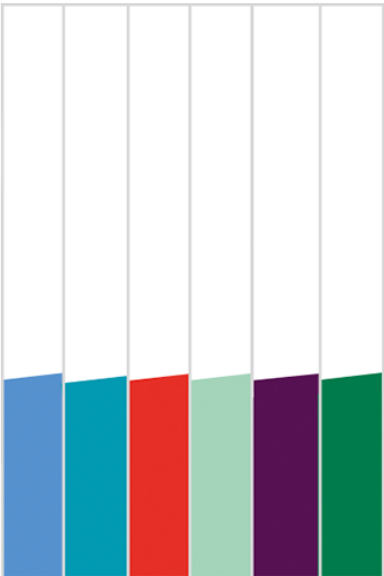


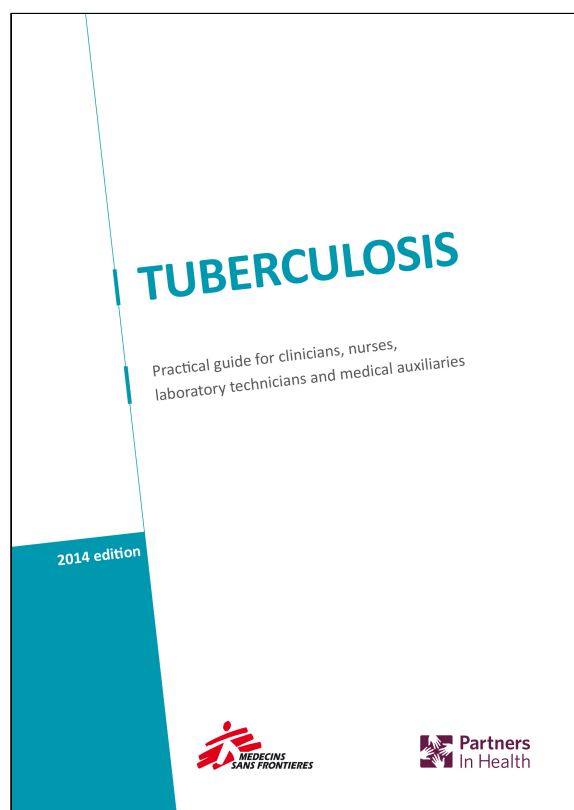
Tuberculosis



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Tuberculosis

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



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Introduction

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

ACH	Air change per hour
AFB	Acid-fast bacilli
AIDS	Acquired immunodeficiency syndrome
Amk	Amikacin
Amx/Clv	Amoxicillin/clavulanic acid
ARI	Annual risk of infection
ART	Antiretroviral therapy
ARV	Antiretroviral
BCG	Bacillus Calmette-Guérin
Bdq	Bedaquiline
CDC	United States Centers for Disease Control and Prevention
Cfz	Clofazimine
Cm	Capreomycin
CMX	Cotrimoxazole
CPC	Cetylpyridinium chloride
CPT	Cotrimoxazole preventive therapy
Cs	Cycloserine
CXR	Chest X-ray
DOT	Directly observed therapy
DR	Drug resistance
DR-TB	Drug-resistant tuberculosis
DST	Drug susceptibility test(ing)
E	Ethambutol

ECG	Electrocardiogram
EPTB	Extrapulmonary tuberculosis
Eto	Ethionamide
FDC	Fixed-dose combination
FNAC	Fine needle aspiration cytology
FQ	Fluoroquinolone
GFR	Glomerular filtration rate
H	Isoniazid
HCW	Health care worker
HIV	Human immunodeficiency virus
HPF	High-power field
IC	Infection control
IM	Intramuscular
Imp/Cln	Imipenem/cilastatin
IPT	Isoniazid preventive therapy
IRIS	Immune reconstitution inflammatory syndrome
IUATLD	International Union against Tuberculosis and Lung Disease
Km	Kanamycin
LFT	Liver function test
Lfx	Levofloxacin
LPA	Line probe assay
Lzd	Linezolid
MDR	Multidrug resistance
MDR-TB	Multidrug-resistant tuberculosis
Mfx	Moxifloxacin
MGIT	Mycobacteria growth indicator tube

MODS	Microscopic observation of drug susceptibility
Mpm	Meropenem
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
NTM	Non tuberculous mycobacteria
Ofx	Ofloxacin
PAS	Para-aminosalicylic acid
PCP	Pneumocystosis
PCR	Polymerase chain reaction
PI	Protease inhibitor
PO	Orally (per os)
Pto	Prothionamide
R	Rifampicin
Rfb	Rifabutin
RR	Rifampicin resistance
S	Streptomycin
TAT	Turn around time
TB	Tuberculosis
Thz	Thioacetazone
TLA	Thin-layer agar
TSH	Thyroid-stimulating hormone
TST	Tuberculin skin test
UVGI	Ultraviolet germicidal irradiation
WHO	World Health Organization
XDR	Extensive drug resistance
XDR-TB	Extensively drug-resistant tuberculosis

Z	Pyrazinamide
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Chapter 1: Introduction and epidemiology

- [1.1 Characteristics of *Mycobacterium tuberculosis* bacillus](#)(see page 13)
- [1.2 Transmission](#)(see page 13)
- [1.3 Evolution of TB infection and disease in humans](#)(see page 14)
- [1.4 Prognosis](#)(see page 16)
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- [References Chapter 1](#)(see page 19)

1.1 Characteristics of *Mycobacterium tuberculosis* bacillus

Mycobacteria are small rod-shaped bacilli that can cause a variety of diseases in humans. They can be thought of in three main groups:

– *Mycobacterium tuberculosis* complex: this group includes *M. tuberculosis*, *M. bovis*, *M. africanum*, *M. microti*, and *M. canetti*. They all can cause “tuberculosis” in humans. The vast majority of tuberculosis is caused by *M. tuberculosis*, with the other organisms being relatively rare. Their treatment is similar (with *M. bovis* being innately resistant to pyrazinamide and *M. africanum* being innately resistant to thioacetazone).

This guide only addresses disease caused by *Mycobacterium tuberculosis* complex.

– *Mycobacterium leprae* causes leprosy.

– Non tuberculous mycobacteria (NTM): this group includes all the other mycobacteria that can cause diseases in humans. NTM sometimes can cause clinical manifestations (in the lungs, skin, bones, or lymph nodes) similar to those of tuberculosis. Most NTM exist in the environment, are not usually spread from person to person and are often non-pathogenic in persons with intact immune system or healthy lung tissue.

All mycobacteria are classical acid-fast organisms and are named so because of the stains used in evaluation of tissue or sputum specimens (i.e. Ziehl-Neelsen stain, [Chapter 3](#)(see page 30)).

M. tuberculosis multiplies more slowly than the majority of bacteria; this is why tuberculosis has a slower evolution (causes disease weeks or even months to years after infection) than most other bacterial infections.

M. tuberculosis is a strictly aerobic bacterium. It therefore multiplies better in pulmonary tissue (in particular at the apex, where oxygen concentration is higher) than in the deeper organs.

1.2 Transmission

M. tuberculosis is transmitted from human-to-human and is mainly spread by airborne route. The source of infection is a patient with pulmonary or laryngeal tuberculosis (TB) who expectorates bacilli. During coughing, speaking, or sneezing, the patient produces tiny infectious droplets. These particles, called droplet nuclei, are about 1 to 5 microns in diameter—about 1-5/1000 of millimetre. Droplet nuclei can remain suspended in the air for several hours, depending on the environment.

Transmission may occur when these infectious droplets are inhaled. Sunlight, UV light and ventilation are effective in decreasing the ability of the droplets reaching the lung ([Chapter 14](#)(see page 120)).

The other modes of transmission are far less common. Cutaneous or mucous inoculation rarely occurs, although such cases have been observed in laboratory personnel. A rare cause of digestive transmission of TB can occur with *M. bovis*, most commonly through cow's milk.

The infectiousness of a patient is linked to the quantity of bacilli contained in his sputa. Patients with sputum smear-positive microscopy are by far the most contagious. Those with smear-negative/culture-positive results are less contagious. Patients whose sputum smear microscopy and culture are both negative are usually not contagious.

Patients who are infected with *M. tuberculosis*, but do not have active disease, cannot transmit TB. Extrapulmonary (EP) forms of TB are only contagious in exceptional circumstances. Children are generally much less contagious 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 three factors:

Contagiousness of the source (the greatest factor):

- Bacteriological status: smear-positive being the most infectious;
- Virulence of the tubercle bacilli: certain strains are very transmissible (and/or more likely to cause active disease).

Environment where the exposure occurred:

- Open air and sunlight are conditions less likely to lead to transmission, whereas small rooms/settings with no ventilation are the conditions most likely to lead to transmission.
- The proximity of the person to the patient is also important (i.e. sleeping next to the patient in the ward versus sleeping 20 meters away).

Duration of exposure:

Close contacts of TB patients are at highest risk of becoming infected with *M. tuberculosis*. They may be family members, roommates, friends, co-workers or others who spend multiple hours per day with the TB patient while the person is infectious.

The best way to stop transmission is to start giving patients effective TB treatment as soon as possible. The length of time required for a TB patient to become non-infectious after starting TB therapy is not exactly known. However, once an effective TB therapy is started, as long as the patient follows the prescribed treatment regimen, there is considerable evidence showing the infectiousness can rapidly decline, even after a few days¹(see page 19),²(see page 19),³(see page 19).

It is estimated that a person with smear-positive TB, undiagnosed and untreated, transmits the bacillus to 10 to 20 people per year (this varies according to lifestyle and environment).

1.3 Evolution of TB infection and disease in humans

- [1.3.1 Primary infection](#)(see page 15)

- [1.3.2 Active TB](#)(see page 15)
- [1.3.3 Risk factors for developing active TB](#)(see page 15)

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 may begin.

1.3.1 Primary 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 represents 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 will be contained and encapsulated with a central zone of parenchymal necrosis (caseous necrosis). It is at this moment that specific TB immunity appears, and a positive skin reaction to tuberculin is observed⁴(see page 19),⁵(see page 19). This stage is usually asymptomatic; however, in some rare cases, hypersensitivity reactions may occur.

Note: a small area of granulomatous inflammation will occur in the alveoli, which is not usually detectable on chest X-ray unless it calcifies or grows substantially. It is called a primary focus.

In the majority of cases (90 to 95% of non-HIV infected patients), the pulmonary lesions gradually heal. In 5 to 10% of the cases, the pulmonary lesion will progress to active disease either by gradual progression and/or spread via lymphatics or blood or by reactivation (often many years later) of primary or secondary lesions.

1.3.2 Active TB

Before immunity is established, bacilli from the primary infectious focus or from a near-by lymph node can be transported and disseminated throughout the body via the lymph system or the bloodstream. Secondary foci containing bacilli can be born 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 spontaneously resolve. Yet, a number of bacilli may remain latent in the secondary foci for months or even years⁶(see page 19).

Different factors can reduce immunity (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 disease”⁵(see page 19).

While active TB may occur after months or years without clinical signs following primary infection, it is estimated that half of the cases of active TB appear in the year following infection.

1.3.3 Risk factors for developing active TB

The risk depends on a number of factors including those that lead to a weakened immune system, damaged lungs, or the intensity and duration of exposure:

Host immune defences:

- HIV infection (risk multiplied by 20-40);
- Diabetes mellitus (risk multiplied by 3-5);
- Malnutrition;
- Prolonged therapy with corticosteroids (such as prednisolone) and other immuno - suppressive therapies;
- Certain types of cancer (e.g., leukaemia, Hodgkin's lymphoma, or cancer of the head and neck);

- Severe kidney disease;
- Alcoholism;
- Substance abuse;
- Age:
 - Young children (children under 5 have twice the risk and higher risks are observed for those under 6 months);
 - Persons over sixty years have 5 times the risk;
- Pregnancy.

Conditions that damage the lung:

- Tobacco smoking;
- Silicosis.

Intensity of exposure (number of inhaled bacilli):

- Contagiousness of the source;
- Environment and proximity in which the exposure took place;
- Duration of exposure;
- Residents and employees of high-risk congregate setting.

1.4 Prognosis

TB is a severe and often deadly disease without treatment. After 5 years without treatment, the outcome of smear-positive pulmonary TB (PTB) in HIV-negative patients is as follows:

- 50-60% die (case fatality ratio for untreated TB);
- 20-25% are cured (spontaneous cure);
- 20-25% develop chronic smear-positive TB.

With adequate treatment, the case fatality ratio (CFR) often falls to less than 2 to 3% under optimal conditions.

Similar CFRs are seen with untreated EPTB and smear-negative PTB, with an equivalent fall in CFR with adequate treatment.

Untreated TB in HIV-infected patients (not on antiretrovirals) is almost always fatal.

Even on antiretrovirals, the CFR is higher than in non-HIV infected patients^{7(see page 19),8(see page 19)}.

1.5 Factors modifying TB epidemiology

- [1.5.1 Socioeconomic development\(see page 17\)](#)
- [1.5.2 TB treatment\(see page 17\)](#)
- [1.5.3 HIV infection\(see page 17\)](#)
- [1.5.4 BCG vaccination\(see page 17\)](#)
- [1.5.5 Other factors\(see page 18\)](#)

There are four major factors that influence TB epidemiology: (1) socioeconomic development; (2) TB treatment; (3) HIV infection; and (4) BCG vaccination.

1.5.1 Socioeconomic development

In European countries, the incidence and specific mortality of TB have diminished by 5 to 6% per year since 1850. This progressive improvement dates back to before the era of vaccination and antibiotics and was correlated with socioeconomic development (improvement of living conditions, nutritional status of populations, etc.). TB is a disease of the poor: over 95% of cases occur in resource-constrained countries and in poor communities. In industrialised countries, TB generally affects the most disadvantaged social groups.

1.5.2 TB treatment

Diagnosing and initiating effective treatment in a patient early in the course of their TB disease, before they can infect many people, is considered the most effective preventive measure against TB. Effective treatment substantially reduces or eliminates disease transmission from smear-positive patients in less than one month after initiation of treatment.

Since the introduction of anti-TB treatment, a rapid reduction of the annual risk of infection (ARI) has been observed in many industrialised countries, with the infection risk diminishing by approximately 50% every 5 to 7 years during this period⁹(see page 19). This tendency was observed in countries having a BCG vaccination programme, as well as, in those without one. This reduction of the risk of infection is a direct consequence of detection programmes, diagnosis and treatment.

1.5.3 HIV infection

Immunodeficiency induced by HIV infection is a major risk factor for progression of TB infection and has a dramatic impact on the epidemiology of TB. While the lifetime risk of TB disease after infection is approximately 10%, patients infected with both by HIV and *M. tuberculosis* have an approximate risk of 10% annually. Approximately 12 to 14% of TB cases in the world are at present among HIV patients¹⁰(see page 19). The African region accounts for 82% of the TB cases among HIV patients¹¹(see page 19),¹²(see page 19). The impact of HIV on TB epidemiology can only increase with the spread of the HIV epidemic in Asia, where two-thirds of the world's *M. tuberculosis*-infected population lives.

1.5.4 BCG vaccination

The effect of BCG vaccination is controversial. Two notions may be distinguished: the effectiveness of BCG at an individual level and the epidemiological impact of this vaccination.

Effectiveness of BCG at an individual level

Even though results of controlled surveys are contradictory (efficacy ranging from 0 to 80%), it is acknowledged that BCG, if administered before primary infection (as is done in the practice of giving it at birth), confers a protection of 40 to 70% for a period of approximately 10 to 15 years¹³(see page 19),¹⁴(see page 19),¹⁵(see page 19),¹⁶(see page 19). Protection from the severe forms of TB in children (miliary and meningitis) is estimated at 80%.

Epidemiological impact of vaccination

The analysis of public health statistics of some European countries has shown that BCG vaccination reduces the number of active TB cases in vaccinated subjects as compared to those unvaccinated. Models demonstrate that even moderately effective vaccines could have a significant effect on reducing tuberculosis epidemics if they can be coupled with moderate to high treatment rates¹⁷(see page 19). Despite some protection of the BCG vaccination, the impact of BCG vaccination on TB transmission and the TB epidemic is generally considered quite minimal¹⁸(see page 19) and more effective vaccines are needed.

1.5.5 Other factors

Other modifying factors include infection control measures ([Chapter 14](#)[\(see page 120\)](#)) and isoniazid preventive therapy for latent TB ([Chapter 16](#)[\(see page 130\)](#)). The degree to which the TB epidemiology is affected by these measures is not known.

1.6 Epidemiological indicators

When a National TB Programme (NTP) is functioning well, indicators from the local authorities and NTP can be obtained.

If not, the WHO developed a TB country profile sheet for each country [1](#)[\(see page 0\)](#) where there are estimated TB incidences and prevalence, as well as, the HIV co-infection rate and estimated MDR-TB rates among new and previously treated TB cases.

The following are the most common indicators:

– **Annual incidence rate of all TB cases**

Number of new cases of TB (all forms) that develop in a population of individuals during one year. The standard is to express it for 100,000 inhabitants.

– **Annual incidence rate of smear-positive TB cases**

Number of new smear-positive cases of PTB that develop in a population of individuals during one year. The standard is to express it for 100,000 inhabitants.

– **Prevalence of smear-positive TB**

Proportion of a population presenting with smear-positive TB at a specific time, usually one year, and reported per 100,000 population. Prevalence represents approximately double the incidence.

– **Proportion of MDR-TB among new and previously treated cases** ([Chapter 7](#)[\(see page 61\)](#)).

– **HIV positivity rate among all TB patients**

Proportion of HIV positive patients among all TB patients diagnosed during a given period of time.

[1](#)[\(see page 0\)](#) http://apps.who.int/iris/bitstream/10665/75938/1/9789241564502_eng.pdf

1.7 Estimation of the burden of TB worldwide

TB today is second only to HIV/AIDS as the major cause of death from an infectious disease.

In 2011, there were 8.7 million estimated incident cases of TB and 1.4 million estimated deaths, including almost 1 million deaths from HIV-negative individuals and an additional 430,000 deaths from HIV-associated TB [7](#)[\(see page 19\)](#), [19](#)[\(see page 19\)](#). While the absolute number of TB cases has been slightly decreasing since 2006, there are many parts of the world where the number of TB cases is still increasing [19](#)[\(see page 19\)](#).

1.8 Drug-resistant TB worldwide

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

Multidrug-resistant TB (MDR-TB) is defined as TB that is resistant to at least isoniazid and rifampicin.

Extensively drug-resistant TB (XDR-TB) is defined as TB that is resistant to isoniazid and rifampin, any fluoroquinolone and at least one of three injectable second-line drugs (amikacin, kanamycin or capreomycin).

In 2008, an estimated 390,000 to 510,000 MDR-TB cases emerged globally (best point estimate is 440,000 cases)⁷(see page 19). Among incident TB cases globally, 3.7% of new cases and 20% of previously treated cases are estimated to have (MDR-TB)¹⁹(see page 19). In 2008, MDR-TB caused an estimated 150,000 deaths.

In some parts of the world, like the former Soviet Union and Eastern Europe, the percent of new and previously treated TB cases with DR-TB is alarmingly high with some areas reporting greater than 30% in new cases and greater than 70% in retreatment cases (e.g. Belarus).

In contrast, in countries like China and India, the percentage of new cases with MDR-TB is low, but due to the high TB incidence and population density, these countries yield a disturbingly high estimate of absolute number of MDR-TB cases. It is estimated that almost 50% of the world's cases of MDR-TB occur in China and India alone.

Africa does not have survey data for DR-TB for all countries. However the limited survey data in the continent suggests that the MDR-TB burden is significant in some regions, especially in Southern Africa.

As of 2012, XDR-TB, has been identified in 84 countries, such that the average proportion of MDR-TB cases with XDR-TB is estimated to be 9%¹⁹(see page 19).

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Chapter 2: Clinical presentation

- 2.1 Pulmonary tuberculosis (PTB)(see page 21)
- 2.2 Extrapulmonary tuberculosis (EPTB)(see page 22)
- 2.3 Disseminated or miliary tuberculosis(see page 25)
- 2.4 Clinical presentation in HIV-infected patients(see page 25)
- 2.5 Summary of clinical presentations of tuberculosis(see page 27)
- References Chapter 2(see page 28)

2.1 Pulmonary tuberculosis (PTB)

Certain signs of PTB are quite typical: prolonged cough (lasting more than 2 weeks) and sputum production, while others are less so: weight loss, anorexia, fatigue, shortness of breath, chest pain, moderate fever, and night sweats.

Haemoptysis (blood in sputum) is a characteristic sign present in about one third of patients¹(see page 28),²(see page 28).

All these signs are variable and evolve in a chronic, insidious manner. History taking and questioning the patient are therefore of the utmost importance.

Advanced forms and complications are not uncommon. These include:

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

In an endemic area, the diagnosis of PTB is to be considered, in practice, for all patients who have experienced respiratory symptoms for more than 2 weeks.

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

Table 2.1 - Differential diagnosis for PTB (non-HIV infected patients)

Diseases	Comments
Bacterial pneumonia	<ul style="list-style-type: none"> • Usually more acute and shorter in duration; high fever often present. • Response to broad-spectrum antibiotics with no anti-TB activity suggests bacterial pneumonia. • Lobar consolidation is typical of bacterial pneumonia, however, X-ray alone cannot differentiate TB from bacterial pneumonia.
Pulmonary abscess	<ul style="list-style-type: none"> • Usually arises from aspiration in individuals with impaired consciousness (coma, intoxication with alcohol/drugs, etc.). • Bad smelling, purulent sputum. • Cavities typically have a thick-wall and air-fluid levels.

Bronchiectasis	<ul style="list-style-type: none"> • Frequent complication of successive, poorly treated bronchopulmonary infections in tropical regions. • Haemoptysis, usually mild, can be present.
Lung cancer	<ul style="list-style-type: none"> • History of smoking or exposure to environmental toxins (working in a mine, etc.). • Haemoptysis in 20 to 50% of patients.
Paragonimiasis (lung flukes)	<ul style="list-style-type: none"> • To be ruled out in TB suspect cases in endemic areas (certain areas of South- Eastern Asia, Western Africa and Latin America).
Pulmonary echinococcosis (hydatid disease)	<ul style="list-style-type: none"> • In Latin America, the Middle East, some sub-Saharan African countries, China. • Lung involvement may cause chronic cough with or without haemoptysis. • Cysts can mimic TB cavities.
Pneumocystosis	<ul style="list-style-type: none"> • In immunocompromised patients on corticosteroids or cancer chemotherapy agents.
Less common diseases	<ul style="list-style-type: none"> • Silicosis, sarcoidosis, berylliosis, melioidosis, cryptococcosis, aspergillosis, histoplasmosis.

For differential diagnosis in HIV-infected patients, see [Section 2.4](#)(see page 25).

2.2 Extrapulmonary tuberculosis (EPTB)

- [2.2.1 Lymph node tuberculosis](#)(see page 23)
- [2.2.2 Tuberculous meningitis](#)(see page 23)
- [2.2.3 Tuberculosis of bones and joints](#)(see page 23)
- [2.2.4 Genitourinary tuberculosis](#)(see page 24)
- [2.2.5 Abdominal tuberculosis](#)(see page 24)
- [2.2.6 Tuberculous pleural effusion](#)(see page 24)
- [2.2.7 Tuberculous pericardial effusion](#)(see page 24)
- [2.2.8 Cutaneous tuberculosis](#)(see page 25)

Starting from a pulmonary localisation (primary infection), *M. tuberculosis* can spread to other organs during a silent phase, generally at the beginning of the infection ([Chapter 1](#)(see page 13)). Active TB can develop in many other parts of the body, in particular lymph nodes, meninges, vertebrae, joints, kidneys, genital organs and the abdominal cavity.

EPTB forms can develop at any age. Young children and HIV infected adults are more susceptible.

EPTB forms present with a variety of clinical characteristics. However, a common characteristic is the insidious evolution with gradual deterioration of the physical condition. Furthermore, there is a lack of response to symptomatic or non-tuberculosis anti-infective treatments. EPTB may be associated with a pulmonary localisation, which should be searched for when ever EPTB is diagnosed or suspected. [Table 2.3](#)(see page 27), at the end of this chapter, summarizes the characteristics of EPTB.

2.2.1 Lymph node tuberculosis

Lymph node TB is a common presentation particularly in certain areas of Africa and Asia, where it represents up to 25% of TB cases³(see page 28),⁴(see page 28). This form is more common in children and HIV-infected patients.

The presentation of lymph node tuberculosis is non-inflammatory adenopathies, cold and painless, single or multiple, usually bilateral, evolving in a chronic mode towards softening and fistulisation. Cervical localisation is most frequent, ahead of axillary and mediastinal forms. They are associated with other localisation in 10 to 30% of cases.

Diagnosis is mainly clinical, however fine needle aspiration can be done if the diagnosis is in question (Chapter 3, [Section 3.10](#)(see page 37)).

Adenopathies usually disappear in less than 3 months after treatment initiation. Paradoxical reactions may be observed at the beginning of treatment (appearance of the lymph node getting worse with abscesses, fistulas or other lymph nodes appearing) and often a change in the treatment is not needed.

Differential diagnosis includes 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

Meningitis due to tuberculosis is most common in children below 2 years of age⁵(see page 28) and in HIV-infected adults. Headaches, irritability, fever, and an altered mental status accompany the beginning of the disease, often in a variable manner, which is progressive in nature. The meningeal syndrome (stiff neck, hypotonia in infants, photophobia and headache) is present in most cases. Vomiting may be present. The impairment of the third cranial nerve is a sign that can accompany TB meningitis (oculomotor paralysis).

The main differential diagnoses are other forms of meningitis where the cerebrospinal fluid (CSF) is clear – viral/fungal meningitis or incompletely treated bacterial meningitis are the most common.

TB meningitis is a medical emergency, and any delay in diagnosis/treatment may result in irreversible neurological sequelae⁵(see page 28).

2.2.3 Tuberculosis of bones and joints

Tuberculosis of bones and joints is mostly found in children, probably because of better vascularisation and oxygenation of osteo-articular structures during growth.

Arthritis: Often arthritis due to TB is a chronic monoarthritis, starting insidiously, with little or no pain and accompanied by joint destruction. The joints most often affected are the hips, knees, elbows and wrists. Half of the patients with TB arthritis have PTB at the same time.

Osteitis: This is the less frequent presentation of TB of the bones. It may be a primary osteitis or an osteitis complicating arthritis. It affects long bones and is occasionally accompanied by cold abscesses. Like arthritis, it is distinguished from common bacterial infections by the contrast of slight symptoms and the extent of destruction detected by radiography.

Spondylodiscitis (TB of the spine or Pott's disease): TB of the spine affects vertebrae and disks, bringing about destruction and deformation of the spine. A missed diagnosis of thoracic or cervical spinal TB can result in paralysis. Dorsal localisation is the most frequent followed by lumbar and lumbosacral areas. Localised pain may precede the appearance of the first radiological anomalies (destruction of an inter-vertebral disk) by several months. A para-vertebral cold abscess may accompany osteo-articular lesions, yet neurological signs may complicate them.

The diagnosis is often made based on the clinical history and X-ray, as biopsy and culture is difficult to perform in resource-constrained settings. Deterioration of physical condition and prolonged and insidious clinical history of osteitis or arthritis are in favour of TB aetiology as opposed to bacterial osteomyelitis or brucellosis. The patient may have a history of not responding to broad-spectrum antibiotics.

2.2.4 Genitourinary tuberculosis

Renal involvement is frequent and may be asymptomatic for a lengthy period of time, with a slow development of genitourinary signs and symptoms including: dysuria, urinary frequency, nocturia, urgency, back and flank pain, abdominal pain, tenderness/swelling of the testes or epididymitis and haematuria. General physical condition is preserved most of the time with only about 20% of patients having constitutional symptoms⁶(see page 28).

Diagnosis is suspected in the presence of pyuria (white blood cells in the urine) and micro or macroscopic haematuria, which does not respond to broad-spectrum antibiotics. Examination of the urine aids in diagnosis (Chapter 3, [Section 3.10](#)(see page 37)).

In women, genital tract contamination can also happen by a haematogenous path. Abdominal pain, leucorrhoea and vaginal bleeding are variable, non-specific signs of genital tract tuberculosis. Extension may be found in the peritoneum with resulting ascites. The presenting complaint leading to the diagnosis of genitourinary disease is often sterility.

In men, genital localisation is secondary to renal localisation. It is manifested most often by epididymitis with scrotal pain.

2.2.5 Abdominal tuberculosis

Abdominal TB commonly presents as ascites resulting from the peritoneal localisation of the infection. The frequency of chronic ascites in tropical regions, with its many different causes, makes this relatively uncommon form of TB a common diagnostic challenge⁷(see page 28). Diagnosis is assisted greatly by examination of the ascitic fluid via paracentesis (Chapter 3, [Section 3.10](#)(see page 37)).

Besides ascites, clinical symptoms are non-specific: abdominal pain, diarrhoea and constitutional symptoms (fever, night sweats, malaise, weight loss). The ascites may mask weight loss.

2.2.6 Tuberculous pleural effusion

TB pleural effusion by itself is often asymptomatic, especially if less than 300 ml. When the effusion is large, shortness of breath may be present. Sputum production and cough may only be present if there is also pulmonary involvement, which is common. Constitutional symptoms such as fever, weight loss, night sweats, anorexia and malaise may also be present.

This form of TB is more frequent in young adults⁸(see page 28). Diagnosis is assisted by examination of the pleural fluid via paracentesis (Chapter 3, [Section 3.10](#)(see page 37)).

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. The clinical examination may show pericardial friction rub, raised jugular pressure and tachycardia. The radiography and ultrasounds are key elements for diagnosis (Chapter 3, [Section 3.7](#)(see page 35)).

Pericardiocentesis may be necessary in the event of acute heart failure resulting in haemodynamic compromise. It must be performed by experienced personnel in well-equipped hospitals.

2.2.8 Cutaneous tuberculosis

The clinical presentation of cutaneous tuberculosis is chronic, painless, non-pathognomonic lesions, ranging from small papula and erythema to large tuberculomas. The diagnosis is based on culture from a biopsy⁹(see page 28).

2.3 Disseminated or miliary tuberculosis

Miliary TB is a generalised massive infection characterized by diffusion of bacteria throughout the body. The disease may manifest as a miliary pattern or very small nodular elements (“millet seeds”) in the lungs. It can occur immediately after primary infection or during reactivation of a latent site; it is thought to occur during haematological spread¹⁰(see page 28).

The classic acute form is mostly found in children, young adults and HIV patients. The presentation can be either abrupt or insidious, marked by a progressive deterioration of the patient’s physical condition. The clinical picture is often completed within one to two weeks and is characterized by a profoundly altered physical condition, marked wasting, headaches and constant high fever. Discrete dyspnoea and coughing suggest a pulmonary focus; however, lungs can often be clear on auscultation. A moderate hepatosplenomegaly is occasionally found. Certain forms of miliary TB evolve in a subacute fashion over several months.

Given this non-specific clinical picture, typhoid fever and septicaemia should be considered in a differential diagnosis.

Diagnosis of miliary TB is confirmed by chest X-ray (Chapter 3, Section 3.7(see page 35)). When feasible, fundoscopy would reveal choroidal tubercles. Generally, sputum smear examination is negative. When there is no possibility of obtaining chest X-rays, the lack of response to broad-spectrum antibiotics is an argument in favour of miliary TB.

In children, the risk of meningeal involvement is high (60-70%)¹¹(see page 28),¹²(see page 28). Lumbar puncture should be routinely performed if miliary TB is suspected.

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

Miliary TB is a medical emergency.

2.4 Clinical presentation in HIV-infected patients

TB is a leading cause of HIV-related morbidity and mortality, and it is one of the main opportunistic diseases¹³(see page 28). According to the WHO clinical staging of HIV/AIDS, HIV patients with pulmonary TB are in clinical stage III and HIV patients with extrapulmonary TB are in clinical stage IV¹⁴(see page 28).

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 HIV-negative individuals.

As the immune system deteriorates in later stages of the disease, the patterns of TB presentation become increasingly atypical, with pulmonary smear-negative, disseminated, and extrapulmonary TB

forms becoming more common. These cases are more difficult to diagnose and have a higher fatality rate than smear-positive cases. Algorithms presented in Chapter 4, [Section 4.2](#)(see page 44) use clinical criteria combined with laboratory and other investigations to help diagnose TB in HIV-infected individuals.

HIV patients with PTB tend to experience more fever and weight loss compared to those who are HIV-negative. Yet, these patients suffer with less coughing and haemoptysis due to lesser inflammation and cavity formation. Smear microscopy is more often negative.

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

Table 2.2 - Differential diagnosis for PTB in HIV-infected patients

Diseases	Comments
Other pneumonia (bacterial, viral, atypical)	<ul style="list-style-type: none"> Bacterial pneumonia (most often <i>S. pneumoniae</i>, <i>H. influenzae</i>) is common at all stages of HIV infection. Atypical pneumonia (<i>M. pneumoniae</i>, <i>C. pneumoniae</i>) and viral pneumonia (respiratory syncytial virus, cytomegalovirus) are possible at any CD4 count, except cytomegalovirus which occurs at CD4 < 50.
Pneumocystosis (<i>Pneumocystis jirovecii</i> pneumonia or PCP)	<ul style="list-style-type: none"> PCP has many characteristics in common with TB (insidious onset, persistent cough, fever) but tends to occur in the latter stages of HIV infection (CD4 < 200). It imparts a greater degree of dyspnoea, rarely produces effusions, and is not usually accompanied by haemoptysis. For more information, see Diagnostic algorithm 2(see page 47), Chapter 4.
Pulmonary Kaposi's sarcoma (KS)	<ul style="list-style-type: none"> KS can resemble TB, with slow-onset of cough, fever, haemoptysis, night sweats and weight loss. It is a disease of late-stage HIV, and in most cases, is preceded or accompanied by lesions involving the skin and mucus membranes.
Less common diseases	<ul style="list-style-type: none"> Pulmonary cryptococcosis, histoplasmosis and other fungal infections. Pulmonary nocardiosis: on direct smear, nocardia are weakly acid-fast, similar in appearance to mycobacteria (although they are branching filamentous bacilli, particularly on Gram staining).

In HIV adult patients, the most common non-pulmonary forms of TB are lymphadenopathy, pleural effusion, pericarditis, meningitis, as well as, miliary (disseminated) TB. In HIV-infected children, miliary TB, TB meningitis and diffuse lymphadenopathy are the most common non-pulmonary forms.

PTB is also present in patients with EPTB.

Immune reconstitution inflammatory syndrome (IRIS) is a clinical presentation of TB in patients starting antiretroviral therapy. See Chapter 12, [Section 12.7](#)(see page 113) for clinical presentation and management of IRIS¹⁵(see page 28).

2.5 Summary of clinical presentations of tuberculosis

Table 2.3 - Clinical presentations and considerations for HIV-infected patients

Site	Clinical presentation	Considerations for HIV infected patients
Pulmonary	<ul style="list-style-type: none"> • Prolonged cough (> 2 weeks), sputum production, chest pain, shortness of breath. • Haemoptysis • Constitutional symptoms often present: fever, night sweats, weight loss, anorexia, fatigue. 	<ul style="list-style-type: none"> • See algorithms Chapter 4(see page 44).
Disseminated, miliary TB	<ul style="list-style-type: none"> • Non specific symptoms: high fever, headache, weight loss. • Deterioration over days to weeks. • Simultaneous involvement of multiple organs. • High risk of meningitis in children (60- 70%). 	<ul style="list-style-type: none"> • Miliary TB can be under-diagnosed, as it may be confused with severe wasting in advanced stages of HIV infection. • 90% have miliary findings on X-ray. • TB can sometimes be isolated from blood cultures in HIV-infected individuals (which rarely is the case in non-HIV individuals).
Lymph nodes	<ul style="list-style-type: none"> • Non-painful, non-inflamed lymphadenopathy (> 4 weeks, > 2 cm). • Softening and fistulising to become chronic. • Most often in cervical region. • Often associated with other TB sites. 	<ul style="list-style-type: none"> • Lymphadenopathy is relatively common in HIV and can result from HIV infection. In persistent generalized lymphadenopathy (PGL), lymph nodes are symmetrical, not tender. Posterior cervical or epitrochlear nodes are often involved. • Other causes of lymphadenopathy are more common: lymphoma, carcinomatous metastases, Kaposi's sarcoma.
Meningitis	<ul style="list-style-type: none"> • Subacute, developing over days to weeks. • Fever, irritability, poor feeding, headaches, behaviour change. • Vomiting, neck stiffness and photophobia usually present. • Often associated with miliary TB. 	<ul style="list-style-type: none"> • Often insidious onset compared to other meningitis that can occur with HIV patients. • Perform antigen test CrAg LFA (Lateral Flow Assay) on serum and CSF to rule out cryptococcal meningitis.
Osteoarticular TB	<ul style="list-style-type: none"> • Monoarthritis with little or no pain, accompanied by joint destruction. 	<ul style="list-style-type: none"> • More common in HIV-positive. • Multifocal disease is more common.
Spinal TB (Pott's disease)	<ul style="list-style-type: none"> • Deformation of the spine. 	<ul style="list-style-type: none"> • More common in HIV-positive.

Abdominal TB	<ul style="list-style-type: none"> • Ascites (rule out other possible causes) • Abdominal mass (25-50% in the right lower quadrant), pain or diarrhoea. • Usually fever > 2 weeks. 	<ul style="list-style-type: none"> • Higher rate of PTB present than in HIV-negative.
Pleural effusion	<ul style="list-style-type: none"> • Pleuritic chest pain, dyspnoea. • More common in young adults. 	<ul style="list-style-type: none"> • Serious effusions are common in HIV.
Pericardial effusion	<ul style="list-style-type: none"> • Chest pain, dyspnoea, lower limb oedema or ascites, pericardial friction rub. 	<ul style="list-style-type: none"> • In the presence of a pericardial effusion (in high TB-HIV prevalence areas), TB is often the most likely treatable cause.

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Chapter 3: Diagnostic investigations

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- [3.3 Phenotypic drug susceptibility tests \(DST\)](#)(see page 31)
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- [3.8 Tuberculin skin test \(TST\)](#)(see page 36)
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3.1 Sputum smear microscopy

Sputum smear microscopy allows a rapid and reliable identification of patients with pulmonary tuberculosis (PTB) where there are more than 5000 bacilli/ml of sputum.

If the sputum has less than 5000 bacilli/ml, smear microscopy is highly unlikely to diagnose PTB, thus has an overall low sensitivity for PTB¹(see page 39),²(see page 39),³(see page 39).

Another shortcoming of smear microscopy is its non-specificity, such that *M. tuberculosis* appears the same as non tuberculous mycobacteria (NTM). However, in areas of high TB prevalence, positive smears have a very high probability of being *M. tuberculosis*.

The reliability of sputum microscopy depends on the quality of sputum collection. Sputum produced on early morning often shows a higher concentration of *M. tuberculosis*. Importantly, the reliability of sputum microscopy depends on the proper preparation and interpretation of slides. Thus, laboratory technicians must be properly trained and quality control checks must be regularly carried out in a supervising laboratory.

It is recommended that all patients suspected of PTB should submit at least two sputum specimens. Studies have shown that, when collection and examination techniques are correctly conducted, about 80% of sputum smear-positive patients are found during the first sputum examination and over 15% more during the second. Successive, repeated examinations yield fewer positives⁴(see page 39).

Usually, a first sample is collected at the time of the consultation when the patient is identified as a suspected TB case. A second sample is collected in the early morning the day after the initial consultation (and the patient brings the sample to the health facility if it is collected at home).

In order to limit the number of visits to the health facility, “frontloaded microscopy” (also referred to as 'same day' or 'spot-spot' microscopy) can be performed. Two sputum specimens are collected one hour apart. This strategy has shown similar results to the standard strategy over two days (spot-morning-spot) in terms of diagnostic yield⁵(see page 39).

See [Appendix 1](#)(see page 149) for sputum specimen collection, storage and shipment.

The staining methods uses a technique where the mycobacteria retain a primary stain after exposure to decolourising acid-alcohol, hence the term “acid-fast bacilli” (AFB). The two most common methods of staining, which determine the acid-fast nature of the mycobacteria, are Ziehl-Neelsen staining and auramine staining ([Appendix 2](#)(see page 153))⁶(see page 39).

Auramine staining has the advantage of permitting a more rapid slide reading. It is recommended in laboratories with a high workload defined as ≥ 20 slides per reader per day. It requires trained, experienced technicians and a fluorescent microscope. LED (lightemitting-diodes) modules that can be adapted to ordinary microscopes or new LED microscopes are simpler, cheaper and safer alternatives to traditional mercury vapor lamp microscopes and do not require dark room.

Concentration techniques ([Appendix 4](#)([see page 160](#))) increase the sensitivity of sputum smear microscopy and fluorescence and have also been shown to increase the detection up to 20% in some settings with high HIV prevalence⁷([see page 39](#)).

3.2 Culture

Culture allows diagnostic confirmation of TB and is more sensitive than microscopy, 10-100 bacilli/ml are required to obtain a positive result³([see page 39](#)). Only specialized laboratories with regular quality assurance procedures in place can be relied upon for culture.

After decontamination of the sputum specimen to eliminate other organisms, the sample is centrifuged. The sediment is cultured in a special medium, in an incubator at 37°C. For specimen storage and shipment, see [Appendix 1](#)([see page 149](#)).

M. tuberculosis is a slow-growing pathogen thus, culture results are obtained after several days. The turn around time (TAT) for these techniques is summarized in [Section 3.5](#)([see page 34](#)), Table 3.1.

Culture should play a bigger role in diagnosis and patient follow-up due to the limited value of direct microscopy for:

- Confirmation of failures;
- Diagnosis of EPTB;
- Confirmation of smear negative TB when the diagnosis is in doubt;
- Distinction between *M. tuberculosis* complex and NTM;
- Monitoring treatment and outcome evaluation for patients on second-line anti-TB drugs.

Once there is growth on either a solid or liquid media, the organism must be identified. There are a number of ways to identify *M. tuberculosis*. The tests can be phenotypic (the most common being the niacin test) or genotypic (which use DNA analysis, [Section 3.4](#)([see page 32](#))). Given the complexities associated with phenotypic identification, genetic tests are preferred. The drawback is their cost. Nonetheless, laboratories performing cultures, at a minimum, should be able to conduct identification tests for *M. tuberculosis* that follow international guidelines.

3.3 Phenotypic drug susceptibility tests (DST)

Phenotypic DST determines if a strain is resistant to an anti-TB drug by evaluating the growth (or metabolic activity) in the presence of the drug⁸([see page 39](#)). The laboratory performing phenotypic DST should be specialised in mycobacterial cultures, reliable and subject to external quality assessment, often by a supranational laboratory or national reference laboratory.

The turn around time (TAT) for these techniques is summarized in [Section 3.5](#)([see page 34](#)), Table 3.1.

The reliability of DST varies from one drug to another. For Group 1 anti-TB drugs, DST is very reliable for rifampicin and isoniazid but less so for pyrazinamide and much less for ethambutol. DST for aminoglycosides, polypeptides and fluoroquinolones have been tested in different laboratories and shown to have relatively good reliability and reproducibility. DST to other second-line drugs (para-aminosalicylic acid, ethionamide and cycloserine) is much less reliable and reproducible⁹(see page 39).

3.4 Molecular techniques

- 3.4.1 Automated real time PCR (Xpert MTB/RIF)(see page 32)
- 3.4.2 Line probe assays (LPA)(see page 33)

Molecular (or genotypic) tests can be used to diagnose TB through the amplification of nucleic acids (DNA or RNA). They are also used to detect drug resistance through identifying genetic mutations (drug-resistant alleles) in the bacterium responsible (genotypic DST). Different assays and platforms have been developed.

3.4.1 Automated real time PCR (Xpert MTB/RIF)

This test can diagnose TB and resistance to rifampicin. In contrast to other techniques (*in vitro* culture, DST and conventional molecular techniques) the Xpert MTB/RIF can be used in peripheral laboratories and does not require sophisticated equipment or highly-skilled personnel¹⁰(see page 39),¹¹(see page 39),¹²(see page 39),¹³(see page 39).

The test is based on real-time PCR, targeting specific nucleic acid sequences in the *M. tuberculosis* complex genome, while also simultaneously providing information about the most common mutations related to rifampicin resistance.

It is a highly automated test (only 3 manual steps required), which is run in a closed system with one cartridge per sample. Thus, it is less prone to contamination than other PCR-based tests. Each instrument can process 4 samples at one time, with a processing time of just under 2 hours. Higher capacity machines are available. See [Appendix 3](#)(see page 156) for more information on Xpert MTB/RIF instruments.

The performances of this test are almost similar to that of the culture. Published results have shown that for PTB detection, the assay has sensitivities of 98% for smear-positive, culture-positive samples, and 72% for smear-negative, culture-positive samples (sensitivity can reach 90% if the test is repeated 3 times)¹⁴(see page 39),¹⁵(see page 39).

The test Xpert MTB/RIF also has good sensitivity (80%) and excellent specificity (> 98%) when performed on cerebrospinal fluid, lymph node material and gastric fluid¹⁶(see page 39).

Because of its excellent performance, its quick turn around time and its ease of use, this test should be used as an initial diagnostic test in HIV-infected patients and when multidrug-resistant TB (MDR-TB) or TB meningitis are suspected, in both adults and children.

It can also be used for diagnosis of lymph node TB. As the sensitivity of the Xpert test in pleural fluid is low, its use is not recommended.

The sensitivity for the detection of rifampicin resistance compared with conventional DST on culture is 97.6%. The test has a high negative predictive value, therefore, non rifampicin resistant results can be considered to be true susceptible.

In populations where the prevalence of MDR-TB is below 10%, the positive predictive value is below 85% ([Appendix 3](#) (see page 156)). Therefore when a Xpert with RIF positive results is found, the test should be immediately repeated in order to rule out possible labelling or clerical errors. If the second Xpert MTB/RIF test does not show rifampicin resistance, the patient can be considered as having a susceptible TB. If the result of the second Xpert MTB/RIF test also shows rifampicin resistance, it should be confirmed by a phenotypic DST or a different genotypic DST method.

Xpert MTB/RIF does not eliminate the need for conventional microscopy, culture and DST, which are required to monitor treatment progress and to detect resistance to drugs other than rifampicin.

3.4.2 Line probe assays (LPA)

To date no fully automated LPA exist. These molecular tests can only be performed by specialized laboratories with strict quality assurance procedures in place.

There are a number of different molecular assays available:

- Conventional Nucleic Acid Amplification (NAA) amplifies *M. tuberculosis*-specific nucleic acid sequences with a nucleic acid probe, enabling direct detection of the bacillus. The current NAA tests available show a lower sensitivity than culture and therefore, are not recommended for the diagnosis of TB. They are also too labour-intensive to be implemented for routine diagnosis in most laboratories.
- Two molecular techniques are commercially available:
 - Hain assays: GenoType® MTBDR*plus* assay and GenoType® MTBDR*s/* (Hain Lifescience GmbH, Nehren, Germany). The GenoType® MTBDR*plus* assay has been shown to be good at detecting rifampicin resistance but less so for isoniazid resistance among smearpositive patients (sensitivity and specificity values for rifampicin and isoniazid were 95.3% and 95.5% and, 89.9 and 87.1%, respectively)¹⁷ (see page 39),¹⁸ (see page 39). The GenoType® MTBDR*s/* assay can detect resistance to fluoroquinolones and injectables drugs with a good specificity but a lower specificity (85% for fluoroquinolones and 43 to 84% for injectables)¹⁹ (see page 39).
 - The INNO-LiPA Rif. TB® line probe assay (Innogenetics, Belgium)²⁰ (see page 39).

The GenoType® MTBDR*plus* assay can identify mutations on the KatG or on the InhA genes:

- Mutation on KatG gene corresponds to resistance to high-dose isoniazid;
- Mutation on InhA gene corresponds to resistance to both isoniazid and ethionamide, but not necessarily to high-dose isoniazid.

The GenoType® MTBDR*s/* assay can be used as a triage test on smear-positive patients to guide the initial treatment in extensively drug-resistant TB (XDR-TB) suspects while awaiting confirmatory results from conventional phenotypic testing. However, LPA assays cannot be used as replacement tests for conventional phenotypic second-line anti-TB DST.

These molecular methods have the advantage of giving fast results, within a few hours, for smear-positive patients (referred to as direct testing, because the sputum can be directly tested). For smear negative patients, a primary culture is needed prior to testing (referred to as indirect testing because a culture first has to be grown from the patient's sputum).

In order to benefit from the short turn around time of these tests, good logistical support is required for sample transportation to the reference laboratory with timely return of results. The main constraints remain the high cost, high infrastructure requirements, high level of technical training and the risk of cross-contamination.

3.5 Summary of bacteriological examinations

Table 3.1 - Summary of bacteriological examinations^{3(see page 39),6(see page 39),10(see page 39),21(see page 39),22(see page 39)}

	Sensitivity AFB/ml	Median turn-around time	Additional turn-around time with DST
Smear microscopy (Light, fluorescent)	> 5 000	2 hours	
Culture solid medium LJ standard medium, Middlebrook 7H10 and 7H11	+/- 100	16 days (smear+) 29 days (smear-)	6 weeks
Culture liquid medium (BACTEC®, MGIT®)	+/- 10	8 days (smear+) 16 days (smear-)	2 weeks (smear+) 2 weeks (smear-)
Culture microcolonies (TLA, MODS)	+/- 10	14 days	0 (H and R)
LPA (Hain®, INNO-LiPA®)	Only on positive smear	1 day (direct testing)	0 (H and R) 21 days (indirect testing)
Automated real-time PCR (Xpert MTB/RIF)	+/-10	2 hours	0 (R only)

3.6 Indications for DST

Ideally, genotypic DST is indicated for all patients at the start of TB treatment, as to ensure that the most appropriate therapy for each individual can be determined^{23(see page 39)}.

At the very least, the following patients should have DST performed to isoniazid and rifampicin, or rifampicin alone:

- Previously treated patients;
- Persons who develop active TB after exposure to a patient with documented MDR-TB;
- Patients who remain smear-positive after two months of therapy;
- New patients in countries with high prevalence of MDR-TB.

The following groups are targeted for DST for second-line drugs:

- Patients with a DST showing a resistance to at least rifampicin;
- Patients with a DST showing a resistance to at least isoniazid and another Group 1 drug;
- Patients who remain culture positive on or after Month 4 of an MDR-TB treatment or who reconvert to a

positive culture after Month 4;

– Persons who develop active TB after exposure to a patient with documented MDR-TB.

3.7 Radiology

- [3.7.1 X-rays](#)(see page 35)
- [3.7.2 Ultrasound](#)(see page 35)

3.7.1 X-rays

Chest X-ray is a non-specific investigation for TB. In many national programmes, it is not routinely indicated in sputum smear-positive patients because of limited resources.

Chest X-ray is considered as an additional diagnostic tool given its limitations of nonspecificity. Indeed, several comparative studies have shown that the error rate of under- or over-reading the film by specialists is around 20%. It is often difficult to detect the difference between old healed lesions of fibrosis and active TB. They are rarely conclusive and can only complete the clinical presentation and history to constitute a body of arguments suggestive of TB.

Chest X-ray is however recommended when the smear microscopy results are negative or when TB is suspected in children²⁴(see page 39). It is particularly useful where the proportion of bacteriologically unconfirmed TB (i.e. smear microscopy or Xpert MTB/RIF negative) is likely to be high; for example, in populations with a high incidence of HIV.

In HIV co-infection, infiltrates (especially in advanced immunodeficiency) tend to be more diffuse and located in the lower lung zones; the X-ray may even appear normal in 10% of the cases. Cavitory disease is seen less in those infected with HIV, and in one study, only 33% of HIV-infected patients with PTB had cavities on X-ray when compared to 78% of HIV-negative patients with PTB²⁵(see page 39).

Chest X-rays are valuable tools for the diagnosis of pleural and pericardial effusions, especially at the early stages of the disease when the clinical signs are minimal. The X-ray showing an enlarged heart is a key element for diagnosis of pericardial TB²⁶(see page 39).

Chest X-ray is essential in the diagnosis of miliary TB. It shows small characteristic nodular infiltrations disseminated in both pulmonary fields²⁶(see page 39).

Another use of radiography includes examination of the joints and bones when TB is suspected. Radiography, including the use of computerized tomography scans (CT scans), can be useful for Pott's disease.

3.7.2 Ultrasound

Ultrasound is useful in confirming pleural effusions²⁷(see page 39).

Ultrasound is extremely useful in pericardial TB as it can document that an effusion is the cause of an enlarged heart seen on chest X-ray.

It is moderately useful in diagnosing abdominal TB, whereby documenting multiple enlarged lymph nodes on an abdominal ultrasound is consistent with TB, however, multiple enlarged lymph nodes can be seen in other diseases, especially in HIV. Bowel wall thickening (ileocaecal region) is also suggestive of abdominal TB.

3.8 Tuberculin skin test (TST)

Cutaneous hypersensitivity to tuberculin reflects a delayed hypersensitivity reaction to some *M. tuberculosis* antigens.

A positive reaction signifies that an infection has occurred, but it does not determine if the TB is latent or active. It does not differentiate between infection by *M. tuberculosis* and hypersensitivity due to mycobacterium other than TB.

The TST is done by injecting 5 international units of tuberculin intradermally on the ventral surface (side of arm exposed with palm facing up) of the forearm.

The test is read by a trained health care worker, 48 to 72 hours after the injection. The reaction is the area of induration (swelling that can be felt) around the injection. The diameter of induration is measured with a ruler in millimetres across the forearm. The erythema (redness) around the indurated area is not measured, because the presence of redness does not indicate a reaction.

Tuberculin used for the skin test is also known as purified protein derivative, PPD. The TST is sometimes called PPD test or Mantoux test.

BCG vaccination induces a state of hypersensitivity which can result in a false positive TST, such that the average diameter 1 year after BCG vaccination is 10 mm, with extremes ranging from 4 to 20 mm. A false positive TST due to a vaccine reaction has a tendency to be less reactive with time and disappears 5 to 10 years post-vaccination.

Positive TST

A TST is considered as positive if²⁸ (see page 39):

- Induration is ≥ 5 mm in HIV infected individuals, immunocompromised patients, including those receiving prednisolone therapy of ≥ 15 mg/day for ≥ 1 month, and malnourished children;
- Induration is ≥ 10 mm in all other adults or children (BCG vaccinated or not).

A reaction that appears several minutes or several hours after injection (occasionally even after 24 hours) but which disappears on the day after its appearance is of no value.

In practice, TST has little value as a diagnostic tool when the annual rate of infection and BCG vaccine coverage are high. It can only be used as an element among a body of arguments to establish the diagnosis of active TB, and it is usually only used to help with the diagnosis in children (Chapter 5 (see page 52)).

A highly positive (induration diameter > 20 mm) or phlyctenular reaction should be considered as an argument in favour of active TB, but insufficient in itself for deciding on treatment.

Negative TST

Negative reactions in patients that previously presented positive reactions signify a loss of hypersensitivity. These are considered false negative reactions and can be observed:

Temporally:

- In viral (influenza, measles) or bacterial (whooping cough) infections;
- At the start of the evolution of TB meningitis or miliary TB;
- In patients in poor general condition (e.g. malnutrition);
- During immunosuppressive treatment (e.g. corticosteroids).

Permanently:

- With natural extinction of post-vaccination reaction, observed from the fifth year that follows BCG;

- In a person with a weak immune response, such in very elderly persons;
- In persons with diseases that result in anergy: AIDS, haemopathies, sarcoidosis.

Approximately 30% of children with active TB have negative or doubtful TST when diagnosed.

TST has an essential role in identifying candidates for isoniazid prophylaxis therapy, see [Chapter 16](#)(see [page 130](#)).

3.9 Interferon gamma release assays (IGRAs)

These *in vitro* tests of cellular immunity detect interferon. Individuals who were once exposed to *M. tuberculosis* complex have lymphocytes in their blood that maintain memory for the priming TB antigen. Addition of TB antigen to blood *in vitro* results in rapid stimulation of memory T lymphocytes and release of interferon gamma, which is a specific marker of activation of the immune response²⁹(see [page 39](#)),³⁰(see [page 39](#)).

IGRAs have the advantage that there is no cross reactivity with prior BCG vaccination and with most environmental mycobacteria. However, overall, they offer little advantage over conventional skin testing and may be a less sensitive test in HIV co-infected. In addition, IGRAs remain expensive and are not routinely used in resource-constrained settings.

3.10 Biopsies, laboratory tests on body fluids and other biological tests

- [3.10.1 Biopsies and fine needle aspirate cytology \(FNAC\)](#)(see [page 37](#))
- [3.10.2 Laboratory tests on body fluids](#)(see [page 37](#))
- [3.10.3 Other biological examinations](#)(see [page 38](#))

3.10.1 Biopsies and fine needle aspirate cytology (FNAC)

Biopsies of lymph nodes, bone and pleural lining are often not feasible in resourceconstrained settings given the technical skill and laboratory resources required. The cytology of the lymph nodes from FNAC is easier to perform. Specific granulomatous tissue, the presence of giant Langhans' cells, and/or caseous necrosis strongly correlate with TB. AFBs are not always present. For the procedure for FNAC, see [Appendix 4](#)(see [page 160](#)).

Note: molecular tests can be used on the specimens obtained from FNAC of lymph nodes.

3.10.2 Laboratory tests on body fluids

The diagnosis of some EPTB localisations can be supported or confirmed by a combination of tests performed in respective body fluids.

Table 3.2 - Summary of findings suggestive of TB in body fluids

Fluids	Tests
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Ascitic fluid	<ul style="list-style-type: none"> • Typically translucent yellow-coloured liquid. • Exudate rich in lymphocytes, usually > 300 white cells/mm³; Rivalta test positive (Appendix 5(see page 161)). • Serum-ascites albumin gradient (SAAG) < 1.1 g/dl is consistent with TB (and many other conditions) while a SAAG > 1.1 g/dl makes peritoneal TB unlikely³¹(see page 39). • Adenosine desaminase can be used as a surrogate marker for TB in peritoneal fluid (Appendix 6(see page 163)). • The search for <i>M. tuberculosis</i> by microscopy is most often negative.
Pleural fluid	<ul style="list-style-type: none"> • Typically straw-coloured. • Proteins ≥ 30 g/l (Rivalta test, Appendix 5(see page 161)). • Rich in white cells (1,000-2,500/mm³), with predominant lymphocytes • Adenosine desaminase can be used as a surrogate marker for TB in pleural fluid (Appendix 6(see page 163)). • Microscopy for <i>M. tuberculosis</i> is most often negative. • Xpert MTB/RIF in pleural fluid has a moderate sensitivity, and therefore, is not recommended.
Cerebrospinal fluid	<ul style="list-style-type: none"> • Clear, hyper-concentrated liquid. • Proteins > 0.40 g/l (Pandy test, Appendix 5(see page 161)). • Glucose diminished: < 60 mg/l. • CSF glucose/blood glucose < 0.5. • Between 100 and 1,000 white blood cells/ml, of which over 80% are lymphocytes. • <i>M. tuberculosis</i> can be found by CSF direct microscopy in less than 10%. • Xpert MTB/RIF has a moderate sensitivity that can be increased following centrifugation. Centrifugation is recommended if facilities for efficient and safe centrifugation exist (high-speed centrifuge and biosafety cabinet). • In HIV+ patients, cryptococcal meningitis is a concern. Perform the antigen test with cryptococcal antigen on serum and CSF (CrAgLFA).
Urine	<ul style="list-style-type: none"> • A culture or molecular testing, after centrifugation, are the only measures to confirm diagnosis. • The search for <i>M. tuberculosis</i> in urinary microscopy is almost always negative. • Xpert MTB/RIF has a moderate sensitivity. Priority should be given to patients with CD4 counts < 50 due to demonstrated higher sensitivity in this group³²(see page 39). • The LAM assay is useful in patients with CD4 < 200 (Section 3.10.3(see page 38)).

3.10.3 Other biological examinations

New TB diagnostic tests are in development for point-of-care use. These antigen-detection assays are based on detecting liporabinomannan (LAM): a carbohydrate cell wall antigen that is excreted in the

urine of TB patients. The performances of the LAM urine assay for most populations are poor. An exception is the sensitivity of the LAM assay in patients with CD4 counts < 200³³(see page 39),³⁴(see page 39),³⁵(see page 39). The test may have some utility where advanced HIV-associated immunodeficiency is common.

Sedimentation rate is almost always higher but this examination is very non-specific. A normal sedimentation rate makes TB less likely but still possible.

C-reactive protein is also generally increased but this test also is very non-specific.

There exist commercial rapid blood tests for “serological diagnosis of TB”, but they are so far not very reliable in diagnosing active TB and should not be used.

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Chapter 4: Diagnostic algorithms for pulmonary tuberculosis (PTB) in adults and adolescents

- [4.1 Guiding principles for the use of the algorithms](#)(see page 43)
- [4.2 Adult and adolescent algorithms](#)(see page 44)
- [References Chapter 4](#)(see page 50)

4.1 Guiding principles for the use of the algorithms

- [4.1.1 Clinical assessment](#)(see page 43)
- [4.1.2 Clinical response](#)(see page 43)

The aim of algorithms is to assist the diagnostic process and minimize incorrect diagnosis. The following algorithms are for adults and adolescents. For diagnostic algorithms for children < 10 years, see [Chapter 5](#)(see page 55).

4.1.1 Clinical assessment

See reference [1](#)(see page 50)

– 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.

4.1.2 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

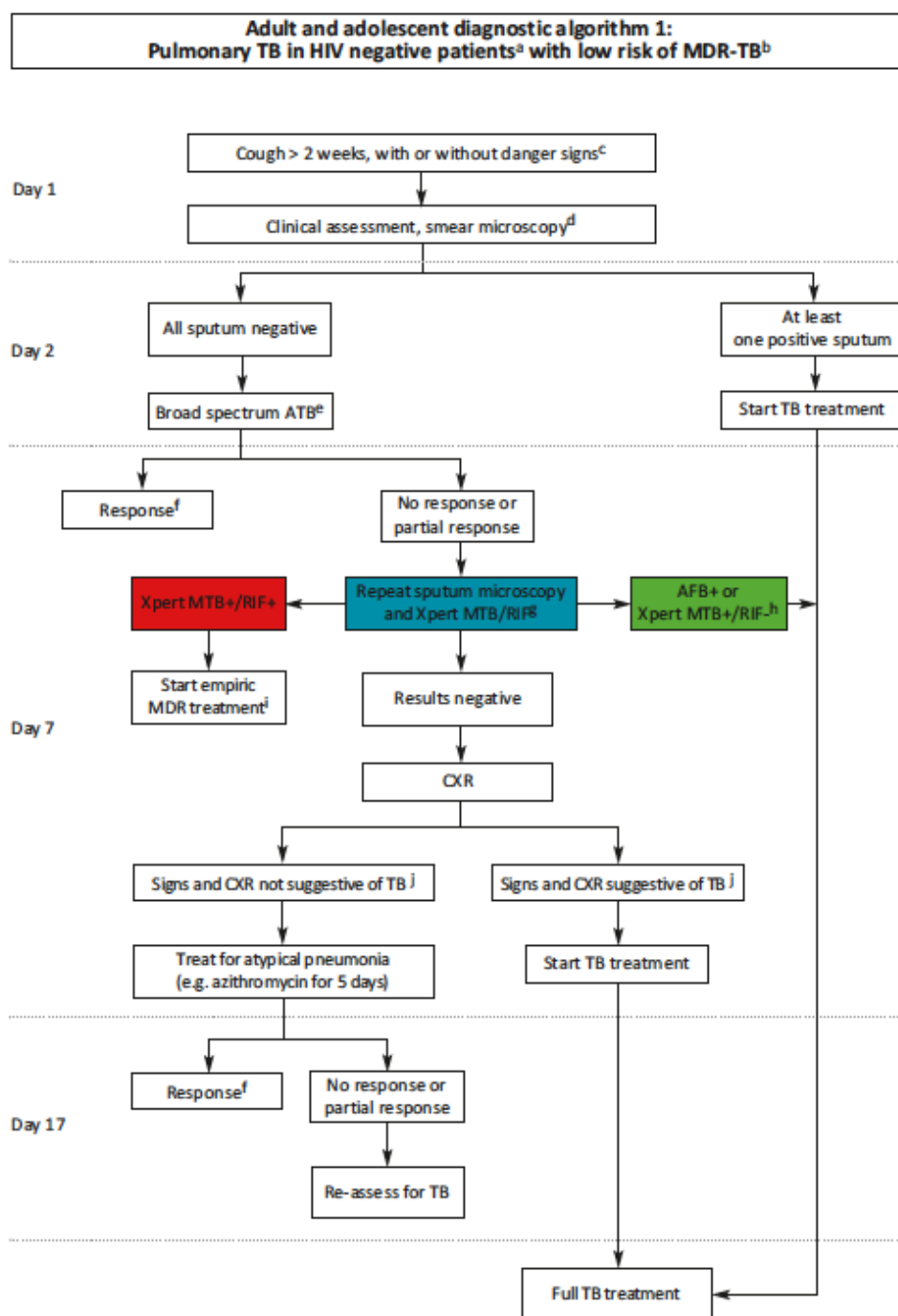
also be treated empirically, with broad-spectrum antibiotics for bacterial pneumonia because benefits outweigh the risks¹(see page 50).

4.2 Adult and adolescent algorithms

- Diagnostic algorithm 1(see page 45)
 - PTB in HIV-negative patients with low risk of MDR-TB(see page 45)
- Diagnostic algorithm 2(see page 47)
 - PTB in HIV-positive patients(see page 47)
- Diagnostic algorithm 3 with Xpert MTB/RIF(see page 50)
 - PTB in patients with high risk of MDR-TB(see page 50)

Diagnostic algorithm 1

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



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

^b. 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).

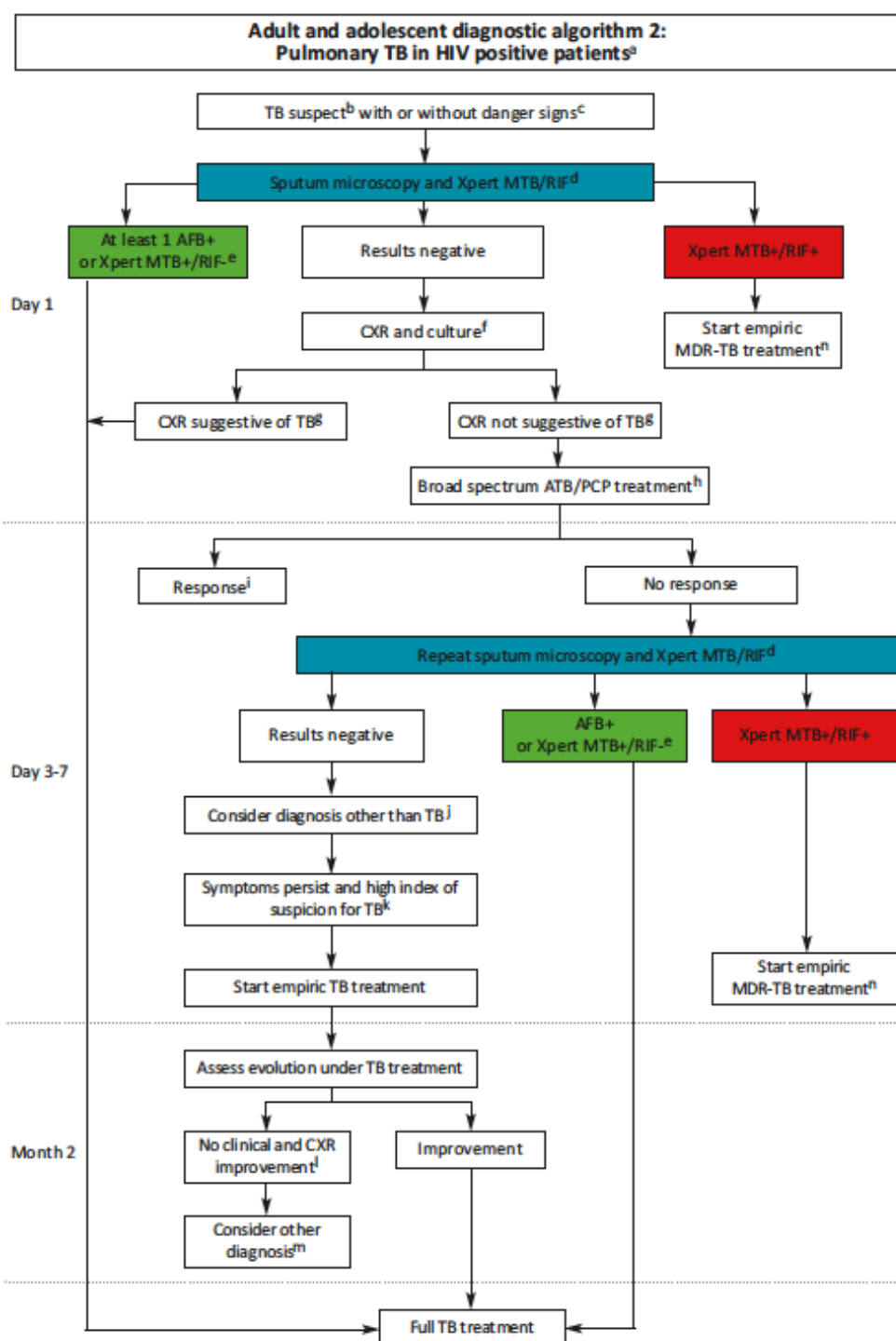
- c. Danger signs: respiratory rate > 30/min and/or fever > 39°C and/or pulse rate > 120/min and/or unable to walk.
- d. Smear microscopy: two sputum examinations performed on the same day.
- e. Broad spectrum ATB:
- If no danger signs: amoxicillin for 7 days (NO fluoroquinolones);
 - If danger signs: parenteral ATB (e.g. ceftriaxone).
- f. Clinical response to a broad spectrum antibiotic does not rule out TB. Patient should be informed to return for reassessment if symptoms recur.
- g. 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.
- h. 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:

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

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



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

^b. 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.

- c. Danger signs: respiratory rate > 30/min and/or fever > 39°C and/or pulse rate > 120/min and/or unable to walk.
- d. 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.
- e. 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.
- f. 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.
- g. TB treatment should be started when clinical signs AND chest X-ray (CXR) are suggestive of TB (Note k).
- h. 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.
- i. 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.
- j. 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
Clinical signs	<ul style="list-style-type: none"> • Current cough • Weight loss • Purulent sputum and haemoptysis less likely if HIV-positive with low CD4 count • Fever • Night sweats • Pleuritic chest pain 	<ul style="list-style-type: none"> • Dry cough • Dyspnoea ++ • Hypoxemia • Not on CPT • More likely if low CD4 count 	<ul style="list-style-type: none"> • Acute onset • High fever

CXR	<ul style="list-style-type: none"> • Upper lobe infiltrates and cavitation only likely in HIV-positive adults with higher CD4 counts. Any lobe of the lung may be affected • In HIV-positive adults with lower CD4 counts, the following 4 patterns are suggestive of TB: <ol style="list-style-type: none"> 1. miliary pattern 2. pleural effusion without airspace (with straw-coloured liquid aspirate) 3. hilar and mediastinal adenopathy 4. large heart (especially if symmetrical and rounded) 	<ul style="list-style-type: none"> • Bilateral interstitial infiltrate with reticulonodular markings that are more pronounced in the lower lobes • Findings lag behind symptoms and may be normal early in the disease 	<ul style="list-style-type: none"> • Lobar consolidation
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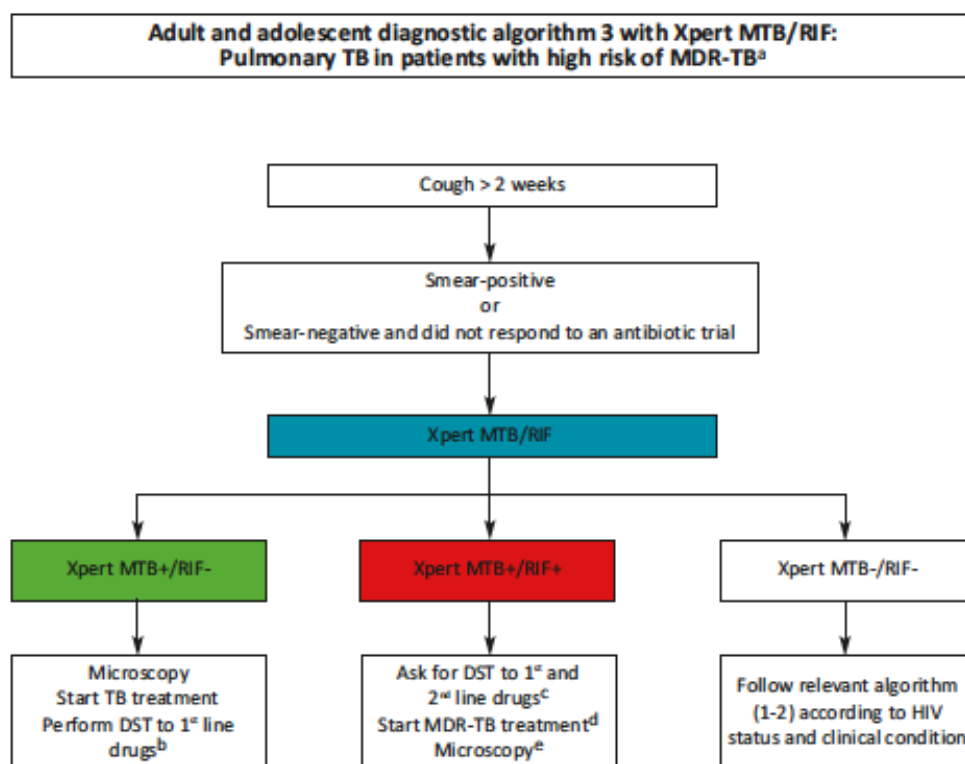
^l. In the absence of any improvement of clinical signs (no weight gain, persistent cough, pain, etc.) AND no improvement on CXR after 2 months of a well conducted TB treatment, diagnosis and treatment should be reconsidered. MDR-TB should also be considered.

^m. In addition to the differential diagnosis in Note k above, DR-TB should be considered.

ⁿ. 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 $\geq 10\%$, 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



^a. 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).

^b. 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.

^c. 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.

^d. • 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.

^e. 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.

References Chapter 4

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Chapter 5: Diagnosis of tuberculosis in children

- [5.1 Background](#)(see page 52)
- [5.2 Characteristics of tuberculosis in children](#)(see page 52)
- [5.3 Diagnostic approach](#)(see page 53)
- [5.4 Key elements of the diagnosis](#)(see page 53)
- [5.5 Collecting sputum specimens in children](#)(see page 55)
- [5.6 Paediatric diagnostic algorithms](#)(see page 55)
- [References Chapter 5](#)(see page 58)

5.1 Background

Tuberculosis (TB) is a significant cause of morbidity and mortality in children in settings of high TB prevalence. The lack of an accurate diagnostic method has contributed to a gross underestimation of its true burden. In high prevalence settings, children < 15 years old are expected to make up 10 to 20% of all TB cases¹(see page 58).

The characteristics of TB disease and approach to diagnosis in children > 10 years old are similar to those for adults. This section focuses on children < 10 years old.

5.2 Characteristics of tuberculosis in children

Children have a high risk of TB infection. In endemic areas, children are likely to be exposed to TB in their household or community. A careful contact history is extremely important in children with signs and symptoms suggestive of TB. In children with diagnosed TB, an effort should be made to detect the source case and any other undiagnosed cases in the household. The younger the child, the more likely it is that a contact can be identified. Equally, all TB cases, especially children or adults who are smear-positive, should be asked about close contact with children ([Chapter 16](#)(see page 130)).

Children have a high risk of progression to active TB disease and of developing severe forms: 90% of young children, who develop TB, do so within 12 months of infection²(see page 58). Children < 3 years and children with immune suppression (e.g. HIV, malnutrition, post-measles) are particularly vulnerable. TB screening with prompt treatment or prophylaxis is especially critical in these children.

Most cases are pulmonary TB (PTB), but smear positivity is rare because children generally have low bacillary loads. Furthermore, sputum samples can be difficult to obtain from children. As a result, smear-positive TB represents only an estimated 10% of all TB observed in the 0 to 14 age group.

Extrapulmonary TB (EPTB) is common in children. The site of EPTB disease is age related. Miliary and meningeal TB is more frequently seen in young children. TB lymphadenitis and osteoarticular TB are more common in older children.

BCG administered at birth offers partial protection against severe forms in young children. It offers little if any protection against pulmonary TB. A history of BCG vaccination does not exclude the possibility of TB in a child with suggestive signs and symptoms.

5.3 Diagnostic approach

For the majority of children, careful history, clinical assessment and follow up alone are sufficient to make a diagnosis of TB, even if confirmation is not possible.

Bacteriology, chest X-ray and tuberculin skin test are useful but not essential in most cases.

A trial of treatment with anti-TB drugs is not recommended as a method to diagnose TB. The decision to treat a child should be carefully considered. Once such a decision is made, the child should be treated with a full course of therapy.

5.4 Key elements of the diagnosis

- [5.4.1 Careful history](#)(see page 53)
- [5.4.2 Clinical examination](#)(see page 53)
- [5.4.3 Re-assessment and follow up](#)(see page 54)
- [5.4.4 HIV testing](#)(see page 54)
- [5.4.5 Diagnostic investigations](#)(see page 54)

Recommendations of how to combine the following elements to arrive at a treatment decision are summarized in the diagnostic algorithms ([Section 5.6](#)(see page 55)).

5.4.1 Careful history

- Contact with a known or presumed TB case:
 - Timing of the exposure: greater risk if exposure occurred in the past 12 months;
 - Closeness of the contact: greater risk if living in same household or sleeping in the same room;
 - Type of TB of the source case: greater risk if smear-positive or cavities on X-ray; resistance pattern of the source case.
- Symptoms suggestive of TB:
 - Cough persistent for > 2 weeks and not improving;
 - Unexplained fever for > 1 week;
 - Unexplained weight loss or failure to thrive;
 - Unexplained fatigue, lethargy or reduced playfulness.

5.4.2 Clinical examination

- Vital signs: fever and increased respiratory rate may be present.
- Growth: weigh the child and compare with previous records. Weight loss or flattening of the growth curve can signal chronic disease.

– Respiratory examination: abnormal auscultation or percussion may be present. Signs of severe respiratory infection: tachypnoea, cyanosis, hypoxemia ($\text{SaO}_2 < 90\%$), nasal flaring, chest indrawing, grunting and feeding difficulties in infants.

– Physical signs of EPTB (see also Chapter 2, [Section 2.2](#)(see page 22)):

Highly suggestive, e.g.:

- Angular deformity of the spine;
- Cervical lymph node with fistula formation.

Non specific requiring further investigation, e.g.:

- Sub-acute meningitis not responding to antibiotic therapy;
- Distended abdomen with ascites;
- Lymphadenopathy without fistula formation;
- Non-painful enlarged joint.

– Other: certain physical findings may point to alternative diagnoses (e.g. asthma) or relevant co-morbidities (e.g. HIV).

5.4.3 Re-assessment and follow up

The diagnosis is rarely made at the first consultation, as the initial clinical presentation is usually non specific. Follow up is critical to assess if signs and symptoms persist despite a trial of well-monitored non-TB antibiotic treatment.

Particularly suggestive of TB disease are:

- Persistent pneumonia after appropriate, well-monitored antibiotic treatment;
- Measured or reliably reported fever of $> 38^\circ\text{C}$ for > 1 week, after common causes such as malaria or pneumonia have been excluded;
- No weight gain despite appropriate nutritional support;
- Persistent or worsening fatigue.

5.4.4 HIV testing

HIV testing should be routinely offered to children with presumed or diagnosed TB.

5.4.5 Diagnostic investigations

The following investigations should be performed in children suspected of TB whenever possible. The unavailability of a test due to resource limitations should not delay the diagnosis of TB.

Tuberculin skin test (TST)

- A positive test can support a diagnosis of TB in a symptomatic child;
- A negative TST does not exclude TB;
- Causes of false positive: BCG, atypical mycobacteria (NTM);
- Causes of false negative: HIV infection, malnutrition.

Chest X-ray

Chest X-ray can be helpful for the diagnosis of intrathoracic TB³(see page 58). Hilar lymphadenopathy is the most common finding. However, obtaining quality films in children and accurately interpreting them may be difficult. This limits their utility in many settings.

Bacteriology

Try to confirm TB, although treatment should not be delayed if clinically indicated.

For EPTB, obtain specimens from the suspected sites for microscopy and, when possible, for culture, cytology or histopathological examination and molecular methods (e.g. Xpert MTB/RIF).

Bacterial yields are higher in older children, and in children of all ages with severe disease. Two sputum specimens should be obtained: an on-the-spot specimen (at first evaluation), and an early morning specimen. Alternatively, two specimens collected one hour apart are an acceptable option (see [Appendix 1](#)(see page 149)).

Xpert MTB/RIF is the initial test of choice in screening for multidrug-resistant TB (MDR-TB). When Xpert MTB/RIF is not available, conventional drug susceptibility test (DST) can be done. DST indications are the same as for adults.

5.5 Collecting sputum specimens in children

Given the importance of trying to obtain confirmation of disease in areas of high drug-resistant TB prevalence or in contact cases of MDR-TB, optimizing the collection of appropriate specimens is critical.

Children < 6 years old, and some as old as 10 years old, may be unable or unwilling to spontaneously expectorate. Explanation and encouragement are important. Chest clapping is a simple, yet, often effective measure to help expectoration.

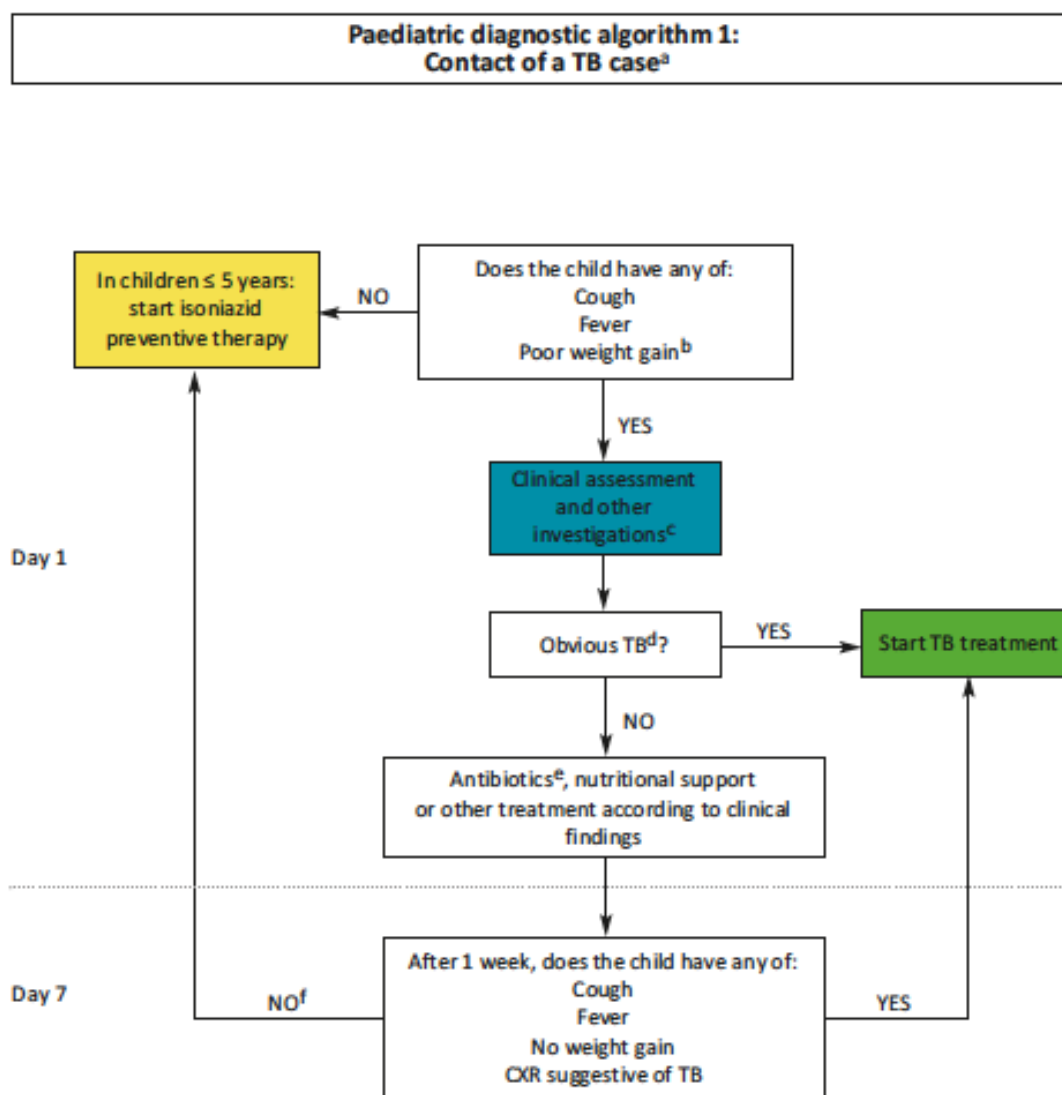
If these measures fail, sputum specimen can be obtained by sputum induction or gastric aspiration ([Appendix 1](#)(see page 149)). Given the distress caused to the child and the generally low yield on smear microscopy, these procedures should only be done if culture or Xpert MTB/RIF is available.

5.6 Paediatric diagnostic algorithms

- [Paediatric diagnostic algorithm 1](#)(see page 56)
 - [Contact of a TB case](#)(see page 56)
- [Paediatric diagnostic algorithm 2](#)(see page 57)
 - [Symptomatic child](#)(see page 57)

Paediatric diagnostic algorithm 1

Contact of a TB case



^a. Contact: child living in the same household or in close and regular contact with any known or suspected TB case in the last 12 months.

^b. Malnutrition or growth curve flattening.

^c. Clinical assessment (including growth assessment), bacteriological tests, HIV testing (in high HIV prevalence areas), and when relevant and available: X-ray (CXR), investigations for EPTB, TST.

^d. Examples of “obvious TB” may include cases of Pott’ disease, TB meningitis, lymph node TB with fistula formation, smear or Xpert MTB/RIF positive or highly suggestive chest X-ray (e.g. hilar lymphadenopathy, upper lobe infiltrates, miliary picture).

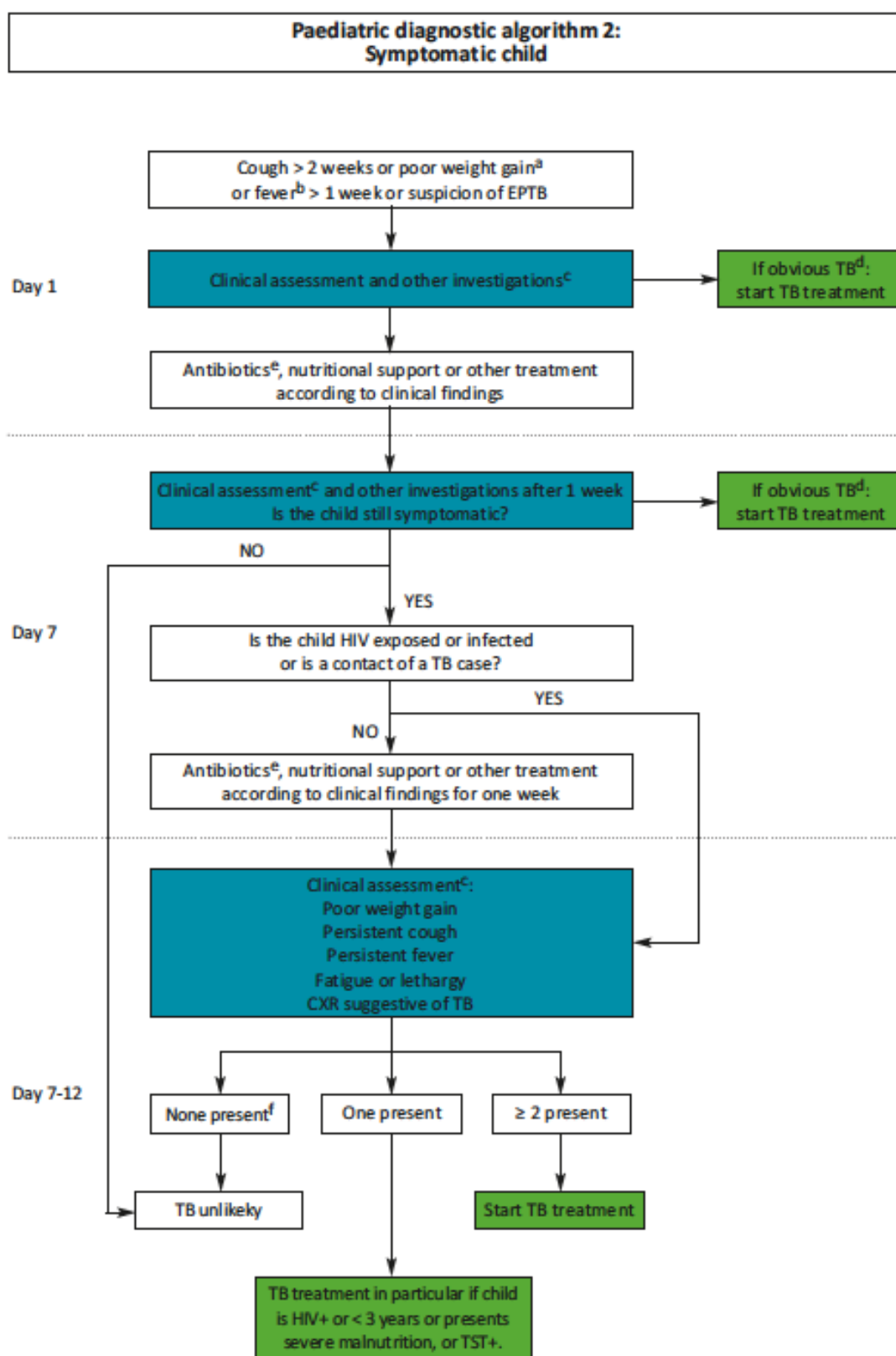
^e. Broad spectrum ATB:

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

^f. Clinical response to a broad-spectrum antibiotic does not rule out TB. Carer should be informed to consult if symptoms re-occur.

Paediatric diagnostic algorithm 2

Symptomatic child



^a. Malnutrition or growth curve flattening.

- b. Temperature > 38°C.
- c. Clinical assessment (including growth assessment), bacteriological tests, HIV testing (in high HIV prevalence areas), and when relevant and available: X-ray (CXR), investigations for EPTB, TST.
- d. Smear microscopy positive or Xpert MTB/RIF positive, CXR showing suggestive lesions (e.g. hilar lymphadenopathy, upper lobe infiltrates, miliary picture), gibbus.
- e. Broad spectrum antibiotics:
 - If no signs of severity:
 - first-line: amoxicillin PO for 7 days (NO fluoroquinolones). Advise carer to return with the child if no improvement after 48 hours of antibiotics;
 - if a second course of antibiotic if needed: azithromycin PO for 5 days.
 - If signs of severity: parenteral antibiotics (ceftriaxone ± cloxacillin if *S. aureus* is suspected). In addition: PCP treatment should be given presumptively to all HIV-exposed or HIV-infected children < 1 year of age, and any older child with severe immune suppression and not on CTX prophylaxis. For all other HIV-exposed or HIV-infected children, it should be considered if there is poor response to broad spectrum antibiotics after 48 hours.
- f. Clinical response to a broad-spectrum antibiotic does not rule out TB. Carer should be informed to consult if symptoms re-occur.

References Chapter 5

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<http://www.theunion.org/index.php/en/resources/scientific-publications/item/110-diagnostic-atlas-of-intrathoracic-tuberculosis-in-children>⁵

⁵ <http://www.theunion.org/index.php/en/resources/scientific-publications/item/110-diagnostic-atlas-of-intrathoracic-tuberculosis-in-children>

Chapter 6: Intensive case finding in HIV-infected individuals

- [6.1 Routine screening](#)(see page 59)
- [6.2 Purposes of screening](#)(see page 59)
- [References Chapter 6](#)(see page 60)

6.1 Routine screening

Intensive case-finding (ICF) should be in place in all projects providing care to HIV-infected patients. Screening can be performed at multiple points in time by different levels of health care workers (e.g. counsellors during HIV testing, health care providers during clinical consultations).

All children and adults should be regularly screened for TB using the following criteria:

Table 6.1 - Screening criteria/symptoms in children and adults¹(see page 60)

Children	Adults
<ul style="list-style-type: none"> • Current cough* • Fever • Poor weight gain** • Contact with a contagious person 	<ul style="list-style-type: none"> • Current cough* • Fever • Weight loss • Night sweats

* Asking about “current cough”, rather than cough for 2 weeks, is more sensitive for TB disease in HIV-infected individuals²(see page 60).

** Poor weight gain is defined as reported weight loss or underweight or confirmed weight loss > 5% since last visit, or growth curve flattening.

6.2 Purposes of screening

- [6.2.1 Early detection and treatment of active TB](#)(see page 59)
- [6.2.2 Identification of patients eligible for isoniazid preventive therapy \(IPT\)](#)(see page 60)

6.2.1 Early detection and treatment of active TB

Children and adults found to have one or more of the above symptoms/criteria during screening may have active TB, and they should be evaluated with an appropriate TB diagnostic algorithm in order to rapidly diagnose those who do have TB (see Diagnostic algorithms, [Chapter 4](#)(see page 44) and [Chapter 5](#)(see page 55)).

6.2.2 Identification of patients eligible for isoniazid preventive therapy (IPT)

The significant proportion of asymptomatic active TB described in patients eligible for ART (15 to 20%)²(see page 60),³(see page 60) leads to use this screening method with caution. It should only be used for ruling out TB in patients not yet eligible for antiretroviral therapy (CD4 greater than 350 and no WHO stage III or IV illnesses) or after three months of treatment in patients started under antiretroviral therapy in order to allow for possible unmasking of TB.

For IPT, see [Chapter 16](#)(see page 130).

References Chapter 6

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Chapter 7: Case definitions for registration

- [7.1 Definition of a tuberculosis case](#)(see page 61)
- [7.2 History of prior anti-TB treatment](#)(see page 61)
- [7.3 Anatomical site of the disease](#)(see page 62)
- [7.4 Bacteriological status](#)(see page 62)
- [7.5 HIV status](#)(see page 63)
- [7.6 Other co-morbidities](#)(see page 63)
- [7.7 Summary of patient registration](#)(see page 63)
- [References Chapter 7](#)(see page 64)

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 between¹(see page 64):

- **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](#)(see page 135) for outcome definitions for failure);
 - **Treatment interruption:** patients who interrupted (see [Chapter 17](#)(see page 135) 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).

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 [\(see page 0\)](#).

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.

[\(see page 0\)](#) If possible, obtain histological or bacteriological evidence (microscopy, culture or molecular test).

7.4 Bacteriological status

- [7.4.1 Detection of *M. tuberculosis*\(see page 62\)](#)
- [7.4.2 Strain sensitivity/resistance\(see page 62\)](#)

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 treatment²(see page 64)

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

References Chapter 7

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<http://www.who.int/tb/strategy/en/>
2. Treatment of Tuberculosis Guidelines 4th edition. World Health Organization, Geneva. 2009. (WHO/HTM/TB/2009.420).
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Chapter 8: Anti-TB drugs and treatment regimens

- [8.1 Introduction](#)(see page 65)
- [8.2 Anti-TB drug formulations](#)(see page 67)
- [8.3 Quality-assured anti-TB drugs](#)(see page 68)
- [8.4 Dosing of anti-TB drugs](#)(see page 69)
- [8.5 Cross resistance](#)(see page 69)
- [References Chapter 8](#)(see page 70)

8.1 Introduction

- [8.1.1 Standard code for TB treatment regimens](#)(see page 65)
- [8.1.2 Treatment approaches](#)(see page 66)

A combination of several antibacterial drugs is necessary for treating the disease and avoiding the emergence of resistance. Treatment regimens define the specific drug combinations used and the intended length of treatment.

Anti-TB drugs are classified into 5 groups based on efficacy, experience of use and drug class. Not all drugs in the same group have the same efficacy, mechanisms of action, adverse effect profile or safety. Each drug has a specific action on one or more bacillary populations but none on dormant bacilli [\(see page 65\)](#).

Treatment regimens are expressed in a standardised and abbreviated manner.

8.1.1 Standard code for TB treatment regimens

Anti-TB drugs

Table 8.1 - Drug groups and abbreviations (adapted from the WHO¹[\(see page 70\)](#))

Group name	Anti-TB drug	Abbreviation
GROUP 1 First-line oral agents	Isoniazid Rifampicin Pyrazinamide Ethambutol Rifabutin	H R Z E Rfb
GROUP 2 Injectable agents	Streptomycin Amikacin Kanamycin Capreomycin	S Amk Km Cm

Group name	Anti-TB drug	Abbreviation
GROUP 3 Fluoroquinolones (FQs)	Moxifloxacin Levofloxacin Ofloxacin	Mfx Lfx Ofx
GROUP 4 Oral bacteriostatic second-line anti-TB drugs	Ethionamide Prothionamide Cycloserine Para-aminosalicylic acid	Eto Pto Cs PAS
GROUP 5 Drugs with limited data on efficacy and/or long-term safety in the treatment of DR-TB	Bedaquiline Linezolid Clofazimine Amoxicillin/clavulanic acid Isoniazid high dose Thioacetazone Imipenem/cilastatin Meropenem	Bdq Lzd Cfz Amx/Clv High dose H Thz Ipm/Cln Mpm

Notes:

- The traditional “first-line anti-TB drugs”: H, R, Z, E and streptomycin (S) are now referred to as Group 1 drugs, with the exception of S, which is included in Group 2. Groups 2 (except S) to 5 are usually reserved for drug-resistant (DR) TB and are referred to as “second-line anti-TB drugs”.
- In these guidelines, clarithromycin (Clr) is not included in the Group 5 drugs until further data on its efficacy is available.

Treatment regimens

TB regimens are abbreviated according to the following system:

- Drugs are listed using their abbreviations.
- Treatment is divided into two phases, initial (or intensive) phase and continuation phase. These two phases are divided by a slash.
- The number before each phase represents the duration of that phase in months.
- A number in subscript (e.g. 3) after a letter means that intermittent dosing is used (H3R3 means isoniazid and rifampicin are given 3 times weekly).
- No number in subscript means that medications must be taken every day.
- When drugs are placed in brackets, it means that fixed-dose combinations (FDC) are used.
- When drugs are not placed in brackets, individual drugs are used.
- Second line drugs are separated by a hyphen.

Examples:

- 2 (HRZE)/4 (HR): the patient receives a FDC containing four drugs (isoniazid, rifampicin, pyrazinamide, ethambutol) daily for two months, then a FDC containing two drugs (isoniazid, rifampicin) daily for four months.
- 8 Km-Lfx-Eto-Cs-Z/14 Lfx-Eto-Cs-Z: the patient receives a combination of five individual drugs daily for eight months, then a combination of four individual drugs daily for fourteen months. The injectable drug is mentioned first, the fluoroquinolone second, Group 1 drug(s) are mentioned last.

8.1.2 Treatment approaches

Standardized treatment or regimen:

All patients in a defined group receive the same regimen. Different groups might receive a different regimen.

For example:

- All patients with a strain susceptible to first-line drugs receive the same standard treatment for 6 months, or for 12 months, depending on the site involved.
- Patients who failed to respond to the first-line drugs may start an empiric standardized regimen for multidrug-resistant TB (MDR-TB), based on drug resistance data of first- and second-line anti-TB drugs from representative patient populations, until the full drug susceptibility testing (DST) returns and the patient's regimen is individualized.

Individualized treatment or regimen:

Each regimen is designed based on the patient's previous history of TB treatment and individual DST results.

DR-TB programmes often use a combination of the standardized and individualized approaches. However, in situations where DST is unavailable or limited to only one or two first-line drugs, programmes will most commonly use a purely standardized approach.



An active TB lesion contains distinct *M. tuberculosis* populations: actively multiplying bacilli in open cavities (responsible for transmission); slowly multiplying bacilli in acidic inflammatory tissue; sporadically multiplying bacilli in tissues and dormant bacilli in solid lesions.

8.2 Anti-TB drug formulations

- [8.2.1 Fixed-dose combinations \(FDCs\)](#)(see page 67)
- [8.2.2 Single drug formulations](#)(see page 68)
- [8.2.3 Paediatric formulations](#)(see page 68)

8.2.1 Fixed-dose combinations (FDCs)

FDC formulations incorporate several (2, 3 or 4) individual drugs in the same tablet. FDCs are recommended as they have many advantages in improving adherence, removing the risk of patients taking only part of the prescribed medications, reducing the risk of failure and development of resistance. Quality assured FDC formations only exist for Group 1 drugs, and their composition is provided in Table 8.2

Table 8.2 - Quality-assured FDC formulations

FDC tablets	Formulations available for daily treatment*
<i>Treatment in adults:</i>	
4 drug FDC	E 275 mg/ H 75 mg/ Z 400 mg/ R 150 mg
3 drug FDC	E 275 mg/ H 75 mg/ R 150 mg
3 drug FDC	H 75 mg/ Z 400 mg/ R 150 mg
2 drug FDC	H 75 mg/ R 150 mg
<i>Treatment in children:</i>	
3 drug FDC	H 50 mg/ Z 150 mg/ R 75 mg

FDC tablets	Formulations available for daily treatment*
3 drug FDC*	H 30 mg/ Z 150 mg/ R 60 mg
2 drug FDC	H 50 mg/ R 75 mg
2 drug FDC*	H 30 mg/ R 60 mg
2 drug FDC*	H 60 mg/ R 60 mg

* These formulations must be phased out if new paediatric FDCs are available that correspond to the WHO recommended doses for children².(see page 70)

8.2.2 Single drug formulations

Quality assured FDCs do not exist for drugs in Groups 2 to 5. Therefore, the treatment of MDR-TB is provided by using a combination of individual drugs.

8.2.3 Paediatric formulations

Paediatric formulations are not available for all medicines, and the dosing thereof can be problematic. For some drugs, the only option is to manipulate the commercial formulations available for adults by doing the following:

- Splitting of tablets: if available use tablets with a score line. However not all tablets are meant to be split, as this can affect the bioavailability and the efficacy of the drug (e.g. ingredients protected from stomach acidity by an enteric coating).
- Crushing of tablets and opening of capsules: a fraction of the powder is estimated to deliver the required dose. The remaining powder should be discarded right after the administration. These powders can be mixed with food or liquid vehicles like juice, etc. Such manipulations should be done immediately before administering the medicine. There is little information on the impact of mixing drugs with food or liquids. In some cases, interactions might occur that may change the bioavailability.
- An alternative to the manipulation of adult dosages are extemporaneous formulations. However, this can only be considered when qualified staffs are available to ensure the preparation of these formulations following good compounding procedures.

8.3 Quality-assured anti-TB drugs

Using sub-standard anti-TB drugs can be disastrous both to the individual and the community. This includes treatment failure resulting in death or resistance and transmission of resistant strains to other individuals. Only quality-assured drugs must be used.

There are several internationally recognized mechanisms that evaluate the quality of TB drugs. These mechanisms are: the WHO pre-qualification programme¹(see page 0), approval by Stringent Regulatory Authorities²(see page 0) or evaluation and temporary approval by the Expert Review Panel of Global Fund/Global Drug Facility³(see page 0).

¹(see page 0) WHO Prequalification Scheme: <http://apps.who.int/prequal/>

²(see page 0) The national drug regulatory authorities, which are members of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) are considered as Stringent Regulatory Authority (SRA) as per the Global Fund Quality Assurance Policy for pharmaceutical products from July 1, 2009.

³(see page 0) http://www.stoptb.org/gdf/drugsupply/quality_sourcing_process.asp

8.4 Dosing of anti-TB drugs

For the daily dose of anti-TB drugs to be administered:

- See [Appendix 8](#)(see page 164) for FDC tablets to be administered (number of tablets/day) based on the weight of the patient.
- See [Appendix 9](#)(see page 171) for individual drugs.

8.5 Cross resistance

There is well-known cross-resistance between some of the antibacterial drugs used in treatment of TB. Resistance mutations to one anti-TB drug may confer resistance to some or all of the members of the drug family, and less commonly, to members of other families. For example, among aminoglycosides, resistance to kanamycin is associated with near complete cross-resistance to amikacin. In contrast, cross-resistance between kanamycin and streptomycin is generally low. Moreover, TB isolates that are resistant to kanamycin at high doses may be resistant to capreomycin (a polypeptide).

Table 8.3 - Summary on cross-resistance between anti-TB agents³(see page 70)

Drugs class	Cross-resistance
Rifamycins	R and Rfb have high levels of cross-resistance.
Isoniazid	Eto/Pto can have cross-resistance to H if the inhA mutation is present.
Aminoglycosides and polypeptides	Amk and Km have very high cross-resistance. Km (or Amk) and Cm have low to moderate cross-resistance. S has low cross resistance with Amk and Km.
Fluoroquinolones	FQs are believed to have variable cross-resistance between each other. Some <i>in vitro</i> data show that strains can be susceptible to some later-generation FQs when resistant to earlier-generation FQs (Ofx). In these cases, it is unknown if the later-generation FQs remain clinically effective.
Thioamides	Eto and Pto have 100% cross-resistance.
Thioacetazone	Thz cross-resistance to H, Eto/Pto, and PAS has been reported, but is generally considered low.

References Chapter 8

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<http://www.pih.org/publications/entry/pih-guide-to-the-medical-management-ofmultidrug-resistant-tuberculosis>⁶

⁶ <http://www.pih.org/publications/entry/pih-guide-to-the-medical-management-ofmultidrug-resistant-tuberculosis>

Chapter 9: Treatment of drug-susceptible tuberculosis

- 9.1 Standard first-line treatment regimens(see page 71)
- 9.2 Special situations(see page 73)
- 9.3 Adjunctive corticosteroid therapy(see page 74)
- 9.4 Follow-up for patients treated with first-line regimens(see page 75)
- 9.5 Management of adverse effects in patients on first-line regimens(see page 78)
- 9.6 Management of treatment interruption in patients on first-line regimens(see page 81)
- References Chapter 9(see page 83)

9.1 Standard first-line treatment regimens

- 9.1.1 New patient regimens(see page 71)
 - Pulmonary TB and extrapulmonary TB(see page 71)
 - TB meningitis and osteoarticular/spinal TB(see page 72)
- 9.1.2 Previously treated patient regimens(see page 72)

Standard first-line regimens are used for patients with presumed drug-susceptible tuberculosis (TB), documented drug-susceptible TB or while waiting for drug susceptibility testing (DST) results when drug-resistant (DR) TB is unknown but considered a low probability.

9.1.1 New patient regimens

New patients are defined as those who have no history of anti-TB treatment or who have received less than one month of anti-TB drugs. New patients may have smear positive or smear negative pulmonary TB (PTB) or extrapulmonary TB (EPTB).

Pulmonary TB and extrapulmonary TB

(except TB meningitis and osteoarticular/spinal TB)¹(see page 83),²(see page 83)

2 (HRZE)/4 (HR)

The treatment lasts 6 months with an intensive phase of 2 months with 4 anti-TB drugs and a continuation phase of 4 months with 2 anti-TB drugs.

In lymph node TB, adenopathies usually disappear in less than 3 months after treatment initiation. Paradoxical reactions may be observed at the beginning of treatment (appearance of abscesses, fistulas or other lymph nodes) and should not lead to a change in treatment. Non-steroidal anti-inflammatory drugs can be used in patients that experience paradoxical reactions.

This regimen should NOT be used :

– In patients who develop active TB after close contact with a known DR-TB case:

Obtain DST and while waiting for results, start a regimen based on the DST of the presumed source case (Chapter 10(see page 84)).

– In areas with high prevalence of resistance to isoniazid:

In these areas, all patients should get a DST at the start of treatment. The regimen 2 (HRZE)/4 (HR)E can be used¹(see page 83) in places where DST is not available or while waiting for DST result. This

recommendation is based only on expert opinion. As a result, many patients will receive ethambutol unnecessarily if the DST is not available, but this could prevent rifampicin resistance in theory.

Notes:

- An 8-month regimen 2 (HRZE)/6 (HE) or 2 S(HRZ)/6 (HE) is still used by some countries however, it has been demonstrated that it gives more frequent relapses and failures than the 6-month regimen. It should be replaced by the above 6-month regimen.
- Three times a week regimens are not recommended as a routine practice. However, for patients who are: (1) under strict directly observed therapy and (2) not HIV-infected, three times a week regimen for the continuation phase can be considered. Three times weekly administration during the intensive phase should not be done in any situation.

TB meningitis and osteoarticular/spinal TB

2 (HRZE)/10 (HR)

TB meningitis

Treatment of TB meningitis lasts 12 months^{2(see page 83),3(see page 83)}. Although 6 months are probably sufficient in most cases, treatment lasts longer because of the uncertain cerebrospinal fluid penetration of some anti-TB drugs. It is also recommended that all patients with TB meningitis receive a course of corticosteroids (Section 9.3(see page 74)).

Osteoarticular TB and spinal TB (Pott's disease)

Although there is limited evidence to the benefit of extending the treatment, treating for 12 months with 2 (HRZE)/10 (HR)^{2(see page 83),3(see page 83)} is recommended mainly because it is difficult to assess the response to the treatment. Pott's disease is a severe form of TB that should be treated as a priority because of the risk of neurological sequelae due to the chronic compression of the spinal nerve. In the absence of significant deformity and neurological deficit, most cases of spinal TB can be successfully treated with rest, back support bracing and anti-TB drugs. Surgery should be considered for patients with neurological deficit, an unstable spine lesion, and/or when they are not responding to therapy.

9.1.2 Previously treated patient regimens

See reference 1(see page 83)

Previously treated patients are defined as those who have received one month or more of anti-TB drugs in the past. It is critical in these patients to detect drug resistance, especially multidrug-resistant TB (MDR-TB) so that an effective drug regimen can be used. First-line drug regimens are not effective against MDR strains and their use can result in mortality and morbidity, amplification of resistance and spread of MDR-TB.

Strategy in previously treated patients:

Drug-resistance should be determined in all previously treated patients at or before the start of treatment. Xpert MTB/RIF is the preferred screening method for MDR-TB because of its sensitivity and quick turnaround time. The following are strategies depending on the availability of DST:

1 - Xpert MTB/RIF is available^{4(see page 83)}: Xpert MTB/RIF indicating rifampicin resistance in previously treated patients should lead to an empiric MDR regimen (see Adult and adolescent diagnostic algorithm 3, Chapter 4(see page 50)). Previously treated patients with an Xpert MTB/RIF test indicating no rifampicin resistance should have DST to first-line drugs and be started on a first-line retreatment regimen^{1(see page 0)}.

2 - Only conventional DST is available: Patients whose treatment has failed^{2(see page 0)}^{3(see page 0)} or other patients with a high likelihood of MDR-TB (close contacts) should be started on an empiric MDR regimen while waiting for DST results. Relapse patients or patients returning after interruption may receive a

retreatment regimen with first-line drugs ¹(see page 0) while waiting DST ⁵(see page 83). When DST result becomes available, the regimen should be adjusted. If the clinical condition does not improve or deteriorates on the retreatment regimen with first-line drugs while waiting DST results, change to an empiric MDR regimen.

3 - DST is not available: Strategies without DST for previously treated patients are not recommended. Some programmes may have no choice but to care for patients under these circumstances. In this case, it is advised for TB patients whose previous treatment has failed ²(see page 0) ³(see page 0) or other patients with a high likelihood of MDR-TB (close contacts) to be started on an empiric MDR regimen. Patients with low to moderate risk of having MDR-TB (relapse or returning after interruption) may receive a retreatment regimen with first-line drugs: 2 (HRZE) ⁴(see page 0) /1 (HRZE)/5 (HR)E. If no response is seen, the patient should be switched to an empiric MDR regimen. The MDR regimen should be continued throughout the course of treatment.

Empiric MDR regimens are described in [Chapter 10](#)(see page 84).

¹(see page 0) Most national TB programmes use 2 S(HRZE)/1 (HRZE)/5 (HR)E while waiting DST. These guidelines suggest using HRZE until DST returns, as the benefits of streptomycin are minimal and the daily injections discomforting.

[^a(see page 0) ^b(see page 0)]

²(see page 0) For PTB, failure should be confirmed with either: a positive culture OR a positive smear and the presence of clinical deterioration. This indicates that the patient is a true failure and not a case of being smear-positive with dead bacilli.

[^a(see page 0) ^b(see page 0)]

³(see page 0) MDR-TB rates of failures should be documented in all programmes to determine if their rates of MDR-TB are high enough to warrant empiric MDR-TB treatment while waiting DST.

[^a(see page 0) ^b(see page 0)]

⁴(see page 0) Most national TB programmes use 2 S(HRZE)/1 (HRZE)/5 (HR)E. These guidelines suggest using HRZE as the benefits of streptomycin are minimal and the daily injections discomforting.

9.2 Special situations

See references ¹(see page 83) and ⁵(see page 83)

- [9.2.1 Women](#)(see page 73)
- [9.2.2 Children](#)(see page 74)

9.2.1 Women

Pregnant women

All first-line oral drugs can be administered.

Streptomycin is contra-indicated (ototoxic to the fetus).

Rifampicin can increase the metabolism of vitamin K, resulting in clotting disorders. Prophylactic administration of vitamin K to the mother and the neonate is recommended when the mother has received rifampicin during pregnancy:

– For the mother:

phytomenadione (vitamin K) PO: 10 mg/day for the 15 days prior to expected date of delivery. Even with this maternal prevention, the infant still needs prophylactic IM vitamin K to prevent haemorrhagic disease of the newborn.

– For the newborn infant:

phytomenadione (vitamin K) IM: 1 mg as a single dose, the day of birth

All pregnant women should also receive preventive treatment for isoniazid-related peripheral neuropathy (**pyridoxine** PO: 10 mg/day along with their anti-TB drugs).

Breast-feeding women

Breast-feeding women should routinely receive preventive treatment for isoniazid-related peripheral neuropathy (**pyridoxine** PO: 10 mg/day along with their anti-TB drugs). In addition, the breast-fed infant should receive **pyridoxine** PO: 5 mg/day.

Women under contraception

Rifampicin and rifabutin interact with hormonal contraceptives and decreases their efficacy. Patients may choose between: use of medroxyprogesterone IM or barrier methods (diaphragm, condom, UID), or as a last resort, an oral contraceptive containing a high dose of estrogen (50 microgrammes/tab), throughout the course of treatment.

9.2.2 Children

Children should be treated with 2 (HRZE)/4 (HR)^{2(see page 83)}, except for TB meningitis and osteoarticular TB where the treatment is 2 (HRZE)/10 (HR).

Ethambutol is considered safe regardless of child's age, in particular regarding ocular toxicity^{6(see page 83)}, provided it is correctly dosed at 20 mg/kg/day. It is routinely used in drug-susceptible TB in children.

Streptomycin should be avoided in children because irreversible auditory nerve damage may occur and the injections are painful. Thus, the retreatment regimen is not recommended in children.

Children with TB are often malnourished. Therapeutic feeding should be initiated in children with severe malnutrition. Children not severely malnourished should receive nutritional supplementation with a standard food package or ready-to-use food for at least the first two months of treatment wherever possible.

9.3 Adjunctive corticosteroid therapy

Corticosteroids are indicated for:

- Meningitis of all stages of severity;
- Effusions: pleural effusion with severe respiratory difficulties; pericardial effusion;
- Compressions: laryngitis with obstruction of upper airways; urinary tract TB (in order to prevent ureteric stenosis); lymph node hypertrophy with bronchial or arterial compression;
- Severe hypersensitivity to TB drugs (although effectiveness has not been demonstrated);
- Life-threatening paradoxical reactions (immune reconstitution inflammatory syndrome) at the beginning of antiretroviral therapy or TB treatment (Chapter 12, [Section 12.7\(see page 113\)](#))^{1(see page 07)}.

The suggested treatment is **prednisolone** PO (or prednisone) for 6 to 12 weeks according to the severity of symptoms and clinical response:

- Children: 2 mg/kg once daily in the morning, up to 4 mg/kg once daily in severely ill children (max. 60

mg once daily)

– Adults: 40 to 60 mg once daily in the morning

The dose should be tapered off in the last 2 weeks. For adults, decrease the dose by 5-10 mg every 2 to 3 days. Stopping the corticosteroids abruptly may result in adrenal crisis.



Though corticosteroids are immunosuppressive, they may still be used safely in many HIV patients, depending on the immune status and concurrent infections. Never start corticosteroid treatment before anti-TB therapy.

9.4 Follow-up for patients treated with first-line regimens

- [9.4.1 Clinical visits](#)(see page 75)
- [9.4.2 Bacteriological examinations](#)(see page 75)
 - [Smears at the end of intensive phase](#)(see page 75)
 - [Smears in middle of continuation phase](#)(see page 76)
 - [End of treatment sputum examination](#)(see page 76)
- [9.4.3 Patient information and adherence interviews](#)(see page 77)
- [9.4.4 Follow-up schedules](#)(see page 77)

Patients should be followed for the entire duration of treatment. Follow-up includes, in particular, assessing the treatment results, adjusting the treatment if necessary, and detecting and managing adverse effects and adherence problems.

9.4.1 Clinical visits

Frequency of visits will depend on the patient's clinical condition and evolution. On average, for an outpatient who is not having any particular problem, the recommendation is weekly visits during the first month, a visit every other week during the second month and once a month thereafter.

The patient should be weighed at each visit and the doses should be adjusted, if necessary.

The occurrence of adverse effects should be asked at each visit.

Visits should coincide with bacteriological testing, when done. In EPTB, the clinical evolution is essential to assess the treatment response. The resolution of the symptoms and weight gain are important elements for monitoring response to treatment.

9.4.2 Bacteriological examinations

For EPTB, sputum smears are only performed if the patient develops pulmonary signs.

Patients with PTB should have their sputum examined as follows:

Smears at the end of intensive phase

All PTB (smear-positive and smear-negative) should have sputum smear performed at the end of Month 2 (new patients) or end of Month 3 (retreatment patients).

If the smear is negative, start the continuation phase.

If the smear is positive:

Xpert available	<p>Evaluate for resistance to rifampicin:</p> <p>Xpert RIF–: start continuation phase with first-line anti-TB drugs for one month then repeat smear.</p> <p>Xpert RIF+: switch to empiric MDR regimen (Chapter 10(see page 84)), perform culture and DST and adapt treatment accordingly.</p>
Xpert not available	<p>Initially smear-positive patients: Start continuation phase, repeat smear one month later. In most patients, sputum will test negative a month later (patients who started out with high bacillary loads may still have dead bacilli in their sputum at the end of the intensive phase but this is less likely a month later). A patient with positive smear at Month 3 (new patients) and Month 4 (retreatment patients) should have a culture and DST performed. If clinically deteriorating, consider switching to empiric MDR treatment while waiting for DST. If the results show a DR-TB, adapt treatment accordingly.</p> <p>Initially smear-negative patients: Suspect a treatment failure; perform culture and DST. If clinically deteriorating, consider switching to empiric MDR treatment while waiting for DST. If the results show a DR-TB, adapt treatment accordingly.</p>

Smears in middle of continuation phase

If smear is negative at the end of Month 4 (new patients) or at the end of Month 5 (retreatment patients), continue treatment until the end.

A positive smear at the end of Month 4 (end of Month 5 for retreatment patients) meets the standard definition of “treatment failure”.

Be careful when defining failure on the basis of microscopy alone; a positive smear might be due to the presence of dead bacilli, especially in patients who started out with a high bacillary load.

Always try to confirm the failure:

- By rapid culture;
- By clinical evaluation of the patient (if culture is not available, clinical evaluation can be sufficient).

If the culture is negative, and clinical evolution is good: a positive smear alone at Month 4 or Month 5 may not automatically indicate treatment failure. If the patient is considered highly likely not to be a failure despite the positive smear, then continue the present treatment and monitor every two weeks with clinical visits, smears and cultures, until it is determined with certainty the patient has been cured.

Xpert MTB/RIF (or other molecular methods) should not be used to monitor therapy. However it can be useful to show that a positive smear during the follow-up has rifampicin resistance, making it likely that the current therapy is not working.

End of treatment sputum examination

The sputum smear performed at the end of Month 6 (new patients) or Month 8 (retreatment patients) helps establish the final outcome of the treatment. Outcome definitions are discussed in [Chapter 17](#)(see page 135).

9.4.3 Patient information and adherence interviews

The clinician who makes the diagnosis and prescribes treatment should inform the patient about his disease and its treatment. Nevertheless, this initial interview alone is not sufficient to ensure that all the information has been given and taken in.

Interviews are recommended:

- At the start of treatment: two interviews devoted to informing the patient (one for informing him/her, the second for making sure the information has been absorbed);
- At the end of the intensive phase: an interview to explain the treatment changes that accompany the change in treatment phase;
- Throughout the treatment at all consultations: an interview to help assess and encourage adherence should be performed.

See [Chapter 13](#) (see page 116) for more information on adherence and patient's support.

When there are a large number of patients, interviews devoted to treatment adherence with specially trained personnel may be justified.

9.4.4 Follow-up schedules

See reference [1](#) (see page 83)

New patients on 6 month first-line regimen

Month	0	1	2	3	4	5	6
Clinical visits ^a	***	**	*	*	*	*	*
Bacteriological monitoring ^d	*		*		*b,c		*
Adherence	***	**	*	*	*	*	

^a. If the patient's clinical condition is not improving or deteriorating, a DST or a molecular test for resistance should be performed.

^b. Smear-positivity or culture-positivity at Month 4 or later is defined as "treatment failure" and necessitates re-registration as "previously treated patient" and a change of treatment as described in [Section 9.1.2](#) (see page 72).

^c. It is not necessary to perform smear microscopy after Month 2 if patient was not bacteriologically confirmed at the start of treatment, smear was negative at Month 2, and patient is clinically improving.

^d. Bacteriological monitoring is not needed for EPTB, except if lung involvement is suspected.

Patients on retreatment 8 month first-line regimen

Month	0	1	2	3	4	5	6	7	8
Clinical visits ^a	***	**	*	*	*	*	*	*	*
Bacteriological monitoring ^d	*			*b		*c			*
Adherence	***	**	*	*	*	*	*	*	*

- ^a. If the patient's clinical condition is not improving or deteriorating at any time a DST or a molecular test for resistance should be performed.
- ^b. If a positive smear microscopy is found at Month 3, a DST or a molecular test should be performed.
- ^c. Smear- or culture-positivity at Month 5 or later is defined as treatment failure and necessitates reregistration and a change of treatment as described in [Section 9.1.2](#)(see page 72).
- ^d. Bacteriological monitoring is not needed for EPTB, except if lung involvement is suspected.

9.5 Management of adverse effects in patients on first-line regimens

- [9.5.1 Symptom-based approach to managing adverse effects](#)(see page 78)
- [9.5.2 Cutaneous or generalized hypersensitivity](#)(see page 79)
- [9.5.3 Hepatotoxicity](#)(see page 80)
- [9.5.4 Isoniazid-associated neuropathy](#)(see page 80)

9.5.1 Symptom-based approach to managing adverse effects

The drugs used to treat TB may cause adverse reactions. Managing drug reactions rapidly and aggressively is an important means to increase tolerance. Generally with minor adverse effects, drugs need not be stopped and encouragement to the patient and use of ancillary medicines is all that is necessary. With major adverse effects, the drugs often have to be stopped and modified regimen continued.

Table 9.1 - Main adverse effects and probably responsible drugs

Adverse effects	Drug(s) probably responsible	Management
Minor		
Nausea, vomiting	R, H, Z	See Appendix 10 (see page 214)
Arthralgia	Z	See Appendix 10 (see page 214)
Peripheral neuropathy	H	See Section 9.5.4 (see page 80)
Orange/red urine, tears, etc.	R	Patients should be told when starting treatment that this is normal.
Major		
Skin rash	S, E, Z, R, H	See Section 9.5.2 (see page 79)
Auditory toxicity	S	See Appendix 10 (see page 214)
Vestibular toxicity	S	See Appendix 10 (see page 214)
Nephrotoxicity	S	See Appendix 10 (see page 214)
Hepatitis	Z, H, R	See Section 9.5.3 (see page 80)

Adverse effects	Drug(s) probably responsible	Management
Optic neuritis	E	See Appendix 10(see page 214)
Thrombocytopenic purpura	R	See Appendix 10(see page 214)

Generally it is not necessary to monitor renal or liver function, or blood counts unless there are clinical reasons to do so (e.g. a history of liver disease).

For more information, see individual drug sheets in [Appendix 9\(see page 171\)](#).

9.5.2 Cutaneous or generalized hypersensitivity

Hypersensitivity reactions usually appear early during treatment, often in the first month, but rarely during the first week. The drug the most likely to provoke these reactions is streptomycin however, other drugs can be involved. Consider also other causes of skin rash (e.g. scabies).

Hypersensitivity reactions show up in the form of itching and skin rashes. General signs, such as fever, dizziness, vomiting and headache, may occur.

Severe—even lethal—exfoliative dermatitis may occur very occasionally (Stevens-Johnson's syndrome), particularly if administration of the drug continues after signs of hypersensitivity appear.

In the event of simple itching: symptomatic treatment (e.g. antihistaminics), without interrupting or modifying treatment.

In the event of skin rash with or without itching:

1 - Stop anti-TB drugs; give symptomatic treatment (no corticosteroids except in emergencies) and wait for disappearance of symptoms.

2 - Identify the drug that caused the reaction in order to re-start treatment as rapidly as possible. Use trial doses as in the table below. Test first the drugs least likely to have caused the reaction: start with isoniazid over 3 days then add rifampicin over 3 days, etc.

For patients on re-treatment regimen including streptomycin: if isoniazid, rifampicin, pyrazinamide and ethambutol have been all re-introduced without recurrence of rash, streptomycin should be discontinued without testing.

Table 9.2 - Re-challenge of first-line anti-TB oral drugs and streptomycin (adapted from the WHO^{7(see page 83)})

Drug	Likelihood	Trial doses		From Day 3
		Day 1	Day 2	
H	least likely	50 mg	Full dose	Full dose
R		75 mg	300 mg	Full dose
Z		250 mg	1000 mg	Full dose
E		100 mg	500 mg	Full dose
S	most likely	125 mg	500 mg	Full dose

Note: if the initial reaction to treatment was severe, a weaker trial dose should be used (approximately 1/10th of the dose indicated for Day 1).

9.5.3 Hepatotoxicity

All anti-TB drugs may cause hepatotoxicity. Pyrazinamide is the most hepatotoxic and isoniazid the second but to a much lesser extent. Some combinations, such as rifampicin/pyrazinamide potentiate the hepatotoxic effect of each drug.

Clinical aspects resemble that of viral hepatitis: anorexia, nausea, vomiting, jaundice, etc.

If available, laboratory examination of liver injury is useful in diagnosing and following liver toxicity. Serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are elevated in liver toxicity.

AST or ALT or serum bilirubin > 3 times upper limit of normal with symptoms or > 5 times normal limit in the absence of symptoms are considered elevated. An AST or ALT or serum bilirubin < 5 times normal limit defines mild toxicity; 5 to 10 times normal limit defines moderate toxicity and > than 10 times normal limit defines severe toxicity.

When such symptoms occur or if liver enzymes are moderately or severely elevated, all anti-TB drugs should be stopped while waiting for resolution of signs. Treatment with the same drugs may, most of the time, be resumed without incident. The objective is to resume treatment either with the initial regimen or with another, and as rapidly as possible.

When the clinical status of the patient does not allow interruption of TB treatment, the least toxic drugs, streptomycin and ethambutol, can be used while waiting for clinical resolution of the hepatitis.

If symptoms reappear, it might be wise to reintroduce the drugs one by one and stopping the last drug re-introduced if symptoms recur or liver tests become abnormal. Some authors recommend starting with rifampicin (and ethambutol) and reintroduce isoniazid 3 to 7 days later. If rifampicin, ethambutol and isoniazid have been introduced and the biochemical abnormalities have not recurred, do not introduce pyrazinamide as it is most likely the causative agent.

The alternative regimen depends of the drug causing the toxic hepatitis, these regimen are similar to those recommended in case of resistance to the given drug.

- Pyrazinamide is involved: 2 S(HR)/7 (HR) or 2 (HR)E/7 (HR)
- Isoniazid is involved: 9 RZE
- Rifampicin is involved: 3 S-Lfx-HZE/12 Lfx-HZE or 3 Km-Lfx-HZE/12 Lfx-HZE
- Pyrazinamide and rifampicin are involved: 3 S-Lfx-HE/12 Lfx-HE or 3 Km-Lfx-HE/12 Lfx-HE

In the rare event of rifampicin and isoniazid are involved the treatment regimen is as an MDR regimen.

9.5.4 Isoniazid-associated neuropathy

Peripheral neuropathy refers to damage to the nerves located outside of the central nervous system. This usually occurs more commonly in pregnant and breastfeeding women and patients with HIV infection, alcohol dependency, malnutrition, diabetes, chronic liver disease, and renal impairment. These patients should receive preventive treatment with **pyridoxine** PO (5 to 10 mg/day in children; 10 mg/day in adults) along with their anti-TB drugs. Other guidelines recommend 25 mg/day but there is some evidence that this dose may overcome the antibiotic action of isoniazid. If only 25 mg tablets are available give 3 times weekly or cut in half and give daily.

If peripheral neuropathy develops, administer **pyridoxine** PO:

- Children less than 12 years: 20 to 40 mg/day in 2 divided doses
- Children over 12 years: 60 to 100 mg/day in 2 divided doses
- Adults: 100 to 200 mg daily

9.6 Management of treatment interruption in patients on first-line regimens

- [9.6.1 New patients on first-line regimens](#)(see page 81)
- [9.6.2 Retreatment patients on first-line regimens](#)(see page 82)

The approach depends on initial bacteriological status, the moment when the patient returns, and the length of previous treatment. The questions of whether or not a patient still presents an active form of the disease, and whether or not he has developed a resistance should always be determined. Treatment interruption can be for any reason.

Every effort should be made to re-start or complete TB treatment in patients who experience treatment interruption.

The approach is, in theory, standardised as described in [Table 9.3](#)(see page 81) and [Table 9.4](#)(see page 82). However, it is often complex and should be based on rigorous study of the patient's history, meticulous clinical examination, and bacteriological examination results. A chest X-ray might be useful, especially if previous ones are available for comparison.

A patient who interrupted his treatment is more at risk of interrupting again. The patient should be followed even more closely and re-motivated with the greatest attention: retreatment regimen may be the last chance of cure, and adapted strategies should be considered to support patient's adherence ([Chapter 13](#)(see page 116)).

9.6.1 New patients on first-line regimens

Table 9.3 - Management of new patients who interrupted treatment

Length of treatment	Length of interruption	Sputum result at return	Treatment outcome	Classification at return	Treatment action and registration
< 1 month	< 2 weeks	Not needed	–	–	Continue treatment at the point it was stopped.
	2-7 weeks	Not needed	–	–	Re-start treatment.
	≥ 8 weeks	Smear+ Smear–	Interruption	New	Re-start treatment, perform DST ^b .
1-2 months	< 2 weeks	Not needed	–	–	Continue treatment at the point it was stopped.
	2-7 weeks	Smear+	–	–	• Re-start treatment, perform DST ^b .
		Smear–	–	–	• Continue treatment at the point it was stopped.

Length of treatment	Length of interruption	Sputum result at return	Treatment outcome	Classification at return	Treatment action and registration
	≥ 8 weeks	Smear+ Smear–	Interruption	TAI ^a TAI ^a	Start retreatment, perform DST ^b and give a new number to the patient.
≥ 2 months	< 2 weeks	Not needed	–	–	Continue treatment at the point it was stopped.
	2-7 weeks	Smear+	Cancel previous registration	Others	• Start retreatment, perform DST ^b , register as “Others”.
		Smear–	–	–	• Continue treatment at the point it was stopped.
	≥ 8 weeks ^c	Smear+ Smear–	Interruption	TAI ^a TAI ^a	Start retreatment, perform for DST ^b and give the patient a new number.

^a. TAI = Treatment after interruption.

^b. Xpert MTB/RIF and conventional DST if available.

^c. For patients having received adequate treatment for four months or more who return smear-negative and in good clinical condition, the decision to start a retreatment will be considered on a case by case basis.

9.6.2 Retreatment patients on first-line regimens

Table 9.4 - Management of retreatment patients who interrupted treatment

Length of treatment	Length of interruption	Sputum result at return	Treatment outcome	Classification at return	Treatment action and registration
< 1 month	< 2 weeks	Not needed	–	–	Continue retreatment at the point it was stopped.
	2-7 weeks	Not needed	–	–	Re-start retreatment.
	≥ 8 weeks	Smear+ Smear–	Interruption Interruption	Same as previous registration	Re-start retreatment and give the patient a new number.
> 1 month	< 2 weeks	Not needed	–	–	Continue retreatment at the point it was stopped.
	2-7 weeks	Smear+	–	–	• Re-start retreatment, ask for DST ^b .

		Smear–	–	–	• Continue retreatment at the point it was stopped, ask for DST ^b .
	≥ 8 weeks	Smear+ Smear–	Interruption Interruption	TAI ^a TAI ^a	Re-start retreatment, give a new number to the patient, ask for DST ^b .

^a. TAI = Treatment after interruption.

^b. Xpert MTB/RIF and conventional DST if available.

References Chapter 9

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Chapter 10: Treatment of multidrug-resistant TB (MDR-TB)

- 10.1 Design of therapeutic regimens in MDR-TB(see page 84)
- 10.2 Selection of anti-TB drugs in MDR-TB regimens(see page 85)
- 10.3 Building a treatment regimen for MDR-TB(see page 88)
- 10.4 Duration of MDR-TB regimens(see page 91)
- 10.5 Follow-up for patients treated for MDR-TB(see page 91)
- 10.6 Management of adverse effects in patients on second-line regimens(see page 93)
- 10.7 Surgery as an adjunctive treatment measure(see page 94)
- 10.8 Management of patients whose treatment failed and palliative care(see page 95)
- 10.9 Special situations(see page 95)
- 10.10 Treatment of extensively drug-resistant TB (XDR-TB)(see page 97)
- References Chapter 10(see page 98)

10.1 Design of therapeutic regimens in MDR-TB

The following are the basic principles involved in MDR-TB regimen design¹(see page 98):

- The intensive phase includes at least four core Group 2 to 4 anti-TB drugs likely to be effective, including an injectable agent – plus pyrazinamide (Z).
- In the case of unclear evidence about the effectiveness of a certain drug, it can be part of the regimen but it should not be counted as one of the four core second-line anti-TB drugs.
- An anti-TB drug is considered “likely to be effective” when:
 - 1** - The drug has not been used in a regimen that failed for the individual patient;
 - 2** - Drug susceptibility testing (DST) performed on the patient’s strain indicates that the strain is susceptible. Only DST for isoniazid, rifampicin, Group 2 and 3 drugs is considered reliable;
 - 3** - No known resistance to drugs with high cross-resistance;
 - 4** - No known close contacts with a patient infected with a strain resistant to the drug;
 - 5** - In the absence of DST or for drugs in which individual DST is not reliable, a drug resistance survey demonstrates that resistance to the drug is rare in patients with similar TB history.
- It is not always possible that all five criteria can be ascertained and clinical judgment is often necessary on whether to count a drug as “likely effective”.
- An important pitfall in designing MDR-TB regimens is due to the turnaround time necessary for DST, the patient may have already received months of a treatment by the time DST results become available from the laboratory. The possibility of further acquired resistance during this time must be considered. If there is a high probability of acquired resistance to a drug after the specimen for DST was collected, this drug should not be counted as one of the four second-line anti-TB drugs in the core regimen, but can be included as an adjunctive agent.
- The most effective regimens for MDR-TB include at least a fluoroquinolone (preferably a third-generation), an injectable agent, ethionamide (or prothionamide), either cycloserine or para-aminosalicylic acid, and pyrazinamide.

- There are conditions when more than five drugs may be started, as is the case if the susceptibility pattern is unknown or the effectiveness is questionable for a drug(s).
- A drug should not be used when patient is known to have a major contraindication of usage (e.g. known major drug-drug interactions, history of allergic reaction, pregnancy).
- Each dose is given under directly observed therapy (DOT) throughout the treatment. A treatment card is marked for each observed dose. DOT can be performed either facility-based or home-based (often referred to as community-based). See [Chapter 13](#) (see page 116).
- Treatment is given six or seven days a week. Six days a week is chosen for those patients managed in outpatient settings where DOT cannot be done everyday.

10.2 Selection of anti-TB drugs in MDR-TB regimens

See reference [2](#) (see page 98)

- [Group 1 \(Oral first-line agents\)](#) (see page 85)
- [Group 2 \(Injectable agents\)](#) (see page 85)
- [Group 3 \(Fluoroquinolones\)](#) (see page 86)
- [Group 4 \(Oral bacteriostatic second-line anti-TB drugs\)](#) (see page 86)
- [Group 5 \(Drugs with limited data on efficacy and/or long-term safety\)](#) (see page 86)

Group 1 (Oral first-line agents)

Pyrazinamide is routinely added to MDR regimens if susceptibility (by DST) is documented or if DST is unknown. If well tolerated it is used for the entire treatment, although patients doing well and with minimal lung disease can have it stopped with the injectable agent and continue with at least three likely effective drugs.

Ethambutol is not routinely added to MDR regimens, however it can be added if the criteria of it being a likely effective drug are met.

For patients with strains resistant to low concentrations of isoniazid, but susceptible to higher concentrations, the use of high-dose isoniazid may have some benefit (see [Group 5](#) (see page 86)).

The newer rifamycins, such as rifabutin have very high cross-resistance to rifampicin and are not used in MDR regimens.

Group 2 (Injectable agents)

All patients should receive a Group 2 injectable agent if susceptibility is documented or the drug is considered likely to be effective.

Kanamycin or amikacin are the first choice injectable agent. Both are low cost, and have been used extensively for the treatment of MDR-TB. They are considered to be very similar and have a high frequency of cross-resistance.

Given the high rates of resistance to streptomycin in patients with MDR-TB, streptomycin is not used in MDR-TB treatment regimens.

If the strain is susceptible to capreomycin or if resistance is rare in the patient population and if aminoglycosides are contra-indicated or poorly tolerated or ineffective on the patient's strain,

capreomycin should be used. Capreomycin should also be used while waiting for the DST results in places where resistance to kanamycin and amikacin is common.

Group 3 (Fluoroquinolones)

The most potent available fluoroquinolones in descending order based on *in vitro* activity and animal studies are: moxifloxacin > levofloxacin > ofloxacin^{3(see page 98),4(see page 98)}.

This guide recommends not using ofloxacin (second-generation fluoroquinolone) as it has inferior performance against TB compared to the other Group 3 fluoroquinolones. In addition, resistance may develop more easily to the fluoroquinolone group when ofloxacin is used in a multidrug regimen. Ciprofloxacin (second-generation fluoroquinolone) is not included in Group 3 and should never be used to treat drug-susceptible or DR-TB because of its low efficacy against TB bacilli^{5(see page 98)}.

Third-generation fluoroquinolones (moxifloxacin and levofloxacin) may have some efficacy against ofloxacin-resistant strains^{6(see page 98)}.

Mostly based on cost and availability, levofloxacin is often the fluoroquinolone used in most MDR-TB regimens, whereas moxifloxacin is reserved for cases of high resistance (resistance to ofloxacin, injectable agents, or other second-line anti-TB drugs).

In case of resistance to fluoroquinolones, the use of bedaquiline should be considered (see below).

Group 4 (Oral bacteriostatic second-line anti-TB drugs)

Ethionamide and prothionamide are considered the most potent Group 4 drugs^{1(see page 98)}. However it should be noted that these drugs do have some cross-resistance with isoniazid. Ethionamide and prothionamide can be included in the regimen if *inhA* gene is detected but should not be counted as a likely effective drug.

Cycloserine and/or para-aminosalicylic acid should be included in MDR-TB regimens. Both share no cross-resistance to other anti-TB drugs. Since the combination of ethionamide or prothionamide and para-aminosalicylic acid often causes a high incidence of gastrointestinal disturbances and hypothyroidism, these agents are usually used together only when three Group 4 agents are needed.

The drugs in Group 4 may be started at a low dose and escalated over 1 to 2 weeks to improve tolerance.

Group 5 (Drugs with limited data on efficacy and/or long-term safety)

Group 5 drugs are recommended in cases where adequate regimens are impossible to design with the drugs from Groups 1 to 4.

Compared to other drugs in this group bedaquiline is the only one with proven efficacy against TB. While there is no clear evidence for the hierarchy of use of Group 5 drugs, these guidelines propose that the three most attractive agents from this group in order of preference are: bedaquiline, linezolid, clofazimine.

Bedaquiline^{1(see page 0),7(see page 98),8(see page 98),9(see page 98)}: Bedaquiline is a diarylquinoline with bactericidal anti-mycobacterial activity. This new drug was registered by the US FDA in December 2012^{2(see page 0)} for MDR-TB patients with no other therapeutic options. It is recommended in case of resistance to fluoroquinolones or when it is not possible to have four effective anti-TB drugs from Group 2 to 4 in the regimen. The dosage in adult is 400 mg once daily for 2 weeks followed by 200 mg 3 times per week for 22 weeks.

The drug is not yet recommended for children or pregnant women. The main adverse effects are nausea, arthralgia, headache and QT prolongation. QT prolongation can result in cardiac arrhythmia and sudden death. Baseline and regular electrocardiogram (ECG) monitoring should be performed. QT prolongation

is more pronounced when combined with clofazimine. Combination with other QT prolonging drugs (moxifloxacin, ondansetron, etc.) should be avoided or closely monitored. Bedaquiline must not be combined with rifamycins and some antiretrovirals (see [Chapter 12](#) (see page 109)). Bedaquiline is not registered in most high burden countries and only available through compassionate use (see also [Appendix 11](#) (see page 227)).

For situations that require the use of Group 5 drugs other than bedaquiline (or when bedaquiline is not available), use at least two other drugs from Group 5 given the limited knowledge of their efficacy.

Linezolid: Linezolid has good activity *in vitro* and in animal studies. There are also a number of reports and case series in MDR-TB and XDR-TB¹⁰(see page 98),¹¹(see page 98),¹²(see page 98),¹³(see page 98),¹⁴(see page 98),¹⁵(see page 98),¹⁶(see page 98),¹⁷(see page 98) and a recent study showing efficacy in XDR-TB¹⁸(see page 98). It has numerous severe adverse effects including myelo-suppression and irreversible peripheral neuropathy. It is presently very expensive.

Clofazimine: There is a moderate amount of experience with clofazimine in MDR-TB treatment but no clear *in vivo* data on efficacy against TB. It is usually added to regimens for XDR-TB.

Amoxicillin/clavulanic acid: Generally the B-lactam antibiotics are not regarded as very useful drugs in TB. However, the addition of the B-lactamase inhibitor makes them active *in vitro* against TB. There is one *in vivo* study that showed good early bactericidal activity. While amoxicillin/clavulanic acid is probably a relatively weak anti-TB drug, it is often included because it is available, inexpensive and causes only minor adverse effects.

High-dose isoniazid: High-dose isoniazid (16-20 mg/kg/day) can be used as a Group 5 drug in the presence of resistance to low concentrations of isoniazid¹⁹(see page 98) (> 1% of bacilli resistant to 0.2 mcg/ml but susceptible to 1 mcg/ml of isoniazid). Isoniazid is not recommended for high-dose resistance (> 1% of bacilli resistant to 1 mcg/ml of isoniazid)²⁰(see page 98) or in presence of katG gene mutation (see LPA, Chapter 3, [Section 3.4.2](#) (see page 33)).

Notes:


– **Gatifloxacin** (Group 3): Although gatifloxacin is similar to moxifloxacin in efficacy against TB, it is associated with serious hypo/hyperglycaemia, and new onset diabetes. Thus, its use is not recommended.

– **Terizidone** (Group 4): It is unknown whether this drug is equally efficacious as cycloserine, therefore these guidelines recommends the use of cycloserine over terizidone.

– **Imipenem/cilastatin** and **meropenem** (Group 5): These beta-lactam/carbapenems are only given intravenously. Given the cost and difficulty of the twice-daily intravenous administration, it is not commonly used in resource-constrained settings. Meropenem is preferred in children as there is more experience with its use. Meropenem can be combined with oral doses of clavulanate. These drugs are commonly used for a duration of two months past conversion.

– **Clarithromycin** (Group 5): This drug is included in various TB manuals²¹(see page 98) yet evidence to support its efficacy in MDR-TB is minimal. It may have a synergistic effect on first-line anti-TB drugs with enhanced intracellular effectiveness against the TB bacilli. However, until more information on effectiveness in TB and MDR-TB, its use is not recommended.

– **Thioacetazone** (Group 5): While thioacetazone is known to be active against TB bacilli, it is placed in Group 5 because its role in DR-TB treatment is not well established. Thioacetazone has cross-resistance with some of the other anti-TB agents (Chapter 8, [Section 8.5](#) (see page 69)) and overall is a weakly bacteriostatic drug. It is contraindicated in HIV-infected individuals²²(see page 98) due to a risk of serious adverse reactions (Stevens-Johnson syndrome and death). Persons of Asian descent also have a higher incidence of Stevens-Johnson syndrome. For these reasons, thioacetazone is rarely added as a Group 5 drug. Until there is more information in its role in MDR-TB therapy, its use is not recommended.

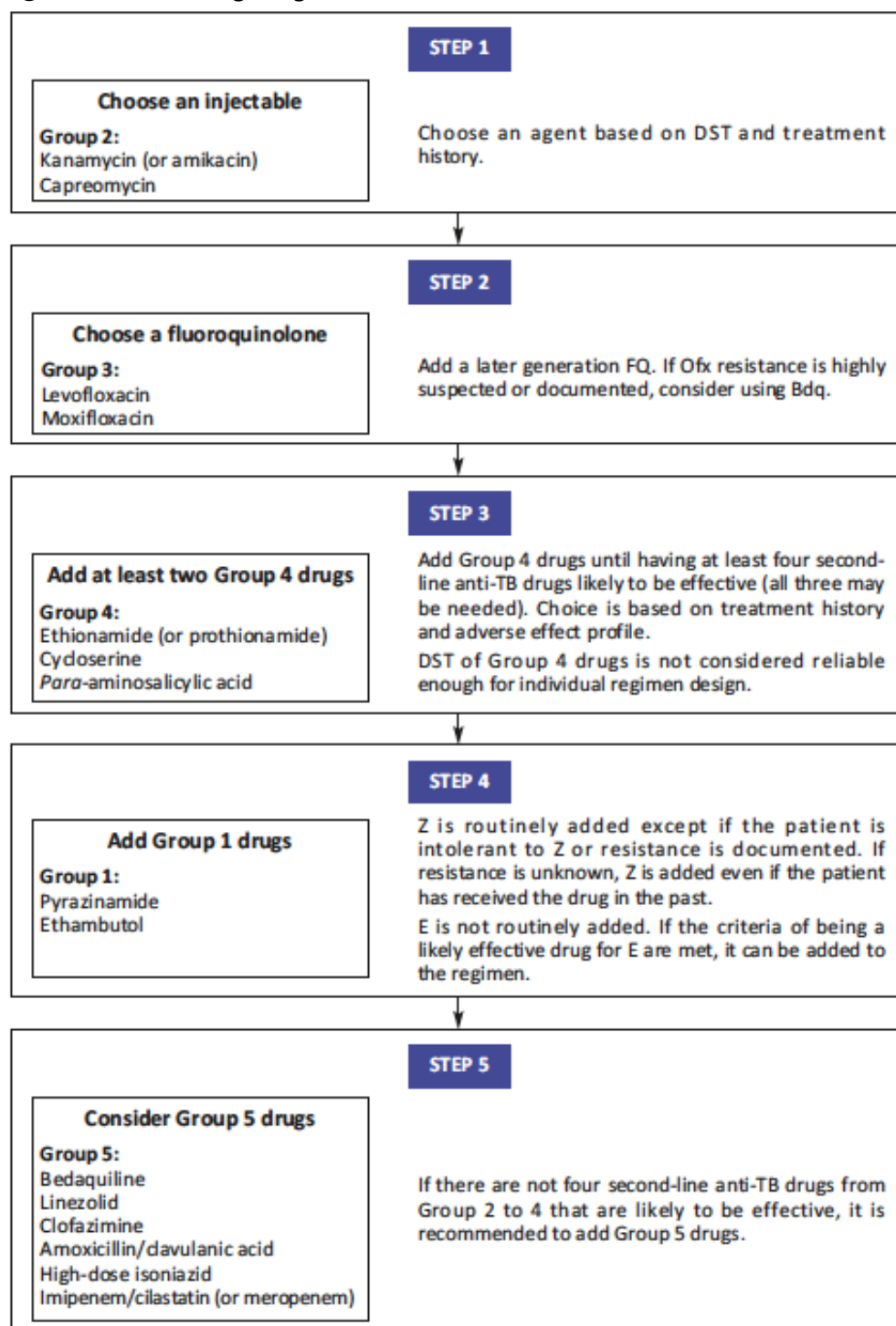
 Bedaquiline is relatively well tolerated. Data and experience on its use is very limited. In a blinded randomized placebo-control study there were an increase number of deaths in the study arm that received bedaquiline. While none of the deaths were considered directly related to the drug, the possibility that the use of the drug carries an increase risk of death cannot be ruled out. The risks and benefits of receiving this drug should be fully explained to the patient.

 <http://www.accessdata.fda.gov/drugsatfdadocs/label/2012/204384s000lbl.pdf>

10.3 Building a treatment regimen for MDR-TB

Adapted from Drug-resistant tuberculosis: a survival guide for clinicians. San Francisco, Francis J. Curry National Tuberculosis Center and California Department of Health Services, 2004.

Individual regimens are designed based on DST of the infecting strain, history of TB treatment, and contact history. Figure 10.1 describes the steps to build a regimen for MDR-TB treatment.

Figure 10.1 - Building a regimen for MDR-TB**Box 10.1** - Examples of how to initiate and design MDR-TB regimens

Example 1 - patient doing poorly on first-line treatment

A patient receiving first-line treatment for new patients (2 HRZE/4 HR) continues to be smear positive at Month 3 with symptoms including weight loss, fever, shortness of breath and cough. The patient feels the shortness of breath is getting severe and he spends more than 50% of the day in bed. No DST was performed at the start of treatment. Xpert MTB/RIF performed at Month 3 shows MTB+ and rifampicin resistance. What should be done?

Answer: A positive Xpert MTB/RIF at Month 3 in a patient doing poorly on a first-line regimen that shows R resistance is highly likely to be a true positive. This patient should be placed on MDR-TB therapy. A confirmatory DST with conventional methods to at least H and R and if possible to injectable agents and fluoroquinolones should be performed.

If a rapid molecular test was not available, this patient should be placed on an MDR-TB regimen while waiting conventional DST results.

- If there is low second-line drug resistance in patient's strains with MDR-TB in the area then a common regimen is: Km-Lfx-Eto (or Pto)-Cs-ZE.
- If there is moderate to high second-line drug resistance in MDR-TB strains in the area or if the level of resistance to second-line drugs is not known: Cm-Mfx-Eto (or Pto)-Cs-PASZE. Once DST becomes available the regimen can be adjusted. In this case, the infecting strain was determined to be resistant to H-R-S and susceptible to Km-Cm-Ofx-E; resistance to Z was unknown. Given the DST results, it is recommended to continue with Km-Lfx-Eto (or Pto)-Cs-ZE and drop the PAS if it was used in the initial regimen.

Example 2 - Xpert RIF positive in a patient with low probability of MDR-TB

A HIV-negative smear-negative TB suspect is referred to Xpert MTB/RIF to establish the diagnosis of TB. The result of the Xpert is MTB+ and rifampicin resistance. The patient has never been diagnosed with TB. The MDR-TB prevalence for new patients in the area is 1%. The patient only complains of a mild cough for 3 weeks and X-ray shows minimal lesions. What should be done?

Answer: The RIF resistance positive predictive value (PPV) for the Xpert MTB/RIF in the setting of 1% rifampicin resistance prevalence is 32% ([Appendix 3](#)(see page 156)). Because of the relatively low PPV of the Xpert MTB/RIF under these circumstances and the fact that patient is HIV-negative and not seriously ill, he can be placed on a first-line drug regimen while waiting confirmation DST. If possible, DST confirmation should be done through a rapid phenotypic method or using LPA on culture (indirect method). If the patient deteriorates clinically at any time while waiting confirmation DST, an empirical MDR-TB regimen should be started. When the DST returns, the regimen should be adjusted if the resistance to rifampicin is confirmed.

Note:

An alternative shorter 9 month standard regimen (4 Km-Gfx-Pto-Cfz-high dose H-ZE/5 Gfx- Cfz-ZE) [1](#)(see page 98) has shown good effectiveness in a study in Bangladesh²³(see page 98). Adaptations are made in some countries in Western Africa²⁴(see page 98) with moxifloxacin replacing gatifloxacin and extension of the regimen to 12 months. At present, this regimen is still considered experimental²⁵(see page 98).

Given the limited evidence supporting this regimen these guidelines recommend the following:

- Obtain country-level and institutional ethical approval before implementation.
- Implement it under operational research conditions following good practices.
- Consider this regimen on a case-by-case basis for programmes with proper follow-up and outcome documentation in unstable settings where a 2 year-treatment is not an option.
- Perform DST to the fluoroquinolones in a liquid medium and do not use in any patient with documented fluoroquinolone resistance (the third-generation fluoroquinolones are the backbone of the regimen and the regimen does not perform well against strains resistant to fluoroquinolones).

- Use only in HIV-negative patients until more information is published on the regimen and its use in HIV-positive patients.
- Do not use in areas with a high prevalence of resistance to second-line anti-TB drugs until more information is published.

 (see page 0) The recommended dosing in the 9-month regimen is described in: Aït-Khaled N, Alarcón E, Armengol R, Bissell K, Boillot F, Caminero J A, Chiang C-Y, Clevenbergh P, Dlodlo R, Enarson D A, Enarson P, Fujiwara P I, Harries A D, Heldal E, Hinderaker S G, Lienhardt C, Monedero I, Rieder H L, Rusen I D, Trébucq A, Van Deun A, Wilson N. Management of tuberculosis: a guide to the essentials of good practice. Paris, France: International Union Against Tuberculosis and Lung Disease, 2010.

10.4 Duration of MDR-TB regimens

- [10.4.1 Intensive phase](#)(see page 91)
- [10.4.2 Length of treatment](#)(see page 91)

10.4.1 Intensive phase

Duration of intensive phase is guided by culture. The injectable agent should be continued for at least 8 months¹(see page 98) and at least 4 months after the patient becomes culture negative – which ever is longer.

The use of an individualized approach which reviews the cultures, smears, X-rays and the patient's clinical status may also aid in deciding whether or not to continue an injectable agent longer than the above recommendation, particularly in the case of patients for whom the susceptibility pattern is unknown, effectiveness is questionable for an agent(s) or extensive or bilateral pulmonary disease is present.

A change to intermittent therapy with the injectable agent (3 times weekly) is done when signs of toxicity are noticed. Three times a week therapy is recommended in patients after 6 months of an injectable agent and who have had culture conversion, as toxicity becomes a greater risk to patients with longer periods of the injectable agent.

10.4.2 Length of treatment

The duration of treatment is guided by culture. It is recommended continuing therapy for a minimum of 20 months¹(see page 98) and at least 18 months after the patient becomes culture negative.

Extension of therapy to 24 months may be indicated in chronic cases with extensive pulmonary damage.

10.5 Follow-up for patients treated for MDR-TB

Table 10.1 - Routine patient monitoring

Evaluation	Frequency
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Assessment by a clinician	<p><i>During intensive phase:</i> every day during the first weeks if hospitalized and at least every week if treated as outpatient, until the treatment is well tolerated. Once stable, the patient is seen once or twice monthly.</p> <p><i>During continuation phase:</i> monthly assessment unless there is a medical necessity to see the patient more often.</p> <p>The DOT supporter sees the patient daily and signals any concerns to the clinician.</p>
Treatment adherence and tolerance	Daily at every DOT encounters by the DOT supporter.
Sputum smear and cultures	<p>Monthly until the end of treatment.</p> <p><i>Note:</i> programmes with very limited culture capacity may consider doing smears monthly but cultures every other month for the continuation phase.</p>
Weight	At baseline and then monthly.
DST	At baseline and for any positive culture during treatment.
Chest X-rays	At baseline and then every three to six months.
Serum creatinine Serum potassium (K+)	At baseline, then twice a month for the first two months, then monthly while receiving an injectable agent. Every one to three weeks in HIV-infected patients, diabetics throughout the course of the injectable agent.
Thyroid stimulating hormone (TSH)	Every six months if receiving Eto/Pto and/or PAS (every three months in HIV positive patients) and whenever signs/symptoms of hypothyroidism are present. TSH is sufficient for screening for hypothyroidism and it is not necessary to measure hormone thyroid levels.
Liver serum enzymes	At baseline then monthly during the intensive phase. Every 3 months thereafter. Monthly monitoring for HIV-infected. In patients with viral hepatitis: once weekly for the first month, then every one to four weeks. Monthly for patients taking Bdq.
Bilirubine	Monthly for patients taking Bdq.
HIV screening	At baseline then repeat when clinically indicated or every 6 months in high HIV prevalence settings.
Pregnancy tests	At baseline for women of childbearing age, and repeat if indicated.

Haemoglobin White blood count	If on Lzd, weekly during the first month, then monthly or as needed based on symptoms; there is little clinical experience with prolonged use of Lzd. For HIV-infected patients on AZT: monthly initially and then as needed based on symptoms. If patient not on Lzd or AZT, routine monitoring is not indicated.
Hearing tests	Baseline audiogram, then monthly during intensive phase (and whenever clinically indicated). Ask patient about changes in hearing at every clinic visit and evaluate their ability to participate in normal conversation.
Vision tests	For patients on long-term E or Lzd, use the Ishihara test (test for changes in the vision of colour). Perform at baseline as a certain percentage of the population has colour blindness. Then monthly in patients taking Lzd.
Psycho-social consultation	At baseline by trained personnel in the skills of psycho-social management, during treatment and repeat as indicated. Refer to psychiatrist when indicated.
ECG	Patients taking Bdq: at baseline then, after 2 weeks then, monthly.

10.6 Management of adverse effects in patients on second-line regimens

Treating rapidly and aggressively adverse reactions is an important means to increase tolerance and is critical to improve outcomes.

All patients should be informed that they are likely to experience adverse effects. Adverse effects appear most commonly at the start of therapy, especially during the first few weeks of treatment where the patient can feel quite lousy – with nausea and vomiting being the most common adverse effect. Patients should be informed that many of the common minor adverse effects will improve with time and medical treatment.

Patients are monitored for general toxicities and drug-specific toxicity at every DOT encounter. They should be educated that if serious adverse effects appear (e.g. hearing loss, dizziness, ringing in the ears, jaundice, edema, decreased urine output, skin rash or burning in the legs), they must inform the health care worker immediately.

It is often difficult to ascertain whether a given adverse effect is due to a single drug or is the result of several drugs given simultaneously. If after management of adverse effects the patient remains intolerably symptomatic, a dose reduction or elimination of one of the drugs may be necessary. Permanent dose reduction or definitive elimination of a drug should be considered only after all other possibilities have been exhausted i.e., in cases of significant organ dysfunction or intractable intolerance. Ideally, any drug eliminated from a treatment regimen should be replaced with an equally effective drug, as to not compromise the overall effectiveness of the regimen.

Dose reduction can be done in a systematic manner by starting with the most likely offending drug for one week to see whether the symptoms diminish or disappear. If symptoms persist, the drug is returned

to its original dose and the same process repeated for the other drugs, until all potentially responsible drugs have been tested. Systematic dose reduction of multiple drugs simultaneously would be the next option.

Whenever reducing or holding a drug to determine the cause of an adverse effect, tell the patient that this is a test to determine which drug is involved and that the drug dose will be increased back to therapeutic dose in a manner that will be better tolerated. Returning back to therapeutic doses gradually (over one to two weeks) while implementing strategies to decrease a specific adverse effect can often allow the patient to better tolerate it.

Treatment supporters and nurses working with TB programmes should report an adverse event to the physician at the earliest appropriate time. Only the managing physician should do dose changes or eliminate a specific anti-TB drug.

Often, if an adverse effect cannot be completely eliminated, patients may be asked to tolerate symptoms until they subside. Often reassurance and emotional support can result in the avoidance of adding yet another medication to the high burden of medications the patient is already receiving.

For specific management of common adverse effects, see [Appendix 10](#) (see page 214).

Ancillary medicines (anti-emetics, potassium replacement, thyroid hormone, medicines for psychiatric conditions, etc.) should be provided free of charge to the patient.

10.7 Surgery as an adjunctive treatment measure

Surgery can be considered only in optimal surgical facilities with trained thoracic surgeons. Specialized surgical facilities should include stringent infection control measures since infectious substances and aerosols are generated in large quantities during surgery, during mechanical ventilation and post-operative pulmonary hygiene manoeuvres.

General indications for surgery for programmes with limited access to surgery include patients with resistance to a large number of drugs and localized pulmonary disease. Computerized tomography, pulmonary function testing, and quantitative lung perfusion/ventilation are recommended as part of the preoperative work-up.

The most common operative procedure in patients with MDR-TB is resection of part or all of a lung. Large case series analysis suggest surgical resection can be effective and safe under appropriate surgical conditions²⁶(see page 98),²⁷(see page 98). It is considered an adjunct to chemotherapy and appears to be beneficial for patients when skilled thoracic surgeons and excellent postoperative care are available²⁸(see page 98). It is not indicated in patients with extensive bilateral disease.

Resection surgery should be timed so as to offer the patient the best possible chances of cure with the least morbidity. Thus, the timing of surgery may be earlier in the course of the disease when the patient's risk of morbidity and mortality are lower, for example, when the disease is still localized to one lung or one lobe. Furthermore, bacilli excretion during treatment has a "window" when the bacilli load decreases under pressure of anti-TB drugs and it can be registered by decreasing or even disappearing of mycobacteria in smear and/or culture. This "window" is the best time for surgery. It is critical to operate before the mycobacterial count begins to rise. The best time for surgery is usually considered to be between two and six months after initiation of treatment²⁸(see page 98),²⁹(see page 98),³⁰(see page 98). Surgery should not be considered a last resort.

Even with successful resection, an additional 12 to 24 months of chemotherapy should be given.

10.8 Management of patients whose treatment failed and palliative care

When it has been determined a patient is failing therapy for DR-TB, the first priority is to design a new regimen using the principles described in Sections 10.1 to Section 10.3. The new regimen should contain at least two new effective drugs.

The employment of newly developed TB drugs available for compassionate use ([Appendix 11](#)(see page 227)) is encouraged. For some of these drugs (delamanid), approval is expected in 2013.

When no therapeutic option or new regimen is possible, the patient can be continued on an anti-TB regimen that is reasonably tolerated (and if the patient desires) or the regimen can be completely stopped. The decision to stop therapy should be made after careful evaluation and consultation with the patient, the family and the MDR-TB treatment team.

Palliative/supportive care should be continued. Supportive measures for minimizing suffering due to the disease or the therapy should be implemented according to the patient needs.

Supportive measures may include:

- Relief of respiratory symptoms: oxygen should be used to alleviate shortness of breath; corticosteroids (prednisolone) are beneficial in severe respiratory insufficiency; codeine helps control cough.
- Identification, assessment and treatment of pain: according to the standard recommendations (non opioids/mild opioids/strong opioids adapted to the level of pain).
- All necessary ancillary medications needed should be used.
- Patients with poor nutritional status should receive nutritional support.
- In debilitated patients, important measures for making patients comfortable and preventing complications must be taken. Regular scheduled movement of the bedridden patients prevents bedsores. Bathing and oral care assistance keeps patients clean and comfortable, while preventing skin infections.
- Disorders such as anxiety or depression due to prolonged sickness, separation from family, difficult living conditions, etc. should be addressed when present. The patient as well as the family may need support.
- Potential social problems should also be addressed. When necessary, hospice-like care should be offered to families who want to keep the patient at home. Inpatient end-of-life care should be available to those for whom home care is not available.

Note: the above palliative/supportive measures should be implemented to all DR-TB patients if indicated whether or not they are failing treatment. Some measures may even need to be continued after a patient's TB has cured, but the patient still remains with significant respiratory damage.

10.9 Special situations

- [10.9.1 Pregnant women](#)(see page 96)
- [10.9.2 Breastfeeding women](#)(see page 96)
- [10.9.3 Women of child-bearing age](#)(see page 96)
- [10.9.4 Children](#)(see page 97)
- [10.9.5 Extrapulmonary drug-resistant TB](#)(see page 97)
- [10.9.6 Renal insufficiency](#)(see page 97)

10.9.1 Pregnant women

Pregnant women should be carefully evaluated, such that the risks and benefits of treatment considered according to gestational age and severity of disease.

- The primary goal is culture conversion to protect the health of the mother and child, both before and after birth.
- If the patient is very stable with minimum disease, treatment may be delayed and started in the second trimester with 3 or 4 drugs known to be safe in pregnancy and active on the infecting strain. In most cases of moderate to severe disease the treatment should be started right away with the risks and benefits explained to the mother.
- Aminoglycosides are contraindicated. If an injectable agent is required, capreomycin is the only option as there are case reports of safe use in pregnancy.
- Ethionamide and prothiomamide should be avoided due to data suggesting teratogenicity in animals.
- Fluoroquinolones are considered acceptable to use despite limited data.
- Moxifloxacin, para-aminosalicylic acid, cycloserine and amoxicillin/clavulanic acid is an appropriate initial regimen with a consideration of capreomycin in cases of advanced disease (extensive parenchymal damage or life-threatening condition).
- If some drugs were withheld because of the pregnancy, they can be added back postpartum if needed to make a more complete regimen.

The child should receive BCG at birth.

10.9.2 Breastfeeding women

Most anti-TB drugs will be found in the breast milk in concentrations that would equal only a small fraction of the therapeutic dose used in an infant. Effects on infants of such exposure during the full course of DR-TB treatment have not been established. Therefore, when resources and training are available, it is recommended to provide infant formula as an alternative to breastfeeding. If infant formula is used, the infant formula, clean water, fuel for boiling water and the apparatus (stove, heating pans and bottles) must be provided to the mother, as well as training on how to prepare and use the infant formula. If infant formula cannot be provided regularly and used safely, the child should be breastfed and the risks/benefits explained to the mother.

Treatment administered timely and properly is the best way to prevent transmission of tubercle bacilli to the breastfed infant.

If a mother is smear-positive and there is a possibility the mother is failing treatment, the care of the infant should be entrusted to family members until she becomes smear-negative, if feasible. Otherwise, nursing mothers with DR-TB should not be separated from their infants.

10.9.3 Women of child-bearing age

A pregnancy test should be performed before starting anti-TB therapy (to be repeated if indicated).

Women of child-bearing age should be provided contraception in addition to MDR-TB treatment.

Patients should be advised to take their oral contraceptives at times well away from when they may experience vomiting caused by the anti-TB drugs. Patients who vomit within the first two hours of taking the contraceptive tablet should use a barrier method of contraception for the duration of symptoms and for seven days after recovery.

Note: for patients with mono- and poly-drug resistant TB susceptible to rifampicin ([Chapter 11](#)(see page 102)), rifampicin interacts with hormonal contraceptives and decreases their efficacy. Patients may choose between these options, throughout the course of anti-TB treatment: medroxyprogesterone IM or barrier methods (diaphragm, condom, UID) or, as a last resort, oral contraceptive containing a high dose of estrogen (50 micrograms/tablet).

10.9.4 Children

Children with DR-TB generally have primary resistance transmitted from an adult contact with DR-TB.

Culture and DST, if available, should be used to guide therapy. In other cases, the child should be treated empirically, guided by the DST pattern of the index case. However, every effort should be made to obtain a sample from the child for culture and DST.

Given the severity of DR-TB, there are no drugs that are absolutely contraindicated in children.

Children generally tolerate well second-line anti-TB drugs.

The administration of second-line drugs can be problematic due to the lack of commercially available paediatric formulations.

10.9.5 Extrapulmonary drug-resistant TB

Regimen construction and duration for extrapulmonary DR-TB is the same as for pulmonary DR-TB.

If a patient with DR-TB has symptoms suggestive of central nervous system involvement, the regimen should include drugs with good cerebrospinal fluid (CSF) penetration^{31(see page 98),32(see page 98)}:

- Ethionamide or prothionamide and cycloserine have good penetration into the CSF.
- Kanamycin, amikacin, and capreomycin do so only in the presence of meningeal inflammation.
- Para-aminosalicylic acid and ethambutol have little or no penetration.
- Fluoroquinolones have variable CSF penetration, with better penetration seen in the higher generations.

10.9.6 Renal insufficiency

Renal insufficiency may be due an injectable anti-TB drug or other aetiologies including longstanding TB infection.

In patients with renal insufficiency, the creatinine clearance should be calculated. If less < 30 ml/min, anti-TB drugs should be adjusted. The formula to estimate the creatinine clearance, and the dose of anti-TB drugs in renal insufficiency are presented in [Appendix 12\(see page 228\)](#).

10.10 Treatment of extensively drug-resistant TB (XDR-TB)

XDR-TB is much more difficult to treat than other MDR-TB and extremely difficult to treat in HIV-infected patients^{33(see page 98),34(see page 98)}. While reports of HIV-infected patients being promptly diagnosed with XDR-TB and placed on adequate regimen are non-existent to date, a few reports of cohorts of HIV-negative patients have been shown to have cure rates that exceed 50%^{33(see page 98),35(see page 98)}.

There is very limited data on different clinical approaches to XDR-TB. Management of a patient with documented, or almost certain, XDR-TB should be as follows^{7(see page 98),21(see page 98)}:

1 - Consider a longer duration of use for the injectable agent (12 months or possibly the whole treatment). If the patient's strain is resistant to all injectable agents, use one the patient has never used before^{1(see page 0)}.

- 2** - Use a third-generation fluoroquinolone such as moxifloxacin. The potential benefit of moxifloxacin should be weighed against the increased risk of QT prolongation when combined with bedaquiline.
- 3** - Use all Group 4 agents that have not been used extensively in a previous regimen or any that are likely to be effective.
- 4** - Use two or more agents from Group 5. Add bedaquiline. Consider high-dose H if lowlevel resistance is documented or no *katG* mutation is detected.
- 5** - Use any likely effective Group 1 drugs.
- 6** - Consider adjuvant surgery if there is localized disease.
- 7** - Consider compassionate use of new agents ([Appendix 11](#)(see page 227)).

Extension of therapy to 24 months is the suggested minimum length of treatment for XDR-TB.

Box 10.2 - A case of XDR-TB and example regimen

Example:


A patient is receiving Km-Ofx-Eto-Cs-Z and remains smear-positive and culture-positive after 8 months of treatment. In addition the patient is not improving clinically. The DST performed on a sputum collected 2 months ago reveals resistance to H, R, Z, E, S, Km, Cm and Ofx. This patient has XDR-TB.

The regimen should be designed based on the principles described in [Section 10.1](#)(see page 84). Bdq should be considered. A higher generation FQ may have some effect.

The recommended regimen to be considered in this patient would be:

Lfx-Cs-PAS-Bdq-Lzd-plus two Group 5 drugs (Cfz-Amx/Clv).

- Lfx causes less QT prolongation than Mfx.
- Cfz has an additive effect to the QT prolongation when used with Bdq.
- ECG monitoring is required.
- The risk of sudden death versus the benefits of Bdq should be fully explained to the patient.
- Consider also compassionate use of new anti-TB agents under development.

 [\(see page 0\)](#) While the reproducibility and reliability of DST to injectables is good, there is little data on clinical relevance of the test. Options with XDR-TB are very limited and some strains may be affected *in vivo* by an injectable agent even though they are testing resistant *in vitro*.

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Chapter 11: Treatment of mono- and poly-drug resistant tuberculosis (PDR-TB)

- [11.1 Treatment schemes](#)(see page 102)
- [11.2 Treatment algorithms for PDR-TB](#)(see page 104)
- [References Chapter 11](#)(see page 107)

11.1 Treatment schemes

- [11.1.1 Choice of the treatment scheme](#)(see page 102)
- [11.1.2 PDR Scheme A for cases with H or HS resistance](#)(see page 103)
- [11.1.3 PDR Scheme B for cases with HE or HES resistance](#)(see page 103)
- [11.1.4 PDR Scheme C for cases with R or RS or RE or RES resistance](#)(see page 104)

11.1.1 Choice of the treatment scheme

Mono- and poly-drug resistant tuberculosis (PDR-TB) management is based on the PDR treatment schemes presented in Table 11.1.

Table 11.1 - Resistance pattern and recommended treatment schemes

Resistance category	H	R	E	S	Treatment scheme
H-R susceptible	Sus.	Sus.	Sus.	Sus.	New case regimen
	Sus.	Sus.	Sus.	Res.	New case regimen
	Sus.	Sus.	Res.	Sus.	New case regimen
	Sus.	Sus.	Res.	Res.	New case regimen
H-resistance	Res.	Sus.	Sus.	Sus.	PDR Scheme A*
	Res.	Sus.	Sus.	Res.	PDR Scheme A*
	Res.	Sus.	Res.	Sus.	PDR Scheme B
	Res.	Sus.	Res.	Res.	PDR Scheme B
R-resistance	Sus.	Res.	Sus.	Sus.	PDR Scheme C
	Sus.	Res.	Sus.	Res.	PDR Scheme C
	Sus.	Res.	Res.	Sus.	PDR Scheme C
	Sus.	Res.	Res.	Res.	PDR Scheme C

Sus. = susceptible; Res. = resistant.

* Except previously treated patients, for whom PDR Scheme B + ethambutol is preferred.

The treatment schemes of mono/PDR-TB are based on the assumption that a full baseline drug susceptibility testing (DST) is performed before or at the start of treatment with firstline anti-TB drugs.

There is little published evidence to determine the best treatment for mono/PDR-TB. The treatment schemes are therefore based on the principles of TB treatment and expert opinion¹(see page 107),²(see page 107),³(see page 107).

At least 3, ideally 4, likely effective drugs are included in the regimen. DST results at baseline and previous treatment history are used to choose the appropriate scheme.

The use of Xpert MTB/RIF can greatly aid in getting patients on the proper regimens when isoniazid resistance is present and amplification of resistance to rifampicin is a possibility.

Perform second-line DST if patients come from a region of high second-line resistance and if there is a history of second-line anti-TB drug use. Resistance to second-line anti-TB drugs will impact the choice of regimen.

11.1.2 PDR Scheme A for cases with H or HS resistance

For new patients, the treatment regimen is 9 RZE. However, the combination HRZE can be used if more convenient since it can be given as fixed-dose combination.

At Month 2, perform smear, Xpert MTB/RIF, and culture:

Xpert available	Xpert RIF+ : switch to empiric MDR regimen while waiting for full DST results then, adapt treatment accordingly. Xpert RIF- : continue PDR Scheme A.
Xpert not available	Culture+ : switch to empiric MDR regimen with the inclusion of R while waiting for full DST results. <ul style="list-style-type: none"> DST is unchanged (H or HS resistance only): stop the MDR regimen, and resume PDR Scheme A; DST has changed: adapt treatment accordingly. Culture- : continue PDR Scheme A.

Perform smear and culture every other month. If cultures or smears are positive, switch to MDR regimen while waiting for full DST results then, adapt treatment accordingly.

For previously treated patients, it is safer to use Scheme B plus ethambutol, as DST to this drug should not be relied upon if the patient has already received it.

11.1.3 PDR Scheme B for cases with HE or HES resistance

Start patients on 3 Cm (or Km)-Lfx-RZ/7 Lfx-RZ regardless of smear status at the time of diagnosis.

At Month 2, perform smear, Xpert MTB/RIF and culture:

Xpert available	Xpert RIF+ : switch to empiric MDR regimen while waiting for full DST results then, adapt treatment accordingly. Xpert RIF- : continue PDR Scheme B.

Xpert not available	<p>Culture+: switch to empiric MDR regimen with the inclusion of R while waiting for full DST results.</p> <ul style="list-style-type: none"> • DST is unchanged (HE or HES resistance only): stop the MDR regimen, and resume PDR Scheme B; • DST has changed: adapt treatment accordingly. <p>Culture–: continue PDR Scheme B.</p>
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At Month 3, perform smear, Xpert MTB/RIF, and culture. If Xpert shows RIF+ or if the culture is still positive, this regimen is declared “failure”. Switch to MDR treatment.

Even if found susceptible, streptomycin should not be used given the high rates of resistance to this drug in patients with DR-TB and the poor reliability of the DST.

11.1.4 PDR Scheme C for cases with R or RS or RE or RES resistance

Start patient on MDR regimen until confirmation that the strain is susceptible to fluoroquinolones and injectable agents.

When DST results confirm resistance to R, RS, RE or RES and susceptibility to H, fluoroquinolones and an injectable agent, there are two options:

- 1** - Continue the full course of MDR-TB treatment plus isoniazid. This is a reasonable consideration given that DST reliability is not 100%. This is recommended if the suspicion for MDR-TB is high (i.e. a contact of an MDR-TB patient or failure of a first-line regimen).
- 2** - Start PDR Scheme C: 3 Cm (or Km)-Lfx-HZ (+/-E)/12 Lfx-HZ (+/- E). Ethambutol is added if it is likely to be effective.

Even if found susceptible, streptomycin should not be used given the high rates of resistance to this drug in patients with DR-TB and the poor reliability of the DST.

At Month 2, perform smear and culture:

Culture+: start empiric MDR regimen and repeat DST.

- DST is unchanged: resume PDR Scheme C;
- DST has changed: adapt treatment accordingly.

Culture–: complete PDR Scheme C.

At Month 3, perform smear and culture. If the culture is still positive, this regimen is declared “failure.” Switch to MDR treatment.

Note: if the baseline DST is performed by LPA (Hain® test), only DST for R and H are available. In order to avoid possible resistance amplification, the worst scenario should be assumed:

- If only resistance to H is detected, treat with Scheme B, even new patients while waiting for full DST.
- If only resistance to R is detected, treat as MDR-TB as sensitivity of Hain® test for H resistance is low.

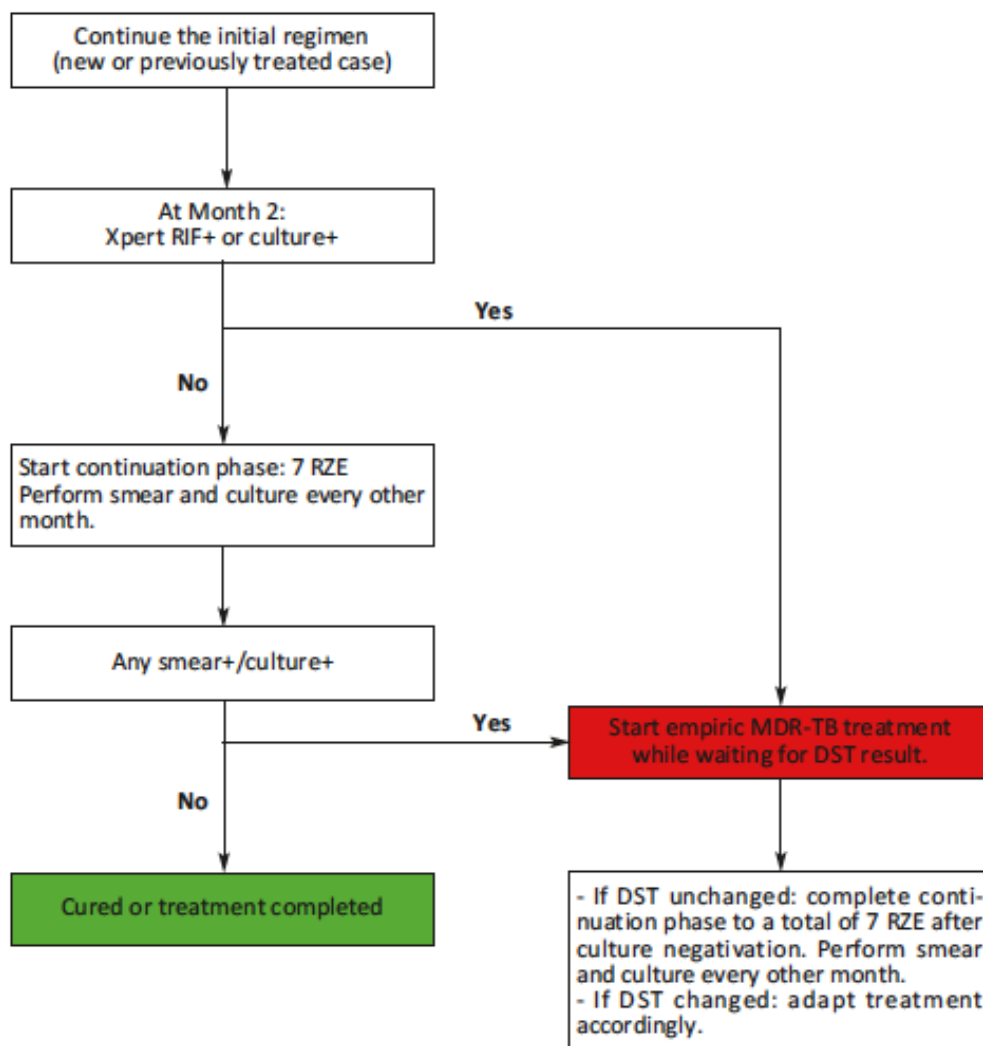
11.2 Treatment algorithms for PDR-TB

- [PDR scheme A\(see page 105\)](#)
- [PDR scheme B\(see page 106\)](#)
- [PDR scheme C\(see page 107\)](#)

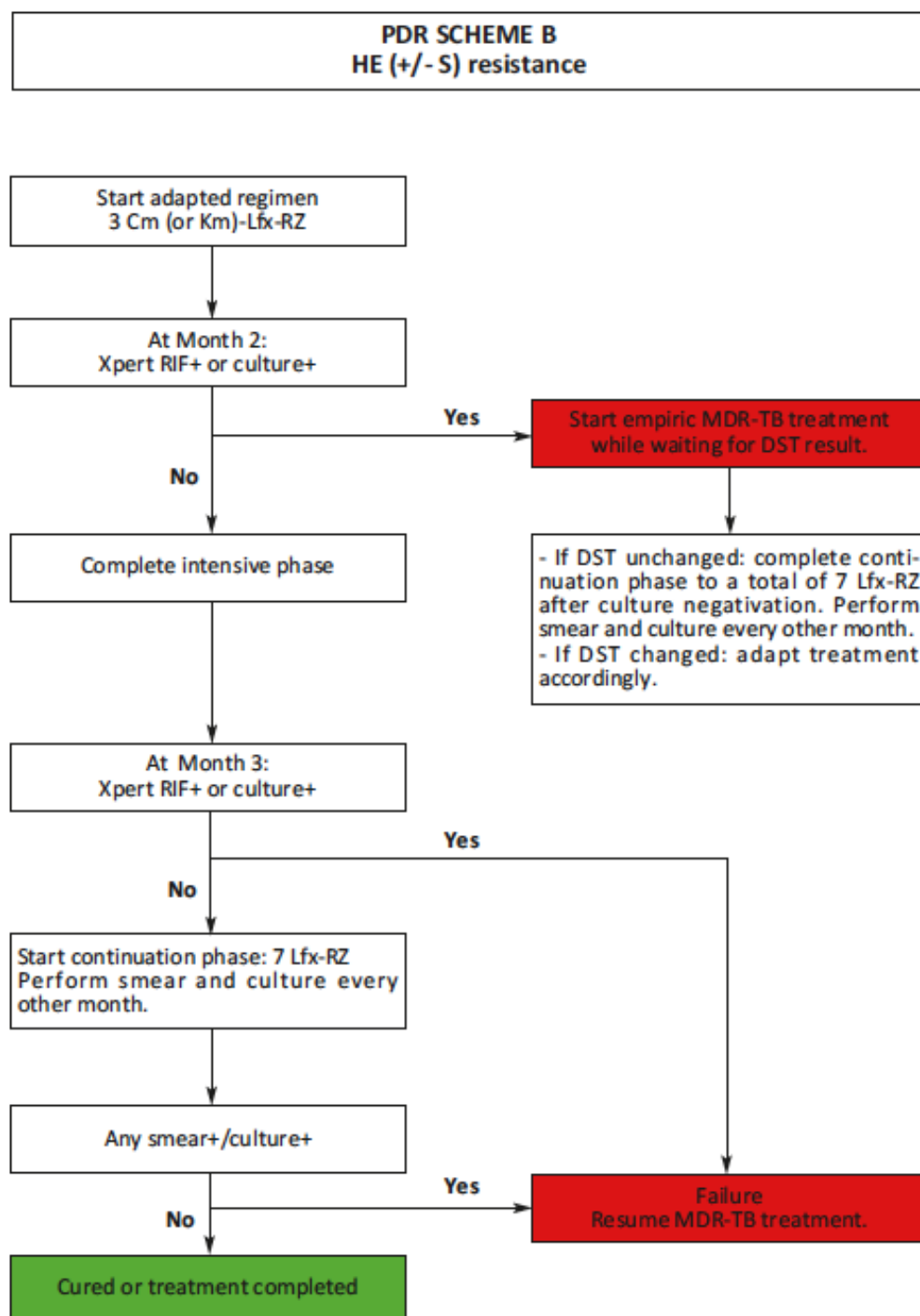
PDR scheme A

PDR SCHEME A H (+/- S) resistance

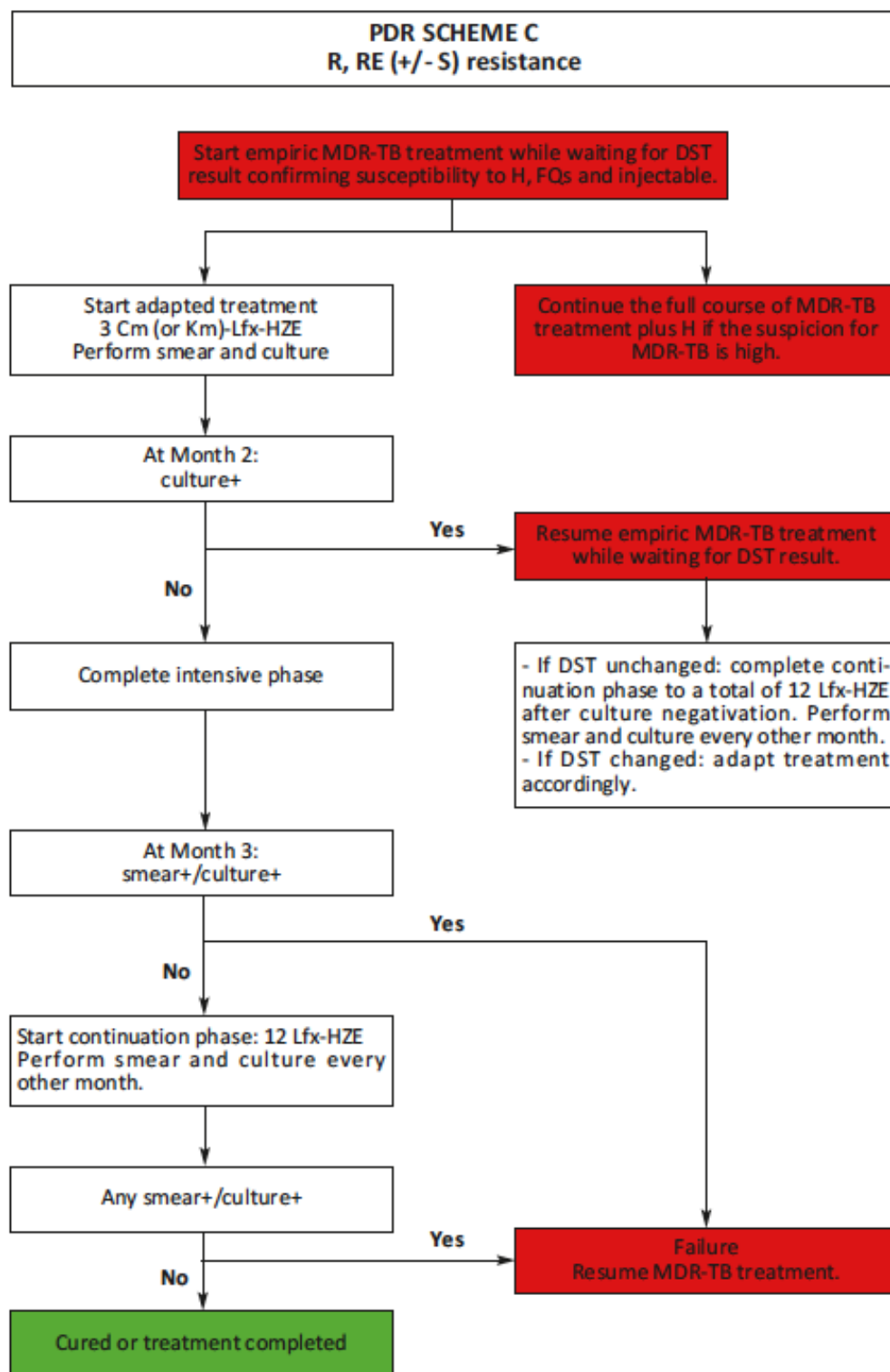
Note: for previously treated patients it is safer to use Scheme B + ethambutol.



PDR scheme B



PDR scheme C



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Chapter 12: Co-management and treatment of HIV in TB disease

- [12.1 HIV testing and counselling for patients known or suspected to have TB](#)(see page 109)
- [12.2 Prophylaxis against opportunistic infections](#)(see page 109)
- [12.3 Anti-TB regimens in HIV patients](#)(see page 109)
- [12.4 Concomitant treatment TB and HIV](#)(see page 110)
- [12.5 Drug interactions](#)(see page 110)
- [12.6 Overlapping toxicities with anti-TB drugs and antiretrovirals](#)(see page 113)
- [12.7 Immune reconstitution inflammatory syndrome \(IRIS\)](#)(see page 113)
- [12.8 HIV-infected children with TB](#)(see page 114)
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- [12.10 HIV-infected patients with DR-TB](#)(see page 114)
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12.1 HIV testing and counselling for patients known or suspected to have TB

HIV testing is recommended for all patients with signs and symptoms of tuberculosis (TB), whether TB is suspected or already confirmed. HIV testing should be offered as part of an “opt out” approach, which means the patients will have to specifically decline the HIV test after receiving the pre-test counselling if they do not want the test performed.

HIV-infected TB patients may have household members who are also living with HIV. Testing for HIV is recommended in immediate family members where horizontal or vertical transmission may have occurred.

12.2 Prophylaxis against opportunistic infections

It is recommended that cotrimoxazole preventive therapy (CPT) be initiated or continued during TB treatment, as it is associated with a reduced risk of death. CPT prevents a number of infections such as pneumocystosis, toxoplasmosis, some diarrhoea and other bacterial infections (respiratory, urinary tract, etc.) and malaria.

If the patient is receiving prophylaxis against other opportunistic infections, the prophylaxis should continue during TB therapy.

12.3 Anti-TB regimens in HIV patients

HIV patients follow the usual first-line or second-line TB regimens. Intermittent regimens should not be used in HIV-positive TB patients.

Case definitions, treatment categories, sputum examination follow-up, and treatment outcomes are equally applicable for HIV-infected TB patients.

12.4 Concomitant treatment TB and HIV

Antiretroviral therapy (ART) dramatically improves survival in HIV-infected patients. In addition, ART reduces TB rates greatly both at individual and population levels.

ART must be initiated in all HIV positive patients with active TB irrespective of the CD4 cell count. Start the anti-TB treatment first, followed by ART as soon as possible and within eight weeks of starting TB treatment^{1(see page 115),2(see page 115),3(see page 115)}.

For the following patients, at high risk of mortality, consider starting ART within the first two weeks:

- Patients with low CD4 count (especially CD4 < 50);
- Young children (especially < 1 year of age);
- Patients with drug-resistant TB (DR-TB).

The first-line ART regimen should contain two nucleoside reverse transcriptase inhibitors (NRTIs) plus one non nucleoside reverse transcriptase inhibitor (NNRTI). The preferred NNRTI in patients starting ART while on TB treatment is efavirenz (EFV), since there is less interaction between EFV and rifamycins compared to other NNRTIs. The preferred NRTI in the first-line ART regimen is tenofovir (TDF), combined with either lamivudine (3TC) or emtricitabine (FTC). If TDF is not available, then zidovudine (AZT) is preferred over stavudine (d4T) due to the long-term adverse effects.

In summary, for adults and adolescents:

- Tenofovir/lamivudine/efavirenz (TDF/3TC/EFV) is the preferred first-line ART regimen because of the once daily dosing and the availability of a fixed-dose combination.
- In the event of severe central nervous system intolerance to EFV:
 - a) Give triple NRTI ART regimen: zidovudine/lamivudine/abacavir (AZT/3TC/ABC);
 - or
 - b) Replace rifampicin (R) with rifabutin (Rfb, 300 mg daily) and start nevirapine (NVP) based ART regimen with lead-in dosing of NVP for 2 weeks;
 - or
 - c) Give NVP based ART regimen tenofovir/lamivudine/nevirapine (TDF/3TC/NVP) but without lead-in dose when used with rifampicin containing first-line TB treatment. In patients with CD4 > 250, close clinical and ALT monitoring at 4, 8 and 12 weeks is recommended.

12.5 Drug interactions

- [12.5.1 Antituberculous and antiretrovirals\(see page 111\)](#)
- [12.5.2 Other interactions\(see page 112\)](#)

12.5.1 Antituberculous and antiretrovirals

Rifamycins and antiretrovirals

Interactions between rifamycins and 2 groups of antiretrovirals (ARVs) —NNRTIs and protease inhibitors (PIs) —must be expected due to liver enzyme induction of the rifamycins.

For possible combinations of ARVs and rifamycins, see Table 12.1.

Patients receiving NVP when TB is diagnosed:

- If rifabutin is available, give 2 months of HZE-Rfb followed by 4 months of H-Rfb.
- If rifabutin is not available, replace NVP with EFV 600 mg. When the TB treatment is completed, NVP may be resumed [\(see page 0\)](#).
- If rifabutin is not available and EFV is contraindicated, see options in previous section.

Patients receiving protease inhibitors (PI):

- When PIs and rifamycins are given to the same patient, PI serum levels can decrease to sub-therapeutic levels, while the serum levels of rifamycins could rise to toxic levels.
- Rifabutin is a less potent enzyme inducer than rifampicin; rifabutin is the preferred drug in patients using PIs.
- If rifabutin is not available, dosages of lopinavir and ritonavir (LPV/r) must be significantly increased in patients taking both LPV/r and rifampicin (see Table 12.1). Liver enzymes should be monitored.

Table 12.1 Possible combinations of ARVs and rifamycins

	Rifampicin	Rifabutin
NNRTIs		
Nevirapine (NVP)	Do not combine unless Rfb is not available and there are no other options.	Rfb: 300 mg/day NVP: usual dose
Efavirenz (EFV)	May be combined. R: usual dose EFV: 600 mg/day	–
NRTIs		
Abacavir (ABC)	May be combined without dose adjustments.	–
Didanosine (ddl)		
Lamivudine (3TC)		
Stavudine (d4T)		
Zidovudine (AZT)		
Tenofovir (TDF)		
PIs		
Indinavir (IDV)	Do not combine	Rfb: 300 mg/day IDV: 1 g every 8 hours

	Rifampicin	Rifabutin
Nelfinavir (NFV)	Do not combine	Rfb: 300 mg/day NFV: usual dose
Lopinavir/ritonavir (LPV/r)	May be combined if Rfb is not available. LPV/r: double dose of LPV/r (800 mg/ 200 mg twice daily) R: usual dosage	Rfb: 150 mg/day ^{4(see page 115)} LPV/r: usual dose
Atazanavir/ritonavir (ATZ/r)	Do not combine	Rfb: 150 mg/3 times a week ^{5(see page 115)} ATZ/r: usual dose

Bedaquiline and antiretrovirals^{6,7}

Data from drug-drug interaction studies with bedaquiline and ARVs to date are extremely limited.

- NNRTI: EFV (enzyme inducer) is estimated to decrease bedaquiline concentrations by 50%. Nevirapine does not significantly affect bedaquiline concentrations.
- NRTI are unlikely to affect bedaquiline concentrations.
- PI: ritonavir is an enzyme inhibitor. The use of ritonavir-boosted lopinavir (LPV/r) with bedaquiline may result in a significant accumulation of bedaquiline and its metabolites. This combination is therefore not recommended.

The following ART regimens can therefore be considered in association with bedaquiline:

- 1) 2 NRTIs + nevirapine: e.g. AZT/3TC or FTC/NVP or TDF-3TC-NVP;
- or
- 2) 3 NRTIs: e.g. AZT/3TC/ABC.

Fluoroquinolones and didanosine


Buffered didanosine contains an aluminium/magnesium-based antacid that, if given with a fluoroquinolone, can result in its decreased absorption. If it is not possible to avoid prescribing these drugs together, didanosine should be given 2 hours apart fluoroquinolone administration. The enteric-coated formulation of didanosine can be given without such precaution.

Other drug-drug interactions can occur between anti-TB drugs and ARVs, further complicating treatment. Most of the drugs used in the treatment of DR-TB have not had drug-drug interaction studies performed with ARVs.

12.5.2 Other interactions

Rifampicin can interact with drugs commonly used in opportunistic infections.

Interaction occurs with fluconazole. Rifampicin may decrease blood levels of fluconazole by as much as 25-50%. The two drugs can be taken 12 hours apart (i.e. rifampicin in the morning, fluconazole in the evening) without dosage adaptation. However, the patient's clinical condition should be carefully monitored, as the dosage of fluconazole may need to be increased if clinical improvement is suboptimal. For the treatment oral candidiasis, miconazole mucoadhesive tablets (gum patches) can be used (no interaction with rifampicin).

 If a patient is changed from EFV back to NVP on completion of TB treatment, no lead-in dosing of NVP is necessary.

12.6 Overlapping toxicities with anti-TB drugs and antiretrovirals

The main potential overlapping toxicities between anti-TB drugs and ARVs are:

- Hepatic reactions;
- Cutaneous reactions;
- Neuropathy;
- Nephrotoxicity.

The use of agents with shared adverse effect profiles should be avoided if possible. Often, however, the benefit of using drugs that have overlapping toxicities outweighs the risk. Thus, if two drugs with overlapping toxicities are essential in a regimen, increased monitoring for potential adverse effects is recommended rather than avoidance of a certain combination.

Important points:

- HIV patients are more likely to develop isoniazid-related peripheral neuropathy. Thus, all patients on isoniazid should receive **pyridoxine** PO (vitamin B₆): 10 mg daily or 25 mg twice a week.
- The use of thioacetazone is contraindicated in HIV patients due to the high frequency of Stevens-Johnson syndrome and corresponding risk of mortality.
- Due to reports of increased renal toxicity during concurrent use of TDF and injectable agents (kanamycin, amikacin, and capreomycin), the use of TDF is not recommended during the intensive (i.e. injectable) phase of DR-TB treatment. If TDF is absolutely necessary, serum creatinine and creatinine clearance, and electrolytes should be monitored frequently.

For potential overlapping toxicities of antiretrovirals and anti-TB drugs, see [Appendix 13](#)(see page 230).

12.7 Immune reconstitution inflammatory syndrome (IRIS)

Immune reconstitution inflammatory syndrome (IRIS) occurs after initiation of ART, in the presence of a previously unrecognized, often subclinical, opportunistic infection. Patients present with paradoxical worsening of their clinical status as the immune system recovers on ART.

Symptoms vary according to the infection, but can include fever, enlarging lymph nodes, worsening pulmonary infiltrates, respiratory distress, neurologic signs, or exacerbation of inflammatory changes at other sites.

IRIS can occur anytime between 10 and 180 days after ART initiation (usually 2-4 weeks) and is more common with CD4 count < 50. Mild to moderate forms of IRIS are relatively common in TB patients who are started on ART (seen in up to one third of patients in some studies); however, severe IRIS is relatively rare.

IRIS occurs with respect to TB in two circumstances:

1 - Paradoxical TB IRIS: A patient is diagnosed with TB, starts TB treatment, followed by ART after a few weeks, and then develops IRIS.

2 - Unmasking TB IRIS: A patient is screened for TB before initiation of ART and no TB is found. The patient then starts ART, followed by onset of TB symptoms and signs.

It is important to note that IRIS with respect to TB is a diagnosis of exclusion. Patients with advanced HIV infection may show clinical deterioration for a number of other reasons (all of which should be ruled out before giving the diagnosis of IRIS):

- Clinical worsening due to new opportunistic infections;
- Other subclinical infections unmasked following immune reconstitution with ART initiation;
- TB treatment failure due to DR-TB.

The management of IRIS depends on the clinical status of the patient and the site and extent of involvement. Nonsteroidal anti-inflammatory drugs are used in mild to moderate IRIS cases and corticosteroids in severe IRIS cases (Chapter 9, [Section 9.3](#)(see page 74)). The use of corticosteroids can be dangerous if IRIS is misdiagnosed and the clinical deterioration is in fact DR-TB or a different opportunistic infection.

Most cases of IRIS can be treated without interruption of ART; in very severe forms of IRIS, ART may need to be suspended.

12.8 HIV-infected children with TB

Most HIV-positive children with TB respond well to the 6-month TB regimen, similar to HIV-uninfected children. If the clinical response is slow, other causes should be considered such as poor adherence to therapy, inadequate drug absorption, DR-TB, and other infections.

The following ARV regimens are preferred in children on TB treatment:

- Child < 3 years old or < 10 kg: AZT *preferred* or D4T/3TC + ABC;
- Child > 3 years and > 10 kg: AZT *preferred* or ABC or D4T/3TC + EFV.

TDF is considered safe in children above 3 years of age.

12.9 HIV-infected pregnant women with TB

TB in HIV-positive pregnant/postpartum women is associated with significant maternal and infant mortality. ART in pregnant women with TB is summarized below:

- TDF is the preferred NRTI and is safe to use throughout pregnancy.
- Safety of EFV is considered acceptable during pregnancy⁸(see page 115).

12.10 HIV-infected patients with DR-TB

DR-TB does not appear to be more prevalent in HIV-infected patients compared to HIV-uninfected patients. However, high mortality rates have been reported in patients coinfecting with HIV and DR-TB.

Prompt initiation of appropriate DR-TB therapy (and subsequent initiation of ART) can help to reduce mortality.

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Chapter 13: Adherence to treatment

- [13.1 Treatment delivery and accompaniment](#)(see page 116)
- [13.2 Factors that influence adherence](#)(see page 116)
- [13.3 Patient support](#)(see page 118)
- [13.4 Additional patient support for patients on DR-TB treatment](#)(see page 118)
- [References Chapter 13](#)(see page 119)

13.1 Treatment delivery and accompaniment

Good adherence is when the patient follows the treatment as prescribed. Failure to take anti-TB drugs consistently, in an inappropriate way or stopping the treatment too soon, can lead to treatment failure or relapse. Additionally, it may contribute to the development of resistance, which may complicate subsequent treatment, thereby, decreasing the chances of successful outcomes¹(see page 119).

In order to achieve good adherence, treatment is sometimes delivered under direct observation therapy (DOT)²(see page 119), but DOT can be limiting for patients and is labour intensive to implement. DOT has not been proven to improve results for drug-susceptible TB when compared to self-administered treatment in controlled trials³(see page 119).

Therefore, when there is no factor that would make it difficult to adhere to therapy, treatment can be self-administrated as long as it is accompanied with adequate patient support ([Section 13.3](#)(see page 118)).

Experience with other chronic diseases and with TB therapy has shown that with strong guidance and support, patients can reach high treatment success with self-administrated treatment.

Patient commitment to follow instructions and prescriptions (drug dosages and schedule, length of treatment, diligence in coming in for follow-up visits, etc.) is needed for the entire length of the treatment. It is crucial that the patient understands the treatment, and that the clinic is organized in such a way that the patient can follow the treatment properly all the way to completion.

There are some situations in which DOT is required:

- Second-line treatment: drugs are poorly tolerated and multidrug-resistant TB (MDR-TB) treatment requires a huge pill burden for a long period of time. Missing doses can result in resistance amplification with fatal consequences for the patient. For these reasons, strict DOT is recommended during the entire duration of the treatment.
- First-line treatment:
 - Patients in whom adherence is an issue due to mental health problems or serious socioeconomic challenges (e.g. homelessness) and all patients incapable of taking drugs on their own;
 - Prisoners: risk of drugs being sold, stolen or not taken.

13.2 Factors that influence adherence

See reference [2](#)(see page 119)

- [13.2.1 Patient-related factors](#)(see page 117)
- [13.2.2 Treatment-related factors](#)(see page 117)

- **13.2.3 Factors related to the therapeutic environment**(see page 117)

There are several factors that can influence adherence, being barriers related to the patient, the treatment or the therapeutic environment. While it is not always possible to control all of these factors — particularly those related to the patient— it is possible to at least control the treatment and therapeutic environment-related factors.

13.2.1 Patient-related factors

- Socioeconomic factors such as having a job, a home, family or other support, being stigmatized or marginalized;
- Psychological factors such as feelings of discouragement;
- Understanding and perception of the disease and treatment: a patient might continue or abandon treatment because s/he sees, or does not see, improvement. S/he might also have trouble taking an active part in treatment if s/he attributes the illness to supernatural causes, etc.

Personal difficulties should be discussed at patient visits. Solutions will depend on the context and the patient's problem, and need to be found on a case-by-case basis.

13.2.2 Treatment-related factors

- Simplicity of treatment improves adherence. The use of fixed-dose combinations (FDCs) simplifies the treatment by reducing the number of tablets. In addition, it also prevents the patient from removing one or more medications from the treatment.
- Adverse effects are often the reason why patients interrupt their treatment and must be quickly detected and adequately managed.

For drug-resistant TB (DR-TB), the number of tablets to be taken every day, the lack of FDCs, and the frequency and severity of adverse reactions make daily accompaniment necessary (see [Section 13.3](#)(see page 118)).

13.2.3 Factors related to the therapeutic environment

- Patients' welcome is essential. Waiting times at clinics should be reasonable. For hospitalized patients, accommodations (comfort, food, heating, etc.) should be adequate.
- The proximity of drug distribution centres limits the number of patients who abandon due to transportation problems.
- The relationship between the health care worker and the patient influences the adherence. If a patient trusts or has confidence in his/her health care worker, s/he is more likely to follow instructions and advice and to collaborate with the health care worker. Patients may also be more likely to bring questions and concerns to the health care worker's attention.
- Hospitalization should be limited. Most cases can be treated as outpatients. If hospitalisation is required, the duration of stay should be as short as possible. Patients should be discharged as soon as their clinical condition allows.
- Free care (visits, laboratory tests and treatment, including those relating to adverse effects) limits the number of patients who abandon for financial reasons.
- The co-management of HIV infection and TB requires coordination between the TB and HIV/AIDS programmes at all levels. Systems that set up a "one-stop service", where patients receive both TB and HIV care, reduces the number of visits and decreases waiting times resulting in higher patient satisfaction and better results.

- Coordination for other diseases, like diabetes and hypertension, can also take place in the same clinic to decrease the burden on the patient.
- Drug supply management must be rigorous. It is essential to avoid shortages, which can lead to treatment interruption and negatively impact adherence (patients waste time in pointless travel, lose confidence in the clinic, etc.).
- To anticipate possible problems, give the patient a few extra days' worth of treatment, in case s/he cannot come get his/her drugs on the scheduled date.

13.3 Patient support

See reference [5](#)(see page 119)

Patient support is the shared responsibility of the entire health care team (clinicians, nurses, treatment supporters, social workers, etc.). It is a continuous process because adherence to treatment varies over time, and any patient can go through phases of treatment acceptance and rejection. In large-scale programmes, the health care team sometimes includes a team of counsellors to provide information and support.

Patient education

Patient education consists of:

- Helping the patient to understand his/her disease and treatment;
- Enabling the patient to acquire and maintain skills that allow him/her to optimally manage his/her disease in daily life;
- Answering the patient's questions throughout the entire treatment.

For more information, see [Appendix 14](#)(see page 232).

Emotional support

Listen to the patient, give encouragement, and gain his/her trust, so that s/he does not have to hide the fact that s/he has forgotten or made a mistake in his/her treatment. These things happen fairly often, and it is important to know about them in order to help find solutions.

Social support

Implement social support measures for patients with limited resources. Depending on the specific needs of patients:

- Social workers can help to obtain disability allowances, housing assistance, shelter for the homeless, etc.
- The programme can provide meals or food; vouchers or money for transportation, or can reimburse the costs of transportation, fuel, etc.

13.4 Additional patient support for patients on DR-TB treatment

See reference [1](#)(see page 119)

DOT where the patient must take public transport daily or walk long distances to go to the clinic (referred to as clinic-based DOT) can actually have a negative effect. Furthermore, there can be infection control issues for the patient and staff with clinic-based DOT. Thus, home-based DOT (referred to as daily accompaniment) is preferred over clinic-based DOT when possible. Home-based DOT has been shown to be equally effective as clinic-based DOT⁴(see page 119). DOT is usually provided by trained, supervised, and compensated treatment supporters.

The profile and the roles and responsibilities of treatment supporters for DR-TB patients are presented in [Appendix 15](#)(see page 234).

Due to the duration of treatment, socio-economic support to patients is essential.

References Chapter 13

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Chapter 14: Tuberculosis infection control

- 14.1 Introduction(see page 120)
- 14.2 Implementation of TB IC strategies(see page 120)
- 14.3 Administrative controls(see page 122)
- 14.4 Environmental controls(see page 123)
- 14.5 Personal protective measures(see page 125)
- 14.6 Hospital hygiene(see page 126)
- 14.7 Patients' homes(see page 126)
- References Chapter 14(see page 127)

14.1 Introduction

The largest source of *M. tuberculosis* transmission is the contagious patients with respiratory tuberculosis not yet diagnosed and put on treatment. Therefore, tuberculosis infection control (TB IC) relies, above all, on:

– Early diagnosis (including in clinics and any non-tuberculosis medical wards, whereby active case finding through cough surveillance of all admissions should avoid days or weeks of transmission from unsuspected TB cases);

AND

– Prompt implementation of effective treatment. With effective treatment, contagiousness decreases even after a few days and may be considered nil after 2 to 3 weeks of treatment^{1(see page 127),2(see page 127),3(see page 127),4(see page 127)}. It is essential the treatment is “effective,” as multidrug-resistant TB (MDR-TB) patients that are placed on first-line anti-TB drugs are likely to remain contagious.

However, in health care facilities where TB patients or persons suspected of having TB congregate, additional measures are needed to reduce the risk of transmission between patients, to health care staff and to vulnerable (particularly immunocompromised) patients/visitors^{5(see page 127)}.

TB infection control (IC)^{1(see page 0)} consists in different strategies for preventing transmission of TB in health care facilities.

^{1(see page 0)} This chapter reviews the basic TB IC strategies. More in depth information can be found from the Tuberculosis Coalition for Technical Assistance which has published a framework and developed a website (<http://www.tbcta.org/Library>) that provides a comprehensive set of examples.

14.2 Implementation of TB IC strategies

- 14.2.1 Infection control practitioner(see page 121)
- 14.2.2 Infection control committee(see page 121)
- 14.2.3 Infection control plan(see page 121)

There is a trio of infection control levels, which include (1) administrative, (2) environmental and (3) personal protective controls⁵(see page 127). The implementation of these measures requires a dedicated staff and an IC plan.

14.2.1 Infection control practitioner

A person should be clearly identified and designated as responsible for TB IC. This person should have the support and authority to conduct, apply and evaluate TB IC policies. This person in some settings is also known as IC officer.

14.2.2 Infection control committee

The IC practitioner would evaluate the need to create an infection control committee (ICC). The ICC might include doctors, nurses, laboratory technicians, logisticians and administration staff (including representation from the maintenance and housekeeping services). According to the context and degree of risk, experts in IC may be needed.

14.2.3 Infection control plan

All facilities should have a detailed written IC plan that is at least annually updated and distributed to healthcare staff.

A simplified version of the plan must be accessible to all healthcare workers including staff not directly involved in TB patients' management, such as cleaners, kitchen staff, etc.

The first step in developing an IC plan is assessing the health care facility's risk for TB transmission⁶(see page 127). This should be performed by the IC practitioner. The plan must be specific to each facility.

An example of risk assessment tool is given in [Appendix 16](#)(see page 235).

The IC plan should include the different types of measures—administrative, environmental and personal. Information on specific precautions and procedures for high-risk areas should be detailed.

It is recommended to draw a floor plan of the facility with the different areas, including the patient flow and identifying areas of high risk.

Listed below from highest to lowest level of risk:

Highest risk

- Smear-positive inpatient unit
- Diagnosis department
- Culture/drug susceptibility test (DST) and sputum smear preparation area (laboratory)
- Sputum collection area
- Radiology department
- Waiting area

Limited risk

- Children inpatient ward
- Extrapulmonary TB (EPTB) and smear-negative unit
- Sputum reception and smear reading area (laboratory)
- Waste management area

Lowest risk (non-TB zone)

- Kitchen area
- Administration

14.3 Administrative controls

- [14.3.1 Patients triage](#)(see page 122)
- [14.3.2 Patient, visitors and attendants' flow](#)(see page 122)
- [14.3.3 Segregation of hospitalized patients](#)(see page 122)
- [14.3.4 TB IC training](#)(see page 123)

The administrative controls aim at preventing the exposure to infectious droplet nuclei.

14.3.1 Patients triage

Upon entry into the health facility, a member of the medical staff should identify patients with a cough as soon as possible. Patients with a cough over two weeks should be sent to a separate waiting room if possible.

All patients with cough (including patients with less than two weeks of cough) should receive tissues or face masks, and they should be requested to cover their mouth and nose when they cough.

14.3.2 Patient, visitors and attendants' flow

Inside the TB department, circulation of patients and attendants is controlled:

- Encourage patients/attendants to spend as much time as possible outdoors if weather permits or in areas that are open on three or four sides.
- Have visible signage on entry doors to TB wards that forbid visitors to enter.
- Limit visitation duration, particularly for contagious patients.
- Encourage visits outside the building, especially for contagious patients.
- Have visiting areas well identified with signage.
- Before any visit, the nurse should provide information on transmission risk, including the usage of respirators if carers need to go in high risk areas, such as smear-positive, drug-resistant TB (DR-TB), re-treatment smear-positive inpatient units and areas or clinics where diagnosis of TB is being undertaken.
- Avoid that known or suspect TB patients go through areas where they may infect other patients, and vice versa, that patients without TB go through areas where they are unnecessarily exposed to the bacillus.

14.3.3 Segregation of hospitalized patients

Patients should preferably be treated in ambulatory care. Hospitalisation should be limited and reserved for clinically unwell patients.

TB wards must be separated from the others wards in the health structure compound.

Ideally, within the TB department, patients should be placed in single rooms. If this is not possible, cohort isolation must be implemented and different sections should be labelled according to the degree of contagiousness (smear/culture status) and risk of resistance.

The following is one scheme of separation. It does involve the use of some single isolation rooms (all TB inpatient facilities should have some isolation rooms. If none exist, a very high priority is to add some).

- Smear-positive patients with proven or suspected DR-TB, including chronic cases and retreatment cases that are likely to have MDR-TB. MDR-TB cases should have single isolation rooms (place in 2 to 4

person rooms with other MDR-TB patients if there are no single rooms and try to match DST patterns). It is particularly important not to mix MDRTB patients with extensively drug-resistant TB (XDR-TB) patients.

- Smear-positive patients with fully susceptible TB.
- Smear-negative patients (or patients who have converted), with proven or suspected DRTB (once patients are on effective treatment, they rapidly become non-contagious).
- Less or non-contagious TB: patients with smear-negative pulmonary TB (PTB), EPTB, patients having converted their sputum/culture and most children.
- Patients who are undergoing diagnosis as suspected cases: when possible do not hospitalize patients for diagnosis. If hospitalization is necessary, these patients need isolation rooms. Never put a patient who is not receiving TB medications in a TB ward.

If women and men are to be separated, this scheme requires at least 8 different wards and enough single rooms for suspect cases and MDR-TB patients.

14.3.4 TB IC training

All healthcare personnel should receive initial training on TB transmission, information on high-risk areas in the facility and on protective measures. Continuing education should be offered annually.

The training should also include how staff can teach patients, visitors and attendants about the risk of TB transmission and how to avoid it (cough etiquette, use of masks and respirators).

14.4 Environmental controls

- [14.4.1 Ventilation](#)(see page 123)
- [14.4.2 Architectural considerations](#)(see page 124)
- [14.4.3 Ultra-violet germicidal irradiation](#)(see page 124)
- [14.4.4 Areas requiring specific measures](#)(see page 124)

The environmental measures aim at reducing the concentration of infectious droplet nuclei in the air.

14.4.1 Ventilation

Ventilation (replacement of inside air with outside air) is the most effective means for reducing the concentration of *M. tuberculosis* in the air, and as a result, the risk of transmission.

The WHO recommends that in areas where TB transmission might occur, a minimum ventilation rate of 12 air changes per hour (ACH)⁶(see page 127) should be achieved. See [Appendix 17](#)(see page 235) for recommendations on ACH measurement.

Effective ventilation can be obtained by natural (assisted or not) or mechanical means.

Natural ventilation

Natural ventilation, especially cross-ventilation (windows/doors in opposite sides of the room), has the best cost-effective ratio. It should be done with the windows and outside doors open (as much as weather conditions permit). Inside doors should be closed so that the flow of air is directed outside and not toward the corridors.

Create shady spaces so that patients, attendants and visitors can stay outside during the day. Wind-driven roof turbines (whirly birds) or chimneys can also be used to improve natural ventilation, in that they can keep the principle of directing room air towards the exterior. In addition, fans can be used when the natural ventilation flow rate is too low (assisted natural ventilation).

Mechanical ventilation

When natural ventilation cannot reach adequate rates, centralised mechanical ventilation should be considered in some settings, such as within cold climates. Centralised mechanical ventilation relies on the use of mechanical equipment to maintain an air pressure difference between two areas in order to draw air into a room and vent it to the outside. It requires continuous and meticulous maintenance, which renders it costly and difficult to implement and operate.

Advantages and disadvantages of each ventilation technique are presented in [Appendix 18](#) (see page 236).

14.4.2 Architectural considerations

Airborne infection control should be always considered during the planning/construction stages of new health facilities and those being modified. It is important to achieve the following:

- Building layout and design with maximised natural ventilation (assisted or not) and sunlight. Waiting areas should be open on three sides. Design of TB wards should avoid internal hallways with doors from the rooms and wards opening into them. Instead, doors should open to outside hallways that are open to air (this may not be feasible in cold climates).
- Specific areas (open air, sputum collection booth, etc.) should be reserved for procedures with a high risk of *M. tuberculosis* transmission (e.g. sputum collection, sputum induction, etc.).
- Allow patient flow that reduces exposure of patients at risk to patients that are infectious (e.g. separate waiting rooms for different cohorts, one patient per room in a hospital). If designing a new TB ward, incorporate plenty of single rooms or at least small rooms with 2 to 4 beds for easier separation of the different cohorts of patients. General hospitals should also have isolation rooms available for TB suspects and contagious patients.

Rehabilitation of existing structures in order to maximise natural ventilation could be a viable economical option instead of building expensive systems, like centralised mechanical ventilation.

14.4.3 Ultra-violet germicidal irradiation

Ultra-violet germicidal irradiation (UVGI) lamps [1](#) (see page 0) may be used when adequate ventilation cannot be achieved in high-risk areas. When properly installed, designed, maintained and operated, an UVGI system, in addition to 6-12 ACH ventilation, could be the equivalent of 10-25 ACH ⁷ (see page 127).

For technical information on upper room UVGI, see [Appendix 19](#) (see page 237).

- Main requirements and constraints in UV lamps usage include:
 - Expertise in installation and testing;
 - Rigorous monitoring and maintenance;
 - Electricity, relative humidity less than 70%, good air mixing.
- Potential hazards include: Transient eye and skin injuries from overexposure, mercury poisoning (broken or mishandled lamp).

14.4.4 Areas requiring specific measures

Sputum collection areas

These areas must be settled, wherever possible, outside in open air where bacilli will naturally be dispersed by wind rather than in a closed room where the concentration of bacilli will be high.

In cold regions, sputum collection should be performed in very well ventilated indoor rooms (at least 20 ACH) or in well ventilated rooms (at least 12 ACH) equipped with a UVGI system.

Another option for sputum collection areas in cold climate regions is to assign a specific room of small size (1 m²) with one single glass door opening outside. Keep the door largely open for 5 minutes between each patient. The small volume of air in this room facilitates rapid ventilation.


Laboratory

All laboratories should undergo a risk assessment, and IC measures should be adapted accordingly. In any case, limit the access to all TB laboratories.

The use of ventilated workstation ([Appendix 7](#)(see page 163)) is strongly recommended for smear preparation (microscopy and test Xpert). In laboratories where culture are carried out, biological safety cabinets type II must be used.

Laboratories must have easy to clean working surfaces (avoid wood) to allow proper disinfection. They should also have large windows to let in sunlight and allow natural ventilation if the laboratory has no mechanical ventilation.

Water-filters should be used to avoid contamination by saprophyte mycobacteria that are sometimes present in the water.

 [\(see page 0\)](#) UVGI inactivate bacilli. Natural light dries the droplet but does not inactivate bacilli.

14.5 Personal protective measures

- [14.5.1 Respirators \(or high-filtration masks or anti-inhalation masks\)](#)(see page 125)
- [14.5.2 Face or surgical masks](#)(see page 125)

Personal protective measures aim at minimising the risk of bacillus transmission by providing barriers to inhaling or exhaling infectious droplet nuclei.

14.5.1 Respirators (or high-filtration masks or anti-inhalation masks)

A respirator is personal protective equipment that prevents inhalation of infectious droplet nuclei by the person who wears it.

Exposed staff

Staff must wear a respirator, regardless if they are the caregiver or not. Respirators should be worn:

- When in contact with contagious patients (suspect or confirmed TB case);
- When collecting sputum samples;
- When collecting and disposing of sputum containers;
- In areas where droplet nuclei could be present (i.e. a room that has been occupied by a TB case, prior to the time required for air cleaning).

Using respirators needs proper training, fit testing and continuous supervision. This also applies to home-based DOT supervisors.

Visitors/attendants

Visitors and attendants must wear a respirator when entering a contagious TB patient's room.

For more information on respirators, see [Appendix 20](#)(see page 240).

14.5.2 Face or surgical masks

Face masks are medical devices that prevent patients from spreading infectious droplets when talking, coughing or sneezing. They should be worn by contagious patients (suspect or confirmed) when they leave their rooms to go to another department or any other enclosed area. They should not be worn when the patient is alone in his/her room and outdoors.

For more information on surgical masks, see [Appendix 21](#)(see page 242).

Using a mask in public areas could be stigmatizing. Patients can use a cloth scarf to achieve the same purpose.

14.6 Hospital hygiene

- [14.6.1 Hygiene and disinfection](#)(see page 126)
- [14.6.2 Waste management](#)(see page 126)

14.6.1 Hygiene and disinfection

Sputum containers

Patients with pulmonary TB produce sputum that may contain tubercle bacilli.

– In the wards, patients' sputum containers should be large (about 200-ml), non-sterile, and sealable. They are to be replaced daily and cannot be re-used.

– In the laboratories, containers for sample collection are smaller (25-35 ml), with hermetic screw cap, non-sterile and for single use.

Environmental cleaning

Sterilization or the use of disinfecting chemicals in a TB patient's room is not necessary. Ordinary cleaning of rooms and objects (linens, dishes, etc.) used by TB patients is sufficient. After the patient is discharged, air the empty room well according to the calculated ACH.

Reusable medical items

Standard operating procedures for reprocessing items should be followed. There are no specific measures for TB services.

Standard precautions

Standard precautions (hand hygiene, gowns, etc.) apply in TB wards, as they do in any other hospital department.

14.6.2 Waste management

Standard operating procedures for handling and the disposal of healthcare waste (including soft, sharp, etc.) should be followed. There are no specific measures for TB services.

Note: used sputum containers should be collected in a leak proof trash bag and incinerated without filling the containers with chlorine solution before incineration (this can produce toxic gases).

14.7 Patients' homes

In settings where DR-TB (and HIV) is highly prevalent, systematic TB IC evaluations on patients' homes are recommended.

TB IC at patients' homes follows the same principles and measures as in healthcare facilities.

Administrative, environmental and personal measures should be followed at least until patient's smear is negative, ideally until culture conversion.

Administrative measures

– Assess the risk of TB transmission: gather information on the number of people that live in the house, number of rooms, etc.

– Screen contacts for TB.

– Children under 5 should spend as little time as possible in the same spaces as culture-positive patient (although the risk to the child is greatly reduced once a patient starts an effective regimen). The mother

should use a surgical mask while taking care of the child until she becomes smear-negative.

- Offer education on TB transmission, airborne precautions (cough etiquette, masks), clinical symptoms and waste management of sputum containers or tissues (do not empty the container; throw it in the latrines or enclose it hermetically in plastic bags and discard in the normal waste).

Environmental measures

- Ideally, the patient should sleep in a separated room, with door closed off to the rest of the house.
- Common spaces should be well ventilated (often done by keeping windows open at all times).
- The patient should be encouraged to spend time outside in a shaded area if weather permits.

Personal protective measures

- If smear-positive or not responding to the regimen, the patient should wear surgical masks when in contact with persons in areas poorly ventilated. Once smear-negative, the patient can be considered non-infectious and no longer needs to wear masks.
- Any person attending to the patient in enclosed spaces should wear a respirator. A fit test should be performed, and the person should be educated on the proper use of respirators. Once the patient is smear-negative, respirators are no longer necessary.

References Chapter 14

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Chapter 15: Follow-up of staff exposed to tuberculosis

- [15.1 Initial assessment](#)(see page 128)
- [15.2 BCG vaccination](#)(see page 128)
- [15.3 Follow-up](#)(see page 129)
- [References Chapter 15](#)(see page 129)

Note: this chapter only provides general recommendations, which should be adapted to the regulations and context of each country.

15.1 Initial assessment

New staff entering a TB facility and who will be in contact with potentially contagious patients and/or clinical laboratory specimens must undergo baseline assessment:

- Determine the BCG immunization status (BCG scar check);
- Perform a baseline chest X-ray;
- Perform a baseline tuberculin skin test (TST);
- HIV testing is strongly recommended.

In addition, the following information should be provided:

- *M. tuberculosis* occupational transmission;
- TB infection control measures and good practices for preventing transmission;
- Higher risk of active TB in immunocompromised (mainly HIV-infected, diabetics, pregnant women);
- Suggestive symptoms of TB.

Immunocompromised health staff should not work in settings where the risk of exposure to the bacillus is high ([Section 14.2.3](#)(see page 121)).

Pregnant women should not work in TB facilities, or at least should not be exposed to potentially contagious patients.

15.2 BCG vaccination

Recommendations vary between countries, with some countries requiring health staff to be BCG vaccinated if never vaccinated and TST negative. There is limited evidence regarding the benefits of BCG vaccination in adults¹(see page 129) who have previously not had BCG vaccination.

Despite the limited evidence of efficacy, it is generally recommended to vaccinate healthcare personnel with negative TST, particularly in situations with a significant exposure to MDR-TB¹(see page 129) (facilities treating MDR-TB, prisons or within regions with high prevalence of MDR-TB).

BCG vaccine should only be administered if:

- The person is HIV negative;
- The person is not pregnant¹(see page 0);

- The person has previously never had BCG vaccination;
- The person has previously never had active TB;
- The person is TST negative.

Inform the person vaccinated that BCG does not confer complete protection and that tuberculosis may still occur if other protective measures are not used.

Testing for TST response soon after BCG vaccination is not recommended. More information on BCG vaccine is provided in [Appendix 22](#)(see page 243).



Pregnancy is not an absolute contra-indication but generally live vaccines should not be administered. Women staff's vaccination status should be determined before they become pregnant.

15.3 Follow-up

Follow-up of the staff routinely exposed includes:

- Clinical examination once per year;
- Assessment of TB and HIV for any symptomatic staff;
- Chest X-rays if clinical signs are observed (not routinely).

Staff presenting with a recent risk of an immunocompromised state (HIV infection, immuno-suppressive treatment, etc.) and newly pregnant women should not remain exposed. According to the context and the level of risk, they should be transferred to another department or to the least TB-exposed position ([Section 14.2.3](#)(see page 121)).

Long-term (at least 36 months) isoniazid preventive therapy is recommended for all HIV-infected health staff known to be TST-positive, including those who convert from TST-negative to TST-positive (see [Chapter 16](#)(see page 130) for more information).

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Chapter 16: Chemoprophylaxis

- [16.1 Isoniazid preventive therapy \(IPT\)](#)(see page 130)
- [16.2 Benefit and limitations of IPT](#)(see page 130)
- [16.3 IPT in children](#)(see page 130)
- [16.4 IPT in HIV-infected individuals](#)(see page 131)
- [16.5 Chemoprophylaxis and drug-resistant tuberculosis](#)(see page 133)
- [References Chapter 16](#)(see page 133)

16.1 Isoniazid preventive therapy (IPT)

IPT (or isoniazid prophylaxis) is most often the treatment for primary infection in order to sterilize lesions and prevent the development of active tuberculosis (TB). It is more a treatment than a prophylaxis.

It consists of the daily administration of isoniazid (H) for 6 months, at a dose of [1](#)(see page 133):

Isoniazid PO:

Newborns and children less than 30 kg: 10 mg/kg once daily (7 to 15 mg/kg/day)

Children over 30 kg and adults: 5 mg/kg once daily (4 to 6 mg/kg/day)

Maximum dose: 300 mg/day

16.2 Benefit and limitations of IPT

Prophylaxis of drug-susceptible TB is effective when properly done. It may reduce the risk of developing TB by up to 90% in a patient with primary infection.

However:

- It is often difficult to rule out active TB with certainty, but it is essential to do so; administering prophylaxis to a patient with active TB would be the equivalent of giving the patient isoniazid in monotherapy.
- Most studies reveal poor adherence (28-60%)²(see page 133),³(see page 133), since asymptomatic patients do not see the point of what they consider a long, restrictive treatment.
- The effectiveness of prophylaxis depends on the strain sensitivity to isoniazid.
- The risk of isoniazid-induced hepatitis is not insignificant. It is low in young subjects and progressively increases with age, attaining over 2% in subjects over 50 years⁴(see page 133).
- Isoniazid is contraindicated in patients with severe or chronic active hepatitis. It should be administered with caution to patients who regularly consume alcohol.

16.3 IPT in children

- [16.3.1 Newborn infants of mothers with active tuberculosis](#)(see page 131)
- [16.3.2 Children under five years of age in contact with a TB patient](#)(see page 131)

16.3.1 Newborn infants of mothers with active tuberculosis

IPT is administered to the child for 6 months. BCG vaccination is done just after IPT (BCG vaccine should not be given during isoniazid administration).

- If a child immediately or subsequently presents signs of TB, which is generally only evident after approximately 2 to 8 weeks, he should undergo complete anti-TB treatment after exclusion of other possible medical causes. This case scenario is unlikely if IPT is correctly administered, but it is not impossible in cases of primary resistance to isoniazid.
- If a tuberculin skin test (TST) is possible, the approach is:
 - To administer isoniazid for 3 months, then do a TST;
 - If the TST is positive, continue isoniazid for 3 more months;
 - If the TST is negative, stop isoniazid and administer the BCG vaccine.

Notes:

- The child should not be separated from her/his mother unless she is severely ill. Breastfeeding should continue.
- It is possible that isoniazid is not effective if primary resistance against this drug exists (varies according to the area) or if there is a problem of secondary resistance in the mother. The child must therefore be closely monitored in all cases.

16.3.2 Children under five years of age in contact with a TB patient

See Diagnosis of tuberculosis in children, [Chapter 5](#)(see page 52).

If the child presents no cough, no fever and no weight loss (failure to thrive), then administer IPT for 6 months, regardless of the vaccination status of the child. If it is not possible to administer IPT, vaccinate if not vaccinated and monitor the child.

16.4 IPT in HIV-infected individuals

- [16.4.1 HIV-infected adults and adolescents](#)(see page 131)
- [16.4.2 HIV-exposed and HIV-infected children](#)(see page 132)
- [16.4.3 Health care workers with HIV](#)(see page 132)

IPT can only be implemented if intensive case-finding for HIV-infected TB patients is already in place ([Chapter 6](#)(see page 59)).

16.4.1 HIV-infected adults and adolescents

IPT is safe and effective in HIV-infected patients; it reduces the risk of active TB by 33-64%¹(see page 133). It should be implemented in all settings having a high prevalence of TB and HIV.

Current evidence suggests that only HIV-infected adults having a positive TST benefit from IPT⁵(see page 133). HIV-infected adults and adolescents without any of the four TB symptoms (cough, fever, weight loss, night sweats), and having a positive TST, should be offered long-term IPT (at least 36 months).

TST is not a prerequisite for IPT. In settings where TST is not feasible, HIV-infected adults and adolescents without any TB symptoms should be offered 6 months of IPT, which should be repeated every 3 years.

In eligible adults and adolescents, IPT should be initiated after 3 months of anti retroviral therapy (ART). Patients should have attended at least 2 clinic appointments, and they should have a good understanding of why IPT is being prescribed.

IPT has been shown to offer additional protection against TB in those on ART. However, initiation of ART should take priority over initiation of IPT.

In the subgroup of patients eligible and/or in the process of being started on ART, there is a high prevalence of undiagnosed TB, including a considerable proportion with no TB symptoms^{6(see page 133)}. In this subgroup, it is reasonable to wait 3 months^{1(see page 0)} before considering initiation of IPT. During this time, TB symptom screening should be repeated at each clinic visit.

16.4.2 HIV-exposed and HIV-infected children

^{2(see page 0)}

IPT should be given to children in 3 situations as long as symptom-based TB screening is negative (no current cough, no fever and no poor weight gain) or evaluation has not found active TB:

- Routinely: all HIV-exposed and HIV-infected children between the ages of 12 months and 15 years, regardless of contact history, should be given 6 months of IPT every 3 years;
- After contact^{3(see page 0)} with any case of TB (smear positive, smear negative and extrapulmonary): all HIV-exposed and HIV-infected children < 15 years of age should be given 6 months of IPT;
- Post-TB treatment: all HIV-exposed and HIV-infected children < 15 years of age should be given 6 months of IPT immediately after the successful completion of TB treatment^{1(see page 133)}.

TST does not have a role in determining which child will benefit from IPT. TST can, however, be used to evaluate a child for active TB.

16.4.3 Health care workers with HIV

Long-term IPT (at least 36 months) is recommended for HIV-infected health workers known to be TST-positive, including those who convert from TST-negative to TST-positive.

Notes on IPT in HIV-infected individuals:


- All adults, adolescents, and children on IPT should be routinely given vitamin B6 in order to decrease the risk of peripheral neuropathy (**pyridoxine** PO: 10 mg daily).
- Before initiating IPT, it is important to assess for risk factors (viral hepatitis, chronic alcohol consumption, use of potentially hepatotoxic medication, etc.) and signs of liver disease. Baseline liver function tests (LFTs) should be considered in these cases and the benefit of IPT weighed against the potential risk that isoniazid might aggravate the liver disease. Routine monitoring of liver transaminases (ALT) is not necessary in all those taking IPT. LFTs should be considered only when clinically indicated and/or in those at significant risk for liver disease.
- If an adult or adolescent develops active TB while on IPT, a specimen should be sent for TB culture and drug susceptibility testing (DST). Adapted treatment (i.e. for drug-resistant TB) must be prescribed to those found to have active TB resistant to isoniazid.
- Children developing active TB while on IPT should be initiated on TB treatment that uses 4 drugs in the intensive phase (i.e. HRZE). If possible, perform culture and DST. It should be noted that the risk of a child developing drug-resistant TB in this scenario is much less compared to an adult.

^{1(see page 0)}

A 3-month time lag allows any undiagnosed TB to be ‘unmasked’ by ART.

^{2(see page 0)}

HIV-exposed infants are infants born to HIV-positive women (the infant is of unknown HIV infection status but may be HIV infected).

 (see page 0) Contact is defined as living in the same household, or in close and regular contact with, any known or suspected TB case within the last 12 months.

16.5 Chemoprophylaxis and drug-resistant tuberculosis

Contacts of multidrug-resistant TB (MDR-TB) patients in whom latent infection is diagnosed are often infected with the same strain as the index case. Studies from high-burden TB areas have shown that approximately two-thirds or more of household members will have the same strain of TB⁷(see page 133),⁸(see page 133),⁹(see page 133),¹⁰(see page 133).

There have been very few studies of the use of second-line anti-TB drugs to prevent disease in MDR-TB contacts. Due to the lack of evidence, lack of consensus about whether close contacts of MDR-TB patients should be given chemoprophylaxis and which drugs should be given, routine chemoprophylaxis for close contacts of MDR-TB patients cannot be recommended at this time.

Close contacts of drug-resistant TB patients should be followed for at least two years. If active disease develops, prompt initiation of treatment with a regimen designed to treat the index case is recommended.

References Chapter 16

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Chapter 17: Monitoring and evaluation

- [17.1 Introduction](#)(see page 135)
- [17.2 Definitions of treatment outcomes](#)(see page 135)
- [17.3 Recording tools](#)(see page 138)
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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](#)(see page 61).

17.2 Definitions of treatment outcomes

- [17.2.1 Interim outcomes for drug-susceptible TB and MDR-TB](#)(see page 135)
- [17.2.2 Final outcomes for drug-susceptible TB and DR-TB](#)(see page 136)

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 [1](#)(see page 0)).
- 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
Drug-susceptible TB	At 2-3 and 4-5 months: <ul style="list-style-type: none"> • Bacteriological status (smear negative/positive/no information) • Final outcomes in patient who had already interrupted or died
MDR-TB	At 6 months: <ul style="list-style-type: none"> • Bacteriological status (negative/positive/no information) based on smear and culture • Final outcomes in patient who had already interrupted or died

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^{1(see page 147),2(see page 147)}

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.

Outcomes	TB	Definitions
Failure	DS TB	<p>Patient with signs of continued active disease or deterioration requiring a treatment change:</p> <ul style="list-style-type: none"> Any patient with positive smear or culture at 4-5 months of treatment or thereafter. 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.
	DR-TB ^{a,b,c}	<p>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:</p> <ul style="list-style-type: none"> Lack of monitoring cultures converting to negative by 6 months for MDR-TB (3 months for PDR-TB), and/or Resistance amplification to rifampicin or isoniazid (PDR-TB) or to Group 2 or Group 3 drugs (MDR-TB), and/or Bacteriological reversion (at least two positive smears or cultures at least 7 days apart after monitoring smears or cultures have become negative), or A clinical decision has been made to terminate treatment early due to poor response or adverse events. 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^{d,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 2nd 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

 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.

17.3 Recording tools

- [17.3.1 Drug-susceptible TB treatment card and drug-susceptible TB register](#)(see page 138)
- [17.3.2 DR-TB treatment card and DR-TB register](#)(see page 138)
- [17.3.3 Laboratory request form\(s\) and register\(s\)](#)(see page 138)
- [17.3.4 Drug-O-Gram](#)(see page 138)

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 ([Appendix 23](#)(see page 245) and [Appendix 24](#)(see page 245)) 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 ([Appendix 25](#)(see page 246)) 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 ([Appendix 26](#)(see page 246)) 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 ([Appendix 24](#)(see page 245)).

17.3.3 Laboratory request form(s) and register(s)

- Request form for microscopy and Xpert MTB/RIF ([Appendix 27](#)(see page 247));
- Request form for sputum culture, LPA and DST ([Appendix 28](#)(see page 247));
- Sputum smear microscopy register ([Appendix 29](#)(see page 248));
- Xpert MTB/RIF register ([Appendix 30](#)(see page 248)).

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 31](#)(see page 249)).

17.4 Reporting

- [17.4.1 Case detection and enrolment report for TB](#)(see page 139)
- [17.4.2 Case detection and enrolment report for DR-TB](#)(see page 140)
- [17.4.3 Interim treatment outcomes for drug-susceptible TB and DR-TB](#)(see page 141)
- [17.4.4 Final treatment outcomes for TB](#)(see page 142)

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](#)(see page 135)).

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](#)(see page 61).

See Quarterly report for case enrolment, [Appendix 32](#)(see page 249).

Main indicators

– *Proportion of confirmed pulmonary TB (PTB)*

= *Number of PTB cases confirmed enrolled/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*

= *Number of smear-negative PTB cases enrolled/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*

= *Number of smear-positive PTB cases enrolled/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*

= *Number of new TB cases enrolled/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*

= *Number of TB patients less than 15 years enrolled/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*

= *Number of cases enrolled under treatment/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*

= *Number of new smear-positive PTB cases detected/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

See standard DR-TB case detection and enrolment reports in [Appendix 33](#)(see page 250).

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 ([Appendix 26](#)(see page 246)), the laboratory register for culture and DST and the Xpert register ([Appendix 30](#)(see page 248)).

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.

All data can be extracted from the DR-TB register ([Appendix 26](#)(see page 246)).

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

See standard TB treatment outcomes reports ([Appendix 32](#)(see page 249) and [Appendix 33](#)(see page 250)).

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 evaluated³(see page 147).

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.

17.5 Programme assessment

- [17.5.1 Organization](#)(see page 144)
- [17.5.2 Procedures](#)(see page 146)
- [17.5.3 Human resources](#)(see page 147)

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
Access to care	<ul style="list-style-type: none"> • Accessibility of treatment facilities, decentralization, etc. • Home-based treatment available when appropriate. 	Easy access to care during the intensive/continuation phases
Patient comfort	<ul style="list-style-type: none"> • Patient welcome • Condition of the facility, heating (or cooling), overall organization and cleanliness. • Food during hospitalization and/or for outpatients (supplemental rations, quantities, organization in charge). • Bed occupancy rate of the TB ward. 	<ul style="list-style-type: none"> • According to needs • Bed occupancy rate ≤ 100%
Information and therapeutic education	Patient interviews conducted.	Patient understanding of treatment
Hospital hygiene	<ul style="list-style-type: none"> • Equipment (respirators, masks, gloves, gowns, autoclaves, cleaning supplies, etc.) • Waste management (sorting, incinerator, etc.) 	All necessary equipment is available and used.
Constant supply of lab materials	<ul style="list-style-type: none"> • Supplied by (government, agency or facility, other) • Buffer stock • Number and duration of shortages 	<ul style="list-style-type: none"> • 3-month buffer stock • No shortages

Criteria	Indicators	Goals
Constant supply of quality-assured anti-TB drugs	<ul style="list-style-type: none"> • Stock card maintenance • Order frequency, delivery time, buffer stock • Shortage(s) • Drug sources • Institution in charge of supply • Use of FDCs first-line drugs • Storage conditions • Organization of supply for peripheral facilities 	<ul style="list-style-type: none"> • Stock cards up-to-dated • One person in charge of the pharmacy • All adequate • No shortages • WHO-prequalified sources (or equivalent) • Use of FDCs • Appropriate storage conditions • Regular supply
Case detection	<ul style="list-style-type: none"> • Type of case detection (active or passive) • Contacts screening • Detection rate of new smear-positive cases • Percentage of smear-positive patients out of the total number of patients who had a sputum smear. • Detection rate of MDR-TB 	<p>Know the type, in order to interpret the quantitative results of case detection</p> <ul style="list-style-type: none"> • 100% • Depends on the context • < 20% • Depends on the context
Diagnosis of smear-negative PTB and EP forms	<ul style="list-style-type: none"> • Automated molecular test • Culture or molecular techniques • X-rays • Others (e.g. ADA, Pandy, Rivalta, FNAC) • Algorithms used 	<ul style="list-style-type: none"> • Yes • Yes • Yes • Yes • Yes
DST	DST possible (methods, quality control)	Detection of DR-TB
Treatment support	Number of patients receiving treatment support/month	100% of those eligible for support
Identification of non-adherent patients	<ul style="list-style-type: none"> • System for identifying and looking for non-adherent patients • Percentage of patients who resumed treatment among those missing for less than 2 months who had to be looked for 	<ul style="list-style-type: none"> • Yes • > 90%
Integrated TB/HIV care	<ul style="list-style-type: none"> • Access to voluntary counselling and testing (VCT) • Access to ART • Access to cotrimoxazole prophylaxis • HIV treatment integrated in the TB service (or TB treatment in the HIV service) 	<ul style="list-style-type: none"> • Yes • Yes • Yes • Yes

17.5.2 Procedures

Criteria	Indicators	Goals
Registers/ records	Description of the documents <ul style="list-style-type: none"> • Consistency between TB registers and treatment cards • Consistency between TB register and lab registers 	Records reliable <ul style="list-style-type: none"> • 100% • 100%
Standard case definitions	Percentage of patients with exact case definition out of a randomized sample of patients	100%
Adequate standard treatment regimens and follow-up	<ul style="list-style-type: none"> • Percentage of new cases correctly treated (combinations, dosage, duration) out of a randomized sample of patients • Percentage of patients who did not have bacteriological follow-up according to schedule out of a randomized sample of patients • Percentage of MDR-TB patients who did not have biochemistry tests according to schedule out of a randomized sample of patients 	<ul style="list-style-type: none"> • > 95% • < 10% • < 10%
HIV testing	Percentage of new cases tested for HIV	100%
ART	Percentage of HIV-positive TB cases started on ART ART started within: < 2 weeks; 2 weeks-< 2 months; ≥ 2 months	100%
Criteria for cure	Percentage of confirmed cases declared cured who actually met the definition of cure out of a randomized sample of patients	> 90%
Regular monitoring of drug-susceptible TB and DR-TB	<ul style="list-style-type: none"> • Quarterly report and cohort analysis for drug-susceptible TB • Bi-annual report and cohort analysis for DR-TB 	<ul style="list-style-type: none"> • Quantitative data on inclusions and results collected • Rapid detection of potential problems
Adherence monitoring	<ul style="list-style-type: none"> • Percentage of patients coming in for their appointment out of number of patients expected • Percentage of doses given under DOT for DR-TB treatment in a randomized sample of patients 	<ul style="list-style-type: none"> • > 90% in both the intensive and continuation phases • 100%

Criteria	Indicators	Goals
Prevention of <i>M. tuberculosis</i> airborne transmission in TB facilities	<ul style="list-style-type: none"> • Isolation • 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) • Written prevention plan? • Person in charge identified? 	<ul style="list-style-type: none"> • Isolation of smear positive patients • Isolation of DR smear positive patients • Appropriate use of means • Yes • Yes
Standard precautions	Description	Standard precautions followed
Laboratory quality control	<ul style="list-style-type: none"> • Regular evaluation of laboratory functioning • Quarterly EQA of smear microscopy • Annual EQA of DST 	<ul style="list-style-type: none"> • Ensure the quality of laboratory analyses for bacteriological diagnosis • Results according to standards • Results according to standards

17.5.3 Human resources

Criteria	Indicators	Goals
Staff	<ul style="list-style-type: none"> • Job descriptions (doctors, nurses, lab technicians, cleaning staff, etc.) • Medical staff-to-patient ratio 	On average: <ul style="list-style-type: none"> • One nurse for 10-15 patients • One doctor for 40-50 patients
Training	Refer to training programme evaluation criteria	Competent staff
Other contributors	Description: other NGOs, local associations, etc.	

A grid for evaluating TB clinic operations can be found in [Appendix 35](#) (see page 251). Each criterion is rated either “satisfactory” or “unsatisfactory”.

References Chapter 17

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Appendices

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- [Appendix 32. Quaterly report\(see page 249\)](#)
- [Appendix 33. Report on detection and enrolment of TB cases with rifampicin and multidrug-resistance\(see page 250\)](#)
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Appendix 1. Sputum specimen: collection, storage and shipment

- [1.1 Sputum collection techniques\(see page 150\)](#)
 - [1.1.1 Sputum obtained spontaneously\(see page 150\)](#)
 - [1.1.2 Sputum induction\(see page 150\)](#)
 - [1.1.3 Gastric aspiration\(see page 151\)](#)
- [1.2 Sputum specimen storage\(see page 152\)](#)
- [1.3 Sputum specimen shipment\(see page 152\)](#)

1.1 Sputum collection techniques

Regardless the collection technique used, staff member present during sputum collection should wear a respirator to prevent bacilli inhalation.

1.1.1 Sputum obtained spontaneously

Two specimens are to be collected. When possible, specimens should be collected outside in the open air and far away from other people.

The first sample is collected on the spot, at the consultation, when the patient is identified as suspected TB case. If the patient has recently eaten, ask him/her to rinse his/her mouth with water in order to avoid the presence of food in the sample.

The second sample is collected the day after, in the early morning, right after the patient wakes up and before eating. The second sample may be collected at home then the patient brings it to the health facility.

Alternatively, two sputum specimens can be collected one hour apart (frontloaded microscopy).

Collection technique:

- The patient must be given a labelled sputum container (or a Falcon® tube, if the sample is to be shipped by air).
- Have the patient take a deep breath, hold for a few seconds, exhale, repeat two or three times, then cough: sputum is material brought up from the lungs after a productive cough. One or two minutes of chest clapping are of benefit.
- Collect at least 3 ml and close the container hermetically.

The quality of sample determines the reliability of the result. Always check that the sample contains solid or purulent material and not only saliva. Take a new sample if unsatisfactory.

If the sample is collected at home, make sure that the patient has understood the technique, including closing the container hermetically after collecting the sputum.

1.1.2 Sputum induction

Sputum induction is sometimes used in children when sputa cannot be spontaneously expectorated, and only in order to perform cultures or Xpert MTB/RIF.

Sputum induction must be performed under close medical supervision. The child should be observed for respiratory distress during, and for 15 minutes after, the procedure. Bronchospasm may occur. Salbutamol spray and oxygen must be ready at hand.

Equipment

- Gloves and respirator
- Suction catheter (6, 7, 8F)
- Sputum container
- 50 ml syringe, needle
- Mask and tubing for nebulizer
- Holding chamber with child's mask (to be sterilized between each patient)
- Sterile hypertonic solution of 5% sodium chloride (to be kept refrigerated)
- Sterile solution of 0.9% sodium chloride (for the specimen)
- Salbutamol spray
- Oxygen

Procedure

The child should fast for at least 2 hours before the procedure.

– Prior to nebulization:

- Explain the procedure to the child and/or the person accompanying him/her (this person must wear a respirator).
- Place the child in a sitting position in the adult's arms.
- Administer 2 puffs of salbutamol via a holding chamber, 10 minutes before nebulization.
- Prepare a sputum container.

– Nebulization:

- Fill the nebulizer with 5 ml of 5% hypertonic saline solution (sputum inducer).
- Place the nebulizer mask over the child's mouth.
- Leave the child to inhale until the reservoir is empty.

– Nasopharyngeal suction:

- Do 1 to 2 minutes of clapping.
- Clean out the nasal cavity.
- During suction, the child is laid on his /her side, back to the operator, who is behind him/her.
- Fit a suction catheter to a 50 ml syringe. Lubricate the end of the catheter.
- Measure the distance from the tip of the nose to the angle of the jaw. Insert the suction catheter to that depth.
- When inserting and withdrawing the tube, pull on the plunger of the syringe to create suction.
- Once the syringe is filled with air and mucus, disconnect it from the suction catheter and purge the air (tip facing upward), so that only mucus is left in the syringe.
- To collect the mucus: draw 2 ml of 0.9% sodium chloride into the syringe to rinse, then empty contents into the sample container.

1.1.3 Gastric aspiration

Gastric aspiration is sometimes used in children when sputa cannot be spontaneously expectorated nor induced using hypertonic saline, and only in order to perform cultures or Xpert MTB/RIF.

Equipment

- Gloves and respirator
- Suction catheter (6, 7, 8F)
- Sputum container
- 50 ml syringe
- Sterile water

Procedure

– Prior to inserting the suction catheter:

- Explain the procedure to the child and/or the person accompanying him/her (this person must wear a respirator);
- 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.

– First suction to collect the gastric fluid and place it in the sputum container, then rinse the stomach with 30 ml of sterile water and suction again. Add the suctioned fluid to the first sample.

– Start culture within 4 hours of collecting the sample. If there will be more than four hours' delay, neutralize with 100 mg of sodium bicarbonate.

1.2 Sputum specimen storage

When examinations are not performed on the site of collection:

Specimen for smear microscopy

Smears should be performed within three-four days of collection and in the meanwhile stored refrigerated (2 to 8°C) and protected from light.

Contamination does not affect microscopy but heat make specimen liquefy, with selection of mucopurulent part of the sample more difficult.

Specimen for culture in liquid medium

Keep the specimen refrigerated (2 to 8°C), protected from light. Do not use cethylpyrodiminium chloride (CPC) as it is not compatible with MGIT.

The specimen should be processed as soon as possible.

Specimen for culture on Lowenstein-Jensen medium (LJ)

– *Specimens that can be cultured in less than 3 days after collection:*

Keep refrigerated (2 to 8°C) and protected from light until transport OR immediately transport to the laboratory for processing.

– *Specimens that will be cultured more than 3 days after collection:*

Use Falcon tubes and add 1% CPC to preserve the specimen for up to 2 weeks. Specimens with CPC should not be refrigerated, as the CPC will crystallize and be ineffective.

Samples with CPC can be inoculated on LJ. For inoculation on agar, they require prior neutralization by neutralizing buffer (Difco).

CPC can be used for specimens tested by Xpert MTB/RIF.

1.3 Sputum specimen shipment

To a local laboratory

- Without CPC transport medium: between 2 and 8°C and protected from light;
- With CPC transport medium: should not be refrigerated because at low temperatures the CPC will crystallize and ruin the sample. Specimens should be kept at room temperature, protected from heat and light.

By air to a reference laboratory for culture

Samples are collected and shipped in 50 ml Falcon® conical tubes with screw caps. The tubes are labelled UN 3373, corresponding to Category B infectious substances. If transport times are less than 12 hours, even specimens without CPC can be transported at room temperature.

Samples are triple-packaged, in accordance with IATA packing instruction 650:

1. Primary container holding the sputum sample: tube tightly closed and placed into a latex glove;
2. Secondary container intended to protect the primary container: leak-proof box with enough absorbent material to absorb the entire sample, should the primary container break;
3. Outer packaging intended to protect the secondary container, with UN 3373 labelling.

Information to be provided:

- Primary container: label with the patient's name or identification number and the sample collection date and location;

– Outer package: indicate the name of the receiving laboratory, the complete address (name, street, postal code, locality, country), and telephone number.

All samples must be accompanied by the corresponding laboratory test request form (including clinical information).

Notes:

- Procedures for shipping bacterial strains obtained after culture are different, more complicated, and rarely feasible in practice. Cultures are classified as Category A infectious substances (UN 2814).
- For a detailed description of the shipment procedures, see *MSF Medical catalogue*, volume 4.

Appendix 2. Sputum smear process

- [2.1 Ziehl-Neelsen staining \(hot method\)](#)(see page 153)
- [2.2 Auramin O staining](#)(see page 154)
- [2.3 Bleach sedimentation](#)(see page 155)

2.1 Ziehl-Neelsen staining (hot method)

Equipment

- Gloves and respirator
- Water, distilled or filtered
- Carbol fuchsin
- 3% acid-alcohol (ethanol + hydrochloric acid)
- 0.3% methylene blue

Technique

- Flood the slide with carbol fuchsin (after filtering the carbol fuchsin).
- Gently heat the slide. Begin timing as soon as steam appears; let it steam for 5 minutes, without allowing the slide boil or dry out.
- Gently rinse the slide with distilled or filtered water until the water runs clear; drain.
- Cover the slide with 3% acid-alcohol solution, leave on for 3 minutes, then drain. Repeat this operation 2 or 3 times, until the slide is completely decolourized.
- Rinse the slide with distilled or filtered water, and drain.
- Cover the slide with methylene blue, and leave on for one minute.
- Gently rinse the slide with distilled or filtered water until the water runs clear, then allow to air dry.

Reading

A slide should be examined by an experienced laboratory technician on at least 300 fields (15 minutes on average) before giving a negative result. As a maximum, a technician can read 20-25 slides per day, otherwise quality is likely to suffer.

Tuberculosis bacilli stain red on a blue background, are straight or slightly curved, and often cluster in groups of 3 to 10.

Reporting

There are two types of grading scales: one by the World Health Organization and the International Union against Tuberculosis and Lung Disease (WHO-IUATLD) and one by the US Centre of Disease Control and American Thoracic Society (CDC-ATS). Each field is a high powered field (HPF).

Grading AFB scale (WHO-IUATLD)

Number of acid-fast bacilli (AFB)	Report
No AFB	0
1–9 AFB per 100 fields	Scanty (report number of AFB)
10–99 AFB per 100 fields	1+
1–10 AFB per field	2+
More than 10 AFB per field	3+

Note that seeing 1-9 AFB per 100 HPF is reported as “scanty” and the exact number of bacilli should be recorded. For example, a report of “scanty 3” means there were three AFB seen per 100 HPFs and is not the same as a report of “AFB 3+”. Scanty results are considered as positive result.

Grading AFB scale (CDC-ATS)

Number of AFB	Report
0	Negative
1–2 AFB per 300 fields	+/-
1–9 AFB per 100 fields	+
1–9 AFB per 10 fields	++
1–9 AFB per 1 field	+++
More than 9 AFB per 1 field	++++

2.2 Auramin O staining

Equipment

- Gloves and respirator
- Water, distilled or filtered
- 0.1% auramin O solution
- 0.5 % acid alcohol
- 0.5% potassium permanganate solution
- Fluorescence microscope (or a LED device that can be attached to a standard light microscope)

Technique

- Flood the smear with 0.1% auramin solution and allow staining for 15 minutes ensuring that smears remain covered with stain.
- Rinse with distilled or filtered water until water runs clear and drain excess water from the slide. Do not use water containing chlorine (risk of interference with the fluorescence).

- Flood the smear with 0.5% acid-alcohol for 2 minutes to decolourize it.
- Rinse with distilled or filtered water and drain excess water from the slide.
- Flood the smear with 0.5% potassium permanganate solution and allow to counterstain for 2 minutes. Time is critical because counterstaining for longer may quench the fluorescence of AFB.
- Rinse with distilled or filtered water and drain excess water from the slide. Wipe the back of the slide with tissue paper.
- Allow smears to air-dry. Read as soon as possible after staining.

Note: to control the quality of the colouration, it is essential to include at least a known positive smear in the batch.

Reading

- 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.
- Look aspect of smear: black background without debris or artefacts.
- Read one length of the smear (about 40 fields).

Reporting

Number of AFB	Report
0 AFB per 1 length	Negative
1–19 AFB per 1 length	Scanty (report number of AFB)
20–199 AFB per 1 length	1+
5–50 AFB per 1 field	2+
More than 50 AFB per 1 field	3+

Notes:

- The technique need a skilled reader (artefacts are frequent).
- The fluorescence stain remains stable only for 3 days when sheltered from light. Quality control has to be organised accordingly.

2.3 Bleach sedimentation

Equipment

- Gloves and respirator
- 15 ml plastic conical screw capped tube
- 3.5% bleach solution (12° chl) [\(see page 0\)](#)
- Vortex (optional)
- Transfer pipettes
- Slides

Technique

- Transfer the sputum to the 15-ml tube.
- Add an equal amount of 3.5% bleach.
- Screw the cap back tightly. Shake vigorously until the mixture is homogeneous.

- Let stand for sedimentation at room temperature for 15 to 18 hours.
- Using a pipette, carefully transfer the supernatant to a waste container containing a 1% chlorine solution.
- Mix the sediment with the remaining fluid.
- Transfer 2 drops of the sediment to a slide.
- Make a smear and let it air dry in a horizontal position.
- When the smear is completely dry, fix it by passing the smear through a flame 3 times.

 (see page 0) Check the actual available chlorine content of the bleach with a pool tester.

Appendix 3. Xpert MTB/RIF

- [3.1 Sample processing](#)(see page 156)
- [3.2 Interpretation of the results](#)(see page 157)
- [3.3 Storage of samples and cartridges](#)(see page 157)
- [3.4 Logistic requirements](#)(see page 158)
- [3.5 Predictive values for detection of rifampicin resistance with Xpert MTB/RIF](#)(see page 159)

Xpert MTB/RIF assay is based on hemi-nested real time PCR for simultaneous detection of *M. tuberculosis* (MTB) and rifampicin (RIF) resistance. The target is the *rpoB* gene, critical for detection of mutations associated to rifampicin resistance.

Xpert MTB/RIF automates all aspects of real time PCR analysis, with results available in 2 hours.




3.1 Sample processing

The test can be performed using fresh sputum samples or decontaminated samples prior culture inoculation.

Procedure with fresh sputum samples

- Ask the patient to rinse the mouth twice before collecting the sample.
- Collect a minimum of 1.5 ml good quality sputum.
- Follow the procedures outlined below:

Procedure for Xpert MTB/RIF*

<p>Step 1</p>  <p>Add the reagent 2:1 (v/v) to the sample and shake 10-20 times. Incubate at room temperature for 15 min.; during incubation repeat once shaking for 10- 20 times.</p>	<p>Step 2</p>  <p>With a pipette transfer the diluted sample into a cartridge.</p>	<p>Step 3</p>  <p>Insert the cartridge in the machine and start the test.</p>
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* Source: National Health Laboratory Services, South Africa.

Procedure for sediment samples

- Sediments can be prepared according to standard decontamination procedure (NALCNaOH method) and re-suspend with phosphate buffer.
- Ensure 0.5 ml is available for the test; add 1.5 ml of reagent for 0.5 ml of re-suspended sediment.
- Follow the procedure described in the above figure.

3.2 Interpretation of the results

Proper test performance is ensured by 2 internal controls:

- Sample processing control (SPC) ensures adequate processing and monitors presence of inhibition.
- Probe check control (PCC) verifies that the steps of the tests (rehydration, filling of the cartridge, etc.) take place correctly.

When the test is completed the display can show:

- “MTB detected” expressed by levels (the higher the level, the higher the amount of MTB detected in the sample) or “MTB not detected”;
- RIF results expressed as “detected”, “not detected” or “indeterminate” are available only if MTB is detected.

Other possible results:

- Invalid: MTB invalid and SPC failed due to one of several reasons, such as inhibition;
- Error: MTB no result, SPC no result, PCC failed; fail of system components;
- No result: e.g. tests stopped during processing.

3.3 Storage of samples and cartridges

Samples

- For a period ≤ 3 days: store at 35°C maximum. A cold chain is not required for up to 3 days after collection. During this period of time, overgrowth of normal flora does not have negative influence on the test. However, if a cold chain is available, samples should be stored at 2 to 8°C in order to help their preservation.
- For a period of 4 to 10 days: store refrigerated at 2 to 8°C. If samples require other testing (i.e. smear microscopy and/or culture), sample storing conditions adequate for microscopy and culture have to be followed. CPC does not interfere with Xpert MTB/RIF testing.

Cartridges

- To be stored at 2 to 28°C.
- The cartridge should be used within 30 minutes of opening the cartridge lid.
- Cartridges are stable for 7 days after opening the packaging.

3.4 Logistic requirements

Power supply

The device requires stable and uninterrupted power supply.

Each GeneXpert instrument will need a uninterruptible power supply (UPS).

The minimum requirement for the functioning of the GeneXpert instrument is to have a 800VA UPS.

Operating temperature

The operating temperature for GeneXpert instrument device is 15 to 30°C. According to climate conditions, the installation of air conditioning can be recommended to keep the area within the temperature ranges indicated by the manufacturer.

Calibration

The GeneXpert modules require annual calibration, which must be performed by an authorised service provider or carried out by swapping out the modules. A detailed commercial sales contract and customer support plan should be negotiated with the supplier, guaranteeing regular maintenance, calibration, repair and replacement (when needed).

Cartridges and reagents shelf-life

12 months from date of production.

Storage space

Each kit contains 10 cartridges and all reagents necessary to run 10 tests.

The dimensions of the kit are 27 x 20 x 17 cm and the weight is 800 g.

Lab space

The GeneXpert IV instrument (4 modules allowing the processing of 4 specimens at the same time) has the following dimensions:

29.8 cm wide, 35.6 cm high, 31.1 cm deep; weight: 12 kg.

It is designed for indoor use only.

Provide at least 5 cm of clearance on each side of the instrument to ensure adequate ventilation.

Do not place the instrument close to the vents of other instruments or air-handling units.

Safety

The personal protection requirements for microscopy should be adopted, including use of gloves and respirators.

Waste disposal

Same procedure as for sputum containers. To be noted is the large volume of additional waste generated by Xpert MTB/RIF compared to smear microscopy.

3.5 Predictive values for detection of rifampicin resistance with Xpert MTB/RIF

Positive predictive value (PPV) is defined as the proportion of subjects with a positive test result who are correctly diagnosed. A high PPV means that when the test yields a positive result, it is most likely correct. Negative predictive value (NPV) is defined as the proportion of subjects with a negative test result who are correctly diagnosed. A high NPV means that when the test yields a negative result, it is most likely correct. PPV and NPV are influenced by the prevalence of disease in the population being tested.

Predictive values according to the prevalence of rifampicin resistance

Source: World Health Organization. *Rapid implementation of the Xpert MTB/RIF diagnostic test*¹(see page 251).

Rifampicin resistance prevalence	PPV	NPV	True positive*	False negative*	False positive*	True negative*
1%	32.4%	99.9%	9.5	0.5	19.8	970.2
2%	49.2%	99.9%	19	1	19.6	960.4
3%	59.5%	99.8%	28.5	1.5	19.4	950.6
4%	66.4%	99.8%	38	2	19.2	940.8
5%	71.4%	99.7%	47.5	2.5	19	931
6%	75.2%	99.7%	57	3	18.8	921.2
7%	78.1%	99.6%	66.5	3.5	18.6	911.4
8%	80.5%	99.6%	76	4	18.4	901.6
9%	82.4%	99.5%	85.5	4.5	18.2	891.8
10%	84.1%	99.4%	95	5	18	882
11%	85.4%	99.4%	104.5	5.5	17.8	872.2
12%	86.6%	99.3%	114	6	17.6	862.4
13%	87.7%	99.2%	123.5	6.5	17.4	852.6
14%	88.5%	99.2%	133	7	17.2	842.8
15%	89.3%	99.1%	142.5	7.5	17	833

Rifampicin resistance prevalence	PPV	NPV	True positive*	False negative*	False positive*	True negative*
20%	92.2%	98.7%	190	10	16	784
25%	94.1%	98.3%	237.5	12.5	15	735

* Sensitivity (95%) and specificity (98%) for Xpert MTB/RIF rifampicin resistance, compared with reference method (culture).

Appendix 4. Fine needle aspirate cytology (FNAC)

FNAC is used to obtain material from lymph nodes. The material is expressed onto slides and prepared for examination.

Two smears will be prepared with Giemsa stain [1\(see page 0\)](#) [2\(see page 251\)](#) to look for caseum, granuloma, giants cells, and epithelioid cells or histocytes and 1 or 2 will be prepared with Ziehl-Neelsen (ZN) stain to look for acid-fast bacilli (AFB).

Equipment

- Needle 23G (in very few cases, it would be possible to use 19G)
- 10 ml syringe
- 2 slides for Giemsa + one or 2 slides for ZN stain
- 10% polyvidone iodine, sterile gauze, gloves

Technique

- Disinfect the area.
- With the needle attached to the syringe, insert the needle deep into the lymph node.
- After the needle has entered the mass, pull back on the syringe plunger to create a vacuum.
- Rapidly move the needle in a to-and-fro fashion to allow material entering the needle.
- When blood or material appears in the needle hub the aspiration should be stopped. Try to aspirate as much as possible of materials, the amount of materials that has been aspirated would have effect on the specificity and sensitivity of diagnosis.
- Release the negative pressure before to take out the needle from the lymph node. Do not continue sucking while taking out the needle, this will avoid aspiration of materiel into the barrel of the syringe and avoid mixing the sample with the possible peripheral blood in the skin.

Slide preparation

Slide should be identified prior to the aspiration and prepared immediately after the aspiration.

- Detach the needle from the syringe immediately after the aspiration.
- Fill the syringe with air (needle is still detached).

Prepare the smear as follow:

– *Giemsa*

- Reattach the needle to the syringe and carefully release one small drop of sample onto one end of the slide by pushing down the plunger of the syringe (if the drop is placed in the middle of slide it would be difficult to make smear afterwards).
- Put another slide over the sample.
- Slide the two slides against each other, in opposite directions, to spread the sample out completely between them. Do not press the slides together forcefully, to avoid crushing the cells.
- Allow to air dry.
- Fix the smears by methanol when they are completely dry.
- Proceed to Giemsa staining.

– *Ziehl-Neelsen*

- Place a small drop of ganglion aspirate on the slide.
- Make a smear that is neither too thin or too thick.
- Allow to air dry.
- Fix the smear by flame when it is completely dry.
- Proceed to ZN staining.

Reading after Giemsa staining

On each slide, one or several of the following aspects can be found:

- Caseation necrosis (caseum): a uniform, acellular, pinkish substance.
- Granuloma: cluster of epithelioid cells and lymphocytes scattered through out smear with or without caseous necrosis.
- Epithelioid cells: elongated, often semi-lunar cells with a fine granular nuclear chromatin surrounded by pink cytoplasm.
- Giant cells: huge multinuclear cells.

Notes:

- It would be better to look for granuloma and necrosis with the 10x and 40x power of microscope then to look for epithelioid cells and giant cells with 100x power.
- Observation of smear requires a competent reader with skills in cytology. Slides have to be sent to a referral cytopathology laboratory for quality control or confirmation.
- The quality of the specimen and the preparation are essential. The smear is to be done by skilled technicians.



(see page 0) The golden standard of diagnosis for TB on tissue samples is hematoxylin-eosin stain, but Giemsa stain can be used as an alternative in remote areas with limited equipment.

Appendix 5. Protein estimation

- [5.1 Pandy test\(see page 161\)](#)
- [5.2 Rivalta test\(see page 162\)](#)

5.1 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 0.20-0.45 g/litre.

The Pandy test is positive when protein is superior to 0.45 g/litre.

Equipment

- 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 in a 1000 ml bottle.
- Add 500 ml of distilled water and shake vigorously.
- Leave to stand for one day.
- Check whether any 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 day before filtering.

Pandy reagent is a highly corrosive and toxic solution:

- Label the bottle and mark it corrosive and poisonous.
- Wash hands after the 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.
- In order 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.

5.2 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

- 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 in 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.
- In order 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 6. Adenosine desaminase assay (ADA)

Adenosine desaminase is an enzyme that is necessary for the maturation and differentiation of lymphoid cells. It is useful surrogate marker for TB in pleural and peritoneal fluids.

ADA testing is not widely available but can be done relatively easily and cheaply if a spectrophotometer is available^{2(see page 251)}. Kits can be purchased to perform the test (see MSF *Medical catalogue*, volume 4).

Pleural fluid

ADA is typically greater than 50 U/litre in TB pleural effusions. Pleural effusions with an ADA level below 40 U/litre are much less likely due to TB. The specificity is increased when ADA is greater than 50 and the lymphocyte-neutrophil ratio is greater than 0.75^{3(see page 251)}.

Peritoneal fluid

A meta-analysis suggests the optimal cut off values of greater than 39 U/litre^{4(see page 251)} likely to be due to TB. However, the sensitivity of ADA in peritoneal fluid is substantially lower in patients with cirrhosis.

Notes:

- HIV-infected patients and patients already on TB medications may have lower levels of ADA.
- ADA is generally not a good test in cerebrospinal fluid.

Appendix 7. Ventilated work station (VWS) and bio-safety cabinet (BSC)

- [7.1 Ventilated workstation \(VWS\)\(see page 163\)](#)
- [7.2 Class II BSC\(see page 164\)](#)

7.1 Ventilated workstation (VWS)

The VWS provides a safe work environment while preparing **sputum smears for AFB staining and Xpert MTB/RIF**. It is used when adequate natural ventilation cannot be achieved. Designed to be placed over a bench, it is constituted by a rectangular box ducted to the outside, where the duct is connected to an extraction fan.

VWS are used without filter and do not provide product protection. They should never be used for preparing cultures.

7.2 Class II BSC

A Class II BSC protects not only the operator and the environment, but also the material being manipulated inside the cabinet.

The room air and the air circulating within the cabinet are drawn by a downward flowing current through a grate then, through a HEPA filter, which protects both the operator and the product. The air exiting the cabinet is filtered through a HEPA filter to protect the environment.

Class II BSCs are required for performing **cultures**.

Notes:

- Class I BSCs cannot be used for performing cultures and VWS are sufficient for preparing samples for microscopy and tests Xpert MTB/RIF. Therefore, their use is not recommended in this manual.
- Class III BSCs are generally not used for TB.

Appendix 8. Daily dose of anti-TB drugs using FDCs

- [Appendix 8a. New paediatric FDCs](#)(see page 164)
- [Appendix 8b. Former paediatric FDCs](#)(see page 167)

Appendix 8a. New paediatric FDCs

- [Intensive phase](#)(see page 164)
- [Continuation phase](#)(see page 166)

Intensive phase

Weight (kg)	Paediatric formulations		Adult formulations		
	HZR 50/150/75	E 100	E 400	H 100	EHZR 275/75/400/150
4	1 tab	1 tab			
5	1 tab	1 tab			
6	1 tab	1 tab			
7	1 tab	1 tab			
8	2 tab	2 tab			
9	2 tab	2 tab			
10	2 tab	2 tab			

11	2 tab	2 tab			
12	3 tab	3 tab			
13	3 tab	3 tab			
14	3 tab	3 tab			
15	3 tab	3 tab			
16	4 tab	–	1 tab		
17	4 tab	–	1 tab		
18	4 tab	–	1 tab		
19	4 tab	–	1 tab		
20	4 tab	–	1 tab		
21	4 tab	–	1 tab		
22	4 tab	–	1 tab		
23	–	–	–	1 tab	2 tab
24	–	–	–	1 tab	2 tab
25	–	–	–	1 tab	2 tab
26	–	–	–	1 tab	2 tab
27	–	–	–	1 tab	2 tab
28	–	–	–	1 tab	2 tab
29	–	–	–	1 tab	2 tab
30-34	–	–	–	–	2 tab
35-39	–	–	–	–	2½ tab
40-54	–	–	–	–	3 tab
55-70	–	–	–	–	4 tab
> 70	–	–	–	–	5 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.

TABLETS ARE TO BE TAKEN ON A EMPTY STOMACH.

Continuation phase

Weight (kg)	Paediatric formulation	Adult formulation
	HR 50/75	HR 75/150
4	1 tab	
5	1 tab	
6	1 tab	
7	1 tab	
8	2 tab	
9	2 tab	
10	2 tab	
11	2 tab	
12	3 tab	
13	3 tab	
14	3 tab	
15	–	2 tab
16	–	2 tab
17	–	2 tab
18	–	2 tab
19	–	2 tab
20	–	2 tab
21	–	2 tab
22	–	3 tab
23	–	3 tab

24	–	3 tab
25	–	3 tab
26	–	3 tab
27	–	3 tab
28	–	3 tab
29	–	3 tab
30-34	–	2 tab
35-39	–	2½ tab
40-54	–	3 tab
55-70	–	4 tab
> 70	–	5 tab

	Daily dosing in patients < 30 kg	Daily dosing in patients ≥ 30 kg
E	15 to 25 mg/kg once daily	15 to 25 mg/kg once daily
H	7 to 15 mg/kg once daily	4 to 6 mg/kg once daily
Z	30 to 40 mg/kg once daily	20 to 30 mg/kg once daily
R	10 to 20 mg/kg once daily	8 to 12 mg/kg once daily

Appendix 8b. Former paediatric FDCs

- [Intensive phase](#)(see page 167)
- [Continuation phase](#)(see page 169)

Intensive phase

Weight (kg)	Paediatric formulations		Adult formulations		
	HZR 30/150/60	E 100	E 400	H 100	EHZR 275/75/400/150
4	1 tab	1 tab			
5	1 tab	1 tab			

6	2 tab	1 tab			
7	2 tab	1 tab			
8	2 tab	2 tab			
9	2 tab	2 tab			
10	3 tab	2 tab			
11	3 tab	2 tab			
12	3 tab	2 tab			
13	3 tab	2 tab			
14	3 tab	2 tab			
15	4 tab	3 tab			
16	4 tab	3 tab			
17	4 tab	3 tab			
18	4 tab	3 tab			
19	5 tab	3 tab			
20	5 tab	–	1 tab		
21	5 tab	–	1 tab		
22	5 tab	–	1 tab		
23	–	–	–	1 tab	2 tab
24	–	–	–	1 tab	2 tab
25	–	–	–	1 tab	2 tab
26	–	–	–	1 tab	2 tab
27	–	–	–	1 tab	2 tab
28	–	–	–	1 tab	2 tab
29	–	–	–	1 tab	2 tab

30-34	–	–	–	–	2 tab
35-39	–	–	–	–	2½ tab
40-54	–	–	–	–	3 tab
55-70	–	–	–	–	4 tab
> 70	–	–	–	–	5 tab

For example:

- A child weighing 9 kg takes 2 tablets of HZR (30 mg/150 mg/60 mg) + 2 tablets of E (100 mg) once daily.
- A child weighing 20 kg takes 5 tablets of HZR (30 mg/150 mg/60 mg) + 1 tablet of E (400 mg) once daily.

TABLETS ARE TO BE TAKEN ON A EMPTY STOMACH.

Continuation phase

Weight (kg)	Paediatric formulation	Adult formulation
	HR 30/60	HR 75/150
4	1 tab	
5	1 tab	
6	2 tab	
7	2 tab	
8	2 tab	
9	2 tab	
10	3 tab	
11	3 tab	
12	3 tab	
13	3 tab	
14	3 tab	
15	–	2 tab
16	–	2 tab
17	–	2 tab

18	–	2 tab
19	–	2 tab
20	–	2 tab
21	–	2 tab
22	–	3 tab
23	–	3 tab
24	–	3 tab
25	–	3 tab
26	–	3 tab
27	–	3 tab
28	–	3 tab
29	–	3 tab
30-34	–	2 tab
35-39	–	2½ tab
40-54	–	3 tab
55-70	–	4 tab
> 70	–	5 tab

	Daily dosing in patients < 30 kg	Daily dosing in patients ≥ 30 kg
E	15 to 25 mg/kg once daily	15 to 25 mg/kg once daily
H	7 to 15 mg/kg once daily	4 to 6 mg/kg once daily
Z	30 to 40 mg/kg once daily	20 to 30 mg/kg once daily
R	10 to 20 mg/kg once daily	8 to 12 mg/kg once daily

Appendix 9. Anti-TB drug sheets and patient instructions

- **Group 1**(see page 171)
 - Isoniazid (H)(see page 171)
 - Rifampicin (R)(see page 174)
 - Pyrazinamide (Z)(see page 176)
 - Ethambutol (E)(see page 178)
 - Rifabutin (Rfb)(see page 180)
- **Group 2**(see page 183)
 - Streptomycin (S)(see page 183)
 - Kanamycin (Km)(see page 185)
 - Amikacin (Amk)(see page 187)
 - Capreomycin (Cm)(see page 190)
- **Group 3**(see page 192)
 - Levofloxacin (Lfx)(see page 192)
 - Moxifloxacin (Mfx)(see page 195)
 - Ofloxacin (Ofx)(see page 197)
- **Group 4**(see page 199)
 - Ethionamide (Eto) and Prothionamide (Pto)(see page 199)
 - Cycloserine (Cs)(see page 202)
 - Para-aminosalicylic acid (PAS) and sodium salt of PAS(see page 204)
- **Group 5**(see page 206)
 - Clofazimine (Cfz)(see page 207)
 - Linezolid (Lzd)(see page 209)
 - Amoxicillin/Clavulanic acid (Amx/Clv)(see page 211)
- **Patient instructions**(see page 213)
 - Patients under first-line regimen(see page 214)
 - Patients treated for DR-TB(see page 214)

Group 1

- Isoniazid (H)(see page 171)
- Rifampicin (R)(see page 174)
- Pyrazinamide (Z)(see page 176)
- Ethambutol (E)(see page 178)
- Rifabutin (Rfb)(see page 180)

Isoniazid (H)

- Therapeutic action(see page 172)
- Presentation(see page 172)
- Dosage(see page 172)
- Contra-indications, adverse effects, precautions(see page 173)
- Monitoring(see page 173)
- Patient instructions(see page 173)
- Remarks(see page 174)

Therapeutic action

- Antibacterial with bactericidal activity

Presentation

- 100 mg and 300 mg tablets
- 50 mg/5 ml oral solution

Dosage

- Child under 30 kg: 10 mg/kg (7 to 15 mg/kg) once daily
- Child over 30 kg and adult: 5 mg/kg (4 to 6 mg/kg) once daily
- Maximum dose: 300 mg daily

Weight (kg)	Daily dose (mg)	300 mg tablet	100 mg tablet	50 mg per 5 ml oral solution
5	35-75	–	–	5 ml
6	42-90	–	–	6 ml
7	49-105	–	–	7 ml
8	56-120	–	–	8 ml
9	63-135	–	–	9 ml
10	70-150	–	–	10 ml
11	77-165	–	–	11 ml
12	84-180	–	–	12 ml
13	91-195	–	–	13 ml
14	98-210	–	–	14 ml
15	105-225	–	–	15 ml
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	200	–	2 tab	–
46-55	300	1 tab	–	–
56-70	300	1 tab	–	–
> 70	300	1 tab	–	–

Contra-indications, adverse effects, precautions

- Do not administer to patients with severe hepatic impairment.
- May cause:
 - peripheral neuropathy, especially in malnourished, alcoholic, diabetic, HIV-infected patients, pregnant and breast-feeding women, patients with renal impairment or chronic hepatic disease and patients receiving high doses of isoniazid;
 - hepatic disorders, especially in alcoholic patients, patients taking rifampicin, patients > 35 years;
 - hypersensitivity reactions; psychotic reactions.
- For the management of adverse effects, see [Chapter 9](#)(see page 71) and [Appendix 10](#)(see page 214).
- Administer with caution and monitor patients taking phenytoin, carbamazepine, benzodiazepines (risk of toxicity), warfarin (risk of bleeding), cycloserine (increased risk of peripheral neuropathy, drowsiness, dizziness).
- Administer concomitantly pyridoxine (vitamin B₆) to patients at risk of peripheral neuropathy (child: 5 to 10 mg/day; adult: 10 mg/day).
- *Pregnancy and breast-feeding: no contra-indication. To prevent peripheral neuropathy, administer pyridoxine (10 mg/day). In addition, supplement the breast-fed infant with pyridoxine (5 mg/day).*



Monitoring

- Symptomatic monitoring

Patient instructions

- Take without food.
- Avoid alcohol during treatment.

Remarks

- For patients on first-line treatment, isoniazid is given as part of a fixed dose combination.
- Isoniazid is included in Group 1 however, when used in high doses (16 to 20 mg/kg/day), it is included in Group 5.
- *Storage: below 25°C* -  - 

Rifampicin (R)

- [Therapeutic action](#)(see page 174)
- [Presentation](#)(see page 174)
- [Dosage](#)(see page 174)
- [Contra-indications, adverse effects, precautions](#)(see page 175)
- [Monitoring](#)(see page 176)
- [Patient instructions](#)(see page 176)
- [Remarks](#)(see page 176)

Therapeutic action

- Antibacterial (rifamycin) with bactericidal activity

Presentation

- 150 mg and 300 mg tablets or capsules
- Also comes in 100 mg/5 ml oral suspension.

Dosage

- Child under 30 kg: 15 mg/kg (10 to 20 mg/kg) once daily
- Child over 30 kg and adult: 10 mg/kg (8 to 12 mg/kg) once daily
- Maximum dose: 600 mg daily

Weight (kg)	Daily dose (mg)	300 mg tablet or capsule	150 mg tablet <small>1(see page 0)</small>	100 mg per 5 ml oral suspension
5	50-100	–	–	4 ml
6	60-120	–	–	5 ml
7	70-140	–	–	5 ml
8	80-160	–	–	6 ml
9	90-180	–	–	7 ml
10	100-200	–	–	8 ml
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 jaundice, history of allergy or severe blood disorders (thrombocytopenia, purpura) during a previous treatment with a rifamycin.
- Avoid or administer with caution to patients with hepatic impairment (do not exceed 8 mg/kg/day).
- Do not combine with bedaquiline. In patients taking nevirapine, indinavir, nelfinavir, lopinavir/ritonavir, atazanavir/ritonavir, use rifabutin in place of rifampicin.
- May cause:

- orange-red discolouration of body fluids;
- gastrointestinal disturbances, headache, drowsiness, hepatic disorders;
- thrombocytopenia, hypersensitivity reactions.
- For the management of adverse effects, see [Chapter 9](#)(see page 71) and [Appendix 10](#)(see page 214).
- Rifampicin reduces the effect of many drugs (antimicrobials, some antiretrovirals, some hormones, antidiabetics, corticoids, phenytoin, etc.):
- In women under contraception, use injectable medroxyprogesterone or a non-hormonal contraception or, as a last resort, an oral contraceptive used contains 50 µg ethinylestradiol per tablet.
- For concomitant fluconazole administration, administer each drug 12 hours apart (rifampicin in the morning, fluconazole in the evening).
- For other drugs, adjust dosage if necessary.
- *Pregnancy and breast-feeding: no contra-indication. If used in late pregnancy, administer phytomenadione (vitamin K) to the mother and the newborn to reduce the risk of bleeding disorders.*



Monitoring

- Symptomatic monitoring, liver function in elderly patients and patients with hepatic disease

Patient instructions

- Take without food on an empty stomach.
- Rifampicin causes a harmless orange-red discoloration of the urine, faeces, sweat, saliva, sputum, tears, and other body fluids.

Remarks

- For patients on first-line treatment, rifampicin is given as part of a fixed dose combination.
- *Storage: below 25°C* -  - 



(see page 0) If only 150 mg capsules are available: 1 capsule daily for children 8 to 15 kg.

Pyrazinamide (Z)

- [Therapeutic action](#)(see page 176)
- [Presentation](#)(see page 176)
- [Dosage](#)(see page 176)
- [Contra-indications, adverse effects, precautions](#)(see page 178)
- [Monitoring](#)(see page 178)
- [Patient instructions](#)(see page 178)
- [Remarks](#)(see page 178)

Therapeutic action

- Antibacterial with sterilising and bactericidal activity

Presentation

- 400 mg tablet

Dosage

- Child under 30 kg: 35 mg/kg (30 to 40 mg/kg) once daily
- Child over 30 kg and adult: 25 mg/kg (20 to 30 mg/kg) once daily

- Maximum dose: 2000 mg daily
- Patient with renal impairment: 25 mg/kg/dose, 3 times per week

Weight (kg)	Daily dose (mg)	400 mg tablet
5	150-200	½ tab
6	180-240	½ tab
7	210-280	½ tab
8	240-320	¾ tab
9	270-360	¾ tab
10	300-400	1 tab
11	330-440	1 tab
12	360-480	1 tab
13	390-520	1 tab
14	420-560	1 tab
15	450-600	1½ tab
16	480-640	1½ tab
17	510-680	1½ tab
18	540-720	1½ tab
19	570-760	1½ tab
20	600-800	1½ tab
21	630-840	2 tab
22	660-880	2 tab
23	690-920	2 tab
24	720-960	2 tab
25	750-1000	2 tab
26	780-1040	2 tab
27	810-1080	2 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 history of allergy to pyrazinamide, severe hepatic impairment or severe gout.
- May cause: gout and arthralgias, hepatic disorders, photosensitivity, rash, gastrointestinal disturbances, hypersensitivity reactions.
- For the management of adverse effects, see [Chapter 9](#)(see page 71) and [Appendix 10](#)(see page 214).
- *Pregnancy: safety in the first trimester is not definitely established. However, given the severity of the disease, it may be used during pregnancy.*
- *Breast-feeding: no contra-indication*



Monitoring

- Symptomatic monitoring

Patient instructions

- Take with or without food.
- Protect your skin from sun.

Remarks

- For patients on first-line treatment, pyrazinamide is given as part of a fixed dose combination.
- *Storage: below 25°C* -  - 

Ethambutol (E)

- [Therapeutic action](#)(see page 179)
- [Presentation](#)(see page 179)
- [Dosage](#)(see page 179)
- [Contra-indications, adverse effects, precautions](#)(see page 180)
- [Monitoring](#)(see page 180)
- [Patient instructions](#)(see page 180)
- [Remarks](#)(see page 180)

Therapeutic action

- Antibacterial with bacteriostatic activity

Presentation

- 100 mg and 400 mg tablets

Dosage

- Child under 30 kg: 20 mg/kg (15 to 25 mg/kg) once daily
- Child over 30 kg and adult: 15 mg/kg (15 to 25 mg/kg) once daily
- Maximum dose: 1200 mg daily
- Patient with renal impairment: 15 to 25 mg/kg/dose, 3 times per week

Weight (kg)	Daily dose (mg)	400 mg tablet	100 mg tablet
5	75-125	–	1 tab
6	90-150	–	1 tab
7	105-175	–	1 tab
8	120-200	½ tab	–
9	135-225	½ tab	–
10	150-250	½ tab	–
11	165-275	½ tab	–
12	180-300	½ tab	–
13	195-325	½ 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	600	1½ tab	–
36-45	800	2 tab	–
46-55	1000	2 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: retrobulbar optic neuritis.
- The dosage must be carefully adjusted to the weight (adverse effects are dose-dependant), especially for children under 5 years, as it is more difficult to detect visual alterations at this age.
- For the management of adverse effects, see [Appendix 10](#)(see page 214).
- *Pregnancy: no contra-indication*
- *Breast-feeding: no contra-indication*



Monitoring

- Visual acuity and colour discrimination before and during treatment

Patient instructions

- Take with or without food.

Remarks

- For patients on first-line treatment, ethambutol is given as part of a fixed dose combination.
- *Storage: below 25°C* -  - 

Rifabutin (Rfb)

- [Therapeutic action](#)(see page 181)
- [Presentation](#)(see page 181)
- [Dosage](#)(see page 181)
- [Contra-indications, adverse effects, precautions](#)(see page 182)
- [Monitoring](#)(see page 183)
- [Patient instructions](#)(see page 183)
- [Remarks](#)(see page 183)

Therapeutic action

– Antibacterial (rifamycin) with bactericidal activity

Presentation

– 150 mg capsule

Dosage

– Child and adult: 5 to 10 mg/kg once daily
 – Maximum dose: 300 mg daily
 – Patient with severe renal impairment: reduce the dose by half
 Dose adjustment may be required when combined with some antiretrovirals.

Weight (kg)	Daily dose (mg)	150 mg capsule
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	1 caps
16	80-160	1 caps
17	85-170	1 caps
18	90-180	1 caps

19	95-190	1 caps
20	100-200	1 caps
21	105-210	1 caps
22	110-220	1 caps
23	115-230	1 caps
24	120-240	1 caps
25	125-250	1 caps
26	130-260	1 caps
27	135-270	1 caps
28	140-280	1 caps
29	145-290	1 caps
30-35	300	2 caps
36-45	300	2 caps
46-55	300	2 caps
56-70	300	2 caps
> 70	300	2 caps

Contra-indications, adverse effects, precautions

- Do not administer to patients with history of allergy or severe blood disorders (thrombocytopenia, purpura) during a previous treatment with rifamycins.
- Administer with caution to patients with severe hepatic or renal impairment, or with blood disorders.
- May cause: orange-red discolouration of skin and body fluid, gastrointestinal disturbances, hypersensitivity reactions, blood disorders (leukopenia, anaemia, thrombocytopenia), reversible uveitis, hepatic disorders.
- For the management of adverse effects, see [Appendix 10](#)(see page 214).
- Monitor combination with fluconazole (increased risk of ocular toxicity).
- Rifabutin reduces the effect of many drugs (antimicrobials, some hormones, antidiabetics, corticoids, phenytoin, etc.):
 - In women under contraception, use injectable medroxyprogesterone or a nonhormonal contraception or, as a last resort, an oral contraceptive used contains 50 µg ethinylestradiol per tablet.
 - Do not combine with bedaquiline.
 - For other drugs, adjust dosage if necessary.
- *Pregnancy and breast-feeding: avoid except is vital (safety is not established). If used in late pregnancy, administer phytomenadione (vitamin K) to the mother and the newborn to reduce the risk of bleeding disorders.*

Monitoring

- Symptomatic monitoring, liver function in elderly and patients with hepatic disease

Patient instructions

- Take with or without food.
- Rifabutin causes a harmless orange-red discoloration of the skin, urine, saliva and other body fluids.

Remarks

- Rifabutin is use in place of rifampicin in patients taking nevirapine, indinavir, nelfinavir, lopinavir/ritonavir, atazanavir/ritonavir.
- *Storage: below 25°C*

Group 2

- Streptomycin (S)(see page 183)
- Kanamycin (Km)(see page 185)
- Amikacin (Amk)(see page 187)
- Capreomycin (Cm)(see page 190)

Streptomycin (S)

- Therapeutic action(see page 183)
- Presentation(see page 183)
- Dosage(see page 183)
- Contra-indications, adverse effects, precautions(see page 184)
- Monitoring(see page 184)
- Patient instructions(see page 184)
- Remarks(see page 185)

Therapeutic action

- Antibacterial (aminoglycoside) with bactericidal activity

Presentation

- Streptomycin sulfate, eq. 1 g base, vial of powder for injection, for IM injection. DO NOT ADMINISTER BY IV INJECTION.

Dosage

- Child over 30 kg and adult: 12 to 18 mg/kg once daily
- Maximum dose: 1000 mg daily
- Patient over 60 years: 500 to 750 mg once daily
- Patient with severe renal impairment: 12 to 15 mg/kg/dose, 2 or 3 times per week

The daily doses take into account the displacement volume (see note below).

Weight (kg)	Daily dose (mg)	Daily dose - 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

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 the displacement volume is ignored. The risk of error increases the greater the weight of the powder and the smaller the volume of solvent used. For example, when reconstituting capreomycin, the increase in volume due to the displacement value of the powder is 0.7 ml. Therefore if 2 ml of solvent are added to the vial of powder for injection, the final volume will be 2.7 ml and the final concentration 1 g in 2.7 ml, i.e. 390 mg/ml (and not 1 g in 2 ml or 500 mg/ml).

Contra-indications, adverse effects, precautions

- Do not administer to children under 30 kg and patients with history of allergy to an aminoglycoside.
- Administer with caution to patients over 60 years or with pre-existing renal, vestibular or auditory impairment.
- May cause:
 - ototoxicity (vestibular and auditory toxicity), renal toxicity, electrolyte disturbances; rarely, hypersensitivity reactions;
 - local pain after injection.
- For the management of adverse effects, see [Appendix 10](#)(see page 214).
- Avoid or monitor combination with other ototoxic and/or nephrotoxic drugs (furosemide, amphotericin B, tenofovir, etc.).
- *Pregnancy: **CONTRA-INDICATED.** Use capreomycin if an injectable agent is required.*
- *Breast-feeding: no contra-indication*

Monitoring

- Symptomatic monitoring, in particular early detection of ototoxicity (dizziness, tinnitus or hearing loss)

Patient instructions

- Maintain a good fluid intake to limit renal problems.

Remarks

– Storage: below 25°C - 

Reconstituted solution can be kept 24 hours below 25°C and protected from light.

Kanamycin (Km)

- [Therapeutic action](#)(see page 185)
- [Presentation](#)(see page 185)
- [Dosage](#)(see page 185)
- [Contra-indications, adverse effects, precautions](#)(see page 187)
- [Monitoring](#)(see page 187)
- [Patient instructions](#)(see page 187)
- [Remarks](#)(see page 187)

Therapeutic action

– Antibacterial (aminoglycoside) with bactericidal activity

Presentation

– Kanamycin sulfate, eq. 1 g base, vial of powder for injection, for IM injection
Also comes in 1 g base ampoule (250 mg/ml, 4 ml), for IM injection

Dosage

- Child under 30 kg: 15 to 30 mg/kg once daily
- Child over 30 kg and adult: 15 to 20 mg/kg once daily
- Maximum dose: 1000 mg daily
- Patient over 60 years: 10 mg/kg once daily (max. 750 mg daily)
- Patient with severe renal impairment: 12 to 15 mg/kg/dose, 2 or 3 times per week

For the powder for injection, the daily doses take into account the displacement volume (see the [note on displacement volume](#)(see page 184) - powders for injection).

Weight (kg)	Daily dose (mg)	Daily dose - IM injection 1 (see page 0) solution 250 mg/ml	Daily dose - IM injection 1 (see page 0) (1 g powder in 4 ml of water for injection; final volume 4.71 ml; 212 mg/ml)
5	75-150	0.5 ml	0.6 ml
6	90-180	0.5 ml	0.6 ml
7	105-210	0.5 ml	0.6 ml
8	120-240	0.5 ml	0.6 ml
9	135-270	0.8 ml	0.9 ml
10	150-300	0.8 ml	0.9 ml
11	165-330	0.8 ml	0.9 ml

12	180-360	1 ml	1.2 ml
13	195-390	1 ml	1.2 ml
14	210-420	1 ml	1.2 ml
15	225-450	1 ml	1.2 ml
16	240-480	1 ml	1.2 ml
17	255-510	1.5 ml	1.8 ml
18	270-540	1.5 ml	1.8 ml
19	285-570	1.5 ml	1.8 ml
20	300-600	1.5 ml	1.8 ml
21	315-630	1.5 ml	1.8 ml
22	330-660	1.5 ml	1.8 ml
23	345-690	1.5 ml	1.8 ml
24	360-720	1.5 ml	1.8 ml
25	375-750	2 ml	2.4 ml
26	390-780	2 ml	2.4 ml
27	405-810	2 ml	2.4 ml
28	420-840	2 ml	2.4 ml
29	435-870	2 ml	2.4 ml
30-33	500	2 ml	2.4 ml
34-40	625	2.4 ml	3 ml
41-45	750	3 ml	3.4 ml
46-50	875	3.4 ml	4 ml
51-70	1000	4 ml	Entire volume
> 70	1000	4 ml	Entire volume

Contra-indications, adverse effects, precautions

- Do not administer to patients with history of allergy to an aminoglycoside.
- Administer with caution to patients over 60 years or with pre-existing renal, vestibular or auditory impairment.
- May cause:
 - nephrotoxicity, ototoxicity (auditory and vestibular toxicity), electrolyte disturbances; rarely hypersensitivity reactions;
 - local pain after injection.
- For the management of adverse effects, see [Appendix 10](#)(see page 214).
- Avoid or monitor combination with other ototoxic and/or nephrotoxic drugs (furosemide, amphotericin B, tenofovir, etc.).
- Pregnancy: **CONTRA-INDICATED**. Use capreomycin if an injectable agent is required.
- Breast-feeding: no contra-indication

Monitoring

- Symptomatic monitoring, serum creatinine and electrolytes, audiometric test before and during treatment

Patient instructions

- Maintain a good fluid intake to limit renal problems.

Remarks

- Do not mix with other drugs in the same syringe.
- Storage: below 25°C
Reconstituted solution can be kept 24 hours below 25°C; it may darken during the storage but this does not indicate a loss of potency.



(see page 0) For doses less than 1 ml, use a 1 ml syringe graduated in 0.01 ml.

[a(see page 0) b(see page 0)]

Amikacin (Amk)

- [Therapeutic action](#)(see page 187)
- [Presentation](#)(see page 187)
- [Dosage](#)(see page 188)
- [Contra-indications, adverse effects, precautions](#)(see page 189)
- [Monitoring](#)(see page 189)
- [Patient instructions](#)(see page 189)
- [Remarks](#)(see page 189)

Therapeutic action

- Antibacterial (aminoglycoside) with bactericidal activity

Presentation

- Amikacin sulfate, eq. 500 mg base in 2 ml ampoule (250 mg/ml), for IM injection
 - Amikacin sulfate, eq. 500 mg base, vial of powder for injection, for IM injection
- Also comes in 100 mg and 1 g base vials of powder for injection.

Dosage

- Child under 30 kg: 15 to 30 mg/kg once daily
- Child over 30 kg and adult: 15 to 20 mg/kg once daily
- Maximum dose: 1000 mg daily
- Patient over 60 years: 10 mg/kg once daily (max. 750 mg daily)
- Patient with severe renal impairment: 12 to 15 mg/kg/dose, 2 or 3 times per week

Weight (kg)	Daily dose (mg)	Daily dose - IM injection ¹(see page 0) (500 mg in 2 ml ampoule = 250 mg/ml)
5	75-150	0.5 ml
6	90-180	0.5 ml
7	105-210	0.5 ml
8	120-240	0.5 ml
9	135-270	0.8 ml
10	150-300	0.8 ml
11	165-330	0.8 ml
12	180-360	1 ml
13	195-390	1 ml
14	210-420	1 ml
15	225-450	1 ml
16	240-480	1 ml
17	255-510	1.5 ml
18	270-540	1.5 ml
19	285-570	1.5 ml
20	300-600	1.5 ml
21	315-630	1.5 ml
22	330-660	1.5 ml
23	345-690	1.5 ml
24	360-720	1.5 ml
25	375-750	2 ml

26	390-780	2 ml
27	405-810	2 ml
28	420-840	2 ml
29	435-870	2 ml
30-33	500	2 ml
34-40	625	2.5 ml
41-45	750	3 ml
46-50	875	3.5 ml
51-70	1000	4 ml
> 70	1000	4 ml

Contra-indications, adverse effects, precautions

- Do not administer to patients with history of allergy to an aminoglycoside.
- Administer with caution to patients over 60 years or with pre-existing renal, vestibular or auditory impairment.
- May cause:
 - nephrotoxicity, ototoxicity (auditory and vestibular toxicity), electrolyte disturbances; rarely hypersensitivity reactions;
 - local pain after injection.
- For the management of adverse effects, see [Appendix 10](#)(see page 214).
- Avoid or monitor combination with other ototoxic and/or nephrotoxic drugs (furosemide, amphotericin B, tenofovir, etc.).
- *Pregnancy: **CONTRA-INDICATED**. Use capreomycin if an injectable agent is required.*
- *Breast-feeding: no contra-indication*

Monitoring


- Symptomatic monitoring, serum creatinine and electrolytes, audiometric test before and during treatment

Patient instructions

- Maintain a good fluid intake to limit renal problems.

Remarks

- Do not mix with other drugs in the same syringe.
- *Storage: below 25°C - ~~⚡~~*
Reconstituted solution can be kept 24 hours below 25°C; it may darken during the storage but this does not indicate a loss of potency.

 (see page 0) For doses less than 1 ml, use a 1 ml syringe graduated in 0.01 ml.

Capreomycin (Cm)

- [Therapeutic action](#)(see page 190)
- [Presentation](#)(see page 190)
- [Dosage](#)(see page 190)
- [Contra-indications, adverse effects, precautions](#)(see page 191)
- [Monitoring](#)(see page 192)
- [Patient instructions](#)(see page 192)
- [Remarks](#)(see page 192)

Therapeutic action

– Antibacterial (cyclic polypeptide) with bactericidal activity

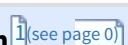
Presentation

– Capreomycin sulfate, eq. 1 g base, vial of powder for injection, for deep IM injection

Dosage

- Child under 30 kg: 15 to 30 mg/kg once daily
- Child over 30 kg and adult: 15 to 20 mg/kg once daily
- Maximum dose: 1000 mg daily
- Patient over 60 years: 10 mg/kg once daily (max. 750 mg daily)
- Patient with severe renal impairment: 12 to 15 mg/kg/dose, 2 or 3 times per week

The daily doses take into account the displacement volume (see the [note on displacement volume](#)(see page 184) - powders for injection).

Weight (kg)	Daily dose (mg)	Daily dose - Deep IM injection  (1 g dans 2 ml d'eau ppi; volume final 2,7 ml; 390 mg/ml)
5	75-150	0.3 ml
6	90-180	0.3 ml
7	105-210	0.4 ml
8	120-240	0.4 ml
9	135-270	0.5 ml
10	150-300	0.5 ml
11	165-330	0.5 ml
12	180-360	0.6 ml

13	195-390	0.6 ml
14	210-420	0.6 ml
15	225-450	0.8 ml
16	240-480	0.8 ml
17	255-510	0.8 ml
18	270-540	0.8 ml
19	285-570	0.8 ml
20	300-600	1 ml
21	315-630	1 ml
22	330-660	1 ml
23	345-690	1 ml
24	360-720	1 ml
25	375-750	1.3 ml
26	390-780	1.3 ml
27	405-810	1.3 ml
28	420-840	1.3 ml
29	435-870	1.3 ml
30-33	500	1.3 ml
34-40	600	1.6 ml
41-45	750	1.8 ml
46-50	800	2 ml
51-70	1000	Entire volume
> 70	1000	Entire volume

Contra-indications, adverse effects, precautions

- Do not administer to patients with history of allergy to capreomycin.
- Administer with caution to patients over 60 years or with pre-existing renal, vestibular or auditory impairment.

- May cause:
 - electrolyte disturbances, nephrotoxicity, ototoxicity (vestibular and auditory toxicity); rarely, hypersensitivity reaction.
 - local pain after injection.
- For the management of adverse effects, see [Appendix 10](#)(see page 214).
- Avoid or monitor combination with other ototoxic and/or nephrotoxic drugs (furosemide, amphotericin B, tenofovir, etc.).
- *Pregnancy: safety is not established however capreomycin is the only option if an injectable agent is required, as aminoglycosides are contra-indicated during pregnancy.*
- *Breast-feeding: no contra-indication*

Monitoring

- Symptomatic monitoring, serum creatinine and electrolytes, audiometric test before and during treatment


Patient instructions

- Maintain a good fluid intake to limit renal problems.

Remarks

- *Storage: below 25°C*

Reconstituted solution must be kept refrigerated (2°C to 8°C) and may be used for up to 24 hours; it may develop a straw colour during the storage but this does not indicate a loss of potency.

 [\(see page 0\)](#) For doses less than 1 ml, use a 1 ml syringe graduated in 0.01 ml.

Group 3

- [Levofloxacin \(Lfx\)](#)(see page 192)
- [Moxifloxacin \(Mfx\)](#)(see page 195)
- [Ofloxacin \(Ofx\)](#)(see page 197)

Levofloxacin (Lfx)

- [Therapeutic action](#)(see page 192)
- [Presentation](#)(see page 192)
- [Dosage](#)(see page 193)
- [Contra-indications, adverse effects, precautions](#)(see page 194)
- [Monitoring](#)(see page 194)
- [Patient instructions](#)(see page 194)
- [Remarks](#)(see page 194)

Therapeutic action

- Antibacterial (fluoroquinolone) with bactericidal activity

Presentation

- 250 mg and 500 mg tablets

Dosage

- Child under 30 kg:
 - 6 months-under 5 years: 15 to 20 mg/kg/day in 2 divided doses
 - 5 years and over: 10 mg/kg once daily
- Child over 30 kg and adult: 750 to 1000 mg once daily
- Maximum dose: 1000 mg daily
- Patient with severe renal impairment: 750 to 1000 mg/dose, 3 times per week

Weight (kg)	Daily dose (mg)	500 mg tablet	250 mg tablet
5	75-100	–	–
6	90-120	–	–
7	105-140	–	–
8	120-160	–	–
9	135-180	–	–
10	150-200	–	–
11	165-220	–	½ tab x 2
12	180-240	–	½ tab x 2
13	195-260	–	½ tab x 2
14	210-280	–	½ tab x 2
15	225-300	–	½ tab x 2
16	240-320	–	½ tab x 2
17	255-340	–	½ tab x 2
18	270-360	–	½ tab x 2
19	285-380	–	½ tab x 2
20	200	–	1 tab
21	210	–	1 tab
22	220	–	1 tab
23	230	–	1 tab
24	240	–	1 tab
25	250	–	1 tab

26	260	–	1 tab
27	270	–	1 tab
28	280	–	1 tab
29	290	–	1 tab
30-35	750	–	3 tab
36-45	750	–	3 tab
46-55	1000	2 tab	–
56-70	1000	2 tab	–
> 70	1000	2 tab	–

Contra-indications, adverse effects, precautions

- Do not administer to patients with history of allergy or tendon damage during a previous treatment with a fluoroquinolone.
- Administer with caution to children, adolescents and patients over 60 years (increased risk of tendon damage); patients with risk factors for QT interval prolongation (heart failure, bradycardia, hypokalaemia, etc.) or history of psychiatric disorders or seizures.
- May cause: gastrointestinal disturbances, headache, central nervous system disorders (dizziness, insomnia, depression, etc.), hypersensitivity reactions, photosensitivity, peripheral neuropathy, myalgia, tendinitis, tendon rupture; rarely, crystalluria.
- For the management of adverse effects, see [Appendix 10](#)(see page 214).
- Avoid or monitor combination with drugs that prolong QT interval (amiodarone, bedaquiline, clofazimine, erythromycin, fluconazole, lopinavir, mefloquine, ondansetron, pentamidine, quinine, etc.) and warfarin.
- Do not administer simultaneously with antacids containing magnesium or aluminium, calcium, iron and zinc salts, didanosine (except enteric-coated formulation): administer 2 hours apart.
- *Pregnancy and breastfeeding: safety is not established, considered as acceptable if vital for the mother.*

Monitoring

- Symptomatic monitoring

Patient instructions

- May be taken with food but do not take milk-based product or antacids or multivitamins when taking a tablet, wait two hours.
- Maintain a good fluid intake.
- Protect your skin from sun.

Remarks

- An oral suspension (25 mg/ml) is available, however because of its high concentration of benzyl alcohol, it is contraindicated in children under 3 years. For long-term use in children no safety data are

available.

– Storage: below 25°C -  - 

Moxifloxacin (Mfx)

- [Therapeutic action](#)(see page 195)
- [Presentation](#)(see page 195)
- [Dosage](#)(see page 195)
- [Contra-indications, adverse effects, precautions](#)(see page 196)
- [Monitoring](#)(see page 197)
- [Patient instructions](#)(see page 197)
- [Remarks](#)(see page 197)

Therapeutic action

– Antibacterial (fluoroquinolone) with bactericidal activity

Presentation

– 400 mg tablet

Dosage

- Child under 30 kg: 7.5 to 10 mg/kg once daily
- Child over 30 kg and adult: 400 mg once daily
- Maximum dose: 400 mg daily

Weight (kg)	Daily dose (mg)	400 mg tablet
5	37.5-50	–
6	45-60	–
7	52.5-70	–
8	60-80	–
9	67.5-90	–
10	75-100	¼ tab
11	82.5-110	¼ tab
12	90-120	¼ tab
13	97.5-130	¼ tab
14	105-140	¼ tab
15	112.5-150	¼ tab

16	120-160	¼ tab
17	127.5-170	¼ tab
18	135-180	½ tab
19	142.5-190	½ tab
20	150-200	½ tab
21	157.5-210	½ tab
22	165-220	½ tab
23	172.5-230	½ tab
24	180-240	½ tab
25	187.5-250	½ tab
26	195-260	½ tab
27	202.5-270	½ tab
28	210-280	½ tab
29	217.5-290	½ 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 history of allergy or tendon damage during a previous treatment with a fluoroquinolone.
- Administer with caution to children, adolescents and patients over 60 years (increased risk of tendon damage); patients with risk factors for QT interval prolongation (heart failure, bradycardia, hypokalaemia, etc.) or history of psychiatric disorders or seizures.
- May cause: gastrointestinal disturbances, headache, central nervous system disorders (dizziness, insomnia, depression, etc.), hypersensitivity reactions, photosensitivity, peripheral neuropathy, myalgia, tendinitis, tendon rupture, QT prolongation; rarely, crystalluria.
- For the management of adverse effects see [Appendix 10](#)(see page 214).
- Avoid or monitor combination with drugs that prolong QT interval (amiodarone, bedaquiline, clofazimine, erythromycin, fluconazole, lopinavir, mefloquine, ondansetron, pentamidine, quinine, etc.) and warfarin.

- Do not administer simultaneously with antacids containing magnesium or aluminium, calcium, iron and zinc salts, didanosine (except enteric-coated formulation): administer 2 hours apart.
- *Pregnancy and breastfeeding: safety is not established, considered as acceptable when vital for the mother.*


Monitoring

- Symptomatic monitoring

Patient instructions

- May be taken with food but do not take milk-based product and antacids and multivitamins when taking a tablet, wait two hours.
- Maintain a good fluid intake.
- Protect your skin from sun.

Remarks

- Moxifloxacin is more frequently associated with QT prolongation than levofloxacin and ofloxacin.
- *Storage: below 25°C* - 

Ofloxacin (Ofx)

- [Therapeutic action](#)(see page 197)
- [Presentation](#)(see page 197)
- [Dosage](#)(see page 197)
- [Contra-indications, adverse effects, precautions](#)(see page 199)
- [Monitoring](#)(see page 199)
- [Patient instructions](#)(see page 199)
- [Remarks](#)(see page 199)

Therapeutic action

- Antibacterial (fluoroquinolone) with bactericidal activity

Presentation

- 200 mg and 400 mg tablets

Dosage

- Child under 30 kg: 15 to 20 mg/kg/day in 2 divided doses
- Child over 30 kg and adult: 800 mg/day in 2 divided doses
- Maximum dose: 800 mg daily
- Patient with severe renal impairment: 600 to 800 mg/dose, 3 times per week

Weight (kg)	Daily dose (mg)	400 mg tablet	200 mg tablet
5	75-100	–	–
6	90-120	–	–
7	105-140	–	–

8	120-160	–	–
9	135-180	–	–
10	150-200	–	½ tab x 2
11	165-220	–	½ tab x 2
12	180-240	–	½ tab x 2
13	195-260	–	½ tab x 2
14	210-280	–	½ tab x 2
15	225-300	–	1 tab (morning) + ½ tab (evening)
16	240-320	–	1 tab (morning) + ½ tab (evening)
17	255-340	–	1 tab (morning) + ½ tab (evening)
18	270-360	–	1 tab (morning) + ½ tab (evening)
19	285-380	–	1 tab (morning) + ½ tab (evening)
20	300-400	–	1 tab x 2
21	315-420	–	1 tab x 2
22	330-440	–	1 tab x 2
23	345-460	–	1 tab x 2
24	360-480	–	1 tab x 2
25	375-500	–	1 tab x 2
26	390-520	–	1 tab x 2
27	405-540	–	1 tab x 2
28	420-560	–	1 tab x 2
29	435-580	–	1 tab x 2
30-35	800	1 tab x 2	–
36-45	800	1 tab x 2	–
46-55	800	1 tab x 2	–
56-70	800	1 tab x 2	–

> 70	800	1 tab x 2	–
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Contra-indications, adverse effects, precautions

- Do not administer to patients with history of allergy or tendon damage during a previous treatment with a fluoroquinolone.
- Administer with caution to children, adolescents and patients over 60 years (increased risk of tendon damage); patients with risk factors for QT interval prolongation (heart failure, bradycardia, hypokalaemia, etc.) or history of psychiatric disorders or seizures.
- May cause: gastrointestinal disturbances, headache, central nervous system disorders (dizziness, insomnia, depression, etc.), hypersensitivity reaction, photosensitivity, peripheral neuropathy, myalgia, tendinitis, tendon rupture; rarely, crystalluria.
- Avoid or monitor combination with drugs that prolong QT interval (amiodarone, bedaquiline, clofazimine, erythromycin, fluconazole, lopinavir, mefloquine, ondansetron, pentamidine, quinine, etc.) and warfarin.
- For the management of adverse effects, see [Appendix 10](#)(see page 214).
- Do not administer simultaneously with antacids containing magnesium or aluminium, calcium, iron and zinc salts, didanosine (except enteric-coated formulation): administer 2 hours apart.
- *Pregnancy and breastfeeding: safety is not established, considered as acceptable when vital for the mother.*

Monitoring

- Symptomatic monitoring

Patient instructions

- May be taken with food but do not take milk-based product and antacids and multivitamins when taking a tablet, wait two hours.
- Maintain a good fluid intake.
- Protect your skin from sun.

Remarks

- *Storage: below 25°C*

Group 4

- [Ethionamide \(Eto\) and Prothionamide \(Pto\)](#)(see page 199)
- [Cycloserine \(Cs\)](#)(see page 202)
- [Para-aminosalicylic acid \(PAS\) and sodium salt of PAS](#)(see page 204)

Ethionamide (Eto) and Prothionamide (Pto)

- [Therapeutic action](#)(see page 200)
- [Presentation](#)(see page 200)
- [Dosage](#)(see page 200)
- [Contra-indications, adverse effects, precautions](#)(see page 201)
- [Monitoring](#)(see page 201)
- [Patient instructions](#)(see page 201)

- [Remarks\(see page 202\)](#)

Therapeutic action

– Antibacterials (thioamides) with bactericidal and bacteriostatic activity

Presentation

– 250 mg tablet

Dosage

- Child under 30 kg: 15 to 20 mg/kg/day in 2 divided doses or once daily if tolerated
- Child over 30 kg and adult: 500 to 750 mg/day in 2 divided doses or once daily if tolerated
- Maximum dose: 1000 mg daily
- Patient with severe renal impairment: 250 to 500 mg/day

Weight (kg)	Daily dose (mg)	250 mg tablet
5	75-100	–
6	90-120	–
7	105-140	½ tab
8	120-160	½ tab
9	135-180	½ tab
10	150-200	½ tab
11	165-220	1 tab
12	180-240	1 tab
13	195-260	1 tab
14	210-280	1 tab
15	225-300	1 tab
16	240-320	1 tab
17	255-340	1 tab
18	270-360	1 tab
19	285-380	1½ tab
20	300-400	1½ tab
21	315-420	1 ½ tab

22	330-440	1½ tab
23	345-460	1½ tab
24	360-480	1½ 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 mellitus or depression.
- May cause:
 - frequent gastrointestinal disturbances (nausea, vomiting, gastritis, stomatitis, diarrhoea, abdominal pain, metallic taste, etc.);
 - occasionally: endocrine disorders (hypothyroidism, gynecomastia, alopecia, etc.), hypoglycaemia, depression, anxiety, dizziness, hepatitis, peripheral or optic neuropathy, hypersensitivity reactions.
- For the management of adverse effects, see [Appendix 10](#)(see page 214).
- Monitor combination with cycloserine (increased risk of seizure) and para-aminosalicylic acid (increased risk of hypothyroidism and gastrointestinal disturbances).
- *Pregnancy: avoid (potentially teratogenic)*
- *Breast-feeding: may be used. Observe the infant for adverse effects.*


Monitoring

- Symptomatic monitoring, liver and thyroid function

Patient instructions

- Take with food or at bedtime to limit gastrointestinal disturbances.
- Avoid alcohol during treatment.

Remarks

- To increase tolerance, start with a low dose (250 mg/day) then, increase the dose over 1 to 2 weeks to achieve the target dose.
- Ethionamide and prothionamide are used for the same indication at the same dosage.
- Storage: below 25°C - 

Cycloserine (Cs)

- [Therapeutic action](#)(see page 202)
- [Presentation](#)(see page 202)
- [Dosage](#)(see page 202)
- [Contra-indications, adverse effects, precautions](#)(see page 203)
- [Monitoring](#)(see page 204)
- [Patient instructions](#)(see page 204)
- [Remarks](#)(see page 204)

Therapeutic action

- Antibacterial with bacteriostatic activity

Presentation

- 250 mg capsule

Dosage

- Child under 30 kg: 10 to 20 mg/kg/day in 2 divided doses, or once daily depending on available formulation and tolerance
- Child over 30 kg and adult: 500 to 750 mg/day in 2 divided doses; some patients may tolerate once daily dosing.
- Maximum dose: 1000 mg daily
- Patients with severe renal impairment: 250 mg once daily or 500 mg/dose, 3 times per week

Weight (kg)	Daily dose (mg)	250 mg capsule
5	50-100	–
6	60-120	–
7	70-140	–
8	80-160	–
9	90-180	–
10	100-200	–
11	110-220	–
12	120-240	–

13	130-260	1 caps
14	140-280	1 caps
15	150-300	1 caps
16	160-320	1 caps
17	170-340	1 caps
18	180-360	1 caps
19	190-380	1 caps
20	200-400	1 caps
21	210-420	1 caps
22	220-440	1 caps
23	230-460	1 caps
24	240-480	1 caps
25	250-500	1 caps
26	260-520	1 caps x 2
27	270-540	1 caps x 2
28	280-560	1 caps x 2
29	290-580	1 caps x 2
30-35	500	1 caps x 2
36-45	500	1 caps x 2
46-55	500	1 caps x 2
56-70	750	1 caps (morning) + 2 caps (evening)
> 70	750	1 caps (morning) + 2 caps (evening)

Contra-indications, adverse effects, precautions

- Avoid if possible in patients with epilepsy, depression, psychosis, severe anxiety, history of neurological or psychiatric disorders, alcohol dependence. However, if cycloserine is essential to the regimen, it can be administered under close monitoring.
- Administer with caution to patients with renal impairment.
- May cause:

- neurotoxic effects: seizure, headache, lethargy, confusion, personality change, dizziness, drowsiness, anxiety, psychosis, depression, suicidal ideation; rarely, peripheral neuropathy.
- hypersensitivity reactions.
- For the management of adverse effects, see [Appendix 10](#)(see page 214).
- Avoid or monitor combination with isoniazid, ethionamide, prothionamide (increased risk of neurotoxic effects).
- Administer concomitantly pyridoxine (vitamin B₆) to prevent neurotoxic effects (child: 5 to 10 mg/day; adult: 50 mg per 250 mg of cycloserine/day).
- *Pregnancy: safety is not established, no known teratogenicity. To prevent neurotoxic effects, administer pyridoxine as above.*
- *Breast-feeding: no contra-indication. To prevent neurotoxic effects, administer pyridoxine as above. Supplement the breast-fed infant with pyridoxine (5 mg/day).*


Monitoring

- Symptomatic monitoring, in particular early detection of depression and behaviour changes

Patient instructions

- Take capsules with water before or after meals.
- Avoid alcohol during treatment.

Remarks

- To increase tolerance, start with a low dose (250 mg/day) then, increase the dose over 1 to 2 weeks to achieve the target dose.
- *Storage: below 25°C* - 

Para-aminosalicylic acid (PAS) and sodium salt of PAS

- [Therapeutic action](#)(see page 204)
- [Presentation](#)(see page 204)
- [Dosage \(expressed in PAS\)](#)(see page 205)
- [Contra-indications, adverse effects, precautions](#)(see page 206)
- [Monitoring](#)(see page 206)
- [Patient instructions](#)(see page 206)
- [Remarks](#)(see page 206)

Therapeutic action

- Antibacterial with bacteriostatic activity

Presentation

- Para-aminosalicylic acid (PAS): delayed-release granules, 4 g sachet (PASER® Jacobus)
- Para-aminosalicylate sodium (sodium salt of PAS or PAS-sodium):
- Powder for oral solution, 5.52 g sachet (PAS-Na® Olainfarm)
- 60% w/w delayed-release granules, 9.2 g sachet or 100 g jar (MONOPAS® Macleods)

One 4 g sachet of PAS (PASER® Jacobus) = one 5.52 g sachet of PAS-sodium (PAS-Na® Olainfarm) = one 9.2 g sachet of PAS sodium 60 % w/w (MONOPAS® Macleods).

Dosage (expressed in PAS)

- Child under 30 kg: 200 to 300 mg/kg/day in 2 to 3 divided doses (max. 8 g daily)
- Child over 30 kg and adult: 8 g once daily if tolerated or in 2 divided doses (max. 12 g daily)
- Patient with severe renal impairment: 8 g/day in 2 divided doses

For paediatric dosing: PAS (Jacobus) comes with a dosage scoop graduated in milligrams; PAS sodium (Macleods) with a measuring spoon graduated in grams.

Weight (kg)	Daily dose (in mg of PAS)	PASER® Jacobus (mg)	PAS-Na® Olainfarm (sachet)	MONOPAS 9.2 g® Mcleods (g)
5	1000-1500	500 mg x 2	–	1.5 g x 2
6	1200-1800	750 mg x 2	–	1.5 g x 2
7	1400-2100	750 mg x 2	–	2 g x 2
8	1600-2400	1000 mg x 2	–	2 g x 2
9	1800-2700	1000 mg x 2	–	3 g x 2
10	2000-3000	1000 mg x 2	–	3 g x 2
11	2200-3300	1500 mg x 2	–	3 g x 2
12	2400-3600	1500 mg x 2	–	3 g x 2
13	2600-3900	1500 mg x 2	–	3 g x 2
14	2800-4200	1500 mg x 2	–	4 g x 2
15	3000-4500	2000 mg x 2	–	4 g x 2
16	3200-4800	2000 mg x 2	–	4 g x 2
17	3400-5100	2000 mg x 2	–	4 g x 2
18	3600-5400	2000 mg x 2	–	4 g x 2
19	3800-5700	2500 mg x 2	–	6 g x 2
20	4000-6000	2500 mg x 2	–	6 g x 2
21	4200-6300	2500 mg x 2	–	6 g x 2
22	4400-6600	2500 mg x 2	–	6 g x 2
23	4600-6900	3000 mg x 2	–	6 g x 2
24	4800-7200	3000 mg x 2	–	6 g x 2
25	5000-7500	3000 mg x 2	–	8 g x 2

26	5200-7800	3000 mg x 2	–	8 g x 2
27	5400-8000	3500 mg x 2	–	8 g x 2
28	5600-8000	3500 mg x 2	–	8 g x 2
29	5800-8000	3500 mg x 2	–	8 g x 2
30-70	8 g	2 sachets	2 sachets	2 sachets
> 70	8-12 g	2-3 sachets	2-3 sachets	2-3 sachets

Contra-indications, adverse effects, precautions

- Avoid or administer with caution to patients with hepatic or renal impairment or gastric ulcer.
- May cause:
 - frequent gastrointestinal disturbances (nausea, vomiting, gastritis, diarrhoea);
 - rarely: hypothyroidism, hepatitis, blood disorders, hypersensitivity reactions.
- For the management of adverse effects, see [Appendix 10](#)(see page 214).
- Monitor combination with ethionamide/prothionamide (increased risk of hypothyroidism and gastrointestinal disturbances).
- *Pregnancy: safety is not established, no known teratogenicity.*
- *Breast-feeding: no contra-indication*



Monitoring

- Symptomatic monitoring, liver and thyroid function

Patient instructions

- Take the granules mixed with acidic juices (apple or orange).
- Do not chew the granules.
- Do not use if the sachet is swollen or if granules are dark brown or purple.
- Shells of the granules may appear in the stool.

Remarks

- To increase tolerance, start with a low dose (4 g/day in 2 divided doses) then, increase the dose over 1 to 2 weeks to achieve the target dose.
- PAS and PAS-sodium may come in various strengths or proportions. As daily dosages are expressed in PAS, always check the content of PAS in the product: 1 g of PAS is equivalent to 1.38 g of PAS-sodium (e.g. one 9.2 g sachet of MONOPAS® 60% w/w contains 600 mg of PAS-sodium equivalent to approximately 435 mg of PAS per 1 g of granules).
- *Storage:*
 - PAS: below 15°C; may be stored at 40°C for 8 weeks maximum;
 - PAS-sodium: below 25°C -  - 

Group 5

- Clofazimine (Cfz)(see page 207)
- Linezolid (Lzd)(see page 209)

- [Amoxicillin/Clavulanic acid \(Amx/Clv\)](#)(see page 211)

Clofazimine (Cfz)

- [Therapeutic action](#)(see page 207)
- [Presentation](#)(see page 207)
- [Dosage](#)(see page 207)
- [Contra-indications, adverse effects, precautions](#)(see page 208)
- [Monitoring](#)(see page 209)
- [Patient instructions](#)(see page 209)
- [Remarks](#)(see page 209)

Therapeutic action

– Antibacterial with in vitro activity (no evidence in vivo)

Presentation

– 50 mg and 100 mg soft capsules

Dosage

– Child under 30 kg: 2 to 3 mg/kg/day

– Child over 30 kg and adult: 200 to 300 mg/day for 2 months then 100 mg/day

The daily dose is administered in 2 divided doses or once daily, depending on tolerance and available formulation.

Weight (kg)	Daily dose (mg)	100 mg capsule	50 mg capsule
5	10-15	–	–
6	12-18	–	–
7	14-21	–	–
8	16-24	–	–
9	18-27	–	–
10	20-30	–	–
11	22-33	–	–
12	24-36	–	–
13	26-39	–	–
14	28-42	–	–
15	30-45	–	–

16	32-48	–	1 caps
17	34-51	–	1 caps
18	36-54	–	1 caps
19	38-57	–	1 caps
20	40-60	–	1 caps
21	42-63	–	1 caps
22	44-66	–	1 caps
23	46-69	–	1 caps
24	48-72	–	1 caps
25	50-75	–	1 caps
26	52-78	–	1 caps
27	54-81	–	1 caps
28	56-84	–	1 caps
29	58-87	–	1 caps
30-35	First 2 months: 200 to 300 mg then reduce to 100 mg	First 2 months: 1 caps x 2 or 2 caps (morning) + 1 caps (evening) then 1 caps	–
36-45			–
46-55			–
56-70			–
> 70			–

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:
 - gastrointestinal disturbances (nausea, vomiting, abdominal pain, diarrhoea) sometimes severe (acute abdomen presentation, intestinal bleeding);
 - pink, red or brownish-black discolouration of skin, body fluids and faeces;
 - eye and skin dryness and irritation, hypersensitivity reactions, photosensitivity;
 - QT prolongation (newly reported).
- For the management of adverse effects, see [Appendix 10](#)(see page 214).
- Pregnancy: not recommended (safety is not established)

– *Breast-feeding: can be used; may cause breast milk discolouration and reversible skin discolouration in breastfed infants.*


Monitoring

– Symptomatic monitoring

Patient instructions

– Take with food to improve gastrointestinal tolerance.
 – Protect your skin from sun.
 – Clofazimine may cause reversible discolouration of the skin, conjunctiva, faeces, urine, sweat, tears, saliva, sputum, breast-milk, etc. However, it may take months to years to disappear after stopping treatment.

Remarks

– *Storage: below 25°C* - 

Linezolid (Lzd)

- [Therapeutic action](#)(see page 209)
- [Presentation](#)(see page 209)
- [Dosage](#)(see page 209)
- [Contra-indications, adverse effects, precautions](#)(see page 211)
- [Monitoring](#)(see page 211)
- [Patient instructions](#)(see page 211)
- [Remarks](#)(see page 211)

Therapeutic action

– Antibacterial (oxazolidinone) with bactericidal activity

Presentation

– 600 mg tablet

Also comes in 400 mg tablet and 100 mg/5 ml powder for oral suspension.

Dosage

– Child under 30 kg: 30 mg/kg/day in 3 divided doses
 – Child over 30 kg and adult: 600 mg once daily
 – Maximum dose: 600 mg daily

Weight (kg)	Daily dose (mg)	600 mg tablet	100 mg per 5 ml oral suspension
5	150	–	2.5 ml x 3
6	180	–	3 ml x 3
7	210	–	3.5 ml x 3

8	240	–	4 ml x 3
9	270	–	4.5 ml x 3
10	300	–	5 ml x 3
11	330	–	5.5 ml x 3
12	360	–	6 ml x 3
13	390	–	6.5 ml x 3
14	420	–	7 ml x 3
15	450	–	7.5 ml x 3
16	480	–	8 ml x 3
17	510	–	8.5 ml x 3
18	540	–	9 ml x 3
19	570	–	9.5 ml x 3
20	600	–	10 ml x 3
21	600	–	10 ml x 3
22	600	–	10 ml x 3
23	600	–	10 ml x 3
24	600	–	10 ml x 3
25	600	–	10 ml x 3
26	600	–	10 ml x 3
27	600	–	10 ml x 3
28	600	–	10 ml x 3
29	600	–	10 ml x 3
30-35	600	1 tab	–
36-45	600	1 tab	–
46-55	600	1 tab	–
56-70	600	1 tab	–

> 70	600	1 tab	–
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Contra-indications, adverse effects, precautions

- Administer with caution to patients with blood disorders or hypertension.
- May cause:
 - myelosuppression (decreased level of platelets after 10-14 days of treatment, decreased level of white blood cells, and anaemia), lactic acidosis;
 - optic and peripheral neuropathy (can be irreversible), diarrhoea, nausea.
- For the management of adverse effects, see [Appendix 10](#)(see page 214).
- Avoid or monitor combination with serotonergic drugs such as tricyclic antidepressants (e.g. amitriptyline), selective serotonin reuptake inhibitors (e.g. fluoxetine, paroxetine), lithium, etc., as it may cause a serotonin syndrome.
- Administer concomitantly pyridoxine (vitamin B₆) to prevent neurotoxic effects (child: 5 to 10 mg/day; adult: 50 mg/day).
- *Pregnancy: avoid (safety is not established), except if vital. To prevent neurotoxic effects, administer pyridoxine as above.*
- *Breast-feeding: avoid (safety is not established), except if vital. To prevent neurotoxic effects, administer pyridoxine as above. Supplement the breast-fed infant with pyridoxine (5 mg/day).*

Monitoring

- Symptomatic monitoring, visual acuity and colour discrimination before and during treatment; complete blood count weekly (first month), then monthly, and as needed based on symptoms

Patient instructions

- Take with or without food.

Remarks

- *Storage: no special temperature requirements*

Amoxicillin/Clavulanic acid (Amx/Clv)

- [Therapeutic action](#)(see page 211)
- [Presentation](#)(see page 211)
- [Dosage \(expressed in amoxicillin\)](#)(see page 212)
- [Contra-indications, adverse effects, precautions](#)(see page 213)
- [Monitoring](#)(see page 213)
- [Patient instructions](#)(see page 213)
- [Remarks](#)(see page 213)

Therapeutic action

- Antibacterial (penicillin) with possible bactericidal activity

Presentation

- 875 mg amoxicillin/125 mg clavulanic acid tablet (ratio 7:1)
- 400 mg amoxicillin/57 mg clavulanic acid/5 ml, powder for oral suspension (ratio 7:1)
- 500 mg amoxicillin/62.5 mg clavulanic acid tablet (ratio 8:1)
- 500 mg amoxicillin/62.5 mg clavulanic acid/5 ml, powder for oral suspension (ratio 8:1)

Dosage (expressed in amoxicillin)

- Child and adult: 80 mg/kg/day in 2 divided doses
- Maximum dose: 3000 mg daily
- Patient with severe renal impairment: 1000 mg/day in 2 divided doses

Weight (kg)	Daily dose (mg)	875 mg/125 mg tablet	400 mg/57 mg per 5 ml oral suspension
5	400	–	2.5 ml x 2
6	480	–	3 ml x 2
7	560	–	3.5 ml x 2
8	640	–	4 ml x 2
9	720	–	4.5 ml x 2
10	800	–	5 ml x 2
11	880	–	5.5 ml x 2
12	960	–	6 ml x 2
13	1040	–	6.5 ml x 2
14	1120	–	7 ml x 2
15	1200	–	7.5 ml x 2
16	1280	–	8 ml x 2
17	1360	–	8.5 ml x 2
18	1440	–	9 ml x 2
19	1520	–	9.5 ml x 2
20	1600	–	10 ml x 2
21	1680	1 tab x 2	–
22	1760	1 tab x 2	–
23	1840	1 tab x 2	–
24	1920	1 tab x 2	–
25	2000	1 tab x 2	–
26	2080	1 tab (morning) + 1 ½ tab (evening)	–

27	2160	1 tab (morning) + 1 ½ tab (evening)	–
28	2240	1 tab (morning) + 1 ½ tab (evening)	–
29	2320	1 tab (morning) + 1 ½ tab (evening)	–
30-35	2600	1 tab (morning) + 2 tab (evening)	–
36-45	2600	1 tab (morning) + 2 tab (evening)	–
46-55	2600	1 tab (morning) + 2 tab (evening)	–
56-70	2600	1 tab (morning) + 2 tab (evening)	–
> 70	2600	1 tab (morning) + 2 tab (evening)	–

Contra-indications, adverse effects, precautions

- Do not administer to patients with history of allergy to penicillins or hepatic disorders during a previous treatment with amoxicillin/clavulanic acid.
- Administer with caution to patients with hepatic impairment or history of allergy to cephalosporins (cross-sensitivity may occur).
- May cause: diarrhoea, hypersensitivity reactions, jaundice and cholestatic hepatitis.
- *Pregnancy: no contra-indication*
- *Breast-feeding: no contra-indication*

Monitoring

- Symptomatic monitoring


Patient instructions

- Take with food.

Remarks

- The ratio of amoxicillin/clavulanic acid varies according to the manufacturer (2/1, 4/1, 6/1, 8/1, 7/1, 14/1, 16/1). The daily dose and administration schedule may vary depending on the formulation used.

– *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.

Patient instructions

- [Patients under first-line regimen](#)(see page 214)
- [Patients treated for DR-TB](#)(see page 214)

Patients under first-line regimen

First-line anti-TB drugs are usually well tolerated. However, inform the patient that s/he 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;
- Dizziness or hearing loss;
- Blurred vision, reduced visual acuity, blind spot, green-red colour blindness, eye pain, sensitivity to light;
- Muscle twitching or weakness;
- Pain or swelling in the joints.

Patients treated for DR-TB

Inform the patient that s/he should seek urgent 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;
- Dizziness or hearing loss;
- Blurred vision, reduced visual acuity, blind spot, green-red colour blindness, eye pain, sensitivity to light;
- Muscle twitching or weakness;
- Pain or swelling in the joints;
- Personality changes (depression, aggressive behaviour, anxiety);
- Severe abdominal upset or severe nausea, vomiting, black or bloody stools;
- Pain, burning, swelling of a tendon or muscle;
- Unusual bleeding.

Appendix 10. Management of common adverse effects in adults on DR-TB regimens

See references [5](#)(see page 251) and [6](#)(see page 251)

The management of common adverse effects for first-line regimens is described in Chapter 9, [Section 9.5](#)(see page 78). However, as some patients on second-line regimens are also on first-line anti-TB drugs, the first-line anti-TB drugs are also included in this appendix.

- [Abdominal pain](#)(see page 215)
- [Alopecia](#)(see page 215)
- [Arthralgias](#)(see page 215)
- [Auditory toxicity \(hearing loss\)](#)(see page 216)

- Depression(see page 216)
- Diarrhoea(see page 216)
- Electrolyte loss(see page 217)
- Fungal infection(see page 217)
- Gastritis(see page 217)
- Gynecomastia(see page 218)
- Haematologic abnormalities(see page 218)
- Hepatitis(see page 218)
- Hypothyroidism(see page 219)
- Lactic acidosis(see page 219)
- Metallic taste(see page 220)
- Nausea/vomiting(see page 220)
- Nephrotoxicity(see page 221)
- Optic neuritis(see page 222)
- Peripheral neuropathy(see page 222)
- Photosensitivity(see page 222)
- Psychosis(see page 223)
- QT prolongation(see page 223)
- Seizures(see page 224)
- Skin reactions(see page 225)
- Suicidal ideation(see page 226)
- Tendinitis/tendon rupture(see page 226)
- Vestibular toxicity(see page 227)

Abdominal pain

Suspected agents: Eto/Pto, Cfz, Lzd

Abdominal pain is most commonly [gastritis\(see page 217\)](#). However, abdominal pain can also be the early sign of serious adverse effects such as hepatitis, pancreatitis, and lactic acidosis in particular when Lzd is used. See also management of [hepatitis\(see page 218\)](#) and [lactic acidosis\(see page 219\)](#). Amylase (and if possible lipase) and lactate testing should be available to programmes using second-line anti-TB drugs, especially if used in conjunction with ART.

Deposition of Cfz crystals can be associated with severe abdominal pain (acute abdomen presentation). Cfz should be stopped in patients presenting with painful abdomen.

Alopecia

Suspected agents: H, Eto/Pto

Temporary and mild hair loss can occur with either H or Eto/Pto in the first months of treatment. Significant cosmetic change has not been reported.

Arthralgias

Suspected agents: Z, FQs, Bdq

Arthralgias generally diminish over time. Serum uric acid levels may be elevated, but this is of little clinical relevance and anti-hyperuricemic therapy is of no proven benefit in these patients.

Begin therapy with an anti-inflammatory agent, e.g. **ibuprofen** PO: 400 to 800 mg 3 times daily.

Paracetamol PO: 500 to 1000 mg 2 to 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) provided this does not compromise the effectiveness of the treatment.

Auditory toxicity (hearing loss)

Suspected agents: aminoglycosides, Cm

Hearing loss and/or tinnitus are signs of auditory toxicity. Auditory toxicity is most commonly observed in patients receiving large cumulative doses of aminoglycosides or Cm.

Concomitant use of loop diuretics (furosemide), particularly in the setting of renal insufficiency, may exacerbate ototoxicity. Patients starting therapy with hearing loss at baseline are at the highest risk.

Hearing loss is generally not reversible upon discontinuation of therapy. Audiometry for baseline and/or follow-up testing is required to pick up early hearing loss. Change to Cm three times a week if currently on an aminoglycoside. If no improvement, consider replacing the drug responsible by an oral Group 4 anti-TB drug or Bdq. If replacement is not possible, consider reducing the dose or discontinuing the agent provided this does not significantly compromise the effectiveness of the treatment. Progression can be prevented once the offending agent is discontinued. However, continuation of injectable therapy despite hearing loss almost always results in deafness.

Depression

Suspected agents: Cs, FQs, Eto/Pto

Anti-TB therapy may contribute to depression. Depressive symptoms may fluctuate during therapy. History of depression may increase the risk of developing depression during treatment but is not a contraindication to use of any of the above agents.

Interventions include psychological support to patient (and family if needed) as well as antidepressant therapy at usual doses if necessary.

Avoid serotonin reuptake inhibitors and tricyclic antidepressants with Lzd (risk of serotonin syndrome).

Always give pyridoxine to patients receiving Cs (50 mg of pyridoxine for every 250 mg of Cs).

Consider lowering the dose or discontinuing a suspected anti-TB drug, provided this does not compromise the effectiveness of the treatment.

Diarrhoea

Suspected agents: PAS, FQs, Eto/Pto, Amx/Clv, lpm/Cln

Diarrhoea, along with increased flatus and cramping, can cause significant difficulty for patients, but very rarely does it lead to discontinuation of medication.

PAS often causes diarrhoea with the initiation of medication. Inform patients that diarrhoea usually resolves or improves considerably after some weeks.

For diarrhoea with no blood in stools and no fever, **loperamide** PO (4 mg followed by 2 mg after each loose stool to a maximum of 10 mg/day) may be used intermittently, especially when patients need to attend social functions or return to work, but not daily. Encourage patients to tolerate some degree of loose stools and flatulence. Prevent (encourage fluid intake) or treat dehydration.

For severe diarrhoea, particularly if associated with blood in stools, severe abdominal pain, or fever $> 38.5^{\circ}\text{C}$, consider other causes such as acute bacterial enteritis, or pseudomembranous colitis (*C. difficile*) related to FQs. Do not use loperamide in bloody diarrhoea or diarrhoea associated with fever.

Electrolyte loss

Suspected agents: Cm, aminoglycosides

Electrolyte abnormalities are much more commonly seen with Cm but can occur with any of the injectable agents. Consider switching Cm to an aminoglycoside if possible. Electrolyte abnormalities are typically reversible with discontinuation of therapy.

Other potential causes of electrolyte deficiency (vomiting and diarrhoea the two most common) should be treated if present.

Serum electrolytes should be routinely measured before treatment, then as described in Chapter 10.

Mild to moderate hypokalaemia (serum potassium level of 2.5-3.4 mmol/L) requires potassium replacement: **potassium chloride** PO, 10 to 20 mmol 2 to 4 times per day (20 to 80 mmol/day), depending upon the severity of the hypokalaemia. Sequential monitoring of serum potassium levels is essential to monitor the response.

For anyone found to have hypokalaemia, consider empiric oral magnesium replacement if serum magnesium level cannot be measured. Untreated hypomagnesaemia may lead to a syndrome of "resistance" to correction of hypokalaemia. Magnesium should be taken at least 2 hours before or 4 to 6 hours after the FQs.

If clinical signs of severe hypokalaemia develop (i.e., marked muscle weakness, cardiac arrhythmias) or if serum potassium level is < 2.5 mmol/L, IV replacement is urgently required.

Fungal infection

Suspected agents: FQs

Vaginal, penile, skin fold and oral candidiasis may occur, especially in patients taking FQs. Topical antifungals or short-course oral antifungals are usually effective.

Gastritis

Suspected agents: PAS, Eto/Pto, FQs, H, E, Z

Gastritis is characterised by epigastric burning or discomfort, a sour taste in the mouth, abdominal pain prior to or relieved by eating.

Haematemesis and melena (black stools) are symptoms of a bleeding gastric ulcer and require urgent intervention.

For gastritis, dyspepsia, belching, hyperacidity, and epigastric pain:

omeprazole PO: 10 to 20 mg once daily. The dose can be increased to 20 mg twice daily.

For acid-related dyspepsia: histamine H₂-antagonists such as ranitidine may be an alternative.

Antacids should not be administered simultaneously with FQs as they can interfere with the absorption of FQs.

Gynecomastia

Suspected agents: Eto/Pto

Eto/Pto may cause breast enlargement that can be a troublesome, especially for male patients.

Galactorrhoea has also been reported. Encourage patients to tolerate this adverse effect. Symptoms resolve when treatment is stopped.

Haematologic abnormalities

Suspected agents: Lzd, R, Rfb, all anti-TB drugs

Leukopenia, thrombocytopenia, anaemia, and coagulation abnormalities can exceptionally occur with a number of anti-TB drugs.

Thrombocytopenic purpura is more common with intermittent use of R. Stop R immediately and treat aggressively, shock, renal failure and thrombocytopenia. R should never be reintroduced.

Lzd can cause profound myelosuppression (suppression of white blood cells, red blood cells and platelets). In this case, stop Lzd and manage with blood transfusions if needed. Lzd should never be reintroduced.

Hepatitis

Suspected agents: Z, H, R, Eto/Pto, PAS

Symptoms include nausea, vomiting, jaundice, scleral icterus, tea-colored urine, pale stool, and diminished appetite.

Other causes of hepatitis include infections (e.g., hepatitis A, B, C, D, E; cytomegalovirus, leptospirosis, Epstein-Barr virus, yellow fever, rubella), alcohol use, and other medications (e.g., anti-epileptics, paracetamol, sulfa drugs, erythromycin).

Routine screening of liver function is recommended as describe in Chapter 10. A mild transient elevation of transaminases may be observed in the first months of therapy and usually remains asymptomatic. However, a significant hepatitis is usually symptomatic and the diagnosis is confirmed by a significant elevation in serum transaminases.

If the patient has symptoms of hepatitis, check liver function:

- If liver enzymes are elevated but less than 5 times normal, continue anti-TB therapy but follow liver function each week.
- If liver enzymes are greater than 5 times normal limit, stop all anti-TB medications and control liver function weekly. If liver enzymes continue to increase, then progressive drug-induced hepatitis or an unrelated cause must be suspected.
- If liver enzymes plateau or revert to normal and symptoms resolve, restart anti-TB drugs, beginning with the agents least likely to be hepatotoxic (Cm or the aminoglycoside-E-FQ-Cs) and then the following agents can be resumed one at a time over a period of one week, while checking liver enzymes at the end of each week: PAS-Eto/Pto-R-Z and H. The offending agent can generally be identified in this manner and discontinued or replaced. Many providers add the most likely culprit last in the challenge,

Hypothyroidism

Suspected agents: Eto/Pto, PAS

Symptoms of hypothyroidism include fatigue, somnolence, cold intolerance, dry skin, coarse hair, and constipation, as well as occasional depression and psychosis.

Thyroid enlargement and delayed deep tendon reflexes may be encountered on examination.

In cases of hypothyroidism, the diagnosis is confirmed by a serum level of thyroid stimulating hormone (TSH) greater than 10.0 IU/ml.

Both Eto/Pto and PAS interfere with hormone synthesis and when used together, hypothyroidism can be common. In most cases of treatment-induced hypothyroidism, the patient can be continued on both medicines with replacement hormone therapy.

Most adults require **levothyroxine** 100 to 150 micrograms daily. Adjust the dose in the following manner:

- Start levothyroxine with:
 - 75 to 100 micrograms daily in young adults;
 - 50 micrograms daily in older patients;
 - 25 micrograms daily in patients with significant cardiovascular disease.
- Monitor TSH every one to two months and increase dose by 12.5-25 micrograms until TSH normalizes below 5.00 IU/ml. Adjust dose more slowly in the elderly and patients with cardiovascular disease.

Thyroid dysfunction resolves upon discontinuation of TB therapy. Hormone replacement may be discontinued several months after treatment completion.

Lactic acidosis

Suspected agent: Lzd

Lactic acidosis is a potentially life-threatening build up of lactic acid in the body, due to mitochondrial toxicity of certain drugs. Signs and symptoms include nausea and vomiting, abdominal pain, and increased respiration rate. It can be detected by measurement of blood lactate and pH. It can occur with prolonged use of Lzd. Stop Lzd if it occurs.

Lactic acidosis can also be associated with ART.

Metallic taste

Suspected agents: Eto/Pto, FQs

Encourage the patient to tolerate this adverse effect. Normal taste returns when treatment is stopped.

Nausea/vomiting

Suspected agents: Eto/Pto, PAS, Z, Amx/Clv, Cfz, Lzd, Ipm/Cln, Bdq

Nausea and vomiting are frequent, especially during the first few weeks of therapy.

Eto/Pto and PAS can be initiated with gradual increase over 1 to 2 weeks to help avoid nausea and vomiting.

Anti-emetics are commonly used either as needed or on a daily standing basis (typically 30 minutes before the drugs intake). Histamine H₂-antagonists (ranitidine) or proton pump inhibitors (omeprazole) can also provide relief.

For patients with significant vomiting (especially if diarrhoea is associated), hydration status should be assessed and dehydration corrected as necessary.

Rarely for refractory vomiting, temporary discontinuation or dose reduction of the suspected agent is warranted.

A strategy to figure out which medicine is causing the nausea and vomiting is to give a trial stoppage of a medicine for two or three days and then add it back gradually increasing the dose (advise the patient the medicine will be increased back to a therapeutic dose in a manner that will be better tolerated). Stop first Eto/Pto or PAS as they are more likely to cause nausea and vomiting.

The following describes a stepwise approach to the management of nausea and vomiting:

Always check for danger signs associated with nausea and vomiting:

- Signs of dehydration (thirst, dry mouth, sunken eyes, low blood pressure)
- Serum electrolytes if vomiting
- Signs of hepatitis (jaundice, right-sided abdominal pain)
- Ask if there is any blood in the vomit and melena, if so address possible bleeding ulcers

For all patients, nausea and vomiting should be aggressively treated with a three phase approach:

– **First phase - Adjust drug administration without lowering doses:**

- Administer drugs causing nausea at night.
- Administer PAS one hour after taking other anti-TB drugs.
- If the patient receives PAS once daily, give in 2 divided doses (DOT must be done for both doses).
- Encourage the patient: nausea and vomiting often improve over the first weeks and may resolve entirely with time.

– **Second phase - Administer anti-emetics:**

- Start with **metoclopramide** PO: 10 mg 30 minutes before anti-TB drugs, maximum 15 mg twice daily. Do not use metoclopramide if neurological problems develop.
- If symptoms persist, metoclopramide can be continued with the addition of ondansetron or promethazine:

ondansetron PO: 8 mg twice daily (30 minutes before anti-TB drugs). Ondansetron can increase the QT interval and it is recommended to avoid this drug in patients taking medicines that significantly increase the QT interval.

If ondansetron is not available: **promethazine** PO: 25 mg 30 minutes before anti-TB drugs. If necessary, the dose of promethazine may be increased to 50 mg 3 times daily.

– **Third phase - Reduce the dose or stop temporarily the drug:**

- If taking Eto/Pto, consider reducing dose by one weight class. For example, if taking 1000 mg/day reduce to 750 mg, if taking 750 mg/day reduce to 500 mg. Avoid giving an adult that weighs more than 33 kg less than 500 mg/day of Eto/Pto.
- If taking Cfz, reduce to 100 mg/day.
- If absolutely necessary, stop all anti-TB drugs until symptoms resolve.

Notes:

- Ondansetron is serotonin 5-HT₃ receptor antagonist with strong anti-emetic properties. A number of other anti-emetics from this class exist and sometimes a patient may respond better to one than another.
- Omeprazole decreases the acid production in the stomach is also useful in the treatment of nausea (20 mg at bedtime, and if not effective, 20 mg twice daily for 1 to 2 months – longer if necessary).
- In any of the phases, if there is excessive anxiety over the nausea caused by medications, consider adding a short-acting benzodiazepine (e.g. diazepam 5 mg PO) 30 minutes prior to giving the medications. This can help a condition called “anticipation nausea”. Once nausea is improved, stop the diazepam. The treatment must be short as benzodiazepines can cause dependence and tolerance. Do not give diazepam for longer than 2 weeks.

Nephrotoxicity

Suspected agents: aminoglycosides, Cm

Nephrotoxicity is readily 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 creatinine while on the injectable agent.

Symptomatic cases may present with any of the following findings: decreased urine production; evidence of volume overload such as edema, anasarca, or shortness of breath; or uremic symptoms such as mental status changes (confusion, somnolence) or serositis.

Co-morbid conditions such as diabetes or chronic renal failure are not a contraindication to treatment with the above agents, though greater caution must be exercised in such circumstances. Renal impairment may be permanent.

If renal failure occurs:

- Stop the nephrotoxic agent.
- Rule out other causes of renal failure (e.g. diabetes, dehydration, medications, congestive heart failure, urinary obstruction, urinary tract infection, prostate hypertrophy).
- Follow serum creatinine and electrolytes closely, every 1 to 2 weeks until stable.
- If renal function stabilizes or improves, resume the injectable agent, switching to Cm if an aminoglycoside was being used previously. Change dosing to 3-times-weekly.

Risk of nephrotoxicity can be minimized by encouraging fluids and avoiding other nephrotoxic drugs in patients receiving parenteral therapy.

Additionally, any patient with renal insufficiency requires specific dosing of anti-TB drugs, which should be adjusted based on creatinine clearance. Dosing in renal insufficiency is provided in [Appendix 12](#)(see [page 228](#)).

Optic neuritis

Suspected agents: E, and rarely Eto/Pto, Lzd

This rare adverse effect is typically due to E and usually reversible after discontinuation of the drug. Loss of red-green colour distinction is usually the first sign. In this case, stop the causative agent permanently.

Peripheral neuropathy

Suspected agents: Cs, Lzd, H, and rarely Eto/Pto, aminoglycosides, Cm, E, FQs

Peripheral neuropathy refers to damage to the nerves located outside of the central nervous system. This adverse effect is associated with numerous anti-TB drugs but is common with Cs, Lzd, and H. Linezolid-associated peripheral neuropathy is extremely painful and can be non-reversible.

The usual dose of **pyridoxine** PO for prophylaxis is:

- 50 mg daily for every 250 mg of Cs in all patients receiving Cs;
- 50 mg daily in all patients receiving Lzd;
- 10 mg daily in patients at risk of peripheral neuropathy receiving H.

Aside from prophylaxis, correction of vitamin deficiencies in patients with nutritional compromise is needed.

Neuropathy occurs most commonly in the lower extremities, with 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.

If peripheral neuropathy is diagnosed:

- If the patient receives Lzd, stop Lzd immediately, and do not reintroduce it.
- If the patient receives Km and is known to be susceptible to Cm, consider changing Km to Cm.
- Other contributing causes should be addressed (i.e. diabetes or malnutrition).
- **Pyridoxine** PO: 100 to 200 mg/day in adults until symptoms resolve.
- Non-steroidal anti-inflammatory drugs or paracetamol may help alleviate symptoms.
- Physical therapy focusing on the affected regions may be of benefit.

If these measures are insufficient, the following combination can be tried:

- **amitriptyline** PO: start with 25 mg/day at bedtime for one week, then 50 mg/day at bedtime for one week, then 75 mg/day at bedtime. Do not use tricyclic antidepressant in patients receiving Lzd.
- carbamazepine PO: start with 200 mg once daily for one week, then 200 mg twice daily for one week, then 200 mg 3 times per day.

If not controlled, decrease dose of responsible medication if considered essential to the regimen. Rarely, medication may be discontinued, but only if an alternative drug is available and the regimen is not compromised.

Photosensitivity

Suspected agents: Cfz, FQs

Recommend the patient to avoid direct exposure to the sun, to wear protecting clothes (long sleeves) and to use sunscreens.

Psychosis

Suspected agents: Cs, FQs, H

Visual or auditory hallucinations, delusions, paranoia, and bizarre behaviour are hallmarks of psychosis. Caregivers should be familiar with these symptoms in order to allow early detection. History of psychosis is not a contraindication to the use of the above agents, though psychiatric symptoms are more likely to occur. Some patients may need antipsychotic medication throughout the duration of anti-TB therapy. Adverse effects are generally reversible upon discontinuation of treatment.

Cs is the medicine most commonly associated with psychosis; however psychotic symptoms may occur with H, FQs and Eto/Pto.

For acute psychosis:

- If the patient is at risk of harming himself/herself or others: urgent hospitalization.
- Stop the Cs.
- Treat the acute psychosis.

Cs may be resumed once the patient is no longer psychotic, usually at a lower dose. Some patients will not be able to tolerate re-initiation of Cs, and the use of other agents should be considered. Once all symptoms have resolved, antipsychotic therapy may often be tapered.

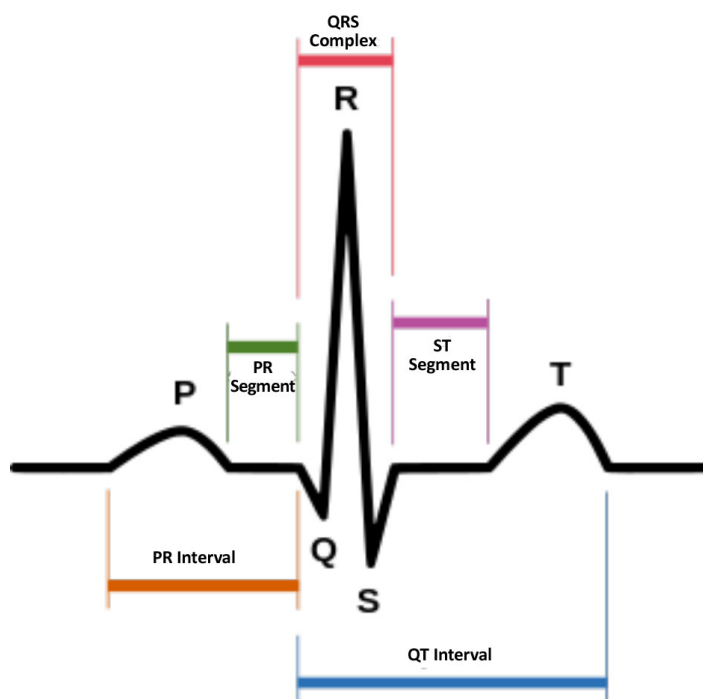
If Cs is continued, some patients will require antipsychotic therapy throughout treatment. In such patients, antipsychotic therapy may usually be slowly (not abruptly) discontinued upon completion of anti-TB therapy.

Whenever psychosis occurs in a patient taking Cs, check the creatinine. Cs is 100% renally excreted and if there is a decrease in renal function (elevated creatinine) this can result in toxic levels of Cs. In this case, a temporary suspension of Cs and re-introduction at a renally adjusted dose may be needed (see [Appendix 12](#)(see page 228)).

QT prolongation

Suspected agents: Bdq, FQs, Cfz

Certain drugs can cause QT prolongation and, thus, predispose to torsades de pointes, arrhythmias and sudden death.



The QT interval is measured from the beginning of Q-wave to the end of the T wave. Its duration varies depending on the heart rate. Its measurement must be corrected according to the heart rate. It is recommended to use the Fredericia method to calculate the QTcF. The formula is $QTcF = QT / \text{cube root of the interval between two waves R}$.

$$QTcF = \frac{QT}{\sqrt[3]{RR}}$$

Bedaquiline: an electrocardiogram (ECG) should be performed before starting treatment then monthly throughout the whole course of treatment.

- If the QTcF interval is between 480 and 500 ms, the patient is stable and electrolytes within normal range: ECG should be performed weekly.
- In case of ventricular arrhythmia or QTcF > 500 ms, stop Bdq and other QT prolonging drugs.

Fluoroquinolones: Mfx causes the greatest QT prolongation. Lfx and Ofx have a lower risk of QT prolongation. Although the overall risk of QT prolongation is minimal, avoid (if possible) or monitor combination of FQs with other drugs that prolong QT interval. In addition, care should be to keep electrolytes within normal range. The patient's renal function should be monitored and the dose of FQ adjusted if needed. ECG monitoring prior to, and during, TB therapy is not routinely recommended as the benefits of the FQ in this case outweigh the risk of QT prolongation.

Cfz (and ondansetron) can also cause significant QT prolongation and should be avoided or used with caution in patients taking Bdq.

Seizures

Suspected agents: Cs, H, FQs

Cs, H, and the FQs have been associated with seizures, while there are other causes (e.g. epilepsy, meningitis, encephalitis, alcohol withdrawal, hypoglycaemia, cerebrovascular accident, malignancy or toxoplasmosis in HIV-infected individuals).

Check serum potassium, calcium and magnesium if possible. Check serum glucose.

Whenever a seizure occurs in a patient taking Cs, check the creatinine. Cs is 100% renally excreted and if there is a decrease in renal function (elevated creatinine), this can result in toxic levels of Cs responsible for the seizure. Renally adjusted dose may be needed (see [Appendix 12](#) (see page 228)).

A history of seizures is not an absolute contraindication to the use of Cs, FQs, and H. However, do not include Cs if an alternative drug is available. In patients with a history of seizures, they should be controlled with anti-epileptics before starting TB treatment.

Sub-therapeutic levels of anti-seizure drugs can be caused by drug-drug interactions between anti-seizure drugs and anti-TB drugs, especially H and R.

Seizures that appear for the first time during TB treatment are likely to be caused by an anti-TB drug. They are not a permanent sequel of treatment with any of the above agents.

If patient experiences a seizure for the first time:

- Stop Cs for a short period.
- Initiate anti-epileptic treatment (carbamazepine, phenytoin, or valproic acid are most commonly used), especially for cases where seizures repeat after holding the dose of Cs.
- Reintroduce Cs if it is essential to the regime. Usually, Cs can be restarted and maintained at a lesser dose, but the usual dose effective should be achieved as soon as possible.

Anti-epileptic treatment may be needed for the remainder of anti-TB therapy.

Skin reactions

Suspected agents: all anti-TB drugs

Major skin reactions

- Stop all anti-TB drugs.
- In the case of anaphylaxis, manage with standard emergency protocols (including the use of epinephrine, etc.).
- In the event of severe generalized rash, a parenteral corticosteroid (i.e., dexamethasone IM or IV: 2 to 4 mg 4 times daily) may be needed.
- Once the reaction has resolved, try to determine which drug caused the reaction: see rechallenge of anti-TB drugs below.

Any drug resulting in Stevens-Johnson syndrome or anaphylaxis should never be reintroduced.

Minor skin reactions

In case of localized and mild skin rash:

- Rule out other possible causes not related to drugs (i.e., scabies, contact dermatitis due to an environmental allergen).
- If no obvious cause, stop all anti-TB drugs.
- Give an antihistamine PO up to 3 to 4 times daily.
- Try to determine which drug caused the reaction: once the reaction has resolved, anti-TB drugs can be reinstated as a “challenge” – a partial dose – in a serial fashion. A typical sequence is the following order: H-R-Z-Eto/Pto-FQ-Cs-E-PAS-Cm or the aminoglycoside.

If the rash was particularly severe, start with 1/10th of the original dose and increase more slowly. Add the most likely culprit last in the challenge. If the most likely culprit drug is not essential, consider not reintroducing it in the challenge.

Re-challenge of anti-TB drugs

Drug	Day 1	Day 2	Day 3
H	50 mg	Full dose	Full dose
R	75 mg	300 mg	Full dose
Z	250 mg	1000 mg	Full dose
Eto/Pto	125 mg	250 mg	Full dose
FQ	50 mg	200-250 mg	Full dose
Cs	125 mg	250 mg	Full dose
E	100 mg	500 mg	Full dose
PAS	1 g	4 g	Full dose
Cm	125 mg	500 mg	Full dose
Km	125 mg	500 mg	Full dose
Amk	125 mg	500 mg	Full dose

If a test dose of any drug causes a reaction, discontinue this drug, unless it is deemed essential to the regimen. If that is the case, desensitization can be considered.

Give the drugs in a setting where a health care provider can respond to any severe allergic reaction.

Note: If a rash appears while patient is on Thz, it should never be given again.

Suicidal ideation

Suspected agents: Cs, H, Eto/Pto

Suicidal ideation is more commonly associated with Cs. Evidence of suicidal ideation should prompt immediate action:

- Keep the patient in the hospital until risk of suicide has passed.
- Discontinue Cs.
- Lower the dose of Eto/Pto to 500 mg daily until the patient is stable.
- Request psychiatric consultation.
- Initiate antidepressant therapy.
- If no improvement occurs after holding Cs, hold H and Eto/Pto.

Tendinitis/tendon rupture

Suspected agents: FQs

Tendon rupture is more common in elderly patients and diabetics.

When significant inflammation of tendons or tendon sheaths occur:

- Rest the joint involved, give a non-steroidal anti-inflammatory drug.
- If the TB treatment is likely to fail without the FQ, try to continue the FQ. Inform the patient that tendon damage may occur, but that FQ is essential to prevent treatment failure.

Vestibular toxicity

Suspected agents: aminoglycosides, Cm, Cs, FQs, H, Eto/Pto, Lzd

Early symptoms of vestibular toxicity include: sensation of ear fullness and intermittent ringing in the ears. When these symptoms are reported, it may be possible to change the dosing interval of the injectable agent (2 or 3 times a week, not daily) then continue without the symptoms progressing. If an aminoglycoside is being used, Cm can be tried but vestibular toxicity may still occur.

If tinnitus and unsteadiness develop and these are attributed to vestibular toxicity, stop the injectable agent to stop ongoing severe disability and ataxia. Symptoms of vestibular toxicity generally do not improve even after stopping the injectable agent. This is one of the few adverse reactions that cause permanent intolerable toxicity and necessitate discontinuation of a class of agents.

Disequilibrium is most commonly caused by injectable agents but can also be caused, more rarely, by Cs, FQs, Eto/Pto, H or Lzd. If stopping the injectable agent does not improve symptoms, other drugs or all drugs can be held for several days to see if the symptoms improve, then adding them back in groups one by one to see if symptoms return.

Appendix 11. Compassionate use

- [11.1 Definitions](#)(see page 227)
- [11.2 Indications](#)(see page 227)
- [11.3 Minimal requirements](#)(see page 228)
- [11.4 National regulations](#)(see page 228)

11.1 Definitions

The term “compassionate use” refers to the use of potentially life-saving experimental treatments to patients suffering from a disease for which no satisfactory authorised therapy exists and/or who cannot enter a clinical trial. For many patients, these treatments represent their last hope. Experimental treatment is below referred to as investigational new drug (IND).

11.2 Indications

Both MDR-TB and XDR-TB can be life-threatening diseases for which approved drugs alone may be ineffective. In some cases, experimental TB drugs, used in combination with approved drugs, could potentially be effective or life-saving.

Compassionate use may be considered for patients presenting with a life-threatening condition (e.g. deteriorating clinical condition due to TB and/or severe immune depression) when:

- Available treatments have failed or are very likely to fail (e.g. regimen comprises less than 3 highly likely effective drugs and/or clinical evolution shows that the treatment is not effective).
- No medical or surgical options are appropriate.
- At least one highly likely effective drug is available (based in the DST result and previous use by the

patient). The IND should never be used in monotherapy. It should always be used in conjunction with other drug(s) with proven or probable efficacy in order to prevent emergence of resistance to the IND. In that respect, will be taken into consideration on a case by case basis:

- the number of remaining drug(s) and their bactericidal or bacteriostatic activity: at least one bactericidal or 2 bacteriostatic drugs could be considered as a minimum;
- the reliability of the DST to the remaining drug(s), treatment history prior to the last DST result;
- the vulnerability to resistance amplification of the IND if known;
- the use of the IND does not result in the discontinuation of an essential effective drug. Special attention will be paid if the use of the IND imposes the replacement of an anti- TB drug by a less effective one.

Compassionate use might be considered for a single patient or a group of patients presenting similar characteristics.

The use of two INDs would basically follow the same indications and conditions. Possible interactions and overlapping toxicity between the INDs have to be taken into consideration.

11.3 Minimal requirements

Compassionate use should only be considered if conditions for an adequate management of DR-TB patients are in place: optimal treatment regimen; clinical, biological and bacteriological monitoring; adherence support and follow-up. Results of DST by a validated laboratory are critical to decision making.

In addition to the basic components of regular DR-TB case management a specific monitoring might be required for the use of an IND.

It is essential that a reporting system is in place in order to diligently report any adverse events.

11.4 National regulations

In most countries, only drugs for which a marketing authorization has been granted by the national regulatory agency can be used in humans. Some national regulatory agencies have developed mechanisms to facilitate the access to new drugs at different stages of development, but before market approval. In this case, a party can apply for approval of an IND and then seek the proper permission to import the drug to a country. The use of an IND requires permission from the proper national regulatory authorities and/or country ethic boards.

Appendix 12. Dose adjustments in renal insufficiency

- [12.1 Normal values for the creatinine clearance\(see page 228\)](#)
- [12.2 Calculation of creatinine clearance\(see page 229\)](#)
- [12.3 Adjustment of anti-TB drugs in renal insufficiency\(see page 229\)](#)

12.1 Normal values for the creatinine clearance

Men: 97 to 137 ml/min

Women: 88 to 128 ml/min

12.2 Calculation of creatinine clearance

Weight (kg) x (140 – age) x (constant)

Serum creatinine (μmol/L)

The constant = 1.23 for men and 1.04 for women

Example:

A female patient under capreomycin (Cm), weight 50 kg, age 46, has a serum creatinine = 212 μmol/L:

Step 1: Calculate the creatinine clearance

$50 \times (140 - 46) \times (1.04) / 212 = 23.0 \text{ ml/min}$

Step 2: As creatinine clearance is < 30, administer 12 to 15 mg/kg of Cm 3 times weekly (ie. 600 to 750 mg of Cm per dose 3 times weekly).

If the creatinine continues to increase, consider suspension of the injectable agent.

Step 3: Adjust every drug in the regimen as necessary according to the following table.

12.3 Adjustment of anti-TB drugs in renal insufficiency

Dosing of anti-TB drugs in renal insufficiency^{6(see page 251),7(see page 251)}

Drugs	Dose and frequency if creatinine clearance < 30 ml/min
H	No change
R	No change
Z	25 mg/kg 3 times per week (not daily)
E	15-25 mg/kg 3 times per week (not daily)
Rfb	2.5-5 mg/kg per day
S ^a	12-15 mg/kg 2 or 3 times per week (not daily)
Km ^a	12-15 mg/kg 2 or 3 times per week (not daily)
Amk ^a	12-15 mg/kg 2 or 3 times per week (not daily)
Cm ^a	12-15 mg/kg 2 or 3 times per week (not daily)
Lfx	750-1000 mg 3 times per week (not daily)
Mfx	No change
Ofx	600-800 mg 3 times per week (not daily)
Eto/Pto	250-500 mg per day

Cs ^b	250 mg once daily or 500 mg 3 times per week
PAS ^c	8 g per day in 2 divided doses
Cfz	No change
Amx/Clv	1000 mg per day in 2 divided doses
Lzd	No change
lpm/Cln	500 mg every 8 hours for creatinine clearance 20-40 ml/min 500 mg every 12 hours for creatinine clearance < 20 ml/min

^a. Use injectable agents with caution in patients with impaired renal function (increased risk of ototoxicity and nephrotoxicity).

^b. Monitor carefully for signs of neurotoxicity.

^c. Sodium salt formulations of PAS may result in excessive sodium load and should be avoided in patients with kidney disease.

Appendix 13. Potential overlapping toxicities of ARVs and anti-TB drugs

Note: drugs that are more strongly associated with the listed toxicities appear in bold lettering.

Toxicity	ARV agent	Anti-TB agent	Comments
Abdominal pain	All ARVs	Eto/Pto, PAS, Cfz, FQs, H, Lzd, E, Z	Abdominal pain is common and often benign; however, it may be an early symptom of severe adverse effects such as pancreatitis, hepatitis or lactic acidosis.
Central nervous system (CNS) toxicity	EFV	Cs, H, Eto/Pto, FQs	EFV has a high rate of CNS adverse effects (dizziness, impaired concentration, depersonalization, abnormal dreams, insomnia and confusion) in the first 2-3 weeks of use, but they typically resolve on their own. If they do not resolve, consider substitution of the agent. There are limited data on the use of EFV with Cs; concurrent use is accepted practice as long as there is frequent monitoring for CNS toxicity.
Depression	EFV	Cs, FQ, Eto/Pto	Severe depression can be seen in 2.4% of patients receiving EFV. Consider substitution of EFV if severe depression develops.
Diarrhoea	All protease inhibitors, ddi (buffered formulation)	Eto/Pto, PAS, FQs, Amx/Clv, lpm/Cln	Diarrhoea is common. Also consider opportunistic infections as a cause of diarrhoea, or <i>Clostridium difficile</i> (pseudomembranous colitis).

Dysglycaemia (disturbed blood sugar regulation)	Protease inhibitors	Eto/Pto	PI tend to cause insulin resistance and hyperglycaemia. Eto/Pto may cause hypoglycaemia and poor glucose regulation in diabetics.
Electrolyte disturbances	TDF (rare)	Cm, aminoglycosides	
Headache	AZT, EFV	Cs	Rule out more serious causes of headache such as bacterial or cryptococcal meningitis, toxo- plasmosis, etc. Use of analgesics (ibuprofen, paracetamol) and good hydration may help. Headaches secondary to AZT, EFV and Cs are usually self-limited.
Hepatitis	NVP, EFV, all protease inhibitors (RTV)	Z, H, R, E, PAS, Eto/Pto	When severe, stop both the ART and TB medications, and restart the TB medications first. Also consider CMX as a cause of hepatotoxicity if the patient is receiving this medication.
Hypothyroidism	d4T	Eto/Pto, PAS	Several studies show subclinical hypothyroidism associated with d4T.
Lactic acidosis	d4T, ddl, AZT, 3TC	Lzd	Early detection and management of hyperlactatemia in order to prevent development of lactic acidosis.
Myelosuppression	AZT	Lzd	Monitor blood counts regularly. Replace AZT if bone marrow suppression develops. Consider suspension of Lzd. Also consider CMX as a cause if the patient is receiving this medication. Consider adding folinic acid supplements, especially if the patient is receiving CMX.
Nausea and vomiting	RTV, d4T, NVP, and most others	Eto/Pto, PAS, Z, Amx/Clv, Cfz, Lzd, Ipm/Cln	Persistent vomiting may be a result of developing lactic acidosis (especially common with long-term d4T use) and/or hepatitis secondary to medications.
Nephrotoxicity	TDF, IDV	Aminoglycosides, Cm	TDF may cause renal injury with the characteristic features of Fanconi syndrome, hypophosphataemia, hypo-uricaemia, proteinuria, normoglycaemic glycosuria and, in some cases, acute renal failure. Avoid TDF in patients receiving aminoglycosides or Cm. If TDF is absolutely necessary, serum creatinine and electrolytes should be monitored at least every 2 weeks.
Optic neuritis	ddl	E, Eto/Pto, Lzd	Suspend agent responsible for optic neuritis permanently and replace with an agent that does not cause optic neuritis.

Pancreatitis	d4T, ddI	Lzd	Avoid concomitant use of these agents. If an agent causes pancreatitis, suspend it permanently and do not use any of the potentially pancreatitis-producing ARVs (d4T or ddI) in the future.
Peripheral neuropathy	d4T, ddI	Lzd, Cs, H, Eto/Pto, S, Km, Amk, Cm, E, FQs	Avoid use of d4T or ddI in combination with Cs or Lzd (increased risk of peripheral neuropathy).
QT prolongation	RTV boosted PI	Bdq, Cfz, Mfx, other FQs	
Skin rash	ABC, NVP, EFV, d4T and others	All anti-TB drugs	Do not re-challenge with ABC (risk of life-threatening anaphylaxis). Do not re-challenge with any agent that may have caused Stevens-Johnson syndrome. Also consider CMX as a cause of skin rash if the patient is receiving this medication.

Adapted from WHO Guidelines for the programmatic management of drug-resistant tuberculosis⁸(see page 251).

Appendix 14. Informing the patient

- [14.1 At the start of treatment](#)(see page 232)
 - [Outpatients](#)(see page 232)
 - [Hospitalized patients](#)(see page 233)
- [14.2 In the course of treatment](#)(see page 234)

14.1 At the start of treatment

Arrange two interviews (allow about 20 minutes for each): one to supply the patients with the information they need to follow the treatment, the second to make sure they have assimilated the information. These interviews should coincide with the first two clinical visits. The first interview should occur before the treatment begins. Depending on how the clinic is organized, the interviews are done either by the prescribing clinician alone at the time of the clinical visit, or with the help of a specially-trained staff member at an interview just for this purpose. Patients may bring someone with them, if they wish.

Outpatients

First interview

– Explain:

- The disease and how it spreads
For example: this is a serious, but generally curable, infection that affects the lungs and can be spread if not treated (tailor the information according to the focus of the infection, the resistance pattern).
- The treatment process:
Length, intensive/continuation phases, clinical and bacteriological monitoring, visit schedule

(tailor the information according to the regimen); how DOT will work and why it is important when relevant.

- The medications:
 - Management:
 - Where, when, and from whom to get medications;
 - Number of tablets per day; number of doses per day, etc.;
 - Keep tablets in their blister pack until taken, no removing them from their package ahead of time.
 - Main adverse effects and what to do if they occur:
 - For example: for rifampicin, point out that it turns the urine, stools, tear, etc. reddish-orange, that this is normal and not a cause for concern. For ethambutol, advise the patient to consult the doctor immediately if s/he notices a decrease in his/her vision or ability to correctly distinguish colours, etc.
 - Special precautions (depending on concomitant treatment):
 - For example: take rifampicin in the morning, and fluconazole at night.
- Any incentives or enablers the patient may qualify for and how the patient can access them.
- Stress the importance of adherence, anticipate problems, and think about possible solutions.
- Answer any questions.
- Give the date of the second interview (one week later).

Second interview (one week later)

- Check to make sure that information has been assimilated; ask open-ended questions, give the patient time to answer. Give more information, if necessary.
- Answer any questions.
- Remind the patient of the date of the next visit.

Hospitalized patients

First interview

Same as above, plus explain:

- Hospital infection control measures:
 - Isolation and why it is indicated; the importance of covering the mouth when coughing or sneezing, the use of sputum containers, visits outside the building, face masks/respirators (who, when, why), airing out the room, etc.
- Timetable for injections and distribution of drugs.

Second interview (when patient is ready for discharge)

- Explain:
 - Where and when to get medications, the visit schedule;
 - DOT and other treatment support as relevant.
- Make sure that the information the patient needs to continue treatment as an outpatient has been assimilated (treatment process, medications, adverse effects and what to do, etc.).
- Stress the importance of adherence, anticipate problems, and think about possible solutions.
- Answer any questions.

14.2 In the course of treatment

Adherence interviews should take place at least monthly (more frequently if needed) throughout the entire course of treatment. Their purpose is to identify/resolve any problems resulting in poor adherence. Assessment is done either by the clinician at the monthly clinical visit, or by the nurse responsible for individual distribution of drugs.

Adherence interviews should be quick (about 5 minutes); on the other hand, devote as much time as necessary to resolving any problems.

The interview at the end of the intensive phase is more specifically devoted to informing the patient, because of the changes in drug regimen for the continuation phase.

Appendix 15. Treatment supporters for patients under second line therapy

Adapted from USAID TB CARE II (2011) Community-based Care for Drug-resistant Tuberculosis: A Guide for Implementers.

- [15.1 Selecting a treatment supporter](#)(see page 234)
- [15.2 Roles and responsibilities](#)(see page 234)

15.1 Selecting a treatment supporter

The treatment supporter should be someone who:

- Is preferably selected from existing community health workers or other persons with health background;
- Is acceptable to the patient and his/her family;
- Can observe confidentiality of the patient;
- Has a stable living situation;
- Has basic literacy skills (is able to read and write, has basic numeracy skills);
- Is motivated to care for MDR-TB patients;
- Lives near the patient and is able to make twice-daily DOT visits if indicated and to come to the house immediately in case of emergencies;
- Is committed to support the patient for the full length of treatment;
- Should not be immune-suppressed [\(see page 0\)](#) and is in good physical condition;
- Has received basic TB training and DR-TB specific training.

It is not recommended to have family members as treatment supporters. The family relationship may interfere with the ability to monitor MDR-TB treatment.

For children, preferably female DR-TB supporters are recommended; the parents or family members are not especially not appropriate to supervise doses.

15.2 Roles and responsibilities

- Supervises all doses of drugs and keep records on MDR-TB treatment card.
- Detects adverse effects and promptly refers the patient to health facility when necessary.
- Accompanies the patient to all medical consultation.
- Collects and transports monitoring sputum specimens for smear and culture.
- Provides information on the risk of transmission and the infection control measures at home.
- Performs contact tracing.

- Attends refresher trainings.



The most common cause of immunosuppression is HIV/AIDS, but chronic illnesses such as diabetes also alter the immune system and are a risk factor for TB infection and disease.

Appendix 16. Basic TB infection control risk assessment tool



Appendix 17. Air change per hour (ACH) measurement recommendations

The ACH in a mechanically ventilated room should remain more or less constant, whereas natural ventilation will vary according to:

- Whether the doors/windows/vents in that room are open or not;
- Wind speed and direction;
- Temperature and humidity differential between inside and outside.

The ACH rate is one tool among others to assess if:

- The efficiency of the system in delivering the outdoor air and in removing the pollutants to each location in the room;
- The overall airflow direction is from clean to dirty zones.

To calculate the ACH in a given room:

- Start by drawing a sketch of the room;
- Measure the dimensions of the room and calculate the volume (in m³);
- Measure the surface (in m²) of all the openings/vents in the room and air direction across the openings/vents;
- Measure the air speed (in meters per second) using an anemometer.

$$\text{ACH} = \frac{0.65 \times \text{air speed (m/s)} \times \text{opening area (m}^2\text{)} \times 3600}{\text{Room volume (m}^3\text{)}}$$

Room volume (m³)

Summary of proposed specifications:

	Surface (m ²)	Height (m)	ACH	Opening window surface area (m ²)
Single rooms	> 7.5 (2.5 x 3)	> 3	> 12	> 25%
Wards	4.5 m ² /patient	> 3.5	> 12	> 15%
Waiting rooms (preferably outside)	3 m ² /patient	> 3.5	> 12	> 15%
Sputum collection areas (preferably outside)	> 1.5	> 2.5	> 20	> 50%
Toilets	> 1.2	> 2.5	> 12	> 25%
Consultation rooms	> 7.5 (2.5 x 3)	> 3	> 12	> 25%
Central corridors (avoid in new buildings)	> 2	> 3	> 12	> 25%

There are two main techniques to measure the ventilation. The most commonly used is the anemometer that measures the velocity (speed) of air (see manufacturer's recommendations for various types of anemometers). The technique using the gas analyser is difficult and should only be used by trained staff.

Appendix 18. Advantages and disadvantages of ventilation techniques

	Installation/ equipment	Climate		Technical considerations		Cost	Comments
		Cold	Hot	Assessment/ calculation	Installation/ maintenance		
Natural ventilation	Windows and doors	no	yes	simple	very simple	low	Wind depending. No guarantee on direction intensity and frequency.
	Whirly birds	no	yes	very simple	very simple	low	Wind depending (no electricity needed). No guarantee on intensity and frequency.

	Chimney	no	yes	very simple	simple	medium	Climate and wind depending. No guarantee on intensity.
Assisted natural ventilation	Ceiling, wall and desk fans	no	yes	simple	simple	low	Improve dilution. Needs small energy power.
	Extractors/exhaust fans	no	yes	simple	very simple	low	Small energy power needed. Could be solar power (R&D).
Mechanical	Heating ventilation and air conditioning	yes	ideal	difficult	difficult	high	Relative pressure between rooms. High consumption of energy. Could need filter, HEPA filter and heat exchange.

Appendix 19. Upper room ultraviolet germicidal irradiation (UVGI) system

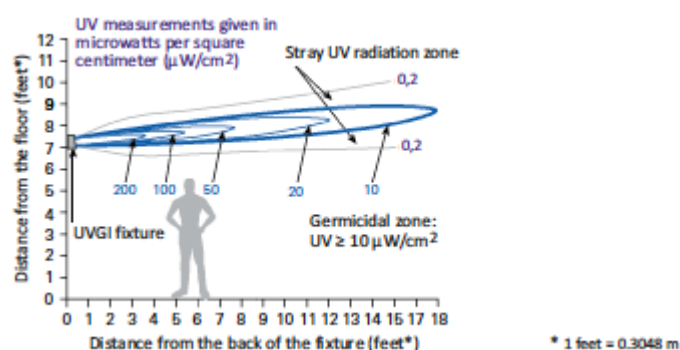
- [19.1 Mechanism of action](#)(see page 237)
- [19.2 Maintenance](#)(see page 238)
- [19.3 Disposal](#)(see page 239)

The use of UVGI in the upper part of rooms may be effective in killing or inactivating *M. tuberculosis* generated by infected persons.

19.1 Mechanism of action

UV lamps are installed into fixtures suspended from a ceiling or mounted on a wall. Fixtures are shielded with louvers or bafflers in order to block radiation below the horizontal plane of the fixtures. UV lights create in the upper portion of the room a germicidal zone where the bacilli are killed (Figure 1). Patients in the lower portion of the room are not exposed to UVGI lights. Good air mixing is needed to transport the air (and thereby the bacilli) to the upper portion of the room. Disinfection is achieved through the rapid dilution of contaminated lower room air with clean irradiated upper room air.

Figure 1

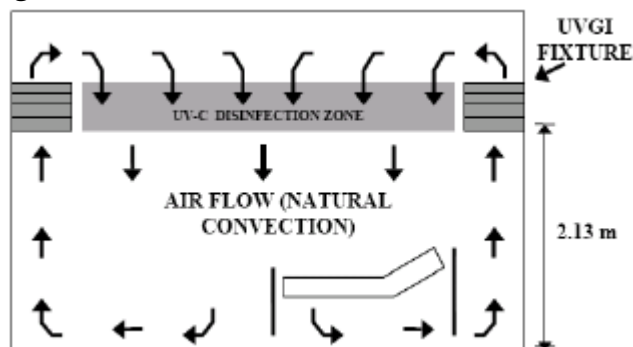


From the WHO, *Implementing the WHO Policy on TB Infection Control in Health-Care Facilities, Congregate Settings and Households*

The lamps should irradiate the entire surface of the upper part of the room (Figure 2), in order to disinfect the largest possible volume of air mixed at a low speed between the upper and lower part of the room.

UVGI Upper-room Irradiation

Figure 2



From Guidelines for the Utilization of Ultraviolet Germicidal Irradiation technology in controlling transmission of tuberculosis in health care facilities in South Africa⁹(see page 251)

Several factors influence the efficiency of UVGI systems:

- Ventilation rate: in controlled environment, at rates up to 6 air change per hour (ACH), UVGI systems increase the effect of air cleaning to > 12 ACH¹⁰(see page 251). But when ventilation rates are increased above 6 ACH, UVGI system effectiveness could be reduced because the time for bacteria irradiation is shorter¹¹(see page 251),¹²(see page 251).
- Effective mixing within the room may be provided by natural convection currents or fans, preferably, ceiling ones. Low velocity ceiling fans boosted UVGI system's effectiveness up to 33% when ACH was below 6¹³(see page 251),¹⁴(see page 251),¹⁵(see page 251).
- Relative humidity: studies¹⁶(see page 251),¹⁷(see page 251),¹⁸(see page 251) have reported rapidly decreasing air cleaning effectiveness in UVGI systems when the relative humidity goes above 70%.
- Installation: the height of the room should be minimum 2.5 m and UVGI fixtures should be installed at the minimum height of 2.1 m. As a thumb rule, a 30W lamp should be sufficient for 18 m² of surface¹⁹(see page 251),²⁰(see page 251), but room shape and type of fixture should be taken into consideration when calculating the needs. For instance, wall-mounted lamps would have a smaller germicidal area than ceiling-mounted ones. Lamps should be on whenever there is a risk of TB transmission. For example, in rooms with hospitalized patients, the lamps should be turned on 24 hours a day.
- Maintenance: see below.

19.2 Maintenance

Dust-covered and/or old UVGI lamps are less effective, hence the need for a careful maintenance, including regular cleaning:

- Lamps and fixture surfaces should be wiped at least monthly (more often if necessary) with a cloth dampened with 70% alcohol. Do not use water and soap or any detergent. The cleaning should be performed when lamps and fixtures are cool.
- Measurement of UVGI level must be done at installation and at least once a year. A UV light meter programmed to detect UV light on a wavelength of 254 nm is needed. Measurements should be performed at eye level in the occupied zone (~ 1.6 m) and in upper irradiated portion of the room, at a distance of 1.2 m from the fixture in all possible directions (imitating a circle with measurements done

while moving in circumference spaced of 1 m). Ideally, all upper room measurements should be around $30 \mu\text{W}/\text{cm}^2$ to $50 \mu\text{W}/\text{cm}^2$. Persons doing these measurements should wear protective equipment (UVprotective glasses, clothing made of tightly woven fabric, soft cotton gloves) and cover exposed skin with opaque creams with solar-protection factors > 15 .

– UV lamps last between 5 000 and 10 000 hours of continue use (7 to 14 months). Check manufacturer's information. After this period, UV lamps rapidly lose effectiveness and need to be changed.

19.3 Disposal

UV lamps contain mercury and quartz and are considered as hazardous waste. Disposal is extremely difficult in many countries; this should be considered before implementing them. If adequate disposal of the lamps by specialized enterprises is not possible in the country, neither their repatriation; UV lamps should be disposed of by encapsulation (sealed in a metal 200 litre drum filled with concrete and then buried away from water sources).

Safety considerations

Reflecting surfaces in the irradiation area of UV lamps must be avoided (i.e. oil painted ceilings, etc.).

At certain wavelengths (including UV-C) UV exposure may be harmful. Skin exposure can produce sunburn (erythema). Exposure of the eyes can produce conjunctivitis (feeling of sand in the eyes, tearing) and/or keratitis (intense pain, sensitivity to light). These symptoms typically commence 6 to 12 hours after exposure.

Despite the fact that these are reversible conditions, health care workers should immediately report them to the IC officer. This could mean that UV irradiation is higher than previously thought at lower room level (lamp poorly positioned? Reflecting surface?).

The USA National Institute for Occupational Safety and Health (NIOSH) states that safe exposure limits are set below those found to initiate eye irritation, the body surface most susceptible to UV. Next table shows the permissible exposure times for given effective irradiances at 254 nm wavelength.

Permissible exposure time*		Effective irradiance ($\mu\text{W}/\text{cm}^2$)
(Units given)	(Seconds)	
8 h	28,800	0.2
4 h	14,400	0.4
2 h	7,200	0.8
1 h	3,600	1.7
30 min	1,800	3.3
15 min	900	6.7
10 min	600	10
5 min	300	20
1 min	60	100
30 s	30	200

10 s	10	600
1 s	1	6,000
0.5 s	0.5	12,000
0.1 s	0.1	60,000

* The occupational exposure limit for UV-C at 254 nm is $6,000 \mu\text{J}/\text{cm}^2$. This can be also calculated with the following formula: $\text{Dose (in } \mu\text{J}/\text{cm}^2) = \text{Time (in seconds)} * \text{Irradiance (in } \mu\text{W}/\text{cm})$.

Exposures exceeding this limit would require the use of personal protection equipment to protect the skin and eyes.

In order to avoid overexposure of UVGI, education of health care workers should include basic information on UVGI systems and their potential harmful effects if overexposure occurs.

Appendix 20. Respirators

- [20.1 Introduction](#)(see page 240)
- [20.2 Instructions for use](#)(see page 240)
- [20.3 Storage](#)(see page 241)
- [20.4 Disposal](#)(see page 241)
- [20.5 Fit testing](#)(see page 241)

20.1 Introduction

Respirators are specially designed masks that act as a personal protective measure to prevent the inhalation of bacilli. Respirators should be used by all staff and carers in areas where the risk of TB transmission is high:

- Smear-positive inpatient units
- Diagnosis department
- Culture/DST and sputum smear preparation area (laboratory)
- Sputum collection area
- Radiology department

The WHO recommends²¹(see page 251) the use of:

- The United States Centre for Disease Control and Prevention/National Institute for Occupational Safety and Health certified N95, with filtering efficiency > 95% if challenged with 0.3μ particles.

OR

- The CE-certified filtering facepiece class 2 EN 149:2001 (FFP2, filtering efficiency 94%, if challenged with 0.3μ particles)

Note: paper or cloth surgical masks do not protect a person against TB.

20.2 Instructions for use

Respirators are for personal use. The same respirator cannot be shared between other staff members, or between other carers.

The respirator should be put before entering the room and removed after exiting the room.

Respirators must be worn covering the nose, the mouth and the chin and providing a tight seal around the edge. Everytime 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 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 fit.
- 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 detected. Otherwise, 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: respirators size and 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 however, the fitting may decrease with frequent wearing.

A respirator extensively used should be discarded after 7 days. If it is only used a few hours 2 to 3 times per week for example, it can be reused for several weeks⁶(see page 251). During this period, the staff can reuse their respirator as long as they are not wet or damaged and provided they do not have loosened straps. Each staff should keep his/her respirator in the pocket of his/her personal gown without creasing it. If the filter material is damaged or the mask has loose straps, the respirator should be immediately discarded.

Note: TB bacillus is trapped in the filter of a mask, and will not be released with shaking or other physical movements of the mask⁶(see page 251).

20.3 Storage

Store in a dry, well ventilated place. Respirators should not be crushed during storage.

20.4 Disposal

Respirators are disposed as “soft waste” and do not need to be disinfected before being discarded.

20.5 Fit testing

Proper fit of a respirator is critical to ensure respiratory protection. Therefore, all staff members who will potentially be exposed to *M. tuberculosis* should perform, before they are required to wear any respirator, a “fit testing” to determine if the respirators being used in the program fit them properly.

At least two models of respirators should be available. If a worker is not able to be fitted with one model, the other one may be used instead.

Testing is performed using a fit testing kit. This kit contains all supplies and instructions needed to perform the test. See *MSF Medical catalogue, volume 2B*.

Fit testing kit



Appendix 21. Face or surgical masks

- [21.1 Introduction](#)(see page 242)
- [21.2 Instructions for use](#)(see page 242)
- [21.3 Storage](#)(see page 242)
- [21.4 Disposal](#)(see page 243)

21.1 Introduction

Face masks or surgical masks should be worn by contagious patients (suspect or confirmed) when they leave their rooms to go to another department or any other enclosed area. Wearing a surgical mask is not necessary when the patient is alone in his/her room or outdoors.

The purpose of the surgical mask is to catch much of the nuclear droplets that are expelled by the patient during talking, breathing or coughing. This results in less bacteria being introduced into areas.

21.2 Instructions for use

Masks are for personal use. The same mask cannot be shared.

- Open the mask.
- Bend the nasal bar (if included).
- Separate the straps; lightly stretch tem.
- Put the chin into the mask.
- Stretch the two straps over the head.
- Put the first strap at neck-height and the second strap on top of the head.

Masks must be replaced if they become wet or damaged, and at least everyday.

It is not recommended to have patients wear masks for large portions of the day or while sleeping as they do restrict air movement and not very comfortable.

21.3 Storage

Store in a dry, well ventilated place.

21.4 Disposal

Masks are disposed as “soft waste” and do not need to be disinfected before being discarded.

Appendix 22. BCG vaccine

- [Composition and presentation](#)(see page 243)
- [Dosage and vaccination schedule](#)(see page 243)
- [Technique and site of administration](#)(see page 243)
- [Contra-indications](#)(see page 243)
- [Adverse effects](#)(see page 243)
- [Precautions](#)(see page 244)
- [Storage](#)(see page 244)

Composition and presentation

- Live attenuated bacterial vaccine
- Powder for injection (lyophilised vaccine) in multidose vial, to be dissolved with the entire vial of the specific solvent supplied by the manufacturer

Dosage and vaccination schedule

- Refer to national immunization recommendations.
- Children under 12 months [1](#)(see page 01) : 0.05 ml as a single dose as soon after birth as possible
- Adults: 0.1 ml as a single dose

Technique and site of administration

- Clean the injection site with clean water, do not use antiseptics (risk of inactivation of live vaccine), allow to dry.
- Administer intradermally. If the injection is correctly done, it should provoke an "orange skin" papula, 5-8 mm in diameter.
- The vaccine is usually administered in the deltoid region of the arm, about one third down the upper arm over the insertion of the deltoid muscle. Follow national recommendations. The vaccine is injected in the same place for all children to make it easy to find the BCG scar subsequently.

Contra-indications

- Do not administer to patients with congenital or acquired immunodeficiency (HIV positive patients, patients with unknown HIV status but symptoms consistent with HIV, patients under immunosuppressive therapy or malignant haemopathy, etc.).
- Vaccination should be postponed in the event of acute extensive dermatosis, acute complicated malnutrition (BCG will be given at discharge from the nutritional centre once the child has recovered), severe acute febrile illness (minor infections are not contra-indications).

Adverse effects

- Complications requiring no specific treatment, with an evolution almost always favourable:
 - normal local reaction 2 to 4 weeks after injection: papule which changes to an ulcer that usually heals spontaneously (dry dressing only) after 2 to 3 months, leaving a permanent scar;
 - persistent ulcer, characterised by serous discharge persisting for over 4 months after injection;

- non-suppurated adenitis, most often axillary, sometimes cervical; cheloid scars;
- abscess at the injection site, due to common germs (red, hot and painful abscess) or poor manipulation during injection or a vaccine with too high a dose (cold and painless abscess).
- Atypical complications:
 - Suppurative lymphadenitis, mostly observed in newborns, usually due to the administration of too high a dose of vaccine. The lymph node, with a diameter at times over 3 cm, evolves toward softening and fistulisation with chronic suppuration.
 - Osteomyelitis in exceptional cases.
 - Disseminated BCG disease, most commonly in immunocompromised infants (110 to 417 cases/100,000 doses in HIV-infected infants²²(see page 251),²³(see page 251)). Mortality in this group could be as high as 75%²⁴(see page 251). If disseminated BCG disease is diagnosed, a full course of 6 months of anti-TB treatment should be administered. This is often indistinguishable from disseminated TB.

Precautions

- If administered simultaneously with EPI vaccines, use different syringes and injection sites.
- Pregnancy: **CONTRA-INDICATED**
- Breast-feeding: no contra-indication

Storage



- *Reconstituted vaccine: between 2°C and 8°C for 6 hours maximum, protected from light.*
- *Powder: between 2°C and 8°C, protected from light. Freezing is possible but unnecessary.*
- *Solvent: a cold chain is not required for storage. 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.*



(see page 0) Expert opinion indicates that vaccination of children older than 12 months of age is usually of limited benefit (although it is not harmful or contraindicated).

Appendix 23. Treatment card for patients on first-line anti-TB therapy



TB-Appendix 23.pdf

Appendix 24. Tuberculosis register for patients on first-line anti-TB therapy



TB-Appendix 24.pdf

Appendix 25. Treatment card for patients on second-line anti-TB therapy



TB-Appendix 25.pdf

Appendix 26. Tuberculosis register for patients on second-line anti-TB therapy



TB-Appendix 26.pdf

Appendix 27. Request form for microscopy and Xpert MTB/RIF



TB-Appendix 27.pdf

Appendix 28. Request form for sputum culture, LPA and DST



TB-Appendix 28.pdf

Appendix 29. Sputum smear microscopy register



TB-Appendix 29.pdf

Appendix 30. Xpert MTB/RIF register



TB-Appendix 30.pdf

Appendix 31. Drug-o-gram



TB-Appendix 31.pdf

Appendix 32. Quaterly report



TB-Appendix 32.pdf

Appendix 33. Report on detection and enrolment of TB cases with rifampicin and multidrug-resistance



TB-Appendix 33.pdf

Appendix 34. Report of final outcomes of drug-resistant tuberculosis



TB-Appendix 34.pdf

Appendix 35. Check-list for the evaluation of a TB service



TB-Appendix 35.pdf

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