-positive patients are the most infectious.
- Virulence of the bacilli: some strains are highly transmissible (and/or more likely to cause active TB).

#### **Environment where the exposure occurred**

- Outdoor environments or those with good ventilation and sunlight are less likely to lead to transmission. Small rooms or rooms with no ventilation are conditions most likely to lead to transmission.
- The proximity of the contact person to the person with TB is also important (e.g. the risk is higher if the contact person sleeps next to the person with TB than if they sleep 20 metres away from the person with TB).

#### **Duration of exposure**

People in close and prolonged contact with a person with TB are at highest risk of becoming infected with *M. tuberculosis*. They may be family members, roommates, friends, co-workers or other people who spend several hours a day with the infectious patient.

The best way to stop transmission is to start effective TB treatment as soon as possible as persons with untreated smear-positive TB transmits the bacillus.

# 1.3 Evolution of tuberculosis infection and disease in humans

When a person inhales infectious droplets containing *M. tuberculosis*, most of the larger droplets become lodged in the upper respiratory tract (nose and throat) where infection is unlikely to develop. However, smaller droplet nuclei may reach the small air sacs of the lung (the alveoli) where infection can occur.

## 1.3.1 Primary infection and latent tuberculosis infection

After transmission, *M. tuberculosis* multiplies slowly, in most cases in the terminal alveoli of the lungs (primary focus) and in the lymph nodes of corresponding drainage areas: this is the primary infection. The primary focus and related hilar lymphadenopathy form the "primary complex".

In one to two months, due to the action of lymphocytes and macrophages (cellular immunity), the primary focus is contained and encapsulated, with a central zone of parenchymal necrosis (caseous lesions). It is not usually detectable on chest x-ray, unless it calcifies or grows substantially. Primary infection is usually asymptomatic. In most cases (90 to 95% of non-HIV infected persons), the pulmonary lesions gradually heal.

During the primary infection, specific immunity develops and a positive skin reaction to tuberculin is observed<sup>[1]</sup>. This immune response may persist without clinical signs of TB. The person is infected, but does not develop the disease. This is referred to as latent tuberculosis infection (LTBI).

Among infected people, on average 5 to 10% will develop active TB over their lifetime<sup>[2]</sup>. For HIV co-infected persons, this risk is much higher.

## 1.3.2 Active tuberculosis

Before immunity is established, bacilli from the primary complex can be disseminated throughout the body via the lymph system or the bloodstream. Secondary foci can develop this way, particularly in the lungs, lymph nodes, serous membranes, meninges, bones and kidneys. As soon as an immune response is mounted, most of these foci resolve spontaneously. However, some bacilli may remain dormant in the secondary foci for months and sometimes years. Different factors can reduce the immune response (e.g. HIV infection) and lead to reactivation of the bacilli and their multiplication in one or more of these foci. This reactivation or progression of the primary or secondary foci results in active TB<sup>[3]</sup>.

An active TB lesion contains actively, slowly or sporadically multiplying bacilli as well as dormant bacilli.

While active TB may occur months or years following primary infection, half of TB cases appear in the year following infection.

## 1.3.3 Risk factors for developing active tuberculosis

Certain factors increase the risk of developing active TB within the first two years of being infected. These factors include immunodepression, damaged lungs and the intensity and duration of exposure.

### Host immune response factors:

- HIV infection
- Children under 5 years<sup>[4][5]</sup>
- Malnutrition
- Persons over 60 years
- Diabetes mellitus
- Other risk factors: prolonged corticosteroid therapy and other immunosuppressive therapies, severe renal disease, alcohol or substance abuse, certain types of cancer (e.g. leukaemia, Hodgkin's lymphoma, cancer of the head and neck); pregnancy

### Conditions that damage the lung:

- Tobacco smoking
- Silicosis
- Chronic obstructive pulmonary disease (COPD)

### Intensity of exposure (high number of inhaled bacilli):

- Highly infectious source
- Poorly ventilated environment
- Proximity with infectious source, including residents and employees of institutions such as detention centres, boarding schools or residential care facilities
- Long duration of exposure

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# 1.4 Prognosis

TB is a severe disease, often fatal if left untreated. After 10 years without treatment, the case fatality rate (CFR) is estimated at 70% for smear-positive PTB and 20% for smear-negative, culture-positive PTB<sup>[1]</sup>.

The CFR is estimated at 3.5% in non-HIV infected patients on TB treatment<sup>[2]</sup>.

The CFR in HIV-infected patients on TB treatment is higher than in non-HIV infected patients<sup>[3]</sup>.

Risk factors for poor outcomes of TB treatment (death and relapse) include resistance to TB drugs, co-morbidities (e.g. untreated HIV infection, diabetes<sup>[4]</sup>), and cavities and high bacillary load<sup>[5]</sup>.

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# 1.5 Factors modifying tuberculosis epidemiology

Five major factors influence TB epidemiology: (1) socioeconomic conditions, (2) TB treatment, (3) HIV infection, (4) diabetes and (5) BCG vaccination.

## 1.5.1 Socioeconomic conditions

The principal factors leading to a reduction in TB cases are improved social and housing conditions. Most cases occur in low-income countries. In industrialised countries, TB generally affects the most disadvantaged social groups.

## 1.5.2 Tuberculosis treatment

Diagnosing and initiating effective treatment in a patient early during their TB disease, before they can infect multiple people, is considered the most effective preventive measure against TB. Once an effective TB treatment is started, there is a rapid reduction in transmission<sup>[1][2]</sup>.

Since the introduction of TB treatment, the risk of TB infection decreased by approximately 10% per year in industrialised countries<sup>[3]</sup>. This trend was observed in countries with a BCG vaccination programme as well as in those without one. Detection programmes, diagnosis and treatment of TB contributed to this reduction in the risk of TB infection.

## 1.5.3 HIV infection

Immunodeficiency induced by HIV infection is a major risk factor for progression to active TB and has a considerable impact on the epidemiology of TB. While the lifetime risk of developing active TB in the general population is 5 to 10% after infection with *M. tuberculosis*, this risk is approximately 10% per year in persons co-infected with HIV and *M. tuberculosis*. Approximately 8% of incident TB cases in the world are among HIV-infected persons (highest in the WHO African Region, more than 50% in parts of southern Africa)<sup>[4]</sup>.

## 1.5.4 Diabetes

The risk of TB among people with diabetes is higher than among those without diabetes. It is estimated that diabetes contributes to 15% of TB cases worldwide<sup>[5]</sup>. Diabetes is also associated with poor absorption of TB drugs and therefore higher rates of drug-resistant TB.

## 1.5.5 BCG vaccination

### Effectiveness of BCG at the individual level

BCG vaccination, if given at birth, is highly effective against the severe forms of TB (miliary and meningitis) in children<sup>[6]</sup>.

### Epidemiological impact of vaccination

Despite some protection from the BCG vaccination, the impact of BCG vaccination on TB transmission and the TB epidemic is considered negligible<sup>[7]</sup>.

## 1.5.6 Other factors

Other modifying factors include infection prevention and control measures ([Chapter 14](#)) and treatment of LTBI ([Chapter 16](#)). The degree to which in a given context the TB epidemiology is affected by these measures is not known.

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# 1.6 Epidemiological indicators

When a National TB Programme (NTP) functions well, indicators can be obtained from the local authorities and NTP. The WHO tuberculosis country profiles also provide an estimation of TB indicators by individual country<sup>a</sup>.

## Box 1.1 – Most common indicators

### Annual incidence rate of TB cases<sup>(a)</sup>

*Numerator:* number of new TB cases (all forms) that occur in a population over one year

*Denominator:* population at the start of the year

### Annual incidence rate of smear-positive PTB cases<sup>(a)</sup>

*Numerator:* number of new smear-positive PTB cases that occur in a population over one year

*Denominator:* population at the start of the year

### Prevalence of smear-positive PTB cases over a given period of time, usually one year<sup>(b)</sup>

*Numerator:* number of smear-positive PTB cases

*Denominator:* population at the start of the period of time

### Proportion of multidrug- and rifampicin-resistant TB cases among TB cases over a given period of time<sup>(c)</sup>

*Numerator:* number of multidrug- and rifampicin-resistant TB cases

*Denominators:*

- Total number of TB cases
- Number of new TB cases
- Number of previously treated TB cases

### Proportion of extensively drug-resistant TB cases among TB cases over a given period of time<sup>(c)</sup>

*Numerator:* number of extensively drug-resistant cases

*Denominators:* as for multidrug- and rifampicin-resistant TB cases

### Proportion of HIV-infected patients among new TB cases over a given period of time<sup>(c)</sup>

*Numerator:* number of HIV-infected patients

*Denominator:* number of new TB cases

(a) The rate is expressed as the number of new TB cases (or new smear-positive PTB cases) per 100,000 population.

(b) Prevalence is expressed as the number of smear-positive PTB cases per 100,000 population. It includes new and pre-existing cases. Prevalence represents approximately double the incidence rate.

(c) Proportion is expressed in %.

## Footnotes

(a) For more information:

[https://worldhealthorg.shinyapps.io/tb\\_profiles/?inputs\\_entity\\_type=%22group%22&lan=%22FR%22](https://worldhealthorg.shinyapps.io/tb_profiles/?inputs_entity_type=%22group%22&lan=%22FR%22)

# 1.7 Global burden of tuberculosis

## 1.7.1 Latent tuberculosis infection

The global prevalence of LTBI is unknown due to difficulties in diagnosis. However, it is estimated that one-quarter of the world's population has LTBI<sup>[1]</sup>.

## 1.7.2 Active tuberculosis

Globally, active TB remains a leading cause of death from infectious disease.

WHO estimated that in 2022 there were 10.6 million incident cases of TB and 1.3 million deaths due to TB, including 1.1 million among non-HIV-infected persons and 167,000 among HIV-infected persons<sup>[2]</sup>.

Patients under 15 years account for 12% of all estimated TB cases<sup>[2]</sup>. However, TB cases in children are frequently undiagnosed and unreported.

While the absolute number of global TB cases is stable, there are large individual country and regional differences in incidence and prevalence.

Most TB cases are in Southeast Asia (46%), Africa (23%) and the Western Pacific (18%), with lower percentages in the Eastern Mediterranean, the Americas and Europe<sup>[2]</sup>.

## 1.7.3 Drug-resistant tuberculosis

Drug-resistant TB (DR-TB) is a growing worldwide problem, and no region is spared.

WHO estimates that annually worldwide there are:

- More than one million rifampicin-susceptible and isoniazid-resistant TB (Hr-TB) cases (11% of all incident TB cases)<sup>[3]</sup>.
- 3.3% of new cases and 17% of previously treated cases, with multidrug-resistant TB (MDR-TB)<sup>a</sup> and rifampicin-resistant TB (RR-TB)<sup>b</sup> representing 410,000 cases and 160,000 deaths<sup>[2]</sup>.

In Eastern Europe and Central Asia, TB incidence is lower than in Southeast Asia and Africa, but up to 30% of new and 65% of retreatment cases exhibit rifampicin-resistance<sup>[3]</sup>.

In China and India, there is a low proportion of rifampicin-resistant cases among all TB cases. However, because of their large populations, these two countries represent 41% of global MDR/RR-TB cases<sup>[3]</sup>.

Resources for detecting drug resistance are limited in many parts of Africa. However, available data suggest that the MDR-TB burden is significant, especially in the south.

The prevalence of extensively drug-resistant TB (XDR-TB)<sup>c</sup>, according to the new WHO definition<sup>[4]</sup>, is currently unknown.

The estimated proportion of pre-XDR TB<sup>d</sup> among MDR/RR-TB cases is 18%<sup>[2]</sup>.

### Footnotes

(a) Multidrug-resistant TB: resistance to at least rifampicin and isoniazid.

(b) Rifampicin-resistant TB: resistance to rifampicin, with or without resistance to other TB drugs.

(c) Extensively drug-resistant TB: MDR/RR-TB with additional resistance to any fluoroquinolone, and at least either bedaquiline or linezolid.

(d) Pre-extensively drug-resistant TB: MDR/RR-TB with additional resistance to any fluoroquinolone.

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# Chapter 2: Clinical presentation

[2.1 Pulmonary tuberculosis](#)

[2.2 Extrapulmonary tuberculosis](#)

[2.3 Disseminated or miliary tuberculosis](#)

[2.4 Clinical presentation in HIV-infected persons](#)

[2.5 Summary of clinical presentations of tuberculosis](#)

Update: January 2022

# 2.1 Pulmonary tuberculosis

Prolonged cough (more than 2 weeks), with or without sputum production, is a common symptom in patients with pulmonary tuberculosis (PTB).

Other frequent, less specific, signs and symptoms include weight loss, anorexia, fatigue, haemoptysis (blood in sputum), shortness of breath, chest pain, moderate fever and night sweats.

Signs and symptoms may vary between individuals and generally evolve in a chronic, insidious manner. History-taking is therefore of the utmost importance.

Advanced forms and complications are common:

- Respiratory insufficiency due to extensive lesions and destroyed lungs;
- Massive haemoptysis due to large cavities with hyper-vascularisation and erosion of vessels;
- Pneumothorax due to the rupture of a cavity in the pleural space.

In endemic areas, the diagnosis of PTB should be considered in any person consulting for respiratory symptoms lasting more than 2 weeks.

Table 2.1 provides a differential diagnosis of PTB for non-HIV infected persons.

**Table 2.1** – Differential diagnosis for PTB

Diseases	Notes
<b>Bacterial pneumonia</b>	<ul style="list-style-type: none"> <li>• Usually more acute and shorter in duration; high fever often present.</li> <li>• Response to antibiotics with no anti-TB activity suggests bacterial pneumonia.</li> <li>• Lobar consolidation is typical of bacterial pneumonia; however, radiography alone cannot differentiate PTB from bacterial pneumonia.</li> </ul>
<b>Pulmonary abscess</b>	<ul style="list-style-type: none"> <li>• May arise from aspiration in individuals with impaired consciousness (coma, intoxication with alcohol/drugs, etc.).</li> <li>• Foul-smelling, purulent sputum.</li> <li>• Cavities typically have a thick wall and air fluid levels.</li> </ul>
<b>Bronchiectasis</b>	<ul style="list-style-type: none"> <li>• Frequent complication of successive, poorly-treated bronchopulmonary infections.</li> <li>• Characterised by chronic or repeated episodes of productive cough.</li> <li>• Haemoptysis, usually mild, can be present.</li> </ul>
<b>Lung cancer</b>	<ul style="list-style-type: none"> <li>• History of smoking or environmental exposure (working in a mine, etc.).</li> <li>• Haemoptysis in 20 to 50% of patients.</li> </ul>
<b>Paragonimiasis</b> (lung flukes)	<ul style="list-style-type: none"> <li>• In certain areas of Southeast Asia, West Africa and Latin America.</li> <li>• To be routinely ruled out in presumed PTB cases.</li> </ul>
<b>Pulmonary echinococcosis</b> (hydatid disease)	<ul style="list-style-type: none"> <li>• In Latin America, the Middle East, some Sub-Saharan African countries and China.</li> <li>• Lung involvement may cause chronic cough, with or without haemoptysis.</li> <li>• Cysts can mimic TB cavities.</li> </ul>
<b>Pneumocystosis</b> ( <i>Pneumocystis jirovecii</i> pneumonia or PCP or PJP)	<ul style="list-style-type: none"> <li>• Common in patients receiving long-term, even low dose, corticosteroid therapy.</li> </ul>
<b>Less common diseases</b>	<ul style="list-style-type: none"> <li>• Silicosis, sarcoidosis, melioidosis.</li> <li>• Cryptococcosis, aspergillosis, histoplasmosis.</li> </ul>

For differential diagnosis in HIV-infected persons, see [Section 2.4](#).

## 2.2 Extrapulmonary tuberculosis

Starting from a pulmonary localisation (primary infection), *M. tuberculosis* can spread to other organs during a silent phase, usually soon after primary infection ([Chapter 1](#)). Active TB can develop in many other parts of the body, particularly in lymph nodes, meninges, bones and joints, kidneys, genital organs and the abdominal cavity.

Due to relative immunodeficiency, young children, HIV-infected persons and malnourished patients are more at risk of developing extrapulmonary tuberculosis (EPTB).

Approximately 16% of global TB cases are classified as EPTB, although this figure varies according the local epidemiology<sup>[1]</sup>.

A patient with EPTB may also have pulmonary involvement (PTB), which should be searched for whenever EPTB is diagnosed or suspected.

[Table 2.3](#) at the end of this chapter summarises the characteristics of EPTB.

### 2.2.1 Lymph node tuberculosis

Lymph node TB is common, particularly in certain areas of Africa and Asia, and especially in children and HIV-infected persons.

The presentation of lymph node TB is a non-inflammatory adenopathy. Nodes are cold and painless, multiple (usually bilateral) or single, evolving in a chronic mode towards softening and fistulisation. Cervical localisation is most frequent. Axillary and mediastinal localisations are also common. Other sites may be involved.

Diagnosis may be clinical, but whenever possible, a lymph node specimen should be collected and tested ([Chapter 3](#)).

Lymph nodes usually disappear within 3 months of treatment initiation. Paradoxical reactions may occur at the beginning of treatment (appearance of abscesses, fistulas or other lymph nodes), but a change in the treatment is not required.

Differential diagnoses include malignancies (lymphoma, leukaemia, ear/nose/throat tumours, Kaposi sarcoma) and other infections (bacterial, viral, non-tuberculosis mycobacteria, toxoplasmosis, HIV infection, syphilis, African trypanosomiasis).

### 2.2.2 Tuberculous meningitis

TB meningitis is a serious form of TB that affects the meninges. It is most common in children under 2 years and in HIV-infected persons. It is a medical emergency. Any delay in diagnosis or treatment will result in irreversible neurological sequelae or death<sup>[2]</sup>.

TB meningitis typically has a subacute insidious course over days or weeks. Symptoms include headache, irritability, fever, vomiting and altered consciousness, which worsen if treatment is delayed. The meningeal syndrome (stiff neck, hypotonia in infants, photophobia and headache) is present in most cases. Third cranial nerve palsy (oculomotor paralysis) may occur.

A CSF specimen should be collected and tested ([Chapter 3](#)).

The main differential diagnoses are other forms of meningitis.

### 2.2.3 Tuberculosis of bones and joints

Up to 40% of patients with TB of bones and joints have concurrent PTB<sup>[3]</sup>.

#### Spinal TB (spondylodiscitis or Pott's disease)

TB can affect vertebrae and intervertebral disks, causing destruction and deformation of the spine. The thoracic spine is the most frequently affected.

Localised back pain may precede by several months the appearance of the first radiological anomalies (destruction of an inter-vertebral disk).

A spinal prominence (gibbus) due to destruction and deformity of the vertebral bodies may be felt.

Paravertebral cold abscesses and/or neurological complications can develop.

A missed diagnosis of thoracic or cervical spinal TB can result in paralysis.

#### Arthritis

TB most frequently causes a chronic mono-arthritis, starting insidiously, with little or no pain and accompanied by joint destruction. The joints most often affected are the hips, knees, elbows and wrists.

#### Osteitis

Osteitis may be a primary osteitis or an osteitis secondary to TB arthritis. Typically, long bones are affected. Cold abscesses may occasionally occur. Like arthritis, it is distinguished from common bacterial infections by the presence of mild symptoms, despite bone and joint destruction.

The diagnosis is based on the patient's history, clinical examination and radiography, as biopsy and culture are difficult to perform in many settings. A history of prolonged osteitis or arthritis associated with a deterioration of the general physical condition favours TB aetiology, as opposed to bacterial osteomyelitis or brucellosis. The patient may have a history of non-response to antibiotics.

### 2.2.4 Urogenital tuberculosis

Renal involvement is frequent and may be asymptomatic for a long period, with a slow development of signs and symptoms: painful urination (dysuria), urinary urgency and frequency (pollakiuria), including during the night (nocturia); back/abdominal pain; tenderness/swelling of the testes or epididymitis or haematuria. There are usually few constitutional symptoms such as fever, night sweats, malaise and weight loss.

Diagnosis is suspected in the presence of pyuria (white blood cells in the urine) and micro- or macroscopic haematuria, which does not respond to antibiotics for urinary infection.

A urine specimen should be collected and tested ([Chapter 3](#)).

In men, genital localisation is secondary to renal involvement. Signs are most often epididymitis with scrotal pain.

In women, genital tract infection can also occur by a hematogenous path. Signs are non-specific: pelvic pain, leucorrhoea and abnormal vaginal bleeding. Infertility is often the reason leading women to seek medical attention.

Extension may be found in the peritoneum, with resulting ascites.

## 2.2.5 Abdominal tuberculosis

Abdominal TB commonly presents as ascites resulting from the peritoneal localisation of the infection.

Abdominal mass (often in the right lower quadrant), pain and diarrhoea may be present. The frequency of chronic ascites in tropical regions, with its many different causes, makes this relatively uncommon form of TB difficult to diagnose<sup>[4]</sup>.

Constitutional symptoms such as fever, night sweats, malaise and weight loss may be present. Accumulation of ascites may mask weight loss.

Ascitic fluid specimen can be collected and tested. Medical imaging can contribute to diagnosis ([Chapter 3](#)).

## 2.2.6 Tuberculous pleural effusion

Tuberculous pleural effusion is one of the most common forms of EPTB.

It is often asymptomatic, especially if less than 300 ml. Shortness of breath and chest pain (often unilateral) occur with large effusion. Sputum production and cough are present in the case of concurrent PTB, which is common.

Constitutional symptoms such as fever, night sweats, malaise and weight loss may be present.

Effusion can progress to tuberculous empyema, with purulent fluid containing large numbers of bacilli. TB empyema is often associated with thickened, scarred and calcified pleura.

Pleural fluid specimen can be collected and tested. Medical imaging can contribute to diagnosis ([Chapter 3](#)).

## 2.2.7 Tuberculous pericardial effusion

Clinical signs of a tuberculous pericardial effusion include chest pain, shortness of breath, oedema of the lower limbs and sometimes ascites.

Clinical examination may show pericardial friction rub, raised jugular pressure and tachycardia.

Medical imaging is key for diagnosis ([Chapter 3](#)).

Pericardiocentesis may be necessary in the event of acute heart failure with haemodynamic compromise. It must be performed by experienced personnel in well-equipped hospitals, and when possible, under direct visualisation with ultrasound.

## 2.2.8 Cutaneous tuberculosis

The clinical presentation of cutaneous TB is chronic, painless, non-pathognomonic lesions, ranging from small papula and erythema to large tuberculomas.

The diagnosis is based on culture from a biopsy.

## References

1. World Health Organization. *Global Tuberculosis Report 2020*. Geneva: World Health Organization; 2020. <https://apps.who.int/iris/rest/bitstreams/1312164/retrieve>
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4. Sinkala, E., et al., *Clinical and ultrasonographic features of abdominal tuberculosis in HIV positive adults in Zambia*. BMC Infect Dis, 2009. 9: p. 44. <https://doi.org/10.1186/1471-2334-9-44>

## 2.3 Disseminated or miliary tuberculosis

Miliary TB is a generalised massive infection characterised by haematogenous diffusion of *M. tuberculosis* throughout the body. It is a medical emergency.

The disease may manifest as a miliary pattern, or very small nodular elements ("millet seeds") in the lungs.

The classic acute form is mostly found in children, young adults and HIV-infected persons. The presentation can be either abrupt or insidious, with progressive deterioration in the patient's physical condition. The clinical picture is often completed within one to two weeks and is characterised by a profoundly altered physical condition, marked wasting, headache and constant high fever. Discrete dyspnoea and coughing suggest a pulmonary focus; however, lungs can often be clear on auscultation. A moderate hepatosplenomegaly may be found. Certain forms of miliary TB evolve in a subacute manner over several months. Given this non-specific clinical picture, typhoid fever and septicaemia should be considered in the differential diagnosis.

Diagnosis of miliary TB is confirmed by CXR ([Chapter 3](#)).

When feasible, fundoscopy may reveal choroidal tubercles.

Sputum smear examination is usually negative. When there is no possibility of obtaining CXR, the lack of response to antibiotics is an argument in favour of miliary TB.

The tuberculin skin test is more likely to be falsely negative than in any other form of TB.

In children, the risk of meningitis (20-40%)<sup>[1]</sup> is high. Lumbar puncture should be performed if miliary TB is suspected.

### References

1. Sharma, S.K., A. Mohan, and A. Sharma. *Miliary tuberculosis: A new look at an old foe*. J Clin Tuberc Other Mycobact Dis, 2016. 3: p. 13-27. <https://doi.org/10.1016/j.jctube.2016.03.003>

## 2.4 Clinical presentation in HIV-infected persons

Among HIV-infected persons, TB is the most common opportunistic infection and a leading cause of morbidity and mortality<sup>[1]</sup>. According to the WHO clinical staging system for HIV/AIDS, individuals with PTB are in clinical stage 3 and patients with EPTB in clinical stage 4<sup>[2]</sup>.

In the early stages of HIV infection, when the immune system is functioning relatively normally, the clinical signs of TB are similar to those in non-infected individuals.

As the immune system deteriorates in later stages of the disease, smear-negative PTB, disseminated TB and EPTB become more common. These cases are more difficult to diagnose, and have a higher fatality rate than smear-positive PTB cases.

Patients may have difficulty expectorating, so more advanced sputum collection techniques may be necessary ([Chapter 3](#) and [Appendix 3](#)).

The algorithm presented in [Chapter 5](#) use clinical criteria combined with laboratory and other investigations to help diagnose TB in HIV-infected persons.

Table 2.2 provides a differential diagnosis of PTB in HIV-infected persons.

**Table 2.2** – Differential diagnosis for PTB

Diseases	Notes
<b>Other pneumonia</b> (bacterial, viral, atypical)	<ul style="list-style-type: none"> <li>Bacterial pneumonia (most often <i>S. pneumoniae</i>, <i>H. influenzae</i>) is common at all stages of HIV infection.</li> <li>Atypical pneumonia (<i>M. pneumoniae</i>, <i>C. pneumoniae</i>) and viral pneumonia are possible at any CD4 count, except in the case of cytomegalovirus, which occurs at CD4 &lt; 50.</li> </ul>
<b>Pneumocystosis</b> ( <i>Pneumocystis jirovecii</i> pneumonia or PCP or PJP)	<ul style="list-style-type: none"> <li>PCP has many characteristics in common with PTB (insidious onset, persistent cough, fever) but tends to occur in the advanced stages of HIV infection (CD4 &lt; 200).</li> <li>PCP is unlikely in patients taking co-trimoxazole prophylaxis.</li> <li>It imparts a greater degree of dyspnoea, rarely produces effusions, and is not usually accompanied by haemoptysis.</li> </ul>
<b>Pulmonary Kaposi's sarcoma</b> (KS)	<ul style="list-style-type: none"> <li>KS can resemble PTB, with slow onset of cough, fever, haemoptysis, night sweats and weight loss. It is a disease of advanced stage HIV, and in most cases, is preceded or accompanied by lesions involving the skin and mucous membranes.</li> </ul>
<b>Less common diseases</b>	<ul style="list-style-type: none"> <li>Pulmonary cryptococcosis, histoplasmosis and other fungal infections.</li> <li>Pulmonary nocardiosis.</li> </ul>

The most common EPTB in HIV-infected persons are miliary TB, TB meningitis and diffuse lymphadenopathy in children, and lymph node TB, pleural effusion, pericarditis, TB meningitis and miliary TB in adults.

Immune reconstitution inflammatory syndrome (IRIS) is a clinical presentation of TB in patients starting antiretroviral therapy. For clinical presentation and management of IRIS, see [Chapter 12](#).

### References

- Ford, N., et al., *TB as a cause of hospitalization and in-hospital mortality among people living with HIV worldwide: a systematic review and meta-analysis*. Journal of the International AIDS Society 2016, 19:20714. <https://doi.org/10.7448/IAS.19.120714>
- World Health Organization. *WHO Case definitions of HIV for Surveillance and Revised Clinical Staging and Immunological Classification of HIV-related disease in adults and children*. Geneva: World Health Organization; 2007. <https://apps.who.int/iris/handle/10665/43699>



## 2.5 Summary of clinical presentations of tuberculosis

**Table 2.3** – Clinical presentations and considerations for HIV-infected persons

Sites	Clinical presentations	Considerations for HIV patients
<b>Pulmonary TB</b>	<ul style="list-style-type: none"> <li>• Prolonged cough (&gt; 2 weeks), with or without sputum production.</li> <li>• Weight loss, anorexia, fatigue, shortness of breath, chest pain, moderate fever, night sweats, haemoptysis.</li> </ul>	<ul style="list-style-type: none"> <li>• Fever and weight loss more common and pronounced.</li> <li>• Cough and haemoptysis may be less common (less inflammation and cavity formation).</li> <li>• See algorithm, <a href="#">Chapter 5</a>.</li> </ul>
<b>Disseminated miliary TB</b>	<ul style="list-style-type: none"> <li>• Non-specific symptoms: high fever, headache, weight loss.</li> <li>• Deterioration over days or weeks.</li> <li>• Simultaneous involvement of multiple organs.</li> <li>• High risk of meningitis in children.</li> <li>• Miliary findings on CXR.</li> </ul>	<ul style="list-style-type: none"> <li>• May be confused with severe wasting in advanced HIV disease.</li> <li>• <i>M. tuberculosis</i> sometimes isolated from blood cultures.</li> </ul>
<b>Lymph node TB</b>	<ul style="list-style-type: none"> <li>• Most often in cervical region.</li> <li>• Non-inflammatory, painless node &gt; 2 cm, chronic (&gt; 4 weeks); fistulisation possible.</li> </ul>	<ul style="list-style-type: none"> <li>• HIV infection can cause persistent generalised lymphadenopathy (PGL). PGL lymph nodes are painless, and symmetrical. Posterior cervical or epitrochlear nodes are often involved.</li> <li>• Other common causes of lymphadenopathy include: lymphoma, carcinomatous metastases, Kaposi sarcoma.</li> </ul>
<b>TB meningitis</b>	<ul style="list-style-type: none"> <li>• Subacute, insidious.</li> <li>• Headache, irritability, fever, altered consciousness.</li> <li>• Meningeal syndrome usually present.</li> </ul>	<ul style="list-style-type: none"> <li>• Rule out cryptococcal meningitis: perform antigen test on serum and CSF.</li> </ul>
<b>Bone and joint TB</b>	<ul style="list-style-type: none"> <li>• Monoarthritis with joint destruction and little or no pain.</li> <li>• Deformity of the spine (Pott's disease).</li> </ul>	<ul style="list-style-type: none"> <li>• Multifocal disease more common.</li> </ul>
<b>Urogenital TB</b>	<ul style="list-style-type: none"> <li>• Renal: urinary symptoms, few constitutional symptoms; suspected when no response to antibiotics for urinary infection.</li> <li>• Non-specific gynaecological symptoms, infertility or epididymitis with scrotal pain.</li> </ul>	
<b>Abdominal TB</b>	<ul style="list-style-type: none"> <li>• Ascites (may mask weight loss).</li> <li>• Abdominal mass, pain, diarrhoea.</li> </ul>	<ul style="list-style-type: none"> <li>• PTB more frequently associated.</li> </ul>
<b>Effusions</b>	<ul style="list-style-type: none"> <li>• Pleural: pleuritic chest pain, dyspnoea.</li> <li>• Pericardial: chest pain, dyspnoea, lower limb oedema or ascites, pericardial friction rub.</li> </ul>	<ul style="list-style-type: none"> <li>• Serious effusions are common.</li> <li>• TB is the most likely aetiology in high TB-HIV prevalence settings.</li> </ul>

# Chapter 3: Diagnosis and follow-up investigations

[3.1 Active tuberculosis](#)

[3.2 Latent tuberculosis infection](#)

[3.3 Other investigations](#)

Update: October 2022

# 3.1 Active tuberculosis

## 3.1.1 Introduction

Active tuberculosis (TB) is bacteriologically confirmed by the detection of *M. tuberculosis* complex through different bacteriological tests. These tests detect either the organism (smear microscopy and culture), or some of its genetic material (genotypic tests, including rapid molecular tests and genome sequencing).

Specimens used for bacteriological testing include respiratory and extrapulmonary specimens ([Table 3.6](#)).

Drug susceptibility testing (DST) is indicated for all patients with confirmed TB. It can be performed using genotypic or phenotypic tests:

- Genotypic DST (gDST) can detect resistance to TB drugs by identifying specific gene mutations.
- Phenotypic DST (pDST) can detect resistance to TB drugs by measuring the growth of *M. tuberculosis* in the presence of the drug.

In case of presumed TB:

- Patients should be tested with a rapid molecular test (RMT) to detect *M. tuberculosis* and rifampicin resistance<sup>a</sup>.
- Whatever the result of the rifampicin susceptibility test (resistance detected or not), all patients, if possible, should be tested with an RMT for isoniazid resistance and at least those with high risk of isoniazid resistance (for definition of high risk of resistance, see below).
- Patients with rifampicin resistance should be tested for resistance to fluoroquinolones and other TB drugs.
- Patients with isoniazid resistance and rifampicin susceptibility should be tested for resistance to fluoroquinolones.
- Culture, pDST and genome sequencing may be required.

In limited-resource settings, resistance to TB drugs should be investigated in priority in patients with:

- High risk of mortality: e.g. HIV-infected patients or patients with extensive disease.
- High risk of resistance: patients with previous TB treatment, or in contact with a TB case resistant to TB drug(s), or coming from an area of high prevalence of resistance to TB drug(s).

**Notes:**

- Negative bacteriological tests for *M. tuberculosis* does not rule out TB.
- A negative DST does not necessarily rule out drug resistance.

Other investigations can assist TB diagnosis. These investigations include: lateral flow urine lipoarabinomannan assay (LF-LAM) which detects an antigen of *M. tuberculosis* cell wall excreted in urine, medical imaging, and some biological tests.

## 3.1.2 Rapid molecular tests

RMTs are nucleic acid amplification tests (NAATs). They can detect *M. tuberculosis* and drug resistance by identifying resistance-conferring mutations in certain genes ([Table 3.1](#)). Other drug resistance-conferring mutations may be present, but not detected by RMTs. In areas where prevalence of these mutations is high, RMT sensitivity may be decreased<sup>[1]</sup>.

**Table 3.1** – Rapid molecular tests and detection of drug resistance

Tests	TB drug resistance (targeted genes)
<p><b>Low complexity NAATs</b></p> <ul style="list-style-type: none"> <li>• Xpert MTB/RIF</li> <li>• Xpert MTB/RIF Ultra</li> <li>• Truenat MTB-RIF Dx</li> </ul> <p><b>Moderate complexity NAATs</b></p> <p><b>High complexity NAATs</b></p> <ul style="list-style-type: none"> <li>• GenoType MTBDRplus (V2.0)</li> <li>• Genoscholar NTM+MDRTB II</li> </ul>	Rifampicin ( <b>rpoB</b> )
<p><b>Low complexity NAATs</b></p> <ul style="list-style-type: none"> <li>• Xpert MTB/XDR</li> </ul> <p><b>Moderate complexity NAATs</b></p> <p><b>High complexity NAATs</b></p> <ul style="list-style-type: none"> <li>• GenoType MTBDRplus (V2.0)</li> <li>• Genoscholar NTM+MDRTB II</li> </ul>	Isoniazid high-level resistance ( <b>katG</b> ) Isoniazid low-level resistance, thionamides <sup>(a)</sup> ( <b>inhA promoter</b> )
<p><b>Low complexity NAATs</b></p> <ul style="list-style-type: none"> <li>• Xpert MTB/XDR</li> </ul> <p><b>High complexity NAATs</b></p> <ul style="list-style-type: none"> <li>• GenoType MTBDRs/ (V2.0)</li> </ul>	Fluoroquinolones ( <b>gyrA, gyrB</b> ) <sup>(b)</sup> Aminoglycosides ( <b>rrs, eis</b> )
<p><b>High complexity NAATs</b></p> <ul style="list-style-type: none"> <li>• Genoscholar PZA-TB II</li> </ul>	Pyrazinamide ( <b>pncA</b> )

- (a) Mutations in other genes can result in resistance to thionamides. Consequently, absence of inhA mutation does not rule out resistance.
- (b) Specific mutations in *gyrA* (e.g. mutations recognized by the probes MUT3B, 3C, 3D) are associated with high-level fluoroquinolones resistance. RMTs have a good specificity, but are less sensitive than culture. Their various levels of complexity determine their use at different levels of health facilities. Low complexity RMTs are preferred in routine practice.

RMTs have a good specificity, but are less sensitive than culture. Their various levels of complexity determine their use at different levels of health facilities. Low complexity RMTs are preferred in routine practice.

## Low complexity nucleic acid amplification tests

### 1) Xpert assays

Xpert assays are almost fully automated. An uninterrupted power supply and a computer are required to perform and read assays.

Xpert assays can be performed on:

- Respiratory specimens (sputum, nasopharyngeal aspirate and, in children, gastric aspirate) and stools in children for PTB.
- Extrapulmonary (EP) specimens:
  - Lymph node biopsy or aspirate: suspicion of lymph node TB or detection of rifampicin resistance in clinically diagnosed lymph node TB;
  - Cerebrospinal fluid (CSF): suspicion of TB meningitis;
  - Pleural fluid: suspicion of TB with pleural effusion;
  - Peritoneal fluid: suspicion of abdominal TB;
  - Pericardial fluid: suspicion of TB with pericardial effusion (sampling to be performed only by experienced clinicians);
  - Synovial fluid: suspicion of TB arthritis;
  - Urine: suspicion of genitourinary TB; suspicion of disseminated TB in HIV-infected patients;
  - Blood: suspicion of disseminated TB in HIV-infected patients.

Xpert MTB/RIF and Xpert MTB/RIF Ultra assays provide simultaneously results for *M. tuberculosis* detection and rifampicin resistance.

Sensitivity of Xpert MTB/RIF Ultra assay is higher than that of Xpert MTB/RIF assay. It provides a result "trace" corresponding to the lowest bacillary load for *M. tuberculosis* detection. It is preferred for HIV-infected patients, children, EP specimens, and sputum smear-negative specimens. Its specificity is lower in patients with a history of TB, as a "trace" result may indicate that the specimen contains fragments of dead bacilli.

WHO has validated their use on lymph node biopsy or aspirate, CSF, pleural fluid, peritoneal fluid, pericardial fluid, synovial fluid, urine, and on stool in children<sup>[2]</sup>. Xpert assays on blood have a low sensitivity compared to culture and are not routinely recommended<sup>[3]</sup>.

Xpert MTB/XDR assay detects resistance to isoniazid (low- and high-level), fluoroquinolones (low- and high-level), aminoglycosides, and thionamides. It does not detect resistance to rifampicin.

Xpert MTB/XDR assay employ the same platform as other Xpert assays, but require a 10-colour module instead of the 6-colour module used for Xpert MTB/RIF and Xpert MTB/RIF Ultra assays. The 10-colour module can also read Xpert MTB/RIF and Xpert MTB/RIF Ultra assays.

Xpert MTB/XDR assay should be used:

- When resistance to rifampicin has been detected by Xpert MTB/RIF or Xpert MTB/RIF Ultra, to detect resistance to other drugs.
- When *M. tuberculosis* has been detected by Xpert MTB/RIF or Xpert MTB/RIF Ultra or culture, to detect resistance to isoniazid in all patients, if possible, and at least those with high risk of isoniazid resistance ([Section 3.1.1](#)).
- Before using a fluoroquinolone containing regimen in isoniazid-resistant TB (Hr-TB), multidrug-resistant (MDR-TB), rifampicin-resistant TB (RR-TB) or drug-susceptible TB treated with the regimen 2HPZ-Mfx/2HP-Mfx.
- Before treating drug-susceptible TB meningitis with the regimen 6HRZ-Eto.
- In patients with fluoroquinolone-susceptible TB, initially treated with a fluoroquinolone-containing regimen, and presenting a smear-positive microscopy at Month 2 or later.

**Table 3.2** – Main performances of Xpert assays

Xpert assays	Performances
<b>MTB/RIF</b>	<p><b>Detection of <i>M. tuberculosis</i> (MTB)</b> compared to culture:</p> <ul style="list-style-type: none"> <li>• Sensitivity in respiratory specimens<sup>[4]</sup>: <ul style="list-style-type: none"> <li>▫ sputum-smear positive: 99%</li> <li>▫ sputum smear-negative: 68%</li> <li>▫ HIV-infected patients: 79%</li> <li>▫ children: see <a href="#">Appendix 1</a>.</li> </ul> </li> <li>• Sensitivity in EP specimen: see <a href="#">Appendix 1</a>.</li> <li>• Specificity: very high in all specimens (99%), i.e. a positive result is unlikely to be a false positive.</li> </ul> <p><b>Detection of rifampicin resistance</b> compared to pDST<sup>[4]</sup>: Sensitivity: 95%; specificity: 98%</p>
<b>MTB/RIF Ultra</b>	<p><b>Detection of MTB</b> in respiratory and EP specimens<sup>[6]</sup>:</p> <ul style="list-style-type: none"> <li>• Sensitivity: + 5% compared to Xpert MTB/RIF</li> <li>• Specificity: - 3.2% compared to Xpert MTB/RIF; - 5.4% in patients with a history of TB</li> </ul> <p>No result for rifampicin resistance if "trace" result.</p>
<b>MTB/XDR</b>	<p><b>Detection of MTB</b> in respiratory and EP specimens (children and adults): As Xpert MTB/RIF.</p> <p><b>Detection of resistances</b> compared to pDST<sup>[6]</sup>:</p> <ul style="list-style-type: none"> <li>• To isoniazid (low- and high-level): sensitivity: 94.2%; specificity: 98%</li> <li>• To fluoroquinolones (low- and high-level): sensitivity: 93.1%; specificity: 98.3%</li> <li>• To aminoglycosides: sensitivity: 86.1%; specificity: 98.9%</li> <li>• To thionamides: sensitivity: 51.7%; specificity: 98.3%</li> </ul>

For more information on specimen processing and Xpert instruments, see [Appendix 1](#).

For interpretation of Xpert assay results, see [Appendix 2](#).

For request form, see [Appendix 34](#).

## 2) Truenat assays

Truenat assays require:

- Several manual steps (pipetting).
- Sequential testing for *M. tuberculosis* detection (Truenat MTB Plus), then for rifampicin resistance detection (Truenat MTB-RIF Dx).
- Separate kits for specimen preparation, DNA extraction, DNA amplification, and detection of *M. tuberculosis* and rifampicin resistance.

Truenat MTB Plus can only be performed on sputum specimens (positive or negative smear microscopy). It is not recommended for other respiratory specimens or EP specimens<sup>[7][8]</sup>.

Specificity is high, i.e. a positive result is unlikely to be a false positive<sup>[9]</sup>.

Tests can be run at room temperatures of up to 40 °C and humidity of up to 80%. Truenat instruments are battery-operated and can be used in peripheral or mobile health facilities.

Interpretation of results is the same as for Xpert ([Appendix 2](#)).

**Table 3.3** – Main performances of Truenat assays

Truenat assays	Performances
<b>MTB Plus</b>	<p><b>Detection of MTB</b> in sputum specimens (children and adults) compared to culture:</p> <ul style="list-style-type: none"> <li>• Sensitivity: <ul style="list-style-type: none"> <li>▫ sputum smear-positive: 80%</li> <li>▫ sputum smear-negative: 55%</li> </ul> </li> <li>• Specificity: 96%<sup>[9]</sup></li> </ul>
<b>MTB-RIF Dx</b>	<p><b>Detection of rifampicin resistance</b> compared to pDST:</p> <p>Performed on the DNA isolated from sputum specimens with Truenat MTB Plus positive result.</p> <ul style="list-style-type: none"> <li>• Sensitivity: 84%</li> <li>• Specificity: 97%</li> </ul>

## 3) TB-LAMP

Although validated by WHO, this test has major limitations:

- It does not detect rifampicin resistance.
- Its sensitivity is lower than that of other low complexity NAATs in HIV-infected or smear-negative patients.
- It cannot be used for the diagnosis of extrapulmonary TB (EPTB)<sup>[7]</sup>.

**Box 3.1** – Choice of low complexity NAATs

**Xpert:** first line tests for the diagnosis of TB in children and adults.  
**Truenat:** if no power supply or operating temperature between 31 and 40 °C.  
**TB-LAMP:** not recommended.

### Moderate complexity nucleic acid amplification tests

WHO recommends these tests for the simultaneous detection of *M. tuberculosis* and resistance to rifampicin and isoniazid, from smear-positive and negative respiratory specimens, in children and adults, including HIV-infected patients.

**Table 3.4** – Performances of moderate complexity NAATs

Tests	Performances
<ul style="list-style-type: none"> <li>• Abbott Real Time MTB and MTB RIF/INH BD MAX MDR-TB</li> <li>• Hain FluoroType MTB and MTBDR</li> <li>• Roche cobas MTB and MTB-INH/RIF</li> </ul>	<p><b>Detection of MTB</b> compared to culture:</p> <ul style="list-style-type: none"> <li>• Sensitivity 93%</li> <li>• Specificity 97.7%</li> </ul> <p><b>Detection of rifampicin resistance</b> compared to pDST:</p> <ul style="list-style-type: none"> <li>• Sensitivity 96.7%</li> <li>• Specificity 98.9%</li> </ul> <p><b>Detection of isoniazid resistance</b> compared to pDST:</p> <ul style="list-style-type: none"> <li>• Sensitivity 86.4%</li> <li>• Specificity 99.8%</li> </ul>

NAATs of moderate complexity have several limitations:

- Need for space, equipment, qualified staff; only feasible in regional laboratories.
- Their use does not eliminate the need for pDST, high complexity NAATs, or genome sequencing to:
  - test susceptibility to other TB drugs;
  - confirm a negative result in patients at high risk of drug resistance.
- Their use on EP specimens is not validated.

### High complexity nucleic acid amplification tests

Line probe assays (LPA) can detect specific rifampicin, isoniazid, fluoroquinolones, aminoglycosides, and pyrazinamide resistance encoding mutations in *M. tuberculosis*.

These tests can be performed on isolates of *M. tuberculosis* (indirect testing). Some can be performed on sputum specimens (direct testing).

NAATs of high complexity have several limitations:

- Need for space, equipment, highly qualified staff; only feasible in reference and national laboratories.
- Risk of cross-contamination (tests are performed in an open system that can lead to the detection of DNA from sources other than the specimen).
- To benefit from the short turnaround time of these tests, efficient logistical support is required to ensure specimens are transported to the laboratory and the results are delivered in a timely manner.
- Their use does not eliminate the need for pDST or genome sequencing to:
  - test sensitivity to other TB drugs;
  - confirm a negative result in patients at high risk of drug resistance.
- Although direct test results can be obtained in 1 to 2 days, for indirect tests, it is necessary to wait the time required for bacterial growth ([Appendix 5](#)).
- Their use on respiratory (non-sputum) or EP specimens is not validated.

**Box 3.2** – WHO validated LPAs<sup>b</sup>

#### First-line LPAs

- GenoType MTBDRplus version 2 ("Hain first line test"): initial test to detect resistance to rifampicin and isoniazid on smear-positive sputum specimens and *M. tuberculosis* isolates. Compared to pDST, sensitivity is 98.2% for rifampicin, and 97.8% for isoniazid; specificity is 95.4% for rifampicin, and 98.8% for isoniazid<sup>[10]</sup>. On smear-negative sputum specimens, sensitivity is low (44.4%), and its use is not recommended<sup>[6]</sup>.
- Genoscholar NTM+MDRTB II ("Nipro test"): performances comparable to GenoType MTBDRplus to detect resistance to rifampicin and isoniazid on smear-positive sputum specimens and *M. tuberculosis* isolates. Not recommended on smear-negative sputum specimens. Can differentiate *M. avium*, *M. intracellulare* and *M. kansasii* from other non-tuberculous mycobacteria.
- Genoscholar PZA-TB II: to detect resistance to pyrazinamide on *M. tuberculosis* isolates. Compared to pDST, sensitivity is 81%, and specificity is 97%<sup>[6]</sup>.

#### Second-line LPA

GenoType MTBDRs/ version 2 ("Hain second line test"): in patients with confirmed MDR/RR-TB, to detect resistance to fluoroquinolones (high- and low-level) and aminoglycosides on smear-positive or smear-negative sputum specimens and *M. tuberculosis* isolates. The number of "indeterminate" results is higher for smear-negative than for smear-positive sputum specimens. For smear-positive sputum specimens, sensitivity is 93% for fluoroquinolones, and 88.9% for aminoglycosides; specificity is 98.3% for fluoroquinolones, and 91.7% for aminoglycosides<sup>[11]</sup>.

### 3.1.3 Genome sequencing

Genome sequencing can only be performed in highly specialized reference laboratories.

It can rapidly:

- Detect mutations associated with TB drug resistance. When available, it is particularly useful to identify:
  - resistance to TB drugs for which pDST is unreliable, or no RMTs are available;
  - mutations missed by RMTs (+ 20% of drug resistance detection compared to RMTs has been described<sup>[12]</sup>).
- Detect mixed infection (infection with distinct *M. tuberculosis* strains).
- Identify heteroresistance (same strain, with different resistance profiles).
- Differentiate treatment relapse and reinfection with a different strain.

Genome sequencing methods include Sanger sequencing (reference method) and next generation sequencing (NGS). The advantage of NGS is that, unlike Sanger sequencing, it provides results for a large number of genes in a single reaction.

NGS results are interpreted by reference laboratories using specific software and mutation databases<sup>o</sup>.

Some mutations associated with resistance to recently introduced drugs (e.g. bedaquiline and delamanid) and their therapeutic implications are still not well-known.

The two main NGS techniques are targeted NGS (tNGS) and whole genome sequencing (WGS):

- tNGS (on smear-positive sputum specimens or culture isolates): detection of resistance conferring mutations on 18 selected genes: first-line TB drugs, fluoroquinolones, aminoglycosides, linezolid, bedaquiline, clofazimine, ethionamide (Deeplex®Myc-TB). Used in routine.
- WGS (on culture isolates): detection of resistance conferring mutations on whole genome (i.e. potentially all TB drugs). Used for research.

### 3.1.4 Smear microscopy

The purpose of smear microscopy is to detect acid-fast bacilli (AFB) in stained specimens.

Smear microscopy has several limitations:

- It has a sensitivity lower than RMTs and culture in respiratory specimens (65% compared to culture<sup>[4]</sup>) and EP specimens (48% compared to culture<sup>[13]</sup>).
- It has a low sensitivity in patients with low bacillary load in sputum (paucibacillary TB), e.g. children and HIV-infected patients.
- It cannot differentiate between *M. tuberculosis* and non-tuberculous mycobacteria. However, in areas with high TB prevalence, AFB detected on smear microscopy are most likely *M. tuberculosis*.
- It does not determine if bacilli are viable (alive) or non-viable (dead).
- It does not determine susceptibility of the bacilli to TB drugs.

Sputum smear microscopy is no longer the recommended initial diagnostic test for PTB. However, it still plays a role:

- When RMTs are not immediately available.
- For assessing the infectiousness of PTB patients.
- For monitoring the response to TB treatment in patients with:
  - drug-susceptible PTB ([Chapter 9](#))
  - drug-resistant PTB. However, culture is also required for monitoring treatment response in these patients ([Chapter 10](#) and [Chapter 11](#)).

For improving the sensitivity of smear microscopy:

- 1) Two sputum specimens should be examined. Approximately 86% of sputum smear-positive patients are identified during the first examination, and an additional 12% during the second. It is not necessary to carry out more than 2 examinations<sup>[14]</sup>.
- 2) Light-emitting diode (LED) fluorescent microscopy to examine auramine-stained smears is preferred to Ziehl-Neelsen microscopy, as it is more sensitive, and reading is more rapid.

Concentration techniques can also increase the sensitivity of smear microscopy<sup>[15]</sup>.

For sputum specimen collection, storage and shipment, see [Appendix 3](#).

For sputum smear preparation and staining techniques, see [Appendix 4](#).

For request form, see [Appendix 34](#).

### 3.1.5 Culture

Culture consists of growing *M. tuberculosis* in specific liquid or solid media.

Culture on liquid medium (automated or manual mycobacterial growth indicator tube, MGIT) is the reference method for the diagnosis of PTB and EPTB.

Given the long turnaround time and equipment required, it is not used as initial diagnostic test.

Culture on solid medium (Lowenstein-Jensen) is cheaper, less prone to contaminations than cultures on liquid media, but its turnaround time is longer.

Other culture techniques are less commonly used<sup>d</sup>.

Culture is necessary to:

- Confirm treatment failure.
- Assess treatment response in patients with drug-resistant PTB ([Chapter 10](#) and [Chapter 11](#)).
- Evaluate treatment outcome in patients with drug-resistant PTB ([Chapter 17](#)).
- Provide isolates for the following tests:
  - First-line LPAs on sputum smear-negative and EP specimens
  - Genoscholar PZA-TB II, regardless of sputum smear positivity
  - First- or second-line LPA when an initial direct LPA gives an invalid result
  - WGS
  - tNGS on smear-negative sputum specimens
- Differentiate between *M. tuberculosis* and non-tuberculosis mycobacteria. Differentiation between species within the *M. tuberculosis* complex is not routinely performed.

Culture may help to diagnose TB when other bacteriological tests are negative or inconclusive:

- In patients with signs and symptoms of TB and a negative RMT, particularly when resistance is suspected.
- In adults with history of TB in the previous 5 years and showing a "trace" result by Xpert MTB/RIF Ultra.

Culture has several limitations:

- Only specialized laboratories implementing systematic quality assurance procedures can be relied upon for culture (often national reference laboratories or supranational).
- *M. tuberculosis* is a slow-growing bacillus. Positive culture results are obtained after 2 to 4 weeks.

For sputum specimen collection, storage and shipment, see [Appendix 3](#).

For the time required to obtain the results, see [Appendix 5](#).

### 3.1.6 Phenotypic drug susceptibility testing

Phenotypic DST (pDST) determines if a strain is resistant to a TB drug by evaluating the growth in the presence of the drug.

It can determine two levels of resistance (low and high) for isoniazid and fluoroquinolones.

The pDST is essential to detect resistance to drugs for which there are no reliable RMTs, and when genome sequencing is not available.

In addition, pDST may be necessary:

- If an RMT indicates *M. tuberculosis* "detected" and drug resistance "indeterminate".
- If an RMT indicates drug susceptibility in a patient at high risk of resistance.
- In areas with a high prevalence of mutations not detected by RMTs.

Phenotypic DST is performed on culture isolates by specialized laboratories (often national reference laboratories or supranational).

The pDST is not reliable for all drugs, even when performed by a highly qualified laboratory<sup>[16]</sup>.

**Table 3.5** – Reliability of pDST for first- and second-line TB drugs



Reliability of pDST	TB drugs
Highly reliable	Isoniazid Rifampicin Fluoroquinolones Aminoglycosides
Unreliable (should not be performed)	Ethambutol Ethionamide Cycloserine or terizidone Para-aminosalicylic acid (or sodium) Delamanid
Reliable, but limited access outside of supranational laboratories	Bedaquiline Linezolid Clofazimine
Reliable when performed in a high-quality laboratory (difficult to perform)	Pyrazinamide

### 3.1.7 Summary of bacteriological tests

The tables below provide an overview of the specimens that can be used for each test, and of the tests that can detect resistance to each TB drug.

**Table 3.6** – Specimens for bacteriological tests

Tests	Specimens
Xpert, microscopy, culture	Respiratory or EP specimens
Truenat	Sputum (smear-positive or negative)
Moderate complexity NAATs	Respiratory specimens
GenoType MTBDRplus version 2 Genoscholar NTM+MDRTB II	Sputum (smear-positive only) <i>M. tuberculosis</i> isolate
Genoscholar PZA-TB II	<i>M. tuberculosis</i> isolate
GenoType MTBDRs/ version 2	Sputum (smear-positive or negative) <i>M. tuberculosis</i> isolate
tNGS	Sputum (smear-positive only) <i>M. tuberculosis</i> isolate
WGS	<i>M. tuberculosis</i> isolate

**Table 3.7** - Tests to detect specific drug resistance

TB drugs	gDST	pDST
Rifampicin	Xpert MTB/RIF and Ultra, Truenat MTB-RIF Dx Moderate complexity NAATs GenoType MTBDRplus, Genoscholar NTM+MDRTB II Genome sequencing	Yes
Isoniazid <sup>(c)</sup>	Xpert MTB/XDR Moderate complexity NAATs GenoType MTBDRplus, Genoscholar NTM+MDRTB II Genome sequencing	Yes
Pyrazinamide	Genoscholar PZA-TB II Genome sequencing	Yes
Ethambutol	Genome sequencing	Unreliable
Fluoroquinolones <sup>(c)</sup>	Xpert MTB/XDR GenoType MTBDRs/ Genome sequencing	Yes
Amikacin	Xpert MTB/XDR GenoType MTBDRs/ Genome sequencing	Yes
Streptomycin	Genome sequencing	Yes <sup>(d)</sup>
Thionamides <sup>(e)</sup>	Xpert MTB/XDR GenoType MTBDRplus, Genoscholar NTM+MDRTB II Genome sequencing	Unreliable
Cycloserine or terizidone Para-aminosalicylic acid (or sodium)	Whole genome sequencing	Unreliable
Bedaquiline Linezolid Clofazimine Delamanid	Genome sequencing	Yes <sup>(d)</sup>

(c) High- and low-level resistance detected by gDST and pDST.

(d) Rarely available in resource-limited settings.

(e) Most mutations conferring resistance to thionamides are not detected by RMTs.

### 3.1.8 Lateral flow urine lipoarabinomannan assay

TB lipoarabinomannan (LF-LAM) is a urine-based point-of-care test that detects lipoarabinomannan (LAM) antigen<sup>9</sup>, which is a marker of active TB.

This test is easy to perform by trained staff, including in peripheral health facilities.

Advantages of LF-LAM over sputum-based tests include:

- Urine specimens easier to collect.
- No risk of staff contamination during specimen collection or processing.
- No specific storage requirements for the urine prior to testing.

The urine is applied to the test strip, left at room temperature for 25 minutes, then read by the naked eye by comparing the band for positivity to a grading scale provided by the manufacturer<sup>f</sup>.

This rapid test should be used in the diagnosis of PTB and EPTB in HIV-infected children and adults. Its rapidly obtained result can contribute to reducing TB mortality among these patients<sup>16</sup>.

Its performances depend on the individual level of immunodeficiency at the time of testing. Its sensitivity is low, but it has an acceptable specificity (see below).

The LF-LAM test is recommended for the following patient groups<sup>17</sup>:

- HIV-infected patients with signs and symptoms of TB or seriously ill<sup>9</sup>, irrespective of CD4 count (sensitivity: 35%; specificity: 95%).
- Hospitalised patients with advanced HIV disease<sup>h</sup> (sensitivity: 64%; specificity: 82%).
- HIV-infected outpatients with CD4 count < 100 cells/mm<sup>3</sup> (sensitivity: 40%; specificity: 87%).

If LF-LAM test is positive: TB treatment should be initiated<sup>1</sup>.

Due to the low sensitivity of the LF-LAM test, a negative result does not rule out TB. The test does not provide information on drug susceptibility. Therefore, all above-mentioned patients should be tested with an RMT, regardless of whether the LF-LAM result is positive or negative.

## 3.1.9 Medical imaging

### Radiography

Chest x-ray (CXR) is used to:

- Detect abnormalities suggestive of PTB and other intra-thoracic TB localisations (pleural, pericardial, miliary).
- Evaluate the severity of intra-thoracic lesions.

It is particularly useful in the diagnosis of PTB in children ([Chapter 4](#)).

For PTB, CXR has a higher sensitivity than TB symptoms<sup>[18]</sup>: a patient with a normal CXR is unlikely to have PTB. For this reason, it can also be used as a screening tool ([Chapter 6](#)) and a triaging tool to identify patients with respiratory symptoms eligible for an RMT.

CXR is also used to:

- Evaluate the response to TB treatment.
- Look for possible complications in case of worsening respiratory symptoms (pneumothorax, tracheal stenosis, etc.).

CXR has several limitations:

- Low specificity: except for cavities or miliary TB, which are specific to TB other abnormalities seen on CXR may be due to other pulmonary diseases.
- Variable quality, depending on several factors:
  - equipment and supply
  - positioning (obtaining quality CXR in children is challenging)
  - reader training and proficiency
- Difficulty distinguishing active from healed lesions
- Error rate of approximately 20%<sup>[19]</sup> (specialists' under/over-reading of the film)

When available, digital CXR has advantages over x-ray films:

- Consistent quality
- Easier image archiving
- No need for reagents and films
- Rapid transmission for teleconsultation and specialist advice
- Immediate results; possibility to screen large numbers of people within a short timeframe
- Lower radiation exposure for staff and patients.

Interpretation of digital CXR can be assisted by computer-aided detection (CAD) software packages. CAD analyses CXR for the presence of PTB-compatible abnormalities, and divides images into "normal" and "abnormal", thereby reducing the number of CXR that need to be read by a clinician. CAD is as sensitive as a radiologist<sup>[20]</sup>.

Computer-aided CXR interpretation assists clinicians when all CXR cannot be read by a radiologist.

However, a radiologist should be consulted locally or via telemedicine to interpret difficult CXR (e.g. in children).

Bone x-ray is used to diagnose and evaluate severity of bone and/or joint TB and assess treatment response.

### Ultrasound

Ultrasound (including point-of-care ultrasound, POCUS) may be useful in:

- PTB: pulmonary consolidation can support the diagnosis of PTB.
- EPTB: if suspected pleural/pericardial effusion or abdominal TB in children and adults, particularly in immunocompromised patients (e.g. HIV-infection, malnutrition).

**Table 3.8** – Medical imaging findings suggestive of TB

Sites	Findings
<b>Pulmonary TB</b>	<p><b>Children</b> See <a href="#">Chapter 4</a>.</p> <p><b>Adolescents and adults</b> CXR can show:</p> <ul style="list-style-type: none"> <li>• Infiltrates typically located in apical and posterior segment of upper lobes and superior segments of lower lobes.</li> <li>• Cavities (specific for TB), patchy, poorly defined consolidations.</li> </ul> <p><b>Patients with TB/HIV</b> As above.</p> <ul style="list-style-type: none"> <li>• In advanced immunodeficiency, infiltrates tend to be more homogeneous, diffuse and located in the lower lungs.</li> <li>• Less cavities than in non-HIV-infected patients.</li> <li>• Mediastinal and hilar lymphadenopathy may be observed.</li> <li>• Miliary pattern.</li> </ul>
<b>Miliary TB</b>	CXR can show miliary nodules (1-3 mm in diameter) disseminated in both fields and uniformly distributed throughout the lung.
<b>Pleural effusion</b>	<ul style="list-style-type: none"> <li>• CXR: effusion (even with minimal clinical signs): <ul style="list-style-type: none"> <li>▫ Mostly unilateral.</li> <li>▫ Obliteration of costophrenic angle.</li> <li>▫ Opacity with curved upper margin.</li> </ul> </li> <li>• Ultrasound: anechogenic fluid on the costophrenic angle (may be echogenic in empyema).</li> </ul>
<b>Pericardial effusion</b>	<ul style="list-style-type: none"> <li>• CXR: cardiac silhouette enlargement, "water bottle" silhouette (very large effusions).</li> <li>• Ultrasound: anechogenic fluid around the heart (may be echogenic if purulent).</li> </ul>
<b>Bone/joint TB</b>	<p>X-ray can show:</p> <ul style="list-style-type: none"> <li>• Any bone/joint: osteopenia (demineralization), bone destruction with relative preservation of cartilage space.</li> <li>• Spine: destruction of an inter-vertebral disk, osteopenia, irregularity of bone margin, bone destruction, paravertebral abscesses.</li> </ul>
<b>Abdominal TB</b>	Ultrasound can show enlarged lymph nodes consistent with TB (and other diseases, especially in HIV infection), bowel wall thickening (ileo-caecal region), hypoechogenic micro-abscesses of liver and/or spleen, ascites.

**Notes:**

- Radiographical and ultrasound findings of EPTB are non-specific. A differential diagnosis should always be considered.
- In HIV-infected patients in settings of high TB prevalence, pleural/pericardial effusion, enlarged abdominal lymph nodes, splenic microabscesses, and ascites are highly suggestive of EPTB <sup>[21]</sup>.
- Adolescents typically have CXR abnormalities similar to those found in adults, however, they may also have abnormalities commonly seen in children, such as enlarged hilar lymph nodes.

### 3.1.10 Other laboratory tests on tissues and body fluids

The diagnosis of TB can be supported by biological tests performed on tissues or body fluids.

**Table 3.9** – Findings suggestive of TB in tissues or body fluids

Tissues/fluids	Findings
<b>Lymph node</b>	Cytology: granulomatous tissue, presence of giant Langhans cells, and/or caseous necrosis. AFBs are not always found by microscopy.
<b>CSF</b>	<ul style="list-style-type: none"> <li>• Clear, hyper-concentrated liquid.</li> <li>• High protein level &gt; 0.40 g/l (see Pandy test, <a href="#">Appendix 8</a>).</li> <li>• Low glucose &lt; 60 mg/l.</li> <li>• Ratio CSF glucose/blood glucose &lt; 0.5.</li> <li>• Between 100 and 1,000 white cells/mm<sup>3</sup>, of which over 80% are lymphocytes.</li> </ul> In HIV-infected patients, rule out cryptococcal meningitis.
<b>Peritoneal fluid</b>	<ul style="list-style-type: none"> <li>• Translucent, yellow-coloured liquid.</li> <li>• Exudate rich in lymphocytes, usually &gt; 300 white cells/mm<sup>3</sup>; Rivalta test positive (<a href="#">Appendix 8</a>).</li> <li>• Serum-ascites albumin gradient (SAAG):               <ul style="list-style-type: none"> <li>&lt; 1.1 g/dl: consistent with TB (and many other conditions).</li> <li>&gt; 1.1 g/dl: peritoneal TB unlikely.</li> </ul> </li> <li>• Adenosine deaminase (ADA) &gt; 39 U/l, likely due to TB <sup>[22]</sup>.</li> </ul>
<b>Pleural fluid</b>	<ul style="list-style-type: none"> <li>• Straw-coloured fluid.</li> <li>• High protein level ≥ 30 g/l (Rivalta test, <a href="#">Appendix 8</a>).</li> <li>• Rich in white cells (1,000-2,500/mm<sup>3</sup>), with predominant lymphocytes.</li> <li>• ADA typically &gt; 50 U/l. Pleural effusion with an ADA &lt; 40 U/l is much less likely due to TB. The specificity is increased when ADA is &gt; 50 U/l and the lymphocyte-neutrophil ratio is &gt; 0.75 <sup>[23]</sup>.</li> </ul>

#### Notes:

- ADA levels increase in TB. ADA is therefore a surrogate marker for TB in pleural and peritoneal fluids. Although not widely available, kits can be purchased to perform the test if a spectrophotometer is available.
- The sensitivity of ADA in peritoneal fluid is lower in patients with cirrhosis.
- HIV-infected patients may have lower levels of ADA.

#### Footnotes

- (a) When microscopy is the only diagnostic test available, specimens should be sent to a facility with capacity to perform RMTs.
- (b) For more information, see: Global Laboratory Initiative. Line probe assays for drug resistant tuberculosis detection Interpretation and reporting guide for laboratory staff and clinicians. [http://stoptb.org/wg/gli/assets/documents/LPA\\_test\\_web\\_ready.pdf](http://stoptb.org/wg/gli/assets/documents/LPA_test_web_ready.pdf)
- (c) For more information :  
 • WHO catalogue of mutations in *M. tuberculosis* complex and their association with drug resistance: <https://www.who.int/publications/i/item/9789240028173>  
 • Relational Sequencing TB (ReSeqTB) Data Platform: <https://c-path.org/programs/cptr/cptr-tools/databases/relational-sequencing-tb-data-platform-reseqtb/>
- (d) Microscopic observation of drug susceptibility (MODS), nitrate reductase assay (NRA), thin layer agar and colorimetric redox indicator (CRI).
- (e) LAM antigen is a component of the mycobacterial cell walls released by *M. tuberculosis* then excreted by the kidneys.
- (f) Alere Determine® TB LAM Ag (Alere Inc, Waltham, MA, USA).
- (g) Seriously ill: respiratory rate > 30/minute, temperature > 39 °C, heart rate > 120/minute and unable to walk unaided.
- (h) For children > 5 years and adults: CD4 count < 200 cells/mm<sup>3</sup> or a WHO clinical stage 3 or 4. All children < 5 years are considered as having advanced HIV disease.
- (i) HIV-infected patients diagnosed with TB using the LF-LAM should be recorded as bacteriologically confirmed TB cases.

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## 3.2 Latent tuberculosis infection

Diagnosis is based on exclusion of active TB and demonstration of latent tuberculosis infection (LTBI).

For demonstrating LTBI, one of the following tests may be performed. However, these tests are not mandatory prior to initiating LTBI treatment in:

- Children under 5 years household contact of a TB case;
- HIV-infected children and adults<sup>[1]</sup>.

### 3.2.1 Tuberculin skin test

A positive tuberculin skin test (TST) indicates that a mycobacterial infection has occurred.

For interpretation of TST results, see [Appendix 9](#).

TST has several limitations:

- It does not distinguish infection by *M. tuberculosis* from exposure to environmental mycobacteria.
- It does not distinguish latent/active TB.
- Prior BCG vaccination can result in a false positive TST.
- False negative TST is common, particularly in HIV-infected patients and malnourished children.

After having ruled out active TB, a positive TST is an indication for treatment of LTBI ([Chapter 16](#)).

**Notes:**

- TST is also used to check the absence of TB in neonates on isoniazid monotherapy ([Chapter 16](#)).
- Other skin tests are available, but have not yet been evaluated by WHO.

### 3.2.2 Interferon gamma release assays

The test is performed in vitro on blood to which *M. tuberculosis* antigens are added. This results in the rapid stimulation of memory T cells and release of interferon-gamma in patients previously exposed to the bacillus.

The following tests measure:

- QuantiFERON-TB Gold In-Tube: the amount of interferon-gamma released.
- T-SPOT.TB test: the number of interferon-gamma producing T cells<sup>[2]</sup>.

The advantage of IGRAs over TST is the absence of cross-reaction with BCG vaccine and most environmental mycobacteria.

IGRAs have some limitations:

- They do not distinguish latent/active TB.
- They are more complex than TST (equipment and trained laboratory technicians) and are not widely available.

A positive test indicates that LTBI is likely; a negative test indicates that it is unlikely.

After having ruled out active TB, a positive IGRA is an indication for treatment of LTBI ([Chapter 16](#)).

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## 3.3 Other investigations

In addition to TB diagnosis tests, the following investigations should be performed at baseline and during treatment. The purpose is to identify common comorbidities, contra-indications, as well as adverse effects of TB drugs.

**Table 3.10** – Other investigations in TB treatment

Tests	Indications
<b>Electrocardiogram (ECG)</b>	Patients on QT prolonging drugs
<b>Brief peripheral neuropathy screen (BPNS)<sup>(a)</sup></b>	Patients on linezolid
<b>Visual function tests</b>	Patients on MDR/RR-TB treatment including ethambutol, linezolid or thionamides
<b>Audiometry<sup>(b)</sup></b>	Patients on aminoglycosides
<b>Full blood count</b>	Patients on linezolid (or rifabutin)
<b>Liver function tests</b> Aspartate aminotransferase (AST) Alanine aminotransferase (ALT)	Patients with pre-existing hepatic disease Patients on MDR/RR-TB treatment
<b>Creatinine</b> Serum creatinine Creatinine clearance	Patients with pre-existing renal disease Patients on aminoglycosides
<b>Serum electrolytes (potassium)</b>	Patients on aminoglycosides
<b>Glycated haemoglobin (HbA1c), or Blood glucose level (fasting or random)</b>	All patients
<b>HIV, hepatitis B and C testing</b>	Patients with undocumented HIV, hepatitis B and C status
<b>CD4 count and viral load</b>	Patients with TB/HIV coinfection
<b>Thyroid stimulating hormone (TSH)</b>	Patients on thionamides or PAS
<b>Pregnancy test</b>	Patients of childbearing age with MDR/RR-TB

(a) BPNS is a clinical examination for detecting peripheral neuropathy and grading the severity of symptoms ([Appendix 16](#)).

(b) For children under 5 years, a specialized equipment and consultation are required.

For more information, see [Chapter 9](#), [Chapter 10](#) and [Chapter 11](#).



# Chapter 4: Diagnosis of active tuberculosis in children

[4.1 Introduction](#)

[4.2 Diagnostic approach](#)

[4.3 Paediatric diagnostic algorithms](#)

Update: March 2023

# 4.1 Introduction

In children, defined in this chapter as patients under 10 years, tuberculosis (TB), pulmonary (PTB) and extrapulmonary (EPTB), is a significant cause of morbidity and mortality.

Globally, WHO estimates that more than one million children develop active TB every year<sup>[1]</sup> and that 60% of TB cases in children are not diagnosed or not reported<sup>[2]</sup>.

After exposure, the risk of TB infection and progression to active TB is high in children under 5 years<sup>[3]</sup>.

Progression to active TB is rapid (within 12 months) in children under 2 years<sup>[4]</sup>.

HIV infection is a significant risk factor for developing TB in children under 1 year<sup>[5]</sup>.

The risk of miliary TB and EPTB, including severe forms such as TB meningitis, is higher in children under 5 years and in immunocompromised children<sup>[3]</sup>. The most common forms of EPTB are lymph node TB and pleural TB (pleural effusion). Osteoarticular TB represents 1 to 2% of TB in children<sup>[4]</sup>.

The risk of death from TB is higher in children under 2 years and children with HIV infection or severe acute malnutrition (SAM)<sup>[3]</sup>. Almost all deaths due to TB in children occur in those not receiving TB treatment, and in the vast majority of cases, in children under 5 years<sup>[6]</sup>.

TB treatment should not be delayed if investigations, or results of investigations, are not immediately available in children at high risk of TB or death from TB.

Children often have the same resistance profile as the index case, i.e. the person who is the presumed source of the infection. If the resistance profile is not available for the child, the resistance profile of the index case should be taken into account for the child's TB treatment.

Children are not considered infectious unless they have extensive lung involvement and/or cavitary PTB or positive smear microscopy.

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## 4.2 Diagnostic approach

Children with TB usually have non-specific symptoms. Clinicians should therefore look for TB, particularly in children:

- Under 2 years of age, or
- With HIV infection or SAM, or
- In contact with a person with TB, or
- Not responding to antibacterial and/or nutritional treatment.

The diagnosis of TB in children, particularly those under 5 years, is often based on a combination of history of exposure to a person with TB, clinical assessment and investigations, such as radiology, when available.

In children at high risk of death from TB, treatment should be initiated as soon a TB diagnosis is considered likely.

In children not at high risk of death from TB, the diagnosis may not be made at the first consultation. A second consultation after one to two weeks is often necessary to reassess the clinical status.

The diagnosis is often made without bacteriological confirmation as:

- Children under 5 years have low bacillary load and bacteriological tests are often negative.
- Specimens for diagnosis of EPTB may be difficult to collect.

TB is bacteriologically confirmed in only 20 to 30% of children<sup>[1]</sup>.

To facilitate the diagnosis of PTB and enable rapid treatment in children, WHO has developed diagnostic algorithms ([Section 4.3](#)).

The diagnosis of EPTB uses the same diagnostic approach. However, no evidence-based algorithms are currently available.

A trial of treatment with TB drugs is not recommended as a method to diagnose TB.

Once a decision is made to treat TB in a child, a full course of treatment should be given.

### 4.2.1 History of exposure to tuberculosis

Children are at risk of TB if they are exposed to a person with TB.

They are at higher risk of TB if:

- The index case is a household or close contact.
- The index case has PTB, sputum smear positive or cavities on chest x-ray.
- The exposure to the index case has occurred in the past 12 months.

**Note:** conversely, when TB is diagnosed in children, it is important to detect the index case and any other undiagnosed household member(s) or close contact(s).

### 4.2.2 Clinical assessment

#### Symptoms suggestive of tuberculosis

Ask if the child has symptoms commonly associated with TB:

- Cough for more than 2 weeks.
- Fever for more than 2 weeks.
- Night sweats that soak the bed or clothes.
- Weight loss or poor/no weight gain.
- Fatigue, reduced playfulness, loss of appetite.
- Haemoptysis (rare in children).
- Non-painful, enlarged cervical, submandibular, or axillary lymph nodes.
- Rapid breathing.

#### Physical examination and growth assessment

Look for signs suggestive of TB:

- Fever, tachypnoea, tachycardia.
- Weight loss, growth curve flattening, underweight or malnourished according to weight for height and/or mid-upper arm circumference.
- Abnormal pulmonary auscultation.
- Signs of respiratory distress and SpO<sub>2</sub> < 90-92%.
- Lethargy, altered mental status (may indicate TB meningitis).
- Signs of EPTB:
  - Highly suggestive, e.g.:
    - Angular deformity of the spine, loss of ability to walk.
    - Cervical lymph node with fistula formation.
  - Requiring further investigation, e.g.:
    - Sub-acute meningitis not responding to antibiotic treatment.
    - Ascites.
    - Lymph node without fistula formation.
    - Non-painful enlarged joint.

HIV status should be assessed in all children with presumed or confirmed TB.

### **Clinical review**

If diagnosis is not made at the first consultation, reassess the child (signs/symptoms suggestive of TB and growth) within one to two weeks maximum.

The following are suggestive of TB:

- Persistent or worsening pneumonia despite non-TB antibiotic treatment.
- No weight gain or weight loss despite nutritional support or treatment.
- Persistent fever after other causes have been ruled out or treated (e.g. malaria).
- Persistent or worsening fatigue, reduced playfulness, loss of appetite.

## **4.2.3 Baseline investigations**

When PTB or EPTB is suspected, perform bacteriological tests, lateral flow urine lipoarabinomannan assay if indicated, and radiography if available.

### **Bacteriological tests**

Rapid molecular tests (RMTs) should be performed on respiratory, stool or extrapulmonary (EP) specimens as the initial diagnostic test.

As the sensitivity of Xpert MTB/RIF Ultra is higher than that of Xpert MTB/RIF, preferably use MTB/RIF Ultra for the detection of TB and rifampicin-resistance ([Chapter 3](#)).

Sputum specimens can be difficult to obtain in children. Explanation and encouragement are important. Chest clapping may help expectoration.

If sputum cannot be obtained spontaneously, more invasive procedures, such as nasopharyngeal aspiration, sputum induction or gastric aspiration ([Appendix 3](#)), can be performed, but only if the specimen is collected for rapid molecular tests, culture or genome sequencing. These procedures should not be performed for smear microscopy.

Stool specimens (which may contain swallowed sputum) are an alternative to respiratory specimens for the diagnosis of PTB in children. Respiratory specimens are more likely to give a positive result, but the use of stool specimens can avoid invasive collection procedures.

For children at risk of DR-TB, i.e. contact with a person with DR-TB or coming from an area with high DR-TB prevalence:

- Multiple specimens (respiratory, stool and EP) should be tested with RMTs. Multiple testing increases the likelihood of detecting TB and obtaining the resistance profile.
- Every effort should be made to perform culture and phenotypic drug susceptibility tests ([Chapter 3](#)).

For the diagnostic accuracy of Xpert MTB/RIF in specimens other than sputum, see [Appendix 1](#).

### **Lateral flow urine lipoarabinomannan assay (LF-LAM)**

LF-LAM should be performed in children with HIV infection:

- With signs and symptoms of TB, or
- Hospitalised with advanced HIV disease, or
- Followed as outpatients with a low CD4 count.

### **Chest x-ray (CXR)**

CXR is particularly useful when bacteriological tests are negative or not available. It is also useful to assess the severity of TB and to determine eligibility for the 4-month drug-susceptible TB regimen ([Chapter 9](#)).

Children with PTB usually have abnormalities on CXR, but a normal CXR does not rule out TB.

For young children unable to stand alone, perform anteroposterior and lateral CXRs if possible (lateral CXR can improve detection of enlarged hilar/mediastinal lymph nodes).

For other children, perform a standard posteroanterior CXR.

CXR findings suggestive of TB in children include<sup>a</sup>: enlarged hilar/mediastinal lymph nodes, miliary pattern, and cavities. Although generally less specific, consolidation and pleural/pericardial effusion in a child not acutely ill is also suggestive of TB.

### **Ultrasound**

See [Chapter 3](#).

### **Tuberculin skin test (TST)**

In children, a positive TST may be one element among many to establish the diagnosis of active TB. However, it has many limitations ([Chapter 3](#) and [Appendix 9](#)).

## **4.2.4 Follow-up investigations**

For children able to expectorate spontaneously, smear microscopy is used to monitor treatment progress ([Chapter 3](#)).

For children unable to expectorate spontaneously, monitoring of treatment progress is clinical. Invasive procedures should not be performed to obtain respiratory specimens for smear microscopy.

## Footnotes

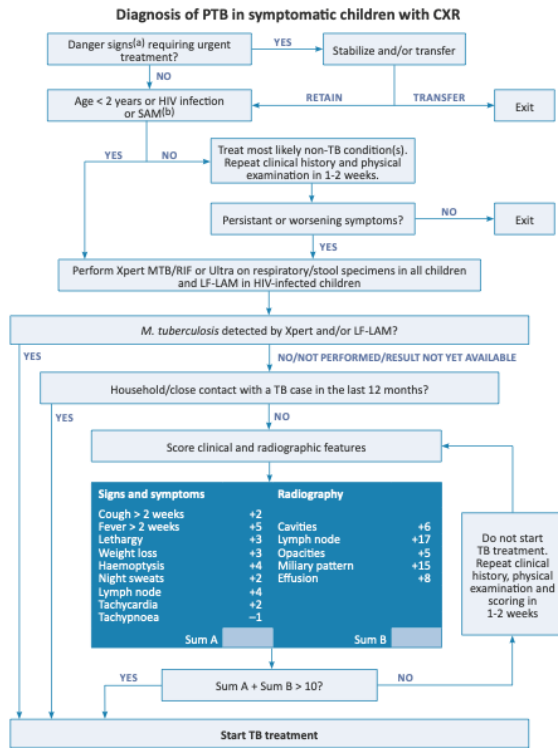
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# 4.3 Paediatric diagnostic algorithms

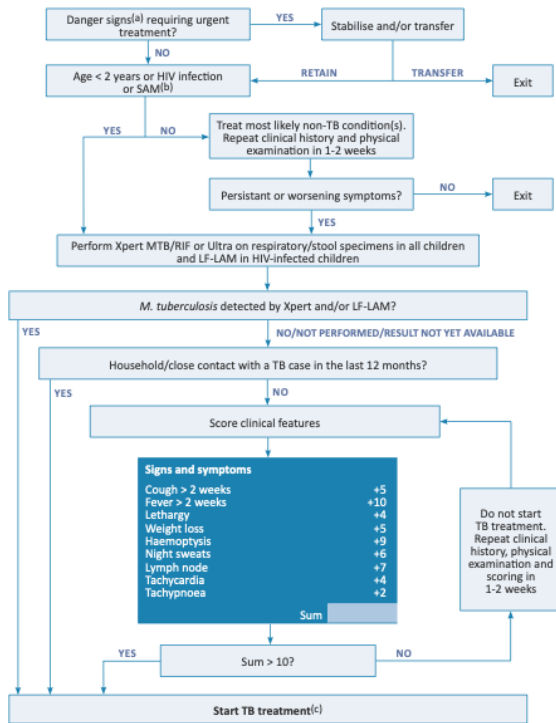
## 4.3.1 Diagnosis of PTB in symptomatic children with CXR



(a) Danger signs:  
 Children < 5 years: age < 2 months; unable to eat or drink; vomiting up everything; severe dehydration; severe pallor; stridor; SpO<sub>2</sub> < 90%; respiratory distress; seizures; profound lethargy or coma; restless, continuously irritable; neck stiffness or bulging fontanelle; fever > 39 °C; SAM.  
 Children ≥ 5 years: diarrhoea with severe dehydration; severe pallor; shock (cold extremities, capillary refill time > 3 seconds, weak and fast pulse); obstructed or absent breathing; respiratory distress; central cyanosis; coma (or seriously altered level of consciousness); seizures; restless, continuously irritable; fever > 39 °C; SAM.  
 (b) SAM: severe acute malnutrition is defined as weight-for-height in Z-score less than -3 or mid-upper arm circumference less than 115 mm.

## 4.3.2 Diagnosis of PTB in symptomatic children without CXR

### Diagnosis of PTB in symptomatic children without CXR



**(a) Danger signs:**

Children < 5 years: age < 2 months; unable to eat or drink; vomiting up everything; severe dehydration; severe pallor; stridor; SpO<sub>2</sub> < 90%; respiratory distress; seizures; profound lethargy or coma; restless, continuously irritable; neck stiffness or bulging fontanelle; fever > 39 °C; SAM.

Children ≥ 5 years: diarrhoea with severe dehydration; severe pallor; shock (cold extremities, capillary refill time > 3 seconds, weak and fast pulse); obstructed or absent breathing; respiratory distress; central cyanosis; coma (or seriously altered level of consciousness); seizures; restless, continuously irritable; fever > 39 °C; SAM.

**(b) SAM:** severe acute malnutrition is defined as weight-for-height in Z-score less than -3 or mid-upper arm circumference less than 115 mm.

**(c)** Once a decision to treat for TB is made, every effort should be made to obtain a CXR to assess the severity of TB.

# Chapter 5: Diagnostic algorithms for pulmonary tuberculosis (PTB) in adults and adolescents

[5.1 Guiding principles for the use of the algorithms](#)

[5.2 Adult and adolescent algorithms](#)

Update: January 2014



# 5.1 Guiding principles for the use of the algorithms

The aim of algorithms is to assist the diagnostic process and minimize incorrect diagnosis. The following algorithms are for adults and adolescents.

## 5.1.1 Clinical assessment<sup>[1]</sup>

– An assessment for danger signs is the first part of the clinical assessment. The adult or adolescent is classified as seriously ill if one or more of the following danger signs are present:

- Respiratory rate > 30/minute;
- Fever > 39°C;
- Pulse rate > 120/minute;
- Unable to walk unaided.

– In cases where there is no bacteriological confirmation of TB, the clinical (and radiological) assessment should determine if the patient needs broad-spectrum antibiotics and/or anti-TB drugs.

– HIV testing should be routinely offered to all individuals suspected of having TB. If testing is refused or unavailable, it might be assumed that a certain patient is likely to be HIVpositive (according to context and/or clinical presentation). In this event, follow the algorithm for HIV-infected patients.

## 5.1.2 Clinical response

For patients who are treated empirically for bacterial pneumonia or pneumocystosis (PCP), a “non-response to antibiotics” increases the likelihood of TB. The converse is not necessarily true, such that a response to antibiotics does not automatically exclude TB in a person suspected of having TB, particularly if respiratory symptoms persist after treatment. Pneumonia or PCP may occur in patients with underlying TB.

Antibiotic treatment is appropriate for HIV-infected patients with cough because bacterial infections are common both with and without TB. All seriously ill patients being started on anti-TB treatment should also be treated empirically, with broad-spectrum antibiotics for bacterial pneumonia because benefits outweigh the risks<sup>[1]</sup>.

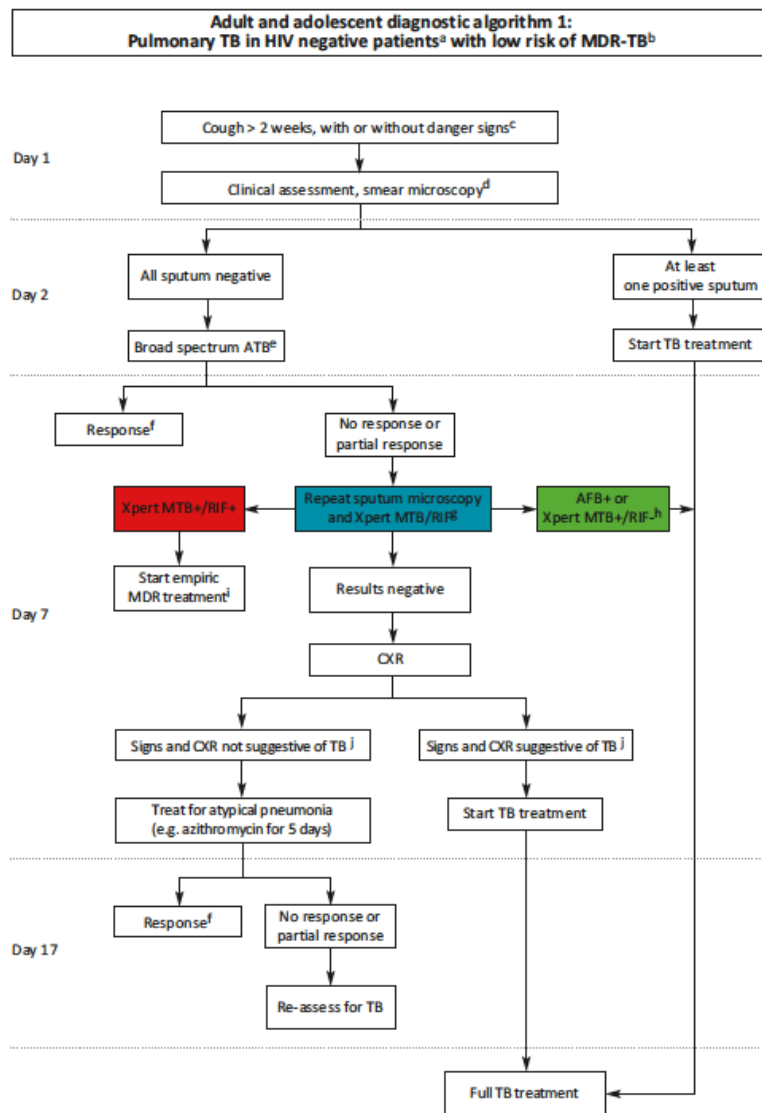
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# 5.2 Adult and adolescent algorithms

## Diagnostic algorithm 1

### PTB in HIV-negative patients with low risk of MDR-TB



<sup>a</sup>. When the patient's serological status is unknown, this algorithm should be used in settings with HIV prevalence < 5%.

<sup>b</sup>. Patients are considered to be at low risk of multidrug-resistant TB (MDR-TB) if they do not meet one of the following criteria: 1) resident in areas with high MDR-TB prevalence; 2) all retreatment categories; 3) exposure to a known MDR-TB case; 4) patient remaining smear + at 2 months; 5) exposure to institutions with high risk of MDR-TB (e.g. prisons).

<sup>c</sup>. Danger signs: respiratory rate > 30/min and/or fever > 39°C and/or pulse rate > 120/min and/or unable to walk.

<sup>d</sup>. Smear microscopy: two sputum examinations performed on the same day.

<sup>e</sup>. Broad spectrum ATB:

- If no danger signs: amoxicillin for 7 days (NO fluoroquinolones);
- If danger signs: parenteral ATB (e.g. ceftriaxone).

<sup>f</sup>. Clinical response to a broad spectrum antibiotic does not rule out TB. Patient should be informed to return for reassessment if symptoms recur.

<sup>g</sup>. According to setting:

- Xpert MTB/RIF available: two sputum smear microscopy on the same day and one Xpert MTB/RIF from one of the samples collected for smear microscopy;
- Xpert MTB/RIF not available: two sputum smear microscopy on the same day.

<sup>h</sup>. In groups of patients with high level of resistance to isoniazid (> 10%) it is recommended to perform a conventional DST at baseline (and/or a line probe assay) in order to provide adequate treatment.

i. According to setting:

- In groups of patients with prevalence of MDR-TB < 10%, patients seriously ill should immediately be initiated under empiric MDR-TB treatment. H and R will be included in the regimen until confirmation of MDR-TB by conventional methods. If the patient is stable, the clinician may choose to wait for confirmation before initiating a MDR treatment.
- In groups of patients with prevalence of MDR-TB ≥ 10%, patients should be initiated under empiric MDR-TB treatment. Consider adding H in settings where mono-resistance to R is not uncommon.

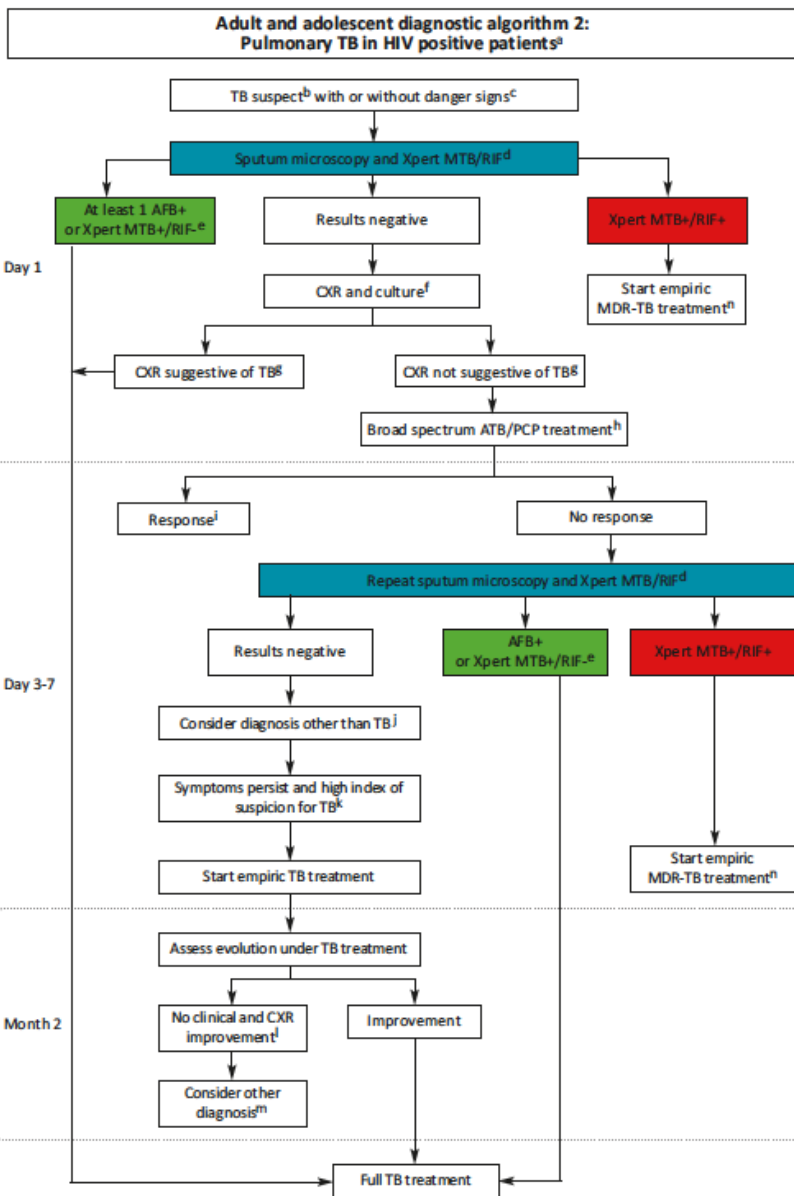
j. Clinical signs and chest X-ray (CXR) findings tend to be more typical in those who are HIV-negative having active TB:

	<b>TB</b>	<b>Bacterial pneumonia</b>
<b>Clinical signs</b>	Weight loss, productive cough, purulent sputum, haemoptysis, pleuritic chest pain	<ul style="list-style-type: none"><li>• Acute onset</li><li>• Fever</li></ul>
<b>CXR</b>	<ul style="list-style-type: none"><li>• Infiltrates, nodules with or without cavitation in the upper lobes and in the superior segments of the lower lobes.</li><li>• Pleural effusions</li><li>• Adenopathy in the mediastinum or hila (rare in TB in adults and adolescents)</li><li>• Miliary disease</li></ul>	<ul style="list-style-type: none"><li>• Lobar consolidation</li></ul>

When clinical signs AND CXR are strongly suggestive of active TB, treatment should be initiated without waiting for diagnosis confirmation.

## Diagnostic algorithm 2

### PTB in HIV-positive patients



<sup>a</sup>. When the patient's serological status is unknown, this algorithm should be used in settings with HIV prevalence > 5%.

<sup>b</sup>. TB suspect is defined as: cough for more than 2 weeks or any cough with at least one of the following signs: loss of weight, night sweats, fever, and suspicion based on clinical judgment.

<sup>c</sup>. Danger signs: respiratory rate > 30/min and/or fever > 39°C and/or pulse rate > 120/min and/or unable to walk.

<sup>d</sup>. According to setting:

- Xpert MTB/RIF available: two sputum smear microscopy on the same day AND one Xpert MTB/RIF from one of the samples collected for smear microscopy;
- Xpert MTB/RIF not available: two sputum smear microscopy on the same day.

<sup>e</sup>. In patients groups with high level of resistance to isoniazid (> 10%) it is recommended to perform a conventional DST at baseline (and/or a line probe assay) in order to provide adequate treatment.

<sup>f</sup>. When possible a culture should be performed. A positive culture result at any point in time in the algorithm should lead to a full TB treatment.

<sup>g</sup>. TB treatment should be started when clinical signs AND chest X-ray (CXR) are suggestive of TB (Note k).

<sup>h</sup>. Broad spectrum ATB/PCP:

- If no danger signs: amoxicillin for 7 days (or recommended oral agent for community-acquired pneumonia in the area). Do NOT use fluoroquinolones;
- If danger signs: parenteral ATB (e.g. ceftriaxone) AND high dose cotrimoxazole.

<sup>i</sup>. If no danger signs: patient should be re-assessed after 7 days.

If danger signs: patient should be assessed daily and if no response, TB treatment should be considered after 3 to 5 days.

Clinical response to broad-spectrum ATB does not rule out TB. Patient should be informed to return for reassessment if symptoms recur.

<sup>j</sup>. Differential diagnosis of a coughing HIV-infected adult/adolescent: bacterial (including atypical) pneumonia, PCP, fungal infection, non-tuberculous mycobacteria, nocardiosis, Kaposi sarcoma and lymphoma.

k. The diagnosis should be based on clinical assessment, CXR and CD4 results, whether cotrimoxazole preventive therapy (CPT) was used, and other treatment already used in the patient. If the index of suspicion for active TB is high, empiric TB treatment should be initiated without waiting for diagnosis confirmation. Other treatments such as broad-spectrum ATB or therapy for PCP may be needed in addition to TB treatment.

	TB	PCP (HIV+)	Bacterial pneumonia
<b>Clinical signs</b>	<ul style="list-style-type: none"> <li>• Current cough</li> <li>• Weight loss</li> <li>• Purulent sputum and haemoptysis less likely if HIV-positive with low CD4 count</li> <li>• Fever</li> <li>• Night sweats</li> <li>• Pleuritic chest pain</li> </ul>	<ul style="list-style-type: none"> <li>• Dry cough</li> <li>• Dyspnoea ++</li> <li>• Hypoxemia</li> <li>• Not on CPT</li> <li>• More likely if low CD4 count</li> </ul>	<ul style="list-style-type: none"> <li>• Acute onset</li> <li>• High fever</li> </ul>
<b>CXR</b>	<ul style="list-style-type: none"> <li>• Upper lobe infiltrates and cavitation only likely in HIV-positive adults with higher CD4 counts. Any lobe of the lung may be affected</li> <li>• In HIV-positive adults with lower CD4 counts, the following 4 patterns are suggestive of TB:               <ol style="list-style-type: none"> <li>1. miliary pattern</li> <li>2. pleural effusion without airspace (with straw-coloured liquid aspirate)</li> <li>3. hilar and mediastinal adenopathy</li> <li>4. large heart (especially if symmetrical and rounded)</li> </ol> </li> </ul>	<ul style="list-style-type: none"> <li>• Bilateral interstitial infiltrate with reticulonodular markings that are more pronounced in the lower lobes</li> <li>• Findings lag behind symptoms and may be normal early in the disease</li> </ul>	<ul style="list-style-type: none"> <li>• Lobar consolidation</li> </ul>

<sup>l</sup>. In the absence of any improvement of clinical signs (no weight gain, persistent cough, pain, etc.) AND no improvement on CXR after 2 months of a well conducted TB treatment, diagnosis and treatment should be reconsidered. MDR-TB should also be considered.

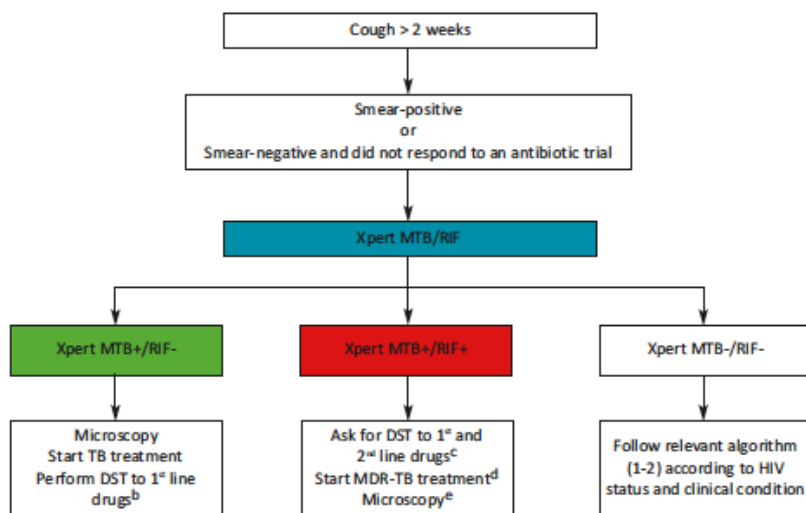
<sup>m</sup>. In addition to the differential diagnosis in Note k above, DR-TB should be considered.

<sup>n</sup>. Immediately start empiric MDR treatment, even if positive predictive value of Xpert MTB/RIF for R resistance is low (this is done to avoid the rapid and high mortality due to untreated MDR-TB in HIV patients). H and R should be included in the regimen until confirmation of MDR-TB by conventional methods if the patient comes from a group with less than a prevalence of MDR-TB < 10%. In groups of patients with prevalence of MDR-TB ≥ 10%, patients should be initiated under an empiric MDR treatment without H or R, although one can consider adding H in settings where mono-resistance to R is not uncommon.

## Diagnostic algorithm 3 with Xpert MTB/RIF

### PTB in patients with high risk of MDR-TB

Adult and adolescent diagnostic algorithm 3 with Xpert MTB/RIF: Pulmonary TB in patients with high risk of MDR-TB<sup>a</sup>



<sup>a</sup>. The following patients are considered to be at high risk of MDR-TB: 1) resident in areas with high MDR-TB prevalence; 2) all retreatment categories; 3) exposure to a known MDR-TB case; 4) patient remaining smear-positive at 2 months; 5) exposure to institutions with high risk of MDR-TB (e.g. prisons).

<sup>b</sup>. Groups of patients at risk of MDR-TB are also at risk of other types of DR-TB as well. DST to the first-line should be performed in order to provide adequate treatment for possible mono- or poly-drug resistance.

- <sup>c</sup>. In populations with a prevalence < 10% of MDR-TB, the resistance to R diagnosed by Xpert MTB/RIF must be confirmed by conventional methods. Drug sensitivity testing (DST) to both first-line drugs and secondline TB drugs should be performed if possible.
- <sup>d</sup>. • In groups of patients with prevalence of MDR-TB < 10%, the decision to start the MDR-TB treatment will be made on clinical presentation of the patient and immunological status. Patients seriously ill and/or HIV+ should be initiated immediately under empiric MDR-TB treatment. H and R will be included in the regimen until confirmation by conventional methods.
- In groups of patients with prevalence of MDR-TB ≥ 10%, the patient should be initiated using an empiric MDR-TB treatment. Consider adding H in settings where mono-resistance to R is not uncommon.
- <sup>e</sup>. Baseline sputum smear microscopy result on 1 specimen in order to: 1) allow patient follow-up with microscopy; 2) take immediate decisions related to TB infection control.

# Chapter 6: Screening for active tuberculosis

[6.1 Introduction](#)

[6.2 High-risk groups](#)

[6.3 Screening strategies and screening outcomes](#)

Update: October 2023

# 6.1 Introduction

Globally, up to 30% of people with tuberculosis (TB) are estimated to be undetected and thus untreated<sup>[1]</sup>.

The purpose of screening for active TB (also referred to as "intensive case finding for TB") is to improve case detection.

It aims to identify, within groups at high risk of TB (e.g. contacts of a person with TB, HIV-infected persons), individuals most at risk who should undergo a TB diagnostic test.

Screening allows for early diagnosis, and consequently early treatment, which contributes to improving treatment outcomes and reducing TB transmission.

Screening also allows the identification of people who may benefit from diagnosis and/or treatment of latent TB infection (LTBI).

Screening for active TB should be undertaken only if adequate capacity is available for the diagnosis and treatment of active TB.

## References

1. World Health Organization. *WHO consolidated guidelines on tuberculosis. Module 2: screening – systematic screening for tuberculosis disease*. Geneva: World Health Organization; 2021. Licence: CC BY-NC-SA 3.0 IGO.  
<https://www.who.int/publications/i/item/9789240022676>



## 6.2 High-risk groups

### 6.2.1 Contacts of a person with tuberculosis

- If the index patient has bacteriologically confirmed pulmonary TB (PTB): screening should be rapidly performed in all household and close contacts, regardless of age and HIV status.
- If the index patient has clinically diagnosed PTB or extrapulmonary TB (EPTB): screening should be rapidly performed in household and close contacts under 15 years and/or with HIV infection.

Depending on resources and national recommendations, screening for active TB can be extended to all household and close contacts, regardless of the form of TB of the index patient and regardless of age and HIV status of the contact.

For more information on screening strategies, see [Table 6.1](#).

#### Box 6.1 – WHO definitions for contacts<sup>[1]</sup>

- A **household contact** is a person who shared the same enclosed living space for one or more nights or for frequent or extended periods during the day with the index case during the 3 months before the start of current treatment.
- A **close contact** is a person who does not live in the household, but who shared an enclosed space, such as a social gathering place, workplace or facility, with the index case for extended periods during the day during the 3 months before the current disease episode commenced.

### 6.2.2 HIV-infected patients

- In HIV-infected outpatients, screening for active TB should be performed at each contact with a trained health worker (e.g. counsellor, nurse)<sup>[1][2]</sup>.
  - For children, screening is based on the presence of symptoms and/or a history of close contact with a person with TB.
  - For adolescents and adults, screening is based on the WHO four-symptom screen (W4SS).
- In HIV-infected inpatients, upfront diagnostic testing is recommended (lateral flow urine lipoarabinomannan assay and rapid molecular tests, see [Chapter 3](#)).

For more information on screening strategies, see [Table 6.1](#).

### 6.2.3 Other high-risk groups

Screening for active TB should be routinely performed in:

- Detained persons.
- Miners, and other persons with current or past exposure to silica, and patients with silicosis.

Screening for active TB can be considered, depending on local epidemiology, context, and resources, in:

- Patients with malnutrition, chronic diseases (e.g. diabetes, chronic obstructive pulmonary disease), persons over 60 years or previously treated for TB.
- Pregnant women.
- Staff of health facilities exposed to TB ([Chapter 15](#)).
- Urban population living in slums, homeless people, migrants from countries with a TB prevalence estimated to be 100/100,000 or higher.
- General population in areas with a TB prevalence estimated to be 500/100,000 or higher.

For more information on screening strategies, see [Table 6.1](#).

## References

1. World Health Organization. *WHO operational handbook on tuberculosis. Module 2: screening - systematic screening for tuberculosis disease*. Geneva: World Health Organization; 2021. Licence: CC BY-NC-SA 3.0 IGO. <https://www.who.int/publications/i/item/9789240022614>
2. World Health Organization. *WHO consolidated guidelines on tuberculosis. Module 2: screening – systematic screening for tuberculosis disease*. Geneva: World Health Organization; 2021. Licence: CC BY-NC-SA 3.0 IGO. <https://www.who.int/publications/i/item/9789240022676>

## 6.3 Screening strategies and screening outcomes

People screening positive should be referred for active TB diagnosis ([Chapter 3](#)).

People screening negative are unlikely to have active TB and should be referred for diagnosis and/or treatment of LTBI ([Chapter 16](#)).

**Table 6.1** – Examples of screening strategies by target group

Screening strategies	Positive screening
<b>Contacts and other high-risk groups<sup>(a)</sup></b>	
Ask for cough AND Perform CXR	Presence of cough AND/OR Abnormal CXR
Ask for cough THEN Perform CXR for those without cough	Presence of cough OR Abnormal CXR
Ask for any TB symptom: • Cough • Fever • Weight loss or poor weight gain • Night sweats • Haemoptysis • Reduced playfulness or lethargy in young children AND Perform CXR	Presence of at least one symptom AND/OR Abnormal CXR
Ask for any TB symptom (as above) THEN Perform CXR for those without any symptom	Presence of at least one symptom OR Abnormal CXR
Ask for any TB symptom <sup>(b)</sup> (as above)	Presence of at least one symptom
<b>Outpatient HIV-infected children &lt; 10 years<sup>(c)</sup></b>	
Ask for: • Cough • Fever • Poor weight gain <sup>(d)</sup> • Contact with a patient with TB	Presence of at least one symptom AND/OR Contact with a patient with TB
<b>Outpatient HIV-infected adolescents (&gt; 10 years) and adults on ART<sup>(e)(f)</sup></b>	
Ask for W4SS: • Cough • Fever • Weight loss • Night sweats AND Perform CXR	Presence of at least one symptom AND/OR Abnormal CXR
Ask for W4SS (as above) THEN Perform CXR for those without any W4SS	Presence of at least one symptom OR Abnormal CXR
Ask for W4SS (as above) <sup>(b)</sup>	Presence of at least one symptom

(a) In patients with chronic diseases (diabetes, etc.), detained persons and miners, symptom screening can be repeated as often as needed while CXR should be performed once a year.

- (b) Only if CXR is not available.
- (c) In HIV-infected children, CXR is not used as a screening tool.
- (d) Including: underweight, growth curve flattening, weight loss.
- (e) Symptom screening can be repeated as often as needed while CXR should be performed once a year.
- (f) In HIV-infected adolescents and adults stable on ART and pregnant women, combination of W4SS + CXR allows detection of the largest number of active TB cases.

Other screening strategies are possible depending on resources and/or national recommendations. For example:

- In contacts and other high-risk groups, screening can be based on CXR only.
- In HIV-infected adolescents and adults not on antiretroviral therapy, C-reactive protein (CRP) may be used in combination with other screening tools.

**Note:** digital CXR is preferred over X-ray film. Computer-aided detection (CAD) is particularly useful when CXR screening is performed in large populations ([Chapter 3](#)).

# Chapter 7: Case definitions for registration

[7.1 Definition of a tuberculosis case](#)

[7.2 History of prior anti-TB treatment](#)

[7.3 Anatomical site of the disease](#)

[7.4 Bacteriological status](#)

[7.5 HIV status](#)

[7.6 Other co-morbidities](#)

[7.7 Summary of patient registration](#)

**Update: January 2014**

## 7.1 Definition of a tuberculosis case

A tuberculosis (TB) case is a patient that has been diagnosed as such by a clinician, regardless if the diagnosis has been confirmed bacteriologically or not.

The elements necessary for defining a TB case are: the TB treatment history, the bacteriological status, the anatomical site of the disease and the patient's HIV status.

**Note:** any person receiving treatment for TB should be recorded as a TB case.

## 7.2 History of prior anti-TB treatment

Patients who have interrupted or failed a previous anti-TB treatment have a higher risk of developing drug-resistance (DR). Therefore, it is important to question patients about their previous treatment prior to treatment initiation.

Case registration distinguishes between<sup>[1]</sup>:

- **New patients:** patients who have never been treated for TB or have taken anti-TB drugs for less than 1 month.
- **Previously treated patients:** patients who have received 1 month or more of anti-TB drugs in the past.  
Previously treated patients are further sub-classified into relapse, failure and return after treatment interruption:
  - **Relapse:** patients who were cured or completed treatment on their last TB treatment;
  - **Failure:** patients who have failed their most recent treatment (see [Chapter 17](#) for outcome definitions for failure);
  - **Treatment interruption:** patients who interrupted (see [Chapter 17](#) for outcome definition of treatment interruption) their last treatment should be classified as "Return after treatment interruption".
- **Others:** patients who cannot be included in one of the above categories (e.g. patients who have previously been treated via an erratic or unknown TB regimen).

### References

1. World Health Organization. *Implementing the WHO STOP TB strategy: A handbook for national tuberculosis control programmes*. World Health Organization, Geneva. (WHO/HTM/TB/2008.401. 2008).  
<http://www.who.int/tb/strategy/en/>

## 7.3 Anatomical site of the disease

### **Pulmonary TB (PTB)**

Refers to a case of TB presenting with involvement of the lung parenchyma.

#### **Notes:**

- Miliary TB is also classified as PTB because there are lesions in the lungs.
- Any patient presenting with PTB and an EPTB form at the same time is classified as a PTB case for recording purposes.

### **Extrapulmonary TB (EPTB)**

Refers to a case of TB involving organs other than the lungs. Diagnosis is based on clinical signs corresponding to extrapulmonary active TB and a decision by a clinician to treat with a full course of anti-TB drugs<sup>a</sup>.

#### **Notes:**

- Sputum smear microscopy should always be done, and if possible culture and/or molecular test.
- Patients presenting with tuberculous pleural effusion, or mediastinal lymphadenopathy without evidence of parenchymal localization are classified in this category.

### **Footnotes**

(a) If possible, obtain histological or bacteriological evidence (microscopy, culture or molecular test).

## 7.4 Bacteriological status

Bacteriological status refers to the detection of *M. tuberculosis* by smear, culture or molecular methods. The bacteriological status can be further sub-classified on the basis of drug sensitive and drug resistant cases.

### 7.4.1 Detection of *M. tuberculosis*

Every TB case should be classified into one of two categories:

- **Confirmed TB case:** a case with a positive bacteriological result (microscopy, culture or molecular method).
- **Non-confirmed TB case:** a case where investigations are negative (microscopy, culture or molecular method) and for whom a clinician prescribes anti-TB treatment.

Confirmed TB cases are further sub-classified as:

1. smear positive/negative/not done
2. culture positive/negative/not done
3. molecular test positive/negative/not done

### 7.4.2 Strain sensitivity/resistance

When possible, culture and DST should be done to determine if the strain presents resistance to some drugs:

- **Susceptible TB:** the strain is not resistant to any first-line anti-TB drugs.
- **Drug-resistant TB:**
  - **Monodrug-resistant TB:** resistance to one first-line anti-TB drug only;
  - **Polydrug-resistant TB (PDR-TB):** resistance to more than one first-line anti-TB drug, other than isoniazid and rifampicin;
  - **Multidrug-resistant TB (MDR-TB):** resistance to at least isoniazid and rifampicin;
  - **Extensively drug-resistant TB (XDR-TB):** MDR-TB resistant to at least one fluoroquinolone and at least one second-line injectable drug (Km, Amk, Cm).

Patients with DR-TB should be classified in the following manner:

- **Confirmed isoniazid resistance and rifampicin susceptible:** resistance to isoniazid but not rifampicin. Resistance to first and second-line anti-TB drugs may be present.
- **Confirmed rifampicin resistant TB (RR-TB):** resistance to rifampicin confirmed by phenotypic drug susceptibility test or line probe assay or Xpert MTB/RIF (isoniazid susceptible or unknown).
- **Confirmed MDR-TB:** resistance to isoniazid and rifampicin, with or without resistance to first and second-line anti-TB drugs.
- **Confirmed XDR-TB:** resistance to isoniazid and rifampicin, and to at least one fluoroquinolone, and one second-line injectable drug (Km, Amk, Cm).
- **Unconfirmed DR-TB:** patients treated as DR-TB but without DST results (e.g. children who are contacts of a known case, patients with clinical failure and for whom no DST was available for some reason).



## 7.5 HIV status

Determining and recording the patient's HIV status is critical for treatment decisions, as well as for assessing programme performances. The TB treatment card and TB register, which should be treated as confidential documents, should include: dates and results of HIV tests, starting date of cotrimoxazole and antiretroviral therapy.

## 7.6 Other co-morbidities

Any other significant diseases, such as diabetes, hepatitis B or C, cancer and malnutrition, should be noted at registration.

# 7.7 Summary of patient registration

Table 7.1 summarizes the elements necessary for defining a TB case.

**Table 7.1** - Patient registration by outcome of most recent TB treatment<sup>[1]</sup>

Registration groups based on treatment history		Further classification
New		<ol style="list-style-type: none"> <li>1. <b>PTB or EPTB?</b> If EPTB, indicate site.</li> <li>2. <b>Bacteriologically confirmed or non-confirmed TB case?</b></li> <li>3. <b>Sub-category of bacteriological status:</b> <ul style="list-style-type: none"> <li>▫ Smear positive/negative/not done</li> <li>▫ Culture positive/negative/not done</li> <li>▫ Molecular test positive/negative/not done</li> </ul> </li> <li>4. <b>If previously treated:</b> <ul style="list-style-type: none"> <li>▫ Document last regimen received</li> <li>▫ History of second-line drug use</li> </ul> </li> <li>5. <b>DST pattern:</b> susceptible to H and R, confirmed H resistance and R susceptible, RR-TB, MDR-TB or XDR-TB</li> <li>6. <b>HIV status</b> (negative/positive/not done)</li> <li>7. <b>Other co-morbidities?</b></li> </ol>
Previously treated	Relapse	
	Failure	
	Treatment interruption	
Other		

## References

1. World Health Organization. *Treatment of Tuberculosis Guidelines 4<sup>th</sup> edition*. World Health Organization, Geneva. 2009. (WHO/HTM/TB/2009.420). [http://whqlibdoc.who.int/publications/2010/9789241547833\\_eng.pdf](http://whqlibdoc.who.int/publications/2010/9789241547833_eng.pdf)

# Chapter 8: Tuberculosis drugs and treatment regimens

[8.1 Introduction](#)

[8.2 Standard code for treatment regimens](#)

[8.3 Drugs for drug-susceptible tuberculosis](#)

[8.4 Drugs for drug-resistant tuberculosis](#)

[8.5 Tuberculosis drug formulations](#)

Update: October 2022

# 8.1 Introduction

A combination of several antituberculosis drugs is needed to treat tuberculosis (TB) and prevent the emergence of resistance. Each TB drug has a specific action on one or more bacillary populations, but none on dormant bacilli.

TB drugs are classified into two categories:

- Drugs for drug-susceptible TB (DS-TB), also referred to as "first-line TB drugs".
- Drugs for drug-resistant TB (DR-TB), also referred to as "second-line TB drugs". WHO has further classified DR-TB drugs in groups based on their effectiveness and safety profile.

Treatment regimens define the TB drug combinations used and the intended duration of TB treatment.

For more information on the TB drugs, see [Appendix 10](#).

# 8.2 Standard code for treatment regimens

## 8.2.1 Tuberculosis drugs

Each TB drug has an abbreviation.

**Table 8.1** – Categories and abbreviations of TB drugs

Categories	TB drugs	Abbreviations
<b>Drug-susceptible TB</b> (first-line drugs)		
	Isoniazid (standard dose) Rifampicin Pyrazinamide Ethambutol Rifabutin Rifapentine	H R Z E Rfb P
<b>Drug-resistant TB</b> (second-line drugs)		
<b>Group A</b>	Levofloxacin or moxifloxacin Bedaquiline Linezolid	Lfx or Mfx Bdq Lzd
<b>Group B</b>	Clofazimine Cycloserine or terizidone	Cfz Cs or Trd
<b>Group C</b>	Delamanid Ethambutol Pyrazinamide Imipenem/cilastatin or meropenem Amikacin or streptomycin Ethionamide or prothionamide Para-aminosalicylate sodium or para-aminosalicylic acid Isoniazid (high-dose)	Dlm E Z Ipm/Cln or Mpm Am or S Eto or Pto PAS H <sup>h</sup>
<b>Ungrouped</b>	Pretomanid	Pa

**Notes:**

- High-dose isoniazid, although not a Group C drug according to the WHO classification, is considered in this guide as a Group C drug as it is used as such when building a treatment regimen for DR-TB.
- Pretomanid is not categorized in the WHO classification and is only used in standard treatment regimens for DR-TB ([Chapter 10](#)).

## 8.2.2 Treatment regimens

TB treatment regimens are expressed as follows:

- Drugs are designated by their abbreviation.
- For some regimens, the treatment is divided into two phases: initial (or intensive) phase, and continuation phase. The phases are separated by a slash /.
- Letters in brackets ( ) indicate fixed-dose combinations (FDCs).
- Letters that are not in brackets indicate individual drugs.
- Second-line drugs are separated by a hyphen.
- Letters in square brackets [ ] indicate that drugs are used, but not considered as likely effective ([Chapter 10](#)).
- A superscript h (<sup>h</sup>) indicates that the drug is administered in a high dose.
- Numbers before letters indicate the duration (in months) of the treatment or of each phase.
- Numbers in subscript and angle brackets < > after a drug indicate the duration (in months) of the treatment with this drug.

**Box 8.1** – Examples

**2(HRZE)/4(HR)**: the initial phase lasts 2 months with an FDC containing 4 drugs; the continuation phase lasts 4 months, with an FDC containing 2 drugs.

**18Bdq-Lzd-Cfz-Cs-Dlm-[Z]**: the treatment lasts 18 months with 6 individual drugs; Z is used, but not considered as a likely effective drug.

**4Bdq<sub>6</sub>-Lfx-Cfz-Z-E-H<sup>h</sup>-Lzd<sub>2</sub>/5Lfx-Cfz-Z-E**: the initial phase lasts 4 months but bedaquiline is given for 6 months and linezolid for 2 months only; the continuation phase lasts 5 months.

## 8.3 Drugs for drug-susceptible tuberculosis

All drugs used for DS-TB treatment are taken 7 days a week.

### 8.3.1 First-line drugs

Table 8.2 – Main characteristics of first-line TB drugs

TB drugs	Activity	Resistance
Isoniazid	Bactericidal	<ul style="list-style-type: none"><li>• High level of resistance in some regions.</li><li>• Cross-resistance with thionamides.</li></ul>
Rifampicin Rifabutin Rifapentine	Bactericidal	<ul style="list-style-type: none"><li>• High level of resistance to rifampicin in some regions.</li><li>• High level of cross-resistance between rifamycins.</li></ul>
Ethambutol	Bacteriostatic	Unknown (no reliable drug susceptibility test for ethambutol).
Pyrazinamide	Weakly bactericidal	High level of resistance in regions where rifampicin resistance is frequent.

#### Isoniazid

Isoniazid is usually well tolerated at recommended doses.

It may cause peripheral neuropathy, hepatotoxicity, and hypersensitivity reactions.

Peripheral neuropathy can be prevented by administration of pyridoxine (vitamin B<sub>6</sub>). See [Appendix 17](#).

#### Rifamycins (rifampicin, rifabutin, rifapentine)

Rifamycins are usually well tolerated at recommended doses.

They may cause hypersensitivity reactions, hepatotoxicity, and thrombocytopenia.

They are strong inducers of cytochrome P450 and can affect the plasma concentrations of many drugs ([Appendix 19](#)).

Rifampicin is the most used rifamycin in the treatment of DS-TB.

Rifabutin is used instead of rifampicin in patients taking certain antiretrovirals ([Appendix 19](#)).

Rifapentine is only used in the 4-month regimen 2HPZ-Mfx/2HP-Mfx.

**Note:** rifampicin and rifapentine are also used to treat latent TB infection ([Chapter 16](#)).

#### Ethambutol

Ethambutol is usually well tolerated, including in children, particularly with respect to ocular toxicity<sup>[1]</sup>. Ocular toxicity is dose- and duration-dependent. It is uncommon when ethambutol is used at the recommended dose for 2 months.

#### Pyrazinamide

Pyrazinamide is usually well tolerated however, it may cause hepatotoxicity, gout, arthralgias and photosensitivity.

### 8.3.2 Other drugs

Two second-line drugs are also used in the treatment of DS-TB: moxifloxacin ([Section 8.4.1](#)) and ethionamide ([Section 8.4.3](#)).

## References

1. World Health Organization. *Guidance for national tuberculosis programmes on the management of tuberculosis in children*. Geneva: World Health Organization; 2014. [https://apps.who.int/iris/bitstream/handle/10665/112360/9789241548748\\_eng.pdf?sequence=1](https://apps.who.int/iris/bitstream/handle/10665/112360/9789241548748_eng.pdf?sequence=1)



## 8.4 Drugs for drug-resistant tuberculosis

Drugs used for DR-TB treatment (except bedaquiline) are taken 7 days a week.

### 8.4.1 Group A drugs

Table 8.3 – Main characteristics of TB drugs Group A

TB drugs	Classes	Activity	Resistance
<b>Levofloxacin</b> <b>Moxifloxacin</b>	Fluoroquinolones (FQs)	Bactericidal	<ul style="list-style-type: none"> <li>Resistance common in some regions.</li> <li>Cross-resistance between FQs.</li> </ul>
<b>Bedaquiline</b>	Diarylquinolines	Bactericidal	<ul style="list-style-type: none"> <li>Partial cross-resistance with Cfz.</li> <li>Growing resistance as use increases.</li> </ul>
<b>Linezolid</b>	Oxazolidinones	Bactericidal	Resistance assumed to be rare due to its limited use.

#### Fluoroquinolones (levofloxacin, moxifloxacin)

FQs are usually well tolerated.

They may cause tendinopathy and QT prolongation.

Moxifloxacin is sometimes used at high dose (Mfx<sup>h</sup>) in the presence of low-level resistance to FQs.

#### Bedaquiline

Bedaquiline is usually well tolerated. It may cause hepatotoxicity and QT prolongation.

Bedaquiline has a long half-life (5.5 months). Therefore, adverse effects can persist after the drug is stopped, and if TB is still active, resistance can develop.

Bedaquiline is metabolized in the liver by the cytochrome P450 (CYP450) system enzymes. Drugs, which induce or inhibit CYP450, can affect bedaquiline plasma concentrations and should be avoided ([Appendix 19](#)).

The extent of cross-resistance bedaquiline/clofazimine and the clinical implications are not fully understood<sup>[1][2][3]</sup>.

#### Linezolid

Linezolid may cause myelosuppression, dose- and duration-dependent neuropathy and lactic acidosis.

Pyridoxine supplementation (vitamin B<sub>6</sub>) is recommended for all patients on linezolid, although there is no evidence that pyridoxine can prevent linezolid-induced neuropathy.

Adverse effects frequently lead to reducing the dose or discontinuing linezolid. The optimal dose and duration of treatment are not established.

Linezolid has many interactions and overlapping toxicities with other drugs (e.g. risk of serotonin syndrome when administered with serotonergic drugs<sup>[4]</sup>). However, it is not always possible to avoid concomitant use of these drugs (e.g. even on linezolid, a patient with depression may require an antidepressant).

### 8.4.2 Group B drugs

Table 8.4 – Main characteristics of TB drugs Group B

TB drugs	Classes	Activity	Resistance
<b>Clofazimine</b>	Riminophenazine (anti-leprosy drug)	Probably bacteriostatic	<ul style="list-style-type: none"> <li>Partial cross-resistance with Bdq.</li> <li>Growing resistance as use increases.</li> </ul>
<b>Cycloserine</b> <b>Terizidone</b>	Analogue of D-alanine	Bacteriostatic	<ul style="list-style-type: none"> <li>Resistance common in areas where it has been used extensively.</li> <li>Full cross-resistance between the 2 drugs.</li> </ul>

#### Clofazimine

Clofazimine is a QT-prolonging drug.

Orange-pink to brownish-black discolouration of the skin and body fluids occur in almost all patients. These changes are reversible and not harmful.

Clofazimine has a long half-life (approximately 70 days). Consequently, its adverse effects can persist for several weeks or months after the drug is stopped.

#### Cycloserine or terizidone

Cycloserine and terizidone are structural analogues used at the same dose.

Both drugs may cause neurotoxicity including psychiatric adverse events.

To prevent neurotoxicity, pyridoxine (vitamin B<sub>6</sub>) should be administered along with these drugs throughout the course of treatment ([Appendix 17](#)).

## 8.4.3 Group C drugs

**Table 8.5** – Main characteristics of TB drugs Group C

TB drugs	Classes	Activity	Resistance
<b>Delamanid</b>	Nitroimidazooxazines	Bactericidal	<ul style="list-style-type: none"> <li>• Potential cross-resistance with pretomanid.</li> <li>• Resistance assumed to be rare due to its limited use.</li> </ul>
<b>Ethambutol</b>		Bacteriostatic	High prevalence of resistance among MDR/RR-TB patients (> 49% in some settings <sup>[5][6]</sup> ).
<b>Pyrazinamide</b>		Bactericidal	High prevalence among MDR/RR-TB patients (> 80% in some areas <sup>[7][8]</sup> ).
<b>Imipenem/cilastatin</b> <b>Meropenem</b>	Carbapenems		Full cross-resistance between carbapenems.
<b>Amikacin</b> <b>Streptomycin</b>	Aminoglycosides	Bactericidal	Partial cross-resistance between the 2 drugs.
<b>Ethionamide</b> <b>Prothionamide</b>	Thionamides	Weak bacteriostatic	<ul style="list-style-type: none"> <li>• Full cross-resistance between thionamides.</li> <li>• Cross-resistance with isoniazid if inhA mutation present.</li> <li>• High prevalence of resistance among MDR-TB patients in some areas<sup>[9]</sup>.</li> </ul>
<b>Para-aminosalicylate sodium</b> <b>Para-aminosalicylic acid</b>		Weak bacteriostatic	Common in some regions.
<b>Isoniazid high-dose</b>			Cross-resistance with thionamides if inhA mutation present.

### Delamanid

Delamanid is usually well tolerated.

It may cause QT prolongation<sup>[10]</sup>.

It is particularly useful in patients with pre-existing hepatic disease (no reported hepatotoxicity) or HIV infection (no significant drug interactions or overlapping toxicities with antiretrovirals).

It is also useful for replacing a Group A or B drug causing toxicity.

### Ethambutol

See [Section 8.3.1](#). Vision monitoring is required when ethambutol is administered for more than 2 months (risk of optic neuritis).

### Pyrazinamide

See [Section 8.3.1](#).

### Carbapenems (imipenem/cilastatin, meropenem)

Imipenem is always combined with cilastatin. Cilastatin has no antibacterial activity, its role is to inhibit a renal enzyme that inactivates imipenem.

Meropenem does not need to be combined with cilastatin, as it is metabolised through a different pathway.

High cost and difficulty with administration limits the use of carbapenems.

Carbapenems may cause gastrointestinal disturbances, neurotoxicity and hypersensitivity reactions.

Meropenem should be used in children and adolescents under 15 years, and if possible, in epileptic patients and patients with TB meningitis (risk of seizures lower than with imipenem/cilastatin).

The first dose is always administered in a health facility so that an eventual hypersensitivity reaction can be managed. If conditions permit, carbapenems can be continued as an outpatient.

Amoxicillin/clavulanic acid is routinely administered prior to carbapenems, as clavulanic acid prevents the development of carbapenem resistance.

### Aminoglycosides (amikacin, streptomycin)

Aminoglycosides should only be used when no alternative is available. Most patients with DR-TB can be treated without aminoglycosides, including some cases of extensively drug-resistant TB (XDR-TB).

Aminoglycosides are nephrotoxic and ototoxic drugs. Streptomycin is less nephrotoxic than other aminoglycosides, but causes vestibular toxicity<sup>[11]</sup> more frequently. If an aminoglycoside is used, close monitoring is essential (audiometry, electrolytes and renal function). If close monitoring cannot be ensured, aminoglycosides should not be used.

**Note:** kanamycin and capreomycin are no longer recommended, as their use is associated with higher rates of treatment failure and death<sup>[12]</sup>.

#### **Thionamides (ethionamide, prothionamide)**

Ethionamide and prothionamide are used at the same dose.

They may cause gastrointestinal disturbances, hypothyroidism (especially if co-administered with para-aminosalicylic acid), neuropathy and hepatotoxicity. In patients with diabetes, the dose of antidiabetics may need to be adjusted.

#### **Para-aminosalicylate sodium or para-aminosalicylic acid**

PAS often causes gastrointestinal disturbances and can decrease the absorption of other TB drugs. It may also cause hypothyroidism, especially when co-administered with a thionamide.

#### **High-dose isoniazid**

See [Section 8.3.1](#). There is limited evidence to support the use of high-dose isoniazid.

High-dose isoniazid may cause more adverse effects than the standard dose.

It has overlapping toxicity with linezolid (neuropathy) and hepatotoxic drugs.

To prevent peripheral neuropathy, pyridoxine (vitamin B<sub>6</sub>) should be administered to all patients throughout the course of treatment ([Appendix 17](#)).

## **8.4.4 Ungrouped drugs**

#### **Pretomanid**

Pretomanid belongs to the same class as delamanid and has bactericidal activity.

It is used only as part of standard regimens for DR-TB in the following combinations: BPaLM, BPaL (and BPaLC in operational research conditions), see [Chapter 10](#).

Regimens that include bedaquiline, pretomanid and linezolid may cause hepatotoxicity, lactic acidosis, myelosuppression, neuropathy and QT prolongation. Pretomanid/delamanid cross-resistance is likely.

## **8.4.5 Other drugs**

#### **Amoxicillin/clavulanic acid**

Amoxicillin/clavulanic acid is administered before each dose of carbapenem.

The clavulanic acid component prevents the development of carbapenem resistance.

Only formulations with a ratio of 4:1 (e.g. 500/125 mg) or 2:1 (e.g. 250/125 mg) are suitable for this indication. Do not use formulations with a ratio of 8:1 or 7:1.

## **References**

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## 8.5 Tuberculosis drug formulations

Only quality-assured drugs should be used. Several internationally recognized mechanisms ensure the quality of TB drugs<sup>a, b</sup>.

### 8.5.1 Fixed-dose combinations

FDC formulations combine several TB drugs (2, 3 or 4) in the same tablet. FDCs are only available for first-line TB drugs. FDCs improve adherence (decreased pill burden, decreased risk of omission of one or more drugs).

Table 8.6 – Quality-assured FDC formulations

FDCs	Available formulations
<b>Children</b>	
HZR	H50 mg/Z150 mg/R75 mg
HR	H50 mg/R75 mg
<b>Adults</b>	
EHZR	E275 mg/H75 mg/Z400 mg/R150 mg
EHR	E275 mg/H75 mg/R150 mg
HR	H75 mg/R150 mg

**Note:** when needed in children, ethambutol is given as a single formulation, in addition to the paediatric FDCs.

### 8.5.2 Individual drugs

Quality-assured single drug formulations are available for all first-line TB drugs. It may be necessary to use them when FDCs cannot be used due to adverse effects or drug interactions.

There are no quality-assured FDCs for second-line TB drugs. The treatment of DR-TB is based on a combination of individual drugs.

### 8.5.3 Paediatric formulations

Paediatric formulations should be used whenever possible.

However, they are not available for all TB drugs. When the only option is to manipulate the adult formulations:

- Preferably use scored tablets.
- Ensure that tablets/capsules can be split, crushed or opened (e.g. active ingredients may be protected from gastric acidity by an enteric coating).
- If tablets must be crushed (or capsules opened), a fraction of the powder corresponding to the required dose is mixed with food or liquids. Such manipulations should be done immediately before administering the drug. Any remaining powder should be discarded.
- The preparation of extemporaneous formulations using adult formulations is an alternative, however, this can only be considered if there are qualified personnel to ensure preparation in compliance with the appropriate compounding procedures.

#### Footnotes

(a) Quality assurance:

- WHO Prequalification Scheme: <http://apps.who.int/prequal/>
- Stringent Regulatory Authorities (SRA): <https://www.who.int/initiatives/who-listed-authority-reg-authorities/SRAs>

(b) Supply:

- Global Drug Facility: <https://www.stoptb.org/facilitate-access-to-tb-drugs-diagnostics/global-drug-facility-gdf>

# Chapter 9: Treatment of drug-susceptible tuberculosis

[9.1 Introduction](#)

[9.2 Conventional treatment regimens](#)

[9.3 Alternative treatment regimens](#)

[9.4 Special situations](#)

[9.5 Adjunctive therapy](#)

[9.6 Patient monitoring](#)

[9.7 Adverse effects](#)

[9.8 Treatment adaptation and change of treatment](#)

[9.9 Treatment interruptions](#)

Update: October 2022

# 9.1 Introduction

Drug-susceptible tuberculosis (DS-TB) treatment is indicated:

- When susceptibility to rifampicin and isoniazid is confirmed by drug susceptibility testing (DST), or
- If the probability of resistance to rifampicin and isoniazid is low:
  - while waiting for DST results for rifampicin and/or isoniazid,
  - when susceptibility to rifampicin is confirmed and susceptibility to isoniazid cannot be tested.

The probability of resistance is considered low in the following situations:

- No previous TB treatment;
- No contact with a drug-resistant TB (DR-TB) patient;
- The patient comes from an area of low prevalence of resistance according to drug resistance surveys.

Patients with DS-TB should start a conventional regimen based on first-line drugs ([Table 9.1](#)) or, if eligible, an alternative regimen ([Table 9.2](#)).

All regimens for DS-TB are standard regimens.

For dosages of fixed-dose combinations, see [Appendix 13](#).

For dosages of individual drugs, see [Appendix 10](#).

## 9.2 Conventional treatment regimens

**Table 9.1** – Conventional DS-TB regimens according to the infection site

Regimens Duration	Eligibility
<b>2(HRZE)/2(HR)</b> 4 months	Children > 3 months and adolescents < 16 years with <sup>[1]</sup> : <b>Pulmonary TB (PTB)</b> <ul style="list-style-type: none"> <li>microscopy smear-negative or Xpert result "negative", "trace", "very low" and "low"</li> </ul> or <ul style="list-style-type: none"> <li>clinically diagnosed with TB lesions confined to one lobe and no cavities on chest x-ray (CXR)</li> </ul> <b>Extrapulmonary TB (EPTB)</b> non severe, i.e.: <ul style="list-style-type: none"> <li>pleural effusion without complications (e.g. no empyema, pneumothorax or fistula)</li> <li>extra- or intra-thoracic lymph node TB with no airway obstruction</li> </ul>
<b>2(HRZE)/4(HR)</b> 6 months	<b>PTB and EPTB (except miliary TB, TB meningitis and bone and joint TB)</b> <sup>[2]</sup> Adolescents ≥ 16 years and adults Children and adolescents < 16 years not eligible for the 4-month regimen or when the national protocol does not include the 4-month regimen.
<b>2(HRZE)/10(HR)</b> 12 months	<b>Miliary TB and TB meningitis</b> <sup>[3]</sup> All children, adolescents and adults.
<b>2(HRZE)/7-10(HR)</b> 9-12 months	<b>Bone and joint TB</b> <sup>[4]</sup> All children, adolescents and adults.

If bacteriological testing and/or CXR are not available, children meeting the following criteria are eligible for the 4-month regimen 2(HRZE)/2(HR):

- Signs and symptoms not requiring hospitalisation<sup>a</sup>.
- Extra-thoracic lymph node TB without involvement of other EP sites.

If after one month of treatment symptoms have completely resolved, continue treatment until the end. If symptoms have not completely resolved, further investigations are needed.

If after 4 months of treatment symptoms have not completely resolved and/or there is no weight gain, further investigation is needed. The treatment can be extended to 6 months if causes of non-response to treatment (including DR-TB, non-adherence and non-TB disease) are ruled out or unlikely.

Ethambutol can be removed from the 4- and 6-month regimens in non-HIV-infected children living in areas where the prevalence of HIV and/or isoniazid resistance is low with:

- PTB microscopy smear-negative, or
- Extra- or intra-thoracic lymph node TB<sup>[5]</sup>.

For spinal TB, rest and back support bracing are indicated in addition to drug therapy. For patients with neurological deficit or unstable spine lesion, surgery can also be considered.

### Footnotes

- (a) Symptoms requiring hospitalisation: signs of severe respiratory disease or distress, severe acute malnutrition, fever > 39 °C, severe pallor, restlessness, irritability or lethargy, etc.

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## 9.3 Alternative treatment regimens

**Table 9.2** – Alternative DS-TB regimens according to the infection site

Regimens Duration	Eligibility
<b>2HPZ-Mfx/2HP-Mfx</b> 4 months	<b>PTB and non-severe EPTB</b> <sup>[1][2]</sup> Adolescents ≥ 12 years and adults meeting all the following criteria: <ul style="list-style-type: none"> <li>• Weight ≥ 40 kg</li> <li>• CD4 ≥ 100 if HIV-infected</li> <li>• No resistance to fluoroquinolones (FQs) or living in areas where the prevalence of FQs resistance is low.</li> </ul>
<b>6HRZ-Eto</b> 6 months	<b>TB meningitis</b> <sup>[3]</sup> Non-HIV infected children and adolescents under 20 years without inhA mutation detected.

### Regimen 2HPZ-Mfx/2HP-Mfx

- This regimen is an alternative to the conventional regimens for PTB and EPTB in eligible patients.
- Implementation requires DST to FQs and supply of rifapentine.
- There are no fixed-dose combinations (FDC) for this regimen which makes treatment adherence more difficult.

### Regimen 6HRZ-Eto

- Small studies have shown lower mortality, but more neurological sequelae with the 6HRZ-Eto regimen compared to the 12-month conventional regimen. However, no clinical trials have been conducted to compare the two regimens<sup>[3]</sup>.
- The advantages of this regimen are short duration and better central nervous system penetration of ethionamide compared to ethambutol.
- Implementation requires supply of ethionamide.
- There are no FDC for this regimen which makes treatment adherence more difficult.
- The daily doses of TB drugs in this regimen are higher than those of other regimens:
  - isoniazid 20 mg/kg daily (max. 400 mg)
  - rifampicin 20 mg/kg daily (max. 600 mg)
  - pyrazinamide 40 mg/kg daily (max. 2 g)
  - ethionamide 20 mg/kg daily (max. 750 mg)

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## 9.4 Special situations

### 9.4.1 Women (pregnant or breastfeeding or of childbearing age)

#### Pregnant or breastfeeding women

- All TB drugs used in conventional regimens, except rifabutin, can be used during pregnancy and breastfeeding<sup>[1]</sup>.
- Isoniazid may cause peripheral neuropathy due to vitamin B<sub>6</sub> (pyridoxine) deficiency:
  - Pregnant and breastfeeding women should receive **pyridoxine** PO (10 mg once daily) throughout the course of TB treatment.
  - Breast-fed neonates or infants should receive **pyridoxine** PO (5 mg once daily).
- Rifampicin may cause clotting disorders due to increased vitamin K (phytomenadione) metabolism:
  - Women in late pregnancy on rifampicin (or rifabutin) should receive **phytomenadione** PO (10 mg once daily) for 2 weeks prior to expected date of delivery.
  - Neonates should also receive **phytomenadione** IM at birth (1 mg single dose) to prevent haemorrhagic disease of the newborn.
- Alternative regimens containing rifapentine, moxifloxacin<sup>[2]</sup> and/or ethionamide cannot be used to treat DS-TB in pregnant and breastfeeding women.

#### Women of childbearing age

Women on contraception should use an intra-uterine device or a progestogen-only injectable throughout the courses of TB treatment, as rifamycins reduce the effectiveness of implants and oral contraceptives.

### 9.4.2 Malnutrition or risk of malnutrition

- For patients with malnutrition, therapeutic feeding should be initiated.
- For children with severe acute malnutrition, a 6-month regimen is preferred over a 4-month regimen until more data on the efficacy of the 4-month regimen in these patients become available.
- For at-risk populations, such as children, pregnant and breastfeeding women and the elderly, nutritional supplementation with a standard food package or ready-to-use food may be considered during the first 2 months of treatment.

### 9.4.3 Diabetes

TB can impair glycaemic control in patients with diabetes<sup>[3]</sup>. It is necessary to increase blood glucose monitoring in these patients.

TB drugs can exacerbate complications of diabetes (e.g. peripheral neuropathy). Avoid prescribing ethambutol in patients with pre-existing diabetic retinopathy.

Rifampicin can reduce the effect of sulfonylureas (e.g. glibenclamide, gliclazide). In contrast, first-line TB drugs have no interactions with metformin.

If diabetes is diagnosed, treat and monitor according to standard protocols.

At the end of TB treatment, it is recommended to schedule a specialist consultation for a complete evaluation and, if necessary, adjust antidiabetic treatment.

### 9.4.4 Renal insufficiency

In patients with renal insufficiency, creatinine clearance should be calculated. If it is less than 30 ml/minute, doses of certain TB drugs should be adjusted.

For the formula to estimate the creatinine clearance and dose adjustments in renal insufficiency, see [Appendix 12](#).

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# 9.5 Adjunctive therapy

## 9.5.1 Pyridoxine prophylaxis

Pyridoxine (vitamin B<sub>6</sub>) prophylaxis is indicated for all patients at risk of peripheral neuropathy, i.e. pregnant or breastfeeding women and patients with HIV infection, chronic alcohol use, malnutrition, diabetes, chronic hepatic disease or renal impairment (see Peripheral neuropathy, [Appendix 17](#)).

## 9.5.2 Corticosteroid therapy

Corticosteroid therapy is indicated for:

- TB meningitis<sup>[1]</sup> and pericarditis<sup>[2]</sup>;
- Treatment and prevention of TB-associated immune reconstitution inflammatory syndrome (TB-IRIS). See [Chapter 12](#).

There is insufficient evidence regarding the use of corticosteroids in other indications<sup>[3][4]</sup>.

**Table 9.3** – Corticosteroid treatment

Indications	Dosage and duration
<b>TB meningitis<sup>[5]</sup></b>	<b>dexamethasone IV/PO</b> Child: 0.6 mg/kg once daily for 4 weeks, tapered off over 4 weeks Adult: 0.4 mg/kg once daily for 7 days, tapered off over 6 to 8 weeks
<b>TB pericarditis</b>	<b>prednisolone PO</b> Child: 1.5 mg/kg once daily for 4 weeks, tapered off over 6 weeks Adult: 60 mg once daily for 4 weeks, tapered off over 6 weeks

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# 9.6 Patient monitoring

Patients should be assessed at baseline, then, regardless of the regimen prescribed, monitored throughout the course of treatment.

Monitoring includes:

- Assessment of treatment response
- Detection of adverse effects and adherence issues.

For the schedule of follow-up examinations, see [Appendix 14](#).

Baseline and follow-up findings should be noted in the patient file to enable the detection and interpretation of potential changes.

## 9.6.1 Clinical visits

### Baseline assessment

Assessment includes:

- Symptoms of TB and their severity (cough, fever, night sweats, weight loss, shortness of breath, ability to perform daily activities).
- Vital signs and weight.
- Comorbidities and other risk factors for adverse effects requiring monitoring adaptation.
- Psychological assessment.

Other investigations may be needed depending on the drugs used in the regimen prescribed ([Section 9.6.3](#)).

Clinical assessment should be performed by a clinician. Psychological assessment should be performed whenever possible by personnel with appropriate training.

All patients starting treatment should be given the information they need to understand the disease and its treatment ([Appendix 21](#)).

### Follow-up visits

Each follow-up visit, assessment includes:

- Clinical progress, vital signs and weight. Dosages should be adjusted to the weight if necessary.
- Occurrence of adverse effects.
- Adherence to treatment ([Appendix 22](#)).
- Psychological condition.

Frequency of visits depends on the patient's clinical condition and evolution:

- A visit every other week for the first month, then once a month if there is no particular problem.
- Additional visits may be required in case of comorbidities, severe or multiple adverse effects, pregnancy, etc.

Visits should coincide with bacteriological examinations and other investigations when possible.

The clinician should take into account any information and concerns regarding treatment tolerance and adherence reported by the patient or the team responsible for the patient's follow-up and support.

## 9.6.2 Bacteriological tests

To assess treatment response in patients with:

- PTB: bacteriological tests are essential.
- EPTB: evaluation is based on clinical evolution. However, bacteriological tests are required if patients also develop PTB.

### Baseline tests

Baseline tests are those performed on specimens collected just prior to treatment initiation. They include:

- Rapid molecular tests (RMTs) for detection of *M. tuberculosis* and rifampicin and isoniazid resistance.
- Smear microscopy to monitor treatment progress.
- Culture and phenotypic DST (pDST) when indicated.

For more information, see [Chapter 3](#).

### Follow-up tests

- Smear microscopy

Microscopy should be performed every 2 months until treatment completion.

If treatment is effective, microscopy at Month 2, 4 and 6 should be negative.

#### Notes:

- Patients with high bacillary load at baseline may have dead bacilli in their sputum for several months.
- As microscopy cannot distinguish dead from live bacilli, a positive result does not necessarily indicate that the treatment has failed.

- Rapid molecular tests

RMTs cannot be used to monitor treatment progress. However, if microscopy or culture is positive at Month 2 or later, RMTs should be performed to detect the emergence of new drug resistance not present at baseline ([Chapter 3](#)).

- Culture and pDST

Culture and pDST should be performed:

- at Month 2 or later, if RMTs show a new resistance to rifampicin or isoniazid;
- at Month 4, if microscopy is positive.

Full pDST (for first- and second-line drugs) should be performed on any positive culture.

**Note:** bacteriological tests are performed at the end of the month (e.g. Month 2 means the end of the 2<sup>nd</sup> month of treatment).

Regardless of the above schedule, RMTs, culture and pDST should be performed if the patient's clinical condition deteriorates.

#### End-of-treatment test

Microscopy should be performed at end of treatment to confirm the end-of-treatment outcome ([Chapter 17](#)).

## 9.6.3 Other investigations

#### Radiography

- CXR: for children with presumptive PTB, patients with non-bacteriologically confirmed PTB, suspicion of other intra-thoracic TB at baseline, then if indicated (e.g. worsening respiratory symptoms, non-response to TB treatment).
- Bone x-ray: for patients with osteoarticular and spinal TB at baseline, then every 6 months.

#### Biological tests

**Table 9.4** – Blood tests at baseline and during treatment

Tests	Indications
Full blood count <sup>(a)</sup>	HIV-infected patients on rifabutin or zidovudine (AZT), at baseline, then once a month for the first 2 months, then if indicated.
Liver function tests <sup>(b)</sup>	Patients with pre-existing hepatic disease, at baseline, then once a month.
Serum creatinine <sup>(c)</sup>	Patients with renal insufficiency at baseline, then if indicated.
HbA1C and/or blood glucose level	All patients, at baseline, to detect diabetes. If diabetes is detected, monitor according to standard protocols.
HIV, hepatitis B and C	For patients with undocumented HIV, hepatitis B and C status; HIV test every 6 months in high HIV prevalence areas. Tests can be repeated in case of recent exposure.
CD4 count and viral load	HIV-infected patients: at baseline, then every 6 months.

(a) Haemoglobin, red and white blood cells, platelets.

(b) Aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Bilirubin if elevated liver enzymes.

(c) For estimation of creatinine clearance see [Appendix 12](#).

## 9.7 Adverse effects

Rapid management of adverse effects is essential to increase tolerance and improve outcomes.

- In the event of minor adverse effects, drugs should not be stopped. Providing support and using ancillary medicines is all that is necessary.
- In the event of major adverse effects, the regimen may need to be adapted.

**Table 9.5** – Main adverse effects and likely responsible drugs

Adverse effects	Drug(s) likely responsible	Management
<b>Minor</b>		
Nausea, vomiting	Eto, Z	<a href="#">Appendix 17</a>
Arthralgia	Z	<a href="#">Appendix 17</a>
Peripheral neuropathy	H, Eto	<a href="#">Appendix 17</a>
Orange/red urine, tears, etc.	R, P	Patients should be told that this is normal before starting treatment.
<b>Major</b>		
Skin reactions	E, Z, R, H, P, Mfx, Eto	<a href="#">Appendix 17</a>
Hepatotoxicity	Z, H, R, P, Eto	<a href="#">Appendix 17</a>
Optic neuritis	E	<a href="#">Appendix 17</a>
Haematologic disorders	R, P, H, E	<a href="#">Appendix 17</a>

For more information on individual drugs, see [Appendix 10](#).

# 9.8 Treatment adaptation and change of treatment

## 9.8.1 Treatment adaptation

The whole treatment or individual drug(s) may be temporarily interrupted by the clinician in case of severe adverse effects ([Appendix 17](#)). This is considered as treatment adaptation, as long as it does not meet the definition of "treatment failure" ([Chapter 17](#)).

## 9.8.2 Change of treatment

The clinician should replace the DS-TB treatment with:

- A treatment for isoniazid-resistant TB (Hr-TB) when RMT or pDST shows:
  - the development of isoniazid resistance ([Chapter 11](#)) after treatment initiation, or
  - undetected isoniazid resistance at baseline, for any reason.
- A treatment for multidrug-resistant or rifampicin-resistant TB (MDR/RR-TB, [Chapter 10](#)) in the following circumstances<sup>[1]</sup>:
  - Development of rifampicin resistance after treatment initiation.
  - Rifampicin resistance not detected at baseline, for any reason.
  - No bacteriological conversion or bacteriological reversion ([Chapter 17](#)).
  - Insufficient clinical response to treatment in patients:
    - with non-bacteriologically confirmed TB (e.g. miliary TB, some forms of EPTB, TB in children).
    - with bacteriologically confirmed TB, when the bacteriological response cannot be assessed, or the result is inconclusive.

The above treatment changes meet the outcome definition of "treatment failure" ([Chapter 17](#)), except when the reason for change is a resistance undetected at baseline<sup>[1]</sup>.

## References

1. World Health Organization. *Meeting report of the WHO expert consultation on drug-resistant tuberculosis treatment outcome definitions*, 17-19 November 2020. Geneva: World Health Organization; 2021. <https://www.who.int/publications/i/item/9789240022195>



## 9.9 Treatment interruptions

Treatment interruptions can lead to the emergence of resistances.

Problems of treatment interruption by the patient (e.g. discontinuation of certain drugs, recurrent treatment interruptions) should be detected and addressed (management of adverse effects if necessary and reinforcement of patient support measures).

Interruption of the entire treatment for two consecutive months or more meet the definition of "lost to follow-up" ([Chapter 17](#)).

**Table 9.6** – Management of patients who interrupt treatment

Length of treatment before interruption	Length of interruption	Management
< 1 month	< 2 weeks	Continue treatment at the point it was stopped. Doses missed during interruption must be made up to complete the treatment.
	2-7 weeks	Restart treatment or perform RMTs (see below) depending on patient's clinical evolution.
	≥ 8 weeks	Perform RMTs: <ul style="list-style-type: none"> <li>• if no resistance, restart treatment.</li> <li>• if resistance, start DR-TB treatment.</li> </ul>
≥ 1 month	< 2 weeks	Continue treatment at the point it was stopped. Doses missed during interruption must be made up to complete treatment.
	≥ 4 weeks	Perform RMTs: <ul style="list-style-type: none"> <li>• if no resistance, restart treatment.</li> <li>• if resistance, start DR-TB treatment.</li> </ul>

For patients on 6-month regimen who have received adequate treatment for 4 months or more, who return smear negative, are in good clinical condition and with no resistance detected, the decision to re-start a treatment is considered on a case-by-case basis.

When a DST is not feasible (e.g. miliary TB, some forms of EPTB, TB in children), clinical and radiological evaluation should guide the decision to either restart DS-TB treatment or switch to an DR-TB treatment.

# Chapter 10: Treatment of multidrug-resistant and rifampicin-resistant tuberculosis

[10.1 Introduction](#)

[10.2 Treatment regimens in programmatic conditions](#)

[10.3 Treatment regimens in operational research conditions](#)

[10.4 Special situations](#)

[10.5 Adjunctive therapy](#)

[10.6 Patient monitoring](#)

[10.7 Adverse effects](#)

[10.8 Treatment adaptation and change of treatment](#)

[10.9 Treatment interruptions](#)

[10.10 Surgery](#)

[10.11 Treatment failure and palliative care](#)

Update: February 2023

# 10.1 Introduction

When selecting or building a treatment regimen for multidrug-resistant tuberculosis (MDR-TB) and rifampicin-resistant tuberculosis (RR-TB), the following should be considered:

## 10.1.1 Standard short regimens and individualized long regimens

Patients should receive a standard short treatment regimen (STR) except if they do not meet the eligibility criteria for STRs, or do not tolerate STRs. In such cases, patients require an individualized long treatment regimen (LTR).

It may be necessary to switch from an STR to an LTR, based on the latest drug-susceptibility test (DST) results and/or clinical evolution during treatment course (e.g. drug intolerance, persistence of a positive culture).

## 10.1.2 Likely effective drugs

Treatment is based on a combination of “likely effective” TB drugs.

**Table 10.1** – Definition of likely effective drugs (adapted from WHO<sup>[1]</sup>)

DST	Definition of a likely effective TB drug
Available and reliable	DST indicates susceptibility to the drug.
Unavailable, unreliable, or result pending	The following criteria should be met: <ul style="list-style-type: none"><li>• No resistance detected by DST to a drug with cross-resistance.</li><li>• No resistance to the drug or to a drug with a cross-resistance to it detected by DST in the presumed source case.</li><li>• No previous exposure (&gt; 1 month) to the drug or to a drug with a cross-resistance.</li><li>• The drug has not been widely used in the treatment of TB or drug resistance surveys indicate that drug resistance is rare in the area the patient comes from.</li></ul>

When the criteria of a likely effective drug are not met:

- If the strain of the patient (or the presumed source case) is resistant to clofazimine, bedaquiline can be used but not counted as a likely effective drug until DST demonstrates susceptibility to bedaquiline. The same applies to all drugs with known or potential cross-resistance (e.g. delamanid/pretomanid). For more information on drug resistance and cross-resistance, see [Chapter 8](#).
- If a drug has been widely used and there is no reliable DST for this drug (e.g. ethambutol, cycloserine, para-aminosalicylate sodium): it can be used but never counted as a likely effective drug.
- If a drug has been widely used and there is a reliable DST for this drug (e.g. pyrazinamide): it can be used but not counted as a likely effective drug until DST demonstrates susceptibility.

## 10.1.3 Other considerations

The following should also be considered when choosing or building a treatment regimen:

- Interactions and overlapping toxicities between TB drugs or other drugs the patient may take (see [Appendix 10](#) for individual drugs and [Appendix 19](#) for co-administration of TB drugs and antiretrovirals);
- Comorbidities that can result in increased drug toxicity;
- Absolute contraindications to any drug included in a regimen;
- Pregnancy and breastfeeding ([Appendix 11](#)).

## References

1. World Health Organization. *Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis*. Geneva. 2014. [https://www.ncbi.nlm.nih.gov/books/NBK247420/pdf/Bookshelf\\_NBK247420.pdf](https://www.ncbi.nlm.nih.gov/books/NBK247420/pdf/Bookshelf_NBK247420.pdf)

# 10.2 Treatment regimens in programmatic conditions

## 10.2.1 Short treatment regimens

### A. 6-month BPaLM regimen

#### Eligibility

(adapted from WHO<sup>[1]</sup>)

BPaLM is the preferred treatment regimen for all MDR/RR-TB patients meeting the following criteria:

- 1 - Bedaquiline, pretomanid, linezolid and moxifloxacin are likely effective.
- 2 - Age ≥ 14 years.
- 3 - No miliary TB, osteoarticular TB or TB of the central nervous system (CNS), i.e. brain, spinal cord or meninges.

#### Regimen composition

**Box 10.1** – 6-month BPaLM regimen

**6Bdq-Pa-Lzd-Mfx**

In the BPaLM regimen, the starting dose of linezolid (600 mg once daily) is reduced after 16 weeks to 300 mg once daily.

#### Note:

In the event of resistance to fluoroquinolones (FQs), i.e. pre-XDR-TB, this guide recommends a short four-drug regimen under operational research conditions where possible (Section 10.3). An LTR or BPaL (6-9Bdq-Pa-Lzd with linezolid given at 600 mg for 6 months) can be used in settings where an STR under operational research conditions is not feasible. Note that linezolid causes frequent toxicity. Management of linezolid adverse effects include temporary or early permanent interruption of the drug. If interruptions are recurrent or linezolid is stopped permanently early in the treatment, patients on BPaL would receive a two-drug regimen for a significant period of time, which is not optimal<sup>[1]</sup>.

### B. 9-month bedaquiline-containing regimens<sup>[1]</sup>

#### Eligibility

If pretomanid is not available or for patients not eligible for the BPaLM regimen, a 9-month STR should be used in MDR/RR-TB patients meeting the following criteria<sup>[2]</sup>:

- 1 - Susceptibility to FQs is confirmed by a rapid molecular test (RMT).
- 2 - Other drugs used in the regimen, except isoniazid, are likely effective (Section 10.1.2). High treatment failure rates and amplification of FQ resistance have been observed in some countries<sup>[3]</sup> in patients with strains presenting resistance to other drugs in the STR.
- 3 - No extensive pulmonary TB (PTB):
  - no bilateral lung cavities or extensive lung damage,
  - no cavities or bilateral disease in patients < 15 years.
- 4 - No severe extrapulmonary TB (EPTB):
  - no miliary TB, osteoarticular TB, TB of the CNS, or pericardial TB,
  - no EPTB other than lymph node TB (peripheral nodes or isolated mediastinal mass without compression) in patients < 15 years.
- 5 - No pregnancy or breastfeeding for the ethionamide-containing regimen.

#### Regimen composition

**Box 10.2** – 9-month bedaquiline-containing regimens

**4 to 6Bdq<sub><6></sub>-Lfx-Cfz-Z-E-H<sup>h</sup>-Lzd<sub><2></sub>/5Lfx-Cfz-Z-E**  
or  
**4 to 6Bdq<sub><6></sub>-Lfx-Cfz-Z-E-H<sup>h</sup>-Eto/5Lfx-Cfz-Z-E**

This guide recommends the regimen that includes linezolid (a drug from Group A), rather than the regimen that includes ethionamide.

#### Regimen 4 to 6Bdq<sub><6></sub>-Lfx-Cfz-Z-E-H<sup>h</sup>-Lzd<sub><2></sub>/5Lfx-Cfz-Z-E

- Bdq<sub><6></sub> means that bedaquiline is administered for 6 months (not for 4 months). However, it should be extended to 9 months if the sputum microscopy is positive at Month 4.
- Lzd<sub><2></sub> means that linezolid is administered for 2 months (not for 4 months).
- H<sup>h</sup> is administered for 4 months or extended to 6 months if the sputum microscopy is positive at Month 4.
- Lfx-Cfz-Z-E is administered for 9 months or extended to 11 months if the sputum microscopy is positive at Month 4.
- Moxifloxacin (Mfx) at standard dose can be used instead of levofloxacin.

In practice the patient receives:

A 9-month regimen if microscopy negative at Month 4:

TB drugs	Intensive phase				Continuation phase				
	M1	M2	M3	M4	M5	M6	M7	M8	M9
Months									
Bdq									
Lfx-Cfz-Z-E									
H <sup>h</sup>									
Lzd									

An 11-month regimen if microscopy positive at Month 4:

TB drugs	Intensive phase						Continuation phase				
	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11
Months											
Bdq											
Lfx-Cfz-Z-E											
H <sup>h</sup>											
Lzd											

**Regimen 4 to 6Bdq<sub><6></sub>-Lfx-Cfz-Z-E-H<sup>h</sup>-Eto/5Lfx-Cfz-Z-E**

- Bdq<sub><6></sub> means that bedaquiline is administered for 6 months (not for 4 months). However, it should be extended to 9 months if the sputum microscopy is positive at Month 4.
- H<sup>h</sup>-Eto are administered for 4 months or extended to 6 months if the sputum microscopy is positive at Month 4.
- Lfx-Cfz-Z-E are administered for 9 months or extended to 11 months if the sputum microscopy is positive at Month 4.
- Mfx at standard dose can be used instead of Lfx.

In practice the patient receives:

A 9-month regimen if microscopy negative at Month 4:

TB drugs	Intensive phase				Continuation phase				
	M1	M2	M3	M4	M5	M6	M7	M8	M9
Months									
Bdq									
Lfx-Cfz-Z-E									
H <sup>h</sup> -Eto									

An 11-month regimen if microscopy positive at Month 4:

TB drugs	Intensive phase						Continuation phase				
	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11
Months											
Bdq											
Lfx-Cfz-Z-E											
H <sup>h</sup> -Eto											

## 10.2.2 Long treatment regimens

## Eligibility

All MDR/RR-TB patients not eligible for STRs (programmatically or under operational research).

## Regimen composition

The regimen should include a minimum number of likely effective drugs.

### Box 10.3 – Number of likely effective drugs required in LTRs

At least 4 likely effective TB drugs, including:

- 3 from Group A
- 1 from Group B

If this optimal combination is not feasible:

At least 5 likely effective TB drugs, prioritizing Group A and B drugs and adding Group C drug(s) to bring the total to at least 5 TB drugs.

LTRs may contain more than 5 TB drugs if there is uncertainty of effectiveness in some of the drugs used.

While waiting for full DST results, patients can be treated with:

- An individualized LTR, or
- An empirical<sup>a</sup> LTR according to the known resistance profile.

It may be necessary to switch from an empirical LTR to an individualized LTR, based on the latest DST results and/or clinical evolution during treatment course (e.g. drug intolerance, persistence of a positive culture).

## Individualized long regimens

To build an individualized LTR, a stepwise process is recommended.

Table 10.3 – Steps to build an LTR

Step 1	Use all 3 Group A drugs, unless confirmed resistance or contra-indication.
	<b>1.1 - Levofloxacin (Lfx) or moxifloxacin (Mfx)</b> <ul style="list-style-type: none"><li>• Use Lfx (rather than Mfx) if the patient takes other QT-prolonging drugs.</li><li>• High dose moxifloxacin (Mfx<sup>h</sup>) can be used:<ul style="list-style-type: none"><li>▫ if low-level resistance to FQs is detected, but not counted as a likely effective drug<sup>[1]</sup>.</li><li>▫ with other QT-prolonging drugs, but only if options are very limited (weigh benefits/risks and discuss with the patient).</li></ul></li></ul> <b>1.2 - Bedaquiline (Bdq)</b> <b>1.3 - Linezolid (Lzd)</b>
Step 2	Add 1 or 2 Group B drug(s), unless confirmed or suspected resistance or contra-indication.
	<b>2.1 - Clofazimine (Cfz)</b> Use Cfz rather than Cs or Trd if possible (better safety profile). <b>2.2 - Cycloserine (Cs) or terizidone (Trd)</b> Interchangeable and used at the same dose.
Step 3	Add Group C drugs when the combination of 3 Group A drugs and at least 1 Group B drug is not feasible, to bring the regimen to 5 likely effective drugs.
	<b>3.1 - Delamanid (Dlm)</b> First choice (good safety profile and still limited drug resistance). <b>3.2 - First-line drugs: ethambutol (E), pyrazinamide (Z)</b> <b>3.3 - Imipenem/cilastatin (Ipm/Cln) or meropenem (Mpm)</b> <ul style="list-style-type: none"><li>• If no other option (high cost and difficult to administer).</li><li>• Always administered with amoxicillin/clavulanic acid (Amx/Clv).</li><li>• Use Mpm in patients &lt; 15 years or with a history of epilepsy.</li></ul> <b>3.4 - Amikacin (Am) or streptomycin (S)</b> <ul style="list-style-type: none"><li>• If no other option and confirmed susceptibility.</li><li>• Use Am rather than S. Use S if Am is unavailable or the strain is resistant to Am.</li></ul> <b>3.5 - Ethionamide (Eto) or prothionamide (Pto)</b> Interchangeable and used at the same dose. <b>3.6 - Para-aminosalicylic acid or sodium (PAS)</b> <b>3.7 - High-dose isoniazid (H<sup>h</sup>)</b> Can be used if low-level resistance to H, but not counted as a likely effective drug.

**Note:** isoniazid standard dose can be administered to patients with RR-TB when isoniazid susceptibility is documented. When isoniazid is used in this manner it can be counted as a likely effective drug.

## Empirical long regimens

**Table 10.4** – Examples of empirical long regimens at treatment initiation

Resistance profiles	Examples
<b>Group A and B drugs likely effective</b>	18Lfx-Bdq-Lzd-Cfz If Bdq is contra-indicated: 18Lfx-Lzd-Cfz-Cs-Dlm If Lzd is contra-indicated: 18Lfx-Bdq-Cfz-Cs-Dlm
<b>FQs not likely effective</b> <b>Other Group A and B drugs likely effective</b>	18Bdq-Lzd-Cfz-Cs-Dlm-[Mfx <sup>h</sup> ] <sup>(a)</sup> If Bdq is contra-indicated: 18Lzd-Cfz-Cs-Dlm-lpm/Cln

(a) Moxifloxacin high dose can be used, but not counted if low-level FQ resistance is suspected or found on DST.

## Duration of treatment

At least for 18 months, with at least 15 months after culture conversion (for definition, see [Chapter 17](#)). If well tolerated, all drugs should be taken for the full treatment duration<sup>[4][5]</sup>.

Preliminary evidence suggests that stopping bedaquiline at 6 months is associated with high rates of culture reversion (for definition, see [Chapter 17](#)) in patients with resistance to several drugs or extensive lung damage<sup>[6]</sup>. No safety issues have been reported with bedaquiline treatment longer than 6 months<sup>[2][4][7]</sup>.

Carbapenems are commonly used for a minimum of 2 months after culture conversion. When the number of likely effective drugs included in the regimen is limited, a carbapenem may be required for the entire duration of treatment.

## Footnotes

(a) An empirical regimen is a regimen designed to treat most patients in a region whilst waiting the full DST results.

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- World Health Organization. *WHO operational handbook on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, 2022 update*. <https://www.who.int/publications/i/item/9789240065116>
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# 10.3 Treatment regimens in operational research conditions

MDR/RR-TB patients can be treated under operational research conditions with short regimens other than the standard STRs. Whatever the rationale or results of operational research, they should be communicated as they may complement those of clinical trials.

## 10.3.1 Operational research conditions

The requirements for conducting operational research include:

- A study protocol including 12-month post-end-of-treatment follow-up.
- A clinical treatment guide.
- A patient consent process.
- Approval by an ethics review board and Ministry of Health.
- A pharmacovigilance system (core aDSM<sup>a</sup>).

Study protocol templates are available from the Global Drug-resistant TB Initiative (GDI)<sup>b</sup> and WHO<sup>c</sup>.

## 10.3.2 Treatment regimens under investigation

The following regimens are examples of standardized regimens that can be used under operational research conditions. These regimens have been reviewed by scientific committees and have been tested, or are currently being tested, in clinical trials.

### For FQ-susceptible MDR/RR-TB patients

- The five endTB trial experimental regimens<sup>[1]</sup>:
  - 9Bdq-Lzd-Mfx-Z
  - 9Bdq-Cfz-Lzd-Lfx-Z
  - 9Bdq-Dlm-Lzd-Lfx-Z
  - 9Dlm-Cfz-Lzd-Lfx-Z
  - 9Dlm-Cfz-Mfx-Z
- The TB-PRACTECAL regimen that includes clofazimine<sup>[2]</sup>: 6Bdq-Pa-Lzd-Cfz (BPaLC regimen)

### For FQ-resistant MDR/RR-TB patients

- The endTB-Q trial regimen: 6 or 9Bdq-Dlm-Lzd-Cfz<sup>[3]</sup>
- The TB-PRACTECAL regimen that includes clofazimine: 6Bdq-Pa-Lzd-Cfz (BPaLC regimen)

## Footnotes

- (a) World Health Organization. Active tuberculosis drug-safety monitoring and management (aDSM). Framework for implementation. WHO, Geneva, 2015. [https://apps.who.int/iris/bitstream/handle/10665/204465/WHO\\_HTM\\_TB\\_2015.28\\_eng.pdf;jsessionid=97A194C2FA7D78CF2E18BD60C8C6E3F7?sequence=1](https://apps.who.int/iris/bitstream/handle/10665/204465/WHO_HTM_TB_2015.28_eng.pdf;jsessionid=97A194C2FA7D78CF2E18BD60C8C6E3F7?sequence=1)
- (b) Global Drug Initiative-StopTB Partnership: The Evaluation of Effectiveness and Safety of Novel Shorter Treatment Regimens for Multidrug-Resistant Tuberculosis Operational Research Protocol Template, May 2018. <http://www.stoptb.org/wg/mdrtb/assets/documents/GDI%20OR%20generic%20protocol%20final.pdf>
- (c) World Health Organization. *ShORRT. (Short, all-Oral Regimens for Rifampicin-resistant Tuberculosis) Research Package*. Version 4 June 2020. [https://tdr.who.int/docs/librariesprovider10/shorrt-initiative/shorrt-generic-protocol-june2020\\_en.pdf?sfvrsn=df85f6c1\\_3](https://tdr.who.int/docs/librariesprovider10/shorrt-initiative/shorrt-generic-protocol-june2020_en.pdf?sfvrsn=df85f6c1_3)

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1. <https://clinicaltrials.gov/ct2/show/NCT02754765>
2. <https://clinicaltrials.gov/ct2/show/NCT02589782>
3. <https://clinicaltrials.gov/ct2/show/NCT03896685>



# 10.4 Special situations

## 10.4.1 Women (pregnant or breastfeeding or of childbearing age)

### Pregnant women

Early treatment initiation after diagnosis is recommended. For choosing or building a regimen, see [Appendix 11](#). Pregnancy outcome and any congenital anomalies in the neonate should be documented.

### Breastfeeding women

Use of infant formula is recommended as many second-line drugs should be avoided in breastfeeding women ([Appendix 11](#)). Mothers must be informed of its benefits and risks and provided with infant formula, clean water, fuel for boiling water and a heating device (stove, saucepan and bottles). They must also receive training on how to prepare and use the formula. When infant formula cannot be used safely, infants must be breastfed.

If the mother is smear-positive, mother-infant contact should be maintained, but kept to a minimum. Appropriate infection prevention and control measures should be taken during contact. Care of the infant should be largely entrusted to family members until the mother becomes smear-negative.

### Women of childbearing age

A pregnancy test should be performed before starting treatment and, if necessary, repeated during treatment. A highly effective contraception method (e.g. intra-uterine device or implantable hormonal contraceptive) should be offered prior to starting treatment.

## 10.4.2 Children and adolescents

Given the severity of MDR/RR-TB, no TB drugs are contra-indicated (except pretomanid while waiting data on appropriate dosing)<sup>[1]</sup>. Children and adolescents generally tolerate second-line TB drugs well. They should be treated without delay based on the index case resistance profile when DST is not available (e.g. clinically diagnosed TB, EPTB).

Children and adolescents should receive an STR when eligible, however BPaLM and BPaL regimens are not recommended in patients under 14 years.

Children with non-severe TB receiving an LTR can usually be treated for less than 18 months<sup>[1]</sup>. Some experts suggest that even severe TB could be treated for less than 18 months<sup>[2]</sup>.

## 10.4.3 Patients with malnutrition or risk of malnutrition

See [Chapter 9](#).

## 10.4.4 Extrapulmonary tuberculosis

Patients with some forms of EPTB are not eligible for STRs ([Section 10.2.1](#)) and should be treated with an LTR as described in [Section 10.2.2](#).

For patients with TB of the CNS, drug penetration into the CNS should be taken into account.

**Table 10.5** – Choice of TB drugs for TB of the CNS<sup>[3][4][5]</sup>

Drugs	CNS penetration
<b>Group A</b>	Fluoroquinolones and linezolid: good CNS penetration. Bedaquiline: limited data; can be used, but not counted.
<b>Group B</b>	Cycloserine: good CNS penetration. Clofazimine: limited data; can be used, but not counted.
<b>Group C</b>	Pyrazinamide, carbapenems, thionamides and isoniazid high dose: good CNS penetration. Delamanid: limited data; can be used, but not counted. Ethambutol and PAS: poor CNS penetration. Aminoglycosides: better CNS penetration if meningeal inflammation.
<b>Other</b>	Pretomanid: no data.

If the regimen contains a carbapenem, use preferably meropenem in patients with TB meningitis (less risk of seizures than with imipenem/cilastatin).

## 10.4.5 Diabetes

TB can impair glycaemic control in patients with diabetes<sup>[6]</sup>. It is therefore necessary to increase blood glucose monitoring in these patients.

TB drugs may exacerbate complications of diabetes (e.g. peripheral neuropathy). Avoid prescribing ethambutol or linezolid for patients with pre-existing diabetic retinopathy.

If diabetes is diagnosed, treat and monitor according to standard protocols. At the end of TB treatment, it is recommended to schedule a specialist consultation for a complete evaluation and, if necessary, adjustment of antidiabetic treatment.

## 10.4.6 Renal insufficiency

In patients with renal insufficiency, creatinine clearance should be calculated. If it is less than 30 ml/minute, doses of certain TB drugs should be adjusted. For the formula to estimate creatinine clearance and dose adjustments in renal insufficiency, see [Appendix 12](#).

### References

1. World Health Organization. *WHO consolidated guidelines on tuberculosis. Module 5: management of tuberculosis in children and adolescents*. Geneva: World Health Organization; 2022.  
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## 10.5 Adjunctive therapy

### 10.5.1 Pyridoxine prophylaxis

Pyridoxine (vitamin B<sub>6</sub>) is routinely administered to all patients receiving linezolid, cycloserine or teridizone, thionamides or isoniazid high dose to prevent neurotoxic effects (see Peripheral neuropathy, [Appendix 17](#)).

### 10.5.2 Corticosteroid therapy

See [Chapter 9](#).

# 10.6 Patient monitoring

Patients should be assessed at baseline, then, regardless of the regimen prescribed, monitored throughout the course of treatment.

Monitoring includes:

- Assessment of treatment response.
- Detection of adverse effects and adherence issues.

For the schedule of follow-up examinations, see [Appendix 15](#).

Baseline and follow-up findings should be noted in the patient file to enable the detection and interpretation of potential changes.

## 10.6.1 Clinical visits

### Baseline assessment

Assessment includes:

- Signs and symptoms of TB and severity (cough, fever, night sweats, weight loss, shortness of breath, ability to perform daily activities).
- Vital signs and weight.
- Comorbidities and other risk factors for adverse effects requiring monitoring schedule adaptation.
- Psychological assessment.

Other investigations may be needed depending on the drugs used in the regimen prescribed ([Section 10.6.3](#)).

Clinical assessment should be performed by a clinician. Psychological assessment should be performed whenever possible by personnel with appropriate training.

All patients starting treatment should be given the information they need to understand the disease and its treatment ([Appendix 21](#)).

### Follow-up visits

Each follow-up visit includes assessing:

- Clinical progress, vital signs and weight. Dosages should be adjusted to the weight if necessary.
- Occurrence of adverse effects.
- Adherence to treatment ([Appendix 22](#)).
- Psychological condition.

Frequency depends on the patient's clinical condition and evolution:

- A visit every week for the first month, every other week for the second month, then once a month if there is no particular problem.
- Additional visits may be required in case of comorbidities, severe or multiple adverse effects, pregnancy, etc.

Visits should coincide with bacteriological examinations and other investigations when possible.

The clinician should take into account any information and concerns regarding treatment tolerance and adherence reported by the patient or the team responsible for the patient's follow-up and support.

## 10.6.2 Bacteriological tests

To assess treatment response in patients with:

- PTB: bacteriological tests are essential.
- EPTB: evaluation is based on clinical evolution. However, bacteriological tests are required if patients also develop PTB.

### Baseline tests

Baseline tests are those performed on specimens collected just prior to treatment initiation. Baseline tests include:

- RMTs for detection of *M. tuberculosis* and rifampicin, isoniazid and fluoroquinolone resistance.
- Sputum smear microscopy.
- Culture and full phenotypic DST (pDST) or genome sequencing.

For more information, see [Chapter 3](#).

If DST results are obtained on a specimen collected more than 2 to 3 weeks prior to treatment initiation, a new specimen should be collected just prior to treatment initiation. The new results are considered as baseline results.

### Follow-up tests

- Microscopy: once a month until treatment completion. Although less reliable than culture, it provides immediate results which contribute to the assessment of treatment response.
- Culture: once a month until treatment completion. Culture conversion and reversion are useful markers of whether the treatment is effective or not.
- Full pDST (or genome sequencing): if positive culture at Month 4 or later.
- RMTs: Xpert MTB/XDR (or GenoType MTBDRs/ if Xpert MTB/XDR is not available) if positive microscopy at Month 4 or later, as it can detect resistance-conferring mutations not present at baseline ([Chapter 3](#)).

### End-of-treatment tests

Culture and microscopy should be performed at end of treatment, to confirm the end-of-treatment outcome ([Chapter 17](#)).

#### Post-treatment tests

For patients on BPaLM or BPaL regimen, culture and microscopy should be performed 6 and 12-month post-treatment completion, to detect a relapse.

### 10.6.3 Other investigations

#### Radiography

At baseline, then every 6 months:

- chest x-ray for patients with PTB,
- bone x-ray for patients with osteoarticular and spinal TB.

#### Electrocardiogram

Some TB drugs cause prolongation of the QT interval, which increases the risk of a potentially life-threatening ventricular arrhythmia, including *torsade de pointes* (TdP)<sup>[1]</sup>.

To monitor the QT interval, electrocardiogram (ECG) should be performed:

- At baseline in all patients taking QT-prolonging TB drugs

Then:

- Once a month in patients:
  - taking < 2 moderate or strong QT-prolonging TB drugs,
  - taking < 3 QT-prolonging drugs (TB and non-TB).
- Once a week for one month, then once a month in patients:
  - taking ≥ 2 moderate or strong QT-prolonging TB drugs,
  - taking ≥ 3 QT-prolonging drugs (TB and non-TB),
  - with other risk factors for QT prolongation or TdP:
    - a history of syncopal episodes, TdP or congenital long QT syndrome;
    - uncompensated heart failure, severe coronary disease, bradycardia;
    - untreated hypothyroidism.

Increased ECG monitoring is required in patients in whom a QT prolongation is detected.

For ECG reading, see [Appendix 16](#).

For the management of QT prolongation, see [Appendix 17](#).

For the list of QT prolonging drugs, see [Appendix 19](#).

#### Brief peripheral neuropathy screen

For patients on linezolid: brief peripheral neuropathy screen (BPNS) at baseline, then once a month to detect peripheral neuropathy ([Appendix 16](#)).

#### Visual function tests

For patients on drugs with ocular toxicity: visual acuity and colour vision tests (Ishihara test) at baseline, then once a month to detect the first signs of optic neuritis.

#### Audiometry

For patients on aminoglycosides: at baseline, then once a month to detect hearing loss. Monitoring is particularly important in children, as hearing loss in childhood has negative effects on development.

#### Full blood count

For all patients: haemoglobin, red and white blood cells, and platelets at baseline, then if indicated.

For patients on linezolid: every 2 weeks for the first 2 months, then once a month.

For patients on zidovudine (AZT): once a month for the first 2 months, then if indicated.

#### Liver function tests

For all patients: serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) at baseline, then once a month.

Bilirubin, if AST and ALT are elevated, or if indicated.

Monitor liver function more frequently in case of increase in AST/ALT or other signs of hepatic disorder or risk factors, such as hepatitis B or C.

#### Serum creatinine and potassium level

For all patients: at baseline, then if indicated (e.g. patients with renal insufficiency).

For patients on aminoglycoside: once a month, or more frequently if indicated.

#### Creatinine clearance

For patients with renal insufficiency: at baseline. If < 30 ml/minute, the dose of certain TB drugs should be adjusted ([Appendix 12](#)).

#### Glycated haemoglobin (HbA1c) and/or blood glucose level (BGL)

For all patients: at baseline to detect diabetes. If diabetes is diagnosed, monitor according to standard protocols.

### **HIV, hepatitis B and C**

For all patients with undocumented HIV hepatitis B and C status: at baseline; HIV test every 6 months in high HIV prevalence areas. Tests can be repeated in case of recent exposure.

### **CD4 and viral load**

For HIV-infected patients: at baseline, then every 6 months.

### **Thyroid-stimulating hormone (TSH)**

For patients on thionamides or PAS: at baseline, then every 3 months.

If hypothyroidism is diagnosed: 4 to 12 weeks after levothyroxine initiation and after each levothyroxine dose adjustment until stable, then every 6 months until the end of TB treatment, or for as long as the patient takes levothyroxine.

### **Pregnancy test**

For all adolescents and women of childbearing age: at baseline, then if indicated.

## **References**

1. Roden DM. *Drug-induced prolongation of the QT interval*. *New Engl J Med*. 2004; 350: 1013-1022. <https://doi.org/10.1056/NEJMra032426>

## 10.7 Adverse effects

Rapid and aggressive treatment of adverse effects is essential to improve tolerance and treatment outcomes.

Some adverse effects should be routinely prevented (e.g. peripheral neuropathy).

Most adverse effects cannot be prevented, but can be managed with symptomatic treatment (e.g. arthralgia due to pyrazinamide).

Some adverse effects cannot be eliminated, but are not serious (e.g. skin discoloration due to clofazimine). Patients need reassurance and support to be able to tolerate them until they subside spontaneously.

Some adverse effects can be serious (e.g. optic neuritis due to linezolid), which can lead to dose reduction or temporary or permanent interruption of the drug.

Ascertaining which drug is responsible for a particular adverse effect can be challenging. Temporarily stopping a drug, or reducing the dose, can help identify the responsible drug.

Adverse effects can appear at any time during treatment. Patients should be informed that they are likely to experience adverse effects and should report them immediately to health staff. Treatment supporters and nurses should rapidly report adverse effects to the clinician. Only the managing clinician can modify or stop a TB treatment.

For the management of adverse effects, see [Appendix 17](#).

# 10.8 Treatment adaptation and change of treatment

## 10.8.1 Treatment adaptation

Treatment adaptation may be done by the clinician in case of severe adverse effects ([Appendix 17](#)). The following are considered treatment adaptations:

- For BPaLM and BPaL:
  - permanent interruption of linezolid after Month 4, or
  - interruption < 2 consecutive weeks or < 4 nonconsecutive weeks of individual drug(s) or the whole treatment.
- For 9-month bedaquiline-containing regimens:
  - temporary interruption of individual drug(s) or the whole treatment, or
  - permanent interruption of ethambutol or pyrazinamide during the continuation phase.
- For LTRs:
  - temporary interruption of individual drug(s) or the whole treatment, or
  - change of one drug class in the regimen (no more than one).

In an LTR, at least 4 to 5 likely effective drugs are needed ([Box 10.3](#)). If any of these drugs must be permanently stopped:

- during the first 6 months, the regimen should be modified while maintaining the required number of likely effective drugs.
- after the first 6 months, if the patient clinical status has improved and bacteriological tests are negative, the clinician can decide to continue the treatment if it still includes at least 3 drugs from Group A and/or B.

These modifications are considered as treatment adaptations (not treatment changes, see [Section 10.8.2](#)) as they do not meet the definition of "treatment failure" ([Chapter 17](#)).

## 10.8.2 Change of treatment

Treatment change is defined as the switch from an STR to an LTR or from an LTR to a newly designed LTR.

Treatment should be changed by the clinician in the following circumstances<sup>[1]</sup>:

- Emergence of a new resistance after treatment initiation.
- Resistance not detected at baseline for any reason.
- No bacteriological conversion or bacteriological reversion ([Chapter 17](#)).
- Insufficient clinical response to treatment in patients:
  - with no bacteriologically confirmed TB (e.g. miliary TB, some forms of EPTB, children);
  - with bacteriologically confirmed TB when bacteriological response cannot be assessed, or the result is inconclusive.
- Drug interruption due to severe adverse effects<sup>[2]</sup>:
  - For BPaLM and BPaL:
    - permanent interruption of bedaquiline or pretomanid, or
    - permanent interruption of linezolid before the end of Month 4, or
    - interruption  $\geq 2$  consecutive weeks or  $\geq 4$  nonconsecutive weeks of the whole treatment.
  - For 9-month bedaquiline-containing regimens:
    - permanent interruption of bedaquiline, levofloxacin/moxifloxacin, linezolid, ethionamide or clofazimine, or
    - permanent interruption of both ethambutol and pyrazinamide.
  - For LTRs: change of at least 2 drug classes in the regimen.

**Note:** for BPaLM regimen, if moxifloxacin must be interrupted, see the note in [Section 10.2.1](#).

Treatment changes meet the outcome definition of "treatment failure" ([Chapter 17](#)), except when the reason for change is a resistance not detected at baseline<sup>[1]</sup>.

## References

1. World Health Organization. *Meeting report of the WHO expert consultation on drug-resistant tuberculosis treatment outcome definitions, 17-19 November 2020*. Geneva: World Health Organization; 2021. <https://www.who.int/publications/i/item/9789240022195>
2. World Health Organization. *WHO operational handbook on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, 2022 update*. <https://www.who.int/publications/i/item/9789240065116>



## 10.9 Treatment interruptions

Problems of treatment interruption by the patient (e.g. discontinuation of certain drugs, recurrent treatment interruptions) should be detected and addressed (management of adverse effects if necessary and reinforcement of patient support measures).

Interruptions of individual drug(s) or of the whole treatment may lead to the emergence of new resistances.

Moreover, in case of treatment interruption, drugs with a long half-life such as bedaquiline or clofazimine remain in the blood for several months. In practice, it is as if the patient is receiving bedaquiline and/or clofazimine alone, which increases the risk of developing resistance to these drugs.

Patients who have interrupted the whole treatment for 2 months or more meet the definition of patients "lost to follow-up" ([Chapter 17](#)). If the patient returns, repeat bacteriological tests (RMTs, culture and full pDST or genome sequencing) to detect potential new resistance; start a new individualized regimen.

For patients who have interrupted the whole treatment for 4 weeks or more but less than 2 months, perform new bacteriological tests as above. Further treatment depends on the results of the RMTs (pending full bacteriological tests results) and the patient's clinical status: new individualized regimen or continuation of the same regimen with catch-up of doses missed during interruptions to complete treatment.

For patients on BPaLM/BPaL who have interrupted the whole treatment for 2 weeks or more, perform new bacteriological tests as above and start a new individualized regimen.

# 10.10 Surgery

Surgery is an adjunct to the pharmacological treatment of MDR/RR-TB patients.

It can be performed only by trained thoracic surgeons, in specialized surgical units with excellent postoperative care. These units must implement strict infection prevention and control measures because thoracic surgery, mechanical ventilation and post-operative physiotherapy generate large quantities of aerosols.

When access to surgery is limited, it should be considered in priority for patients with resistance to a large number of drugs and localized lung damage.

Surgery can be performed early, when the disease is still localized (e.g. to a lobe). Partial lung resection (lobectomy or wedge resection) can be effective and safe if performed under appropriate conditions<sup>[1][2][3]</sup>.

At the beginning of treatment, there is a window of opportunity during which the bacillary load decreases transiently under the pressure of TB drugs (decrease in mycobacteria in smears and/or culture). This window is the optimal time for surgery. The prognosis is better when resection is performed after culture conversion<sup>[1][2]</sup>.

It is recommended to perform culture and DST of the resection material. Depending on the results, modification of treatment may be required.

## References

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2. Harris RC, Khan MS, Martin LJ, Allen V, Moore DAJ, Fielding K, et al. *The effect of surgery on the outcome of treatment for multidrug-resistant tuberculosis: a systematic review and meta-analysis*. BMC Infect Dis. 2016; 16(1). <https://doi.org/10.1186/s12879-016-1585-0>
3. World Health Organization. *WHO treatment guidelines for drug-resistant tuberculosis, 2016 update. October 2016 revision*. Geneva. 2016. <https://apps.who.int/iris/bitstream/handle/10665/250125/9789241549639-eng.pdf>

# 10.11 Treatment failure and palliative care

When a treatment is failing, treatment outcome should be recorded as "treatment failure" ([Chapter 17](#)).

A new baseline specimen should be collected, and a new individualized regimen designed according to the principles described in [Section 10.2.2](#).

When the minimum number of likely effective drugs cannot be reached, the use of TB drugs under development available for compassionate use is encouraged ([Appendix 18](#)).

When no therapeutic option or new regimen is possible, the patient can continue a TB regimen that is reasonably tolerated, or the regimen can be stopped. The decision to stop treatment should be made after careful evaluation and consultation with the patient, family, and TB treatment team. Palliative and supportive care should be continued.

Palliative and supportive care is an integral part of patient care throughout their illness<sup>[1][2]</sup>. Some care should be continued after cure if the patient remains with significant respiratory damage.

Palliative and supportive include<sup>[3]</sup>:

- Relief of respiratory symptoms: oxygen for shortness of breath; corticosteroids (prednisolone) for severe respiratory failure; codeine to help control cough.
- Identification, assessment and treatment of pain: non-opioids/mild opioids/strong opioids depending on the intensity of pain.
- Use of all necessary ancillary drugs.
- Nutritional support for undernourished patients.
- Care to improve comfort and prevent complications in debilitated patients; regular position changes in bedridden patients to prevent bedsores; bathing and oral hygiene to improve patient comfort and prevent skin infections
- Management of anxiety or depression (due to prolonged illness, separation from family, difficult living conditions, etc.); support to family as needed.

Offer home care to families who need help. Reserve inpatient rooms for end-of-life patients if they cannot be cared for at home.

## References

1. World Health Organization. *Planning and implementing palliative care services: a guide for programme managers*. Geneva. 2016. <https://apps.who.int/iris/bitstream/handle/10665/250584/9789241565417-eng.pdf?sequence=1&isAllowed=y>.
2. Hughes, J. Snyman, L. *Palliative care for drug-resistant tuberculosis: when new drugs are not enough*. *The Lancet Respiratory Medicine*. Volume 6, Issue 4, P251-252, April 01, 2018. [https://doi.org/10.1016/S2213-2600\(18\)30066-3](https://doi.org/10.1016/S2213-2600(18)30066-3)
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# Chapter 11: Treatment of rifampicin-susceptible and isoniazid-resistant tuberculosis

[11.1 Introduction](#)

[11.2 Standard treatment regimen](#)

[11.3 Other treatment regimens](#)

[11.4 Special situations](#)

[11.5 Adjunctive therapy](#)

[11.6 Patient monitoring](#)

[11.7 Adverse effects](#)

[11.8 Treatment adaptation and change of treatment](#)

[11.9 Treatment interruptions](#)

Update: October 2023

# 11.1 Introduction

Rifampicin-susceptible and isoniazid-resistant tuberculosis (Hr-TB) treatment is indicated in children and adults with pulmonary TB (PTB) and extrapulmonary TB (EPTB) when:

- Susceptibility to rifampicin is confirmed by drug susceptibility testing (DST) and resistance to isoniazid is confirmed by DST,
- or
- Susceptibility to rifampicin is confirmed by DST and resistance to isoniazid is strongly suspected (i.e. household or close contacts of a patient with confirmed Hr-TB), while waiting for DST results for isoniazid, or if susceptibility to isoniazid cannot be tested.

Patient with Hr-TB should be treated with the standard Hr-TB regimen<sup>[1][2]</sup> when:

- Susceptibility to fluoroquinolones is confirmed
- and, if possible
- Susceptibility to pyrazinamide is confirmed.

#### Notes:

- Fluoroquinolone resistance can be detected at the same time as isoniazid resistance by a rapid molecular test (Xpert MTB/XDR).
- Pyrazinamide resistance is detected by more complex tests (phenotypic DST or Genoscholar PZA-TB II) that cannot always be performed, or for which the results are not available at the start of treatment.
- Susceptibility to ethambutol cannot be confirmed as there is no reliable DST.

Other regimens should be considered for patients with additional resistance, contraindication or intolerance to fluoroquinolones and/or pyrazinamide.

## References

1. Fregonese F et al. *Comparison of different treatments for isoniazid-resistant tuberculosis: an individual patient data meta-analysis*. *Lancet Respir Med*. 2018 Apr;6(4):265-275.
2. World Health Organization. *WHO operational handbook on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, 2022 update*. Geneva; 2022. <https://www.who.int/publications/i/item/9789240006997>

# 11.2 Standard treatment regimen

## Box 11.1 – Standard regimen composition for Hr-TB

6(HRZE)-Lfx

Although there is no evidence about the effect of taking isoniazid despite resistance to this drug, the fixed-dose combination (HRZE) is used for the patient's convenience because no fixed-dose combination (RZE) is currently available.

The combination (HRZE) is administered at the same dose as for the intensive phase of drug-susceptible TB (DS-TB) treatment.

In children < 23 kg, ethambutol should be given with the fixed-dose-combination (HRZ). See [Appendix 13](#).

Levofloxacin is preferred over moxifloxacin in the standard Hr-TB regimen (better safety profile). In addition, rifampicin reduces the plasma concentration of moxifloxacin<sup>[1]</sup>.

Treatment prolongation may be considered on a case-by-case basis for patients with lung cavities or with sputum smear still positive after the end of Month 2. However, before prolonging the treatment, the emergence of resistances to rifampicin, fluoroquinolones (and, if possible, pyrazinamide) should be ruled out.

If isoniazid resistance is detected after the patient started a DS-TB treatment, perform a new rapid molecular test (RMT) to rule out the emergence of resistance to rifampicin. Once susceptibility to rifampicin is confirmed, change to a full 6-month standard Hr-TB regimen.

## References

1. Naidoo A, Naidoo K, McIlleron H, Essack S, Padayatchi N. *A Review of Moxifloxacin for the Treatment of Drug-Susceptible Tuberculosis*. J Clin Pharmacol. 2017 Nov;57(11):1369-1386. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5663285/pdf/nihms879749.pdf>

## 11.3 Other treatment regimens

There are no evidence-based treatment recommendations for patients with Hr-TB and additional resistance. The following regimens are examples of regimens that can be used under operational research conditions.

For more information on operational research conditions, see [Chapter 10](#).

### 11.3.1 Additional resistance to levofloxacin

**Box 11.2** – Regimen composition for levofloxacin-resistant Hr-TB

6RZE-Lzd

To avoid the combination of isoniazid and linezolid (increased risk of peripheral neuropathy), the FDC (HRZE) should not be used.

- If linezolid is stopped due to adverse effects:
  - before the end of Month 4: replace linezolid with delamanid until the end of treatment.
  - after the end of Month 4: based on clinical and bacteriological evolution, determine on a case-by-case basis if it is preferable to continue RZE only, or to replace linezolid with delamanid until the end of treatment.
- If linezolid is contraindicated, use the regimen 6RZE-Dlm.

### 11.3.2 Additional resistance to pyrazinamide

**Box 11.3** – Regimen composition for pyrazinamide-resistant Hr-TB

4RE-Lfx-Lzd/2RE-Lfx

- If linezolid is stopped due to adverse effects before the end of Month 4: replace linezolid with delamanid until the end of treatment.
- If linezolid is contraindicated, use the regimen 6RE-Lfx-Dlm.

### 11.3.3 Additional resistance to levofloxacin and pyrazinamide

**Box 11.4** – Regimen composition for levofloxacin and pyrazinamide-resistant Hr-TB

6RE-Lzd-Dlm

# 11.4 Special situations

## 11.4.1 Women (pregnant or breastfeeding or of childbearing age)

### Pregnant or breastfeeding women

- There is no data on the safety of the Hr-TB regimens in pregnant or breastfeeding women. WHO recommends the regimen 6(HRZE)<sup>[1]</sup>. However, there is no absolute contraindication to the use of levofloxacin. In patients with severe TB (e.g. extensive or bilateral lung damage or cavities, miliary TB or TB of the central nervous system) the standard regimen may be considered.
- For prevention of peripheral neuropathy due to isoniazid and clotting disorders due to rifampicin, see [Chapter 9](#).

### Women of childbearing age

- Women on contraception should use an intra-uterine device or a progestogen-only injectable throughout the course of TB treatment, as rifampicin reduces the effectiveness of implants and oral contraceptives.
- For women not on contraception, a pregnancy test should be performed prior to starting Hr-TB treatment and, if necessary, repeated during treatment. An effective contraception method (see above) should be offered prior to starting treatment.

## 11.4.2 Malnutrition or risk of malnutrition

See [Chapter 9](#).

## 11.4.3 Diabetes

TB can impair glycaemic control in patients with diabetes<sup>[2]</sup>. It is therefore necessary to increase blood glucose monitoring in these patients.

TB drugs may exacerbate complications of diabetes (e.g. peripheral neuropathy). Avoid prescribing ethambutol and linezolid in patients with pre-existing diabetic retinopathy. Rifampicin can reduce the effect of sulfonylureas (e.g. glibenclamide, gliclazide). In contrast, first-line TB drugs have no interactions with metformin.

If diabetes is diagnosed, treat and monitor according to standard protocols. At the end of TB treatment, it is recommended to schedule a specialist consultation for a complete evaluation and, if necessary, adjustment of antidiabetic treatment.

## 11.4.4 Renal insufficiency

In patients with renal insufficiency, creatinine clearance should be calculated. If it is less than 30 ml/minute, doses of certain TB drugs should be adjusted. For the formula to estimate creatinine clearance and dose adjustments in renal insufficiency, see [Appendix 12](#).

## References

1. World Health Organization. *WHO operational handbook on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, 2022 update*. Geneva; 2022. <https://www.who.int/publications/i/item/9789240006997>
2. World Health Organization & International Union against Tuberculosis and Lung Disease. (2011). *Collaborative framework for care and control of tuberculosis and diabetes*. World Health Organization. [https://iris.who.int/bitstream/handle/10665/44698/9789241502252\\_eng.pdf?sequence=1](https://iris.who.int/bitstream/handle/10665/44698/9789241502252_eng.pdf?sequence=1)



# 11.5 Adjunctive therapy

## 11.5.1 Pyridoxine prophylaxis

- Pyridoxine (vitamin B<sub>6</sub>) prophylaxis is indicated in patients taking isoniazid if they are at risk of peripheral neuropathy, i.e. pregnant or breastfeeding women and patients with HIV infection, chronic alcohol use, malnutrition, diabetes, chronic hepatic disease or renal impairment.
- All patients on linezolid should receive pyridoxine.

For more information, see Peripheral neuropathy, [Appendix 17](#).

## 11.5.2 Corticosteroid therapy

See [Chapter 9](#).

# 11.6 Patient monitoring

Clinical, bacteriological and radiological monitoring is the same as for patients on DS-TB treatment ([Chapter 9](#)).

- If, after the patient has started the standard Hr-TB regimen:
  - fluoroquinolone resistance is detected: perform a new RMT to rule out the emergence of resistance to rifampicin,
  - pyrazinamide resistance is detected: perform a new RMT to rule out the emergence of resistance to rifampicin or fluoroquinolones.
- Biological monitoring is reinforced and includes the following tests:
  - Patients on pyrazinamide: liver function tests at baseline, then once a month (risk of hepatotoxicity with prolonged use of pyrazinamide).
  - Patients on ethambutol: Ishihara test ([Appendix 16](#)) and visual acuity test at baseline, then once a month (risk of visual toxicity with prolonged use of ethambutol).
  - Patients on linezolid:
    - Full blood count at baseline, every 2 weeks for the first 2 months, then once a month.
    - Peripheral neuropathy screening (BPNS, [Appendix 16](#)) at baseline, then once a month.
    - Ishihara test ([Appendix 16](#)) and visual acuity test at baseline, then once a month.

# 11.7 Adverse effects

Rapid management of adverse effects is essential to increase tolerance and improve outcomes.

- In the event of minor adverse effects, drugs should not be stopped. Providing support and using ancillary medicines is all that is required.
- In the event of major adverse effects, the regimen may need to be adapted.

**Table 11.1** – Main adverse effects and likely responsible drugs

Adverse effects	Drug(s) likely responsible	Management
<b>Minor</b>		
Nausea, vomiting	Z, Lzd	<a href="#">Appendix 17</a>
Arthralgia	Z	<a href="#">Appendix 17</a>
Peripheral neuropathy	H, Lzd, Lfx	<a href="#">Appendix 17</a>
Orange/red urine, tears, etc.	R	Patients should be told when starting treatment that this is normal.
<b>Major</b>		
Skin reactions	E, Z, R, H, Lfx, Lzd, Dlm	<a href="#">Appendix 17</a>
Hepatotoxicity	Z, H, R	<a href="#">Appendix 17</a>
Optic neuritis	Lzd, E	<a href="#">Appendix 17</a>
Haematologic disorders	Lzd, R, H, E	<a href="#">Appendix 17</a>

For more information on individual drugs, see [Appendix 10](#).

# 11.8 Treatment adaptation and change of treatment

## 11.8.1 Treatment adaptation

The whole treatment or individual drug(s) may be temporarily interrupted by the clinician in case of severe adverse effects ([Appendix 17](#)). This is considered as treatment adaptation, as long as it does not meet the definition of "treatment failure" ([Chapter 17](#)).

## 11.8.2 Change of treatment

The clinician should replace the Hr-TB treatment with:

- A treatment for DS-TB if Hr-TB treatment was started before receiving DST result for isoniazid that shows susceptibility to isoniazid.
- A treatment for multidrug-resistant or rifampicin-resistant TB (MDR/RR-TB, [Chapter 10](#)) in the following circumstances<sup>[1]</sup>:
  - Development of rifampicin resistance after treatment initiation.
  - Rifampicin resistance not detected at baseline for any reason.
  - No bacteriological conversion or bacteriological reversion ([Chapter 17](#)).
  - Insufficient clinical response to treatment:
    - in patients with non-bacteriologically confirmed TB (e.g. miliary TB, some forms of EPTB, TB in children),
    - in patients with bacteriologically confirmed TB, when the bacteriological response cannot be assessed, or the result is inconclusive.

The above treatment changes meet the outcome definition of "treatment failure" ([Chapter 17](#)), except when the reason for the change is a resistance not detected at baseline<sup>[1]</sup>.

## References

1. World Health Organization. *Meeting report of the WHO expert consultation on drug-resistant tuberculosis treatment outcome definitions*, 17-19 November 2020. Geneva: World Health Organization; 2021. <https://www.who.int/publications/i/item/9789240022195>

# 11.9 Treatment interruptions

Treatment interruptions can lead to the emergence of new resistances.

Problems of treatment interruption by the patient (e.g. discontinuation of certain drugs, recurrent treatment interruptions) should be detected and addressed (management of adverse events if necessary and reinforcement of patient support measures).

Interruption of the entire treatment for two consecutive months or more meet the definition of "lost to follow-up" ([Chapter 17](#)).

For management of patients who interrupt treatment, see [Chapter 9](#).

# Chapter 12: Tuberculosis and HIV co-infection

[12.1 HIV counselling and testing](#)

[12.2 Concomitant treatment of tuberculosis and HIV co-infection](#)

[12.3 Interactions and overlapping toxicities between tuberculosis drugs and antiretrovirals](#)

[12.4 Prevention of opportunistic infections](#)

[12.5 Immune reconstitution inflammatory syndrome](#)

[12.6 Patient monitoring](#)

**Update: March 2023**

## 12.1 HIV counselling and testing

When HIV status is unknown, HIV counselling and testing is recommended for patients with latent tuberculosis infection (LTBI) and patients with presumed or confirmed active tuberculosis (TB).

The HIV test is performed after counselling, unless the person explicitly declines to be tested.

# 12.2 Concomitant treatment of tuberculosis and HIV co-infection

## 12.2.1 Active tuberculosis

For all HIV-infected patients, treatment of active TB should be started first.

Antiretroviral therapy (ART) should be initiated within 2 weeks of starting treatment of active TB, except for patients with TB meningitis.

For patients with TB meningitis, early initiation of ART is associated with an increased risk of serious adverse events. It is therefore recommended to start ART 4 to 8 weeks after the start of TB treatment<sup>[1]</sup>.

**Table 12.1** – First-line ART for patients with active TB and HIV co-infection<sup>[2]</sup>

ABC: abacavir; AZT: zidovudine; DTG: dolutegravir; EFV: efavirenz; FTC: emtricitabine; LPV/r: lopinavir/ritonavir; RAL: raltegravir; TDF: tenofovir disoproxil fumarate; 3TC: lamivudine

Patients	First choice	Main alternatives
Neonates	AZT + 3TC + RAL <sup>(a)</sup>	AZT + 3TC + LPV/r <sup>(b)(c)</sup>
Children	ABC + 3TC + DTG <sup>(a)</sup>	If paediatric DTG not available: ABC + 3TC + LPV/r <sup>(c)</sup> ABC + 3TC + RAL <sup>(d)</sup>
Adolescents and adults Childbearing-aged and pregnant women	TDF + 3TC (or FTC) + DTG	TDF + 3TC (or FTC) + EFV ABC + 3TC + DTG AZT + 3TC + EFV

(a) Doses of DTG and RAL should be doubled in patients taking rifampicin.

(b) LPV/r paediatric formulation can be administered to children as of the age of 2 weeks.

(c) LPV/r should not be used in children taking bedaquiline. The dose of LPV/r should be adjusted in neonates and children taking rifampicin.

(d) RAL should be used only if LPV/r paediatric formulation is not available.

## 12.2.2 Latent tuberculosis infection

For patients with LTBI not yet on ART, the initiation of ART should take priority over the initiation of LTBI treatment. See [Chapter 16](#).

### References

1. World Health Organization. *Updated recommendations on HIV prevention, infant diagnosis, antiretroviral initiation and monitoring: March 2021*. Geneva: World Health Organization; 2021.  
<https://apps.who.int/iris/rest/bitstreams/1336192/retrieve>
2. World Health Organization. *Update of recommendations on first- and second-line antiretroviral regimens*. Geneva: World Health Organization; 2019.  
<https://apps.who.int/iris/rest/bitstreams/1238289/retrieve>



## 12.3 Interactions and overlapping toxicities between tuberculosis drugs and antiretrovirals

Certain combinations of TB drugs and ARVs are contraindicated or should be avoided or require dose adjustments of TB drugs or ARVs. For more information, see [Appendix 19](#).

**Note:** drug interactions and overlapping toxicities between TB drugs and drugs other than ARVs are common. For example, rifampicin reduces plasma concentrations of fluconazole by 25%. It may be necessary to increase the dose of fluconazole. Conversely, fluconazole increases plasma concentrations of rifabutin. It is necessary to monitor for signs of rifabutin toxicity<sup>[1]</sup>. If patients are taking drugs other than ARVs, clinicians should be aware of potential interactions and overlapping toxicities.

### References

1. European Medical Agency. *Fluconazole: Summary of Product Characteristics*. 2012. [https://www.ema.europa.eu/en/documents/referral/diflucon-article-30-referral-annex-iii\\_en.pdf](https://www.ema.europa.eu/en/documents/referral/diflucon-article-30-referral-annex-iii_en.pdf)

## 12.4 Prevention of opportunistic infections

During TB treatment, cotrimoxazole preventive therapy (CPT) should be started or continued in order to prevent common and opportunistic infections.

# 12.5 Immune reconstitution inflammatory syndrome

TB-associated immune reconstitution inflammatory syndrome (TB-IRIS) can occur in a patient on antiretroviral and/or TB treatment. It is characterised by the onset of new or worsening (after initial improvement) signs and symptoms of TB resulting from the restoration of the immune system by ART.

Most common signs and symptoms of TB-IRIS are fever, lymphadenopathy, pulmonary infiltrates, pleural effusion, respiratory distress, neurological signs<sup>[1]</sup>.

TB-IRIS occurs in two circumstances:

- Paradoxical TB-IRIS: the diagnosis of active TB is made, the patient starts TB treatment, followed by ART and then signs and symptoms of TB worsen.
- Unmasking TB-IRIS: TB is not detected, the patient starts ART and then develops signs and symptoms of TB.

TB-IRIS is more common in patients with low CD4 count. It usually occurs within 3 months of starting ART, most often within the first month<sup>[2]</sup>.

The following differential diagnoses should be considered before making the diagnosis of TB-IRIS:

- New onset of opportunistic infection.
- Other infections unmasked after immune reconstitution due to ART.
- Failure of TB treatment due to drug resistance.

TB-IRIS is considered severe in patients with neurological signs, respiratory distress, or if their condition requires hospitalisation or frequent ambulatory care. Treatment of severe TB-IRIS is based on corticosteroids (except in the case of Kaposi's sarcoma or cryptococcal meningitis, for which corticosteroids are contraindicated).

Patients on corticosteroids should be monitored to detect any other opportunistic infections.

In patients with non severe TB-IRIS, treatment is based on non-steroidal anti-inflammatory drugs.

In case of unmasking TB-IRIS, TB treatment should be started immediately.

ART should not be interrupted, except in case of life-threatening IRIS.

**Table 12.2** – Symptomatic treatment of TB-IRIS

TB-IRIS	Treatment
<b>Severe</b>	<b>prednisolone</b> PO Child and adult: 1.5 mg/kg once daily (2 weeks) then 0.75 mg/kg once daily (2 weeks) <sup>[3]</sup>
<b>Non-severe</b>	<b>ibuprofen</b> PO for the shortest possible duration Child over 3 months: 5 to 10 mg/kg 3 to 4 times daily (max. 30 mg/kg daily) Child 12 years and over and adult: 200 to 400 mg 3 to 4 times daily (max. 1200 mg daily)

## References

1. M. Lanzafame, S. Vento. *Tuberculosis-immune reconstitution inflammatory syndrome*. Journal of Clinical Tuberculosis and Other Mycobacterial Diseases, Volume 3, 2016. <https://doi.org/10.1016/j.jctube.2016.03.002>
2. World Health Organization. *Operational handbook on tuberculosis. Module 5: management of tuberculosis in children and adolescents*. Geneva: World Health Organization; 2022. <https://apps.who.int/iris/bitstream/handle/10665/352523/9789240046832-eng.pdf>
3. Meintjes G, Wilkinson RJ, Morroni C et al. *Randomized placebo-controlled trial of prednisone for paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome*. Aids, 24(15), 2381–2390 (2010). [PubMed: 20808204]. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2940061/>

## 12.6 Patient monitoring

For patients on drug susceptible TB treatment, see [Chapter 9](#).

For patients on multidrug-resistant or rifampicin-resistant TB treatment, see [Chapter 10](#).

For patients on isoniazid-resistant TB treatment, see [Chapter 11](#).

# Chapter 13: Adherence to tuberculosis treatment

[13.1 Introduction](#)

[13.2 Treatment delivery model](#)

[13.3 Factors that influence adherence](#)

[13.4 Therapeutic patient education and patient support services](#)

Update: January 2022

# 13.1 Introduction

Good adherence is when the patient follows the treatment as prescribed. Patient understanding, acceptance and motivation to start and complete TB treatment are essential to maximise chances of cure. Good knowledge of drug dosing, length of treatment, required clinical follow-up and common adverse effects help patients to follow the prescribed therapy.

Failure to take tuberculosis (TB) drugs consistently, or in an inappropriate manner, or stopping the treatment too soon, can lead to treatment failure or relapse. It may also contribute to the development of resistance, which can complicate subsequent treatment, thereby decreasing the chances of a successful outcome.

# 13.2 Treatment delivery model

## 13.2.1 Self-administered treatment

Self-administered treatment (SAT) is taken autonomously by the patient without daily supervision. The patient is seen at a health facility at regular intervals (e.g. monthly) to receive drugs, support and treatment education. SMS telephone reminders may be considered to reinforce adherence.

## 13.2.2 Directly observed therapy

Drugs are sometimes provided daily to the patient and the treatment is taken under direct observation (DOT) by a third party.

DOT may be provided:

- In health facilities (facility-based DOT): in this model, DOT is implemented in a centralised setting and treatment is administered by healthcare workers.
- Outside of health facilities (community or home-based DOT): in this model, DOT is implemented in a decentralised setting and is usually provided by supervised, trained and remunerated treatment supporters.

For the roles and responsibilities of treatment supporters, see [Appendix 20](#).

- Remotely (video-observed therapy or VOT): VOT uses secure Internet connections via a smart phone or computer application to remotely supervise patients taking their treatment.

DOT is labour-intensive to implement and can be inconvenient for patients. Community and home-based DOT and VOT require fewer resources (personnel and transport) than facility-based DOT and may be more convenient for patients.

### Box 13.1 – Recommended treatment delivery models

#### Drug-susceptible TB (DS-TB)

- DOT has not been proven to improve treatment outcomes for DS-TB when compared to SAT in controlled trials<sup>[1]</sup>.
- When there is no factor to complicate adherence, and provided the patient receives appropriate support, treatment should be self-administered.
- There are some situations in which DOT may be preferred:
  - Patients with mental health problems or serious socioeconomic problems (e.g. the homeless) and all patients incapable of taking drugs on their own;
  - Detained persons (risk of drugs being sold or stolen).

#### Drug-resistant TB (DR-TB)

- Due to the lack of fixed-dose combinations (FDC), length of treatment, adverse effects of TB drugs and lack of therapeutic alternatives if treatment fails, patients usually require reinforced support.
- If DOT is considered useful, home-based DOT<sup>[2]</sup> or VOT are preferred to facility-based DOT. A combination of approaches may be required for some patients.

#### Latent TB infection (LTBI)

- LTBI treatment can be self-administered.
- DOT may be considered for patients who have experienced a mild hypersensitivity reaction during treatment with regimens containing HP. However, SAT can be continued if patients are able to seek medical attention rapidly if this adverse effect reoccurs.

## References

1. Karumbi, J. and P. Garner. *Directly observed therapy for treating tuberculosis*. Cochrane Database Syst Rev, 2015(5): p. CD003343. <https://doi.org/10.1002/14651858.CD003343.pub4>
2. Williams et al. *Community-based management versus traditional hospitalization in treatment of drug-resistant tuberculosis: a systematic review and meta-analysis*. Global Health Research and Policy (2016) 1:10. <https://doi.org/10.1186/s41256-016-0010-y>

# 13.3 Factors that influence adherence

Several factors can influence adherence, including barriers related to the patient, the treatment or the therapeutic environment. While it is not always feasible to address all these factors, at the very least it is possible to control the treatment and therapeutic environment-related factors.

## 13.3.1 Patient-related factors

A discussion should be held with the patient prior to treatment initiation and then during every contact they have with the healthcare team. The objective is to identify and anticipate barriers to treatment adherence. Barriers may include:

- Socioeconomic factors (work and home responsibilities, treatment-related costs, decreased income, etc.).
- Psychological factors (feelings of shame, fear of stigma or marginalisation, uncertainty about the future, conceptions about the disease and its treatment, etc.).
- Physical or mental disability.
- Lack of knowledge about the disease and treatment.
- Perception of the disease and treatment (a patient might abandon treatment due to improvement or absence of improvement, a negative experience with a previous treatment, etc.).

Solutions depend on the context and the patient's problem, and therefore should be identified on a case-by-case basis.

## 13.3.2 Treatment-related factors

- Simplicity of treatment improves adherence. The use of FDC simplifies the treatment by reducing the number of tablets. In addition, FDC prevents omission of one or more prescribed TB drugs.
- Adverse effects may lead patients to interrupt their treatment, so these should be detected and managed promptly.

## 13.3.3 Factors related to the therapeutic environment

- To ensure the widest possible access to treatment, TB diagnosis, monitoring and treatment (including TB drugs, drugs for adverse effects and co-morbidities, mental health care) should be provided free of charge.
- The relationship between patients and healthcare staff influences adherence. If patients have confidence in healthcare staff, they are more likely to follow recommendations and engage with the treatment process. Patients are also more likely to bring questions and concerns to the attention of healthcare staff. The same applies to the relationship with treatment supporters.
- In health facilities, the way in which patients are received is essential. Confidentiality of personal, medical, administrative and social information should be assured. Waiting times for diagnosis or follow-up visits should be reasonable.
- Drug supply management must be rigorous. Shortages can lead to treatment interruption and negatively impact adherence (patients waste time in unnecessary travel and lose confidence in the health facility).
- The proximity of drug distribution sites limits the number of patients who abandon due to transportation problems. To anticipate potential problems, give the patients a few extra days of treatment in case they are unable to come to get their drugs as scheduled.
- For the co-management of TB and HIV infection, patients should receive TB and HIV treatment at the same time and in the same place ("one-stop service"). This reduces the number of visits and decreases waiting times, which results in greater patient satisfaction and improved treatment outcomes. Co-management of other co-morbidities (e.g. diabetes, hypertension) should, when possible, use the same approach.
- Hospitalisation should be limited to patients with clinical conditions requiring hospital level care. If hospitalisation is necessary, accommodation (comfort, food, heating, etc.) should be adequate. With the exception of end-of-life patients, the duration of stay should be as short as possible and patients should be discharged as soon as their clinical condition allows.



## 13.4 Therapeutic patient education and patient support services

Therapeutic patient education and patient support require the involvement of the entire healthcare team (clinicians, nurses, treatment supporters, social workers, etc.). The healthcare team sometimes includes trained counsellors who provide information and support.

Therapeutic patient education and patient support may be provided through various channels: organising educational sessions during in-facility or home visits, video and telephone contacts.

Therapeutic patient education and patient support are required throughout treatment, as adherence may vary over time and patients may experience phases of treatment acceptance and rejection.

Due to the toxicity and long duration of treatment, patients on DR-TB treatment usually require substantial support.

### 13.4.1 Therapeutic patient education

Therapeutic patient education consists of:

- Helping patients to understand the disease and treatment;
- Enabling patients to acquire and maintain skills that allow them to manage their treatment and disease in their everyday lives;
- Answering patients' questions throughout the treatment.

For more information, see [Appendix 21](#).

### 13.4.2 Emotional support

Listen to patients and give them encouragement, so that they feel comfortable saying they have forgotten or have made a mistake with their treatment. This is common, and it is important to know so that solutions can be found.

Mental health problems, such as anxiety or depression are frequent, and may have a negative impact on adherence. The healthcare team should be sensitised to their early detection and management.

### 13.4.3 Social support

Implement social support measures for patients with limited resources. Depending on the context and specific needs of patients:

- Social workers can help to obtain disability allowances, housing assistance, shelter for the homeless, etc.
- Meals or food, vouchers or money for transportation or reimburse the cost, etc. can be provided.

# Chapter 14: Infection prevention and control

[14.1 Introduction](#)

[14.2 Administrative measures in health facilities](#)

[14.3 Environmental measures in health facilities](#)

[14.4 Respiratory protection measures in health facilities](#)

[14.5 Patient's homes](#)

Update: October 2023

# 14.1 Introduction

Tuberculosis infection prevention and control (TB-IPC) consists of a combination of 3 types of measures<sup>[1]</sup> :

- Administrative measures
- Environmental measures
- Respiratory protection measures

The aim of these measures is to reduce the risk of exposure to *M. tuberculosis* in health staff, patients, attendants, visitors and household members in contact with an infectious or potentially infectious person.

## Box 14.1 – Potential for TB transmission based on patient characteristics

**Infectious:** patients with smear- or culture-positive pulmonary TB (PTB) untreated, or not treated with an effective treatment, or treated with an effective treatment for less than 2 weeks.

**Potentially infectious:** patients pending TB diagnosis.

**Non-infectious:** patients with both smear- and culture-negative PTB, including those who have smear and culture converted, patients with extrapulmonary TB (EPTB) without concomitant PTB, most children.

## References

1. World Health Organization. *WHO guidelines on tuberculosis infection prevention and control, 2019 update*, Geneva; 2019. License: CC BY-NC-SA 3.0 IGO. <https://apps.who.int/iris/bitstream/handle/10665/311259/9789241550512-eng.pdf?sequence=5&isAllowed=y>

# 14.2 Administrative measures in health facilities

## 14.2.1 Evaluation of the risk of *M. tuberculosis* transmission

The first step is to perform an initial TB risk assessment. This assessment should be performed by the IPC practitioner ([Section 14.2.3](#)).

For an example of risk assessment tool, see [Appendix 23](#).

## 14.2.2 Infection prevention and control plan

Based on the initial assessment, each facility should develop a detailed, written, specific TB-IPC plan for implementing measures to reduce TB transmission.

The TB-IPC plan should be re-evaluated and updated based on periodic (at least annual) TB risk assessments.

A simplified version of this TB-IPC plan should be accessible to staff, i.e. healthcare staff, but also staff not directly involved in the management of patients.

A floor plan indicating the risk of TB transmission in each area should be drawn up and displayed.

### Box 14.2 – Levels of risk in TB facilities

#### High risk

- Sputum and other respiratory specimen collection areas.
- Laboratory (areas for specimen preparation).
- Wards or rooms of infectious TB patients.
- Rooms used for TB diagnosis (clinical consultation, medical imaging).
- Waiting rooms in high TB prevalence areas.

#### Limited risk

- Pediatric wards.
- Wards or rooms for patients with extrapulmonary TB (EPTB) and no concomitant pulmonary TB (PTB) or smear- and culture-negative PTB.
- Laboratory (areas other than those used for specimen preparation, e.g. for specimen reception, smear reading).

#### Low risk (non-TB zones)

- Kitchen.
- Administration.
- Pharmacy.
- Technical services.

## 14.2.3 Infection prevention and control practitioner and committee

An IPC practitioner with the authority, budget, and human resources for implementing TB-IPC measures and conducting TB risk assessments should be assigned.

According to the context, a multidisciplinary TB-IPC committee may be established to assist the IPC practitioner in the development of the TB-IPC plan and ensure its dissemination within the facility. This committee can include doctors, nurses, laboratory technicians, logistic officers, housekeeping staff, transport staff, administration staff.

## 14.2.4 Training of staff

Training on TB symptoms, TB transmission and TB-IPC measures (including respirator fit testing) should be provided to staff when:

- The TB-IPC plan is implemented.
- A TB-IPC measure is introduced or modified.
- A new staff member is hired.

In addition, continuous training sessions should be provided to all staff at least once a year.

## 14.2.5 Patient triage

In waiting rooms in high TB prevalence settings, patients with cough should be quickly identified.

These patients should be promptly isolated and referred/transferred to a unit or facility where TB can be diagnosed and treated.

## 14.2.6 Early diagnosis and treatment of tuberculosis

Patients with PTB are no longer considered as infectious after 2 weeks of effective treatment<sup>[1][2]</sup>.

Therefore, it is essential to promptly:

- Screen patients at risk of TB ([Chapter 6](#)).
- Diagnose TB using rapid diagnostic tests ([Appendix 5](#)).
- Start effective treatment.

## 14.2.7 Separation and isolation

### All health facilities

- Patients with TB (presumed or confirmed): place in isolation; no movements to areas where they could infect other patients.
- Patients without TB: no movements to areas where they could be exposed to the bacillus.

### Outpatient TB facilities

- Favour home-based treatment.
- Limit the frequency and duration of visits to the TB facility.

### Inpatient TB facilities

- Hospitalise only severely ill patients who cannot be diagnosed or treated as outpatients.
- Group patients according to their infectiousness ([Box 14.1](#)) and resistance profile (drug-susceptible/drug-resistant TB, e.g. isoniazid resistance, rifampin resistance, multidrug resistance, extensive drug-resistance).
- Place patients in single rooms if possible.
- If the number of single rooms is limited, they should be given in priority to patients pending diagnosis (potential infectiousness and resistance profile unknown) and patients likely to be the most infectious and/or with the most difficult-to-treat resistance.
- If there are no single rooms, place patients in rooms with 2 to 4 beds max., respecting the principle of separation according to their infectiousness and resistance profile.
- Provide gathering areas for patients to socialize, according to their infectiousness and resistance profile.
- Assign dedicated staff to provide care for patients in isolation.
- Maintain isolation of infectious patients if ambulance transport is required.
- Limit number of attendants.
- Allow visits in dedicated and clearly signaled areas. Limit number of visitors and duration of visits. Avoid visits by children if possible.

## 14.2.8 Respiratory hygiene and cough etiquette

Patients, attendants, visitors and health staff should cover their mouth and nose when they cough or sneeze. Posters to remind respiratory hygiene and cough etiquette should be displayed in various places within the facility.

## 14.2.9 Education for patients, attendants and visitors

Information on the risk of TB transmission and on precautions to be observed (cough etiquette, use of respirators/surgical masks) should be provided by the healthcare staff, using appropriate educational material.

Staff should make sure that patients, attendants and visitors adhere to TB-IPC measures.

## 14.2.10 Health facility hygiene

All standard precautions (hand hygiene; gowns, gloves, facial protection when required; cleaning of floors and surfaces; handling of soiled linen or equipment, and waste) apply in TB facilities, as they do in any health facility.

Sputum containers of inpatients should be replaced daily. Used sputum containers (from wards and laboratory) should be collected in a leak proof trash bag. They should not be filled with chlorine solution before incineration (this can produce toxic gases).

After patient's discharge, the patient's room should be adequately ventilated ([Section 14.3.1](#) and [Appendix 24](#)).

## References

1. Centers of Diseases Control and Prevention. *Core Curriculum on Tuberculosis: What the Clinician Should Know*. Seventh edition, 2021. <https://www.cdc.gov/tb/education/corecurr/pdf/CoreCurriculumTB-508.pdf>
2. Migliori GB, Nardell E, Yedilbayev A, et al. *Reducing tuberculosis transmission: a consensus document from the World Health Organization Regional Office for Europe*. Eur Respir J 2019. <https://doi.org/10.1183/13993003.00391-2019>

# 14.3 Environmental measures in health facilities

## 14.3.1 Ventilation

Ventilation (natural or mechanical) is an effective means for reducing the concentration of *M. tuberculosis* by removing or diluting droplet nuclei suspended in air.

It is measured in air changes per hour (ACH) which is the number of times the entire volume of air in a room is replaced in one hour (for calculation of ACH, see [Appendix 24](#)).

WHO recommends a minimum of 12 ACH in areas where TB transmission may occur (wards or rooms, diagnosis rooms, corridors, etc.)<sup>[1]</sup>.

When planning/constructing a new TB facility or converting an existing facility, the layout of the building must maximise natural ventilation.

- It is preferable that the doors of the rooms open onto outside corridors to facilitate natural ventilation.
- If rooms are distributed along an enclosed central corridor, natural ventilation can be done by opening windows while keeping doors closed so that airflow is directed outside.
- Wind-driven roof turbines (whirly birds) can also be installed to improve natural ventilation.
- When natural ventilation is insufficient, fans can be used (assisted natural ventilation).
- Waiting areas, visiting areas and gathering spaces should be shaded outdoor areas that are open on at least three sides.
- Sputum collection areas should be located in the open air. "Sputum collection booths" (similar to voting booths) can be installed to protect patient privacy.

When adequate natural ventilation cannot be achieved (e.g. cold climate), mechanical ventilation, i.e. the use of equipment to move exhaust air from the room to the outside is necessary.

Sputum collection should be performed in very well-ventilated indoor rooms (at least 20 ACH).

Laboratories should be equipped with:

- ventilated workstation for preparing sputum smears and loading Xpert cartridges if ventilation is < 12 ACH
- biosafety cabinet if specimens are centrifuged or cut/ground regardless of the air change rate<sup>[2]</sup>.

For an overview of ventilation techniques, see [Appendix 25](#).

For ventilated workstation and biosafety cabinet, see [Appendix 6](#).

## 14.3.2 Germicidal ultraviolet lamps

Germicidal ultraviolet (GUV) lamps may be effective in killing or inactivating *M. tuberculosis*. When ventilation is not sufficient (i.e. does not reach 12 or 20 ACH), they should be used as a supplement to ventilation in health care facilities and congregate settings (e.g. detention centres) where the risk of TB transmission is high.

For technical information on GUV lamps see, [Appendix 26](#).

**Note:** the intensity of solar radiation is variable and exposure to the sun should not be relied upon as a means of TB-IPC.

## References

1. World Health Organization. *WHO policy on TB infection control in health-care facilities, congregate settings and households*. World Health Organization; 2009. [https://apps.who.int/iris/bitstream/handle/10665/44148/9789241598323\\_eng.pdf?sequence=1](https://apps.who.int/iris/bitstream/handle/10665/44148/9789241598323_eng.pdf?sequence=1)
2. World Health Organization. *Xpert MTB/RIF implementation manual: technical and operational 'how-to'; practical considerations*. World Health Organization; 2014. [https://apps.who.int/iris/bitstream/handle/10665/112469/9789241506700\\_eng.pdf](https://apps.who.int/iris/bitstream/handle/10665/112469/9789241506700_eng.pdf)

# 14.4 Respiratory protection measures in health facilities

## 14.4.1 Respirators

Medical staff and non-medical staff should wear a respirator ([Appendix 27](#)) when:

- Entering any high-risk area ([Box 14.2](#))
- Entering a room previously occupied by an infectious TB case, if the room has not been ventilated for the time required to remove airborne bacilli ([Appendix 24](#))
- Performing high-risk procedures (sputum or other respiratory specimen collection, pleural paracentesis, pulmonary surgery, etc.)
- Collecting and disposing of sputum containers

Using respirators needs proper training, fit testing and continuous supervision.

Posters to remind staff of when and where to wear respirators should be displayed within the facility.

Attendants should wear a respirator when sharing an enclosed space with an infectious patient:

- Wards or rooms, diagnosis room, sputum or respiratory specimen collection room, etc.
- Ambulance, taxi, or any vehicle

Visitors should wear a respirator when entering wards or rooms of infectious patients.

Visible signs on the entrance doors of departments and rooms should remind attendants and visitors to wear respirators.

Before any visit, the health staff should provide information on the risk of TB transmission and the use of respirators in high-risk areas.

## 14.4.2 Surgical masks

Infectious patients should wear a surgical mask ([Appendix 28](#)) when:

- Leaving their room to go to any other enclosed space, including during transport
- Taking care of young children

Surgical masks should not be worn when patients are alone in their room or when they are outdoors.

## 14.5 Patient's homes

TB-IPC principles and measures (administrative, environmental, and respiratory protection) that apply in health care facilities also apply with adaptations to patients' homes as long as patients are infectious or potentially infectious ([Box 14.1](#)).

### 14.5.1 Screening of household and close contacts

Screening for active TB should be performed in household and close contacts as soon as possible after the patient has been diagnosed ([Chapter 6](#)).

### 14.5.2 Separation and isolation

Patients should:

- Sleep in a separate room, if possible, with the door closed off to the rest of the house.
- Avoid or spend as little time as possible in congregate settings or public transport.

Household members and close contacts should spend as little time as possible in the same enclosed spaces as patients.

### 14.5.3 Respiratory hygiene and cough etiquette

Patients, household members and close contacts should cover their mouth and nose when they cough or sneeze.

### 14.5.4 Ventilation

Patients should spend as much time as possible outdoors if weather permits.

Houses should be adequately ventilated. When it is not possible to keep the windows open, regularly ventilate the patient's room and common spaces.

### 14.5.5 Respiratory protection

- Treatment supporters, household members and close contacts should wear a respirator ([Appendix 27](#)) when sharing an enclosed space (room, vehicle, etc.) with the patient. Treatment supporters and household members should be educated on the proper use of respirators and a fit test should be performed.
- Patients should wear a surgical mask ([Appendix 28](#)) when sharing an enclosed space (room, vehicle, etc.) with other people and when taking care of young children.
- Surgical masks are not necessary when patients are alone in their room or when they are outdoor.

### 14.5.6 Education for patients and household members

Education on the risk of TB transmission and on precautions to be observed should be provided by the healthcare staff:

- Cough etiquette
- Use of respirators/surgical masks
- Waste management: enclose waste (i.e. sputum containers, tissues, respirators/surgical masks) hermetically in plastic bags and discard in the normal waste. Do not empty sputum containers before discarding. Alternatively, tissues can be thrown in the latrine.



# Chapter 15: Follow-up of staff exposed to tuberculosis

[15.1 Introduction](#)

[15.2 Baseline assessment](#)

[15.3 BCG vaccination](#)

[15.4 Follow-up](#)

Update: October 2022

# 15.1 Introduction

The following recommendations apply to staff who work in health facilities and are in contact with tuberculosis (TB) patients and/or infectious laboratory specimens.

They provide general guidance, but should be adapted to the context and regulations of each country.

## 15.2 Baseline assessment

New staff should undergo a baseline assessment. This includes:

- BCG status (BCG scar check)
- Tuberculin skin test (TST) or interferon gamma release assay (IGRA)
- Chest x-ray (CXR)
- HIV test

In addition, the following information should be provided:

- Risk of occupational transmission of *M. tuberculosis*
- Infection prevention and control (IPC) measures to reduce the risk of transmission
- Higher risk of active TB in immunocompromised individuals (e.g. persons with HIV infection, with diabetes) and in pregnant women
- Vigilance required for, and self-reporting of, signs and symptoms suggestive of TB

Immunocompromised staff and pregnant women should not work in TB units or areas where the risk of exposure to *M. tuberculosis* is high ([Chapter 14](#)).

## 15.3 BCG vaccination

Recommendations vary between countries, with some requiring staff to be BCG vaccinated if never vaccinated and TST negative.

There is limited evidence regarding the benefits of BCG vaccination in adults who have not previously had BCG vaccination<sup>[1]</sup>.

Vaccination should be considered on a case-by-case basis in the following situations<sup>[2]</sup>:

- Significant exposure to multidrug-resistant TB (MDR-TB): e.g. facilities treating patients with MDR-TB, detention centres, or areas with high MDR-TB prevalence.
- While corrective actions are implemented:
  - when transmission of MDR-TB to staff has occurred;
  - when IPC measures are inadequate or poorly applied.

The following information should be provided to staff considered for BCG vaccination:

- Benefits and risks of BCG vaccination.
- Impact of BCG on the interpretation of TST results in diagnosing a potential latent TB infection (LTBI).
- No complete protection conferred by the vaccine: TB may still occur if IPC measures are not applied.

BCG vaccine should only be administered if the person:

- Has never had a BCG vaccination.
- Has a HIV test negative result.
- Is not pregnant.
- Has never had active TB.
- Has a TST negative result.

For more information on BCG vaccine, see [Appendix 29](#).

### References

1. Punam Mangtani, Ibrahim Abubakar, Cono Ariti, Rebecca Beynon, Laura Pimpin, Paul E. M. Fine, Laura C. Rodrigues, Peter G. Smith, Marc Lipman, Penny F. Whiting, Jonathan A. Sterne. *Protection by BCG Vaccine Against Tuberculosis: A Systematic Review of Randomized Controlled Trials*. *Clinical Infectious Diseases*, Volume 58, Issue 4, 15 February 2014, Pages 470–480.  
<https://doi.org/10.1093/cid/cit790>
2. Centers for Disease Control and Prevention Fact Sheets on BCG Vaccine.  
<https://www.cdc.gov/tb/publications/factsheets/prevention/bcg.htm>

## 15.4 Follow-up

Follow-up of routinely exposed staff includes:

- An annual clinical evaluation.
- Assessment for TB (including CXR) and HIV, if symptomatic.

For staff who were TST or IGRA negative at baseline, TST may be performed once a year.

Staff working in a TB department and presenting with a recent immunodepression (e.g. HIV infection, immunosuppressive treatment) or a pregnancy, should be transferred to another department or to an area within the TB department where the risk of exposure to *M. tuberculosis* is low ([Chapter 14](#)).

LTBI treatment ([Chapter 16](#)) should be offered, after exclusion of active TB:

- Once to staff who become TST or IGRA-positive.
- To all HIV-infected staff.

# Chapter 16: Treatment of latent tuberculosis infection

[16.1 Introduction](#)

[16.2 Target populations](#)

[16.3 Latent tuberculosis infection treatment regimens](#)

[16.4 Latent tuberculosis infection in HIV-infected patients](#)

[16.5 Latent tuberculosis infection in household contacts](#)

[16.6 Latent tuberculosis infection in other individuals at risk](#)

[16.7 Latent tuberculosis infection and multidrug-resistant tuberculosis](#)

[16.8 Follow-up for patients treated for latent tuberculosis infection](#)

Update: January 2022

# 16.1 Introduction

Exposure to *M. tuberculosis* may result in latent tuberculosis infection (LTBI). WHO defines LTBI as a state of persistent immune response to stimulation by *M. tuberculosis* antigens with no evidence of clinically manifest active tuberculosis (TB)<sup>[1]</sup>. This is also referred to as “tuberculosis infection”.

Identification and treatment of LTBI can reduce TB morbidity and mortality, as well as TB transmission.

Tuberculin skin test (TST) or interferon-gamma release assay (IGRA) can be used to detect LTBI ([Chapter 3](#)).

The goal of LTBI treatment is to reduce the risk of progression to active TB. It must be initiated only once active TB has been ruled out by appropriate evaluation.

If a patient develops signs and symptoms of active TB while on LTBI treatment, a specimen should be taken for diagnosis and detection of drug resistance (Xpert MTB/RIF, Xpert MTB/XDR, culture and drug susceptibility test, DST) and according to the results, TB treatment should be initiated.

## References

1. World Health Organization. *WHO consolidated guidelines on tuberculosis: module 1: prevention: tuberculosis preventive treatment*. Geneva: World Health Organization. 2020.  
<https://www.who.int/publications/i/item/who-consolidated-guidelines-on-tuberculosis-module-1-prevention-tuberculosis-preventive-treatment>

## 16.2 Target populations

TST or IGRA cannot predict which patients with LTBI are likely to develop active TB. Therefore, widespread LTBI testing and treatment are not recommended.

However, in certain populations, the risk of progression to active TB significantly exceeds that of the general population. For these at-risk populations, the benefits of LTBI treatment of preventing active TB and TB transmission outweigh the potential risks.

### **Box 16.1** – Populations who benefit most from LTBI treatment

- HIV-infected individuals.
- Household contacts of patients with bacteriologically confirmed pulmonary TB (PTB), in particular children under 5 years.
- Other individuals or populations at risk (e.g. health staff, detained persons).



# 16.3 Latent tuberculosis infection treatment regimens

There are 3 recommended LTBI treatment regimens and 2 alternative treatment regimens<sup>[1]</sup>. The decision to prescribe one regimen rather than the other should take into consideration:

- Drug-susceptibility of the strain of the presumed source patient, if known.
- Co-morbidities (e.g. HIV infection, pre-existing hepatic disease or neuropathy).
- Risk of drug interactions (especially with antiretrovirals), tolerability, length of treatment and likelihood of adherence.
- Individual characteristics (e.g. age, pregnancy, living conditions, individual preference).
- Epidemiological and programmatic aspects (e.g. HIV prevalence, available drugs, national recommendations).

**Table 16.1** – LTBI treatment regimens

Recommended regimens	
<b>Isoniazid daily for 6 months (6H) or 36 months (36H)</b>	<b>isoniazid</b> PO once daily: < 30 kg: 10 mg/kg (7 to 15 mg/kg) ≥ 30 kg: 5 mg/kg (4 to 6 mg/kg) (max. dose 300 mg daily)
OR <b>Isoniazid + rifapentine weekly for 3 months (3HP)</b>	<b>isoniazid</b> PO once weekly: < 30 kg and ≥ 2 years: 20 to 30 mg/kg ≥ 30 kg: 900 mg + <b>rifapentine</b> PO once weekly <sup>[2]</sup> : 10 to 14 kg and ≥ 2 years: 300 mg 14.1 to 25 kg and ≥ 2 years: 450 mg 25.1 to 32 kg: 600 mg 32.1 to 49.9 kg: 750 mg ≥ 50 kg: 900 mg max.
OR <b>Isoniazid + rifampicin daily for 3 months (3HR)</b>	<b>isoniazid</b> PO once daily: < 30 kg: 10 mg/kg (7 to 15 mg/kg) ≥ 30 kg: 5 mg/kg (4 to 6 mg/kg) (max. dose 300 mg daily) + <b>rifampicin</b> PO once daily: < 30 kg: 15 mg/kg ≥ 30 kg: 10 mg/kg (max. dose 600 mg daily)

Alternative regimens	
<b>Isoniazid + rifapentine daily for 1 month (1HP)</b>	<b>isoniazid</b> PO once daily: ≥ 13 years: 300 mg + <b>rifapentine</b> PO once daily: ≥ 13 years: 600 mg
OR <b>Rifampicin daily for 4 months (4R)</b>	<b>rifampicin</b> PO once daily: < 30 kg: 15 mg/kg ≥ 30 kg: 10 mg/kg (max. dose 600 mg daily)

## 16.3.1 Isoniazid monotherapy

Isoniazid monotherapy (or isoniazid preventive therapy, IPT) is the treatment currently most often used for LTBI. This treatment has proven to be effective in preventing active TB in both HIV-infected and non-HIV-infected patients<sup>[3][4]</sup>.

WHO recommends this treatment in all patients regardless of their HIV status, including children of any age and pregnant women.

The main disadvantage of isoniazid monotherapy is the length of treatment. Patients are usually healthy and may not be motivated to complete a 6-month therapy.

Adverse effects (e.g. peripheral neuropathy, hepatotoxicity) can also lead to treatment interruption.

All patients at risk of peripheral neuropathy should receive pyridoxine (vitamin B<sub>6</sub>) for the entire duration of treatment to prevent this risk (for doses, see [Appendix 17](#)).

In HIV-infected patients, the treatment may be difficult due to additive adverse effects of antiretrovirals and isoniazid, the extending of the duration of treatment to 36 months in some adolescents and adults ([Section 16.4.2](#)) and the high number of tablets to be taken daily. The number of tablets can be reduced using a fixed-dose combination (FDC) of isoniazid/cotrimoxazole/pyridoxine.

## 16.3.2 Rifapentine-containing regimens

### Combination isoniazid-rifapentine once weekly for 3 months (3HP)

This treatment has proven to be effective in preventing active TB in both HIV-infected and non-HIV- infected patients. WHO recommends this treatment in children 2 years and over, adolescents and adults, regardless of their HIV status.

It is short, requires few doses, has a high completion rate and the risk of hepatotoxicity is low<sup>[5][6]</sup>.

The disadvantages of this regimen are the lack of FDC and the development of hypersensitivity reaction in almost 4% of patients<sup>[4]</sup> ([Section 16.8.3](#)).

### Combination isoniazid-rifapentine once daily for 1 month (1HP)

This treatment has proven to be effective in preventing active TB in HIV-infected patients. WHO recommends this treatment as an alternative regimen in patients 13 years and over, regardless of their weight and HIV status.

The treatment is short, has a high completion rate and the risk of hepatotoxicity is low<sup>[7]</sup>. However, cutaneous reactions (rash, itching) are common.

Rifapentine containing regimens are not currently recommended for pregnant women. Despite some reassuring data<sup>[8]</sup>, safety is not definitively established.

## 16.3.3 Rifampicin-containing regimens

### Combination isoniazid-rifampicin once daily for 3 months (3HR)

This treatment has proven to be effective in preventing active TB in both HIV-infected and non-HIV- infected patients. WHO recommends this treatment in all patients regardless of their HIV status, including children of any age and pregnant women.

It is short, safe, has a good completion rate<sup>[3]</sup> and FDC are available for children and adults. Hypersensitivity reaction may occur in approximately 2% of patients<sup>[9]</sup>.

### Rifampicin monotherapy once daily for 4 months (4R)

This treatment has proven to be effective in preventing active TB in non-HIV-infected patients of all ages. WHO recommends this regimen as an alternative regimen in all patients regardless of their HIV status, including children of any age and pregnant women.

The advantages of this regimen (better safety profile and completion rate compared to 6H)<sup>[10]</sup> should be weighed against the risk associated with use of rifampicin in monotherapy (development of resistance to rifampicin in patients with undiagnosed active TB).

#### Notes:

For rifamycin-containing regimens:

- Rifapentine and rifampicin have interactions with many drugs, particularly antiretrovirals ([Appendix 19](#)) and contraceptives ([Chapter 9](#)).
- For pregnant women taking rifampicin, administer phytomenadione (vitamin K) in the last few weeks of pregnancy ([Chapter 9](#)).
- Rifapentine and rifampicin are not interchangeable.
- Rifabutin can replace rifampicin if rifampicin cannot be used due to drug interactions<sup>[2]</sup>.

## References

1. World Health Organization. *WHO consolidated guidelines on tuberculosis: Module 1: prevention: tuberculosis preventive treatment*. Geneva: World Health Organization. 2020.  
<https://www.who.int/publications/i/item/who-consolidated-guidelines-on-tuberculosis-module-1-prevention-tuberculosis-preventive-treatment>
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# 16.4 Latent tuberculosis infection in HIV-infected patients

Treatment of LTBI reduces the risk of active TB by 33-64% [1].

For patients not yet on antiretroviral treatment (ART), ART initiation should take priority over initiation of LTBI treatment.

Among these patients, there is a high proportion of undiagnosed, asymptomatic TB cases and it is important to use all existing diagnostic means to rule out active TB.

**Note:** a treatment programme for LTBI should be combined with a screening programme for active TB in HIV-infected patients (Chapter 6).

## 16.4.1 Children

HIV-exposed children<sup>a</sup> and HIV-infected children and who do not have active TB (for evaluation, see Chapter 4) should receive LTBI treatment:

- After contact with a TB case, including smear-positive, smear-negative and extrapulmonary TB (EPTB), regardless of their age;
- In high TB transmission areas: if aged 12 months and over, regardless of their contact history.

In addition, for children treated for active TB and living in high TB transmission areas, LTBI treatment may also be prescribed immediately after the successful completion of TB treatment to reduce the risk of reinfection.

## 16.4.2 Adolescents and adults

HIV-infected adolescents and adults who do not have active TB should receive LTBI treatment, regardless of contact history and TB prevalence in the area. In areas with high TB transmission, HIV-infected adolescents and adults with a LTBI test positive or unknown and who are unlikely to have active TB (no cough, no fever, no weight loss, no night sweats) should receive the treatment for at least 36 months (long-term regimen).

This regimen is more effective in preventing TB in HIV-infected adults with a positive TST than those with a negative TST [2].

If TST is not feasible, or where the national guidelines do not recommend long-term isoniazid monotherapy, HIV-infected adolescents and adults without any TB symptoms should receive another LTBI treatment (6H or a rifapentine- or rifampicin-containing regimen).

**Table 16.2** – LTBI treatments for HIV-infected patients [3]

Age	Recommended regimens	Alternative regimens
Child < 2 years	6H or 3HR	4R
Child ≥ 2 years	6H or 3HP or 3HR	4R
Adolescent and adult	6H or 3HP or 3HR or 36H	1HP (if ≥ 13 years) or 4R

### Footnotes

(a) HIV-exposed children are children born to HIV-infected women whose HIV status has not been established and/or are still at risk of infection (e.g. still breastfed).

### References

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# 16.5 Latent tuberculosis infection in household contacts

A household contact is a person who has shared the same enclosed living space as the index case for one or more nights or for frequent or extended daytime periods during 3 months before the start of the current treatment<sup>[1]</sup>.

## 16.5.1 Neonates of mothers with active pulmonary tuberculosis

All neonates born to mothers with active PTB should receive treatment for LTBI, after exclusion of active TB, if the mother:

- Has been treated for PTB less than 2 weeks at the time of birth, or
- Has a positive smear microscopy result on a sputum sample collected at birth or close to the time of birth<sup>[2]</sup>.

Xpert MTB/RIF and Xpert MTB/XDR assays should have been performed to rule out resistance to rifampicin and isoniazid in the mother before starting treatment for LTBI in the neonate.

The recommended regimens are 3HR or 6H. For HIV-exposed neonates receiving nevirapine, only 6H is recommended.

BCG vaccine should be administered just after LTBI treatment completion (not during the treatment).

If a TST is feasible and the regimen chosen is 6H:

- Administer isoniazid for 3 months, then perform a TST.
- If the TST is positive, complete isoniazid monotherapy.
- If the TST is negative, stop isoniazid and administer the BCG vaccine.

### Notes:

- A neonate should not be separated from its mother unless severely ill.
- Breastfeeding should continue, and breastfed neonates should receive pyridoxine (vitamin B<sub>6</sub>).

## 16.5.2 Other household contacts

### Children under 5 years

It is not mandatory to perform TST or IGRA prior to LTBI treatment.

All children < 5 years in contact with a confirmed PTB case and who do not have active TB (for evaluation, see [Chapter 4](#)) should receive LTBI treatment, regardless of their HIV and BCG vaccination status.

If LTBI treatment is contra-indicated or in case of parental refusal, monitor the child closely for one year to enable the early detection of active TB.

### Children 5 years and older, adolescents and adults

A TST or IGRA should be performed prior to LTBI treatment. If this is not feasible, LTBI treatment may be considered, weighing benefits and risks.

- Children 5 years and over in contact with a confirmed PTB case and who do not have active TB (for evaluation, see [Chapter 4](#)) may receive LTBI treatment, regardless of their HIV status.
- Adolescents and adults in contact with a confirmed PTB case and who do not have active TB (no TB symptoms and no abnormality on CXR) may receive LTBI treatment, regardless of their HIV status.

**Table 16.3** – LTBI regimens for household contacts<sup>[3]</sup>

Age	Recommended regimens	Alternative regimens
Child < 2 years	6H or 3HR	4R
Child ≥ 2 years	6H or 3HP or 3HR	4R
Adolescent and adult	6H or 3HP or 3HR	1HP (if ≥ 13 years) or 4R

## References

1. World Health Organization. *WHO consolidated guidelines on tuberculosis: Module 1: prevention: tuberculosis preventive treatment*. Geneva: World Health Organization. 2020.  
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<https://www.who.int/publications/i/item/who-consolidated-guidelines-on-tuberculosis-module-1-prevention-tuberculosis-preventive-treatment>



## 16.6 Latent tuberculosis infection in other individuals at risk

Routine LTBI testing (TST or IGRA) and treatment after exclusion of active TB:

- Are recommended for patients with silicosis, on dialysis or taking long-term immunosuppressive therapy.
- Can be considered for health staff, populations in congregate living settings (e.g. detained persons, refugees), migrants from countries with a high TB prevalence, homeless people and drug users.

LTBI testing should be performed periodically (e.g. once a year).

Routine LTBI testing and treatment is not recommended for patients with diabetes, malnutrition or chronic alcohol consumption, unless they belong to the above-mentioned risk groups.

# 16.7 Latent tuberculosis infection and multidrug-resistant tuberculosis

Due to limited evidence, routine LTBI treatment for all household contacts of multidrug-resistant TB (MDR-TB) patients cannot be recommended at this time.

However, treatment of LTBI should be considered in certain high-risk household contacts based on an individual risk-benefit assessment.

Individual assessment includes:

- High risk of progression to active TB: children under 5 years, individuals with HIV infection or on immunosuppressive therapy.
- Resistance pattern of the source case: the LTBI treatment regimen must be individually tailored as contacts of MDR-TB patients are often infected with the same strain<sup>[1]</sup>.
- Intensity of exposure.
- Contra-indication or risk of adverse drug reactions.

A TST or IGRA should be performed prior to LTBI treatment. If not feasible, LTBI treatment may be considered, weighing benefits and risks.

## 16.7.1 Household contacts of multidrug-resistant tuberculosis cases eligible for treatment

Evidence is lacking on the choice of treatment to prevent disease in MDR-TB contacts. Few observational studies, primarily using a fluoroquinolone (FQ) for 6 months, reported promising results<sup>[2][3]</sup>. Randomized clinical trials are ongoing<sup>[4][5]</sup>.

For contacts of FQ-susceptible MDR-TB patients, **levofloxacin** PO for 6 months can be proposed at the following doses:

Weight	5 to 9 kg	10 to 15 kg	16 to 23 kg	24 to 34 kg	35 to 45 kg	> 45 kg
Daily dose	150 mg	200 to 300 mg	300 to 400 mg	500 to 750 mg	750 mg	1 g

If active TB develops during LTBI treatment, DST including resistance to FQs is necessary due to the potential risk associated with use of FQs in monotherapy (development of resistance to FQs in patients with undiagnosed active TB).

In addition to LTBI treatment, monitor these patients for 2 years for the development of active TB.

## 16.7.2 Household contacts of multidrug-resistant tuberculosis cases not eligible for treatment

If the contact is not eligible for LTBI treatment, closely monitor for signs and symptoms of active TB every 3 months for the next 2 years.

If active TB develops, initiate TB treatment promptly with a regimen designed according to the DST. If DST is not feasible, a regimen can be designed according to the resistance profile of the source case.

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# 16.8 Follow-up for patients treated for latent tuberculosis infection

For the modality of administration of LTBI treatments, see [Chapter 13](#).

## 16.8.1 Baseline assessment of liver function

Before initiating LTBI treatment, look for clinical signs of hepatic disease and specific risks of hepatotoxicity.

For patients with hepatic disease, baseline liver function tests (LFTs), i.e. aspartate aminotransferase (AST), alanine aminotransferase (ALT) and bilirubin should be performed.

The benefit of LTBI treatment should be weighed against the potential risk of aggravation of existing hepatic disease. LTBI treatment is contra-indicated in patients with end-stage hepatic disease or LFTs > 5 times the upper limit of normal (ULN) and should be used with caution in patients with LFTs > 3 times ULN<sup>[1]</sup>.

Depending on available resources, baseline LFTs can be performed in groups at risk for hepatotoxicity (e.g. patients with HIV infection, women during pregnancy and post-partum period, chronic alcohol consumption, age > 35 years, concomitant use of hepatotoxic drugs, history of hepatic disease).

## 16.8.2 Follow-up

All patients should be evaluated monthly for signs and symptoms of active TB, adherence ([Appendix 22](#)), and adverse effects.

TST or IGRA should not be repeated.

In patients with pre-existing hepatic disease:

- Baseline LFTs are normal: monitor LFTs monthly.
- Baseline LFTs are elevated or LFTs increase during LTBI treatment: monitor LFTs once a week<sup>[2]</sup>.

Other patients should be tested if they develop symptoms of hepatotoxicity.

Any problems with adherence should be addressed with the patient.

If signs and symptoms of active TB develop, the patient should undergo full evaluation ([Chapter 3](#) and [Chapter 4](#)).

## 16.8.3 Management of adverse effects

### Hepatotoxicity

Clinical features resemble that of viral hepatitis. Early symptoms include malaise, fatigue, loss of appetite, muscle and joint pain. Nausea, vomiting and abdominal pain are common in severe disease. Jaundice, scleral icterus, dark (tea-coloured) urine and discoloured stool are signs of clinical worsening. Clinical hepatitis can be fatal, so action should be taken immediately.

- Patient with symptoms of hepatitis:  
Stop all TB drugs and perform LFTs:
  - AST or ALT or bilirubin  $\geq$  3 times ULN or severe symptoms: do not resume LTBI treatment.
  - AST, ALT, and bilirubin < 3 times ULN and mild symptoms (no jaundice): after discussion with the patient on benefits and risk, treatment may be resumed. Closely monitor the patient and perform LFTs once a week. Continue treatment as long as LFTs levels remain < 3 ULN and there are no signs of worsening hepatitis.
  - LFTs not available: do not resume LTBI treatment.
- Patient without symptoms of hepatitis, but elevated LFTs:
  - AST or ALT  $\geq$  5 times ULN or bilirubin  $\geq$  3 ULN: stop and do not resume LTBI treatment.
  - AST and ALT < 5 times ULN and bilirubin < 3 ULN: stop LTBI treatment. Perform LFTs once a week. If LFTs return to normal, after discussion with the patient on benefits and risk, treatment may be resumed. Closely monitor the patient and perform LFTs once a week.

**Note:** 10 to 20% of patients taking isoniazid alone may have a mild, transient, asymptomatic elevation of LFTs (AST and/or ALT). In most cases, this does not require treatment interruption.

### Hypersensitivity reaction

Possible hypersensitivity reactions have been reported in approximately 2% of patients on 3HR regimen and 4% of patients on 3HP regimens, typically after the first 3 to 4 doses<sup>[3]</sup>.

Symptoms may include flu-like syndrome (fever, chills and malaise, headache), persistent nausea and vomiting and/or watery diarrhoea requiring rehydration in severe cases, cutaneous reactions (rash, with vesicles in severe cases), and more rarely, angioedema, shortness of breath, acute bronchospasm, and hypotension.

In all cases, treatment should be stopped immediately. Symptoms usually resolve within 24 hours after TB drug withdrawal.

In case of mild reaction, consider resuming the treatment. In this case, the patient should be observed at least 4 hours after each dose is administered to detect first signs of hypersensitivity reaction.

In case of moderate to severe reactions, do not resume treatment and consider a regimen without a rifamycin (6H).

## Other adverse effects

See [Appendix 17](#).

## References

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# Chapter 17: Monitoring and evaluation

[17.1 Introduction](#)

[17.2 Definitions of treatment outcomes](#)

[17.3 Recording tools](#)

[17.4 Reporting](#)

[17.5 Programme assessment](#)

Update: January 2014

# 17.1 Introduction

Monitoring and evaluation rely on both quantitative and qualitative information in order to provide information on the following:

- Programme performance (e.g. number of patients started on anti-TB treatment, treatment results, number of patients tested for MDR-TB, etc.);
- Planning for human resources, patient support, diagnostic tests and drug orders, etc.;
- Evaluation of the functioning of the programme (quality of drugs, diagnostics, patient support, etc.).

Recording and reporting are based on a set of standard case and outcome definitions.

Case definitions are presented in [Chapter 7](#).

# 17.2 Definitions of treatment outcomes

For all forms of TB, outcome definitions have many similarities. These are:

- Outcome assignment is standardized, as to permit comparisons across clinicians, time and sites.
- Outcome assignment relies heavily, but not exclusively, on bacteriologic endpoints (smear or culture<sup>a</sup>).
- Outcomes are mutually exclusive and exhaustive.

For all forms of TB, definitions exist for:

- Interim outcomes (intended to have an indication on how the programme is functioning before final outcomes are available);
- Final outcomes (cure, completion, failure, treatment interruption, death or not evaluated).

## 17.2.1 Interim outcomes for drug-susceptible TB and MDR-TB

Given that TB treatment is long (6 to 18 months or more), interim outcomes provide early indicators of programme results. Table 17.1 provides a summary on interim outcomes.

**Table 17.1** - Interim outcomes

TB	Interim outcomes
<b>Drug-susceptible TB</b>	At 2-3 and 4-5 months: <ul style="list-style-type: none"><li>• Bacteriological status (smear negative/positive/no information)</li><li>• Final outcomes in patient who had already interrupted or died</li></ul>
<b>MDR-TB</b>	At 6 months: <ul style="list-style-type: none"><li>• Bacteriological status (negative/positive/no information) based on smear and culture</li><li>• Final outcomes in patient who had already interrupted or died</li></ul>

## 17.2.2 Final outcomes for drug-susceptible TB and DR-TB

Table 17.2 provides definitions for the final outcomes.

**Table 17.2** - Summary table of final outcome definitions<sup>[1][2]</sup>

Outcomes	TB	Definitions
Cured	DS TB	Patient initially bacteriologically confirmed (microscopy, culture or molecular test) who completed treatment AND shows no signs of continued active disease AND has at least 2 negative smears or cultures: one at 4-5 months and the other at the end of treatment AND does not meet the definition of failure.
	PDR-TB	Patient initially bacteriologically confirmed (culture or molecular test), who completed treatment AND has been consistently culture-negative with at least 3 results on sputum tested at least one month apart for the final 6 months of treatment AND does not meet the definition of failure.
	MDR-TB	Patient initially bacteriologically confirmed (culture or molecular test), who completed treatment AND with at least 3 negative cultures in the last 8 months of treatment AND does not meet the definition of failure. If there is a lone positive culture or smear reported during that time, and no concomitant clinical evidence of deterioration, a patient may still be considered cured, provided that this positive culture is followed by a minimum of 3 consecutive negative cultures taken at least 30 days apart.
Completed	All	Patient who completed treatment AND has no signs of continued active disease AND does not meet the bacteriological criteria for cure.
Failure	DS TB	Patient with signs of continued active disease or deterioration requiring a treatment change: <ul style="list-style-type: none"> <li>• Any patient with positive smear or culture at 4-5 months of treatment or thereafter.</li> <li>• Any patient with no significant clinical improvement, no significant gain of weight after 4-5 months of treatment and for whom the diagnosis of failure is established by a clinician.</li> </ul>
	DR-TB (a)(b)(c)	Treatment terminated or need for permanent treatment change of at least 2 classes of anti-TB drugs because of one or more of the following: <ul style="list-style-type: none"> <li>• Lack of monitoring cultures converting to negative by 6 months for MDR-TB (3 months for PDR-TB), and/or</li> <li>• Resistance amplification to rifampicin or isoniazid (PDR-TB) or to Group 2 or Group 3 drugs (MDR-TB), and/or</li> <li>• Bacteriological reversion (at least two positive smears or cultures at least 7 days apart after monitoring smears or cultures have become negative), or</li> <li>• A clinical decision has been made to terminate treatment early due to poor response or adverse events.</li> </ul> These latter failures can be indicated separately in order to do sub-analysis.
Interrupted	All	Patient who interrupted treatment for 2 months or more.
Death	All	Patient who died on TB treatment or while awaiting TB treatment, irrespective of the cause of death. The cause of death should be recorded.
Treatment adapted <sup>(d)</sup> (e)	DS TB	Patient initially treated with a standard regimen and for whom the treatment is secondarily adapted according to the results of DST (and not because of a treatment failure).
Not evaluated	All	Patient whose treatment outcome is unknown (including patients “transferred out” to another treatment centre, for whom the outcome is unknown).

- (a) A patient registered as “failure” can be re-registered as DR-TB “previously treated 2<sup>nd</sup> line” and started again on a new regimen if possible.
- (b) This category does not include the changing of one drug due to an adverse effect or a temporary cessation of drugs in order to manage severe adverse event.
- (c) If a patient was defined as a “failure”, and no appropriate treatment was possible, but the treatment was continued and the patient subsequently interrupted the treatment or died, the outcome is “failure” (the first outcome is recorded).
- (d) For programmes that report using the WHO’s mutually exclusive six outcomes, the “treatment adapted” outcome can be added to failures for reporting purposes, but should also be kept track of separately for good programmatic monitoring and evaluation.
- (e) Not applicable for DR-TB.

If treatment is continuing at the time of a cohort analysis, an outcome of “*still on treatment*” may be provisionally assigned

## Footnotes

- (a) Molecular techniques are not used to monitor treatment response or to declare failure. These tests may identify dead bacilli for a long time and can even be positive after a patient is truly cured.

## References

1. Laserson KF, Thorpe LE, Leimane V, Weyer K, Mitnick CD, Riekstina V, et al. *Speaking the same language: treatment outcome definitions for multidrug-resistant tuberculosis*. *Int. J. Tuberc. Lung Dis.* 2005;9(6):640–5.
2. World Health Organization. *Definitions and reporting framework for tuberculosis - 2013 revision* (WHO/HTM/TB/2013.2). WHO Geneva. 2013. [http://apps.who.int/iris/bitstream/10665/79199/1/9789241505345\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/79199/1/9789241505345_eng.pdf)

## 17.3 Recording tools

Forms used in recording and reporting can be found in the appendices. They are intended to be examples that programmes or country can use to produce their own forms.

### 17.3.1 Drug-susceptible TB treatment card and drug-susceptible TB register

Drug-susceptible TB treatment card and drug-susceptible TB register are used for all new patients or previously treated patients treated by standard first-line regimens (with or without confirmation of the drug susceptibility by a DST).

### 17.3.2 DR-TB treatment card and DR-TB register

DR-TB treatment card tracks, in particular, each dose of each drug taken during the full course of treatment. The number of actually observed doses and the number of expected observed doses are reported each month. In addition to the treatment card, it is recommended to keep a medical chart with a full admission note at the time of enrolment and a progress note at each medical encounter.

DR-TB register includes data on case definition, bacteriological exams (indicate date of specimen collection and not the date of result), type of treatment and treatment outcome. It is a separate register from the drug-susceptible TB register.

Each DR-TB patient detected should be registered, including patients who refuse treatment.

Transfer of patients from the drug-susceptible TB register to the DR-TB register is done usually while on treatment when DST results are available. Patient's outcome is reported as 'treatment adapted' in the comment row of the drug-susceptible TB register.

### 17.3.3 Laboratory request form(s) and register(s)

- Request form for smear microscopy and Xpert assays ([Appendix 34](#));
- Request form for culture, pDST, LPA, genome sequencing ([Appendix 35](#));
- Sputum smear microscopy register;
- Xpert MTB/RIF register.

### 17.3.4 Drug-O-Gram

The Drug-O-Gram is a summary of the patient's treatment history. It includes consecutive DST and treatment changes presented in a chronological order and gives a short summary of the patient status ([Appendix 36](#)).



# 17.4 Reporting

The key evaluation tool for all forms of TB is the periodic report. It must be presented in a standardized manner in two parts: case enrolment and treatment outcomes. The data presented in the report comes from the TB register. It is generally completed by quarter for drug-susceptible TB and by semester for DR-TB.

Evaluation of interim and final treatment outcomes is a fundamental stage in the evaluation. This evaluation is done through a cohort analysis. A "cohort" is a group of individuals presenting certain common characteristics and undergoing the same events. In respect to the evaluation of TB patients, a cohort is represented by patients all put under treatment within a given period of time (usually a quarter for drug-susceptible TB and a semester for DR-TB). At the end of treatment, a final outcome is assigned to each patient ([Table 17.1](#)).

## Notes:

- The number of patients in each group should, in principle, be identical to those registered for the same interval in the *case enrolment* part of the corresponding periodic report. If it is different, an explanation should be given (e.g., patients "interrupting before treatment" can be excluded from the outcome analysis).
- The outcomes of patients "transferred in" should not be included in the outcomes of the facility to which they were transferred. Their outcome results should be recorded in the facility that initially enrolled the patient in TB treatment.

## 17.4.1 Case detection and enrolment report for TB

The elements necessary for defining a TB case (treatment history, bacteriological status, anatomical site of the disease, and HIV status) are defined in [Chapter 7](#).

### Main indicators

- *Proportion of confirmed pulmonary TB (PTB)*  
=  $\text{Number of PTB cases confirmed enrolled} / \text{Total number of TB cases enrolled for the period}$   
With the introduction of automated molecular tests and rapid cultures, it is expected that the proportion of confirmed PTB cases will increase as compared to programmes where only smear microscopy is available.
- *Proportion of smear-negative PTB*  
=  $\text{Number of smear-negative PTB cases enrolled} / \text{Total number of TB cases enrolled for the period}$   
This indicator essentially depends on the following: the quality of microscopy, the number of children under treatment (children are rarely smear-positive), the prevalence of HIV infection within the population (these patients present more smear-negative PTB), and the other diagnostics used (culture, Xpert MTB/RIF, etc).  
The proportion of smear-negative PTB is about 20% when HIV prevalence is low. It is 40 to 60% when HIV prevalence is high. Proportions that differ significantly from these should make one consider the possibility of under- or over-diagnosis of smear-negative forms.
- *Proportion of smear-positive PTB*  
=  $\text{Number of smear-positive PTB cases enrolled} / \text{Total number of TB cases enrolled for the period}$   
In practice, the proportion of smear-positive PTB should correspond to roughly half of all patients. This proportion is lower, however, in areas where HIV prevalence is high. Proportion of smear-positive PTB is around 60% where HIV prevalence is low, and it is 30 to 40% where HIV prevalence is high. Proportions that differ significantly from these should make one consider the possibility of under- or over-diagnosis of smear-negative pulmonary TB and extra-pulmonary B forms.
- *Proportion of new cases*  
=  $\text{Number of new TB cases enrolled} / \text{Total number of cases enrolled for the period}$   
This indicator indirectly reflects the relapse and failure rates and possible parallel treatments outside the programme.
- *Proportion of children*  
=  $\text{Number of TB patients less than 15 years enrolled} / \text{Total number of TB cases enrolled for the period}$   
Children should represent approximately 10 to 15% of the total number of patients. Proportions that differ significantly from these should make one consider the possibility of under- or over-diagnosis of TB in children.
- *Proportion of detected cases enrolled under treatment*  
=  $\text{Number of cases enrolled under treatment} / \text{Total number of cases detected for the period}$   
Patients enrolled are counted from the TB register. Patients detected are counted from the laboratory register and include patients who "interrupted before treatment".
- *Case detection rate*  
=  $\text{Number of new smear-positive PTB cases detected} / \text{Expected number of smear-positive PTB cases for the period}$   
A rough estimate of the expected number of new smear-positive cases can be obtained using the estimated TB incidence given by the WHO in the country profile, which allows an estimate of detection efficacy.

**Note:** even the best programmes often do not detect more than 60 to 70% of expected new smear-positive cases within a population. In addition, patients might come from outside the target area.

## 17.4.2 Case detection and enrolment report for DR-TB

Early detection of resistance is intended to ensure that an appropriate treatment is initiated from the start. DST is usually performed for patients at risk of DR-TB. Target groups vary according to local situation, but should at a minimum always include patients who have been previously treated and contacts of confirmed MDR-TB patients.

The indicators for detection aim at measuring the access of TB patients to DST. The frequency of MDR-TB among individuals in different risk groups is also evaluated.

All patients in whom DR-TB is highly suspected or detected should be started on appropriate treatment in the shortest time possible.

A comparison of enrolled patients under treatment to detected DR-TB cases gives an indication of access to care, though some patients started on treatment may have been detected prior to the period of assessment.

The period of assessment is six calendar months. This is usually counted from January to the end of June and July to the end of December. Indicators are measured three months after the end of the six-month period. All data can be extracted from the DR-TB register, the laboratory register for culture and DST and the Xpert register.

Each indicator should be calculated for all patients and for each risk group of patients, including: all cases, previously treated cases, failures, household contacts and other local risk groups according to the strategy.

### Case detection indicators

- *Proportion of TB patients detected with DST result for isoniazid and rifampicin (for each risk group during the period)*  
= Number of TB cases detected with DST result for both isoniazid and rifampicin/Total number of TB cases detected
- *Proportion of TB patients detected with Xpert MTB/RIF result (for each risk group during the period)*  
= Number of TB cases detected with Xpert MTB/RIF result/Total number of TB cases detected
- *Proportion of confirmed MDR-TB cases detected among TB patients tested for isoniazid and rifampicin DST (for each risk group during the period)*  
= Number of TB cases with confirmed resistance to isoniazid and rifampicin/Total number of TB cases tested for these 2 drugs
- *Proportion of Xpert RIF resistant cases detected among patients tested by Xpert MTB/RIF (for each risk group during the period)*  
= Number of Xpert RIF resistant cases/Total number of TB cases with Xpert MTB/RIF result

### Enrolment indicators

- *Proportion of confirmed MDR-TB cases enrolled on MDR-TB treatment*  
= Number of confirmed MDR-TB cases registered and started on MDR-TB treatment/Total number of confirmed MDR-TB cases detected  
This can also be calculated for rifampicin resistant TB cases.
- *Proportion of confirmed PDR-TB cases enrolled on PDR-TB treatment*  
= Number of confirmed PDR-TB cases registered and started on PDR-TB treatment/Total number of confirmed PDR-TB cases detected  
This calculation does not include rifampicin resistance and unknown isoniazid resistance.

## 17.4.3 Interim treatment outcomes for drug-susceptible TB and DR-TB

Interim analysis should be completed approximately 3 months after all patients who were registered during a particular interval completed the intensive phase of treatment (three months should allow culture results for all those patients).

### Interim treatment outcomes for drug-susceptible TB

Interim results at Month 2 or 3 should be evaluated for all patients treated as new or previously treated patients by standard first-line regimens (with or without confirmation of the drug susceptibility by a DST). These results may be disaggregated by treatment history (new, previously treated, and by type of previous treatment).

At the beginning of a programme, when it is not yet possible to do cohort analysis, the conversion rate at Month 2-3 is a proxy indicator of the effectiveness of treatment, and it allows early detection of potential problems. The smear conversion rate of new smear-positive patients is the proportion of new smear-positive patients who are smear-negative at Month 2. The smear conversion rate of previously treated smear-positive patients is the proportion of previously treated smear-positive patients who are smear-negative at Month 3.

### Interim treatment outcomes for DR-TB

The period of assessment is six calendar months, usually counted from January to end June, July to end December. All patients registered and starting treatment during the period of assessment are included in the calculation. The interim report form should be completed 9 months after the closing day of the cohort. This allows culture information at 6 months of treatment to be included for all patients in the cohort. For instance, interim results of TB patients who started treatment during the first semester of a year (1 January to 30 June), should be calculated at the beginning of April of the following year.

Culture conversion (for confirmed DR-TB cases) and death by six months are used as proxies for final outcomes. Information on treatment interruption by six months is helpful. It is also useful to know how many patients started on second-line drugs for MDR-TB turned out not to be MDR.

At six months:

- *Proportion of death*  
= Number of confirmed MDR-TB cases registered and started on MDR-TB treatment who died of any cause by the end of Month 6/Total number of confirmed MDR-TB cases started on treatment for MDR-TB during the period

- *Proportion of treatment interrupted*  
= Number of confirmed MDR-TB cases started on MDR-TB treatment who interrupted by the end of Month 6/Total number of confirmed MDR-TB cases started on treatment for MDR-TB during the period
- *Proportion with negative culture*  
= Number of bacteriologically confirmed pulmonary MDR-TB cases registered and started on MDR-TB treatment with negative culture at Month 6/Total number of bacteriologically confirmed pulmonary MDR-TB cases registered and started on treatment for MDR-TB during the period
- *Proportion with positive culture*  
= Number of bacteriologically confirmed pulmonary MDR-TB cases registered and started on MDR-TB treatment with positive culture at Month 6/Total number of bacteriologically confirmed pulmonary MDR-TB cases registered and started on treatment for MDR-TB during the period
- *Proportion found not to have MDR-TB*  
= Number of patients started on MDR-TB treatment during the period and later found not to be MDR/Total number of patients started on MDR-TB treatment during the period

## 17.4.4 Final treatment outcomes for TB

The final outcome is the most important direct measurement of the effectiveness of a TB programme in terms of patient care. All patients entered on the TB register should be assigned one of six mutually exclusive outcomes at the end of their therapy. All patients should be assigned the first outcome they experience for the treatment being evaluated<sup>[1]</sup>.

Final treatment outcome cohort analysis could be carried out when all patients admitted in a given period of time had a chance to complete their treatment. In practice:

- For drug-susceptible TB (and all patients treated by standard first-line regimens) cohort results are analysed quarterly, one year after inclusion of the last patient of the cohort (e.g. cohort of patients admitted during the first quarter 2014 will be evaluated at the end of the first quarter 2015).
- For DR-TB, evaluation occurs 27 months after inclusion of the last patient in the cohort in order to have the results of cultures performed at 24 months. The period of assessment is six calendar months, usually counted from January to the end of June and July to the end of December. All patients starting treatment during this period are included in the calculation. Indicators are measured 24 months after the end of the semester of assessment. All data can be extracted from the DR-TB register.

Although the timing of the analysis is different for drug-susceptible TB and DR-TB, the indicators are the same.

Indicators should be calculated for patients treated by standard first-line regimens (with or without confirmation of drug-susceptible TB by a DST), and for patients with PDR-TB and MDR-TB.

The most important indicators are:

- *Proportion of cured*  
= Number of confirmed TB cases declared "cured"/Total number of confirmed TB cases put under treatment during the period  
This indicator is calculated for all confirmed drug-susceptible TB cases and DR-TB cases. It is the best indicator of the success of a programme for confirmed TB patients. Though the effectiveness of the treatment for drug-susceptible TB is theoretically above 90%, the proportion of cure is rarely above 70%. For MDR-TB this indicator rarely exceeds 50%.
- *Proportion of treatment completed*  
= Number of patients registered as "treatment completed"/Total number of patients put under treatment for the period  
A high proportion of patients completing treatment is a positive sign for not confirmed PTB and EPTB. For confirmed TB, it indicates insufficient bacteriological verification at the end of treatment, thus, suggesting that a step should therefore be reinforced.
- *Proportion with successful outcome*  
= Number of patients registered as "cured" or "treatment completed"/Total number of patients put under treatment during the period  
This is the best indicator to measure the efficacy of a programme for all forms of TB (confirmed and not confirmed, PTB and EPTB). This indicator rarely exceeds 80% for drug-susceptible TB and 60% for MDR-TB.
- *Proportion of treatment interrupted*  
= Number of patients registered as "treatment interrupted"/Total number of patients put under treatment during the period  
Patients who interrupted treatment are at risk of not being cured or of relapsing. Treatment interruption indicates a failure of the programme in supporting the patient to be able to successfully complete treatment.
- *Proportion of death*  
= Number of patients registered as "death"/Total number of patients put under treatment during the period  
This ratio usually does not exceed 5% for drug-susceptible TB. Over-mortality may be related to the poor functioning of a programme. It may also be due to a high prevalence of HIV infection among cases or late referrals.
- *Proportion of failure*  
= Number of patients registered as "failures"/Total number of patients put under treatment during the period  
A high failure rate in new cases can be related to poor treatment adherence, high rate of primary resistance or poor quality of anti-TB drugs. The failure rate should not be over 2% in new cases under treatment.
- *Proportion of patients for whom HIV status is known*  
= Number of patients for whom HIV status is known by the end of treatment/Total number of patients put under treatment during the period  
This is one of the indicators that help evaluate the integration of TB and HIV services.
- *TB-HIV co-infection rate*  
= Number of HIV-infected TB patients/Total number of TB patients put under treatment during the period and for whom HIV status is known at the end of

*treatment*

In high HIV-prevalence regions, co-infection rate may exceed 80%. This information is important in assessing other indicators, in particular the proportion of death.

## References

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## 17.5 Programme assessment

To be complete, evaluation should look at how well the programme functions, particularly with respect to three aspects: organization of care, established procedures and human resources. A set of quality criteria is evaluated for each of these aspects. The criteria may be either qualitative (description) or quantitative (indicators). The following tables can be used as a rough guide.

### 17.5.1 Organization

Criteria	Indicators	Goals
<b>Access to care</b>	<ul style="list-style-type: none"> <li>• Accessibility of treatment facilities, decentralization, etc.</li> <li>• Home-based treatment available when appropriate.</li> </ul>	Easy access to care during the intensive/continuation phases
<b>Patient comfort</b>	<ul style="list-style-type: none"> <li>• Patient welcome</li> <li>• Condition of the facility, heating (or cooling), overall organization and cleanliness.</li> <li>• Food during hospitalization and/or for outpatients (supplemental rations, quantities, organization in charge).</li> <li>• Bed occupancy rate of the TB ward.</li> </ul>	<ul style="list-style-type: none"> <li>• According to needs</li> <li>• Bed occupancy rate <math>\leq</math> 100%</li> </ul>
<b>Information and therapeutic education</b>	Patient interviews conducted.	Patient understanding of treatment
<b>Hospital hygiene</b>	<ul style="list-style-type: none"> <li>• Equipment (respirators, masks, gloves, gowns, autoclaves, cleaning supplies, etc.)</li> <li>• Waste management (sorting, incinerator, etc.)</li> </ul>	All necessary equipment is available and used.
<b>Constant supply of lab materials</b>	<ul style="list-style-type: none"> <li>• Supplied by (government, agency or facility, other)</li> <li>• Buffer stock</li> <li>• Number and duration of shortages</li> </ul>	<ul style="list-style-type: none"> <li>• 3-month buffer stock</li> <li>• No shortages</li> </ul>
<b>Constant supply of quality-assured anti-TB drugs</b>	<ul style="list-style-type: none"> <li>• Stock card maintenance</li> <li>• Order frequency, delivery time, buffer stock</li> <li>• Shortage(s)</li> <li>• Drug sources</li> <li>• Institution in charge of supply</li> <li>• Use of FDCs first-line drugs</li> <li>• Storage conditions</li> <li>• Organization of supply for peripheral facilities</li> </ul>	<ul style="list-style-type: none"> <li>• Stock cards up-to-dated</li> <li>• One person in charge of the pharmacy</li> <li>• All adequate</li> <li>• No shortages</li> <li>• WHO-prequalified sources (or equivalent)</li> <li>• Use of FDCs</li> <li>• Appropriate storage conditions</li> <li>• Regular supply</li> </ul>
<b>Case detection</b>	<ul style="list-style-type: none"> <li>• Type of case detection (active or passive)</li> <li>• Contacts screening</li> <li>• Detection rate of new smear-positive cases</li> <li>• Percentage of smear-positive patients out of the total number of patients who had a sputum smear.</li> <li>• Detection rate of MDR-TB</li> </ul>	<p>Know the type, in order to interpret the quantitative results of case detection</p> <ul style="list-style-type: none"> <li>• 100%</li> <li>• Depends on the context</li> <li>• &lt; 20%</li> <li>• Depends on the context</li> </ul>
<b>Diagnosis of smear-negative PTB and EP forms</b>	<ul style="list-style-type: none"> <li>• Automated molecular test</li> <li>• Culture or molecular techniques</li> <li>• X-rays</li> <li>• Others (e.g. ADA, Pandy, Rivalta, FNAC)</li> <li>• Algorithms used</li> </ul>	<ul style="list-style-type: none"> <li>• Yes</li> <li>• Yes</li> <li>• Yes</li> <li>• Yes</li> <li>• Yes</li> </ul>
<b>DST</b>	DST possible (methods, quality control)	Detection of DR-TB
<b>Treatment support</b>	Number of patients receiving treatment support/month	100% of those eligible for support
<b>Identification of non-adherent patients</b>	<ul style="list-style-type: none"> <li>• System for identifying and looking for non-adherent patients</li> <li>• Percentage of patients who resumed treatment among those missing for less than 2 months who had to be looked for</li> </ul>	<ul style="list-style-type: none"> <li>• Yes</li> <li>• &gt; 90%</li> </ul>
<b>Integrated TB/HIV care</b>	<ul style="list-style-type: none"> <li>• Access to voluntary counselling and testing (VCT)</li> <li>• Access to ART</li> <li>• Access to cotrimoxazole prophylaxis</li> <li>• HIV treatment integrated in the TB service (or TB treatment in the HIV service)</li> </ul>	<ul style="list-style-type: none"> <li>• Yes</li> <li>• Yes</li> <li>• Yes</li> <li>• Yes</li> </ul>

## 17.5.2 Procedures

Criteria	Indicators	Goals
<b>Registers/records</b>	Description of the documents <ul style="list-style-type: none"> <li>Consistency between TB registers and treatment cards</li> <li>Consistency between TB register and lab registers</li> </ul>	Records reliable <ul style="list-style-type: none"> <li>100%</li> <li>100%</li> </ul>
<b>Standard case definitions</b>	Percentage of patients with exact case definition out of a randomized sample of patients	100%
<b>Adequate standard treatment regimens and follow-up</b>	<ul style="list-style-type: none"> <li>Percentage of new cases correctly treated (combinations, dosage, duration) out of a randomized sample of patients</li> <li>Percentage of patients who did not have bacteriological follow-up according to schedule out of a randomized sample of patients</li> <li>Percentage of MDR-TB patients who did not have biochemistry tests according to schedule out of a randomized sample of patients</li> </ul>	<ul style="list-style-type: none"> <li>&gt; 95%</li> <li>&lt; 10%</li> <li>&lt; 10%</li> </ul>
<b>HIV testing</b>	Percentage of new cases tested for HIV	100%
<b>ART</b>	Percentage of HIV-positive TB cases started on ART ART started within: < 2 weeks; 2 weeks-< 2 months; ≥ 2 months	100%
<b>Criteria for cure</b>	Percentage of confirmed cases declared cured who actually met the definition of cure out of a randomized sample of patients	> 90%
<b>Regular monitoring of drug-susceptible TB and DR-TB</b>	<ul style="list-style-type: none"> <li>Quarterly report and cohort analysis for drug-susceptible TB</li> <li>Bi-annual report and cohort analysis for DR-TB</li> </ul>	<ul style="list-style-type: none"> <li>Quantitative data on inclusions and results collected</li> <li>Rapid detection of potential problems</li> </ul>
<b>Adherence monitoring</b>	<ul style="list-style-type: none"> <li>Percentage of patients coming in for their appointment out of number of patients expected</li> <li>Percentage of doses given under DOT for DR-TB treatment in a randomized sample of patients</li> </ul>	<ul style="list-style-type: none"> <li>&gt; 90% in both the intensive and continuation phases</li> <li>100%</li> </ul>
<b>Prevention of <i>M. tuberculosis</i> airborne transmission in TB facilities</b>	<ul style="list-style-type: none"> <li>Isolation</li> <li>Building ventilation, lights, UV lamps (hospital wards, outpatient clinics, laboratory); respirators for staff and visitors in contact with contagious patients; masks for contagious patients (if they move about)</li> <li>Written prevention plan?</li> <li>Person in charge identified?</li> </ul>	<ul style="list-style-type: none"> <li>Isolation of smear positive patients</li> <li>Isolation of DR smear positive patients</li> <li>Appropriate use of means</li> <li>Yes</li> <li>Yes</li> </ul>
<b>Standard precautions</b>	Description	Standard precautions followed
<b>Laboratory quality control</b>	<ul style="list-style-type: none"> <li>Regular evaluation of laboratory functioning</li> <li>Quarterly EQA of smear microscopy</li> </ul>	<ul style="list-style-type: none"> <li>Ensure the quality of laboratory analyses for bacteriological diagnosis</li> </ul>

	<ul style="list-style-type: none"> <li>Annual EQA of DST</li> </ul>	<ul style="list-style-type: none"> <li>Results according to standards</li> <li>Results according to standards</li> </ul>
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### 17.5.3 Human resources

Criteria	Indicators	Goals
<b>Staff</b>	<ul style="list-style-type: none"> <li>Job descriptions (doctors, nurses, lab technicians, cleaning staff, etc.)</li> <li>Medical staff-to-patient ratio</li> </ul>	On average: <ul style="list-style-type: none"> <li>One nurse for 10-15 patients</li> <li>One doctor for 40-50 patients</li> </ul>
<b>Training</b>	Refer to training programme evaluation criteria	Competent staff
<b>Other contributors</b>	Description: other NGOs, local associations, etc.	

A grid for evaluating TB clinic operations can be found in [Appendix 39](#).



# Appendices

[Appendix 1. Xpert assays](#)

[Appendix 2. Interpretation of Xpert assay results](#)

[Appendix 3. Collection, storage, and shipment of respiratory specimens](#)

[Appendix 4. Sputum smear microscopy](#)

[Appendix 5. Time required for diagnostic test results](#)

[Appendix 6. Ventilated workstation and biosafety cabinet](#)

[Appendix 7. Lymph node fine needle aspiration](#)

[Appendix 8. Protein estimation](#)

[Appendix 9. Tuberculin skin test](#)

[Appendix 10. Drug information sheets and patient instructions for TB treatment](#)

[Tuberculosis drug information sheets](#)

[Amikacin \(Am\)](#)

[Bedaquiline \(Bdq\)](#)

[Amoxicillin/clavulanic acid ratio 4:1 \(Amx/Clv\)](#)

[Clofazimine \(Cfz\)](#)

[Cycloserine \(Cs\) or terizidone \(Trd\)](#)

[Delamanid \(Dlm\)](#)

[Ethambutol \(E\)](#)

[Ethionamide \(Eto\) or prothionamide \(Pto\)](#)

[Imipenem/cilastatin \(Ipm/Clh\)](#)

[Isoniazid - Standard dose \(H\)](#)

[Isoniazid - High dose \(Hh\)](#)

[Levofloxacin \(Lfx\)](#)

[Linezolid \(Lzd\)](#)

[Meropenem \(Mpm\)](#)

[Moxifloxacin \(Mfx\)](#)

[Para-aminosalicylate sodium \(PAS\)](#)

[Pretomanid \(Pa\)](#)

[Pyrazinamide \(Z\)](#)

[Rifabutin \(Rfb\)](#)

[Rifampicin \(R\)](#)

[Rifapentine \(P\)](#)

[Streptomycin \(S\)](#)

[Patient instructions](#)

[Patients on drug-susceptible TB treatment](#)

[Patients on drug-resistant TB treatment](#)

[Appendix 11. TB drugs in pregnant or breastfeeding women](#)

[Appendix 12. Dose adjustments in renal insufficiency](#)

[Appendix 13. Daily dose of TB drugs using fixed-dose combinations](#)

[Appendix 14. Monitoring of patients on drug-susceptible TB treatment](#)

[Appendix 15. Monitoring of patients on drug-resistant TB treatment](#)

[Appendix 16. Additional investigations in drug-resistant TB](#)

[Appendix 17. Management of adverse effects](#)

[Gastrointestinal disorders](#)

[Abdominal pain](#)

[Diarrhoea](#)

[Epigastric pain](#)

[Hepatotoxicity](#)

[Metallic taste](#)

[Nausea and vomiting](#)

[Neurotoxicity](#)

[Depression](#)

[Headache](#)

[Optic neuritis](#)

[Ototoxicity](#)

[Peripheral neuropathy](#)

[Psychosis](#)

[Seizures](#)

[Endocrine disorders](#)

[Gynecomastia](#)

[Hypothyroidism](#)

[Dermatological disorders](#)

[Alopecia](#)

[Fungal infection](#)

[Photosensitivity](#)

[Skin reactions](#)

[Musculoskeletal disorders](#)

[Arthralgias](#)

[Tendinitis/tendon rupture](#)

[Miscellaneous](#)

[Electrolyte disorders](#)

[Haematologic disorders](#)

[Lactic acidosis](#)

[Nephrotoxicity](#)

[QT prolongation](#)

[Appendix 18. Compassionate use of TB drugs](#)

[Appendix 19. Drug interactions and overlapping toxicities](#)

[Appendix 20. Treatment supporters](#)

[Appendix 21. Therapeutic patient education](#)

[Appendix 22. Assessment of adherence to TB treatment](#)

[Appendix 23. Basic tool for assessing risk of TB transmission](#)

[Appendix 24. Recommendations for air change per hour](#)

[Appendix 25. Overview of ventilation techniques](#)

[Appendix 26. Germicidal ultraviolet lamps](#)

[Appendix 27. Respirators](#)

[Appendix 28. Surgical masks](#)

[Appendix 29. BCG vaccine](#)

[Appendix 34. Request form for smear microscopy and Xpert assays](#)

[Appendix 35. Request form for culture, pDST, LPA, genome sequencing](#)

[Appendix 36. Drug-o-gram](#)

[Appendix 39. TB facility assessment sheet](#)

# Appendix 1. Xpert assays

Update: October 2022

## 1.1 Specimen processing

Staff members present during specimen preparation should wear a respirator (FFP2 or N95) to prevent the inhalation of bacilli. A biosafety cabinet ([Appendix 6](#)) should be used to protect staff from aerosols when the specimen is to be centrifuged or cut/ground.

### 1.1.1 Sputum specimens

See Xpert MTB/RIF package insert:

<https://www.cephheid.com/Package%20Insert%20Files/Xpert-MTB-RIF-ENGLISH-Package-Insert-301-1404-Rev-G.pdf>

See Xpert MTB/XDR package insert:

<https://www.cephheid.com/Package%20Insert%20Files/Xpert%20MTB-XDR%20ENGLISH%20Package%20Insert%20302-3514%20Rev%20C.pdf>

### 1.1.2 Lymph node and other tissue specimens

**Xpert assay performed on a biopsy** (adapted from WHO)<sup>[1]</sup>

- Cut the tissue specimen in small pieces in a sterile mortar (or grinder).
- Add 2 ml of sterile phosphate buffer saline (PBS).
- Grind solution of tissue and PBS to obtain a homogeneous mixture.
- Transfer 0.7 ml of mixture into a centrifuge tube using a transfer pipette. Avoid transferring clumps that are not well homogenized.
- Add 1.4 ml of Xpert Sample Reagent (XSR) using a transfer pipette.
- Shake vigorously 10 to 20 times or vortex for at least 10 seconds.
- Keep at room temperature for 10 minutes.
- Shake vigorously 10 to 20 times or vortex for at least 10 seconds.
- Keep at room temperature for 5 minutes.
- Transfer 2 ml of the mixture to the Xpert cartridge using a transfer pipette.
- Load the cartridge into the Xpert instrument as per the manufacturer's instructions.

**Xpert assay performed on a lymph node specimen obtained by fine needle aspiration (FNA)**

- Flush the needle and syringe into a sterile container containing 1 ml of sterile 0.9% sodium chloride or sterile PBS.
- Transfer 0.7 ml of mixture into a centrifuge tube using a transfer pipette.
- Add 1.4 ml of XSR using a transfer pipette.

For the next steps, continue as above.

For lymph node fine needle aspiration technique, see [Appendix 7](#).

### 1.1.3 Cerebrospinal fluid specimens

Adapted from WHO<sup>[1]</sup>

The processing method for cerebrospinal fluid (CSF) depends on the volume available for testing.

Volume of CSF	Procedure
0.1 to 1 ml	<ul style="list-style-type: none"><li>• Add XSR to the CSF to obtain a final volume of 2 ml.</li><li>• Transfer 2 ml of the mixture into the Xpert cartridge.</li><li>• Load the cartridge into the Xpert instrument as per the manufacturer's instructions.</li></ul>
1 to 5 ml	<ul style="list-style-type: none"><li>• Add an equal volume of XSR to the CSF.</li><li>• Add 2 ml of the mixture directly into the Xpert cartridge.</li><li>• Load the cartridge into the Xpert instrument as per the manufacturer's instructions.</li></ul>
> 5 ml	<ul style="list-style-type: none"><li>• Centrifuge the CSF at 3,000g for 15 minutes.</li><li>• Pour the supernatant and add XSR to the sediment to obtain a final volume of 2 ml.</li><li>• Transfer 2 ml of the mixture into the Xpert cartridge.</li><li>• Load the cartridge into the Xpert instrument as per the manufacturer's instructions.</li></ul>

**Note:** a volume of CSF less than 0.1 ml is insufficient for testing.

### 1.1.4 Stool specimens<sup>[2]</sup>

Stool specimens can be used within 3 hours if kept at room temperature.

- Add 0.8 to 1 g of stool into the 8 ml XSR bottle.
- Shake vigorously for 30 seconds.
- Keep at room temperature for 10 minutes.
- Shake vigorously for 30 seconds.
- Sediment at room temperature for 10 minutes.
- Without disturbing the sediment, transfer 2 ml of the supernatant into the Xpert cartridge.
- Load the cartridge into the Xpert instrument as per the manufacturer's instructions.

### 1.1.5 Urine specimens<sup>[3]</sup>

Urine specimens can be used within 3 hours if kept at room temperature.

- Centrifuge 4 ml of urine at 3,000g for 5 minutes.
- Pour the supernatant and add 2 ml of XSR to the sediment.
- Shake vigorously.
- Transfer 2 ml of the mixture into the Xpert cartridge.
- Load the cartridge into the Xpert instrument as per the manufacturer's instructions.

## 1.2 Diagnostic accuracy of Xpert in specimens other than sputum

Specimens	Performances of Xpert MTB/RIF compared to culture <sup>[4]</sup>
Lymph node biopsy or aspirate	Biopsy: sensitivity: 82%; specificity: 79% Aspirate: sensitivity: 89%; specificity: 86%
CSF	Sensitivity: 70%; specificity: 97%
Pleural fluid	Sensitivity: 50%; specificity: 99%
Pericardial fluid	Sensitivity: 67.6%; specificity: 99.4%
Nasopharyngeal aspirate (children with presumed PTB)	Sensitivity: 46%; specificity: 100%
Gastric aspirate (children with presumed PTB)	Sensitivity: 73%; specificity: 98%
Stool (children with presumed PTB)	Compared to culture of respiratory specimens: <ul style="list-style-type: none"> <li>• No HIV infection: sensitivity: 61%; specificity: 98%</li> <li>• HIV infection: sensitivity: 70%; specificity: 98%</li> </ul>
Urine (presumed genito urinary TB)	Sensitivity: 85%; specificity: 97%
Urine (HIV-infected patients with presumed disseminated TB)	Sensitivity: 40%; specificity: 98% <sup>[5]</sup>
Synovial fluid	Sensitivity: 97%; specificity: 94%
Peritoneal fluid	Sensitivity: 59%; specificity: 97%
Blood (HIV-infected patients with presumed disseminated TB)	Child: sensitivity: 7%; specificity: 99% <sup>[6]</sup> Adult: sensitivity: 56%; specificity: 94%

**Note:** the performances of Xpert MTB/XDR in non-sputum specimens are considered similar to those of Xpert MTB/RIF as the tests are based on similar technologies<sup>[4]</sup>.

## 1.3 Logistic requirements

All Xpert assays are performed with the same instrument.

The 10-colour module can read all Xpert cartridges.

The 6-colour module can read Xpert MTB/RIF and Xpert MTB/RIF Ultra cartridges.

### 1.3.1 Power supply

The instrument requires a constant and stable power supply.

If power cuts are short (less than 10 minutes), use a 1500VA "on line" UPS.

If power cuts are long, the system must be able to sustain a full cycle (approx. 45 minutes). Use a battery charger, a stationary battery, and a voltage stabilizer.

### 1.3.2 Storage and operating temperatures

Storage of cartridges and reagents: between 2 and 28 °C for 12 months from date of manufacture.

Operating temperature for the Xpert instrument: between 15 and 30 °C. According to climate conditions, air conditioning may be required.

### 1.3.3 Calibration

The Xpert modules require annual calibration performed by an authorized service provider or carried out by swapping out the modules. A detailed contract with the supplier should guarantee regular maintenance, calibration, repair, and replacement as and when needed.

### 1.3.4 Required space

The dimensions of the Xpert IV instrument (4 modules enabling the processing of 4 specimens at the same time) are:

Width: 29.8 cm; height 35.6 cm; depth 31.1 cm; weight: 12 kg.

The instrument is designed for indoor use only. Provide at least 5 cm of clearance on each side to ensure adequate ventilation. Do not place the instrument close to the vents of other instruments or air-handling units.

The dimensions of the kits containing cartridges and reagents are:

Xpert MTB/RIF kit 50 tests: 31 cm x 28 cm x 20 cm

Xpert MTB/XDR kit 10 tests: 24 cm x 16 cm x 7 cm

### 1.3.5 Waste disposal

Same procedure as for sputum containers.

Xpert assays generate large volumes of waste.

## References

1. World Health Organization. *Xpert MTB/RIF implementation manual: technical and operational 'how-to'; practical considerations*. Geneva; 2014. <https://apps.who.int/iris/bitstream/handle/10665/112469/9789241506700;jsessionid=44788E3067C3F9DBF836E8BB6BB0F253?sequence=1>
2. de Haas P, Yew B, et al. *The Simple One-Step (SOS) Stool Processing Method for Use with the Xpert MTB/RIF Assay for a Child-Friendly Diagnosis of Tuberculosis Closer to the Point of Care*. *J Clin Microbiol*. 2021 Jul 19;59(8). <https://doi.org/10.1128/JCM.00406-21>
3. MSF South Africa Medical Unit. *SOP: Urine GeneXpert MTB/Rif Assay*.
4. World Health Organization. *WHO consolidated guidelines on tuberculosis. Module 3: diagnosis - rapid diagnostics for tuberculosis detection*. 2021 update. Geneva; 2021. <https://www.who.int/publications/i/item/9789240029415>
5. World Health Organization. *Rapid communication on updated guidance on the management of tuberculosis in children and adolescents*. Geneva: World Health Organization; 2021. <https://www.who.int/publications/i/item/9789240033450>
6. Pohl C, Rutaiwa LK, Haraka F, Nsubuga M, Aloï F, Ntinginya NE, Mapamba D, Heinrich N, Hoelscher M, Marais BJ, Jugheli L, Reither K. *Limited value of whole blood Xpert(®) MTB/RIF for diagnosing tuberculosis in children*. *J Infect*. 2016 Oct;73(4):326-35. <https://doi.org/10.1016/j.jinf.2016.04.041>

# Appendix 2. Interpretation of Xpert assay results

Update: October 2022

## 2.1 Xpert MTB/RIF and Xpert MTB/RIF Ultra

MTB: *M. tuberculosis*; RIF or Rif or R: rifampicin; H: isoniazid

Results	Interpretation and decisions
Invalid/Error/No result	Perform a 2 <sup>nd</sup> test on a new specimen.
MTB not detected	<ul style="list-style-type: none"> <li>Child with presumed PTB: perform a 2<sup>nd</sup> test on a new (respiratory or stool) specimen.</li> <li>Adult: based on clinical judgment, perform a 2<sup>nd</sup> test and/or a culture on a new specimen.</li> </ul>
MTB detected No Rif resistance detected	Perform Xpert MTB/XDR (or LPA or pDST) to detect H resistance <sup>(a)</sup> ; adjust treatment according to DST.
MTB detected Rif resistance detected	<p>Evaluate risk factors for rifampicin resistance (RR):</p> <ul style="list-style-type: none"> <li>High risk of RR<sup>(b)</sup>: treat for MDR/RR-TB.</li> <li>Low risk of RR<sup>(c)</sup>: perform a 2<sup>nd</sup> test on a new specimen<sup>(d)</sup>. If 2<sup>nd</sup> test shows:               <ul style="list-style-type: none"> <li>R susceptibility: treat for DS-TB.</li> <li>R resistance: treat for MDR/RR-TB.</li> </ul> </li> </ul> <p>For patients with MDR/RR-TB, perform:</p> <ul style="list-style-type: none"> <li>Xpert MTB/XDR (or LPA) and culture and pDST (and genome sequencing if available) for resistance to other TB drugs.</li> <li>If discordant results with pDST (R resistance with Xpert, R susceptibility with pDST): treat for MDR/RR-TB<sup>[1]</sup>.</li> </ul>
MTB detected Rif resistance indeterminate	<ul style="list-style-type: none"> <li>Xpert MTB/RIF:               <ul style="list-style-type: none"> <li>Perform a 2<sup>nd</sup> test on a new specimen. If still "indeterminate", treat for DS-TB while investigating RR.</li> <li>Perform pDST (or other gDST) to confirm or rule out RR.</li> <li>Perform Xpert MTB/XDR (or LPA or pDST) to detect H resistance<sup>(a)</sup>.</li> </ul> </li> <li>Xpert MTB/RIF Ultra:               <ul style="list-style-type: none"> <li>Send an extraction of the raw results (gxx file) to a reference laboratory for identification of possible mutations (interpretation of melting curves).</li> <li>If not feasible or still "indeterminate": proceed as for Xpert MTB/RIF.</li> </ul> </li> </ul>
MTB detected "trace" Rif resistance indeterminate (Xpert Ultra)	<ul style="list-style-type: none"> <li>HIV-infected patients, children and EP specimens: a "trace" result should be considered as positive.</li> <li>Adults with history of TB in the previous 5 years: a "trace" result cannot be interpreted, culture should be performed.</li> <li>No interpretation of RR is possible.</li> <li>If suspected resistance to R or other TB drugs: perform pDST (or other gDST). Adjust treatment according to DST.</li> <li>Do not test the specimen with Xpert MTB/XDR as the Xpert MTB/XDR has a higher detection limit than Ultra.</li> </ul>

(a) For all patients if possible, and at least those with high risk of H resistance (patients with previous TB treatment with H, or contact with a TB case resistant to H, or from an area with a prevalence of resistance to H  $\geq$  3%).

(b) Patients with previous TB treatment with R, or contact with a TB case resistant to R, or from an area of high prevalence of resistance to R.

(c) Patients with no previous TB treatment with R, or contact with a TB case resistant to R, and from an area of low prevalence of resistance to R.

(d) A 2<sup>nd</sup> test is necessary because in a population with a prevalence of resistance to rifampicin < 5%, the positive predictive value of one test is < 80%, i.e. > 20% of rifampicin resistant results are false positive.

## 2.2 Xpert MTB/XDR

MTB: *M. tuberculosis*; RIF: rifampicin; INH or H: isoniazid; FLQ or FQs: fluoroquinolones; ETH or Eto: ethionamide; AMK: amikacin; KAN: kanamycin; CAP: capreomycin

Results	Interpretation and decisions
Invalid/Error/No result	Perform a 2 <sup>nd</sup> test on a new specimen.
MTB detected	After a positive Xpert MTB/RIF, an "MTB detected" result is expected because Xpert MTB/XDR and Xpert MTB/RIF have similar detection limit.
MTB not detected No resistance detected	<ul style="list-style-type: none"> <li>After a positive Xpert MTB/RIF: perform a 2<sup>nd</sup> test on a new specimen. If the 2<sup>nd</sup> test is negative, perform culture and pDST.</li> <li>After a "trace" result with Ultra, a negative result is expected because the Xpert MTB/XDR has a higher detection limit than Ultra.</li> </ul>
MTB detected No resistance detected	<ul style="list-style-type: none"> <li>Treat according to the result of Xpert MTB/RIF or Ultra.</li> <li>The test does not rule out all resistances (some resistance-conferring mutations are not detected by Xpert MTB/XDR, e.g. only 30% of Eto resistance conferring mutations are detected).</li> </ul>
MTB detected <ul style="list-style-type: none"> <li>Low INH resistance detected</li> <li>INH resistance detected</li> <li>Low FLQ resistance detected</li> <li>FLQ resistance detected</li> <li>ETH resistance detected</li> <li>AMK, KAN and/or CAP resistance detected</li> </ul>	<p>Evaluate risk factors of resistance for each drug:</p> <ul style="list-style-type: none"> <li>High risk of resistance<sup>(e)</sup>: consider as resistant to the drug. <ul style="list-style-type: none"> <li>If low-level H resistance detected (inhA mutation and no katG mutation): H<sup>h</sup> can be used, but not counted as a likely effective drug.</li> <li>If low-level resistance to FQs detected: Mfx<sup>h</sup> can be used, but not counted as a likely effective drug<sup>[2]</sup>.</li> <li>Resistance to Eto can be detected (inhA mutation). However, a negative result does not rule out resistance. <ul style="list-style-type: none"> <li>Perform pDST for resistance to other TB drugs.</li> </ul> </li> </ul> </li> <li>Low risk of resistance<sup>(f)</sup>: perform a 2<sup>nd</sup> test on a new specimen<sup>(g)</sup>. If the 2<sup>nd</sup> test shows: <ul style="list-style-type: none"> <li>Drug susceptibility: treat with the drug.</li> <li>Drug resistance: consider as resistant (see above for "High risk of resistance").</li> </ul> </li> </ul>
MTB detected Drug resistance indeterminate <sup>(h)</sup>	Perform a 2 <sup>nd</sup> test on a new specimen. If still "indeterminate": treat with likely effective drug(s) while investigating resistance with pDST (or other gDST, e.g. second-line LPA, genome sequencing).

(e) Patients with previous TB treatment with the drug or contact with a TB case resistant to the drug, or from an area of high prevalence of resistance to the drug.

(f) Patients with no previous TB treatment with the drug or contact with a TB case resistant to the drug, and from an area of low prevalence of resistance to the drug.

(g) A 2<sup>nd</sup> test is necessary because in a population with a prevalence of resistance < 5%, the positive predictive value of one test is < 80% (i.e. > 20% of resistant results are false positive).

(h) No "indeterminate" result is given for Eto.

## References

- World Health Organization. *Xpert MTB/RIF implementation manual: technical and operational 'how-to'; practical considerations*. Geneva 2014. <https://apps.who.int/iris/bitstream/handle/10665/112469/9789241506700;jsessionid=44788E3067C3F9DBF836F8BB6BB0F253?sequence=1>
- World Health Organization. *WHO operational handbook on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment*. Geneva 2020. <https://www.who.int/publications/i/item/9789240006997>



# Appendix 3. Collection, storage, and shipment of respiratory specimens

Update: September 2023

## 3.1 Respiratory specimen collection

Staff members (and attendants if necessary) present during sputum collection or collection of any other respiratory specimen should wear a respirator (FFP2 or N95) to prevent bacilli inhalation.

When a patient cannot expectorate spontaneously, respiratory specimens can be obtained by sputum induction (in children and adults) or by nasopharyngeal or gastric aspiration (in children only). These procedures must be performed under close medical supervision and only if the specimen is collected for molecular tests, culture, or genome sequencing.

They should be well explained to the patient and the person accompanying them beforehand.

Specimens are collected in specific containers:

- Sputum containers<sup>a</sup> for sputum obtained spontaneously or by induction
- Conical tubes<sup>b</sup> for specimens obtained by aspiration

Containers should be labelled with the patient's name or identification number, as well as collection date, time and location.

### 3.1.1 Required number of specimens

**Spontaneously obtained sputum:** 2 specimens

- Rapid molecular tests (RMTs): the 2 specimens are collected on the spot. The RMT is performed on the best quality specimen. The second specimen is used if the RMT needs to be repeated. If the patient provides only one specimen on the spot and the RMT needs to be repeated, a new specimen should be collected.
- Microscopy: the first specimen is collected on the spot. The second specimen is preferably collected by the patient in the morning of the next day<sup>c</sup> as soon as they wake up and before eating. The specimen is then brought to the laboratory by the patient. If not feasible, the 2 specimens are collected one hour apart on the spot.
- Culture and phenotypic drug-susceptibility tests (pDST): the 2 specimens are collected on the spot. The 2 specimens are cultured. The second specimen is cultured as a precaution i.e. in case of contamination or negative culture of the first specimen.
- Genome sequencing: the 2 specimens are collected on the spot. The second specimen is used if there is not enough DNA in the first specimen.

**Sputum induction:** if possible, 2 specimens are collected during the same session. However, as this procedure is invasive, if only one specimen is collected, do not repeat the procedure to obtain a second specimen.

**Nasopharyngeal or gastric aspiration:** only one specimen is collected.

### 3.1.2 Quality of specimens

The quality of the specimen determines the reliability of the result. A minimum volume of specimen is required to perform the tests. The specimen should contain mucoid or purulent material.

Rejection criteria: saliva (watery fluid) or specimens containing food particles.

### 3.1.3 Sputum obtained spontaneously

When possible, specimens are collected outside in the open air and far away from other people.

#### Equipment

- Gloves
- Labelled sputum container

#### Procedure

- Ask the patient to rinse their mouth with water.
- Give the patient the sputum container.
- Do 1 to 2 minutes of chest clapping if needed.
- Have the patient take a deep breath, hold for a few seconds, exhale, repeat 2 or 3 times, then cough: sputum is material brought up from the lungs with cough.
- Collect at least 2 ml of sputum and close the container tightly.
- If the specimen is collected at home, make sure that the patient has understood the procedure, including closing the container tightly after sputum collection.
- Take a new specimen if unsatisfactory.

### 3.1.4 Sputum induction

Patients should be observed for respiratory distress (including SpO<sub>2</sub> monitoring) during the procedure and for 15 minutes after the procedure. Oxygen must be ready at hand (risk of bronchospasm).

### Equipment

- Gloves
- Labelled sputum container
- Mask and tubing for nebulizer
- Holding chamber (spacer) with masks of different sizes (to be sterilised between each patient)
- Sterile hypertonic solution of 3 to 6% sodium chloride (sputum inducer)
- Sterile solution of 0.9% sodium chloride (for the specimen)
- Salbutamol metered dose inhaler
- Pulse oximeter and oxygen

### Procedure

Patients should fast for at least 2 hours before the procedure to reduce the risk of vomiting and aspiration.

- Seat the patient comfortably. For young children, sit upright in an adult's arms.
- Give the patient the sputum container.
- Administer 200 micrograms (2 puffs) of salbutamol via a holding chamber, 10 minutes before nebulization.
- Fill the nebulizer with 5 ml of 3 to 6% hypertonic saline solution.
- Place the nebulizer mask over the patient's mouth.
- Leave the patient to inhale until the reservoir is empty.
- Encourage the patient to cough and spit at any time if they feel to urge to do so.
- Collect at least 2 ml of sputum and close the container tightly.
- Terminate the procedure if unsuccessful after 15 minutes.

## 3.1.5 Nasopharyngeal aspiration

### Equipment

- Gloves
- Suction catheter (CH6 for children 1-11 months; CH8 for children 1-10 years)
- 50 ml syringe or equipment for electric suction
- Sterile solution of 0.9% sodium chloride
- Labelled collection container

### Procedure

Children should fast for at least 2 hours before the procedure to reduce the risk of vomiting and aspiration.

- Do 1 to 2 minutes of clapping.
- Clean out the nasal cavity with 0.9% sodium chloride.
- Lie the child on their back or side.
- Lubricate the end of the suction catheter.
- Put 2 drops of 0.9% sodium chloride into each nostril.
- Measure the distance from the tip of the nose to the angle of the jaw, which represents the depth to which the catheter should be inserted. Gently insert the suction catheter to this depth without applying suction.
- Once the catheter is in the posterior nasopharynx, suction with the 50 ml syringe or the electric suction device<sup>d</sup> and slowly pull out the catheter whilst suctioning.
- Collect 2 to 3 ml of respiratory secretions. If insufficient (< 2 ml), put 2 drops of 0.9% sodium chloride into each nostril, then suction on the other nostril.
- Close the container tightly.

## 3.1.6 Gastric aspiration

### Equipment

- Gloves
- Nasogastric tube (CH6 for children 1-11 months; CH8 for children 1-10 years)
- 50 ml syringe
- Sterile water
- Labelled collection container

### Procedure

Children should fast for 4 to 8 hours before the procedure. In practice, the specimen is collected early in the morning in order to obtain the sputum swallowed during the night.

- Place the child in a half-sitting or sitting position in the adult's arms.
- Insert a nasogastric tube and check that it is correctly placed.
- Suction with a 50 ml syringe.

- Collect 5 to 10 ml of gastric fluid. If insufficient (< 5 ml), rinse the stomach with 10 ml of sterile water and suction again.
- Close the container tightly.
- Start culture within 4 hours of collecting the specimen. If there will be more than 4 hours delay, neutralize with an equal volume of sodium bicarbonate.

## 3.2 Specimen inactivation

Two methods can be used for specimen inactivation:

- Add 90 or 95% ethanol to the specimen to reach a final concentration of 70%. Let the solution stand overnight. Transfer 1 ml of the solution into a 2 ml tube.
- Immerse the specimen for 20 minutes in a water bath at 80 °C.

These procedures can be performed in a well-ventilated room or using a ventilated workstation ([Appendix 6](#)).

Inactivated specimens can be used for Sanger sequencing and targeted sequencing.

They cannot be used for cultures, phenotypic drug susceptibility tests or whole genome sequencing.

## 3.3 Specimen storage

If tests are not performed immediately or on the site of collection, specimens should be protected from light. The storage conditions vary according to the test required.

### Fresh specimens

- For RMTs: store at 2-8 °C. Process as soon as possible and within 7 days. Alternatively, if stored at 35 °C max, process within 3 days max.
  - For microscopy: store at 2-8 °C. Process as soon as possible and within 3-4 days. Specimens stored at room temperature liquefy. This makes it more difficult to select mucopurulent material.
  - For cultures:
    - on liquid medium (MGIT): store at 2-8 °C. Culture as soon as possible and within 3-4 days.
    - on solid medium (LJ) cultured ≤ 3 days after collection: store at 2-8 °C. Culture as soon as possible.
    - on solid medium (LJ) cultured > 3 days after collection: use cetylpyridinium chloride (CPC) to preserve specimen (i.e. add an equal volume of CPC to the specimen), store at room temperature (20-30 °C). Culture as soon as possible and preferably within 7 days.
- Do not refrigerate specimens as CPC crystallises and becomes ineffective.
- Note:** CPC is not compatible with MGIT.
- For targeted genome sequencing: store at room temperature (however storage at 2-8 °C will not interfere with the results). Process as soon as possible and preferably within 4 days.

### Inactivated specimens

Store at room temperature.

**Note:** inactivated specimens can be kept for several years.

## 3.4 Specimen shipment

### Fresh specimens

For specimens shipped to reference laboratory by air or road transport company, use a triple packaging as per P650 instructions<sup>e</sup>:

1. Primary receptacle (containing the specimen<sup>f</sup>): leak-proof conical sterile tube tightly closed, labelled with the patient's name and identification number, collection date, time and location.
2. Secondary packaging (to protect the primary container): tightly closed leak-proof plastic box or sachet. The secondary container contains sufficient absorbent material to wrap the primary receptacle and absorb all of the specimen in case of leakage or breakage.
3. Third/outer packaging (to protect the secondary packaging): rigid cardboard box with UN 3373 pictograph Biological substance, Category B.

The outer packaging should display the following information:

- Name, full address and telephone number of the receiving laboratory, as well as name and telephone number of the person to whom the specimen is sent.
- Name, full address and telephone number of the sender.

Specimens stored at 2-8 °C should be shipped in cold chain using an isothermal triple packaging.

### Inactivated specimens

Specimens can be shipped at room temperature without triple-packaging and UN labelling.

If specimens are inactivated with ethanol, the volume of 70% ethanol should not exceed 1 ml per 2 ml tube and 100 ml per package (ethanol is considered a dangerous good).

Any fresh and inactivated specimen should be accompanied by the corresponding laboratory request form ([Appendix 34](#) and [Appendix 35](#)).



In all cases, check specific specimen shipping requirements of the receiving laboratory.

## Footnotes

- (a) Sputum container: plastic, screw top lid, single use, non-sterile, without additive.
- (b) Conical bottom tube, polypropylene, screw top lid, sterile, without additive.
- (c) The concentration of bacilli is higher in the morning sputum, which improves the detection of AFBs.
- (d) If an electric suction device is used, the suction pressure should be 80-100 mmHg for children 1-11 months; 100-120 mmHg for children 1-10 years.
- (e) For more information, see: Guidance on regulations for the transport of infectious substances 2021-2022. Geneva: World Health Organization; 2021. <https://www.who.int/publications/item/9789240019720>
- (f) If the specimen was collected in a sputum container, it should be transferred to a conical tube for shipment.

# Appendix 4. Sputum smear microscopy

Update: January 2022

## 4.1 Sputum smear preparation

Staff members present during sputum smear preparation should wear a respirator (FFP2 or N95) to prevent the inhalation of bacilli. Sputum smears should be prepared promptly after sputum collection.

### Equipment

- Gloves
- New, clean glass slides (never re-use sputum smear slides)
- Wooden applicator sticks

### Technique

- Label one end of the slide with the date of sputum collection and laboratory serial number.
- Select a mucopurulent or blood-stained portion of the sputum specimen.
- Use an applicator stick to transfer to the slide.
- Smear the specimen over an area of 1.5 to 2 cm x 2 to 3 cm. Make it thin enough to be able to read through it.
- Allow the smear to air dry for 15 minutes. Do not dry the smear in direct sunlight or over a flame.
- Fix the smear by passing the underside of the slide through a flame for 2 to 3 seconds. Repeat 3 or 4 times.
- Allow to cool before staining.

## 4.2 Ziehl-Neelsen staining

### Equipment

- Gloves
- Distilled or filtered water
- 0.3% carbol fuchsin
- 3% acid-alcohol
- 0.3% methylene blue
- Binocular microscope with oil immersion objective (100x magnification)

### Technique

- Flood the slide with 0.3% carbol fuchsin (after filtering the carbol fuchsin).
- Gently heat the underside of the slide. Begin timing as soon as steam appears. Let it steam for 5 minutes. Do not let the stain boil or dry.
- Gently rinse the slide until the water runs clear, then drain off excess water.
- Flood the slide with 3% acid-alcohol for 2 to 3 minutes, then drain. Repeat this operation if the slide is not completely decolourised.
- Gently rinse the slide, then drain off excess water.
- Flood the slide with 0.3% methylene blue for one minute, then drain.
- Gently rinse the slide until the water runs clear, then drain off excess water.
- Allow to air dry. Do not wipe or blot.

### Reading

- The slides should be examined by an experienced technician. Technicians must be given sufficient time to accurately read slides.
- Before reading the slide, apply a drop of immersion oil to the left edge of the stained smear. Do not touch the slide with the immersion oil applicator (risk of AFB transfer into the oil bottle and onto another slide).
- Examine at least one length (100 high power fields, HPF) before giving a negative result (this should take at least 5 minutes).
- AFB are red, straight or slightly curved rods. They may be found singly or in small groups. The background stains blue.

### Reporting

Table 4.1 – Grading AFB scale (WHO-IUAT LD)<sup>[1]</sup>

Number of AFB (1000x magnification: one length = 100 HPF)	Reporting
Zero AFB/one length	No AFB
1-9 AFB/one length or 100 HPF	Report exact number of AFB
10-99 AFB/one length or 100 HPF	1+
1-10 AFB/one HPF in at least 50 fields	2+
> 10 AFB/one HPF in at least 20 fields	3+

**Note:** 1-9 AFB in 100 HPF is a positive result. Note that 1-9 AFB in 100 HPF is reported as "scanty" followed by the exact number of AFB seen in 100 HPF (e.g. "scanty 3" means there are 3 AFB in 100 HPF).

Do not confuse "scanty 3" (3 AFB in 100 HPF) with AFB 3+ (more than 10 AFB per HPF).

## 4.3 Auramine O or auramine/rhodamine staining

### Equipment

- Gloves
- Distilled or filtered (not chlorinated) water
- 0.1% auramine O or auramine/rhodamine solution
- 0.5% acid alcohol
- 0.5% potassium permanganate or 0.3% methylene blue
- Fluorescence microscope (or a LED device that can be attached to a standard light microscope)

### Technique

- Flood the slide with auramine O or auramine/rhodamine solution for 15 minutes. Ensure that the staining solution remains on the smear.
- Gently rinse, then drain off excess water. Do not use chlorinated water to avoid disturbing the fluorescence reading.
- Flood the slide with 0.5% acid-alcohol for one minute, then drain.
- Gently rinse, then drain off excess water.
- Flood the slide with 0.5% potassium permanganate solution or 0.3% methylene blue for one minute, then drain.
- Gently rinse, then drain off excess water.
- Allow to air dry. Do not wipe or blot.

**Note:** to control the quality of the colouration include at least one known positive smear in the batch.

### Reading

- The slides should be examined by an experienced technician (artefacts are frequent). Technicians must be given sufficient time to read slides.
- Use a 20x objective to screen the smear.
- Examine one length before giving a negative result.
- Always read the positive control smear first. If the positive control is not positive do not continue with the patient smears, but re-stain the batch.
- AFB are bright yellow, straight or slightly curved rods. They may be found singly or in small groups. The background is dark. Non-specific debris stains pale yellow.

### Reporting

**Table 4.2** – Grading AFB scale (WHO-IUATLD)<sup>[1]</sup>

<b>Number of AFB</b> <b>(200-250x magnification: one length = 300 HPF)</b>	<b>Reporting</b>
Zero AFB/one length	No AFB
1-29 AFB/one length	Report exact number of AFB
30-299 AFB/one length	1+
10-100 AFB/one field on average	2+
> 100 AFB/one field on average	3+

**Notes:**

- 1-29 AFB per length is a positive result. Note that 1-29 AFB per length is reported as "scanty" followed by the exact number of AFB seen per length (e.g. "scanty 3" means there are 3 AFB per length).  
Do not confuse "scanty 3" (3 AFB per length) with AFB 3+ (more than 100 AFB per field).
- The fluorescence stain remains stable when sheltered from light for only 3 days. Quality control should be done within this time.

**References**

1. European Centre for Disease Prevention and Control. *Handbook on tuberculosis laboratory diagnostic methods in the European Union – Updated 2018*. Stockholm: ECDC; 2018.  
<https://www.ecdc.europa.eu/sites/portal/files/documents/TB-handbook-updated-2018.pdf>

# Appendix 5. Time required for diagnostic test results

Update: October 2022

Tests	Estimated time for results	Additional time for DST
<b>Xpert MTB/RIF</b>	110 minutes	–
<b>Xpert MTB/RIF Ultra</b>	< 80 minutes	–
<b>Xpert MTB/XDR</b>	< 90 minutes	–
<b>Truenat</b>	35 minutes (Truenat MTB)	1 hour (Truenat MTB-RIF Dx)
<b>Culture liquid medium</b> (MGIT <sup>(a)</sup> )	8 days (smear+) 16 days (smear–)	2 weeks
<b>Culture solid medium</b> LJ standard medium	16 days (smear+) 29 days (smear–)	6 weeks
<b>Culture microcolonies</b> (TLA <sup>(b)</sup> , MODS <sup>(c)</sup> )	14 days	–
<b>Smear microscopy</b>	2 hours	–
<b>LPA</b> GenoType MTBDRplus (V2.0)	1 to 2 days (direct testing on smear+) 21 days (indirect testing)	–
<b>LPA</b> GenoTypeMTBDRs/ (V2.0)	1 to 2 days (direct testing) 21 days (indirect testing)	–
<b>LF-LAM</b>	25 minutes	–
<b>tNGS</b>	1 to 3 days (direct testing on smear+) 21 days (indirect testing)	–
<b>WGS</b>	21 days (indirect testing)	–

(a) Mycobacteria growth indicator tube.

(b) Thin-layer agar.

(c) Microscopic observation of drug susceptibility.

**Note:** to provide negative results, cultures need to be incubated for 6 to 7 weeks on liquid media and 8 weeks on solid media.



# Appendix 6. Ventilated workstation and biosafety cabinet

Update: October 2023

## 6.1 Ventilated workstation

To ensure a safe work environment when natural or mechanical ventilation is not adequate, WHO recommends the use of a ventilated workstation (VWS) for procedures that do not generate significant amounts of aerosols:

- Preparation of sputum smear for microscopy
- Loading of Xpert cartridges

The VWS is a partially enclosed workspace from which air is drawn inward and exhausted outside of the laboratory. It is intended to be placed on a work-bench. It can be made according to WHO instructions<sup>a</sup>.

## 6.2 Biosafety cabinet

WHO recommends the use of a biosafety cabinet (BSC) Class II A2<sup>[1]</sup> for procedures that may generate significant amounts of aerosols such as decontamination, homogenisation or centrifugation.

Class II A2 BSCs are also required for inoculation of culture media and any procedure requiring manipulation of highly concentrated mycobacteria (e.g. strain identification, drug susceptibility testing).

Installation, certification, monitoring and maintenance should be performed by qualified technicians.

### Footnotes

- (a) For more information, see: CDC, GLI, IUATLD A. *Ventilated Workstation Manual for AFB Smear Microscopy*. 2011. <https://www.stoptb.org/gli-ventilated-workstation-manual-afb-smear-microscopy>.

### References

1. World Health Organization. *Tuberculosis laboratory biosafety manual*. World Health Organization. Geneva, 2012. <https://www.who.int/publications/i/item/9789241504638>

# Appendix 7. Lymph node fine needle aspiration

Update: October 2023

Fine needle aspiration (FNA) is used to obtain specimens from lymph nodes in order to perform Xpert assays.

When Xpert assays are not available, smear microscopy may be performed. However lymph node specimens are paucibacillary and sensitivity of smear microscopy is low<sup>[1]</sup>.

## 7.1 Specimen collection

### Equipment

- Gloves
- Sterile needle 23G (in very few cases, 19G can be used)
- Sterile 5-10 ml syringe
- 10% povidone iodine
- Sterile gauze

### Technique

- Explain the procedure to patient. Position the patient comfortably (according to the location of the lymph node, sitting or lying down).
- Disinfect the skin over and around the lymph node.
- Attach the needle to the syringe and remove the needle cap.
- Maintain the lymph node stable with one hand.
- With the other hand, insert the needle deep into the lymph node mass.
- Aspirate and move the needle in a to-and-fro fashion so that material enters the needle.
- When blood or material appears in the needle hub, stop the aspiration. Try to aspirate as much material as possible into the needle hub to increase the possibility of a positive result.
- Release the negative pressure before pulling the needle out of the lymph node. Do not continue aspirating while removing the needle. This avoids aspirating material into the barrel of the syringe and mixing the specimen with peripheral blood from the skin.

## 7.2 Specimen preparation for Xpert assay

See [Appendix 1](#).

## 7.3 Specimen preparation for smear microscopy

- Place a small drop of material on a slide.
- Make a smear that is neither too thin nor too thick.
- Allow to air dry.
- Fix the smear by flame when completely dry.
- Perform Ziehl-Neelsen staining.

For staining and reading, see [Appendix 4](#).

## References

1. Tadesse M, et al. *GeneXpert MTB/RIF Assay for the Diagnosis of Tuberculous Lymphadenitis on Concentrated Fine Needle Aspirates in High Tuberculosis Burden Settings*. PLoS One. 2015 Sep 14;10(9):e0137471. <https://doi.org/10.1371/journal.pone.0137471>

# Appendix 8. Protein estimation

Update: February 2024

## 8.1 Pandy test

Pandy test is used to detect an increase of protein in the cerebrospinal fluid (CSF).

The normal range of protein in CSF is 0.20 to 0.45 g/litre.

The Pandy test is positive when protein is superior to 0.45 g/litre.

### Equipment

- Disposable gloves
- Pandy reagent
- Pasteur pipettes
- Conical centrifuge glass tube or test tube
- 1 ml pipettes

### Preparation of 500 ml of Pandy reagent

Pandy is a saturated phenol solution.

- Weigh 30 g of phenol and transfer it into a 1000 ml bottle.
- Add 500 ml of distilled water and shake vigorously.
- Leave to stand for one 24 hours.
- Check that some phenol remains undissolved:
  - If so, filter: the solution is ready.
  - If all the phenol has dissolved, add a further 10 g of phenol and wait another 24 hours before filtering.

Pandy reagent is a highly corrosive and toxic solution:

- Label the bottle and mark it corrosive and poisonous.
- Wash hands after preparation.

### Technique

- Place 1 ml of Pandy reagent in a centrifuge tube.
- Add 3 drops of CSF, drop by drop.
- After each drop, look for a white cloud in the tube.
- To facilitate the reading, place a black surface behind the tube.

### Results

- Presence of a white precipitate: Pandy test positive.
- Absence of a white precipitate: Pandy test negative.

## 8.2 Rivalta test

The Rivalta test is used to detect an increase of protein in the body fluid (pleural fluid, ascites).

The test is positive when the proteins are superior to 30 g/litre.

### Equipment

- Disposable gloves
- Rivalta reagent
- Pasteur pipettes
- Conical centrifuge glass tube or test tube
- 5 ml pipette

### Preparation of 100 ml of Rivalta reagent

- Place 50 ml of distilled water in a 100 ml measuring cylinder.
- With a 5 ml pipette, add 3 ml of glacial acetic acid and make up to the 100 ml mark with the remaining 50 ml of distilled water.
- Transfer the solution into a bottle.

### Technique

- Place 2 ml of Rivalta reagent in a centrifuge tube.
- Add 3 drops of pleural fluid/ascites, drop by drop.
- After each drop, look for a white cloud in the tube.

- To facilitate the reading, place a dark surface behind the tube.

### **Results**

- Presence of a white precipitate: Rivalta test positive.
- Absence of a white precipitate: Rivalta test negative.

# Appendix 9. Tuberculin skin test

Update: January 2022

## 9.1 Introduction

A delayed hypersensitivity reaction occurs after an intradermal injection of tuberculin (tuberculin skin test, TST) in persons infected by *M. tuberculosis* or vaccinated with BCG.

The test is performed by injecting 5 IU of tuberculin (purified protein derivative, PPD) intradermally on the ventral surface of the forearm (side of forearm exposed with palm facing up)<sup>a</sup>.

The test, which should be performed by a trained healthcare worker, requires 2 visits. The reading is done on the second visit, 48 to 72 hours after the tuberculin injection.

If the patient does not return within 72 hours, another TST should be performed.

The result is determined by the diameter of the reaction and individual characteristics of the person being tested. It should be recorded in millimetres, not as "positive" or "negative".

The reaction is the area of induration (swelling that can be felt) around the injection site.

Using a ruler, the diameter of induration is measured transversely. The erythema (redness) around the indurated area is not the reaction and should not be measured.

A reaction that appears several minutes, hours or even 24 hours after injection, but disappears on the day after its appearance, is of no significance.

There is no correlation between the diameter of the induration and:

- likelihood of active TB,
- risk of developing active TB,
- protection against TB disease in vaccinated people.

## 9.2 Positive TST

A positive TST result (table below) signifies that a *M. tuberculosis* infection has occurred.

However, TST cannot differentiate between active and latent infection.

A positive test supports the diagnosis of latent TB infection (LTBI) when other diagnostic tools have been used to rule out active TB.

In children, a positive TST may be one element among many to establish the diagnosis of active TB.

Individual characteristics	Diameter of induration
<ul style="list-style-type: none"><li>• Persons with HIV infection</li><li>• Severely malnourished children</li><li>• Persons taking corticosteroids (e.g. prednisolone <math>\geq</math> 15 mg daily <math>\geq</math> 1 month) or immunosuppressants</li><li>• Recent contacts of TB patients</li><li>• Persons with fibrotic changes on CXR consistent with prior TB</li></ul>	$\geq$ 5 mm
<ul style="list-style-type: none"><li>• Persons from countries with high TB prevalence</li><li>• Mycobacteriology laboratory personnel</li><li>• Persons working and/or living in congregate settings, including healthcare facilities, prisons, homeless shelters, etc.</li><li>• Children &lt; 5 years</li><li>• Children &gt; 5 years and adolescents exposed to adults at risk of TB</li><li>• Other at-risk categories (e.g. diabetes, injecting drug users, end-stage renal disease, leukemia, low body mass index)</li></ul>	$\geq$ 10 mm
All other children and adults with no other risk factors or exposure to TB	$\geq$ 15 mm

A reaction highly positive (induration diameter > 20 mm) or phlyctenular (with vesicle) should be considered as an argument in favour of active TB but is not enough to decide on treatment.

Some persons may have a positive TST result even if they have not been infected with *M. tuberculosis*. Causes of false positive results include:

- Errors in tuberculin administration
- Previous BCG vaccination
- Infection with non-tuberculosis mycobacteria
- Low specificity of TST

BCG is given at birth so previous BCG vaccination has limited impact on the interpretation of TST results, except in small children. The average diameter of the TST reaction 1 year after BCG vaccination is 10 mm, with extremes ranging from 4 to 20 mm. The reaction becomes weaker over time and disappears 5 to 10 years post-vaccination.

## 9.3 Negative TST

Usually, a negative TST result signifies that no *M. tuberculosis* infection has occurred. However, a negative TST result does not rule out TB infection. Causes of false negative results include:

- Errors in tuberculin administration
- Recent viral illness or live virus vaccination (e.g. measles)
- Severe TB disease (e.g. TB meningitis or miliary TB)
- Recent (< 12 weeks) or very old (many years) TB infection
- Immunodepression or a weak immune response (e.g. the very elderly, children < 5 years, malnutrition, patients taking corticosteroids or immunosuppressants)
- Persons with diseases that result in anergy (e.g. AIDS, haemopathy, sarcoidosis)
- Natural extinction of post-vaccination reaction from the 5<sup>th</sup> year following BCG

### Footnotes

- (a) For more information on injection technique: WHO operational handbook on tuberculosis. Module 1: prevention - tuberculosis preventive treatment. Geneva: World Health Organization; 2020.  
<https://apps.who.int/iris/rest/bitstreams/1272664/retrieve>

# Appendix 10. Drug information sheets and patient instructions for TB treatment

Update: November 2022

- [Tuberculosis drug information sheets](#)
  - [Amikacin \(Am\)](#)
  - [Amoxicillin/clavulanic acid ratio 4:1 \(Amx/Clv\)](#)
  - [Bedaquiline \(Bdq\)](#)
  - [Clofazimine \(Cfz\)](#)
  - [Cycloserine \(Cs\) or terizidone \(Trd\)](#)
  - [Delamanid \(Dlm\)](#)
  - [Ethambutol \(E\)](#)
  - [Ethionamide \(Eto\) or prothionamide \(Pto\)](#)
  - [Imipenem/cilastatin \(Ipm/Cln\)](#)
  - [Isoniazid - Standard dose \(H\)](#)
  - [Isoniazid - High dose \(H<sup>h</sup>\)](#)
  - [Levofloxacin \(Lfx\)](#)
  - [Linezolid \(Lzd\)](#)
  - [Meropenem \(Mpm\)](#)
  - [Moxifloxacin \(Mfx\)](#)
  - [Para-aminosalicylate sodium \(PAS\)](#)
  - [Pretomanid \(Pa\)](#)
  - [Pyrazinamide \(Z\)](#)
  - [Rifabutin \(Rfb\)](#)
  - [Rifampicin \(B\)](#)
  - [Rifapentine \(P\)](#)
  - [Streptomycin \(S\)](#)
- [Patient instructions](#)
  - [Patients on drug-susceptible TB treatment](#)
  - [Patients on drug-resistant TB treatment](#)

# Tuberculosis drug information sheets

Update: November 2022

- [Amikacin \(Am\)](#)
- [Amoxicillin/clavulanic acid ratio 4:1 \(Amx/Clv\)](#)
- [Bedaquiline \(Bdq\)](#)
- [Clofazimine \(Cfz\)](#)
- [Cycloserine \(Cs\) or terizidone \(Trd\)](#)
- [Delamanid \(Dlm\)](#)
- [Ethambutol \(E\)](#)
- [Ethionamide \(Eto\) or prothionamide \(Pto\)](#)
- [Imipenem/cilastatin \(Ipm/Cln\)](#)
- [Isoniazid - Standard dose \(H\)](#)
- [Isoniazid - High dose \(H<sup>h</sup>\)](#)
- [Levofloxacin \(Lfx\)](#)
- [Linezolid \(Lzd\)](#)
- [Meropenem \(Mpm\)](#)
- [Moxifloxacin \(Mfx\)](#)
- [Para-aminosalicylate sodium \(PAS\)](#)
- [Pretomanid \(Pa\)](#)
- [Pyrazinamide \(Z\)](#)
- [Rifabutin \(Rfb\)](#)
- [Rifampicin \(R\)](#)
- [Rifapentine \(P\)](#)
- [Streptomycin \(S\)](#)



# Amikacin (Am)

Update: January 2022

## Forms, strengths and route of administration

- 500 mg amikacin base in 2 ml ampoule (250 mg/ml), for IM injection

## Dosage

- Child and adult: 15 to 20 mg/kg once daily
- Patient 60 years and over: 15 mg/kg 3 times a week
- Maximum dose: 1000 mg daily
- Renal insufficiency: 12 to 15 mg/kg 2 or 3 times a week

<b>Weight (kg)</b>	<b>Daily dose (mg)</b>	<b>Daily dose (ml) - IM injection<sup>(a)</sup> (500 mg in 2 ml = 250 mg/ml)</b>
5	75-100	0.4 ml
6	90-120	0.4 ml
7	105-140	0.6 ml
8	120-160	0.6 ml
9	135-180	0.6 ml
10	150-200	0.8 ml
11	165-220	0.8 ml
12	180-240	0.8 ml
13	195-260	1 ml
14	210-280	1 ml
15	225-300	1 ml
16	240-320	1.2 ml
17	255-340	1.2 ml
18	270-360	1.2 ml
19	285-380	1.5 ml
20	300-400	1.5 ml
21	315-420	1.5 ml
22	330-440	1.5 ml
23	345-460	1.5 ml
24	360-480	1.5 ml
25	375-500	2 ml
26	390-520	2 ml
27	405-540	2 ml
28	420-560	2 ml
29	435-580	2 ml
30-35	625	2.5 ml
36-45	750	3 ml
46-55	875	3.5 ml
56-70	1000	4 ml
> 70	1000	4 ml

(a) For doses less than 1 ml, use a 1 ml syringe graduated in 0.01 ml.

### **Contra-indications, adverse effects, precautions**

- Do not administer to patients with hypersensitivity to aminoglycosides.
- Administer with caution to patients 60 years and over or patients with pre-existing renal, vestibular, auditory or severe hepatic impairment.
- May cause:
  - nephrotoxicity, ototoxicity, electrolyte disturbances; rarely, hypersensitivity reactions;
  - local pain after injection.
- For the management of adverse effects, see [Appendix 17](#).
- Avoid or monitor combination with other ototoxic and/or nephrotoxic drugs (furosemide, amphotericin B, tenofovir, etc.).
- **Pregnancy:** CONTRA-INDICATED
- **Breastfeeding:** no contra-indication

### **Monitoring**

- Symptomatic monitoring.
- Audiometry, serum creatinine and electrolytes (K, Ca, Mg).

### **Patient instructions**

- Maintain a good fluid intake to limit renal problems.

### **Remarks**

- Use a different site for each injection (absorption may be delayed if the same site is used repeatedly).

### **Storage**

☞ – Below 25 °C

Solution may darken from colourless to a pale yellow, but this does not indicate a loss of potency.

# Bedaquiline (Bdq)

Update: January 2023

## Forms and strengths

- 100 mg tablet
- 20 mg dispersible tablet

## Dosage

- Child up to 15 kg: according to weight and age
- Child 16 to 29 kg: 200 mg once daily for 2 weeks, then 100 mg 3 times a week
- Child 30 kg and over and adult: 400 mg once daily for 2 weeks, then 200 mg 3 times a week

When administered 3 times a week, keep an interval of 48 hours between doses (Monday, Wednesday, Friday = M/W/F).

Weight (kg)	Weeks 1 and 2 Once daily			Subsequent weeks 3 times a week (M/W/F)		
	Dose (mg)	100 mg tablet	20 mg dispersible tablet	Dose (mg)	100 mg tablet	20 mg dispersible tablet
5-6	30-60	-	< 3 months: <b>1½ tab</b> ≥ 3 months: <b>3 tab</b>	10-20	-	< 3 months: <b>½ tab</b> ≥ 3 months: <b>1 tab</b>
7-9	30-80	-	< 3 months: <b>1½ tab</b> ≥ 3 months: <b>3 tab</b> ≥ 6 months: <b>4 tab</b>	10-40	-	< 3 months: <b>½ tab</b> ≥ 3 months: <b>1 tab</b> ≥ 6 months: <b>2 tab</b>
10-15	60-120	-	< 6 months: <b>3 tab</b> ≥ 6 months: <b>6 tab</b>	20-60	-	< 6 months: <b>1 tab</b> ≥ 6 months: <b>3 tab</b>
16-29	200	<b>2 tab</b>	-	100	<b>1 tab</b>	-
≥ 30	400	<b>4 tab</b>	-	200	<b>2 tab</b>	-

- Alternatively, for children 16 to 29 kg: 10 dispersible tablets of 20 mg (200 mg) once daily on Weeks 1 and 2, then 5 dispersible tablets of 20 mg (100 mg) 3 times a week.
- If 20 mg dispersible tablets are not available, 100 mg tablets can be crushed and suspended in 10 ml of water or fruit juice to obtain a solution containing 10 mg of bedaquiline per ml, then administered as follows:

Weight (kg)	Weeks 1 and 2 Once daily		Subsequent weeks 3 times a week (M/W/F)	
	Dose (mg)	100 mg tablet in 10 ml (10 mg/ml)	Dose (mg)	100 mg tablet in 10 ml (10 mg/ml)
5-6	30-60	< 3 months: <b>3 ml</b> ≥ 3 months: <b>6 ml</b>	10-20	< 3 months: <b>1 ml</b> ≥ 3 months: <b>2 ml</b>
7-9	30-80	< 3 months: <b>3 ml</b> ≥ 3 months: <b>6 ml</b> ≥ 6 months: <b>8 ml</b>	10-40	< 3 months: <b>1 ml</b> ≥ 3 months: <b>2 ml</b> ≥ 6 months: <b>4 ml</b>
10-15	60-120	< 6 months: <b>6 ml</b> ≥ 6 months: <b>12 ml</b>	20-60	< 6 months: <b>2 ml</b> ≥ 6 months: <b>6 ml</b>

## Contra-indications, adverse effects, precautions

- Do not administer (or discontinue) to patients with severe hepatic impairment, QTcF > 500 ms or clinically significant ventricular arrhythmia.
  - Avoid or use with caution and under close monitoring in patients with:
    - history of syncopal episodes, *torsades de pointes*, congenital QT prolongation;
    - uncompensated heart failure, severe coronary artery disease, bradycardia;
    - electrolyte disturbances (correct first K, Ca, Mg), hypothyroidism (provide thyroxine);
    - severe renal impairment, end-stage renal disease (optimal dosing not established).
  - May cause:
    - hepatotoxicity, moderate QT prolongation;
    - nausea, vomiting, arthralgia, headache, increased amylase level.
  - For the management of adverse effects see [Appendix 17](#).
  - Avoid or use with caution and under close monitoring in patients taking CYP450 inducers/inhibitors, some ARVs, or other QT prolonging drugs ([Appendix 19](#)).
- Pregnancy:** use if benefits outweigh the risks (safety not established).  
**Breastfeeding:** avoid breastfeeding during treatment (safety not established).

## Monitoring

- Symptomatic monitoring.
- Liver function, ECG, electrolytes (K, Ca, Mg).

## Patient instructions

- Take with food.
- 100 mg tablets can be crushed and mixed with water or fruit juice.
- 20 mg tablets should be dispersed in water, juice, milk, yogurt, porridge, etc.
- Avoid alcohol during treatment.

## Remarks

- For patients over 14 years who receive the regimen BPaL or BPaLM, bedaquiline can be given daily instead of 3 times a week: 200 mg once daily for the first 8 weeks then, 100 mg once daily.

## Storage

☞ – Below 25 °C

# Amoxicillin/clavulanic acid ratio 4:1 (Amx/Clv)

Update: January 2022

## Forms and strengths

- 500 mg amoxicillin/125 mg clavulanic acid tablet
- 250 mg amoxicillin/62.5 mg clavulanic acid per 5 ml, powder for oral suspension

## Dosage (expressed in clavulanic acid)

- Child under 30 kg: 3 mg (0.25 ml)/kg of clavulanic acid 3 times daily, 60 minutes before each dose of meropenem
- Adolescent  $\geq 15$  years and  $\geq 30$  kg and adult: 125 mg of clavulanic acid 2 times daily, 60 minutes before each dose of carbapenem
- Maximum dose: 250 mg daily

Weight (kg)	Daily dose (mg)	500 mg/125 mg tablet	250 mg/62.5 mg per 5 ml oral suspension
5	50	–	1.3 ml x 3
6	60	–	1.5 ml x 3
7	70	–	2 ml x 3
8	80	–	2 ml x 3
9	90	–	2.5 ml x 3
10	100	–	2.5 ml x 3
11	110	–	3 ml x 3
12	120	–	3 ml x 3
13	130	–	3.5 ml x 3
14	140	–	3.5 ml x 3
15	150	–	4 ml x 3
16	160	–	4.5 ml x 3
17	170	–	4.5 ml x 3
18	180	–	5 ml x 3
19	190	–	5 ml x 3
20	200	–	5.5 ml x 3
21	210	–	5.5 ml x 3
22	220	–	6 ml x 3
23	230	–	6 ml x 3
24	240	–	6.5 ml x 3
25	250	–	6.5 ml x 3
26	250	–	6.5 ml x 3
27	250	–	6.5 ml x 3
28	250	–	6.5 ml x 3
29	250	–	6.5 ml x 3
30-35	250	1 tab x 2	–
36-45	250	1 tab x 2	–
46-55	250	1 tab x 2	–
56-70	250	1 tab x 2	–
> 70	250	1 tab x 2	–

## Contra-indications, adverse effects, precautions

- Do not administer to penicillin-allergic patients and patients with history of hepatic disorders during a previous treatment with amoxicillin/clavulanic acid.
- Administer with caution to patients allergic to betalactams (cross-hypersensitivity may occur) and to patients with hepatic impairment.
- May cause: gastrointestinal disturbances (mainly diarrhoea), hypersensitivity reactions, hepatotoxicity.
- For the management of adverse effects, see [Appendix 17](#).
- **Pregnancy:** no contra-indication
- **Breastfeeding:** no contra-indication

## Monitoring

- Symptomatic monitoring

## Patient instructions

- Take with food.

## Storage

☼ – ☞ – Below 25 °C

- Powder for oral suspension: between 15 °C and 25 °C
- Once reconstituted, the oral suspension must be kept refrigerated (between 2 °C and 8 °C) and may be used for up to 7 days.



# Clofazimine (Cfz)

Update: August 2022

## Forms and strengths

- 50 mg and 100 mg soft capsules or tablets

## Dosage

- Child under 10 kg: doses are administered 3 times a week (Monday, Wednesday, Friday = M/W/F)
- Child 10 to 29 kg: 2 to 5 mg/kg once daily
- Child 30 kg and over and adult: 100 mg once daily

<b>Weight (kg)</b>	<b>Daily dose (mg)</b>	<b>100 mg capsule<sup>(a)</sup></b>	<b>50 mg capsule<sup>(a)</sup></b>
5	–	–	<b>1 caps (M/W/F)</b>
6	–	–	<b>1 caps (M/W/F)</b>
7	–	–	<b>1 caps (M/W/F)</b>
8	–	–	<b>1 caps (M/W/F)</b>
9	–	–	<b>1 caps (M/W/F)</b>
10	20-50	–	<b>1 caps</b>
11	22-55	–	<b>1 caps</b>
12	24-60	–	<b>1 caps</b>
13	26-65	–	<b>1 caps</b>
14	28-70	–	<b>1 caps</b>
15	30-75	–	<b>1 caps</b>
16	32-80	–	<b>1 caps</b>
17	34-85	–	<b>1 caps</b>
18	36-90	–	<b>1 caps</b>
19	38-95	–	<b>1 caps</b>
20	40-100	–	<b>1 caps</b>
21	42-105	–	<b>1 caps</b>
22	44-110	–	<b>1 caps</b>
23	46-115	–	<b>1 caps</b>
24	48-120	<b>1 caps</b>	–
25	50-125	<b>1 caps</b>	–
26	52-130	<b>1 caps</b>	–
27	54-135	<b>1 caps</b>	–
28	56-140	<b>1 caps</b>	–
29	58-145	<b>1 caps</b>	–
30-35	100	<b>1 caps</b>	–
36-45	100	<b>1 caps</b>	–
46-55	100	<b>1 caps</b>	–
56-70	100	<b>1 caps</b>	–
> 70	100	<b>1 caps</b>	–

(a) Capsule or tablet

## Contra-indications, adverse effects, precautions

- Do not administer to patients with history of allergy to clofazimine.
- Administer with caution to patients with severe hepatic impairment.
- May cause:
  - orange-brown discolouration of skin and body fluids;
  - strong QT prolongation;
  - gastrointestinal intolerance (nausea, vomiting, abdominal pain);
  - severe abdomen pain, bowel obstruction, intestinal bleeding;
  - eye and skin dryness and irritation, hypersensitivity reactions, photosensitivity.
- For the management of adverse effects, see [Appendix 17](#).
- Avoid or use with caution and under close monitoring in patients taking other QT prolonging drugs ([Appendix 19](#)).
- **Pregnancy:** use only if benefits outweigh the risks (safety is not established).
- **Breast-feeding:** avoid breastfeeding during treatment (safety not established). If used, may cause breast milk discolouration and reversible skin discolouration in breastfed infants.

## Monitoring

- Symptomatic monitoring.
- ECG.

## Patient instructions

- Take with food to improve gastrointestinal tolerance.
- Protect your skin from sun.
- Harmless orange-brown discoloration of the skin and body fluids (urine, sweat, saliva, sputum, tears, breast milk, etc.). It is reversible but may take months to disappear after stopping treatment.

## Storage

🔒 – Below 25 °C

# Cycloserine (Cs) or terizidone (Trd)

Update: January 2022

## Forms and strengths

- 250 mg and 125 mg capsules

## Dosage

- Child under 30 kg: 7.5 to 10 mg/kg 2 times daily (or 15 to 20 mg/kg once daily if tolerated)
- Child 30 kg and over and adult: 5 to 7.5 mg/kg 2 times daily (or 10 to 15 mg/kg once daily if tolerated)
- Maximum dose: 1000 mg daily
- Renal insufficiency: 250 mg once daily or 500 mg 3 times a week

<b>Weight (kg)</b>	<b>Daily dose (mg)</b>	<b>250 mg capsule</b>	<b>125 mg capsule</b>
5	75-100	-	<b>1 caps</b>
6	90-120	-	<b>1 caps</b>
7	105-140	-	<b>1 caps</b>
8	120-160	-	<b>1 caps</b>
9	135-180	-	<b>1 caps</b>
10	150-200	-	<b>1 caps x 2</b>
11	165-220	-	<b>1 caps x 2</b>
12	180-240	-	<b>1 caps x 2</b>
13	195-260	-	<b>1 caps x 2</b>
14	210-280	-	<b>1 caps x 2</b>
15	225-300	-	<b>1 caps x 2</b>
16	240-320	-	<b>1 caps (morning) + 2 caps (evening)</b>
17	255-340	-	<b>1 caps (morning) + 2 caps (evening)</b>
18	270-360	-	<b>1 caps (morning) + 2 caps (evening)</b>
19	285-380	-	<b>1 caps (morning) + 2 caps (evening)</b>
20	300-400	-	<b>1 caps (morning) + 2 caps (evening)</b>
21	315-420	-	<b>1 caps (morning) + 2 caps (evening)</b>
22	330-440	-	<b>1 caps (morning) + 2 caps (evening)</b>
23	345-460	-	<b>1 caps (morning) + 2 caps (evening)</b>
24	360-480	<b>1 caps x 2</b>	-
25	375-500	<b>1 caps x 2</b>	-
26	390-520	<b>1 caps x 2</b>	-
27	405-540	<b>1 caps x 2</b>	-
28	420-560	<b>1 caps x 2</b>	-
29	435-580	<b>1 caps x 2</b>	-
<b>30-35</b>	500	<b>1 caps x 2</b>	-
<b>36-45</b>	500	<b>1 caps x 2</b>	-
<b>46-55</b>	750	<b>1 caps (morning) + 2 caps (evening)</b>	-
<b>56-70</b>	750	<b>1 caps (morning) + 2 caps (evening)</b>	-
<b>&gt; 70</b>	750	<b>1 caps (morning) + 2 caps (evening)</b>	-

## Contra-indications, adverse effects, precautions

- Avoid in patients with epilepsy, depression, psychosis, severe anxiety, history of neurological or psychiatric disorders, chronic alcohol use. However, if essential to the regimen, it can be administered under close monitoring.
- May cause:
  - neurotoxicity: seizure, headache, lethargy, confusion, mood change, drowsiness, anxiety, psychosis, depression, suicidal ideation, peripheral neuropathy; rarely, vestibular toxicity;
  - hypersensitivity reactions.
- For the management of adverse effects, see [Appendix 17](#).
- Avoid or monitor combination with isoniazid and thionamides (increased risk of neurotoxicity).
- Administer concomitantly pyridoxine (vitamin B<sub>6</sub>); child: 1 to 2 mg/kg (usual range: 10 to 50 mg) once daily; adult: 100 mg once daily.
- **Pregnancy:** use if the benefits outweigh the risks. Administer pyridoxine to the mother (as above).
- **Breastfeeding:** no contra-indication. Administer pyridoxine to the mother (as above) and the breast-fed neonate or infant (1 to 2 mg/kg once daily).

## Monitoring

- Symptomatic monitoring.

## Patient instructions

- Take capsules with water before or after meals.
- Avoid alcohol during treatment.

## Remarks

- To increase tolerance, start with a low dose (e.g. 250 mg daily in adults), then increase over 1 to 2 weeks to achieve the requested dose.

## Storage

☞ – Below 25 °C

# Delamanid (Dlm)

Update: September 2022

## Forms and strengths

- 50 mg tablet
- 25 mg dispersible tablet

## Dosage

- Child under 10 kg: according to weight and age
- Child 10 to 15 kg: 25 mg 2 times daily
- Child 16 to 29 kg: 50 mg morning and 25 mg evening
- Child 30 to 45 kg and under 15 years: 50 mg 2 times daily
- Child 46 kg and over and adult: 100 mg 2 times daily

Weight (kg)	Daily dose (mg)	50 mg tablet	25 mg dispersible tablet
5-9	25-50	–	< 3 months: <b>1 tab</b> ≥ 3 months: <b>1 tab x 2</b>
10-15	50	–	<b>1 tab x 2</b>
16-29	75	–	<b>2 tab</b> (morning) + <b>1 tab</b> (evening)
30-45	100-200	< 15 years: <b>1 tab x 2</b> ≥ 15 years: <b>2 tab x 2</b>	–

- If 25 mg dispersible tablets are not available, 50 mg tablets can be crushed and suspended in 10 ml of water or fruit juice to obtain a solution of 5 mg of delamanid per ml, administered as follows:

Weight (kg)	Daily dose (mg)	50 mg tablet in 10 ml (5 mg/ml)
5-9	25-50	< 3 months: <b>5 ml</b> ≥ 3 months: <b>5 ml x 2</b>
10-15	50	<b>5 ml x 2</b>
16-29	75	<b>10 ml</b> (morning) + <b>5 ml</b> (evening)

## Contra-indications, adverse effects, precautions

- Do not administer (or discontinue) to patients with QTcF > 500 ms or albumin level < 2.8 g/dl.
- Avoid or use with caution and under close monitoring in patients with:
  - history of syncopal episodes or *torsades de pointes*, congenital QT prolongation, cardiac disease;
  - electrolyte disturbances (correct first K, Ca, Mg);
  - severe renal or hepatic impairment.
- Use with caution and under close monitoring in patients taking QT-prolonging drugs ([Appendix 19](#)).
- May cause: nausea, vomiting, dizziness, insomnia, mild QT prolongation.
- For the management of adverse effects, see [Appendix 17](#).

**Pregnancy:** use if benefits outweigh the risks (safety not established).

**Breastfeeding:** avoid breastfeeding during treatment (safety not established).

## Monitoring

- Symptomatic monitoring.
- ECG.

## Patient instructions

- Take with food.
- 50 mg tablets should be swallowed whole if possible.
- 25 mg tablets should be dispersed in water or fruit juice.

## **Storage**

☞ - Below 25 °C



# Ethambutol (E)

Update: January 2022

## Forms and strengths

- 100 mg and 400 mg tablets
- 100 mg dispersible tablet, to be dispersed in 10 ml water

## Dosage

- Child and adult: 15 to 25 mg/kg once daily
- Maximum dose: 1200 mg daily
- Renal insufficiency: 15 to 25 mg/kg 3 times a week

<b>Weight (kg)</b>	<b>Daily dose (mg)</b>	<b>400 mg tablet</b>	<b>100 mg tablet</b>
5	75-125	-	1 tab
6	90-150	-	1 tab
7	105-175	-	1 tab
8	120-200	-	2 tab
9	135-225	-	2 tab
10	150-250	-	2 tab
11	165-275	-	2 tab
12	180-300	-	2 tab
13	195-325	-	2 tab
14	210-350	-	3 tab
15	225-375	-	3 tab
16	240-400	-	3 tab
17	255-425	-	3 tab
18	270-450	1 tab	-
19	285-475	1 tab	-
20	300-500	1 tab	-
21	315-525	1 tab	-
22	330-550	1 tab	-
23	345-575	1 tab	-
24	360-600	1 tab	-
25	375-625	1 tab	-
26	390-650	1 tab	-
27	405-675	1½ tab	-
28	420-700	1½ tab	-
29	435-725	1½ tab	-
30-35	800	2 tab	-
36-45	800	2 tab	-
46-55	1200	3 tab	-
56-70	1200	3 tab	-
> 70	1200	3 tab	-

## Contra-indications, adverse effects, precautions

- Do not administer to patients with severe renal impairment or pre-existing optic neuritis (e.g. diabetic retinopathy).
- May cause: dose-related retrobulbar optic neuritis, exacerbated in renal impairment.
- The dosage must be carefully adjusted to the weight, especially for children under 5 years, as it is more difficult to detect visual changes at this age.
- For the management of adverse effects, see [Appendix 17](#).
- **Pregnancy:** no contra-indication
- **Breastfeeding:** no contra-indication

## Monitoring

- Symptomatic monitoring.

## Patient instructions

- Take with or without food.
- 100 mg dispersible tablets should be dispersed in 10 ml water.

## Remarks

- For adults on drug-susceptible TB treatment, ethambutol is given as part of a fixed-dose combination.
- Ethambutol is also used in the treatment of drug-resistant TB treatment for longer duration. For treatment > 2 months, daily doses should be closer to 15 mg/kg and visual acuity and colour discrimination should be monitored.

## Storage

☞ – ☞ – Below 25 °C

# Ethionamide (Eto) or prothionamide (Pto)

Update: January 2022

## Forms and strengths

- 250 mg tablet (ethionamide or prothionamide)
- 125 mg dispersible tablet (ethionamide), to be dispersed in 10 ml water

## Dosage

- Child and adult: 15 to 20 mg/kg once daily
- Maximum dose: 1000 mg daily

<b>Weight (kg)</b>	<b>Daily dose (mg)</b>	<b>250 mg tablet</b>	<b>125 mg dispersible tablet</b>
5	75-100	-	1 tab
6	90-120	-	1 tab
7	105-140	-	1 tab
8	120-160	-	1 tab
9	135-180	-	1½ tab
10	150-200	-	1½ tab
11	165-220	-	2 tab
12	180-240	-	2 tab
13	195-260	-	2 tab
14	210-280	-	2½ tab
15	225-300	-	2½ tab
16	240-320	-	2½ tab
17	255-340	-	2½ tab
18	270-360	-	2½ tab
19	285-380	-	3 tab
20	300-400	-	3 tab
21	315-420	-	3 tab
22	330-440	-	3 tab
23	345-460	-	3 tab
24	360-480	-	3 tab
25	375-500	2 tab	-
26	390-520	2 tab	-
27	405-540	2 tab	-
28	420-560	2 tab	-
29	435-580	2 tab	-
30-35	500	2 tab	-
36-45	500	2 tab	-
46-55	750	3 tab	-
56-70	750	3 tab	-
> 70	1000	4 tab	-

## Contra-indications, adverse effects, precautions

- Do not administer to patients with severe hepatic impairment.
- Administer with caution to patients with hepatic disease, diabetes or depression.
- May cause:
  - frequently: gastrointestinal disturbances (abdominal or epigastric pain, diarrhoea, metallic taste, nausea and vomiting, stomatitis, etc.);
  - occasionally: endocrine disorders (gynecomastia, hypothyroidism), alopecia, depression, anxiety, psychosis, hypoglycaemia, vestibular disorders, hepatotoxicity, peripheral neuropathy, optic neuritis, hypersensitivity reactions, seizures
- For the management of adverse effects, see [Appendix 17](#).
- Monitor combination with: cycloserine or terizidone (increased risk of seizures) and para-aminosalicylic acid (increased risk of gastrointestinal disturbances and hypothyroidism).
- Administer concomitantly pyridoxine (vitamin B<sub>6</sub>); child: 1 to 2 mg/kg (usual range: 10 to 50 mg) once daily; adult: 100 mg once daily.
- **Pregnancy:** CONTRA-INDICATED
- **Breastfeeding:** administer pyridoxine to the mother (as above). Observe the breast-fed neonate or infant for adverse effects and supplement it with pyridoxine (1 to 2 mg/kg once daily).

## Monitoring

- Symptomatic monitoring.
- Liver function and thyroid function.

## Patient instructions

- Take with food and/or at bedtime to limit gastrointestinal disturbances.
- 125 mg tablets should be dispersed in 10 ml water.
- Avoid alcohol during treatment.

## Remarks

- To improve tolerance, start with a low dose (e.g. 250 mg daily in adults), then increase over 1 to 2 weeks to achieve the requested dose.
- For the 6HRZEto regimen for drug-susceptible TB meningitis, the dose is 20 mg/kg once daily (max. 750 mg daily).

## Storage

☼ – ☰ – Below 25 °C

# Imipenem/cilastatin (Ipm/Cln)

Update: January 2022

## Forms, strengths and route of administration

- Powder for injection, in vial of 500 mg imipenem monohydrate/500 mg cilastatin sodium, to be reconstituted with 20 ml of 0.9% sodium chloride (25 mg imipenem/ml).
- Each dose is to be diluted in 100 ml of 0.9% sodium chloride and to be administered by IV infusion:
  - over 30 minutes for doses  $\leq$  500 mg/500 mg
  - over 60 minutes for doses  $>$  500 mg/500 mg
- Use a deep line, preferably an implantable venous access device (Port-a-Cath).

## Dosage (expressed in imipenem)

- Adolescent 15 years and over (and  $\geq$  30 kg) and adult: 1000 mg (2 vials) 2 times daily with 10 hours minimum between infusions
- Maximum dose: 2000 mg daily
- Renal insufficiency: 750 mg every 12 hours for CrCl 20-40 ml/minute; 500 mg every 12 hours for CrCl  $<$  20 ml/minute

Weight (kg)	Daily dose (mg)	Daily dose (ml) - IV infusion (500 mg/500 mg per vial)
5-29	Do not used in patients $<$ 15 years and $<$ 30 kg	
30-33	2000	2 vials (40 ml) in 100 ml of 0.9% NaCl x 2
34-40	2000	2 vials (40 ml) in 100 ml of 0.9% NaCl x 2
41-45	2000	2 vials (40 ml) in 100 ml of 0.9% NaCl x 2
46-50	2000	2 vials (40 ml) in 100 ml of 0.9% NaCl x 2
51-70	2000	2 vials (40 ml) in 100 ml of 0.9% NaCl x 2
$>$ 70	2000	2 vials (40 ml) in 100 ml of 0.9% NaCl x 2

## Contra-indications, adverse effects, precautions

- Do not administer to patients with hypersensitivity to carbapenems.
- Administer with caution to patients allergic to other betalactams (cross-hypersensitivity may occur).
- May cause:
  - nausea, vomiting (the infusion rate may be slowed down in case of nausea), diarrhoea;
  - neurotoxicity: confusional state, seizures (most frequently in patients with history of seizures or renal impairment);
  - hypersensitivity reactions;
  - local reactions (phlebitis/thrombophlebitis).
- For the management of adverse effects, see [Appendix 17](#).
- Avoid or monitor combination with: valproic acid (decreased plasma concentration of valproic acid and risk of seizures), oral or injectable ganciclovir (risk of seizures).
- **Pregnancy and breastfeeding:** avoid unless the benefits outweigh the risks

## Monitoring

- Symptomatic monitoring.

## Remarks

- Administer clavulanic acid 60 minutes before each dose of imipenem/cilastatin.
- Do not mix with Ringer lactate (incompatibility) but may be administered via Y-site.
- Do not mix with other drugs in the infusion bag.

## Storage

☼ – Below 25 °C

- Once reconstituted, solution:
  - remains stable 4 hours at room temperature or 24 hours between 2 to 8 °C,
  - may darken from colourless to yellow (this does not indicate a loss of potency),
  - should be discarded if it becomes brown.



# Isoniazid - Standard dose (H)

Update: January 2022

## Forms and strengths

- 300 mg and 100 mg tablets
- 100 mg and 50 mg dispersible tablets, to be dispersed in 10 ml water

## Dosage

- Child under 30 kg: 10 mg/kg (7 to 15 mg/kg) once daily
- Child 30 kg and over and adult: 5 mg/kg (4 to 6 mg/kg) once daily
- Maximum dose: 300 mg daily

<b>Weight (kg)</b>	<b>Daily dose (mg)</b>	<b>300 mg tablet</b>	<b>100 mg tablet</b>
5	35-75	-	½ tab
6	42-90	-	1 tab
7	49-105	-	1 tab
8	56-120	-	1 tab
9	63-135	-	1 tab
10	70-150	-	1½ tab
11	77-165	-	1½ tab
12	84-180	-	1½ tab
13	91-195	-	2 tab
14	98-210	-	2 tab
15	105-225	-	2 tab
16	112-240	-	2 tab
17	119-255	-	2 tab
18	126-270	-	2 tab
19	133-285	-	2 tab
20	140-300	-	2 tab
21	147-300	1 tab	-
22	154-300	1 tab	-
23	161-300	1 tab	-
24	168-300	1 tab	-
25	175-300	1 tab	-
26	182-300	1 tab	-
27	189-300	1 tab	-
28	196-300	1 tab	-
29	203-300	1 tab	-
30-35	150	½ tab	-
36-45	300	1 tab	-
46-55	300	1 tab	-
56-70	300	1 tab	-
> 70	300	1 tab	-

Alternatively, 50 mg dispersible tablets may be used instead of ½ tablets of 100 mg.

## Contra-indications, adverse effects, precaution

- Do not administer to patients with severe hepatic impairment.
- May cause:
  - peripheral neuropathy;
  - hepatotoxicity;
  - hypersensitivity reactions, arthralgias, optic neuritis, psychotic reactions, seizures and depression.
- Monitor closely:
  - pregnant and breastfeeding women, patients with renal impairment or diabetes; malnourished or HIV-infected patients (increased risk of neuropathy);
  - alcoholic patients (increased risk of neuropathy and hepatotoxicity);
  - patients with chronic hepatic disease or taking rifampicin or ≥ 35 years (increased risk of hepatotoxicity);
  - patients taking anticonvulsants, benzodiazepines (risk of toxicity), warfarin (risk of bleeding). Dose adjustment may be required.
- For the management of adverse effects, see [Appendix 17](#).
- Administer concomitantly pyridoxine (vitamin B<sub>6</sub>) to patients at risk of peripheral neuropathy (child: 5 to 10 mg once daily; adult: 10 mg once daily).
- **Pregnancy and breastfeeding:** no contra-indication. Administer pyridoxine to the mother (as above) and the breast-fed neonate or infant (5 mg once daily).

## Monitoring

- Symptomatic monitoring.
- Liver function in patients with hepatic disease.

## Patient instructions

- Take without food.
- 100 mg dispersible tablet should be dispersed in 10 ml water.
- Avoid alcohol during treatment.

## Remarks

- For patients on drug-susceptible TB treatment, isoniazid is given as part of a fixed-dose combination.
- For the 6HRZ-Eto regimen for drug-susceptible TB meningitis, the dose of isoniazid is 20 mg/kg once daily (max. 400 mg daily).
- Isoniazid is also used in the treatment of latent TB infection and multidrug-resistant TB treatment (at high dose - H<sup>h</sup>).

## Storage

☞ - ☞ - Below 25 °C

# Isoniazid - High dose (Hh)

Update: November 2022

## Forms and strengths

- 300 mg and 100 mg tablets
- 100 mg and 50 mg dispersible tablets, to be dispersed in 10 ml water

## Dosage

- Child under 30 kg: 15 to 20 mg/kg once daily
- Child 30 kg and over and adult: 10 to 15 mg/kg once daily
- Maximum dose: 600 mg daily

<b>Weight (kg)</b>	<b>Daily dose (mg)</b>	<b>300 mg tablet</b>	<b>100 mg tablet</b>
5	75-100	–	<b>1 tab</b>
6	90-120	–	<b>1 tab</b>
7	105-140	–	<b>1½ tab</b>
8	120-160	–	<b>1½ tab</b>
9	135-180	–	<b>1½ tab</b>
10	150-200	–	<b>2 tab</b>
11	165-220	–	<b>2 tab</b>
12	180-240	–	<b>2 tab</b>
13	195-260	–	<b>2 tab</b>
14	210-280	–	<b>2 tab</b>
15	225-300	–	<b>3 tab</b>
16	240-320	–	<b>3 tab</b>
17	255-340	–	<b>3 tab</b>
18	270-360	–	<b>3 tab</b>
19	285-380	–	<b>3 tab</b>
20	300-400	–	<b>3 tab</b>
21	315-420	–	<b>4 tab</b>
22	330-440	–	<b>4 tab</b>
23	345-460	–	<b>4 tab</b>
24	360-480	–	<b>4 tab</b>
25	375-500	–	<b>4 tab</b>
26	390-520	–	<b>4 tab</b>
27	405-540	–	<b>4 tab</b>
28	420-560	–	<b>4½ tab</b>
29	435-580	–	<b>4½ tab</b>
<b>30-35</b>	450	<b>1½ tab</b>	–
<b>36-45</b>	450	<b>1½ tab</b>	–
<b>46-55</b>	600	<b>2 tab</b>	–
<b>56-70</b>	600	<b>2 tab</b>	–
<b>&gt; 70</b>	600	<b>2 tab</b>	–

Alternatively, 50 mg dispersible tablets may be used instead of ½ tablets of 100 mg.

### Contra-indications, adverse effects, precautions

- Do not administer to patients with severe hepatic impairment.
- May cause:
  - peripheral neuropathy;
  - hepatotoxicity;
  - hypersensitivity reactions, arthragias, optic neuritis, psychotic reactions, seizures and depression.
- Monitor closely:
  - pregnant and breastfeeding women, patients with renal impairment or diabetes; malnourished or HIV-infected patients (increased risk of neuropathy);
  - alcoholic patients (increased risk of neuropathy and hepatotoxicity);
  - patients with chronic hepatic disease or taking rifampicin or ≥ 35 years (increased risk of hepatotoxicity);
  - patients taking anticonvulsants, benzodiazepines (risk of toxicity), warfarin (risk of bleeding). Dose adjustment may be required.
- For the management of adverse effects, see [Appendix 17](#).
- Administer concomitantly pyridoxine (vitamin B<sub>6</sub>): child: 1 to 2 mg/kg (usual range: 10 to 50 mg) once daily; adult: 100 mg once daily.
- **Pregnancy and breastfeeding:** no contra-indication. Administer pyridoxine to the mother (as above). Observe the breast-fed neonate or infant for adverse effects and supplement it with pyridoxine (1 to 2 mg/kg once daily).

### Monitoring

- Symptomatic monitoring.
- Liver function.

### Patient instructions

- Take without food.
- Dispersible tablets should be dispersed in 10 ml water.
- Avoid alcohol during treatment.

### Storage

☼ – ☰ – Below 25 °C

# Levofloxacin (Lfx)

Update: September 2022

## Forms and strengths

- 250 mg and 500 mg tablets
- 100 mg dispersible tablet, to be dispersed in 10 ml water

## Dosage

- Child under 30 kg: 15 to 20 mg/kg once daily
- Child 30 kg and over and adult: 750 to 1000 mg once daily
- Maximum dose: 1500 mg daily
- Renal insufficiency: 750 to 1000 mg 3 times a week

<b>Weight (kg)</b>	<b>Daily dose (mg)</b>	<b>500 mg tablet</b>	<b>250 mg tablet</b>	<b>100 mg dispersible tablet</b>
5	75-100	-	-	<b>1 tab</b>
6	90-120	-	-	<b>1 tab</b>
7	105-140	-	-	<b>1½ tab</b>
8	120-160	-	-	<b>1½ tab</b>
9	135-180	-	-	<b>1½ tab</b>
10	150-200	-	-	<b>2 tab</b>
11	165-220	-	-	<b>2 tab</b>
12	180-240	-	-	<b>2 tab</b>
13	195-260	-	-	<b>2 tab</b>
14	210-280	-	-	<b>2 tab</b>
15	225-300	-	-	<b>2 tab</b>
16	240-320	-	-	<b>3 tab</b>
17	255-340	-	-	<b>3 tab</b>
18	270-360	-	-	<b>3 tab</b>
19	285-380	-	-	<b>3 tab</b>
20	300-400	-	-	<b>3 tab</b>
21	315-420	-	-	<b>4 tab</b>
22	330-440	-	-	<b>4 tab</b>
23	345-460	-	-	<b>4 tab</b>
24	360-480	-	-	<b>4 tab</b>
25	375-500	-	<b>2 tab</b>	-
26	390-520	-	<b>2 tab</b>	-
27	405-540	-	<b>2 tab</b>	-
28	420-560	-	<b>2 tab</b>	-
29	435-580	-	<b>2 tab</b>	-
30-35	750	-	<b>3 tab</b>	-
36-45	750	-	<b>3 tab</b>	-
46-55	1000	<b>2 tab</b>	-	-
56-70	1000	<b>2 tab</b>	-	-
> 70	1000	<b>2 tab</b>	-	-



## Contra-indications, adverse effects, precautions

- Do not administer to patients with hypersensitivity or tendon damage during a previous treatment with a fluoroquinolone.
- Administer with caution to patients:
  - over 60 years or on corticosteroid treatment (increased risk of tendon damage);
  - with diabetes or history of mental disorders or seizures.
- May cause:
  - tendinitis, tendon rupture, mild QT prolongation;
  - gastrointestinal disturbances (abdominal or epigastric pain, diarrhoea);
  - neurological disorders (headache, psychosis, seizures, etc.);
  - photosensitivity;
  - hypersensitivity reactions, hypo/hyperglycaemia;
  - rarely: crystalluria, peripheral neuropathy, ototoxicity.
- For the management of adverse effects, see [Appendix 17](#).
- Avoid or use with caution and under close monitoring in patients taking other QT prolonging drugs ([Appendix 19](#)) or warfarin.
- Do not administer simultaneously with: antacids containing magnesium/aluminium, calcium, iron and zinc salts (administer 2 hours apart).

**Pregnancy:** use if benefits outweigh the risks (safety not established).

**Breastfeeding:** avoid breastfeeding during treatment (no absolute contra-indication).

## Monitoring

- Symptomatic monitoring.

## Patient instructions

- Take 2 hours apart from milk-based product, antacids, calcium, iron and zinc salts.
- 100 mg tablets should be dispersed in 10 ml water.
- Maintain a good fluid intake.
- Protect your skin from sun.

## Storage

☼ – ☰ – Below 25 °C

# Linezolid (Lzd)

Update: October 2022

## Forms and strengths

- 600 mg tablet (breakable and non-breakable)
- 150 mg dispersible tablet
- 100 mg/5 ml, granules for oral suspension

## Dosage

- Child under 15 kg: 15 mg/kg once daily
- Child 15 to 45 kg: 10 to 12 mg/kg once daily
- Patient 46 kg and over: 600 mg once daily
- Maximum dose: 600 mg daily

**Note:** in the BPALM therapeutic regimen for patients 15 years and over, the dose of linezolid is 600 mg once daily for 16 weeks then 300 mg once daily up to the end of treatment.

Weight (kg)	Daily dose (mg)	600 mg tablet	150 mg dispersible tablet	100 mg per 5 ml oral suspension
5	75	–	–	3 ml
6	90	–	–	4 ml
7	105	–	–	5 ml
8-9	120-135	–	–	6 ml
10-15	150-180	–	1 tab	–
16-23	160-276	–	1½ tab	–
24-29	240-348	–	2 tab	–
30-35	300	–	2 tab	–
36-45	450	–	3 tab	–
46-55	600	1 tab	–	–
56-70	600	1 tab	–	–
> 70	600	1 tab	–	–

- Alternatively, for children 5 to 6 kg, if oral suspension is not available: one half of a 150 mg dispersible tablet (75 mg) once daily.
- If 150 mg dispersible tablets are not available, 600 mg tablets can be crushed and suspended in 10 ml of water or fruit juice to obtain a solution of 60 mg of linezolid per ml, administered as follows:

Weight (mg)	Daily dose (mg)	600 mg tablet in 10 ml (60 mg/ml)
5	75	1.25 ml
6	90	1.5 ml
7-9	105-135	2 ml
10-15	150-180	2.5 ml

### Contra-indications, adverse effects, precautions

- Administer with caution to patients with haematological disorders or hypertension.
- May cause:
  - anaemia, neutropenia and/or thrombocytopenia;
  - lactic acidosis;
  - peripheral neuropathy (can be irreversible); rarely, optic neuritis;
  - abdominal pain, diarrhoea, nausea.
- For the management of adverse effects, see [Appendix 17](#).
- Avoid or monitor combination with serotonergic drugs such as tricyclic antidepressants (e.g. amitriptyline) or selective serotonin reuptake inhibitors (e.g. fluoxetine, paroxetine): risk of serotonin syndrome.
- Administer concomitantly pyridoxine (vitamin B<sub>6</sub>); child: 1 to 2 mg/kg (usual range: 10 to 50 mg) once daily; adult: 100 mg once daily.
- **Pregnancy:** use if the benefits outweigh the risks. Administer pyridoxine to the mother (as above).
- **Breastfeeding:** avoid breastfeeding during treatment (safety not established).

### Monitoring

- Symptomatic monitoring.
- Full blood count.
- Visual acuity and colour discrimination.

### Patient instructions

- Take with or without food.

### Storage

☞ – ☞ – Below 25 °C

Once reconstituted, the oral suspension may be kept at room temperature for 21 days, protected from light.

# Meropenem (Mpm)

Update: January 2022

## Forms, strengths and route of administration

- Powder for injection, in 500 mg vial, to be reconstituted with 10 ml of water for injection (50 mg meropenem/ml).
- Each dose is to be diluted in 5 ml/kg of 0.9% sodium chloride in children under 20 kg and in 100 ml of 0.9% sodium chloride in children 20 kg and over and adults and to be administered by IV infusion over 15 to 30 minutes.
- Use a deep line, preferably an implantable venous access device (Port-a-Cath).

## Dosage

- Child under 30 kg: 20 to 40 mg/kg every 8 hours
- Child 30 kg and over and adult: 1500 to 2000 mg 2 times daily with 10 hours minimum between infusions
- Maximum dose: 6000 mg daily
- Renal insufficiency: 750 mg every 12 hours for CrCl 20-40 ml/minute; 500 mg every 12 hours for CrCl < 20 ml/minute

<b>Weight (kg)</b>	<b>Daily dose (mg)</b>	<b>Daily dose (ml) – IV infusion (500 mg per vial)</b>
5	300	2 ml in 25 ml of 0.9% NaCl x 3
6	300	2 ml in 30 ml of 0.9% NaCl x 3
7	600	4 ml in 35 ml of 0.9% NaCl x 3
8	600	4 ml in 40 ml of 0.9% NaCl x 3
9	600	4 ml in 45 ml of 0.9% NaCl x 3
10	900	6 ml in 50 ml of 0.9% NaCl x 3
11	900	6 ml in 55 ml of 0.9% NaCl x 3
12	900	6 ml in 60 ml of 0.9% NaCl x 3
13	900	6 ml in 65 ml of 0.9% NaCl x 3
14	900	6 ml in 70 ml of 0.9% NaCl x 3
15	900	6 ml in 75 ml of 0.9% NaCl x 3
16	1200	8 ml in 80 ml of 0.9% NaCl x 3
17	1200	8 ml in 85 ml of 0.9% NaCl x 3
18	1200	8 ml in 90 ml of 0.9% NaCl x 3
19	1200	8 ml in 95 ml of 0.9% NaCl x 3
20	1200	8 ml in 100 ml of 0.9% NaCl x 3
21	1200	8 ml in 100 ml of 0.9% NaCl x 3
22	1200	8 ml in 100 ml of 0.9% NaCl x 3
23	1200	8 ml in 100 ml of 0.9% NaCl x 3
24	1650	11 ml in 100 ml of 0.9% NaCl x 3
25	1650	11 ml in 100 ml of 0.9% NaCl x 3
26	1650	11 ml in 100 ml of 0.9% NaCl x 3
27	1650	11 ml in 100 ml of 0.9% NaCl x 3
28	1650	11 ml in 100 ml of 0.9% NaCl x 3
29	1650	11 ml in 100 ml of 0.9% NaCl x 3
30-33	3000	3 vials (30 ml) in 100 ml of 0.9% NaCl x 2
34-40	3000	3 vials (30 ml) in 100 ml of 0.9% NaCl x 2
41-45	3000	3 vials (30 ml) in 100 ml of 0.9% NaCl x 2
46-50	3000	3 vials (30 ml) in 100 ml of 0.9% NaCl x 2
51-70	4000	4 vials (40 ml) in 100 ml of 0.9% NaCl x 2

> 70	4000	4 vials (40 ml) in 100 ml of 0.9% NaCl x 2
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### Contra-indications, adverse effects, precautions

- Do not administer to patients with hypersensitivity to carbapenems.
- Administer with caution to patients allergic to cephalosporins (cross-hypersensitivity may occur).
- May cause:
  - nausea, vomiting (the infusion rate may be slowed down in case of nausea), diarrhoea;
  - neurotoxicity: confusional state, seizures (rarely compared to imipenem/cilastatin, most frequently in patients with history of seizures or renal impairment);
  - hypersensitivity reactions;
  - local reactions (phlebitis/thrombophlebitis).
- For the management of adverse effects, see [Appendix 17](#).
- Avoid or monitor combination with valproic acid (decreased concentration of valproic acid and risk of seizures).
- **Pregnancy and breastfeeding:** avoid unless the benefits outweigh the risks.

### Monitoring

- Symptomatic monitoring.

### Remarks

- Administer clavulanic acid 60 minutes before each dose of meropenem.
- Do not mix with other drugs in the infusion bag.

### Storage

☼ – Below 25 °C

Once reconstituted, solution should be used immediately (within 1 hour of preparation)

# Moxifloxacin (Mfx)

Update: September 2022

## Forms and strengths

- 400 mg tablet
- 100 mg dispersible tablet, to be dispersed in 10 ml water

## Dosage (standard dose)

- Child under 30 kg: 10 to 15 mg/kg once daily
- Child 30 kg and over and adult: 400 mg once daily
- Maximum dose: 400 mg daily

<b>Weight (kg)</b>	<b>Daily dose (mg)</b>	<b>400 mg tablet</b>	<b>100 mg dispersible tablet</b>
5	50-75	-	7 ml
6	60-90	-	7 ml
7	70-105	-	1 tab
8	80-120	-	1 tab
9	90-135	-	1 tab
10	100-150	-	2 tab
11	110-165	-	2 tab
12	120-180	-	2 tab
13	130-195	-	2 tab
14	140-210	-	2 tab
15	150-225	-	2 tab
16	160-240	-	3 tab
17	170-255	-	3 tab
18	180-270	-	3 tab
19	190-285	-	3 tab
20	200-300	-	3 tab
21	210-315	-	3 tab
22	220-330	-	3 tab
23	230-345	-	3 tab
24	240-360	-	4 tab
25	250-375	-	4 tab
26	260-390	-	4 tab
27	270-405	-	4 tab
28	280-420	-	4 tab
29	290-435	-	4 tab
30-35	400	1 tab	-
36-45	400	1 tab	-
46-55	400	1 tab	-
56-70	400	1 tab	-
> 70	400	1 tab	-



## Contra-indications, adverse effects, precautions

- Do not administer to patients with hypersensitivity or tendon damage during a previous treatment with a fluoroquinolone.
- Administer with caution to patients:
  - over 60 years or on corticosteroid treatment (increased risk of tendon damage);
  - with diabetes or history of mental disorders or seizures.
- May cause:
  - tendinitis, tendon rupture, moderate QT prolongation;
  - gastrointestinal disturbances (abdominal or epigastric pain, diarrhoea);
  - neurological disorders (headache, psychosis, seizures, etc.);
  - photosensitivity;
  - hypersensitivity reactions, hypo/hyperglycaemia;
  - rarely: crystalluria, peripheral neuropathy, ototoxicity.
- For the management of adverse effects, see [Appendix 17](#).
- Avoid or use with caution and under close monitoring in patients taking other QT prolonging drugs ([Appendix 19](#)) or warfarin.
- Do not administer simultaneously with: antacids containing magnesium/aluminium, calcium, iron and zinc salts (administer 2 hours apart).
- **Pregnancy:**
  - DR-TB: use if benefits outweigh the risks (safety not established).
  - DS-TB: do not use.
- **Breastfeeding:**
  - DR-TB: avoid breastfeeding during treatment (no absolute contra-indication).
  - DS-TB: avoid breastfeeding during treatment.

## Monitoring

- Symptomatic monitoring

## Patient instructions

- Take 2 hours apart from milk-based product, antacids, calcium, iron and zinc salts.
- 100 mg tablets should be dispersed in 10 ml water.
- Maintain a good fluid intake.
- Protect your skin from sun.

## Remarks

- Higher dose moxifloxacin (Mfx<sup>h</sup>), i.e. 600 to 800 mg once daily in patients over 30 kg may be used in the presence of certain mutations conferring low level fluoroquinolone resistance. Mfx<sup>h</sup> may cause strong QT prolongation.

## Storage

☼ – ☰ – Below 25 °C

# Para-aminosalicylate sodium (PAS)

Update: October 2022

## Forms and strengths

- Powder for oral solution, 5.52 g sachet of para-aminosalicylate sodium (equivalent to 4 g PAS acid), to be dissolved in 100 ml water

## Dosage (expressed in PAS acid)

- Child under 30 kg: 100 to 150 mg/kg 2 times daily
- Child 30 kg and over and adult: 4 g 2 times daily (max. 12 g daily)

<b>Weight (kg)</b>	<b>Daily dose (mg)</b>	<b>Oral solution or sachet PAS sodium</b>
5	1000-1500	19 ml x 2
6	1200-1800	19 ml x 2
7	1400-2100	25 ml x 2
8	1600-2400	25 ml x 2
9	1800-2700	25 ml x 2
10	2000-3000	50 ml x 2
11	2200-3300	50 ml x 2
12	2400-3600	50 ml x 2
13	2600-3900	50 ml x 2
14	2800-4200	50 ml x 2
15	3000-4500	50 ml x 2
16	3200-4800	75 ml x 2
17	3400-5100	75 ml x 2
18	3600-5400	75 ml x 2
19	3800-5700	75 ml x 2
20	4000-6000	75 ml x 2
21	4200-6300	75 ml x 2
22	4400-6600	75 ml x 2
23	4600-6900	75 ml x 2
24	4800-7200	80 ml x 2
25	5000-7500	80 ml x 2
26	5200-7800	80 ml x 2
27	5400-8000	80 ml x 2
28	5600-8000	80 ml x 2
29	5800-8000	80 ml x 2
30-70	8 g	1 sachet x 2
> 70	8-12 g	1 to 1½ sachet x 2

### **Contra-indications, adverse effects, precautions**

- Avoid in patients with severe renal disease.
- Avoid or use with caution in patients with hepatic impairment or gastric ulcer.

- May cause :
  - frequent gastrointestinal disturbances (nausea, vomiting, gastritis, diarrhoea);
  - hypothyroidism, hepatotoxicity, hypersensitivity reactions.
- Monitor combination with ethionamide/prothionamide (increased risk of gastrointestinal disturbances and hypothyroidism).
- For the management of adverse effects, see [Appendix 17](#).
- **Pregnancy**: use only if benefits outweigh the risks (safety not established).<sup>p</sup>
- **Breastfeeding**: avoid breastfeeding during treatment (safety not established).

## Monitoring

- Symptomatic monitoring.
- Liver and thyroid function.

## Patient instructions

- Mix the powder with 100 ml water.
- Take with food to limit gastrointestinal disturbances.

## Remarks

- To increase gastrointestinal tolerance, start with a low dose, e. g. for an adult : 2 g 2 times daily for 1 to 2 weeks, then 4 g 2 times daily.

## Storage

☞ - ☞ - Below 25 °C

# Pretomanid (Pa)

Update: October 2022

## Forms and strengths

- 200 mg tablet

## Dosage

- Adolescent 15 years and over and adult: 200 mg once daily, in combination with:
  - bedaquiline, linezolid and moxifloxacin (BPaLM)
  - bedaquiline, linezolid and clofazimine (BPaLC)
  - bedaquiline and linezolid (BPaL)
- Maximum dose: 200 mg daily

Age	Daily dose (mg)	200 mg tablet
< 15 years	Do not administer	–
≥ 15 years	200	1

## Contra-indications, adverse effects, precautions

- Do not administer if one of the drugs included in the regimen is contraindicated.
- The contribution of pretomanid to the adverse effects of pretomanid-containing regimens is not determined.
- For adverse effects of companion drugs, see individual [drug information sheets](#).
- **Pregnancy:** use if benefits outweigh the risks (safety not established).
- **Breastfeeding:** avoid breastfeeding during treatment (safety not established).

## Monitoring

- Symptomatic monitoring.
- For monitoring of companion drugs, see individual [drug information sheets](#).

## Patient instructions

- Take with food.

## Storage

☼ – ☰ – Below 25 °C

# Pyrazinamide (Z)

Update: January 2022

## Forms and strengths

- 400 mg tablet
- 150 mg dispersible tablet, to be dispersed in 10 ml water

## Dosage

- Child under 30 kg: 35 mg/kg (30 to 40 mg/kg) once daily
- Child 30 kg and over and adult: 25 mg/kg (20 to 30 mg/kg) once daily
- Maximum dose: 2000 mg daily
- Renal insufficiency: 25 mg/kg 3 times a week

<b>Weight (kg)</b>	<b>Daily dose (mg)</b>	<b>400 mg tablet</b>	<b>150 mg dispersible tablet</b>
5	150-200	–	1 tab
6	180-240	–	1 tab
7	210-280	–	2 tab
8	240-320	–	2 tab
9	270-360	–	2 tab
10	300-400	–	3 tab
11	330-440	–	3 tab
12	360-480	–	3 tab
13	390-520	–	3 tab
14	420-560	–	3 tab
15	450-600	–	3 tab
16	480-640	–	4 tab
17	510-680	–	4 tab
18	540-720	–	4 tab
19	570-760	–	4 tab
20	600-800	–	5 tab
21	630-840	–	5 tab
22	660-880	–	5 tab
23	690-920	–	5 tab
24	720-960	2½ tab	–
25	750-1000	2½ tab	–
26	780-1040	2½ tab	–
27	810-1080	2½ tab	–
28	840-1120	2½ tab	–
29	870-1160	2½ tab	–
30-35	800	2 tab	–
36-45	1000	2½ tab	–
46-55	1200	3 tab	–
56-70	1600	4 tab	–
> 70	2000	5 tab	–

## Contra-indications, adverse effects, precautions

- Do not administer to patients with hypersensitivity to pyrazinamide, severe hepatic impairment or severe gout.
- May cause: gout and arthralgias, hepatotoxicity, gastrointestinal disturbances (epigastric pain, nausea and vomiting), hypersensitivity reactions; rarely, photosensitivity.
- For the management of adverse effects, see [Appendix 17](#).
- **Pregnancy:** no contra-indication
- **Breastfeeding:** no contra-indication

## Monitoring

- Symptomatic monitoring.
- Liver function in patients with hepatic impairment or under drug-resistant TB treatment.

## Patient instructions

- Take with or without food.
- 150 mg tablets should be dispersed in 10 ml water.
- Protect your skin from sun.

## Remarks

- For patients on drug-susceptible TB treatment, pyrazinamide is given as part of a fixed-dose combination.
- For the 6HRZ-Eto regimen for drug-susceptible TB meningitis, the dose of pyrazinamide is 40 mg/kg once daily (max. 2000 mg daily).

## Storage

☞ - ☞ - Below 25 °C



# Rifabutin (Rfb)

Update: January 2022

## Forms and strengths

- 150 mg capsule

## Dosage

- Child and adult: 5 to 10 mg/kg once daily
- Maximum dose: 300 mg daily

<b>Weight (kg)</b>	<b>Daily dose (mg)</b>	<b>150 mg capsule</b>
5	25-50	-
6	30-60	-
7	35-70	-
8	40-80	-
9	45-90	-
10	50-100	-
11	55-110	-
12	60-120	-
13	65-130	-
14	70-140	-
15	75-150	<b>1 caps</b>
16	80-160	<b>1 caps</b>
17	85-170	<b>1 caps</b>
18	90-180	<b>1 caps</b>
19	95-190	<b>1 caps</b>
20	100-200	<b>1 caps</b>
21	105-210	<b>1 caps</b>
22	110-220	<b>1 caps</b>
23	115-230	<b>1 caps</b>
24	120-240	<b>1 caps</b>
25	125-250	<b>1 caps</b>
26	130-260	<b>1 caps</b>
27	135-270	<b>1 caps</b>
28	140-280	<b>1 caps</b>
29	145-290	<b>1 caps</b>
30-35	300	<b>2 caps</b>
36-45	300	<b>2 caps</b>
46-55	300	<b>2 caps</b>
56-70	300	<b>2 caps</b>
> 70	300	<b>2 caps</b>

## Contra-indications, adverse effects, precautions

- Do not administer to patients with hypersensitivity to rifamycins or history of severe haematological disorders (thrombocytopenia, purpura) during a previous treatment with a rifamycin.
- Administer with caution to patients with severe renal impairment or hepatic or haematological disorders.
- May cause:
  - gastrointestinal disturbances, hepatotoxicity;
  - haematological disorders (leukopenia, anaemia, thrombocytopenia), hypersensitivity reactions;
  - reversible uveitis.
- For the management of adverse effects, see [Appendix 17](#).
- Reduce the dose of rifabutin:
  - in patients taking boosted protease inhibitors ([Appendix 19](#));
  - if rifabutin toxicity is suspected in patients taking clarithromycin, fluconazole or itraconazole.
- Rifabutin reduces the effect of many drugs (macrolides, some antiretrovirals, some hormones, warfarin, etc.):
  - in patients taking antiretrovirals, see [Appendix 19](#);
  - in women using contraception, use injectable medroxyprogesterone or an intrauterine device;
  - for the other drugs, adjust dosage if necessary.
- **Pregnancy and breastfeeding:** avoid (safety not established). If used in late pregnancy, administer phytomenadione (vitamin K<sub>1</sub>) to the mother and the neonate.

## Monitoring

- Symptomatic monitoring.
- Liver function in patients with hepatic disease.
- Full blood count.

## Patient instructions

- Take with or without food.
- Harmless orange-red discoloration of the urine, faeces, sweat, saliva, sputum, tears and other body fluids.

## Storage

☼ – ☰ – Below 25 °C

# Rifampicin (R)

Update: January 2022

## Forms and strengths

- 300 mg capsule and 150 mg tablet

## Dosage

- Child under 30 kg: 15 mg/kg (10 to 20 mg/kg) once daily
- Child 30 kg and over and adult: 10 mg/kg (8 to 12 mg/kg) once daily
- Maximum dose: 600 mg daily
- Hepatic impairment: 8 mg/kg once daily max.

<b>Weight (kg)</b>	<b>Daily dose (mg)</b>	<b>300 mg capsule</b>	<b>150 mg tablet</b>
5	50-100	–	½ tab
6	60-120	–	½ tab
7	70-140	–	½ tab
8	80-160	–	1 tab
9	90-180	–	1 tab
10	100-200	–	1 tab
11	110-220	–	1 tab
12	120-240	–	1 tab
13	130-260	–	1½ tab
14	140-280	–	1½ tab
15	150-300	–	1½ tab
16	160-320	1 tab	–
17	170-340	1 tab	–
18	180-360	1 tab	–
19	190-380	1 tab	–
20	200-400	1 tab	–
21	210-420	1 tab	–
22	220-440	1 tab	–
23	230-460	1 tab	–
24	240-480	1 tab	–
25	250-500	1 tab	–
26	260-520	1 tab	–
27	270-540	1 tab	–
28	280-560	1 tab	–
29	290-580	1 tab	–
30-35	300	1 tab	–
36-45	450	1½ tab	–
46-55	450	1½ tab	–
56-70	600	2 tab	–
> 70	600	2 tab	–

## Contra-indications, adverse effects, precautions

- Do not administer to patients with hypersensitivity to rifamycins or history of severe haematological disorders (thrombocytopenia, purpura) during a previous treatment with a rifamycin.
- Avoid or administer with caution to patients with hepatic disorders.
- May cause:
  - hepatotoxicity;
  - influenza-like symptoms, thrombocytopenia, hypersensitivity reactions.
- For the management of adverse effects, see [Appendix 17](#).
- Rifampicin reduces the effect of many drugs (antimicrobials, some antiretrovirals, some hormones, antidiabetics, corticosteroids, phenytoin, direct-acting antivirals for chronic hepatitis C, warfarin, etc.):
  - in patients taking antiretrovirals, see [Appendix 19](#);
  - in women using contraception, use injectable medroxyprogesterone or an intrauterine device;
  - in the event of concomitant fluconazole administration, administer each drug 12 hours apart (rifampicin in the morning, fluconazole in the evening);
  - for the other drugs, adjust dosage if necessary.
- **Pregnancy and breastfeeding:** no contra-indication. If used in late pregnancy, administer phytomenadione (vitamin K<sub>1</sub>) to the mother and the neonate.

## Monitoring

- Symptomatic monitoring.
- Liver function in patients with hepatic disease.

## Patient instructions

- Take without food (or with a small amount of food to increase gastrointestinal tolerance).
- Harmless orange-red discoloration of the urine, faeces, sweat, saliva, sputum, tears and other body fluids.

## Remarks

- For patients on drug-susceptible TB treatment, rifampicin is given as part of a fixed-dose combination.
- For the 6HRZ-Eto regimen for drug-susceptible TB meningitis, the dose of rifampicin is 20 mg/kg once daily (max. 600 mg daily).
- Rifampicin is also used in the treatment of latent TB infection.

## Storage

☼ - ☰ - Below 25 °C

# Rifapentine (P)

Update: October 2022

## Forms and strengths

- 300 mg and 150 mg coated tablets

## Dosage

- Child 12 years and over and adult 40 kg and over: 1200 mg once daily

Age	Daily dose (mg)	300 mg tablet
< 12 years	Do not administer	–
≥ 12 years	1200	4

## Contra-indications, adverse effects, precautions

- Do not administer to patients with hypersensitivity to rifamycins or history of severe haematological disorders (thrombocytopenia, purpura) during a previous treatment with rifamycins.
- Avoid or administer with caution to patients with hepatic disorders.
- May cause:
  - hepatotoxicity;
  - influenza-like symptoms, thrombocytopenia, hypersensitivity reactions.
- For the management of adverse effects see [Appendix 17](#).
- Rifapentine reduces the effect of many drugs (antimicrobials, some antiretrovirals, some hormones, antidiabetics, corticosteroids, phenytoin, direct-acting antivirals for chronic hepatitis C, warfarin, etc.):
  - in patients taking antiretrovirals see [Appendix 19](#).
  - in women using contraception, use injectable medroxyprogesterone or an intrauterine device;
  - in the event of concomitant fluconazole administration, administer each drug 12 hours apart (rifampicin in the morning, fluconazole in the evening);
  - for the other drugs, adjust dosage if necessary.
- **Pregnancy and breastfeeding:** not recommended (safety not established).

## Monitoring

- Symptomatic monitoring.
- Liver function in patients with hepatic disease.

## Patient instructions

- Take with food.
- Harmless orange-red discoloration of the urine, faeces, sweat, saliva, sputum, tears and other body fluids.

## Remarks

- While rifampicin should be taken on an empty stomach, rifapentine is better absorbed if taken with food.
- Also comes in fixed dose combination containing 300 mg of rifapentine/300 mg of isoniazid which can be used in the treatment regimen 2HPZ-Mfx/2HP-Mfx for drug-susceptible TB.
- Rifapentine is also used in the treatment of latent TB infection in children, adolescents, and adults.

## Storage

☞ – ☞ – Below 25 °C

# Streptomycin (S)

Update: January 2022

## Forms, strengths and route of administration

- Powder for injection, in vial of 1 g streptomycin base, to be dissolved in 4 ml of water for injection, for IM injection  
DO NOT ADMINISTER BY IV INJECTION.

## Dosage

- Adolescent 30 kg and over and adult: 12 to 18 mg/kg once daily
- Adult 60 years and over: 15 mg/kg 3 times a week
- Maximum dose: 1000 mg daily
- Renal insufficiency: 12 to 15 mg/kg 2 or 3 times a week

The daily doses take into account the displacement volume (see note below).

Weight (kg)	Daily dose (mg)	Daily dose (ml) - IM injection (1 g in 4 ml of water for injection; final volume 4.83 ml; 207 mg/ml)
5-29	Not used in patients < 30 kg	
30-33	500	2.4 ml
34-40	600	2.8 ml
41-45	700	3.4 ml
46-50	800	4 ml
51-70	900	4.4 ml
> 70	1000	Entire volume

**Note:** displacement volume

Powders for injection are usually formulated such that after reconstitution the final content of the vial corresponds to an adult dose. Errors may occur when only part of the reconstituted solution is to be administered and no allowance is made for the displacement volume. The risk of error increases the greater the weight of the powder and the smaller the volume of solvent used.

## Contra-indications, adverse effects, precautions

- Do not administer to children or adolescents under 30 kg and patients with allergy to aminoglycosides.
- Administer with caution to patients 60 years and over or patients with pre-existing renal, vestibular, auditory or severe hepatic impairment.
- May cause:
  - ototoxicity, nephrotoxicity, electrolyte disturbances; rarely, hypersensitivity reactions;
  - local pain after injection.
- For the management of adverse effects, see [Appendix 17](#).
- Avoid or monitor combination with other ototoxic and/or nephrotoxic drugs (furosemide, amphotericin B, tenofovir, etc.)
- **Pregnancy:** CONTRA-INDICATED
- **Breastfeeding:** no contra-indication

## Monitoring

- Symptomatic monitoring.
- Audiometry, serum creatinine and electrolytes (K, Ca, Mg).

## Patient instructions

- Maintain a good fluid intake to limit renal problems.



## Remarks

- Use a different site for each injection (absorption may be delayed if the same site is used repeatedly).

## Storage

☼ – Below 25 °C

# Patient instructions

Update: January 2022

- [Patients on drug-susceptible TB treatment](#)
- [Patients on drug-resistant TB treatment](#)

# Patients on drug-susceptible TB treatment

TB drugs are usually well tolerated. However, inform patients that they should immediately seek medical attention in the event of:

- Skin rash
- Yellowing of the skin or eyes or dark urine
- Numbness or tingling of fingers or toes
- Decreased urination
- Palpitations
- Blurred vision, reduced visual acuity, blind spot, green-red colour blindness, eye pain, sensitivity to light
- Pain, burning, swelling of a tendon or muscle
- Pain or swelling in the joints

# Patients on drug-resistant TB treatment

Inform patients that they should immediately seek medical attention in the event of:

- Skin rash
- Yellowing of the skin or eyes or dark urine
- Numbness or tingling of fingers or toes
- Decreased urination
- Palpitations
- Dizziness or hearing loss
- Blurred vision, reduced visual acuity, blind spot, green-red colour blindness, eye pain, sensitivity to light
- Muscle cramps, spasms, or weakness
- Pain, burning, swelling of a tendon or muscle
- Pain or swelling in the joints
- Personality changes (depression, aggressive behaviour, anxiety)
- Severe abdominal upset or severe nausea, vomiting, black or bloody stools
- Unusual bleeding

# Appendix 11. TB drugs in pregnant or breastfeeding women

Update: October 2022

TB drugs	Evidence and recommendations
<b>FQs</b>	For DS-TB: do not use the regimen 2HPZ-Mfx/2HP-Mfx in pregnant or breastfeeding women.
	For DR-TB: commonly used in pregnant women despite limited data. Associated with low birth weight in one observational study <sup>[1]</sup> . As FQs reduce mortality from DR-TB, the benefits often outweigh the risks. Avoid breastfeeding if possible <sup>[2]</sup> (no absolute contra-indication).
<b>Bdq</b>	No evidence of fetal harm in animal studies. Associated with low birth weight in one observational study <sup>[1]</sup> . As Bdq reduces mortality from DR-TB, the benefits often outweigh the risks. Avoid breastfeeding if possible (high concentrations in human and animal breast milk) <sup>[3][4]</sup> .
<b>Lzd</b>	Few reported cases of use in pregnant women. Fetal harm in animal studies. As Lzd reduces mortality from DR-TB, the benefits often outweigh the risks. Avoid breastfeeding if possible (no data).
<b>Cfz</b>	Despite common use for leprosy and MDR-TB in pregnant women, few data on pregnancy outcomes. Fetal harm in animal studies. Use during pregnancy only if the benefits outweigh the risks. Avoid breastfeeding if possible (no data). If used, inform mother of possible (and reversible) skin discolouration of the breastfed infant.
<b>Cs, Trd</b>	Use during pregnancy only if the benefits outweigh the risks (no data). No contra-indication during breastfeeding.
<b>Dlm</b>	Use during pregnancy only if benefits outweigh the risks (limited human data, fetal harm in animal studies). Avoid breastfeeding if possible (high concentrations in animal breast milk).
<b>Ipm/Cln, Mpm</b>	Use during pregnancy and breastfeeding only if the benefits outweigh the risks (no data).
<b>Am, S</b>	Contra-indicated in pregnancy. No contra-indication during breastfeeding <sup>[2]</sup> .
<b>Eto, Pto</b>	For DS-TB: do not use the regimen 6HRZ-Eto in pregnant or breastfeeding women.
	For DR-TB: contra-indicated in pregnancy (fetal harm in animal studies <sup>[5]</sup> ). In breastfeeding women, use only if the benefits outweigh the risks (limited data).
<b>PAS</b>	Use in pregnancy only if the benefits outweigh the risks (limited human data, no fetal harm in animal studies). Avoid breastfeeding if possible (no data).
<b>R, Z, H, E</b>	No contra-indication during pregnancy and breastfeeding.
<b>Pa</b>	Use during pregnancy and breastfeeding only if the benefits outweigh the risks (no human data, no fetal harm in animal studies <sup>[6]</sup> ).
<b>P, Rfb</b>	Not recommended during pregnancy and breastfeeding.

For more specific recommendations for pregnant and breastfeeding women, see [Chapter 9](#), [Chapter 10](#), [Chapter 11](#), and [Appendix 10](#).

## References

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# Appendix 12. Dose adjustments in renal insufficiency

Update: January 2022

## 12.1 Normal values for creatinine clearance (CrCl)

Women: 88 to 128 ml/minute

Men: 97 to 137 ml/minute

## 12.2 Estimation of CrCl (Cockcroft-Gault method)

### 12.2.1 If serum creatinine is in $\mu\text{mol/litre}$

$$\frac{\text{Weight (kg)} \times (140 - \text{age}) \times (\text{constant})}{\text{Serum creatinine } (\mu\text{mol/litre})}$$

The constant = 1.04 for women and 1.23 for men

### 12.2.2 If serum creatinine is in mg/dl

$$\frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/dl)}}$$

For women, the result must be multiplied by 0.85.

Example (calculation with serum creatinine in  $\mu\text{mol/litre}$ )<sup>a</sup>:

A woman on cycloserine (Cs), 50 kg, 46 years, serum creatinine = 212  $\mu\text{mol/litre}$

- **Step 1** - Calculate the CrCl:

$$50 \times (140 - 46) \times 1.04 = 4,888$$

$$4,888 \div 212 = 23.1$$

For this patient, the CrCl is 23.1 ml/minute

- **Step 2** - CrCl is < 30 ml/minute, administer 250 mg of Cs once daily or 500 mg 3 times a week.
- **Step 3** - Adjust each drug as required according to the table below.

### 12.2.3 Overweight and obese patients

For overweight (BMI > 25) or obese (BMI > 30) patients, use the ideal body weight (IBW) rather than the actual body weight to avoid overestimation of the CrCl.

The IBW is calculated using the patient's height<sup>b</sup>:

$$\text{IBW women (kg)} = 45.4 + 0.89 (\text{height in cm} - 152.4)$$

$$\text{IBW men (kg)} = 49.9 + 0.89 (\text{height in cm} - 152.4)$$

Example:

A woman, weight 70 kg, height 160 cm (BMI = 27.3, i.e. overweight)

$$45.4 + 0.89 (160 - 152.4) = 45.4 + 0.89 (7.6) = 45.4 + 6.76 = 52.2$$

For this patient, the IBW is 52 kg.

## 12.3 Dosing of TB drugs in renal insufficiency

Drugs	Dose and frequency if CrCl < 30 ml/min
H	No change
R	No change
Z	25 mg/kg 3 times a week (not daily)
E	15-25 mg/kg 3 times a week (not daily)
Rfb	No change
Mfx	No change
Lfx	750-1000 mg 3 times a week (not daily)
Bdq <sup>(a)</sup>	No change
Lzd	No change
Cfz	No change
Cs <sup>(b)</sup>	250 mg once daily or 500 mg 3 times a week
Dlm <sup>(a)</sup>	No change
lpm/Cln	750 mg every 12 hours for CrCl 20-40 ml/min 500 mg every 12 hours for CrCl < 20 ml/min
Mpm	750 mg every 12 hours for CrCl 20-40 ml/min 500 mg every 12 hours for CrCl < 20 ml/min
Am <sup>(c)</sup>	12-15 mg/kg 2 or 3 times a week (not daily)
S <sup>(c)</sup>	12-15 mg/kg 2 or 3 times a week (not daily)
Eto/Pto	No change
PAS <sup>(d)</sup>	4 g 2 times daily
H <sup>h</sup>	No information
Amx/Civ <sup>(e)</sup>	No change
P	No change
Pa	No information

(a) Use with caution in case of severe renal insufficiency or dialysis (limited data).

(b) Monitor carefully for signs of neurotoxicity.

(c) Use with caution in case of severe renal insufficiency or dialysis (increased risk of nephrotoxicity and ototoxicity).

(d) Avoid sodium salt formulations of PAS in patients with severe renal disease (risk of excessive sodium load).

(e) On a case-by-case basis, consider once daily dosing (e.g. 500/125 mg every 24 hours) for patients with CrCl < 10 ml/minute.

## Footnotes

(a) If possible use a calculator to avoid errors, e.g.:

<https://www.mdcalc.com/creatinine-clearance-cockcroft-gault-equation>

(b) If possible use a calculator to avoid errors, e.g.:

<https://www.mdcalc.com/ideal-body-weight-adjusted-body-weight>



# Appendix 13. Daily dose of TB drugs using fixed-dose combinations

Update: October 2022

## 13.1 Conventional regimens for drug-susceptible tuberculosis

### Intensive phase

Weight (kg)	Paediatric formulations		Adult formulations		
	HZR 50/150/75 mg	E 100 mg	E 400 mg	H 100 mg	EHZR 275/75/400/150 mg
4-7	1 tab	1 tab	–	–	–
8-11	2 tab	2 tab	–	–	–
12-13	3 tab	2 tab	–	–	–
14-15	3 tab	3 tab	–	–	–
16-17	4 tab	3 tab	–	–	–
18-22	4 tab	–	1 tab	–	–
23-29	–	–	–	1 tab	2 tab
30-34	–	–	–	–	2 tab
35-39	–	–	–	–	2½ tab
40-54	–	–	–	–	3 tab
55-70	–	–	–	–	4 tab
> 70	–	–	–	–	4 tab

For example:

- A child weighing 9 kg takes 2 tablets of HZR (50 mg/150 mg/75 mg) + 2 tablets of E (100 mg) once daily.
- A child weighing 20 kg takes 4 tablets of HZR (50 mg/150 mg/75 mg) + 1 tablet of E (400 mg) once daily.

**Note:** ethambutol is not routinely given to all children: see [Chapter 9](#).

### Continuation phase

Weight (kg)	Paediatric formulation HR 50/75 mg	Adult formulation HR 75/150 mg
4-7	1 tab	–
8-11	2 tab	–
12-14	3 tab	–
15-21	–	2 tab
22-29	–	3 tab
30-34	–	2 tab
35-39	–	3 tab
40-54	–	3 tab
55-70	–	4 tab
> 70	–	4 tab

TB drugs	Daily dosing in patients < 30 kg	Daily dosing in patients ≥ 30 kg
E	15 to 25 mg/kg	15 to 25 mg/kg
H	7 to 15 mg/kg	4 to 6 mg/kg
Z	30 to 40 mg/kg	20 to 30 mg/kg
R	10 to 20 mg/kg	8 to 12 mg/kg

### 13.2 2HPZ-Mfx/2HP-Mfx regimen for drug-susceptible tuberculosis

Weight (kg)	HP 300/300 mg	P 300 mg	Z 400 mg	Mfx 400 mg
40-49	1 tab	3 tab	4 tab	1 tab
50-64	1 tab	3 tab	4 tab	1 tab
≥ 65	1 tab	3 tab	5 tab	1 tab

TB drugs	Daily dosing in patients < 40 kg	Daily dosing in patients ≥ 40 kg
H	–	300 mg
Z	–	1600 to 2000 mg
P	–	1200 mg
Mfx	–	400 mg

# Appendix 14. Monitoring of patients on drug-susceptible TB treatment

Update: October 2022

A cross "X" with no brackets indicates that the exam should be performed in all patients.

A cross between brackets "(X)" indicates that the exam should only be performed in certain patients.

	Baseline	Treatment								End of treatment	
		W2	M1	M2	M3	M4	M5	M6	Until end of treatment <sup>(a)</sup>		
<b>Clinical visits</b>											
Vital signs, weight, etc.	X	X	X	X	X	X	X	X	X	At each visit	X
Adverse events		X	X	X	X	X	X	X	X	At each visit	X
<b>Bacteriological tests</b>											
Rapid molecular tests <sup>(b)</sup>	X			(X)							
Smear microscopy	X			X		X			X		X
Culture and pDST <sup>(c)</sup>	(X)			(X)		(X)					
<b>Other investigations</b>											
Radiography <sup>(d)</sup>	(X)								(X)	If indicated	If indicated
Full blood count <sup>(e)</sup>	(X)		(X)	(X)						If indicated	
Liver function <sup>(f)</sup>	(X)		(X)	(X)	(X)	(X)	(X)	(X)		If indicated	
Serum creatinine <sup>(g)</sup>	(X)									If indicated	
HbA1c, blood glucose <sup>(h)</sup>	X									If indicated	
HIV, HBV, HCV <sup>(i)</sup>	X								(X)	If indicated	
CD4 and viral load <sup>(i)</sup>	(X)								(X)		(X)

(a) For treatments longer than 6 months.

(b) Rapid molecular tests:

- Xpert MTB/RIF (or Ultra) and Xpert MTB/XDR (or GenoType MTBDRs/if Xpert MTB/XDR not available).
- Repeat RMTs if microscopy or culture is positive at Month 2 or later.

(c) Culture and pDST to first- and second-line drugs:

- At baseline if RMTs are not available, to detect rifampicin and isoniazid resistance or rifampicin resistance mutations not detected by RMTs.
- At Month 2 or later, if RMTs show a new resistance.
- At Month 4, if microscopy is still positive.

(d) Radiography:

- Chest: at baseline for children with presumptive PTB, patients with non-bacteriologically confirmed PTB, suspicion of other intra-thoracic TB, then if indicated (e.g. worsening respiratory symptoms, non-response to TB treatment).
- Bone: at baseline then every 6 months for patients with bone and joint TB.

(e) For patients on AZT or rifabutin.

- (f) For patients with pre-existing hepatic disease: AST and ALT (and bilirubin if AST or ALT are elevated).
- (g) For patients with renal insufficiency.
- (h) For all patients to detect diabetes. If diabetes is detected, monitor according to standard protocols.
- (i) For all patients, unless documented HIV, hepatitis B and C status; HIV test every 6 months in high HIV prevalence areas.
- (j) For HIV-infected patients.

# Appendix 15. Monitoring of patients on drug-resistant TB treatment

Update: June 2023

A cross "X" with no brackets indicates that the exam should be performed in all patients.

A cross between brackets "(X)" indicates that the exam should only be performed in certain patients.

	Baseline	Treatment										End of treatment	Post treatment <sup>(a)</sup>	
		W1	W2	W3	W4	W5	W6	W7	M2	M3	Until end of treatment		M6	M12
<b>Clinical visits</b>														
Vital signs, weight, etc.	X	X	X	X	X		X		X	X	At each visit	X	X	X
Adverse events		X	X	X	X		X		X	X	At each visit	X	X	X
BPNS <sup>(b)</sup>	(X)				(X)				(X)	(X)	(Monthly)	(X)		(X)
Visual function tests <sup>(c)</sup>	(X)				(X)				(X)	(X)	(Monthly)	(X)		(X)
Audiometry <sup>(d)</sup>	(X)				(X)				(X)	(X)	(Monthly)	(X)		(X)
ECG <sup>(e)</sup>	(X)	(X)	(X)	(X)	(X)				(X)	(X)	(Monthly)			
<b>Bacteriological tests</b>														
Smear microscopy	X				X				X	X	Monthly	X	X	X
Culture	X				X				X	X	Monthly	X	X	X
Rapid molecular tests <sup>(f)</sup>	X										If culture or microscopy positive at M4 or later			
Full pDST <sup>(g)</sup>	X										If culture positive at M4 or later			
<b>Other investigations</b>														
Radiography <sup>(h)</sup>	X										(Every 6 months)	X		
Full blood count <sup>(i)</sup>	X		(X)		(X)				(X)	(X)	(Monthly)	(X)		
Liver function <sup>(i)</sup>	X				(X)				(X)	(X)	(Monthly)			
Serum creatinine and potassium <sup>(k)</sup>	X				(X)				(X)	(X)	(Monthly)			
HbA1c, blood glucose <sup>(l)</sup>	X													
HIV, HBV, HCV <sup>(m)</sup>	X										If indicated			
CD4 and viral load <sup>(n)</sup>	(X)										(Every 6 months)			
TSH <sup>(o)</sup>	(X)									(X)	(Every 3 months)			
Pregnancy test <sup>(p)</sup>	X										If indicated			

(a) For patients on BPaLM or BPaL regimen.

(b) For patients on Lzd.

(c) For patients on E, Lzd or thionamides: visual acuity and colour vision deficiency.

(d) For patients on Am or S.

(e) Electrocardiogram, for patients taking:

• < 2 moderate or severe QT-prolonging TB drugs or < 3 QT-prolonging drugs (TB and non-TB): at baseline then monthly.

• ≥ 2 moderate or severe QT-prolonging TB drugs or ≥ 3 QT-prolonging drugs (TB and non-TB) or with other risk factors for QT prolongation or TdP: once a week for the first month, then once a month.

- (f) Rapid molecular tests:
  - Xpert MTB/RIF (or Ultra) and Xpert MTB/XDR (or GenoType MTBDRs/if Xpert MTB/XDR not available).
  - Repeat Xpert MTB/XDR (or GenoType MTBDRs) if culture or microscopy is positive at Month 4 or later.
- (g) For first- and second-line drugs. Repeat if culture is positive at Month 4 or later.
- (h) At baseline, then every 6 months:
  - Chest: for patients with PTB,
  - Bone: for patients with osteoarticular or spinal TB.
- (i) For all patients at baseline, then:
  - Patients on Lzd: every 2 weeks for the first 2 months, then once a month.
  - Patients on AZT: once a month for the first 2 months, then if indicated.
- (j) For all patients: AST and ALT (and bilirubin if AST or ALT are elevated).
- (k) For all patients at baseline. Repeat if indicated. For patients on Am or S: once a month or more frequently if indicated.
- (l) For all patients to detect diabetes. If diabetes is detected, monitor according to standard protocols.
- (m) For all patients, unless documented HIV, hepatitis B and C status; HIV test every 6 months in high HIV prevalence areas.
- (n) For HIV-infected patients.
- (o) For patients on thionamides or PAS.
- (p) For adolescents and women of childbearing age. Repeat if indicated.

# Appendix 16. Additional investigations in drug-resistant TB

Update: October 2022

## 16.1 Electrocardiogram (ECG)

The QT interval is measured in milliseconds (ms) from the start of the QRS complex to the end of the T wave of the ECG. Its value varies depending on the heart rate and should be corrected accordingly (QTc).

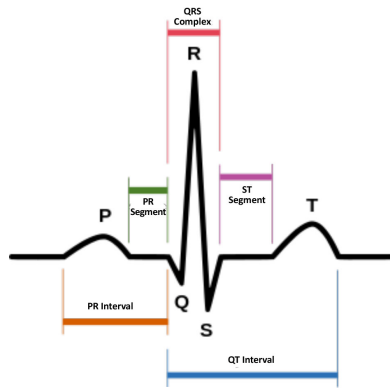
To calculate the QTc interval it is recommended to use the Fridericia formula (QTcF)<sup>a</sup>:

QTcF = QT interval divided by cube root of the interval between two waves R

Normal QTc values:

< 470 ms in women

< 450 ms in men



$$QTcF = \frac{QT}{\sqrt[3]{RR}}$$

## 16.2 Brief peripheral neuropathy screen (BPNS)

Adapted from AIDS Clinical Trial Group (ACTG)<sup>[1][2]</sup>.

### Step 1. Grade subjective symptoms

- Ask the patient to rate the severity of symptoms on a scale from 0 (no symptoms) to 10 (most severe symptoms) for right (R) and left (L) feet and legs.
- Enter the score for each symptom in the corresponding column.

Symptoms	R	L
a. Pain or burning sensation		
b. Pins and needles sensation (tingling sensation)		
c. Numbness (lack of feeling)		

Symptoms may be unilateral or bilateral and of different intensity. Use the highest subjective sensory neuropathy score to obtain the severity grade.

Subjective sensory neuropathy score	Severity grade
0	0
1-3	1
4-6	2
7-10	3



## Step 2. Evaluate vibration perception

- Place the vibrating 128 Hz tuning fork on the top of the distal joint of the right and left big toes and begin counting the seconds.
- Ask the patient to say when they no longer feel the vibration.

There is a decrease in vibration perception if the patient feels the vibration for 10 seconds or less on both sides.

Vibration perception	Result	Grade
Felt > 10 seconds	Normal	0
Felt 6-10 seconds	Mild loss	1
Felt < 5 seconds	Moderate loss	2
Not felt	Severe loss	3

## Step 3. Evaluate tendon reflexes

Using a reflex hammer, tap the Achilles tendon on each ankle.

## Step 4. Make a diagnosis

Diagnosis of peripheral neuropathy is based on the combination of:

- subjective symptoms of grade 1, 2 or 3, and
- at least one bilateral objective finding:
  - reduced vibration perception (grade 1, 2 or 3), or
  - decreased reflexes (absent or hypoactive reflexes)

## 16.3 Ishihara test

The patient is asked to look at a set of plates with circles made of dots of different sizes and colours.

Some circles contain dots that form a number or a shape clearly visible to patients with normal colour vision. Patients who cannot see or have difficulty distinguishing numbers or shapes have a red-green colour vision defect.

Some circles contain dots that form a number or a shape visible to patients with red-green colour vision defect, but invisible to patients with normal colour vision.

The test should be performed as per the manufacturer's instructions.

## Footnotes

- (a) When possible, use a calculator to avoid errors, e.g. <https://www.mdcalc.com/corrected-qt-interval-qt-c>

## References

1. Catherine L. Cherry, Steven L. Wesselingh, Luxshimi Lal, Justin C. McArthur. *Evaluation of a clinical screening tool for HIV-associated sensory neuropathies*. Neurology Dec 2005, 65 (11) 1778-1781. <https://n.neurology.org/content/65/11/1778.long>
2. Mawuntu, Arthur H.P. Mahama, Corry N. et al. *Early detection of peripheral neuropathy using stimulated skin wrinkling test in human immunodeficiency virus infected patients; A cross-sectional study*. Medicine: July 2018 - Volume 97 - Issue 30. [https://journals.lww.com/md-journal/Fulltext/2018/07270/Early\\_detection\\_of\\_peripheral\\_neuropathy\\_using\\_28.aspx](https://journals.lww.com/md-journal/Fulltext/2018/07270/Early_detection_of_peripheral_neuropathy_using_28.aspx)

# Appendix 17. Management of adverse effects

Update: January 2022

- [Gastrointestinal disorders](#)
  - [Abdominal pain](#)
  - [Diarrhoea](#)
  - [Epigastric pain](#)
  - [Hepatotoxicity](#)
  - [Metallic taste](#)
  - [Nausea and vomiting](#)
- [Neurotoxicity](#)
  - [Depression](#)
  - [Headache](#)
  - [Optic neuritis](#)
  - [Ototoxicity](#)
  - [Peripheral neuropathy](#)
  - [Psychosis](#)
  - [Seizures](#)
- [Endocrine disorders](#)
  - [Gynecomastia](#)
  - [Hypothyroidism](#)
- [Dermatological disorders](#)
  - [Alopecia](#)
  - [Fungal infection](#)
  - [Photosensitivity](#)
  - [Skin reactions](#)
- [Musculoskeletal disorders](#)
  - [Arthralgias](#)
  - [Tendinitis/tendon rupture](#)
- [Miscellaneous](#)
  - [Electrolyte disorders](#)
  - [Haematologic disorders](#)
  - [Lactic acidosis](#)
  - [Nephrotoxicity](#)
  - [QT prolongation](#)

# Gastrointestinal disorders

- [Abdominal pain](#)
- [Diarrhoea](#)
- [Epigastric pain](#)
- [Hepatotoxicity](#)
- [Metallic taste](#)
- [Nausea and vomiting](#)

# Abdominal pain

**Eto or Pto, PAS, Cfz, Lzd, FQs, H, Z**

Abdominal pain is common with MDR/RR-TB treatment. It can be the early sign of severe adverse effects such as hepatitis, pancreatitis, or lactic acidosis.

Deposition of Cfz crystals may cause severe abdominal pain (presentation of acute abdomen). In this case, stop Cfz until symptoms resolve.

# Diarrhoea

## PAS, FQs, Eto or Pto, Amx/Clv, Ipm/Cln or Mpm

Diarrhoea, along with cramping, can cause significant difficulty and lead to discontinuation of treatment.

PAS often causes diarrhoea at treatment initiation. It usually resolves or improves substantially after some weeks.

For diarrhoea with no blood in stools and no fever, **loperamide** PO (adult: 4 mg followed by 2 mg after each loose stool to a maximum of 10 mg daily) may be used intermittently, especially when the patient needs to attend social functions or return to work, but not on a daily basis.

Encourage the patient to tolerate some degree of diarrhoea. Prevent (encourage fluid intake including oral rehydration solution) or treat dehydration.

In the event of severe diarrhoea, particularly if associated with blood in stools, severe abdominal pain, or fever > 38.5 °C, consider other causes such as acute bacterial enteritis, or pseudo-membranous colitis (*C. difficile*) due to FQs. Do not use loperamide in bloody diarrhoea or diarrhoea associated with fever.

Monitor serum electrolytes in patients with severe diarrhoea on QT prolonging drugs.

# Epigastric pain

**PAS, Eto or Pto, FQs, E, Z**

Gastritis (epigastric burning or cramp relieved by eating) or dyspepsia (epigastric pain or discomfort following meals, often accompanied by bloating, sensation of fullness and nausea) are frequent with PAS, Eto or Pto.

- For gastritis:
  - **omeprazole** PO: 20 mg once daily in the morning for 7 to 10 days. In severe or recurrent cases, dose may be increased to 40 mg once daily and the treatment may be prolonged for up to 8 weeks.
  - Histamine H<sub>2</sub>-antagonists (e.g., ranitidine) may be an alternative.
- For dyspepsia:
  - **omeprazole** PO: 10 mg once daily in the morning for 4 weeks

Haematemesis (vomiting of blood) and melena (black stools) are symptoms of a bleeding gastric ulcer and require urgent intervention.

# Hepatotoxicity

## Z, H, R, P, Eto or Pto, PAS, Bdq, Amx/Clv

All TB drugs may cause hepatotoxicity. However, certain drugs are likely more responsible than others for this adverse effect.

The liver function tests (LFTs) used for the diagnosis and monitoring of hepatotoxicity are serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin.

A mild, transient elevation of ALT and AST may be observed during treatment and usually remains asymptomatic. Significant hepatotoxicity is usually symptomatic.

Clinical features resemble that of viral hepatitis. Early symptoms include malaise, fatigue, loss of appetite, muscle and joint pain. Nausea, vomiting and abdominal pain are common in severe toxicity. Jaundice, scleral icterus, dark (tea-coloured) urine and discoloured stool are signs of clinical worsening. Differential diagnosis includes infections (e.g. viral hepatitis, cytomegalovirus, leptospirosis, yellow fever, rubella), chronic alcohol use and hepatotoxicity due to other drugs (e.g. anti-epileptics, paracetamol, sulfa drugs, erythromycin).

Clinical hepatitis can be fatal and action should be taken immediately.

### 1) General management

- Patient with symptoms of hepatitis:  
Stop all TB drugs and perform LFTs:
  - a) AST or ALT or bilirubin  $\geq$  3 times upper limit of normal (ULN): wait for resolution of symptoms, perform LFTs weekly and restart TB treatment when LFTs are  $<$  3 times ULN.
  - b) AST, ALT and bilirubin  $<$  3 times ULN and mild symptoms (no jaundice): restart TB treatment, closely monitor the patient and perform LFTs weekly. Continue TB treatment as long as LFTs levels remain  $<$  3 ULN and there are no signs of worsening hepatitis.
- Patient without symptoms of hepatitis, but elevated LFTs:
  - a) AST or ALT  $\geq$  5 times ULN or bilirubin  $\geq$  3 ULN: stop all TB drugs and perform LFTs weekly. Restart TB treatment when LFTs return  $<$  3 times ULN.
  - b) AST and ALT  $<$  5 times ULN and bilirubin  $<$  3 ULN: continue TB treatment and perform LFTs weekly.

If LFTs continue to increase after stopping TB treatment, then ongoing progressive drug-induced hepatitis or an unrelated cause of hepatitis should be suspected.

### 2) Patient on DS-TB treatment

In most cases, the same treatment can be resumed without incident. The objective is to resume the initial regimen or an alternative regimen as rapidly as possible.

If symptoms reappear or LFTs re-increase, try to reintroduce the TB drugs one by one. Start with E and R and reintroduce H three to 7 days later. If E, R and H have been introduced and the LFT abnormalities have not recurred, do not introduce Z as it is most likely the causative agent.

The alternative regimen depends on the drug causing hepatotoxicity:

- Z is involved: 2 (HR)E/7 (HR)
- H is involved: 6RZE-Lfx
- R is involved: treat as MDR/RR-TB

### 3) Patient on DR-TB treatment

When restarting TB treatment, start with the drugs least hepatotoxic (E, Lfx or Mfx, Cs or Trd, Dlm, Am or S, lpm/Clv or Mpm), then drugs moderately hepatotoxic (Bdq, Cfz, Amx/Clav), then give the most hepatotoxic (Z, H, R, Eto or Pto, PAS). Add drugs one at a time every 5 to 7 days, and check LFTs.

The causative agent can generally be identified in this manner. It can be discontinued if not essential and replaced with another less hepatotoxic TB drug.

**Note:** hepatotoxicity may occur in patients receiving regimens containing pretomanid (Pa-Mfx-Z and Bdq-Pa-Lzd). However, the responsible drug has not been determined.

# Metallic taste

Eto or Pto, FQs

Encourage the patient to tolerate this adverse effect. Normal taste returns when TB treatment is stopped.



# Nausea and vomiting

## Eto or Pto, PAS, Z, Amx/Clv, Cfz, Lzd, Ipm/Cln or Mpm, Bdq

Nausea and vomiting are frequent, especially with Eto or Pto and PAS during the first few weeks of treatment. To avoid nausea and vomiting, these drugs can be initiated at low dose with gradual increase over one to 2 weeks.

- Always look for:
  - Signs of dehydration (thirst, dry mouth, sunken eyes)
  - Serum electrolytes disorders if vomiting
  - Signs of hepatitis
  - Haematemesis and melena
- Dehydration and electrolyte disorders should be corrected as necessary.
- Treat nausea and vomiting aggressively, using a stepwise approach:

### First phase - Adjust administration of the responsible drug

- Administer the suspected drug(s) causing nausea at bedtime.
- Patient on Eto or Pto: stop for 3 to 4 days. If signs improve, gradually resume at a lower dose (250 mg, then if tolerated, 500 mg and so on until the full dose is reached).
- Patient on PAS: stop for 3 to 4 days. If signs improve, gradually resume at a lower dose (2 g, then if tolerated, 4 g and so on until the full dose is reached). Take PAS one hour after taking other TB drugs. If PAS is taken once daily, take in 2 divided doses.
- Encourage the patient: nausea and vomiting often improve over the first weeks and may resolve entirely with time.

### Second phase - Administer an antiemetic

**ondansetron** PO 30 minutes before TB drugs:

Child 6 months to < 2 years: 2 mg once daily

Child 2 to < 4 years: 2 mg 2 times daily

Child 4 to < 12 years: 4 mg 2 times daily

Child ≥ 12 years and adult: 4 to 8 mg 2 times daily

Ondansetron is a QT prolonging drug and should be avoided in patients on Cfz, Bdq, Mfx, Dlm, Lfx.

In adults, when ondansetron is not available or is to be avoided:

**metoclopramide** PO:

Adult < 60 kg: 5 mg 3 times daily

Adult ≥ 60 kg: 10 mg 3 times daily

The interval between each dose should be at least 6 hours (even in the event of vomiting). Do not use metoclopramide if neurological problems develop.

or

**promethazine** PO 30 minutes before TB drugs:

Adult: 25 mg

### Third phase - Reduce the dose or temporarily stop the responsible drug

- Patient on Eto or Pto: if the patient does not tolerate full dose, avoid giving an adult less than 500 mg daily.
- Patient on PAS: if the patient does not tolerate full dose, avoid giving an adult less than 6 to 8 g daily.
- Patient on Cfz: reduce the dose by half.
- In the event of intractable nausea and vomiting despite dose reduction or interruption of the suspected drug, stop all TB drugs for 3 to 4 days, until signs resolve.

Permanent interruption of a drug should only be considered if it is not essential to treatment.

**Note:** if there is excessive anxiety over the nausea caused by TB drugs, consider adding **diazepam** PO (adult: 5 mg 30 minutes before TB drugs). This can help to avoid “anticipation nausea”. The treatment must be short as benzodiazepines may cause dependence and tolerance. Do not exceed 10 days of treatment.

# Neurotoxicity

- [Depression](#)
- [Headache](#)
- [Optic neuritis](#)
- [Ototoxicity](#)
- [Peripheral neuropathy](#)
- [Psychosis](#)
- [Seizures](#)

# Depression

## Cs or Trd, Eto or Pto

The treatment of MDR/RR-TB may contribute to depression. Depressive symptoms may fluctuate during TB treatment. History of depression may increase the risk of developing depression during treatment, but is not a contra-indication to use of any of the above TB drugs.

Consider lowering the dose or discontinuing a suspected TB drug, provided this does not compromise the effectiveness of TB treatment.

Other interventions include psychological support to patient (and family if needed) and, when necessary antidepressant treatment. Avoid selective serotonin reuptake inhibitors and tricyclic antidepressants with Lzd (risk of serotonin syndrome).

Suicidal ideation is more commonly associated with Cs or Trd. Evidence of suicidal ideation should prompt immediate action:

- Keep the patient in the hospital for surveillance.
- Stop Cs or Trd.
- Lower the dose of Eto or Pto to 500 mg daily until the patient is stable.
- Refer to mental health consultation.

# Headache

## Cs or Trd, Bdq, Dlm, FQs

Headache is common during the first months of treatment. It can be treated with analgesics.

Headache due to Cs or Trd can be prevented by starting at low dose (250 to 500 mg daily), with gradual increase over 1 to 2 weeks.

# Optic neuritis

**Lzd, E; rarely H, Eto or Pto**

This adverse effect is typically due to Lzd and E.

Symptoms include loss of red-green colour distinction, reduced visual acuity and central scotoma. Loss of red-green colour distinction is the first sign. In this case, stop the suspect drug immediately and permanently.

Symptoms are usually reversible after discontinuation of the drug, but optic neuritis due to Lzd may be irreversible.

# Ototoxicity

## **Aminoglycosides; rarely: Cs or Trd, FQs, Eto or Pto, Lzd**

Hearing loss, tinnitus and/or vestibular disorders (vertigo, dizziness, imbalance) are signs of ototoxicity.

Ototoxicity is most commonly observed in patients receiving large cumulative doses of aminoglycosides. Concomitant use of loop diuretics (furosemide), particularly in patients with renal insufficiency, may exacerbate ototoxicity.

Baseline and follow-up audiometry is required to detect early hearing loss. Hearing loss in high frequencies (> 4000 Hz) is often the first sign of auditory toxicity due to aminoglycosides and can be unnoticed by the patient.

In case of hearing loss, tinnitus or vestibular disorders, discontinue the suspected drug if this does not compromise the effectiveness of TB treatment. If no alternative is available, reduce the dose of aminoglycoside (3 times weekly rather than daily, e.g. on Monday, Wednesday and Friday). Continuation of aminoglycoside therapy despite hearing loss almost always results in deafness.

Tinnitus and vestibular disorders can rarely be due to the following drugs: Cs or Trd, FQs, Eto or Pto and Lzd. If stopping the aminoglycoside does not improve symptoms, other drugs can be discontinued to see if the symptoms improve, then reintroduced one by one to see if symptoms return.

Drug-induced tinnitus and vestibular disorders can be irreversible.

# Peripheral neuropathy

**Lzd, Cs or Trd, H, Eto or Pto; rarely E, FQs**

Peripheral neuropathy refers to damage to the nerves located outside of the central nervous system. This adverse effect is associated to several TB drugs but is commonly due to Lzd, Cs or Trd and H.

Peripheral neuropathy occurs most commonly in the lower extremities. Signs and symptoms include sensory disturbances (e.g. numbness, tingling, burning, pain, loss of temperature sensation), difficulty walking, weakness and decreased or absent deep tendon reflexes. At times, sensory changes may occur in upper extremities.

Linezolid-induced neuropathy is extremely painful and may be non-reversible.

## 1) Patient on DS-TB treatment

- To prevent isoniazid-induced peripheral neuropathy:  
Administer **pyridoxine** PO to patients at risk (pregnant and breastfeeding women, neonates and breastfed infants, and patients with HIV infection, alcohol dependency, malnutrition, diabetes, chronic hepatic disease, and renal impairment) along with their TB treatment:  
Neonate, infant and child < 5 kg: 5 mg once daily  
Child ≥ 5 kg and adult: 10 mg once daily
- If peripheral neuropathy develops:  
Administer **pyridoxine** PO  
Child < 12 years: 10 to 20 mg 2 times daily  
Child ≥ 12 years: 50 mg 2 times daily  
Adult: 50 mg 3 times daily  
For pain management: ibuprofen or paracetamol.

## 2) Patient on DR-TB treatment

- To prevent peripheral neuropathy:  
Administer **pyridoxine** PO:
  - Patient on H: all patients at risk, as for DS-TB.
  - Patient on Cs or Trd, Lzd, H<sup>h</sup> and Eto or Pto:  
Neonate, infant, child: 1 to 2 mg/kg (usual range in child: 10 to 50 mg) once daily  
Adult: 100 mg once daily
- If peripheral neuropathy develops:
  - Patient on Lzd: stop Lzd immediately. For mild symptoms not requiring analgesics, Lzd can be restarted at a lower dose once symptoms subside. For moderate or severe symptoms, stop Lzd permanently. Consider additional TB drugs to reinforce the therapeutic regimen.
  - Patient on Cs or Trd or H<sup>h</sup>: stop these drugs. If they are essential to the regimen, they may be re-introduced once symptoms subside.Other contributing causes should be addressed (e.g., diabetes or malnutrition).  
Administer **pyridoxine** PO: 100 mg daily in adults until symptoms resolve.  
For pain management: ibuprofen or paracetamol.  
Physiotherapy may be of benefit.  
If these measures are insufficient, treat as chronic neuropathic pain, but avoid tricyclic antidepressants in patients on Lzd (risk of serotonin syndrome).  
Do not use carbamazepine (strong CYP450 inducer) in patients on Bdq or Dlm.

# Psychosis

## Cs or Trd, FQs, H, Eto or Pto

Visual or auditory hallucinations, delusions, paranoia and bizarre behaviour are hallmarks of psychosis. Health personnel should be familiar with these symptoms to allow early detection.

The most likely TB drug involved is Cs or Trd, but psychotic symptoms may occur with FQs, H, Eto or Pto.

History of psychosis is not a contra-indication to the use of the above-mentioned drugs, though psychiatric symptoms are more likely to occur in such circumstances.

Some patients may need antipsychotic treatment throughout the duration of TB treatment.

Psychosis is generally reversible upon discontinuation of TB treatment.

For acute psychosis:

- If patients are at risk of harming themselves or others: urgent hospitalisation.
- Stop Cs or Trd.
- Treat the acute psychosis.

Once psychotic symptoms have resolved, antipsychotic treatment can be tapered most of the time. Cs or Trd can be resumed, generally at lower dose.

Antipsychotic treatment should be continued until the end of Cs or Trd treatment and then can usually be stopped gradually (do not stop it abruptly).

If the patient does not tolerate the reintroduction of Cs or Trd, another TB drug should be considered.

Whenever psychosis occurs in a patient on Cs or Trd, check the serum creatinine. Cs or Trd is 100% renally excreted and a decrease in renal function can result in toxic levels of Cs or Trd. In this case, a temporary suspension of Cs or Trd and re-introduction at an adjusted dose may be needed ([Appendix 12](#)).



# Seizures

## **Cs or Trd, H, FQs, Eto or Pto, Ipm/Cln or Mpm**

All the above-mentioned drugs may cause seizures. However, rule out or treat other possible causes (e.g., epilepsy, meningitis, encephalitis, alcohol withdrawal, hypoglycaemia, stroke, cancer, or toxoplasmosis in HIV-infected patients).

In the event of seizures, measure blood glucose level and blood electrolytes. Measure also serum creatinine. With impaired renal function, TB drugs can reach toxic levels, causing seizures. Dosage adjustment may be necessary ([Appendix 12](#)).

A history of seizures is not an absolute contra-indication to the use of the above-mentioned drugs. However, do not use Cs or Trd if there is an alternative. In patients with epilepsy, seizures should be controlled with anti-epileptic therapy before starting TB treatment.

The use of TB drugs (especially H and R) in patients on antiepileptics may lead to decreased blood levels of antiepileptics and seizures.

In patients without history of seizures, a first episode of seizures on TB treatment is likely due to the TB drugs. However, none of the above drugs leave permanent damage.

If a patient has a seizure for the first time:

- Stop suspected TB drugs for a short period.
- Start antiepileptic treatment, especially in the event of repeated seizures after stopping suspected drugs. Do not use carbamazepine or phenytoin in patients receiving Bdq or DIm (strong CYP450 inducers).
- Reintroduce TB drugs that are essential to TB treatment. Usually, they can be resumed at a lower dose, but the effective dose should be reached as soon as possible.

Antiepileptic treatment may be necessary until the end of the TB treatment.

# Endocrine disorders

- [Gynecomastia](#)
- [Hypothyroidism](#)

# Gynecomastia

## Eto or Pto

Eto or Pto may cause breast enlargement in men and women. Galactorrhoea has been reported. Encourage the patient to tolerate this adverse effect. Symptoms resolve when Eto or Pto is stopped.

# Hypothyroidism

## Eto or Pto, PAS

Symptoms appear slowly, are nonspecific and may include fatigue, muscle weakness, daytime sleepiness, excessive sensitivity to cold, dry skin, coarse hair, constipation, facial puffiness, and depression.

Thyroid enlargement and delayed deep tendon reflexes may be seen on examination.

The diagnosis is confirmed by a serum level of thyroid-stimulating hormone (TSH)  $\geq 10$  mIU/litre.

Eto or Pto and PAS may cause hypothyroidism, even more frequently when used together. If possible the responsible TB drugs should be replaced but may be continued if there is no alternative.

In both cases, replacement hormone therapy is required:

### **levothyroxine PO**

Adult < 60 years: initially 75 to 100 micrograms once daily then, adjust in 25 microgram increments every 4 to 12 weeks according to response. Usual maintenance dose is 100 to 200 micrograms daily.

Adult  $\geq 60$  years and/or with significant cardiovascular disease: initially 25 micrograms once daily then, adjust in 25 microgram increments every 4 to 12 weeks according to response. Usual maintenance dose is 100 to 125 micrograms daily.

The daily dose should be taken at the same time each day, 30 to 60 minutes before a meal or a caffeine-containing drink (e.g. coffee, tea) or other drugs to improve absorption.

Monitor TSH until it normalizes below 5 mIU/litre.

Thyroid dysfunction resolves upon discontinuation of TB treatment. Hormone replacement may be discontinued several months after TB treatment completion.

# Dermatological disorders

- [Alopecia](#)
- [Fungal infection](#)
- [Photosensitivity](#)
- [Skin reactions](#)

# Alopecia

## H, Eto or Pto

Temporary and mild hair loss may (rarely) occur in the first months of treatment. Encourage the patient to tolerate this adverse effect. Symptoms resolve when TB treatment is stopped.

# Fungal infection

## FQs

Vaginal, penile, skin fold and oral candidiasis may occur in patients taking FQs. Topical antifungals or short-course oral antifungals are usually effective.

# Photosensitivity

Cfz, FQs; rarely Z

Advise patient to avoid direct exposure to the sun, wear protecting clothes (e.g. long sleeves) and use sunscreen.



# Skin reactions

## All TB drugs

Skin reactions such as itch and skin rash may be hypersensitivity reactions due to any TB drug. General signs of hypersensitivity such as fever, dizziness, vomiting and headache may also occur.

Skin reactions usually appear early during treatment, often in the first month, but rarely during the first week. Most skin reactions are mild or moderate. Severe – even lethal – exfoliative dermatitis (Stevens Johnson's syndrome) may occasionally occur, particularly if administration of the TB drug continues after first signs of hypersensitivity appear.

## Minor skin reactions

- Simple itching: symptomatic treatment (e.g. antihistamine) without interrupting or modifying the TB treatment.
- Localised, mild skin rash, with or without itching:
  - Rule out other possible causes unrelated to TB drugs (i.e. scabies, contact dermatitis).
  - If no obvious other cause, stop all TB drugs.
  - Give symptomatic treatment (an antihistamine, no corticosteroids except in emergencies) and wait for disappearance of symptoms.
  - Once the reaction has resolved, try to determine which drug caused the reaction (see re- challenge of TB drugs below).

## Major skin reactions

- Stop all TB drugs.
- In the event of anaphylaxis, manage according to standard emergency protocol (epinephrine, etc.).
- For severe generalised rash, a parenteral corticosteroid may be needed.
- Once the reaction has resolved, try to determine which TB drug caused the reaction (see re- challenge of TB drugs below).
- Never re-introduce any drug resulting in Stevens-Johnson syndrome or anaphylaxis.

## Rechallenge of TB drugs

Each TB drug can be reinstated as a “challenge” (a test-dose). Introduce one drug at a time, starting with the drugs least likely to have caused the reaction.

Give the drugs in a setting where a health care provider can respond to any severe allergic reaction.

If a test-dose of any drug causes a reaction, discontinue this drug, unless it is deemed essential to the regimen (in this case, desensitisation can be considered).

- First-line TB drugs  
Start with isoniazid over 3 days then add rifampicin over 3 days, etc.

Drug	Likelihood	Trial dose 1	Trial dose 2	Trial dose 3
H	Least likely	50 mg	Full dose	Full dose
R	Least likely	75 mg	300 mg	Full dose
Z	Likely	250 mg	1000 mg	Full dose
E	Likely	100 mg	500 mg	Full dose

**Note:** if the initial reaction to treatment is severe, a weaker trial dose should be used (approximately 1/10<sup>th</sup> of the dose indicated for trial dose 1).

- Second-line TB drugs  
Start with the most important drug in a regimen unless there is suspicion that it is the cause of the reaction. Restart each TB drug one after the other, starting at about 1/10 of the dose on Day 1, half-dose on Day 2 and full dose on Day 3.

# Musculoskeletal disorders

- [Arthralgias](#)
- [Tendinitis/tendon rupture](#)

# Arthralgias

**Z, Rfb, H, Bdq, FQs**

Arthralgias generally diminish over time. Serum uric acid levels are frequently elevated, but this is of little clinical relevance. Anti-hyperuricaemic therapy is of no proven benefit in these patients.

Begin therapy with an anti-inflammatory agent, e.g. **ibuprofen** PO (adult: 400 to 800 mg 3 times daily). **Paracetamol** PO (adult: 500 to 1000 mg 3 times daily) may also help bring relief when given together with an anti-inflammatory drug.

If symptoms fail to resolve, consider lowering the dose of the suspected agent (most often Z), if this does not compromise the effectiveness of TB treatment.

# Tendinitis/tendon rupture

## FQs

In the acute phase, the main symptom of tendinitis is pain when moving the affected joint or palpating the tendon.

In later phase, continuous pain and tendon thickening or nodularity may be present.

The Achilles tendon is involved in most cases, but other joints may be affected (shoulder, hand, etc.).

New and intense physical activities are not recommended during a treatment with a FQ.

Tendinitis is more common in older patients, patients with renal insufficiency or under corticosteroids.

Tendon rupture is a complication of tendinitis. Signs and symptoms include a snap or pop sound at the time of rupture, bruising, inability to move the joint and a lack of continuity of the tendon on palpation.

Early detection of tendinitis, symptomatic treatment, and discontinuation of FQ can prevent tendon rupture. If the TB treatment is likely to fail without the FQ, try to continue the FQ. Inform the patient that tendon rupture may occur, but that FQ is essential to prevent TB treatment failure.

Symptomatic treatment:

- Rest the joint involved.
- Pain management: application of ice, and **ibuprofen** PO:  
Adult: 400 to 600 mg every 4 to 6 hours when required, maximum dose: 2400 mg daily.

# Miscellaneous

- [Electrolyte disorders](#)
- [Haematologic disorders](#)
- [Lactic acidosis](#)
- [Nephrotoxicity](#)
- [QT prolongation](#)

# Electrolyte disorders

## Aminoglycosides

Electrolyte disorders can occur with the aminoglycosides and are typically reversible with discontinuation of therapy.

Other potential causes (vomiting and diarrhoea) should be treated if present.

If clinical signs of mild to moderate hypokalaemia develop (i.e. muscle cramps, spasms or weakness) or if serum potassium level is between 2.5-3.4 mmol/litre, potassium replacement is required:

**potassium chloride PO:**

Child under 45 kg: 2 mmol/kg (2 ml/kg) daily in divided doses

Child 45 kg and over and adult: 30 mmol (30 ml) 3 times daily

If clinical signs of severe hypokalaemia develop (i.e. marked muscle weakness, cardiac arrhythmias) or if serum potassium level is < 2.5 mmol/litre, hospitalise and urgently administer potassium chloride by slow IV infusion.

For a patient with hypokalaemia:

- Monitor serum potassium levels and QT interval until they return to normal.
- Consider magnesium PO if serum magnesium cannot be measured. Untreated hypomagnesaemia may lead to "resistance" to correction of hypokalaemia. Magnesium should be taken at least 2 hours before or 4 to 6 hours after the FQs.

# Haematologic disorders

Lzd, R, P, Rfb, E

Most TB drugs can cause hematological disorders that may involve any blood cells (red cells, white cells, platelets). However, the TB drugs most involved are Lzd and rifamycins.

Severity grade in adults <sup>(a)</sup>	Anaemia	Neutropenia	Thrombocytopenia
<b>Mild</b>	10.5 - 9.5 g/dl	1500 - 1000/mm <sup>3</sup>	100,000 - 75,000/mm <sup>3</sup>
<b>Moderate</b>	< 9.5 - 8.0 g/dl	< 1000 - 750/mm <sup>3</sup>	< 75,000 - 50,000/mm <sup>3</sup>
<b>Severe</b>	< 8.0 - 6.5 g/dl	< 750 - 500/mm <sup>3</sup>	< 50,000 - 20,000/mm <sup>3</sup>
<b>Life-threatening</b>	< 6.5 g/dl	< 500/mm <sup>3</sup>	< 20,000/mm <sup>3</sup>

(a) Adapted from NIAID Division of Microbiology and Infectious Diseases, severity scale, Nov-2007.

## 1) Patient on DS-TB treatment

Rifamycins can cause potentially life-threatening thrombocytopenia. This is more common when used intermittently. Clinical features may include minor haemorrhage (e.g. epistaxis) or severe haemorrhage and thrombocytopenic purpura.

Measure platelets when thrombocytopenia is suspected:

- Moderate thrombocytopenia: stop the rifamycin and monitor platelets weekly until > 75,000/mm<sup>3</sup>.
- Severe thrombocytopenia: stop all TB drugs. Hospitalise. Treat shock or severe haemorrhage.

In any event rifamycins should not be reintroduced.

## 2) Patient on DR-TB treatment

Lzd may cause anemia, neutropenia and/or thrombocytopenia.

Toxicity	Management
<b>Mild to moderate</b>	<ul style="list-style-type: none"> <li>• In all cases:               <ul style="list-style-type: none"> <li>▫ Monitor carefully.</li> <li>▫ Consider reduction of dose of Lzd (e.g. 300 mg once daily or 600 mg 3 times weekly in adults).</li> </ul> </li> <li>• For moderate anemia: consider adding erythropoietin (EPO).</li> <li>• For moderate neutropenia:               <ul style="list-style-type: none"> <li>▫ Stop Lzd.</li> <li>▫ Restart at reduced dose once toxicity has decreased to 'mild'.</li> </ul> </li> </ul>
<b>Severe</b>	<ul style="list-style-type: none"> <li>• In all cases:               <ul style="list-style-type: none"> <li>▫ Stop Lzd and monitor carefully.</li> <li>▫ If Lzd is essential to the regimen, restart at reduced dose once toxicity has decreased to 'mild'.</li> </ul> </li> <li>• For severe anemia: consider adding EPO.</li> </ul>
<b>Life-threatening</b>	<ul style="list-style-type: none"> <li>• Stop Lzd and monitor carefully.</li> <li>• Hospitalise.</li> <li>• Perform blood transfusion</li> <li>• If Lzd is essential to the regimen consider restarting at reduced dose once toxicity has decreased to 'mild'.</li> </ul>

# Lactic acidosis

## Lzd

Lactic acidosis is a rare but potentially life-threatening increase of lactic acid in the bloodstream, that can be due to mitochondrial toxicity of certain TB drugs, usually Lzd.

Signs and symptoms include nausea and vomiting, abdominal pain, extreme fatigue, muscle cramps and increased respiratory rate.

If lactic acidosis is suspected, measure blood lactate and pH. Blood lactate  $\geq 4$  mmol/litre and pH  $< 7.35$  confirm the diagnosis. Stop Lzd and hospitalise for adequate management.

Note that lactic acidosis may also be due to ART (NRTIs).



# Nephrotoxicity

## Aminoglycosides

Nephrotoxicity is diagnosed by a rise in serum creatinine above baseline. In its early form it is usually asymptomatic, which means it is very important to monitor serum creatinine while on aminoglycosides.

Symptomatic cases may present with decreased urine output, evidence of volume overload (edema, anasarca or shortness of breath) or uremic symptoms such as mental status changes (confusion, somnolence).

Comorbidities such as diabetes or chronic renal failure are not a contra-indication to treatment with aminoglycosides, though caution must be exercised in such circumstances.

- If renal failure occurs:
  - Stop the aminoglycoside.
  - Rule out other causes of renal failure (e.g. diabetes, dehydration, other drugs, congestive heart failure, urinary obstruction, urinary tract infection, prostate hypertrophy).
  - Adjust doses of other TB drugs to creatinine clearance ([Appendix 12](#)).
  - Monitor serum creatinine and electrolytes every 1 to 2 weeks until stable.
- If renal function stabilises or improves and if the drug is essential, resume the aminoglycoside adjusted to creatinine clearance ([Appendix 12](#)).

# QT prolongation

**Cfz, Mfx<sup>h</sup>, Bdq, Mfx, DIm, Lfx**

Some TB drugs may cause QT prolongation and predispose to torsades de pointes, arrhythmias, and sudden death.

ECG should be performed before starting TB treatment then monitored throughout the course of treatment in patients taking these drugs.

Possible other causes include other QT prolonging drugs ([Appendix 19](#)), hypothyroidism and genetic causes such as long QT syndrome.

Mild or moderate QT prolongation (QTcF > 470 in women and > 450 ms in men and ≤ 500 ms) is common. Severe QT prolongation (QTcF > 500 ms or increase > 60 ms from baseline) is relatively rare.

- In all cases:
  - Measure serum electrolytes and correct electrolyte disorders if necessary.
  - Measure thyroid stimulating hormone (TSH) and, if necessary, treat hypothyroidism.
- For mild and moderate QT prolongation: monitor ECG at least weekly.
- For severe QT prolongation: stop QT prolonging drugs, hospitalise, perform continuous ECG monitoring until QT returns to normal. Once the patient is stable (normal QTcF and no electrolyte disorders), critical QT prolonging TB drugs can be reintroduced:
  - Patient on Bdq: consider resuming while suspending all other QT prolonging drugs.
  - Patient on Mfx: use Lfx instead.
  - Patient on Cfz or DIm: consider stopping if alternatives are available.
  - Patient on QT prolonging non-TB drug: consider stopping it.

# Appendix 18. Compassionate use of TB drugs

Update: October 2023

## 18.1 Definition

"Compassionate use" (also called "expanded access") is a regulatory framework<sup>[1][2]</sup> that allows the use of an investigational new drug (IND) for patients:

- who have a life-threatening disease, and
- no satisfactory treatment registered by national regulatory authorities (NRA), and
- who cannot enter clinical trials.

## 18.2 National regulations

In most countries, only drugs for which a marketing authorisation has been granted by the NRA can be used in humans.

Some NRAs have developed mechanisms to facilitate access to IND at different stages of development prior to marketing authorisation.

In this case, a clinician or an institution can apply for approval of the use of an IND under compassionate use conditions and seek permission to import it. Approval may be given for a patient or a group of patients, generally after review by a dedicated medical committee.

## 18.3 Indications

Compassionate use may be considered for patients with drug-resistant tuberculosis (DR-TB) when therapeutic regimens composed of drugs with marketing authorisation have failed, or are very likely to fail, and no surgical option is appropriate.

The IND should always be used with other likely effective drug(s), see Chapter 10, [Section 10.1.2](#), to avoid the emergence of resistance to the IND. The number of likely effective drug(s) given with the IND should be, as a minimum, one bactericidal drug or two bacteriostatic drugs.

Possible interactions and overlapping toxicities between the IND and other TB drugs should be taken into consideration. The use of an IND should not result in the discontinuation of an essential likely effective drug.

The use of two INDs should follow the same principles.

## 18.4 Minimal requirements

The minimal requirements for compassionate use of an IND include:

- Adequate patient management (including clinical, bacteriological and biological monitoring, adherence support, etc.).
- Monitoring and management of potential adverse effects specific to the IND.
- A pharmacovigilance system (aDSM)<sup>a</sup>.
- A patient-informed consent process:
  - inform the patient that the safety and efficacy of the IND have not been proven,
  - explain the potential benefits and risks.
- Approval by an ethics review board and by the Ministry of Health.
- Approval by the manufacturer of the IND.

The support of a regulatory affairs pharmacist is necessary regardless of whether the country has a regulatory framework authorising compassionate use.

### Footnotes

- (a) For more information see: World Health Organization. Active tuberculosis drug-safety monitoring and management (aDSM). Framework for implementation. WHO, Geneva, 2015.  
[https://apps.who.int/iris/bitstream/handle/10665/204465/WHO\\_HTM\\_TB\\_2015.28\\_eng.pdf;jsessionid=97A194C2FA7D78CF2E18BD60C8C6E3F7?sequence=1](https://apps.who.int/iris/bitstream/handle/10665/204465/WHO_HTM_TB_2015.28_eng.pdf;jsessionid=97A194C2FA7D78CF2E18BD60C8C6E3F7?sequence=1)

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1. European Medical Agency. *Human Regulatory. Compassionate use* [Accessed 19 April 2023].  
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2. World Health Organization. (2008). *Guidelines for the programmatic management of drug-resistant tuberculosis: emergency update 2008*. World Health Organization.  
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# Appendix 19. Drug interactions and overlapping toxicities

Update: October 2022

## 19.1 Interactions between cytochrome P450 inducers/inhibitors and bedaquiline

Drugs interfering with the cytochrome P450 (CYP450) enzyme system should be avoided with bedaquiline.

Strong CYP450 inducers	Moderate CYP450 inducers	Effect
Rifampicin Phenytoin Carbamazepine Phenobarbital	Efavirenz Rifapentine Rifabutin	Decrease bedaquiline plasma concentrations
Strong CYP450 inhibitors	Moderate CYP450 inhibitors	Effect
Atazanavir Itraconazole Clarithromycin Lopinavir Nelfinavir Ritonavir	Erythromycin Fluconazole Verapamil	Increase bedaquiline plasma concentrations
Drugs metabolized by CYP		Effect
Emtricitabine		Can increase bedaquiline plasma concentrations

This list is not exhaustive. Clinicians should be informed of any cytochrome P450 inducers and inhibitors their patients may be taking.

## 19.2 Overlapping toxicity of QT-prolonging drugs

**TB drugs** (mean QT interval prolongation)

- Mild QT prolongation: delamanid (8.6 ms)<sup>[1]</sup>, levofloxacin (4.6 ms)<sup>[2]</sup>.
- Moderate QT prolongation: bedaquiline (12.3 ms)<sup>[2]</sup>, moxifloxacin (12.3 ms)<sup>[3]</sup>.
- Strong QT prolongation: clofazimine (28.5ms)<sup>[4]</sup>, moxifloxacin high dose (23.14 ms)<sup>[3]</sup>.

**Non-TB drugs**<sup>[5]</sup>

- Antimalarials: artemisinin derivatives (high risk), quinine
- Antipsychotics: haloperidol (high risk), chlorpromazine, fluphenazine, olanzapine, risperidone
- Cardiac drugs: amiodarone (high risk), beta-blockers, digoxin
- Oral azole antifungals: fluconazole, itraconazole
- Macrolides: azithromycin, clarithromycin, erythromycin
- Anti-nausea drugs: ondansetron
- Antiretrovirals: boosted protease inhibitors, efavirenz

This list is not exhaustive. Clinicians should be informed of any QT-prolonging drugs their patients may be taking.

## 19.3 Interactions between TB and antiretroviral drugs

AZT: zidovudine; ATV: atazanavir; 3TC: lamivudine; RAL: raltegravir; ABC: abacavir; DTG: dolutegravir; FTC: emtricitabine; TDF: tenofovir disoproxil fumarate; LPV/r: lopinavir/ritonavir; EFV: efavirenz; RTV or r: ritonavir.  
R: rifampicin; Rfb: rifabutin; P: rifapentine; Bdq: bedaquiline.

<b>TB drugs</b>	<b>NRTI (ABC, 3TC, TDF, AZT)</b>	<b>INI (DTG, RAL)</b>	<b>NNRTI (NVP, EFV)</b>	<b>Boosted PI (LPV/r, ATV/r, DRV/r)</b>
<b>R</b> <sup>[6][7]</sup>	<b>All NRTI</b> <ul style="list-style-type: none"> <li>Can be combined.</li> <li>No dose adjustment.</li> </ul>	<b>DTG</b> <ul style="list-style-type: none"> <li>Can be combined.</li> <li>Double the dose of DTG<sup>(a)</sup>.</li> </ul> <b>RAL</b> <ul style="list-style-type: none"> <li>Can be combined.</li> <li>Double the dose of RAL<sup>(b)</sup>.</li> </ul>	<b>NVP</b> <ul style="list-style-type: none"> <li>Do not combine.</li> <li>Replace NVP with DTG or EFV.</li> <li>If not possible, replace R with Rfb.</li> </ul> <b>EFV</b> <ul style="list-style-type: none"> <li>Can be combined.</li> <li>No dose adjustment.</li> </ul>	<b>ATV/r or DRV/r</b> <ul style="list-style-type: none"> <li>Do not combine.</li> <li>Replace R with Rfb.</li> </ul> <b>LPV/r</b> <ul style="list-style-type: none"> <li>Replace R with Rfb.</li> <li>If not possible and a PI is essential, dose adjustment is required<sup>(c)</sup>.</li> </ul>
<b>Rfb</b> <sup>[7]</sup>	<b>All NRTI</b> <ul style="list-style-type: none"> <li>Can be combined.</li> <li>No dose adjustment.</li> </ul>	<b>All INI</b> <ul style="list-style-type: none"> <li>Can be combined.</li> <li>No dose adjustment.</li> </ul>	<b>NVP</b> <ul style="list-style-type: none"> <li>Can be combined.</li> <li>No dose adjustment.</li> <li>Monitor Rfb toxicity.</li> </ul> <b>EFV</b> <ul style="list-style-type: none"> <li>Do not combine.</li> </ul>	<b>All boosted PI</b> <ul style="list-style-type: none"> <li>Can be combined.</li> <li>Reduce the dose of Rfb by half</li> <li>Monitor Rfb toxicity.</li> </ul>
<b>P</b> <sup>[6][7]</sup>	<b>All NRTI</b> <ul style="list-style-type: none"> <li>Can be combined.</li> <li>No dose adjustment.</li> </ul>	<b>All INI</b> <ul style="list-style-type: none"> <li>Can be combined.</li> <li>No dose adjustment.</li> </ul>	<b>NVP</b> <ul style="list-style-type: none"> <li>Do not combine.</li> <li>Replace NVP with DTG or EFV.</li> </ul> <b>EFV</b> <ul style="list-style-type: none"> <li>Can be combined.</li> <li>No dose adjustment.</li> </ul>	<b>All boosted PI</b> Do not combine.
<b>Bdq</b> <sup>[7]</sup> <sup>[8]</sup>	<ul style="list-style-type: none"> <li>Can be combined.</li> <li>No dose adjustment.</li> </ul>	<b>All INI</b> <ul style="list-style-type: none"> <li>Can be combined.</li> <li>No dose adjustment.</li> </ul>	<b>NVP</b> <ul style="list-style-type: none"> <li>Can be combined.</li> <li>No dose adjustment.</li> </ul> <b>EFV</b> <ul style="list-style-type: none"> <li>Do not combine.</li> <li>Replace EFV with DTG or NVP.</li> </ul>	<b>All boosted PI</b> <ul style="list-style-type: none"> <li>Do not combine.</li> <li>Replace boosted PI with DTG.</li> <li>If no alternative, closely monitor ECG.</li> </ul>

(a) DTG: administer 50 mg 2 times daily, rather than the usual dose of 50 mg once daily.

(b) RAL: e.g. administer 12 mg/kg 2 times daily, rather than the usual dose of 6 mg/kg 2 times daily.

(c) LPV/r:

- Child: increase the dose of RTV to obtain a one-to-one (1:1) LPV/r ratio.

- Adult: double the dose (e.g. 800/200 mg 2 times daily, rather than the usual dose of 400/100 mg 2 times daily).

For more information, see University of Liverpool HIV Drug Interaction Checker: <https://www.hiv-druginteractions.org/checker>.

## 19.4 Overlapping toxicities of antiretrovirals and TB drugs

Drugs strongly associated with the listed toxicities appear in bold lettering.

Toxicity	ARVs	TB drugs	Comments
<b>Abdominal pain</b>	<b>All ARVs</b>	<b>Eto or Pto, PAS, Cfx, Lzd, FQs, H, Z</b>	Common. Often benign, but can be an early symptom of severe adverse effects ( <a href="#">Appendix 17</a> ).
<b>Depression</b>	<b>EFV, DTG</b>	<b>Cs or Trd, FQs, Eto or Pto, H</b>	<ul style="list-style-type: none"> <li>• EFV: consider replacing EFV in the event of severe depression.</li> <li>• DTG: can cause depression, but less frequently<sup>[9]</sup>.</li> </ul>
<b>Diarrhoea</b>	<b>All PI, DTG</b>	<b>Eto or Pto, PAS, FQs, Amx/Clv, Ipm/Cln</b>	Common. Also consider opportunistic infections as a cause of diarrhoea or <i>Clostridium difficile</i> infection (pseudomembranous colitis).
<b>Electrolyte disorders</b>	<b>TDF (rare)</b>	<b>Am, S</b>	See <a href="#">Nephrotoxicity</a> .
<b>Haematological disorders</b>	<b>AZT</b>	<b>Lzd</b>	<ul style="list-style-type: none"> <li>• Monitor full blood count.</li> <li>• Replace AZT in the event of bone marrow suppression.</li> <li>• For Lzd, see <a href="#">Appendix 17</a>.</li> <li>• If the patient takes cotrimoxazole (CMX), also consider CMX as a cause of haematological disorders.</li> </ul>
<b>Headache</b>	<b>AZT, EFV, DTG</b>	<b>Cs or Trd, Bdq, Dlm</b>	Rule out bacterial or cryptococcal meningitis, toxoplasmosis, etc. Headache secondary to AZT, EFV, DTG and Cs or Trd are usually transient.
<b>Hepatotoxicity</b>	<b>NVP, EFV, boosted PIs, DTG</b>	<b>Z, H, R, E, PAS, Eto or Pto, Bdq, Amx/Clav</b>	<ul style="list-style-type: none"> <li>• If severe, stop ART and TB drugs. When treatment is resumed, start the TB drugs first (<a href="#">Appendix 17</a>).</li> <li>• If the patient takes CMX, also consider CMX as a cause of hepatotoxicity.</li> </ul>
<b>Nausea and vomiting</b>	<b>RTV, NVP, and most other ARVs</b>	<b>Eto or Pto, PAS, Z, Amx/Clv, Cfx, Lzd, Ipm/Cln, Bdq</b>	Persistent vomiting can be a result of more severe conditions, such as lactic acidosis and/or drug-induced hepatitis.
<b>Nephrotoxicity</b>	<b>TDF</b>	<b>Am, S</b>	<ul style="list-style-type: none"> <li>• Avoid TDF in patients on aminoglycosides.</li> <li>• If an aminoglycoside is essential: <ul style="list-style-type: none"> <li>▫ For patients already on ART, replace TDF with ABC.</li> <li>▫ For new patients, start with AZT or ABC.</li> </ul> </li> <li>• If TDF and aminoglycoside cannot be avoided, monitor serum creatinine, creatinine clearance and electrolytes at least every 2 weeks.</li> </ul>
<b>Neurotoxicity</b>	<b>EFV, DTG</b>	<b>Cs or Trd, H, Eto or Pto, FQs</b>	<ul style="list-style-type: none"> <li>• EFV: numerous transient effects on the central nervous system during first 2-3 weeks of treatment. If they do not resolve, consider replacing EFV. There are limited data on the use of EFV with Cs or Trd; concomitant use is accepted practice provided the patient is closely monitored for neurotoxicity.</li> <li>• DTG: can cause insomnia and dizziness. Administer in the morning or consider replacing with EFV, a boosted PI or RAL.</li> </ul>
<b>QT prolongation</b>	<b>Boosted PIs, EFV</b>	<b>Cfx, Mfx<sup>h</sup>, Bdq, Mfx, Dlm, Lfx</b>	For monitoring, see <a href="#">Appendix 15</a> .
<b>Skin reactions</b>	<b>ABC, NVP, EFV, and all other ARVs</b>	<b>All TB drugs</b>	<ul style="list-style-type: none"> <li>• Do not re-introduce ABC (risk of anaphylaxis).</li> <li>• Do not re-introduce any agent that may have caused Stevens-Johnson syndrome.</li> <li>• If the patient takes CMX, also consider CMX as a cause of skin reactions.</li> </ul>

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# Appendix 20. Treatment supporters

Update: January 2022

Treatment supporters need specific training to know and understand their role in order to provide the patient with adequate treatment education and support. They should be compensated for their time and services and reimbursed for expenses incurred.

## 20.1 Selecting a treatment supporter

The treatment supporter<sup>a</sup> :

- Is someone from the patient's community;
- Is preferably a community health worker or a person with a background in health (e.g. pharmacist), but can also be a non health worker (co-worker or neighbour);
- Is chosen by, or is acceptable to, the patient and their family (e.g. supporter and patient of the same sex);
- Is able to observe the patient's confidentiality;
- Has a stable living situation;
- Has basic literacy skills (can read and write and has basic numeracy skills);
- Is motivated to care for TB patients and committed to supporting them for the full duration of treatment;
- Lives near enough to the patient to be able to make regular visits (daily or weekly) and go to their home immediately in the event of an emergency;
- Is in good physical condition and not immunedepressed<sup>b</sup>.

It is usually not recommended to have family members as treatment supporters. The family relationship may interfere with the ability to administer TB treatment, especially if the patient is a child.

## 20.2 Roles and responsibilities

Role and responsibilities of a treatment supporter may include:

- Supervision of all drug intakes and keeping records on TB treatment card.
- Detection of adverse effects and, when necessary, prompt referral of the patient to a health facility.
- Accompanying the patient to medical consultations.
- Collection and transport of sputum specimens for bacteriological examinations.
- Provision of health education to family members, including the risk of transmission and implementation of infection prevention and control (IPC) measures in the home.
- Detection of signs and symptoms of TB in family members.
- Participation in refresher trainings.

### Footnotes

(a) From USAID TB CARE II (2017). *Community-based Care for Drug-resistant Tuberculosis: A Guide for Implementers*. Version 3. Updated in 2017. <https://tbcare2.org/wp-content/uploads/2018/09/Community-Based-DR-TB-20180830-1.pdf>

(b) The most common cause of immunosuppression is HIV infection, but chronic illnesses such as diabetes also alter the immune system and are a risk factor for TB infection and active TB.



# Appendix 21. Therapeutic patient education

Update: March 2023

Therapeutic education should be provided promptly after diagnosis, then at each clinical visit and whenever considered necessary by the patient or the health staff, until the end of treatment.

Interviews are done either by the prescribing clinician alone, or with the help of a specially trained staff member or counsellor. Patients may bring someone with them if they wish.

## 21.1 Initial therapeutic education

Two individual interviews should be organised:

- The first interview, before the start of treatment, aims to provide essential information to help the patient understand and manage the disease and treatment.
- The second interview, one week later, aims to verify that the information given previously has been assimilated, and if necessary, complete or clarify it.

### 21.1.1 First interview

- Plan a 30 to 45 minute-session.
- Adapt the information according to the:
  - Stage of disease (latent TB infection, active TB).
  - Site of TB (pulmonary, extrapulmonary).
  - Resistance pattern (drug-susceptible, drug-resistant).
  - Treatment regimen.
  - Comorbidities, especially HIV infection.
- Explain:
  - The disease and how it is transmitted.
  - The treatment:
    - Total duration; duration of phases (intensive/continuation) if relevant.
    - Clinical and bacteriological monitoring.
    - Treatment administration (self-administered or directly observed).
  - The TB drugs:
    - Where, when, and from whom to get them.
    - How to take them: number of tablets (or doses) per day; with or without food, etc.
    - Storage: e.g. do not removed tablets from blister pack ahead of time.
    - Main adverse effects and what to do if they occur.
    - Special precautions according to the situation (e.g. concomitant treatment, pregnancy).
  - Measures the patient and their household members should take to prevent the spread of TB or, if the patient is hospitalised, the hospital infection prevention and control measures in place ([Chapter 14](#)).
  - The importance of HIV testing if not already performed.
- Explain the importance of adherence (regular treatment without omission or interruption). Address patient issues. Identify barriers to adherence and possible solutions. Explain what enablers the patient is eligible for and how to access them ([Chapter 13](#)).
- Answer any questions.
- Give the date of the second interview.

### 21.1.2 Second interview

- Plan a 30-minute session.
- Review patient's knowledge (disease, treatment and other information provided at the first interview).
- Answer any questions.
- Assess adherence ([Appendix 22](#)) and address problems if any ([Chapter 13](#)).
- Give/remind the date of the next clinical visit.

## 21.2 Continuing therapeutic education

An individual interview should be organised at each clinical visit. For the schedule, see [Appendix 14](#) or [Appendix 15](#).

These interviews aim to consolidate the patient's skills and update them if necessary, especially when there is a modification in the treatment regimen (e.g. when moving from intensive to continuation phase; when replacing a treatment regimen with another; when transitioning to outpatient treatment after hospitalisation).

- Explain the changes in treatment if any (composition, duration, adverse effects, precautions, monitoring schedule, etc.).
- Answer any questions.
- Assess adherence ([Appendix 22](#)) and address problems if any ([Chapter 13](#)).
- Give/remind the date of the next clinical visit.

Additional sessions should be scheduled as needed, e.g. if there are learning difficulties or significant changes in the patient's life.

For further information, refer to the specific guidelines on therapeutic patient education.

# Appendix 22. Assessment of adherence to TB treatment

Update: October 2023

Assessment of adherence should be performed at each clinical visit or patient education session.

The adherence assessment is performed as a short interview (± 5 minutes).

For patients with adherence issues, take more time to understand the problems and try to resolve them in a manner adjusted to each person.

## 22.1 Self-administered treatment

When treatment is self-administered, adherence is reported by the patient. To facilitate the assessment, various tools can be used. For example:

### Visual analogue scale

Ask the patient to indicate on the ruler 0-10 how much prescribed TB drugs they have taken since the last visit.

Explain that 0 corresponds to no doses taken at all, 5 to half of the doses taken and 10 to every single dose taken.

For patients with a score less than 10, additional adherence support should be provided.

### Morisky medication adherence scale

Ask the patient these 4 questions:

1. Do you ever forget to take your medicines?
2. Are you careless at times about taking your medicines?<sup>a</sup>
3. When you feel better, do you sometimes stop taking your medicines?
4. If you feel worse when you take your medicines, do you sometimes stop taking them?

Adherence is good if the patient answers “no” to all 4 questions. If the patient answers “yes” to one or more questions, additional adherence support should be provided.

## 22.2 Directly observed treatment

For patients who receive their treatment under supervision, the adherence rate or average DOT rate should be calculated and monitored at the end of each calendar month.

### Adherence rate

The adherence rate measures the patient’s adherence to the overall prescribed treatment:

$$\frac{\text{Number of prescribed days} - (\text{number of missed days} + \text{number of incomplete days})}{\text{Number of prescribed days}} \times 100$$

Number of prescribed days: days in the month that the clinician prescribed TB treatment.

Number of missed days: days in the month that the patient did not take any of the prescribed TB drugs.

Number of incomplete days: days in the month that the patient took some prescribed TB drugs, but not all.

### DOT rate per drug

The DOT rate per drug measures patient’s adherence to each prescribed drug:

$$\frac{\text{Number of prescribed days for the drugs} - \text{number of missed days of the drug}}{\text{Number of prescribed days for the drug}} \times 100$$

### Average DOT rate

The average DOT rate is the average of the DOT rate per drug.

**Box 22.1** – Example of the calculation of monthly adherence rate, DOT rate per drug and average DOT rate

A patient is prescribed Bdq-Lzd-Lfx-Cs from the 10/09 (i.e. the number of prescribed days this month is 20). The patient did not take any treatment on the 20/09 and 21/09 (2 days) and did not take linezolid and cycloserine from the 25/09 to 29/09 (5 days).

- Adherence rate for September:  $20 - (2 + 5) \div 20 \times 100 = 65\%$
- DOT rate per drug for September:
  - for Bdq and Lfx:  $20 - (2) \div 20 \times 100 = 90\%$
  - for Lzd and Cs:  $20 - (2 + 5) \div 20 \times 100 = 65\%$
- Average DOT rate for September:  $90 + 90 + 65 + 65 \div 4 = 77.5\%$

A goal of 100% adherence is ideal as higher treatment adherence results in better treatment outcomes.

This patient has sub-optimal adherence. The reasons why the patient did not take the treatment (especially linezolid and cycloserine) should be explored and additional support should be provided.

## Footnotes

- (a) For example: not taking drugs as scheduled, taking only a part of the prescribed dose, etc.

# Appendix 23. Basic tool for assessing risk of TB transmission

Update: October 2023

This tool can be used for a rapid assessment of the risk of TB transmission and compliance with TB-IPC measures in facilities managing patients with TB, during initial and annual TB-IPC assessments.

[Basic tool for assessing risk of TB transmission.pdf](#)

[Basic tool for assessing risk of TB transmission.docx](#)

# Appendix 24. Recommendations for air change per hour

Update: October 2023

## 24.1 Calculation of air change per hour (ACH)

To calculate the ACH in a room:

- Measure the dimensions of the room and calculate its volume (in cubic meters).
- Measure the dimensions of the openings (e.g. window, vents) and calculate their surface (in square meters).
- Determine the airflow direction across the openings.
- Measure the air speed (in meters per second) using an anemometer.

$$\text{ACH} = \frac{0.65 \times \text{air speed (m/s)} \times \text{opening area (m}^2\text{)} \times 3600}{\text{Volume of the room (m}^3\text{)}}$$

## 24.2 Required ACH

Areas	Required ACH	Remarks
Wards or rooms, diagnosis rooms, corridors, etc.	Minimum 12	Use GUV if required ACH is not reached.
Sputum and other respiratory specimen collection areas	Minimum 20	<ul style="list-style-type: none"><li>• Where possible, perform sputum collection outdoors.</li><li>• Use GUV if required ACH is not reached.</li></ul>

## 24.3 Time required for air cleaning after patient discharge

Rooms should be extensively ventilated between each patient.

The following table shows the ventilation time required to reduce airborne pathogens by 99.9% based on the ACH achieved (adapted from CDC<sup>[1]</sup>).

ACH	Time (in minutes)
6	70
12	35
15	30
20	25

## References

1. Centers for Diseases Control. *Guidelines for Preventing the Transmission of Mycobacterium tuberculosis in Health-Care Settings*. MMWR. December 30, 2005 / 54(RR17);1-141  
[https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5417a1.htm?s\\_cid=rr5417a1\\_e#tab2](https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5417a1.htm?s_cid=rr5417a1_e#tab2)

# Appendix 25. Overview of ventilation techniques

Update: October 2023

Ventilation	Equipment	Installation Maintenance	Cost	Remarks
<b>Natural</b>	Windows and doors	Very simple	Low	<ul style="list-style-type: none"> <li>Adapted to hot climates only.</li> <li>No constant airflow speed and direction.</li> </ul>
	Whirly birds	Very simple	Low	
<b>Assisted natural</b>	Fans (ceiling, wall, desk)	Very simple	Low	<ul style="list-style-type: none"> <li>Adapted to hot climates only.</li> <li>Improves dilution.</li> <li>Power source required.</li> </ul>
	Extractors/ exhaust fans	Simple	Low	<ul style="list-style-type: none"> <li>Adapted to hot climates only.</li> <li>Power source required.</li> </ul>
<b>Mechanical</b>	Heating, ventilation and air conditioning	Very difficult (requires specialised technicians)	Very high	<ul style="list-style-type: none"> <li>Adapted to cold and hot climates.</li> <li>Constant airflow speed and direction if functioning properly.</li> <li>Power source required (high consumption).</li> <li>HEPA filters if air is recirculated.</li> </ul>

For more information on ventilation techniques, refer to specialised guidelines.

# Appendix 26. Germicidal ultraviolet lamps

Update: October 2023

## 26.1 Use

- Germicidal ultraviolet (GUV) lamps emit UV-C rays. They are installed in the upper part of a room to create a "germicidal zone" where bacilli are killed.
- They are suspended from the ceiling or mounted on the wall in fixtures with baffles that prevent the radiation from going downwards and thus reaching the people in the lower part of the room.
- For an effective system:
  - Installation and maintenance should be performed by qualified technicians.
  - Irradiance in the upper part of the room should be in the range of 30 to 50  $\mu\text{W}/\text{cm}^2$ .
  - GUV lamps should irradiate the largest possible volume of the upper part of the room.
  - Effective air mixing is needed to direct the air (and the bacilli) to the germicidal zone. Effective mixing may be provided by natural convection currents or fans. However, when airflow speed is too high, effectiveness can be reduced because the time for bacilli irradiation is shorter.
  - Relative humidity in the room should be below 60%.
  - Room temperature should be between 20 and 24 °C.
  - In rooms with hospitalized patients, the GUV lamps should be switched on 24 hours a day.

## 26.2 Installation

- The height of the room should be minimum 2.5 m and GUV fixtures should be installed at a minimum height of 2.1 m.
- A 30W GUV lamp is usually sufficient for 18 m<sup>2</sup> of room surface. However, the positioning of the lamp influences the size of the germicidal zone (e.g. wall-mounted lamps have a smaller germicidal zone than ceiling-mounted ones).
- Reflective surfaces (i.e. oil painted ceilings, etc.) in the germicidal zone should be avoided.

## 26.3 Maintenance

- A staff member should check every day that the GUV lamps are on and work properly. Keep records of daily inspections.
- Lamps and fixtures should be cleaned at least once a month (more often if necessary). The lamps must be turned off and cool then, wiped with a cloth dampened with 70% alcohol. Do not use water and soap or any type of detergent. Keep records of cleaning.
- GUV level should be measured every 6 months and at least once a year using a GUV light radiometer. Irradiance measurements should be performed:
  - at eye level in different places in the lower occupied area of the room;
  - at 1 m from the fixture centre in all possible directions in upper irradiated area of the room.
- National Institute for Occupational Safety and Health (NIOSH) recommends<sup>[1]</sup>:
  - a maximum of 0.4  $\mu\text{W}/\text{cm}^2$  at eye level in lower occupied area, and
  - an average of 30 to 50  $\mu\text{W}/\text{cm}^2$  in upper irradiated area (for UV-C with a wavelength of 254 nm).
- Staff performing measurements should wear personal protective equipment (UV-protective glasses, thick clothing, and textile gloves) and use sunscreen with solar-protection factor > 15.
- The lifespan of an UV lamp bulb is determined by the manufacturer (typically, 9000 hours of continued use). After this period, UV lamp bulbs rapidly lose effectiveness and must be changed. If a bulb has a 30% decline, it should be replaced before the scheduled time.

## 26.4 Disposal

- GUV lamps contain mercury and quartz and are hazardous waste.
- The disposal process should be discussed before considering the use of GUV lamps.
- Adequate disposal of GUV lamps is performed by specialist companies, not available in all countries. Seek advice from TB-IPC specialists for a context-dependent solution.

## 26.5 Safety considerations

- GUV exposure may be harmful. Skin exposure may cause erythema and eye exposure may cause conjunctivitis (feeling of sand in the eyes, tearing) and/or keratitis (intense pain, photophobia). Symptoms appear 6 to 12 hours after exposure.
- Even if these adverse effects are reversible, staff should report them immediately to the TB-IPC practitioner. It could mean that GUV irradiation is higher than acceptable levels in the lower area of the room.
- Staff training should include basic information on GUV lamps, their potential harmful effects if overexposure occurs, and the personal protective equipment to be used when handling the lamps.

## References

1. National Institute for Occupational Safety and Health. *Environmental control for tuberculosis: basic upper-room ultraviolet germicidal irradiation guidelines for healthcare*





# Appendix 27. Respirators

Update: January 2022

## 27.1 Introduction

Respirators are masks designed to protect the wearer from inhaling bacilli.

Staff must wear a respirator when the risk of TB transmission is high ([Chapter 14](#)).

Attendants and visitors must wear a respirator when entering a ward or room of infectious TB patients.

Recommended respirators include:

- The CE-certified filtering facepiece EN 149 FFP2, filtering efficiency 94% if challenged with 0.4 µm particles; or
- The United States Centre for Disease Control and Prevention/National Institute for Occupational Safety and Health (NIOSH) certified N95, filtering efficiency > 95% if challenged with 0.3 µm particles.

## 27.2 Instructions for use

Respirators are for personal use. The same respirator cannot be shared between staff members or between attendants and visitors.

The respirator should be put on before entering the room and removed after exiting the room.

Respirators must be worn covering the nose, mouth and chin and provide a tight seal around the edge. Every time that a respirator is put on, a seal check has to be performed:

- Fully open the respirator and slightly bend the nose wire to form a curve.
- Separate the two elastic straps and position the respirator under the chin.
- Stretch the two elastic straps over the head, place the first strap at neck-height and the second strap across the top of the head.
- Model the nose wire around the bridge of the nose and secure the edges until you achieve a perfect
- Check for leaks by covering the respirator with both hands and forcefully inhaling and exhaling several times. The respirator should collapse when inhaling and expand when exhaling and no air leak between the face and the respirator should be. Otherwise, elastic straps should be readjusted and/or the respirator repositioned until is sealed properly.

Different factors may not allow proper sealing of respirators to the face: respirator size and/or model; respirator wearer's facial features, including beard and facial hair; headscarves, etc.

There is limited evidence on the acceptable length of time a respirator can be worn with maintained efficiency. The filter materials remain functional for weeks or months, but with frequent wearing the respirator will become less adjusted.

An extensively used respirator should be discarded after 7 days. However, if for example, it is only used a few hours 2 to 3 times a week, it can be reused for several weeks<sup>[1]</sup>. During this period, staff can reuse their respirator provided it is not wet or damaged and its straps are not loosened. Each staff member should keep their respirator in the pocket of their personal gown without creasing it. If the filter material is damaged or the mask has loose straps, the respirator should be discarded immediately.

**Note:** TB bacillus is trapped in the filter of a mask and will not be released with shaking or other physical movements of the mask.

## 27.3 Storage

Store in a dry, well ventilated place. Respirators should not be crushed during storage.

## 27.4 Disposal

Respirators are disposed of as "soft waste" and do not need to be disinfected before being discarded.

## 27.5 Fit testing

All staff members who could be exposed to *M. tuberculosis* should before being required to wear a respirator perform a "fit testing" to determine if the respirators being used fit them properly.

At least two models of respirators should be available. If a worker cannot be fitted with one model, the other one should be used.

Testing is performed using a fit testing kit. The kit contains all the supplies and instructions needed to perform the test.

**Fit testing kit**



## References

1. Roland Diehl, Albert Nienhaus, Peter Witte, Renate Ziegler. *Protection of healthcare workers against transmission of Mycobacterium tuberculosis in hospitals: a review of the evidence*. ERJ Open Research 2020 6: 00317-2019. <https://doi.org/10.1183/23120541.00317-2019>

# Appendix 28. Surgical masks

Update: January 2022

## 28.1 Introduction

The purpose of surgical masks is to catch droplet nuclei that patients expel while talking, breathing or coughing.

Surgical masks should be worn by contagious or potentially contagious patients (confirmed or presumed cases) when they leave their rooms to go to another department or any other enclosed area, or when they take care of young children.

The terms "surgical", "medical" or "procedure" are sometimes used interchangeably to qualify masks. Only masks that conform to the norms EN 14683 or ASTM F2100 should be used.

## 28.2 Instructions for use

Surgical masks are for personal use. The same mask cannot be shared.

- Open the mask.
- Bend the nasal bar (if included).
- Put the chin into the mask.
- Attach the straps behind the head or over the ears.

Surgical masks must be replaced at least once a day and when they become wet or damaged.

It is not recommended to wear masks for large portions of the day or while sleeping, as they are not comfortable.

## 28.3 Storage

Store in a dry, well ventilated place.

## 28.4 Disposal

Masks are disposed of as "soft waste" and do not need to be disinfected before being discarded.

# Appendix 29. BCG vaccine

Update: January 2022

## Composition, forms and route of administration

- Live attenuated bacterial vaccine
- Powder for injection, to be dissolved with the entire vial of the specific solvent supplied by the manufacturer, in multidose vial, for intradermal injection

## Dosage and vaccination schedule

Refer to national recommendations. In countries with a high incidence of TB (> 40 cases per 100,000), WHO recommends<sup>[1]</sup>:

- Child under 12 months: 0.05 ml single dose as soon as possible after birth
- Child 12 months and over<sup>a</sup> and adult: 0.1 ml single dose

## Technique and site of administration

- Clean the injection site with clean water. Do not use antiseptics as risk of inactivation of vaccine). Allow to dry.
- Administer intradermally. If the injection is correctly performed, an "orange-skin" papule measuring 5-8 mm in diameter should appear at the injection site.
- The vaccine is administered in the deltoid region of the arm, about one-third down the upper arm over the insertion of the deltoid muscle.
- The vaccine should be injected in the same place for each child so that the BCG scar is easier to locate.

## Contra-indications

- Do not administer to patients with congenital or acquired immunodeficiency (e.g. HIV infection or serologic status unknown, but symptoms consistent with HIV infection, immunosuppressive therapy, malignant haemopathy).
- Postpone vaccination until recovery in the event of acute extensive dermatosis, acute complicated malnutrition or severe acute febrile illness (minor infections are not contra-indications).

## Adverse effects

- Local reaction 2-4 weeks after injection: papule that ends up as an ulcer and usually heals spontaneously (dry dressing only) after 2 to 5 months, leaving a permanent
- Complications requiring no specific treatment and which almost always evolve favourably:
  - persistent ulcer with serous discharge for over 4 months after injection;
  - non-suppurated adenitis, most often axillary, sometimes cervical;
  - abscess at the injection site due to infection (red, hot and painful abscess) or inadvertent intradermal injection (cold and painless abscess).
- Uncommon complications:
  - suppurative lymphadenitis, mostly in neonates, usually due to inadvertent intradermal injection. The lymph node, which can have a diameter of over 3 cm, evolves toward chronic softening and fistulisation;
  - osteomyelitis (in exceptional cases);
  - disseminated BCG disease<sup>b</sup>, usually in immunocompromised children under 2 years, with a high mortality rate<sup>[2]</sup>.

## Precautions

- If administered simultaneously with other vaccines, use different syringes and injection sites. Do not mix with other vaccines in the same syringe.
- **Pregnancy:** CONTRA-INDICATED
- **Breastfeeding:** no contra-indication

## Storage



- Reconstituted vaccine: between 2 °C and 8 °C for 6 hours max.
- Powder: between 2 °C and 8 °C.
- Solvent: a cold chain is not required for However, at least 24 hours before reconstitution of the vaccine, the solvent must be refrigerated between 2 °C and 8 °C so that the solvent and lyophilised powder are at the same temperature: a temperature difference during reconstitution may reduce vaccine efficacy. Do not freeze.

## Footnotes

(a) BCG vaccine provides high protection for neonates, but only moderate for school age TST negative children.

(b) If disseminated BCG disease is diagnosed, a 6-month TB treatment should be administered.

## References

1. World Health Organization. *BCG vaccines: WHO position paper – February 2018/Vaccins BCG: Note de synthèse de l’OMS – Février 2018*. Weekly epidemiological record/Relevé épidémiologique hebdomadaire, 23 FEBRUARY 2018, 93<sup>th</sup> YEAR/23 FÉVRIER 2018, 93<sup>e</sup> ANNÉE, No 8, 2018, 93, 73–96.  
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2. Hesseling AC, Rabie H, Marais BJ, Manders M, Lips M, Schaaf HS, et al. *Bacille Calmette-Guérin vaccine-induced disease in HIV-infected and HIV-uninfected children*. Clin Infect Dis. 2006;42:548–58.  
<https://doi.org/10.1086/499953>

# Appendix 34. Request form for smear microscopy and Xpert assays

Update: March 2023

[Request form for smear microscopy and Xpert assays.pdf](#)  
[Request form for smear microscopy and Xpert assays.docx](#)

# Appendix 35. Request form for culture, pDST, LPA, genome sequencing

Update: August 2023

[Request form for culture, pDST, LPA, genome sequencing.pdf](#)  
[Request form for culture, pDST, LPA, genome sequencing.docx](#)



# Appendix 36. Drug-o-gram

Update: October 2023

## 36.1 Filling instructions

The drug-o-gram is filled in until the end of treatment. If necessary, add rows to the sections or use several drug-o-gram sheets.

### Section TREATMENT

Each time a drug is prescribed, a dose is changed, or a drug is stopped, note the date (first column) and then in the corresponding row:

- initial dose in mg (except PAS that is prescribed in g)
- new dose (if dose changed)
- a cross (X) if drug stopped

### Section MONITORING

Each time sputum is collected for microscopy and culture/pDST, note the date (first column), then the result in the corresponding row:

- for microscopy: neg; scanty; 1+; 2+; 3+
- for culture: pos; neg; cont (for "contaminated")

Note the date of results (last column).

### Section RMT and section pDST

Each time sputum is collected for a DST, note the date (first column), then the result for each drug tested in the corresponding row:

- R for "resistance"
- S for "susceptibility"
- NR for "invalid, error, no result"

Note the date of results (last column).

### Chest x-ray (CXR)

Each time CXR is performed, note the date and:

- I for "initial"
- IMP for "improvement"
- NC for "no change"
- D for "deterioration"

### Adherence rate (AR)

Note the date and percentage (%), see [Appendix 22](#).

**Note:** for dates, use dd/mm/yyyy format.

## 36.2 Example

This example is not a treatment protocol, but a fictive scenario to explain how to fill in the drug-o-gram.

A period of a few months is shown as an example, but the drug-o-gram should be updated until the end of treatment.

- 28/12/2022 Diagnosis of MDR-TB by Xpert assay. Sputum specimen sent for culture and pDST (n°1). CXR n°1.
- 29/12/2022 Start of treatment (BPALM regimen).
- 15/01/2023 Continuation of BPALM with reduction of Bdq to 3 times a week (Monday, Wednesday, Friday) as per standard protocol.
- 31/01/2023 Culture n°1 result (positive).
- 28/02/2023 pDST n°1 result (confirmation of MDR-TB; sensitivity to other drugs tested).
- 01/03/2023 New specimen sent for culture and pDST n°2 (monthly bacteriological follow-up).
- 02/04/2023 New specimen sent for culture and pDST n°3 (monthly bacteriological follow-up).
- 09/04/2023 Culture n°2 result (positive). New Xpert assay (emergence of FQ resistance). Request for full pDST on culture n°2 (and n°3 given that specimen for culture n°3 has already been sent).
- 10/04/2023 BPALM regimen discontinued (treatment failure). Start of individualised long regimen. Pending results of pDST n°2, continuation of Bdq (used but not counted as probably effective drug).
- 12/05/2023 pDST n°2 result (FQ resistance confirmed; emergence of Bdq resistance). Discontinuation of Bdq and reintroduction of Lzd 300 mg daily as per standard protocol.
- 04/06/2023 pDST n°3 result (confirmation of resistance to FQ and Bdq). Continuation of treatment. CXR n°2.

Etc.

TREATMENT																			MONITORING		
Date	H	R	Z	E	Lfx	Mfx	Bdq	Lzd	Cfz	Cs	Dlm	Am	Eto	PAS	H <sup>h</sup>	Pa	Other	Date collection	AFB	Culture	
29/12/2022						400	400	600								200		28/12/2022	3+	pos	31
15/01/2023						400	200 MWF	600								200		31/01/2023	2+	neg	
						400	200 MWF	600								200		01/03/2023	neg	pos	09 12
						400	200 MWF	600								200		02/04/2023	neg	pos	C 04
10/04/2023						X	200 MWF	X	100	750	200		750	8 g		X					
12/05/2023							X	300	100	750	200		750	8 g				04/05/2023	1+	neg	04
								300	100	750	200		750	8 g				03/06/2023	scanty	neg	

RMT																			
Date collection	H	R	Z	E	Lfx	Mfx	Bdq	Lzd	Cfz	Cs	Dlm	Am	Eto	PAS	H <sup>h</sup>	Pa	Other	Date result	Comments
28/12/2022	R	R			S	S						S						28/12/2023	
09/04/2023	R	R			R	R						S						09/04/2023	New resistance FQs
08/05/2023	R	R			R	R						S						08/05/2023	

pDST																			
Date collection	H	R	Z	E	Lfx	Mfx	Bdq	Lzd	Cfz	Cs	Dlm	Am	Eto	PAS	H <sup>h</sup>	Pa	Other	Date result	Comments
28/12/2022	R	R	S	-	S	S	S		S			S						28/02/2023	
01/03/2023	R	R	S	-	R	R	R	S	S	-	S	S	S	S	-	-		12/05/2023	Resistance FQs + Bdq
02/04/2023	R	R	S	-	R	R	R	S	S	-	S	S	S	S	-	-		04/06/2023	

<b>Date</b>	28/12/2022	15/01/2023	01/02/2023	01/03/2023	10/04/2023	12/05/2023	04/06/2023	dd/mm/yyyy	dd/mm/yyyy	dd/mm/yyyy
<b>Weight (kg)</b>	50.2	49.8	49.3	49	47.2	48	48.4			
<b>CXR</b>	I						NC			
<b>AR (%)</b>			90	90	85	100	90			

## 36.3 Templates

[Drug-o-gram.pdf](#)

[Drug-o-gram.docx](#)

# Appendix 39. TB facility assessment sheet

Update: March 2024

For each component evaluated, the answer (to be entered in the third column) is either:

- "yes" if the objective is met (e.g. FDCs and paediatric formulations are available),
- "no" if the objective is not met,
- the percentage observed (e.g. "100%" if all patients who interrupted their treatment are contacted to resume treatment).

When the answer is "no" or the result is less than 100%, details should be given and corrective action should be taken.

**Note:** for a more specific assessment of infection prevention and control (IPC) performance, see [Appendix 23](#).

[TB facility assessment sheet.pdf](#)

[TB facility assessment sheet.docx](#)

