

TB/HIV Coinfection

Regional Clinical Manual

2017 Update



Pan American
Health
Organization



World Health
Organization
REGIONAL OFFICE FOR THE
Americas

TB/HIV Coinfection
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Also published in Spanish
Coinfección TB/VIH Guía Clínica Regional. Actualización 2017
ISBN: 978-92-75-31985-7

TB/HIV Coinfection Regional Clinical Manual. 2017 Update
ISBN: 978-92-75-11985-3

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Suggested citation. Pan American Health Organization. *TB/HIV Coinfection Regional Clinical Manual. 2017 Update*. Washington, D.C.: PAHO; 2018.

Cataloguing-in-Publication (CIP) data. CIP data are available at <http://iris.paho.org>.

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Acknowledgments

The recommendations in this manual were the product of review, discussion, and consolidation by a group of TB/HIV experts, coordinated by Dr. Rafael López, Advisor on Tuberculosis Prevention and Control, and Dr. Giovanni Ravasi, Advisor on HIV/STI Care and Treatment, at the regional office of the Pan American Health Organization (PAHO), in conjunction with Dr. Mónica Thormann, TB Chapter Coordinator of the Pan American Association of Infectious Diseases (API). PAHO would like to thank the API for its valuable assistance in facilitating opportunities for discussion and bringing several of the revisers together.

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This publication was made possible thanks to the support of the Office of Sustainable Development, Bureau for Latin America and the Caribbean, U.S. Agency for International Development (USAID) under Grant No. AID-OAA-IO-16-00.003. The opinions expressed here are solely the authors' and do not necessarily reflect the opinions of USAID.

Abbreviations and acronyms

ADA	adenosine deaminase
AFB	acid-fast bacilli
AIDS	acquired immunodeficiency syndrome
ALC	absolute lymphocyte count
ART	antiretroviral therapy
ARV	antiretroviral
BCG	bacille Calmette-Guérin (TB vaccine)
CMV	cytomegalovirus
CPT	cotrimoxazole preventive therapy
CSF	cerebrospinal fluid
CXR	chest x-ray
DNA	deoxyribonucleic acid
DOT	directly observed treatment
DR-TB	drug-resistant tuberculosis
DST	drug-susceptibility testing
DTG	dolutegravir
ETB	extrapulmonary tuberculosis
FDC	fixed-dose combination
FNAC	fine-needle aspiration cytology
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IGRA	interferon gamma release assay
IPT	isoniazid preventive therapy
LAC	Latin America and the Caribbean
LDH	lactate dehydrogenase
LF-LAM	lateral-flow lipoarabinomannan assay
LTBI	latent tuberculous infection
MAC	Mycobacterium avium complex
MDR-TB	multidrug-resistant tuberculosis

NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NtRTI	nucleotide reverse transcriptase inhibitor
PAHO	Pan American Health Organization
PCP	Pneumocystis jirovecii pneumonia
PCR	polymerase chain reaction
PGL	persistent generalized lymphadenopathy
PI	protease inhibitor
PPD	purified protein derivative (tuberculin test)
PrEP	pre-exposure prophylaxis
PTB	pulmonary tuberculosis
RAL	raltegravir
RNA	ribonucleic acid
IRIS	immune reconstitution inflammatory syndrome
SM	smear microscopy
STI	sexually transmitted infection
TB	tuberculosis
TB/HIV	tuberculosis/HIV coinfection
TMP/SMX	trimethoprim-sulfamethoxazole (cotrimoxazole)
WHO	World Health Organization
XDR-TB	extensively drug-resistant tuberculosis

Glossary

Active tuberculosis disease	Person with symptoms of the disease caused by <i>M. tuberculosis</i> (cough, fever, weight loss, night sweats), who can infect others (in the case of pulmonary and laryngeal TB). Individuals with pulmonary disease usually have an abnormal chest x-ray and a positive sputum smear. They may also have a positive tuberculin test result; however, this in itself is not enough to diagnose the disease (see latent tuberculous infection).
Atypical mycobacteria	Non-tuberculous mycobacteria.
Bactericide	Treatment that eliminates bacteria.
Bacteriostatic	Treatment that arrests bacterial growth.
Counseling	Process in which a health care provider and a patient or client engage in a dialogue to explore and identify the patient's risks, discuss the challenges for behavior change, and encourage decision-making by setting goals.
Desensitization	A way of overcoming a patient's hypersensitivity to a drug through gradual re-exposure to it.
Empirical treatment	Treatment for a specific disease without a laboratory-confirmed diagnosis.
Exudate	Fluid with a high protein content (>3 g/dL) and inflammatory cells in a space or body compartment.
False negative	A negative result when the patient's actual status is positive.
False positive	A positive result when the patient's actual status is negative.
Failure	A patient with tuberculosis, who, after five months of treatment, still or again has a positive sputum smear.
Hemoptysis	Coughing up fresh blood from the respiratory tract.
Hypersensitivity	Immunological reaction to a small amount of a drug or antigen.
Incubation period	Interval between HIV infection and the appearance of AIDS symptoms--a period of six to ten years.

Latent TB infection	Persistent immune response to previously acquired <i>M. tuberculosis</i> antigens, without clinical manifestations of active TB. To determine whether an individual has latent TB infection, the tuberculin skin test, also known as the Mantoux test or interferon gamma release assay (IGRA), should be performed.
Lost to follow-up	A patient with tuberculosis who has interrupted treatment for more than a month (formerly called a "drop-out").
New case	A patient who has never been treated for TB or has only received treatment for less than a month.
Patient with respiratory symptoms	A person with a cough lasting more than 15 days.
Relapse	An individual who, having been declared cured of pulmonary or extrapulmonary TB after a complete course of TB drug therapy, develops active tuberculosis again.
TB/HIV coinfection	Active TB in a person living with HIV.
Transudate	Fluid with a low protein content (<3 g/dL) in a body space or compartment.
Window period	Interval between HIV infection and the time antibodies are detectable and revealed with a positive (reactive) test.

Introduction

The Region of the Americas has the second highest burden of tuberculosis/human immunodeficiency virus (TB/HIV) coinfection in the world, with an estimated 32,000 cases and 6,000 deaths from this cause in 2015. The official report from the countries of the Region for that year was 21,800 cases of TB with HIV, representing 12% coinfection. Despite the advances in tuberculosis and HIV control, the provision of timely and appropriate diagnosis and treatment of TB/HIV is still problematic, reflected in the persistence of related morbidity and mortality.

Purpose of the manual

The purpose of this manual is to provide updated clinical guidelines for TB/HIV, with emphasis on diagnostic aspects, including new techniques, and current treatment, without losing sight of the public health approach. By compiling and consolidating the latest recommendations of the World Health Organization on the subject, the aim is to provide a reference document for frequent consultation that unifies and standardizes the management of TB/HIV coinfection in health facilities, based on the principle of "two diseases, one patient." The manual also seeks to underpin updates of national standards and guidelines on coinfection and complement the coordinated work that should exist between TB and HIV prevention and control programs at every level, within the framework of the 12 TB/HIV collaborative activities internationally recommended (Table 1).

Target audience

This Regional Clinical Manual is designed for physicians, nurses, and other health care workers involved in the diagnosis, treatment, and follow-up of patients with TB/HIV coinfection in primary and secondary health care facilities in Latin America and the Caribbean. It is also for health care workers in training, national TB and HIV prevention and control programs, and TB/HIV coordination mechanisms at all levels, as well as institutions and organizations involved in care of these diseases.

Preparation of the manual

The manual is based on the initial version published in 2007 and its first update in 2010, which were the product of two meetings of regional TB/HIV experts held in Guatemala City and Panama City, respectively, pursuant to the recommendations of the World Health Organization (WHO) and the Pan American Health Organization (PAHO). For this second update, an expert meeting was held in Quito, Ecuador, in May 2015 during the XVII Congress of the Pan American Association of Infectious Diseases, at which time the scope of the manual and

the issues it should address were determined. These issues included the diagnosis, treatment, and prevention of TB/HIV coinfection, as well as its management in case of resistance, in children and in the presence of other comorbidities.

A subsequent search for the most recent PAHO/WHO diagnostic and treatment recommendations for TB, HIV, and TB/HIV was conducted in response to the issues raised. For this purpose, all the evidence-based guidelines published by WHO since 2010 were identified. This manual therefore reflects, compiles, and consolidates these evidence based recommendations, all of which can be found in bibliography that can be easily-accessed online and duly referenced throughout the text. WHO does not have a specific manual for the management of TB/HIV coinfection; hence, the importance and significance of this manual, which compiled the current recommendations.

Manual implementation

It is expected that this updated version of the manual will follow the path of its predecessors and that, once published, distributed, and disseminated online by PAHO, API, and other partners, it will be adopted by national TB and HIV programs and health care workers responsible for diagnosis and treatment in health facilities and other institutions. Its earlier versions were well-received in the countries of the Region, since they responded to a felt need.

Manual Updates

Updates are expected every three years, as new evidence for TB, HIV, and TB/HIV diagnosis and treatment emerges.

Chapter 1

TB and HIV: basic concepts

1.1 Tuberculosis

1.1.1 Epidemiology

Tuberculosis (TB) remains one of the main public health problems. Along with human immunodeficiency virus (HIV), it is one of the leading causes of death worldwide. In 2014, there were an estimated 9.6 million new cases and 1.5 million deaths from TB, the majority of them in developing countries, predominantly in Asia and Africa. There were also an estimated 1.2 million cases of HIV coinfection, with 390,000 deaths from TB/HIV (1).

Despite the progress made, tuberculosis is still a major public health problem in the Region of the Americas, with an estimated 280,000 cases of all types of TB and 17,000 deaths in 2014 (excluding those involving HIV coinfection), the majority of which were preventable. That same year, the countries reported 228,000 new cases of all forms of TB, 76% of which were bacteriologically confirmed. This represented 77% of the estimated new cases, revealing a gap of nearly 65,000 undiagnosed cases. Roughly 95% of the reported cases were in people over the age of 15, the majority of them male (1.7:1). In 2014, 65% of the new cases reported were concentrated in four countries in the Region: Brazil, Haiti, Mexico, and Peru (1).

1.1.2 Etiology and transmission

Tuberculosis is a chronic bacterial infection caused mainly by *Mycobacterium tuberculosis* and occasionally by *Mycobacterium africanum*, *Mycobacterium canettii*, or *Mycobacterium bovis*. It is characterized by the production of a cell-mediated hypersensitivity reaction and granulomas in the affected tissues. *M. tuberculosis* is an obligate aerobe bacillus that, like all mycobacteria, is distinguished by its surface lipids, which make it resistant to discoloration by the acid-alcohol of certain stains. This is why it is also known as an acid-fast bacillus (AFB).

Tuberculosis is transmitted through the air when people with pulmonary tuberculosis (PTB) or tuberculosis of the respiratory tract cough, speak, sing, spit, or sneeze, producing droplet nuclei of less than five microns in diameter that contain tubercle bacilli, which are inhaled by people who have contact with the patient. *M. bovis* is transmitted through the ingestion of unpasteurized milk or dairy products from infected livestock. Except in the case of laryngeal TB, extrapulmonary tuberculosis (ETB), is not considered transmissible (2).

1.1.3 Pathogenesis and immunology

Primary *M. tuberculosis* infection begins when a person inhales microdroplet nuclei (aerosols) containing microorganisms that are able to bypass the bronchial defenses due to their size and penetrate as far as the alveoli. There, the bacilli are ingested by alveolar macrophages, which transport them to the regional lymph nodes. When the infection is not contained at that level, bacilli can reach the bloodstream and spread. The majority of pulmonary lesions or lesions from dissemination heal. Nevertheless, they become potential reactivation foci. The primary infection produces a nonspecific inflammatory response that is usually asymptomatic. If this dissemination occurs, it can result in potentially fatal miliary TB or tuberculous meningitis, especially in infants and young children (2).

About two to ten weeks after primary infection, a primary lesion appears, sometimes visible on x ray, and cell-mediated hypersensitivity response is completed, this can be confirmed by the tuberculin skin test (also known as PPD [purified protein derivative] or the Mantoux test) or the interferon gamma release assay (IGRA). From an immunological standpoint, lymphocytes enter the infected areas and release interleukins, lymphokines, and other chemotactic factors that attract monocytes; these become macrophages and then histiocytes, which, as components of the inflammatory reaction, develop into granulomas. Mycobacteria can persist within a granuloma for years but are prevented from multiplying and disseminating. Granulomatous lesions calcify and sometimes leave a visible residual lesion in the chest x-ray. The parenchymatous lesion at the portal of entry, or Gohn's focus, satellite adenopathies, and the lymphangitis that links both elements, constitute the primary (or Ranke) complex (2).

Regarding TB incubation period, the majority of immunocompetent people (90%) who have the primary infection do not develop the disease and can remain infected but asymptomatic throughout life without transmitting the microorganism to others. Of the 10% that develops the disease, half do so through progression of the primary infection, and the other 50% through reactivation after primary infection (post-primary TB)—in over half of the cases within two years of the primary infection. Tuberculosis also occurs through reinfection—that is, a new infection that exceeds the immune system's capacity to contain it. In such cases, the patient's immune reaction leads to a characteristic pathological lesion which is localized and frequently presents extensive tissue destruction and cavitation. The highest risk of disease is for children under 5, declines toward the end of childhood, and increases again in young adults, the elderly, immunosuppressed people (with AIDS, collagenopathies, etc.), and people with debilitating diseases (i.e., alcoholism, chronic kidney disease, cancer, diabetes). Since tuberculosis is caused by an obligate aerobic bacterium, pulmonary TB is more common than extrapulmonary TB (ETB) (80% and 20%, respectively). In the general population, ETB is more common in children and HIV-positive people (2).

1.2 HIV infection and AIDS

1.2.1 Epidemiology

In 2014, an estimated two million people in Latin America and the Caribbean (LAC) were living with HIV, 46,000 of them children (aged 0-14). That same year, an estimated 100,000 new infections occurred, along with 50,000 deaths from acquired immunodeficiency syndrome (AIDS). Great strides have been made in reducing the incidence of new cases, however: between 2000 and 2014, there was a 24% reduction in new infections. This reduction was more evident in the Caribbean, where a 50% reduction was observed. The estimated number of new infections in children also fell by 78% from its peak in the period 1999-2001. Similar trends were observed in mortality from AIDS, with a 36% reduction between 2000 and 2014 and a 78% reduction in children. These improvements are largely attributable to the expanded use of antiretroviral drugs in the prevention of mother-to-child transmission and greater access to treatment regimens (3).

In most LAC countries, the epidemics are concentrated in key populations in conditions of vulnerability (transsexual women, gays and other men who have sex with men [MSM], sex workers [both male and female], and drug users), who have a higher prevalence of HIV than the general population. HIV prevalence among MSM ranges from 7% to 20% in Latin America and < 1% to 33% in the Caribbean; it is higher among transsexual women, with figures ranging from 15.5% to 31.9%. HIV prevalence among sex workers is estimated at 6.1% in Latin America and up to 8.4% in the Caribbean. A common cluster of contextual factors contributes to HIV transmission in the Region, the most salient being poverty, inequitable access to education and health services, gender inequality, migration, homophobia and transphobia, stigma, and discrimination (4).

1.2.2 Etiology and transmission

AIDS is the final stage of HIV infection. First described in 1981, its pathogenic agent, HIV, was discovered in 1983. The virus consists of a spherical particulate 80-100 nm in diameter with a three-layer structure: an internal or nucleoid layer containing RNA and the nucleoprotein with the enzymes, an icosahedral capsid, and an envelope derived from the host cell. Two types of HIV have been identified: HIV-1, which is the predominant type globally, and HIV-2, which is seen more often in West Africa. Both cause AIDS and are similarly transmitted, although HIV-2 is transmitted less often and has slower progression to AIDS (5).

HIV is transmitted through blood, semen, vaginal secretions, and breastmilk. Sexual transmission is the most common mode of transmission in LAC, and transmission patterns (heterosexual, bisexual, homosexual, or between other MSM or trans people) varies from country to country and at the subnational level (urban versus rural areas). In some LAC countries, a major mode of transmission, especially in large urban centers, is still in drug use, specifically sharing contaminated syringes. As for vertical (mother-to-child) transmission, around one-third of children of HIV-positive mothers are infected in the absence of any type of preventive intervention—in particular, antiretroviral therapy.

Transmission can occur during pregnancy, delivery (the majority of cases), or breastfeeding (4).

Current policies in the countries for the control of blood and blood products have substantially reduced blood-borne transmission. The risk of occupational HIV transmission through needlestick injuries is very low (0.3%), and the risk of transmission through exposure to mucosa is even lower (6).

1.2.3 Pathogenesis and immunology

Like all viruses, HIV cannot reproduce on its own and must make use of appropriate cells for this purpose. HIV infects cells with molecules of the CD4 antigen on their surface, which enables it to bind and enter the cells. These cells are mainly T lymphocytes of the helper subgroup known as CD4 T lymphocytes, which are key actors in cell-mediated immunity. HIV also needs other cell co-receptors called CCR5 and CXCR4. People with CCR5 variations have a lower probability of becoming infected and, if they do become infected, disease progression is slower.

Once it enters a cell, HIV reproduces through its enzymes. Reverse transcriptase transforms viral RNA into DNA, enabling it to use the cell's genetic apparatus, following its introduction to the cell nucleus through integrase. Protease completes the assembly of the new viral particles. Viral replication causes cell death and a steady decline in the number of CD4 T lymphocytes, as well as impairment in their function, leading to immunodeficiency. HIV also affects B lymphocytes (responsible for humoral immunity), creating mixed immunodeficiency, both cellular and humoral. HIV can also infect macrophages, which act as reservoirs of the virus and help disseminate it to other systems (e.g., the central nervous system).

Acute HIV infection can be unnoticed. However, within two to four weeks of exposure, most people have non-specific symptoms, very similar to any viral process (fever, arthralgia, odynophagia, and adenopathies), known as acute retroviral syndrome. In many cases, this initial syndrome, which disappears in a few days, generally does not lead to an HIV diagnosis since the clinical symptoms are non-specific and may not be recognized, especially if physicians are not familiar with them. Furthermore, at least three weeks must pass after infection for conventional serological tests to detect these antibodies. Fourth-generation antibody and antigen tests (e.g., p24) can detect HIV two weeks after infection. This interval between infection and a positive serological test is known as the "window period."

Symptoms of the disease (AIDS) usually appear after a period of asymptomatic infection (clinical latency) that can last anywhere from six to ten years from the time of infection, although some people may experience rapid progression. People often experience symptoms such as chronic fever and diarrhea, accompanied by significant weight loss; these are the result of opportunistic infections that occur because of the decrease in the number of CD4 lymphocytes caused by viral replication. The CD4 lymphocyte count normally ranges from 600 to 1,500

cells/mm³ and opportunistic infections usually occur when count values are below 200 cells/mm³, except for tuberculosis, which can appear with any CD4 value. The severe forms of TB also entail low CD4 counts and usually lead quickly to death (5).

1.3 TB/HIV coinfection

TB/HIV coinfection is a significant global public health problem. In 2014, 1.2 million new cases of TB/HIV coinfection were estimated worldwide (12% of the total TB cases). In the Americas, WHO estimated 36,000 new TB cases infected with HIV for that year (13% of the total TB cases in the Region), making it the region with the second highest HIV prevalence in new TB cases, after Africa. In the countries of the Region, 169,000 new and previously treated TB cases (74%) were tested for HIV and, of these, 21,900 (13%) were found to be coinfecting. This represents 61% of the estimated figure, indicating that roughly 14,000 cases of coinfection had not yet been detected. Moreover, it was reported that 56,800 HIV-positive people had been screened for TB, a higher number than in previous years but still very low. Tuberculosis is the cause of death in one out of three people with AIDS worldwide, and coinfection accounts for 26% of all deaths from TB. The same percentage is seen in the Americas. In 2014, 52% of cases of TB/HIV coinfection in the Americas received preventive treatment with cotrimoxazole, and 63% of the total cases of TB/HIV coinfection received antiretroviral therapy, indicating a gradual, but still insufficient, increase in recent years. The reported number of HIV patients in treatment with isoniazid was 28,500, a figure that is still very low (1).

The impact of TB/HIV coinfection is reciprocal. As the viral load increases, tuberculosis accelerates the progression of HIV infection to AIDS and, thus, to death. HIV infection, in turn, reduces the CD4 lymphocyte count (critically important for starting and sustaining the immune response) and impacts the clinical presentation and course of tuberculosis, since HIV infection:

- promotes the progression to disease in people infected with TB. The risk of the progression of TB infection to disease is 5% in HIV-negative people in the first two years and then <5% for the rest of their life. In HIV-positive people, that risk is 3-13% per year and increases to more than 30% for the rest of their life.
- increases the TB relapse rate.
- increases the risk of TB transmission in the community (as there are more TB/HIV cases).
- increases mortality.
- increases the demands on the health system.
- boosts the development of extrapulmonary forms of TB and negative sputum smears.

In order to address TB/HIV coinfection, 12 collaborative activities to guide TB/HIV prevention and control were established. Countries have been implementing them since 2004 (Table 1) (7).

Table 1. Collaborative TB/HIV activities

A. Establish and strengthen the mechanisms for delivering integrated TB and HIV services

- A.1. Set up and strengthen a coordinating body for collaborative TB/HIV activities functional at all levels
- A.2. Determine HIV prevalence among TB patients and TB prevalence among people living with HIV
- A.3. Carry out joint TB/HIV planning to integrate the delivery of TB and HIV services
- A.4. Monitor and evaluate collaborative TB/HIV activities

B. Reduce the burden of TB in people living with HIV and initiate early antiretroviral therapy (*the Three I's for HIV/TB*)

- B.1. Intensify TB case-finding and ensure high quality antituberculosis treatment
- B.2. Initiate TB prevention with Isoniazid preventive therapy and early antiretroviral therapy
- B.3. Ensure control of TB Infection in health-care facilities and congregate settings

C. Reduce the burden of HIV in patients with presumptive and diagnosed TB

- C.1. Provide HIV testing and counselling to patients with presumptive and diagnosed TB
- C.2. Provide HIV prevention interventions for patients with presumptive and diagnosed TB
- C.3. Provide co-trimoxazole preventive therapy for TB patients living with HIV
- C.4. Ensure HIV prevention interventions, treatment and care for TB patients living with HIV
- C.5. Provide antiretroviral therapy for TB patients living with HIV

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Chapter 2

TB diagnosis in HIV-positive people

KEY RECOMMENDATIONS

- Screen HIV-positive adults and adolescents for TB using a clinical algorithm. People who report cough, fever, weight loss, or night sweats may have active TB and should be studied for TB and other diseases (Strong recommendation, medium-quality evidence) (1).
- Xpert® MTB/RIF **should** be used as an initial diagnostic test for adults in suspected cases of TB associated with HIV or multidrug-resistant TB (MDR-TB), instead of conventional smear microscopy, culture, and drug susceptibility testing (DST). (Strong recommendation, high-quality evidence) (2).
- Lateral-flow urine lipoarabinomannan assay **can be used** as support in the diagnosis of TB in HIV-positive adults hospitalized with signs or symptoms of TB (pulmonary and/or extrapulmonary) and a CD4 count ≤ 100 cells/ μ L or in gravely ill patients with HIV (with the following danger signs: respiratory rate > 30 /min, temperature $> 39^{\circ}\text{C}$, heart rate > 120 bpm and inability to walk unassisted) regardless of the CD4 count or when the CD4 count is unknown (Conditional recommendation, low-quality evidence) (3).
- For the study of latent tuberculous infection (LTBI) in HIV-positive people, the tuberculin skin test (PPD or Mantoux test) **can** be used in low and lower-middle income countries with a high TB burden (incidence > 100 per 100,000 population). In high or upper-middle-income countries, the PPD or interferon gamma release assay (IGRA) can be used. (Strong recommendation, very low-quality evidence) (4).

Tuberculosis in HIV-positive people can be pulmonary or extrapulmonary. As in the general population, pulmonary TB is the most common type in this group and, therefore, is the most relevant type from a clinical standpoint. Given its contagiousness, it is also the most important from a public health standpoint (1, 4).

2.1 Pulmonary tuberculosis

PTB is diagnosed the same way in HIV-positive and HIV-negative people and is based on:

- Clinical manifestations
- Bacteriological tests
- Diagnostic imaging and other methods

2.1.1 Clinical manifestations

Unlike PTB in an HIV-negative person, who can present florid symptoms, in an HIV-positive person, relevant symptoms may be limited to fever, weight loss, and night sweats. The clinical presentation usually varies. Chronic cough and hemoptysis are less common, because these patients present less cavitation, inflammation, and endobronchial irritation. A cough in an HIV-positive patient should always be investigated through a sputum study for bacteriological diagnosis of TB, regardless of its characteristics or how long the patient has had it. Generally, physical examination does not help distinguish pulmonary TB from other pulmonary infections, and often there are no auscultatory signs (5).

According to the current classification of TB cases based on anatomical location, miliary or disseminated TB is considered PTB and is described below (6).

2.1.1.1 Miliary or disseminated TB (5)

Miliary tuberculosis results from hematogenic and systemic dissemination of the tuberculous bacilli, produced by a recent primary infection or the erosion of a tuberculous lesion to a blood vessel. Patients commonly present constitutional symptoms such as fever or weight loss, rather than respiratory symptoms. Physical examination may reveal choroidal tubercles in the eye fundus and hepatosplenomegaly on abdominal examination. Miliary tuberculosis is an underdiagnosed cause of advanced AIDS wasting syndrome, since it often presents as an insidious and inexplicable febrile process.

Chest x-ray typically shows a diffuse micronodular infiltrate reminiscent of millet (Latin for millet or sorghum), from which the term "miliary" is derived. The x-ray may also appear normal (20-60% of cases) in advanced cases, due to severe immunosuppression and the consequent inability to mount an inflammatory response. A complete hemogram may reveal anemia or pancytopenia, and liver function tests may be abnormal. Definitive diagnosis of miliary tuberculosis is

sometimes possible through Xpert® MTB/RIF or sputum, cerebrospinal fluid (CSF), or blood culture, or bone marrow or liver biopsy.

Differential diagnosis of miliary or disseminated tuberculosis includes histoplasmosis, as well as *Pneumocystis jirovecii* pneumonia, disseminated *Mycobacterium avium* complex infection, and neoplastic syndrome. In children, it should be differentiated from interstitial lymphoid pneumonitis.

In Central and South America, where histoplasmosis is an endemic infection caused by the *Histoplasma capsulatum* fungus, it may present in HIV-positive people as systemic mycosis, which can be an opportunistic infection even more common than tuberculosis. Histoplasmosis tends to exhibit the same clinical manifestations as miliary or disseminated tuberculosis, with fever, weight loss, and hepatosplenomegaly, identical laboratory results showing anemia or pancytopenia, and identical diagnostic imaging with diffuse micronodular infiltrate. Differential diagnosis between these two conditions can be difficult. In addition to hematological alterations, systemic histoplasmosis often involves elevated alkaline phosphatase levels and, above all, marked elevations in lactic dehydrogenase. The fungus can sometimes be seen in a peripheral blood smear; however, given the unavailability of other diagnostic studies such as hemocultures, and the length of time they take, a definitive differential diagnosis can be made only through bone marrow aspiration and biopsy or identification of the fungus in a smear from oral or mucous lesions.

2.1.2 Bacteriological diagnosis (7)

The bacteriological methods are:

- Xpert® MTB/RIF and other molecular assays
- Smear microscopy
- Culture
- Immunochromatography

Every HIV-positive person should be tested for TB if any of the four key symptoms are present: fever, cough, weight loss, and night sweats. The definitive diagnosis of PTB is made with the isolation of *M. tuberculosis* in sputum or samples from bronchoalveolar lavage, preferably through molecular assay. In the absence of this, through smear microscopy and culture (5)

2.1.2.1 Xpert® MTB/RIF and other molecular assays

Detection and direct identification of *M. tuberculosis* in a clinical specimen is possible through nucleic acid amplification methods (real-time polymerase chain reaction, or PCR) such as the Xpert® MTB/RIF assay. These tests have the advantage of being able to detect *M. tuberculosis* quickly.

The Xpert® MTB/RIF assay is currently recommended as the diagnostic method of choice for HIV-positive people. It is fully automated and contained, poses a low biological risk, is appropriate for any laboratory level, and yields results in less

than two hours. It detects the presence of both *M. tuberculosis* and rifampicin resistance. It is 40% more sensitive than smear microscopy. In comparison with culture, its sensitivity in patients with a positive sputum-smear is 98.2% and in patients with a negative sputum smear, 68%. Its specificity is > 99%. In the case of TB/HIV coinfection, its sensitivity is 79%. The Xpert® MTB/RIF assay is also recommended in cases of suspected MDR-TB and for the diagnosis of pediatric TB in pulmonary samples. It is not indicated for bacteriological monitoring of TB treatment (2, 8)

Another molecular bioassay is the molecular line-probe assay (LPA), also known as Genotype or Hain test, which is useful for positive sputum smears or cultures. It detects rifampicin and isoniazid resistance, and its results are available in less than two days. It is recommended for reference laboratories, since it requires a high biosafety level. It is not used for monitoring TB treatment.

2.1.2.2 Smear microscopy

Smear microscopy is the direct microscopic examination of sputum samples for acid-fast bacilli (AFB) using the Ziehl-Neelsen stain. It is inexpensive, easy to use, and the results can be available in a few hours.

Smear microscopy is still useful for diagnosing tuberculosis in HIV positive people in the absence of molecular bioassays. Given its low sensitivity (67%), a culture should be done for all suspected TB cases. Two to three sputum samples are taken from all HIV patients with a cough, regardless of how long they have had it, based on the national standard. Currently, according to WHO recommendations, two sputum samples are sufficient, provided that countries have achieved optimal quality control of smear microscopy, certified through an external quality assurance system.

The best sputum is the first of the morning, and a practical way of collecting two or three samples is the following:

Day 1 (sample 1)

After receiving instructions, the patient gives a sputum sample on the day of his visit to the health facility (the sample should be collected in very-well-ventilated settings, and health workers should ideally use N-95 respirators or collect the sample outdoors). That day, the patient will be given a receptacle for a second sample to bring the next day.

Day 2 (samples 2 and 3)

- The patient collects a sample at home early in the morning and takes it to the health facility.
- The patient gives a third sample in the health facility when he brings the second sample

To prevent the loss of suspected cases, it is important always to take advantage of the first visit and, insofar as possible, avoid the patient's unnecessary return to provide sputum samples. It should be recalled that the probability of obtaining

a positive sputum smear in HIV patients with mild immunodeficiency is the same as for an HIV-negative person. On the other hand, the probability of obtaining positive sputum smear from an HIV patient in the AIDS stage is low. In any case, a negative sputum smear does not rule out a diagnosis of PTB, and a culture should always be done. In suspected cases with a dry cough, sputum induction can be used, provided that infection control measures can be guaranteed to prevent the risk of nosocomial transmission (No. 95 respirators for health workers and negative pressure or very good natural ventilation in the area where the procedure is performed).

The sputum induction technique involves safe, noninvasive collection of sputum through nebulizations that facilitate expectoration. The procedure should be performed in the morning in a fasting state after cleansing the upper respiratory tract to minimize contamination from nasal secretions or saliva. Ten minutes before starting, an inhaled beta-adrenergic should be administered to the patient to prevent bronchoconstriction, followed by nebulization for 10 to 15 minutes with a 3-5% hypertonic solution; the patient should then be instructed to cough and spit. The sputum sample is collected in a container provided for this purpose. The procedure can be repeated once, half an hour later, if the sample is inadequate.

In HIV-positive people with suspected pulmonary TB, a positive sputum smear provides the diagnosis of the disease, and TB treatment should begin immediately. If the sputum smear is negative, the investigation of TB should continue with a culture, DST, and chest x ray.

2.1.2.3 Culture

Sputum culture for *M. tuberculosis* is far more sensitive than smear microscopy for the diagnosis of pulmonary TB and can increase diagnostic confirmation by 15-20%. While more expensive and less accessible because it requires greater training and technological capacity, its contribution to diagnosis is important, though slower (2-8 weeks, depending on the method).

There are two types of culture, based on the medium used:

1) *In solid media:*

- a. **Lowenstein-Jensen medium:** The most common medium worldwide, it is a traditional method that uses a solid, coagulated-egg-based medium with a close-to-neutral pH. Its advantages are its simplicity, the possibility of doing a colony count, and its affordability. Its drawback is that bacterial growth is slow and requires a manual reading. The procedure requires an equipped laboratory with adequate biosafety and skilled personnel. Results are available in 2-8 weeks.
- b. **Ogawa Kudoh:** This is an inexpensive procedure with a low level of complexity and biohazard. Laboratories that perform it must have the same level of biosafety as for smear microscopy. It is very useful in cases where a laboratory has an incubator but no centrifuge. It is also useful for transporting a sputum sample from an outlying area to a reference laboratory. It is sensitive enough to ensure that the culture will help confirm the diagnosis of pulmonary TB in cases with a negative sputum smear and useful for recovering bacilli from the sputum of bacilliferous patients who need drug susceptibility testing. Results are available in 2-8 weeks.

2) *In liquid media*: These techniques are more sensitive than those that employ solid media and serve as reference standard for all cultures. They use enriched semisynthetic media to promote growth of the tuberculous bacillus, and the reading is based on quantification of O₂ reduction and CO₂ increase from reproduction of the bacillus. The reading is automated, using sensors that detect changes in the pressure of these gases. The most widespread type is the BACTEC MGIT[®]. Use of these cultures cuts the average diagnosis time to 10 days; however, they are more expensive than traditional media and require laboratories with a high biosafety level and sufficient numbers of trained personnel.

Sputum culture should be routine in HIV-positive patients, because:

- It increases the diagnosis of PTB, particularly in patients with advanced disease, who tend not to be bacilliferous
- It is necessary for typing tests (to determine whether the agent is *M. tuberculosis* or a non-tuberculous mycobacterium)
- It is required for TB DST (see Chapter 6).

2.1.2.4 Immunochromatography (3)

The lateral flow urine lipoarabinomannan assay (LF-LAM) detects the LAM (lipoarabinomannan) antigen of *M. tuberculosis* in urine. This LAM antigen is a lipopolysaccharide present in the cell wall of the mycobacteria that is released from metabolically active or degenerating cells and appears to be present only in people with active TB. LF-LAM is available commercially. The test is performed manually by applying 60 µL of urine to an immunochromatographic strip and incubating it at room temperature for 25 minutes. It is then inspected with the naked eye. The intensity of any visible band on the strip is compared with a reference standard. This test's advantage over smear microscopy is that urine is easy to collect and store and does not pose the risk of infecting other people that sputum collection does.

LF-LAM is recommended only as support for TB diagnosis in HIV-positive people hospitalized with signs or symptoms of TB (pulmonary and/or extrapulmonary) whose CD4 count is ≤ 100 cells/ μ or in gravely ill HIV-positive patients (with the following danger signs: respiratory rate > 30 /min., temperature $> 39^{\circ}\text{C}$, heart rate > 120 bpm and unable to walk unassisted), regardless of their CD4 count or where the CD4 count is unknown.

2.1.2.5 Drug susceptibility testing

Drug susceptibility testing (DST) involves tests that determine the effectiveness of a particular antimicrobial drug in eliminating or sufficiently inhibiting the pathogen responsible for an infection. In the case of TB, DST for first- and/or second-line drugs is an important part of the diagnosis—mainly in settings where drug resistance is common or poses a high risk to the patient's life, as in the case of HIV-positive people.

The following methods can be used for DST:

1) *Conventional methods*

a) *In solid media*:

- Proportion method in Lowenstein-Jensen medium: The reference standard for DST. It can be done using an indirect technique (by seeding several

centesimal dilutions of bacilli recovered from the culture) or a direct technique (by seeding samples with a high bacillary load). The results are usually available in 4-8 weeks.

- Nitrate reduction method, or Greiss method: It is based on the *M. tuberculosis* property of reducing nitrate to nitrite, which is revealed as a change of color in the culture medium. It is less expensive than DST in liquid media, and its specificity and sensitivity to isoniazid and rifampicin is comparable to that of DST in traditional solid media. Simple to perform with no need for sophisticated equipment, it may be appropriate in resource-constrained laboratories. The results can be available in 7 days.

b) **In liquid media:** A method adapted from the proportion method in solid medium for fluid cultures. The results can be available in 4-14 days. The most commonly used method in the Americas is the MGIT®.

2) Rapid methods

- Molecular assays: These are the most advisable methods, due to the speed with which the results are obtained. These are described under bacteriological molecular assay methods:
 - ⊙ Xpert® MTB/RIF: for rifampicin
 - ⊙ LPA: for rifampicin and isoniazid.

2.1.3 Role of chest x-rays in the diagnosis of pulmonary TB (9, 10)

Pulmonary TB associated with HIV does not exhibit any pathognomonic radiological sign, but chest x-rays are highly sensitive for suspecting the disease. A suspicious reading does not confirm the diagnosis but calls for microbiological studies in any patient where TB is suspected. It should be noted that chest x-rays are less sensitive for TB in HIV positive people than in HIV-negative people.

In a person with PTB and HIV, the degree of immunodeficiency determines the chest x-ray findings (Table 2). In cases of mild immunodeficiency, the chest x-ray is no different than that of a patient without HIV (cavitations, infiltrates in the vertices). In cases of severe immunodeficiency, the radiological findings tend to be atypical, with a predominance of lymphatic involvement and signs of hematogenous dissemination (diffuse interstitial infiltrates or miliary pattern).

Table 2. Findings in chest x-rays of patients with HIV and pulmonary TB

Mild immunodeficiency	Severe immunodeficiency
Cavitation	Cavitation (very rare)
Infiltrates in upper lobes	Infiltrates in lower lobes
Bilateral infiltrates	Unilateral infiltrates
Pleural effusion	Pleural effusion (infrequent)
Intrathoracic lymphadenopathy (infrequent)	Intrathoracic lymphadenopathy
Pulmonary fibrosis and loss of volume	Diffuse interstitial infiltrate
Consolidation	Normal chest x-ray

2.1.4 Differential diagnosis of pulmonary tuberculosis (5)

An HIV patient with suspected PTB and negative bacteriology may not have tuberculosis. It will be necessary to reassess the patient, looking for conditions that could be confused with tuberculosis. Other pathologies must always be considered in an HIV patient who is asymptomatic or has mild immunodeficiency (Table 3). The presence of conditions that indicate advanced immunodeficiency, such as oral candidiasis, could serve to guide the search for other potential opportunistic infections.

Acute bacterial pneumonia is common in people living with HIV. A brief history of symptoms tends to differentiate bacterial pneumonia from PTB. The most common pathogen is *Streptococcus pneumoniae*, which generally responds well to treatment with penicillin or cephalosporins. However, the resistance profile of every context or country should be considered. To preserve future treatment options, it is important not to use fluoroquinolones or aminoglycosides (see second-line TB drugs) if PTB is a possibility.

Pneumocystis jirovecii pneumonia is a common subacute pneumonia with a high mortality rate in HIV-positive people. Definitive diagnosis depends on demonstration of the presence of cysts in induced sputum, bronchoalveolar lavage, or transbronchial biopsy. These studies are not available everywhere, however. Thus, the diagnosis of *P. jirovecii* pneumonia is often based on the clinical manifestations of fever, dry cough, and dyspnea (with or without an x-ray showing diffuse bilateral interstitial infiltrates) and the ruling out of PTB. In this context, the diagnosis is based on the clinical response to the administration of cotrimoxazole (trimethoprim-sulfamethoxazole, TMP/SMX) at high doses and steroids, the latter being indicated when the PaO₂ in arterial gases is < 70 mm Hg. This empirical treatment, combined with oxygen, can save the life of an HIV patient, and when the patient is dyspneic, it should not be deferred for lack of diagnostic tools or arterial gas values. A complete sequential or simultaneous course of TB and *P. jirovecii* pneumonia treatment may be necessary.

Although *P. jirovecii* pneumonia prophylaxis is indicated when the HIV patient has a CD4 lymphocyte count of < 200 cells/mm³, given the frequency and high mortality associated with the disease, every patient with suspected or confirmed TB/HIV coinfection should receive TMP/SMX prophylaxis (one 160/800 mg tablet per day p.o.), at least until the CD4 lymphocyte count is known, because this is a drug that is usually available and has proven to substantially reduce mortality in these patients.

Histoplasmosis, which occurs systemically with mild or no respiratory symptoms in HIV patients, is a very common opportunistic infection in the Region of the Americas and should also be included in the differential diagnosis of PTB with negative smear microscopy.

Table 3 Differential diagnosis of pulmonary tuberculosis in HIV-positive people

Infectious diseases	Noninfectious diseases
<p><i>Bacterial pneumonia:</i> Brief history. Fever. Responds to antibiotics</p>	<p><i>Lung cancer:</i> Risk factors (smoking, advanced age)</p>
<p><i>Lung abscess:</i> Productive cough with abundant fetid purulent sputum. Hydro-aerial level in chest x-ray</p>	<p><i>Congestive heart failure:</i> Symptoms and signs of heart failure (orthopnea, paroxysmal nocturnal dyspnea, hemoptysis, congestive hepatopathy, lower limb edema)</p>
<p><i>Histoplasmosis:</i> Fever and weight loss. Mild or no respiratory symptoms. Pancytopenia. Hepatosplenomegaly. Chest x-ray with diffuse bilateral interstitial infiltrate.</p>	<p><i>Chronic obstructive pulmonary disease:</i> Risk factors (age > 40, smoking, exposure to smoke from firewood, chronic symptoms, episodes of wheezing, dyspnea, symptoms of right-sided heart failure)</p>
<p><i>Bronchiectasis:</i> Cough with abundant sputum. Responds to antibiotics.</p>	<p><i>Asthma:</i> Recurrent intermittent cough and dyspnea, generalized episodes of wheezing. Reverts spontaneously or with bronchodilators. Nocturnal onset.</p>
<p><i>Pneumocystis:</i> Dry cough and dyspnea. Chest x-ray with diffuse bilateral interstitial infiltrate.</p>	

2.2 Extrapulmonary tuberculosis (5, 10)

The ETB case definition is any case of bacteriologically confirmed or clinically diagnosed TB involving organs other than the lungs.

The common forms of HIV-associated ETB are:

- Lymph node
- Pleural
- Meningeal
- Abdominal
- Pericardial
- Other: osteoarticular, genitourinary, cutaneous, ocular, and laryngeal

2.2.1 Clinical manifestations and diagnosis

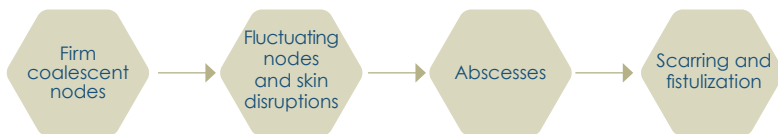
ETB has the same clinical symptoms in HIV-positive and HIV-negative people. ETB patients present with constitutional symptoms (fever, night sweats, or weight loss) and specific symptoms related to the site of the tuberculosis. ETB is generally hard to diagnose. Diagnosis can be presumptive if other conditions can be ruled out.

The diagnosis of ETB depends on the availability of diagnostic tools such as x-rays, ultrasonography, biopsy, and cultures and is not always etiological. Specimens from the site of the suspected ETB should be cultured (e.g., lymph nodes, blood, bone marrow, etc.). The evidence shows that Xpert® MTB/RIF is useful for the diagnosis of meningial and lymph node TB, but the evidence of its usefulness for other forms of ETB is still out.

Every patient with ETB should be tested for PTB, preferably with Xpert® MTB/RIF or other molecular assays, or with smear microscopy and a chest x-ray. Many patients with ETB do not have concomitant PTB, however. If the two are present, the case is classified as PTB. The main forms of ETB are described below.

2.2.2 Lymph node tuberculosis

This is the most common form of ETB in HIV-positive or negative patients. The most commonly affected lymph nodes are the cervical nodes. However, other lymph nodes, such as the axillary and mediastinal nodes, can also be affected. The natural progression of the mode of lymph node compromise should be borne in mind when suspecting lymph node tuberculosis:



Assessment of a patient with lymphadenopathies should begin with a clinical history and a complete physical examination. If that does not explain the enlarged nodes, they should be studied. In adults and adolescents with HIV, differential diagnosis of lymph node tuberculosis includes:

- Persistent generalized lymphadenopathy (PGL)
- Histoplasmosis
- Lymphoma

PGL appears in up to 50% of patients with recent HIV infection, is self-limited, and does not require specific treatment. This diagnosis is suggested by adenopathies with the following characteristics:

- Diameter < 1 cm
- 2 or more extrainguinal sites
- Duration of 3 months or more

The lymph nodes are symmetrical, not painful on palpation, and often appear in the posterior cervical and epitrochlear region. This condition progresses slowly during the course of HIV infection and disappears before the patient develops AIDS. It is a clinical diagnosis that requires investigation only if there are symptoms

or signs of another disease. Differential diagnosis in children includes bacterial abscesses and lymphoma.

Lymph node characteristics that warrant investigation are:

- Large (> 4 cm in diameter) or growing
- Asymmetrical
- Sensitive or painful and not associated with local infections
- Fluctuating and coalescent
- Accompanied by constitutional symptoms (fever, night sweats, weight loss)
- Parahilar or mediastinal nodes visible in chest x-ray

The investigation of lymphadenopathies includes two procedures: fine-needle aspiration cytology (FNAC) and biopsy. FNAC is a simple procedure that usually takes a few minutes and is done on an outpatient basis (Annex 1). When cytotechnologists or pathologists are available, an immediate diagnosis can be made (Table 4). If FNAC does not yield the diagnosis or suggests malignancy, a lymph node biopsy is performed to contribute to the diagnosis (Table 5).

Table 4. Diagnosis using FNAC

Study	Results	Diagnosis
Observation of the aspirated material	Caseous material (cheese-like)	TB
Smear for AFB	AFB present	TB
Smear for cytology	Malignant cells	Malignancy

FNAC: Fine-needle aspiration cytology; TB: tuberculosis; AFB: acid-fast bacilli.

Table 5 Diagnosis with biopsy

Study	Results	Diagnosis
Observation of the sliced sample	Caseous material (Cheese-like)	TB
Fresh-slice smear for AFB	AFB present	TB *
Freshly processed lymph node	Positive TB culture	TB
Lymph node in formalin for histology	Granuloma and AFB Malignant cells	TB Malignancy

* Non-tuberculous mycobacteria can also produce lymphadenopathies with AFB present in the smear. AFB: acid-fast bacillus; TB: tuberculosis.

When lymph node tuberculosis is suspected, interpretation of the biopsy results should take the effects of immunosuppression into account. In cases of mild immunosuppression, it is more common to find cheese-like lesions (caseous

necrosis) with few or no AFB. In cases of severe immunosuppression, there may be little cellular reaction with high AFB counts.

2.2.3 Pleural tuberculosis

The clinical manifestations of pleural tuberculosis are a combination of constitutional symptoms: fever, night sweats, and weight loss; with localized symptoms or findings produced by pleural effusion, including:

- Pleuritic chest pain
- Dyspnea
- Shifting of the trachea and mediastinum towards the opposite side of the effusion
- Reduced chest expansion
- Dull percussion sounds on the side of the effusion
- Decreased breath sounds on the side of the effusion

The chest x-ray typically shows:

- Unilateral homogeneous radiopacity
- Concave superior edge (Damoiseau line).

In a person with HIV and pleural effusion, diagnostic thoracentesis is always necessary (see procedure in Annex 2) and, ideally, a pleural biopsy.

In pleural tuberculosis, the pleural fluid is typically characterized by:

- Yellowish color, occasionally blood-stained
- Moderate lymphocyte-predominant leukocytosis
- Exudate (proteins > 3 g/dL).

When a cytochemical analysis of the pleural fluid is not possible, an exudate can be diagnosed if, after letting the fluid stand, it coagulates. For this reason, a low protein concentration result in pleural fluid that has been transported with delay or left standing in the laboratory, should be interpreted with caution. Microscopic examination rarely reveals the presence of AFB, and *M. tuberculosis* cultures take too long to guide immediate clinical management. A positive biochemical marker such as adenosine deaminase (ADA) contributes to the diagnosis of pleural tuberculosis. In a study, the sensitivity, specificity, positive predictive value, and negative predictive value were 93%, 95%, 96%, and 90%, respectively, in HIV patients, with a cut-off point of 35 IU/L (11).

A blind pleural biopsy using an Abrams needle can make an histopathological diagnosis of pleural tuberculosis possible. However, since distribution of the lesions in the pleura is not uniform, the procedure yields a diagnosis in only 75% of cases. Biopsies must be repeated to improve diagnostic performance. A pleuroscopy-guided biopsy of the pleura offers greater diagnostic potential, since it allows a direct visualization of the lesions before specimen collection. Both procedures are not necessary if symptoms are compatible with tuberculosis and a lymphocytic exudate was obtained with thoracentesis.

Differential diagnosis of pleural tuberculosis includes:

1. Cancer
2. Parapneumonic effusion
3. Pulmonary embolism
4. Amebic liver abscess (right-sided pleural effusion)

A tuberculous empyema can appear when a tuberculous cavity ruptures toward the pleural space. Aspiration yields thick, white-yellowish pus. In some cases, chest tube placement for pus drainage is necessary; pus should be examined for AFB and non-AFB, since it needs to be differentiated from a bacterial empyema. In this latter case, the patient is considered more compromised and toxic.

2.2.4 Tuberculous meningitis

The most common form of central nervous system tuberculosis is tuberculous meningitis. The spread of *M. tuberculosis* to the meninges occurs through hematogenic dissemination or rupture of a cerebral tuberculoma into the subarachnoid space. A high index of suspicion is necessary to make the diagnosis. Onset is marked by malaise, headache, and fever, followed by two or three weeks of persistent headache, meningism, vomiting, confusion, and focal neurological signs. The paralysis of cranial nerve pairs, most commonly the III but also of the IV and VI, resulting from the development of exudates and inflammation in skull base, should suggest tuberculous meningitis. Tuberculomas and vascular occlusion can produce focal neurological deficits and seizures. Rapid clinical deterioration is associated with the development of communicating hydrocephalus.

The diagnosis of tuberculous meningitis is based on clinical manifestations and analysis of CSF obtained through lumbar puncture (see procedure in Annex 3). In TB meningitis, the opening CSF pressure is high. The fluid is clear or slightly cloudy (xanthochromic). Generally, the leukocyte count reveals lymphocyte predominance. However, in the first 48 hours there may be a predominance of polymorphonuclear leukocytes, elevated proteins, and normal or slightly low glucose levels. Microscopic examination of the CSF rarely reveals the presence of AFB. CSF culture takes time and is often negative. An elevated ADA in CSF contributes to the diagnosis. It is important to validate the ranges of positivity for each country or population through research (the cut-off point usually ranges from 9 to 10 IU/L). CSF PCR has high specificity but low sensitivity, meaning that a negative result does not rule out the diagnosis.

If the patient has a focal neurological deficit (cerebral space-occupying lesion) or if the fundus of the eye shows papilledema (increased intracranial pressure), a CT scan of the brain prior to the lumbar puncture is recommended, if available. When there are clear signs of intracranial hypertension, if a CT scan is not feasible and TB meningitis is a possibility, it is recommended to start empirical treatment for TB immediately instead of risking the patient's life with a lumbar puncture or delaying treatment.

In HIV-positive people, a Gram stain and an India ink stain of the CSF should always be ordered, in addition to the Ziehl-Neelsen stain, due to the need to differentiate tuberculous meningitis from bacterial meningitis and, especially, cryptococcal meningitis, which could have very similar clinical manifestations and CSF characteristics (Table 6).

Cryptococcus neoformans fungus infection is contracted from the environment through inhalation but rarely produces respiratory symptoms and is never contagious. It is the most common form of meningitis in HIV-positive people, its onset is insidious and the symptoms nonspecific. The most common symptoms are fever and persistent headache. On physical examination, less than 20% of patients have a stiff neck or other focal neurological signs. Given the similarities between tuberculous meningitis and cryptococcal meningitis, in terms of CSF alterations and the frequency with which India ink staining is negative in the latter (20-40%), definitive differentiation of the diseases is possible only by detecting the cryptococcal antigen or culturing the cerebrospinal fluid.

Table 6. Analysis of cerebrospinal fluid to rule out diagnoses other than TB

CSF	Appearance	Leukocytes	Proteins (mg/dL)	Glucose (mg/dL)	Microscopy
Normal	Clear	< 5/mm ³	20-45	50-80	Negative
Tuberculous meningitis	Clear or slightly cloudy (xanthochromic)	Elevated PMN > L (early) L > PMN	Elevated	Normal or slightly low	Positive AFB: < 20%
Cryptococcal meningitis	Clear or slightly cloudy	Elevated L > PMN	Elevated	Low	Positive India ink: 60-80%
Bacterial meningitis	Demonstrably cloudy	Elevated Presence of PMN	Elevated	Low	Gram stain: Presence of bacteria
Viral meningitis	Clear	Elevated PMN > L (early) L > PMN	Elevated	Normal	Negative
Neurosiphilis	Clear or cloudy	L > PMN	Elevated	Normal	Negative
Neoplasia	Clear or xanthochromic	> L/ normal	Elevated or normal	Low or normal	Negative
Leptospirosis	Clear	Elevated L > PMN	Elevated	Normal or low	Negative

CSF: cerebrospinal fluid; L: lymphocytes; PMN: polymorphonuclear

2.2.5 Abdominal tuberculosis

Abdominal tuberculosis can be:

- Gastrointestinal
- Mesenteric
- Peritoneal

Tuberculosis of the gastrointestinal tract can present simply as an abdominal mass in either the stomach area or cecum. In the latter case, a mass in the lower right quadrant of the abdomen can sometimes be palpated. In its intestinal, mesenteric, and genitourinary variants, abdominal tuberculosis may often present as an acute abdomen. It is most commonly located in the mesenteric lymph nodes or small intestine, and when disseminated to the peritoneum, it produces ascites. In addition to ascites, patients with peritoneal tuberculosis exhibit constitutional symptoms such as fever and weight loss. Hepatomegaly and adenopathies or abdominal masses may be present. In these cases, physical examination reveals ascites.

Abdominal tuberculosis is usually diagnosed during surgery for acute abdomen or an exploratory laparotomy, since it is unlikely to be suspected clinically, given the insidious and nonspecific nature of the symptoms: fever, diarrhea, abdominal pain, and weight loss.

The diagnosis of peritoneal tuberculosis is generally presumptive and is made through paracentesis (see procedure in Annex 4). Analysis of the ascitic fluid shows a yellowish fluid that is sometimes cloudy or blood-stained, indicative of lymphocytic exudate. Microscopic examination or culture of ascites rarely shows the presence of AFB. It should be borne in mind that a gravely ill emaciated patient has low levels of serum albumin and, therefore, the fluid does not exceed the conventional protein threshold of > 3 g/dL to classify it as an exudate. In such cases, it is important to calculate the quotient of the protein concentration in the ascites fluid and the serum, which, when > 0.5 , indicates exudate. A positive ADA in ascitic fluid contributes to the diagnosis (with a cut-off point of 39 IU/L, with sensitivity and specificity values of 100% and 97%, respectively). Abdominal ultrasound can yield findings compatible with tuberculosis, such as enlarged mesenteric or retroperitoneal lymph nodes. A CT scan of the abdomen can reveal necrotic adenopathies or psoas abscesses. A chest x-ray should be taken to rule out concomitant PTB (12).

Differential diagnosis of abdominal tuberculosis should consider amebiasis, lymphoma, colon cancer, appendiceal plastron, and Crohn's disease. Tubo-ovarian TB should be differentiated from a salpingitis, abscess, or ruptured ectopic pregnancy.

Other differential diagnoses based on the characteristics of the ascitic fluid are:

- Transudates: congestive heart failure, renal failure, nephrotic syndrome, portal hypertension.
- Exudates: neoplasia, other infections that cause peritonitis.

2.2.6 Pericardial tuberculosis

Patients with tuberculous pericarditis present with constitutional symptoms, such as fever and weight loss, and cardiovascular symptoms, such as chest pain, dyspnea, cough, ascites, and lower limb edema. On physical examination, tachycardia, low blood pressure, muffled heart sounds, pericardial friction rub, and signs of right-sided heart failure can be found. Chest x ray reveals a jug-handle type of cardiac silhouette, and electrocardiogram shows changes in the ST segment and T wave, with low-voltage QRS complexes.

The definitive diagnosis is made through a pericardiocentesis, a pericardial window with biopsy, or both. This is only safe when an echocardiogram and an experienced surgeon are available. The pericardial fluid is a lymphocytic exudate. A positive ADA in the pericardial fluid contributes to the diagnosis (with a cut-off point of ≥ 40 IU/L, sensitivity of 88%, and specificity of 83%). Pericardial effusions rarely reveal the presence of AFB. An emergency therapeutic pericardiocentesis is necessary if there is cardiac tamponade.

In regions where TB and HIV are present, tuberculosis is always the most likely cause of pericardial effusion. Other differential diagnoses of pericardial effusion, based on the characteristics of the fluid, are (Table 7):

- Transudates: heart failure, renal failure, liver failure, hypothyroidism.
- Exudates: neoplasia, bacterial or viral pericarditis, collagenopathy.

Table 7. Characteristics of exudates and transudates that make it possible to evaluate pleural, abdominal, and pericardial fluids

Test	Exudate	Transudate
Proteins	> 3 g /dL	< 3 g /dL
Fluid/serum protein ratio	> 0.5	< 0.5
LDH fluid	> 200 IU/dL	< 200 IU/dL
Fluid/serum LDH	> 0.6	< 0.6

LDH: lactate dehydrogenase; IU: international units.

Figure 1 shows the algorithm for clinical diagnosis of ETB (10):

Figure 1. Algorithm for clinical diagnosis of ETB.

Suspect ETB in patients with:

Cough lasting two or more weeks, or

- Involuntary weight loss with:
- Night sweats
- Temperature >37.5°C or feverish
- Dyspnea (effusion or pericarditis)
- Cervical or axillary adenopathies
- Chest x-ray
 - ◊ Miliary or diffuse opacities
 - ◊ Cardiac dilation (especially if asymmetrical and rounded)
 - ◊ Pleural effusion
- Intrathoracic adenopathies
- Subacute or chronic headache or altered consciousness

Suspect disseminated tuberculosis in all HIV positive people who experience rapid or extreme weight loss, fever, and night sweats.

If TB is suspected, determine HIV status

If HIV status is unknown or the last test is negative, counsel and order a rapid HIV test.

- Explain that this will affect the way the disease will be investigated and treated
- Discuss the need for antiretroviral therapy in the event that HIV-related TB is diagnosed
- If the patient consents, try to get the test done the same day

Look for and pay attention to:

Cervical, axillary, or inguinal adenopathies (if present with other types of ETB, they may be the only way to confirm the diagnosis)

Possible tuberculous lymphadenitis

Signs of fluid in the thorax:

- Absence of breath sounds
- Reduced chest wall movements
- Dullness to percussion

Possible tuberculous pleural effusion

Signs of the presence of fluid around the heart:

- Distant cardiac sounds
- Lower-limb or abdominal edema
- Engorgement of neck veins and hands when arm is kept above the shoulder

Possible tuberculous pericarditis

Signs of meningitis:

- Stiff neck
- Confusion
- Abnormal eye movements

Possible tuberculous meningitis

2.3 Latent tuberculosis infection ⁽³⁾

Latent tuberculous infection (LTBI) is a state of persistent immunologic response to antigens of previously acquired *Mycobacterium tuberculosis*. The vast majority of infected people exhibit no signs nor symptoms but are at risk of developing active TB, which can be prevented with prophylactic treatment. For the study of LTBI in HIV-positive people, the following is recommended, when available:

- Tuberculin skin test (PPD or Mantoux test) in low- or middle-low-income countries with a high TB burden (incidence > 100 per 100,000 pop.).
- In upper-middle- or high-income countries with a low TB burden (incidence < 100 per 100,000 pop.), PPD or interferon gamma release assay (IGRA) can be used.

In the tuberculin test, 0.1 mL of PPD is injected subcutaneously in the forearm. In 48 to 72 hours, the induration reaction is measured. This indicates the presence of *M. tuberculosis* infection but does not diagnose the disease. In children who previously received the BCG vaccine, it may lead to a false positive result. In AIDS patients, as well as patients with severe malnutrition or miliary tuberculosis, PPD can be negative even when they have active tuberculosis. In HIV patients, PPD is considered positive when the induration is greater than 5 mm in diameter.

The IGRA consists of mixing a blood sample with antigens representing two *M. tuberculosis* proteins, incubating it for 16 to 24 hours, and then measuring the amount of interferon gamma released. In infected patients, white blood cells will release interferon gamma as a response to their contact with those antigens. The advantages of this test over the PPD include: quick results, the objectivity of the reading, the non potentiation of the response to repeated use, and the fact that BCG does not influence the results. The disadvantages include the fact that it does not differentiate between LTBI and active tuberculosis, the cost, the need to process the sample within 12 hours of collection, and mistakes during sample collection and transport. IGRA is not recommended in countries with a high TB burden.

The treatment of LTBI is described in section 6.1.2.

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Chapter 3

HIV diagnosis in TB patients

KEY RECOMMENDATIONS

- Regardless of the epidemiological context (generalized or concentrated HIV epidemic¹), it is recommended that health care providers systematically offer and administer an HIV test to every patient (adult, adolescent, or child) with suspected or diagnosed tuberculosis (Strong recommendation, low-quality evidence) (1).
- Health care providers should offer an HIV test to the sexual partner of patients with TB/HIV coinfection, encouraging both individuals to mutually know their HIV status (Strong recommendation, low-quality evidence) (1).

The recommendations issued in this chapter are based on WHO Consolidated guidelines on HIV testing services (1).

Timely HIV diagnosis in people with TB is essential to provide integrated management, start antiretroviral therapy (ART) in a timely manner, and reduce the risk of complications and mortality in people with TB/HIV coinfection.

The availability of diagnostic tools will determine the promptness of the diagnosis, but efforts should always be made to ensure it is obtained as quickly as possible—ideally, in the same facility in which the TB patient is treated. Among the HIV diagnostic tests available nowadays for people with suspected or diagnosed TB, the use of rapid tests at the point of care shortens the time between diagnosis and referral to care and treatment.

3.1 Laboratory diagnosis of HIV infection

HIV infection can be determined through tests for:

- Antibodies against the virus
- Virus antigens
- Viral RNA/DNA
- Virus culture

¹ In a concentrated HIV epidemic, the infection has spread rapidly through one or more subpopulations but not to the general population yet. Its prevalence is typically > 5% in subpopulations and < 1% in the general population.

A generalized HIV epidemic is self-sustained through heterosexual transmission. In a generalized epidemic, HIV prevalence in pregnant women seeking prenatal care tends to be > 1%. (2)

In clinical practice, the blood or serum tests performed are for the detection of antibodies or a combination of antibodies and viral antigens (certain rapid tests can use saliva samples). The most common tests of this type are usually:

- Rapid tests
- Enzyme-linked immunosorbent assay (ELISA)

These are reliable tests with over 99% sensitivity and specificity. However, like all serological tests, they are faced with a “window period,” which is the time between infection with HIV and the appearance of detectable antibodies or antigens that will yield a positive (also known as reactive) result in the serological test. This period can be from two weeks (with fourth-generation tests) to three months from the time of infection, depending on the type of serological test and the individual's immune status.

For HIV diagnosis, the use of sequential serological tests based on national algorithms is recommended: the first should be highly sensitive ($\geq 99\%$ for rapid tests and 100% for ELISA) and highly specific $\geq 98\%$ for screening; and the second, highly sensitive ($\geq 99\%$ for rapid tests and 100% for ELISA) and highly specific ($\geq 99\%$) for confirmation. Given the high reliability of these tests, anyone with a repeatedly reactive test for HIV antibodies should be considered infected.

In the case of sequential tests with conflicting results, the diagnosis can be confirmed using another methodology (serological or virological), always following the national algorithms.

The frequency of false positives in serological tests is very low (0.0004-0.0007%). False positives are caused by:

- Recent influenza vaccination
- Pregnancy (especially multiparous)
- Collagen disease (systemic lupus erythematosus)
- Chronic renal failure
- Error in sample labeling or handling

False negatives are also very rare and are almost always due to the window period mentioned above. Depending on the infection's prevalence in the population, false negatives can range from 0.03% to less than 0.001%. False negatives are caused by:

- The window period
- Advanced AIDS (very rare)
- Error in sample labeling or handling

On rare occasions, serological tests can yield indeterminate results, since they are not negative but do not meet the criteria for positivity, meaning that they could be reported as positive. Indeterminate results are caused by:

- Acute HIV infection
- Advanced AIDS
- Antibody cross-reactivity (lymphoma, multiple sclerosis, recent vaccination)
- Error in sample handling

Anyone with an indeterminate result should be assessed for risk factors for HIV infection.

Presence of risk factors must prompt repeat testing for consecutive control in 14 days.

If no risk factors are present, the indeterminate result should not be dismissed, and the test should be repeated while ruling out conditions other than HIV.

3.2 Recommendations for services offering HIV testing

The following basic principles should be applied to all models of HIV screening in all circumstances. The principle of the “five Cs” is explained in detail in the box below.

1. Consent
2. Confidentiality
3. Counseling
4. Correct test results
5. Connections to care, treatment and prevention services

Guiding principles for HIV screening tests and counseling

- Before being screened for HIV, people must give their informed consent and should receive the pertinent counseling. Verbal consent is usually sufficient, but every individual should have the opportunity to refuse the test in private. Compulsory testing is never justified.
- Testing and counseling services are confidential, meaning that the information shared by the professional and the patient will not be revealed to third parties without the patient's express consent. The counselor should raise, among other issues, who else the patient may wish to inform and how the information should be conveyed. Sharing the information with the patient's intimate partner or family members and loved ones, as well as health professionals, tends to be highly beneficial.
- Testing and counseling services must be accompanied by pre-test information (which can be provided in a group setting in some contexts). Testing must be followed by appropriate, high-quality counseling. It is important to have quality assurance mechanisms and auxiliary supervision and counseling systems in place to guarantee quality counseling.
- The professionals providing testing and counseling should do their utmost to offer quality services, quality assurance mechanisms must be in place to guarantee users receive correct results. Quality assurance mechanisms, may include both internal and external measures, should be supported by the national reference laboratory, as needed.
- Connection to prevention, care, and treatment should include an effective system for referring each case to appropriate complementary services, including long-term prevention and treatment support services.

People must receive clear and relevant information according to their circumstances, before HIV screening. This can be provided individually or in groups, and should cover:

- benefits of HIV testing
- meaning of a positive result and the steps to confirm the diagnosis
- meaning of a negative result
- available services in the case of an HIV diagnosis
- confidentiality of test results and any information shared by the client
- the individual's right to refuse testing
- informed consent for the test (may be verbal, and written consent is not required).
- opportunity for additional questions

The post-testing information for people with a negative result should include:

- an explanation of the test result
- education about HIV prevention methods
- provision of male and female condoms, lubricant, and instructions on their use
- emphasis on the importance of knowing the HIV status of their sexual partner and information about how partners can access testing.
- referral and connection to HIV prevention services, including harm reduction services, as appropriate

Individuals who test negative and report recent risk behavior must be counseled to repeat the test in four weeks. Individuals with no recent risk factors do not need to repeat the test.

Recommendations for HIV-positive test result counselling:

- explain the test results and HIV diagnosis.
- give the person time to consider the results and provide him/her with emotional support
- discuss immediate concerns and help the person decide who can offer immediate support.
- assess the risk of intimate partner violence risk and discuss possible measures to guarantee the person's physical safety.
- assess suicide risk, depression, and other mental health consequences of an HIV diagnosis.
- provide clear information about antiretroviral therapy and its benefits for health and HIV transmission risk-reduction.
- convey the need for immediate connection with a health care and treatment service.
- agree on a specific date and time for the patient's referral to a health care and treatment service for HIV-positive people.
- provide information on how to prevent HIV transmission.

- provide male or female condoms and lubricants and instructions on their use.
- discuss the possibility of result disclosure, its risks and benefits, especially with intimate partners and contacts.
- offer support for the couple's mutual disclosure of their HIV status.
- promote HIV testing and offer the test to the person's sexual partners, children, and other family members.
- provide additional referrals for prevention, counseling, support, and other services, as appropriate.
- offer an opportunity for additional questions.

HIV testing services must ensure that all user results and information remain confidential. Although disclosing the information to friends, sexual contacts, supportive family members and health care providers can often be beneficial, this should only be done by the tested person or by someone who has their consent to do so. It is the ethical and professional responsibility of the person who provides the test results to follow national and international guidelines to guarantee they are correct.

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Chapter 4

TB treatment for HIV patients

KEY RECOMMENDATIONS

- TB treatment for patients with TB/HIV coinfection should be at least as long as for TB patients without HIV (Strong recommendation, high quality of evidence) (1).
- Patients with TB/HIV coinfection should be treated for tuberculosis with four drugs, including rifampicin, for at least 6 months. During the intensive and continuous phases, treatment should be administered daily (Strong recommendation, high quality of evidence) (1, 2).
- For patients with drug-susceptible pulmonary TB with HIV coinfection who receive ART during their TB treatment, a 6-month treatment regimen is recommended over a regimen of 8 months or more (Conditional recommendation, very low quality of evidence) (1).
- Every patient with pulmonary TB and HIV should be monitored through smear microscopy, culture, and DST (Strong recommendation, high quality of evidence) (3).
- Patients in treatment for tuberculosis should be counseled and educated about TB and treatment adherence (Strong recommendation, moderate-quality of evidence) (1).

TB treatment for HIV-positive patients is a priority once the diagnosis is made and should ideally begin the day of diagnosis or as soon as possible, regardless of the patient's condition. The promptness with which treatment begins will determine the reduction in the risk of death in advanced cases or cases with marked physical deterioration (2).

4.1 General comments

As a rule, the same drugs, dosages, and length of treatment are used to treat TB in HIV positive and HIV-negative patients (1).

Clinical staff should use the case definitions for registering and reporting TB cases used by TB control programs, since these definitions differentiate between new and previously treated patients, making it possible to determine the treatment.

The following TB case definitions are based on the level of diagnostic certainty and whether laboratory confirmation is available (4).

Presumptive TB case: anyone with symptoms or signs that suggest tuberculosis (formerly known as “suspected TB”).

Bacteriologically confirmed TB case: anyone with a positive sputum smear, culture, or rapid test (Xpert® MTB/RIF and other molecular assays, or immunochromatography).

Clinically diagnosed TB case: anyone who does not meet the criteria for bacteriological confirmation but has been diagnosed with active TB by a physician or other clinician who has decided to administer a full course of TB treatment to the patient. This definition includes cases diagnosed on the basis of anomalous x-ray findings or suggestive histology and extrapulmonary cases without laboratory confirmation. If these clinically diagnosed cases subsequently have positive bacteriology (before or after beginning the treatment), they should be reclassified as bacteriologically confirmed.

Tuberculosis cases are also classified by:

1. Anatomical site of the disease
2. History of previous treatment
3. Resistance to TB drugs
4. Serological results of HIV test

1. Anatomical site of the disease: Determining the location is important to identify infectious cases (pulmonary or laryngeal TB). The treatment regimens are generally the same, regardless of the TB location. There are some exceptions, which are mentioned further on.

- **Pulmonary TB (PTB)** refers to any bacteriologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or tracheobronchial tree. Miliary TB is classified as PTB because there are lung lesions. A patient with both pulmonary and extrapulmonary TB is classified as a PTB case.
- **Extrapulmonary TB (ETB)** refers to any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs—e.g., pleura, lymph nodes, abdomen, genitourinary tract, skin, joints, bones, and meninges. Intrathoracic tuberculous lymphadenopathies (mediastinal and/or hilar) and tuberculous pleural effusion, without radiographic lung abnormalities, constitute ETB.

2. History of previous TB treatment: This classification focuses on previous treatment history and is independent of bacteriological confirmation or site of disease:

- **New cases:** Patients who have never been treated for TB or have taken TB drugs for less than a month.
- **Previously treated cases:** Patients who have received a month or more of TB drugs in the past. They are classified by the outcome of their recent course of treatment as follows:

- ◇ **Relapse:** Patients who have previously been treated for TB, were declared *cured or treatment completed* at the end of their most recent course of treatment, and now are diagnosed with TB (reactivation or a new infection).
- ◇ **Treatment after failure:** Patients who have previously been treated for TB but whose treatment failed (positive sputum smear or culture at month 5 or subsequently during treatment).
- ◇ **Treatment after loss to follow-up:** Patients who have previously been treated for TB and were declared lost to follow-up at the end of their most recent course of treatment (people diagnosed with TB who did not begin treatment or whose treatment was interrupted for a month or more). These were previously known as *treatment after default* patients.
- ◇ **Other previously treated cases:** Patients who have previously been treated for TB but whose outcome after their most recent course of treatment is unknown or undocumented.
- **Patients with unknown previous TB treatment history:** Patients who do not fit into any of categories listed.

New cases and relapses are considered incident TB cases.

3) TB drug resistance: This classification is based on drug susceptibility testing (DST) in clinical isolates confirmed to be *M. tuberculosis*.

- **Mono-resistance:** resistance to one first-line anti-TB drug only
- **Poly-resistance:** resistance to more than one first-line anti-TB drug (other than both isoniazid and rifampicin)
- **Multidrug resistance:** resistance to at least both isoniazid and rifampicin.
- **Extensive drug resistance:** resistance to any fluoroquinolone and at least one of three second-line injectable drugs (capreomycin, kanamycin, and amikacin), in addition to multidrug resistance.
- **Rifampicin resistance:** resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other TB drugs. It includes any resistance to rifampicin, whether monoresistance, multidrug resistance, polydrug resistance, or extensive drug resistance.

4) Serological HIV test result: TB/HIV coinfection diagnosis will be determinant in the conduct to follow:

- **HIV-positive TB patient** refers to any bacteriologically confirmed or clinically diagnosed case of TB with an HIV-positive test result at the time of TB diagnosis or other documented evidence of enrollment in HIV care, with or without ART.
- **HIV-negative TB patient** refers to any bacteriologically confirmed or clinically diagnosed case of TB who has a negative result from HIV testing at the time of TB diagnosis. Any HIV-negative TB patient subsequently found to be HIV positive should be reclassified accordingly.

- **Unknown HIV status TB patient** refers to any bacteriologically confirmed or clinically diagnosed case of TB who has no result of HIV testing and no other documented evidence of enrollment in HIV care. If the patient's HIV status is subsequently determined, the case should be reclassified accordingly.

4.2 Standard TB treatment regimen for HIV-positive people⁽¹⁻³⁾

The Pan American Health Organization/World Health Organization (PAHO/WHO) and the International Union against Tuberculosis and Lung Disease recommend standard treatment regimens. Table 8 shows drugs for treatment of new TB cases, including people with HIV (3).

Table 8 First-line TB drugs for the treatment of HIV-positive people

Drug (abbreviation)	Mechanism of action	Potency	Recommended daily dose (mg/kg weight)	
			Average (range)	Maximum dose (mg)
Isoniazid (H)	Bactericide	High	5 (4-6)	300
Rifampicin (R)	Bactericide	High	10 (8-12)	600
Pyrazinamide (Z)	Bactericide	Low	25 (20-30)	-
Ethambutol (E)	Bacteriostatic	Low	15 (15-20)	-

There is a standard code for TB treatment regimens. Each drug has an abbreviation, as seen in Table 8. A regimen has two phases, each consisting of a drug combination. The number before a phase is the length of that phase in months. A subscript number after a letter represents the number of weekly doses of that drug. When there is no subscript number after a letter, treatment with the drug is daily. For example: 2HRZE means 2 months of isoniazid, rifampicin, pyrazinamide, and ethambutol daily. (3)

For new cases, including HIV-positive people without TB drug resistance, the standard regimen is:

2HRZE/4HR

Initial or intensive phase	Second or continuation phase
2 months of HRZE	4 months of HR

In this regimen, the initial, or intensive, phase lasts two months. This 4-drug cocktail (HRZE) rapidly eliminates bacilli in active division, contributing to reduced contagiousness; prevents selection of drug-resistant strains, especially isoniazid; and contributes to the patient's clinical improvement. In the second, or continuation, phase, which lasts four months, two drugs (HR) are used to eliminate bacilli in intermittent division (1-3).

It is recommended that these drugs be administered in presentations with fixed-dose combinations (FDC) for each phase (1, 3).

In both the first and second phase of TB treatment, **daily** drug administration is recommended for HIV-positive people (ideally, 7 days a week, but operationally, 5 or 6 days is considered acceptable). All drug intake should be directly observed by health care providers or an individual trained for this purpose; this method is known as directly observed treatment (DOT). In TB/HIV coinfection cases, treatment administration three times per week is not recommended (1, 2, 5).

For relapsed or lost to follow-up patients who have been treated before for a single episode, the standard regimen for new cases should be administered until the DST results are in. In cases with risk or suspicion of drug-resistant TB (DR-TB), the treatment regimen will depend on DST and is described in Chapter 6.

4.3 Treatment considerations in special cases

In exceptional cases of ETB with a serious risk of disability and difficult evaluation of treatment response (bone or joint tuberculosis) or a high mortality risk (central nervous system tuberculosis), the second phase of TB treatment may be extended to 9 to 12 months, respectively, according to some experts (3, 5).

Treatment of tuberculous meningitis should begin as soon as clinical manifestations and CSF findings suggest it. Treatment delay is associated with higher mortality. Although TB can be cured after a 6-month therapy, in HIV-positive or negative patients, it is recommended to extend it to 9-12 months, given the risk of disability and mortality. Although corticosteroid therapy is immunosuppressive, its use as an adjuvant treatment for a limited time has been associated with lower mortality and fewer sequelae. Steroids such as prednisone (1 mg/kg/day) or dexamethasone (0.3 to 0.4 mg/kg/day) can be used; with a progressive dose reduction after one to two weeks, depending on the symptoms, and stopping them after 4 to 6 weeks use. Due to clinical and CSF similarities with cryptococcal meningitis, as well as the diagnostic difficulties mentioned earlier, cryptococcal meningitis should always be ruled out in these patients (6).

In cases of tuberculous pericarditis in remote locations, TB treatment can be initiated based on the patient's history and physical examination. This can be life-saving. Although empirical treatment with steroids and TB drugs tends to resolve the symptoms, the definitive treatment includes a pericardiectomy to avoid the subsequent appearance of constrictive pericarditis due to scarring (6).

4.4 TB treatment monitoring

All TB patients should be monitored to evaluate their treatment response. Weight should be recorded every month and drug dosages adjusted as necessary. All patients should be instructed to report the persistence or reappearance of TB symptoms (including weight loss), adverse drug reactions, or treatment interruptions. Usually, evaluation of treatment response in ETB patients is clinical, weight recording being a very important tool. Bacteriological monitoring is more useful in PTB smear-positive cases than in smear-negative ones, and in both cases, chest x-rays for monitoring TB treatment are unnecessary and unreliable (3).

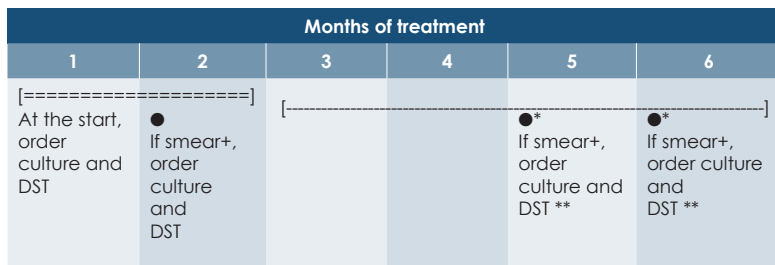
4.4.1 Evaluation of treatment response (3)

Before the start of TB treatment, a culture and DST should be performed in all HIV positive people. Smear microscopy should be done for new pulmonary TB patients at the end of the initial, or intensive, treatment phase (second month). When smear is negative, the new patient moves on to the second phase and is monitored with a new sputum smear at the end of the fifth and sixth month of treatment. If possible, monthly sputum smears should be performed. When the result at the end of the second month of treatment turns out positive, the first phase should be extended until the DST results are in, and based on these results, the patient should either move on to the second phase or the treatment should be changed. If the result is compatible with MDR-TB, the case is no longer considered drug-susceptible TB and is reclassified as a new case of MDR TB. Furthermore, the potential causes of the persistent positive smear should be explored. They include the following:

- Initial phase of treatment was poorly supervised and as a result, patient's treatment adherence was also poor.
- Drug dosages were lower than recommended.
- Patient had extensive pulmonary cavities and a high initial bacillary load.
- Presence of comorbidities that interfered with either adherence or the response.
- Non-viable bacteria were still visible through microscopic examination.
- Patient had drug-resistant TB that did not respond to treatment with first-line drugs.
- Dubious drug quality.

When the sputum smear at the end of the fifth or sixth month is positive, a culture and DST should be ordered and the case classified as treatment failure (Figure 2). Based on the result, the treatment is changed (see Chapter 6).

Figure 2. TB treatment monitoring in new HIV-positive pulmonary TB patients



References:

[=====] First, or intensive, phase (HRZE)

[-----] Second, or continuation, phase (HR)

● Smear microscopy

Smear+ Positive smear microscopy

* Omit if patient had a negative smear at the start of treatment.

** Positive smear or culture at month 5 or subsequently (or detection of MDR-TB at any time) is considered treatment failure; the case should be reclassified accordingly and the treatment changed

4.4.2. Classification of TB patients by treatment outcome (4)

All patients with a diagnosis of TB, except for those with drug resistance, are classified by treatment outcome into the following seven groups:

Cured: A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who was smear- or culture-negative in the last month of treatment and on at least one previous occasion.

Treatment completed: A TB patient who completed treatment without evidence of failure but with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or because results are unavailable.

Treatment failed: A TB patient whose sputum smear or culture is positive at month 5 or later during treatment.

Died: A TB patient who died for any reason before starting or during the course of treatment.

Lost to follow-up: A TB patient who did not start treatment or whose treatment was interrupted for one month or more.

Not evaluated: A TB patient for whom no treatment outcome is assigned. This includes cases "transferred" to another treatment unit, as well as cases for whom the treatment outcome is unknown.

Treatment success: The sum of *cured* and *treatment completed*.

4.5 Identification and management of adverse reactions to TB drugs

Most HIV-positive people complete their TB treatment without significant adverse drug reactions. It has been described, however, that adverse drug reactions are more common in HIV-positive than HIV-negative people, especially as immunosuppression progresses, which is why good clinical monitoring is necessary. Systematic monitoring with laboratory tests is not recommended.

Adverse reactions can be prevented when the physician is familiar with them and is aware of the patient's pathologies or baseline conditions (HIV, alcoholism, diabetes, renal failure, pregnancy). Part of good clinical monitoring is educating patients and their families about adverse drug reactions and inquiring about them during each office visit (3, 6).

4.5.1 Main adverse reactions to TB treatment (3, 6)

TB drugs produce different adverse reactions, some of them common and others occasional (Table 9). They are classified as mild and severe adverse reactions, depending on the severity of the symptoms (Table 10). Mild adverse reactions should be handled with information, specific measures, and patient encouragement to complete treatment. In these cases, anti-TB drug administration should continue and dosage should be revised. Serious adverse reactions should lead to immediate suspension of suspected drug and hospitalization.

Table 9. Adverse reactions to TB drugs

Drug	Common adverse reactions	Occasional adverse reactions
Isoniazid	Peripheral neuropathy Hepatitis (> 40 years) Drowsiness or lethargy	Seizures Joint pain Exanthema Lupoid reactions Pellagra Agranulocytosis Acute psychosis
Rifampicin	Gastrointestinal: anorexia, nausea, vomiting abdominal pain Hepatitis Reduced effectiveness of oral contraceptives	Renal failure Thrombocytopenia Influenza-like syndrome Pseudomembranous colitis Osteomalacia Hemolytic anemia Shock Exanthema
Pyrazinamide	Arthralgia Hepatitis	Gastrointestinal symptoms Exanthema Sideroblastic anemia

Drug	Common adverse reactions	Occasional adverse reactions
Streptomycin	Ototoxicity and vestibular nerve damage (in the fetus as well) Nephrotoxicity	Exanthema
Ethambutol	Optic neuritis	Exanthema Arthralgia Peripheral neuropathy
Rifabutin	Neutropenia Leukopenia Elevated liver enzymes Skin eruptions Gastrointestinal symptoms	Uveitis

Table 10. Sign- or symptom-based management of adverse TB drug reactions

Adverse reactions	Drug(s) likely responsible	Management
Mild signs or symptoms		
Anorexia, nausea, abdominal pain	Pyrazinamide Rifampicin Isoniazid	Give tablets with small meals or at night, before bedtime. Advise the patient to take the tablets slowly with a sip of water. If symptoms persist or worsen, or the patient experiences persistent vomiting or signs of hemorrhage, consider the reaction severe and refer
Arthralgia	Pyrazinamide	Give aspirin, nonsteroidal anti-inflammatories, or acetaminophen
Neuropathy with tingling, burning, or numbness in hands or feet	Isoniazid	Give pyridoxine (50-75 mg /day)
Drowsiness	Isoniazid	Explain this to the patient. Give the tablets before bedtime.
Red or orange urine	Rifampicin	Counsel the patient. Prior to treatment, the patient should be informed that this can happen and is normal
Severe signs or symptoms		
Exanthema with or without pruritus	Streptomycin Pyrazinamide Rifampicin Isoniazid	Stop all drugs

Adverse reactions	Drug(s) likely responsible	Management
Severe signs or symptoms		
Hypoacusis	Streptomycin	Stop the drug
Dizziness (vertigo and nystagmus)	Streptomycin	Stop the drug
Jaundice (rule out other causes) and hepatitis	Isoniazid Pyrazinamide Rifampicin	Stop anti-TB drugs
Confusion (suspect acute liver failure if jaundice is present)	Almost all TB drugs	Stop TB drugs and order urgent liver function tests
Visual anomalies (rule out other causes)	Ethambutol	Stop the drug
Shock, purpura, and acute renal failure	Rifampicin	Stop the drug and do not use it again
Reduced diuresis	Streptomycin	Stop the drug
Arthralgia	Rifabutin	Stop the drug

4.5.2 Management of drug-induced hepatitis (3, 6)

When hepatitis from TB treatment is suspected, it is important to rule out other potential causes, such as acute viral hepatitis – especially in HIV-positive people. Jaundice should not be considered proof of hepatitis, since a drug such as rifampicin can cause asymptomatic cholestatic jaundice. Liver function tests should always be performed: in drug-induced hepatitis, they will be characterized by a marked increase in aspartate aminotransferase (AST) levels and a relatively small increase in alanine aminotransferase (ALT). It should be recalled that in HIV-positive patients, there are other reasons for discrete elevations in aminotransferases, such as certain opportunistic infections and their treatment drugs.

Most TB drugs can produce hepatotoxicity; this occurs most often with isoniazid, rifampicin, and pyrazinamide. In the case of drug-induced hepatitis, evidenced by an elevation in liver function test results to levels more than five times higher than normal, drug administration should be stopped until test results return to normal. When liver function tests cannot be done, the recommendation is that treatment not be resumed until approximately two weeks after jaundice disappears. In most cases, the patient can resume the same initial regimen without the return of hepatitis.

The most hepatotoxic of all TB drugs is pyrazinamide. Thus, if drug-induced hepatitis has put the patient's life at risk, it is safer to use a regimen with isoniazid and rifampicin and two non-hepatotoxic drugs—for example, 2SHRE and 6HR, which would be indicated for a patient with severe liver disease.

Critically ill TB patients with drug-induced hepatitis, including those who are HIV-positive, should receive two or more of the least hepatotoxic drugs, such as streptomycin and ethambutol. Once the hepatitis has cleared, the usual treatment should resume, beginning with the least hepatotoxic drug.

4.6 Management of allergic reactions^(3, 6)

It is important to determine whether certain reactions, such as pruritus and exanthema, were present before the start of the TB treatment, since many HIV-positive people suffer from pruriginous cutaneous eruptions (scabies, superficial mycoses, eosinophilic dermatitis, etc.) or are taking other drugs that provoke these skin reactions (TMP/SMX, pyrimethamine, etc.).

If a patient reports pruritus, and other obvious causes are ruled out, antihistamines can be used while continuing the TB treatment, keeping the patient under close observation. If exanthema develops, it will be necessary to suspend the TB treatment and wait for the skin problem to clear up.

Table 11 shows the standard approach for reintroducing TB drugs when the responsible drug is unknown, in order to identify it.

Table 11. Sequential reintroduction of TB drugs after the appearance of cutaneous reactions

Drug	Test dose		
	Day 1	Day 2	Day 3
Isoniazid	50 mg	300 mg	300 mg
Rifampicin	75 mg	300 mg	Full dose
Pyrazinamide	250 mg	1g	Full dose
Ethambutol	100 mg	500 mg	Full dose

The test dose begins with isoniazid, the TB drug least likely to be responsible for the skin reaction. The small initial dose allows only for a minor reaction than the full dose. The procedure is repeated, adding one drug at a time, until the reaction after the addition of a drug makes it possible to identify the responsible drug.

If the drug responsible for the reaction is pyrazinamide or ethambutol, TB treatment will have to resume without that drug. If possible, after consultation with a specialist, it should be replaced with another effective anti-TB drug. If the adverse reaction requires a change of more than one drug, the case should be declared as a failure, and once the reaction subsides, a new course of treatment should begin.

In rare cases, patients develop hypersensitivity reactions to the two most powerful TB drugs: isoniazid and rifampicin, which are the backbone of the short-course treatment. Desensitization of TB/HIV patients who develop hypersensitivity

reactions should be considered, but with caution, given the risk of severe toxicity. The following desensitization method can be used, under the supervision of a specialist:

- a. Begin desensitization with one-tenth the normal dose.
- b. Increase the dose by one-tenth the normal dose every day until the patient receives the full dose on the tenth day.

Once desensitization is complete, the drug is administered as part of the usual treatment regimen. If possible, during desensitization, two drugs that the patient has not already taken should be administered to prevent the risk of his developing drug resistance during the desensitization process.

4.7 TB treatment in patients with additional comorbidities^(3, 6)

4.7.1 Treatment of patients with previous liver disease

Carriers of hepatitis virus with a history of acute hepatitis and alcohol abuse can receive the customary TB treatment regimen, provided there is no evidence of chronic decompensated liver disease. For patients with unstable or advanced liver disease, liver function tests should be ordered before beginning the treatment. When alanine aminotransferase enzyme [ALT] is elevated more than three times its normal value prior to treatment, a specialist should be consulted to determine which treatment regimens to select and ensure careful clinical and laboratory monitoring.

4.7.2 Treatment of patients with renal failure

The initial treatment regimen in patients with severe renal failure is with isoniazid, pyrazinamide, rifampicin, and ethambutol, followed by 4 months of isoniazid and rifampicin. Isoniazid and rifampicin are eliminated through biliary excretion; thus, there is no need for dosage adjustment. Ethambutol and pyrazinamide metabolites produce significant renal excretion; thus, the dosage must be adjusted. Administration of the conventional average dose of these drugs is recommended: pyrazinamide 25 mg/kg/day and ethambutol 15 mg/kg/day, three times a week.

Due to the higher risk of nephrotoxicity and ototoxicity, patients with renal failure should avoid streptomycin. If streptomycin must be used, the indicated dosage should be 15 mg/kg/day two or three times a week, with a maximum of 1 g.

All patients with renal failure should receive pyridoxine while receiving isoniazid to prevent peripheral neuropathy.

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Chapter 5

HIV treatment in TB patients

KEY RECOMMENDATIONS

- Every HIV-positive TB patient should receive antiretroviral therapy (ART), regardless of his CD4 count (Strong recommendation, high-quality evidence) (1, 2).
- TB treatment should be initiated first. ART should begin as soon as possible, within 8 weeks of the start of the TB treatment (Strong recommendation, high-quality evidence) (2).
- Antiretroviral therapy is recommended for all HIV-positive drug-resistant TB patients who require second-line TB drugs, regardless of their CD4 count. ART should begin as soon as possible, within 8 weeks of the start of the TB treatment (Strong recommendation, very low-quality evidence) (1, 2).
- Every TB/HIV patient with severe immunosuppression ($CD4 < 50/mm^3$) should receive ART within a maximum of 2 weeks after the start of TB treatment (Strong recommendation; high-quality evidence) (2).
- In people with TB/HIV coinfection who start ART, the recommended first-line regimen is TDF + 3TC (or FTC) + EFV in a fixed dose combination (Strong recommendation, moderate-quality evidence) (1).

TDF: tenofovir; 3TC: lamivudine; FTC: emtricitabine; EFV: efavirenz.

The recommendations in this chapter are based on the WHO Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection of 2016 (1).

5.1 Antiretroviral therapy in patients with TB/HIV coinfection

5.1.1 General information on antiretroviral therapy

Highly active antiretroviral therapy (HAART) was introduced in 1996 and consists of a cocktail of at least three antiretroviral drugs (ARV). The combination of different

classes of drugs and mechanisms of action to inhibit viral replication is efficient and reduces drug resistance risk. Antiretroviral therapy (ART) is for life and is very effective, since it achieves significant reductions in morbidity and mortality in HIV-positive people. It does so through two mechanisms: reduction of the viral load to undetectable levels (< 40 or 50 copies/mm³), which, in turn, permits gradual restoration of the immune system (increase in CD4 lymphocytes).

ARV drugs are currently divided into five therapeutic classes, based on their mechanism of action (Table 12) (3).

1. Nucleoside or nucleotide reverse transcriptase inhibitors (NRTI or NtRTI, respectively)
2. Non-nucleoside reverse transcriptase inhibitors (NNRTI)
3. Protease inhibitors (PI)
4. Fusion and entry inhibitors (FI and EI)
5. Integrase inhibitors (INSTI)

Table 12. Classification of antiretrovirals by their mechanism of action

NRTI/NtRTI	NNRTI	PI	FI/EI	INSTI
Abacavir (ABC)	Efavirenz (EFV)	Atazanavir (ATV)	Enfuvirtide (T20)	Raltegravir (RAL)
Didanosine (ddI)	Nevirapine (NVP)	Darunavir (DRV)	Maraviroc (MVC)	Dolutegravir (DTG)
Emtricitabine (FTC)	Etravirine (ETV)	Lopinavir (LPV)		
Lamivudine (3TC)		Ritonavir (RTV)		
Tenofovir (TDF)		Saquinavir (SQV)		
Zidovudine (AZT)				

Note: The complete list of WHO prequalified ARV drugs can be found at <http://apps.who.int/prequal/query/ProductRegistry.aspx>

Since 2015, WHO has recommended the administration of ART to all HIV-positive individuals (adults and adolescents), regardless of disease stage and CD4 count. To begin ART, insofar as possible, the use of simplified, less toxic, and more practical regimens in fixed dose combinations is recommended. Table 13 presents the regimens of choice and alternatives recommended by WHO for starting antiretroviral therapy in adults and adolescents (1).

Table 13. Recommended antiretroviral therapies in adults and adolescents

First-line ART	Preferred first-line regimens	Alternative first-line regimens ¹
Adults (including adults with tuberculosis or coinfection with the hepatitis B virus)	TDF + 3TC (o FTC) + EFV	AZT + 3TC + EFV (or NVP) TDF + 3TC (or FTC) + DTG ² TDF + 3TC (or FTC) + EFV ₄₀₀ ^{2,3} TDF + 3TC (or FTC) + NVP
Pregnant or lactating women	TDF + 3TC (o FTC) + EFV	AZT + 3TC + EFV (o NVP) TDF + 3TC (o FTC) + NVP
Adolescents	TDF + 3TC (o FTC) + EFV	AZT + 3TC + EFV (or NVP) TDF (o ABC) + 3TC (or FTC) + DTG ² TDF (o ABC) + 3TC (or FTC) + EFV ₄₀₀ ^{2,3} TDF (o ABC) + 3TC (or FTC) + NVP

ART: antiretroviral therapy.

¹In special cases, ABC or boosted protease inhibitors (ATV/r, DRV/r, LPV/r).

²There is no data yet about safety and efficacy of DTG and EFV400 in pregnant women, people with TB/HIV coinfection, and children and adolescents under the age of 12.

³EFV in a lower daily dose (400 mg).

During ART, careful clinical, virological, and immunological patient monitoring is necessary to evaluate the treatment response. This is done through periodic visits to the treating physician to assess clinical improvement (weight gain and reduction in the frequency and severity of opportunistic infections) and monitoring CD4 lymphocyte count and viral load. After treatment initiation, it is recommended to monitor HIV viral load at month six and twelve, and at least once a year after complete viral suppression is reached.

Viral load is the preferred monitoring method for detection and confirmation of treatment failure. Treatment failure is defined as a viral load of over 1,000 copies/mL, confirmed in two consecutive measurements after at least 6 months of ART in the absence of treatment adherence problems. In the event of treatment failure, the therapeutic regimen must be switched. Table 14 presents the recommended second- and third-line regimens by population and first-line regimen at the time of treatment failure (1).

Table 14. Second- and third-line antiretroviral therapy by target population and first-line regimen

Population	1st-line regimen	2nd-line regimen	3rd-line regimen
Adults	2 NRTI + EFV	2 NRTI + ATV/r or LPV/r or DRV/r	DRV/r + DTG (or RAL) ± 1–2 NRTI
	2 NRTI + DTG	2 NRTI + ATV/r or LPV/r	DRV/r + 2 NRTI ± NNRTI
Pregnant or breastfeeding women	2 NRTI + EFV	2 NRTI + DRV/r	Optimized genotype-based regimen
		2 NRTI + ATV/r or LPV/r	DRV/r + DTG (or RAL) ± 1–2 NRTI

2 NRTI: cocktail of 2 nucleos(t)ide reverse transcriptase inhibitors.

Table 15 shows daily recommended dose of antiretrovirals as part of ART (3).

Table 15. Daily dose of antiretrovirals for HIV-positive adults

Drug	Oral dosage
Nucleoside reverse transcriptase inhibitors (NRTI)	
Abacavir (ABC)	300 mg q.12h or 600 mg /24 h
Didanosine (ddI)	250 mg/24 h (< 60 kg) or 400 mg/24 h (> 60 kg)
Emtricitabine (FTC)	200 mg/day
Lamivudine (3TC)	150 mg q. 12h or 300 mg/24 h
Zidovudine (AZT)	300 mg q. 12h
Nucleotide reverse transcriptase inhibitor (NRTI)	
Tenofovir (TDF)	300 mg/day
Non-nucleoside reverse transcriptase inhibitors (NNRTI)	
Efavirenz (EFV) ¹	600 mg/day (before bedtime)
Etravirine (ETV)	200 mg q. 12h
Nevirapine (NVP)	200 mg q. 12h ²
Protease inhibitors (PI)	
Lopinavir (LPV)/ritonavir (RTV)	400/100 mg q. 12h ³
Atazanavir (ATV)/RTV	300 mg/day + RTV 100 mg/day
Saquinavir (SQV)/RTV	1 000 mg q. 12h + RTV 100 mg q.12h
Darunavir (DRV)/RTV	800 mg + 100 mg/day
	600 mg + 100 mg q. 12h (in patients with previous exposure to PI)

Drug	Oral dosage
Integrase inhibitors	
Raltegravir (RAL)	400 mg q.12h
Dolutegravir (DTG)	50 mg/day
Entry/fusion inhibitors	
Maraviroc (MVC)	150 mg q.12h ⁴
Enfuvirtide (T20)	90 mg (1 ml) q.12h (subcutaneously)

¹ Can be administered with or without food, but not with fatty foods.

² Start with half the dose the two first weeks.

³ In people with TB/HIV coinfection and in TB treatment with rifampicin, the administration of LPV/r with an adjusted boosted dose of RTV (LPV/r 400 mg/400 mg twice a day) or double the daily dose of LPV/r (LPV/r 800 mg/200 mg twice a day) can be considered.

⁴ Use only when the virus is confirmed to have R5 tropism.

5.1.2 Antiretroviral therapy in TB patients

To reduce mortality from TB/HIV coinfection, reduce TB transmission, and generally improve TB management, the following is recommended:

- Start ARVs to all HIV-positive people with active tuberculosis, regardless of their CD4 lymphocyte count. ART should also be initiated for TB/HIV patients with MDR-TB, regardless of their CD4 count.
- Begin the TB treatment first, followed by ARVs as soon as possible, within 8 weeks of the start of TB treatment. TB/HIV patients with severe immunosuppression (CD4 count < 50/mm³) should begin ART 2 weeks after the start of anti-TB treatment.

In individual patient management, it is important for the clinician to bear in mind that there may be reasons to defer treatment with ARVs, such as:

- Avoiding drug interactions
- Simplify adverse drug reaction identification
- Improve TB treatment adherence

When ART should only be deferred to give the patient enough time to get adjusted to anti-TB treatment.

Antiretroviral therapy and its monitoring in HIV/TB coinfecting people does not differ greatly from that of people without TB. Since there are no significant interactions between NRTIs and NNRTIs and TB drugs, including rifampicin, ART is constructed in a similar manner. In the case of NNRTIs, rifampicin reduces their plasma concentration but not significantly. Therefore, from a clinical standpoint, a conventional dose of both efavirenz and nevirapine can be administered; nevertheless, given nevirapine's risk of hepatotoxicity, its use is recommended only when efavirenz is not an option.

In patients with TB/HIV coinfection, the recommended first-line regimen is:

TDF + 3TC (or FTC) + EFV

In TB/HIV coinfecting patients in treatment for TB with contraindications or TDF-associated adverse events, TDF/3TC or TDF/FTC can be replaced with another combination of two NRTIs (e.g., AZT/3TC or ABC/3TC or ABC/FTC).

In people with contraindications, toxicity, or EFV intolerance or who are receiving or need to begin second- or third-line ART, the prescription of ART requires an individualized approach by a specialist with extensive experience in the use of antiretrovirals and their pharmacological interactions with TB drugs. TB drugs (rifampicin in particular) can have pharmacological interactions with PIs and INSTIs, and it is always important to consider the risk of interactions and the need for necessary posology adjustments (see section 5.2.2 on interactions between ARV and TB drugs and their management).

5.2 Adverse reactions to ARVs and interactions with TB drugs

5.2.1 Adverse reactions to ARVs

All ARVs have adverse effects and are potentially toxic. The toxicity ranges from self-limiting discomfort to risk of death. It is essential for treatment adherence and patient safety that adverse reactions are identified and managed. ARVs have many common adverse effects, which are listed in Table 16 (1). The ARVs causing these effects and their management recommendations are summarized in Table 17 (1).

Table 16. Common adverse reactions to ARVs

Adverse reaction	Causative ARV and symptoms and signs
Gastrointestinal	Virtually all ARVs can produce nausea, diarrhea, and vomiting
Hematotoxicity	Bone marrow suppression (anemia, neutropenia), generally associated with AZT
Mitochondrial dysfunction	Mainly all NRTIs (most frequently d4T, ddI). It includes lactic acidosis, hepatotoxicity, pancreatitis, peripheral neuropathy, lipodystrophy, and myopathy
Hepatotoxicity	In the NNRTI class: NVP In the PI class: RTV and DRV. In the entry or fusion inhibitor class: MVC. Acute and severe hepatitis exacerbation can occur in patients coinfecting with HBV that discontinue 3TC, FTC or TDF ATV can produce indirect asymptomatic hyperbilirubinemia

Adverse reaction	Causative ARV and symptoms and signs
Renal toxicity	Nephrolithiasis (rarely, with ATV) TDF-associated renal tubular dysfunction
Other metabolic abnormalities	More common with PIs Include hyperlipidemia, fat accumulation, insulin resistance, diabetes, and osteopenia
Allergic reactions	Exanthema and hypersensitivity reactions more common with NNRTIs, including ETV although they also occur with some NRTIs, such as ABC. Some PIs, such as DRV, can produce exanthemas and should be used with caution in people allergic to sulfamides.

Table 17. Recommended management of adverse reactions to ARVs

Adverse reaction	ARVs involved	Recommendations
Acute pancreatitis	ddl	Discontinue ddl; provide supportive treatment and laboratory monitoring Resume treatment with other NRTIs: AZT, ABC, TDF, 3TC
Diarrhea	ddl LPV/r SQV/r	Tends be self-limiting; symptomatic treatment is indicated
Skin eruptions (mild to severe; they include Stevens-Johnson syndrome or toxic epidermal necrolysis)	NVP Less frequently EFV ETV DRV/r	Mild: antihistamines Moderate (without compromised mucous membranes): Change NVP by EFV Moderate (with compromised mucous membranes) or severe: stop ARV treatment and after reaction subsides, resume with 3 NRTIs or 2 NRTIs + IP
Dyslipidemia and hyperglycemia	PI	Substitute suspected PI with a PI with less metabolic risk: ATV Diet Exercise Consider hypolipidemic drugs
Gastrointestinal intolerance (nausea, vomiting, abdominal pain)	All ARVs. Less frequently: 3TC, FTC, ABC	Self-limiting Symptomatic treatment

Adverse reaction	ARVs involved	Recommendations
Hematoxicity (anemia and leukopenia)	AZT	Transfusions Replace with TDF or ABC
Hyperbilirubinemia	ATV	Monitor Substitute another PI
Hypersensitivity reaction with fever and respiratory symptoms	ABC. Less frequently: ETV, T20	Discontinue ABC and DO NOT RESUME Substitute another drug
Lactic acidosis	All NRTIs (particularly ddI)	Discontinue treatment with the ARV Supportive treatment Substitute the NRTI(s) involved with ABC, TDF, or 3TC
Lipoatrophy and lipodystrophy	All NRTIs Protease inhibitors	Early substitution with TDF or ABC Exercise and surgery Counseling
Neuropsychiatric: insomnia, drowsiness, depression, behavioral and personality changes	EFV	Tends be self-limiting Symptomatic treatment Consider substituting with another PI
Renal toxicity (renal tubular dysfunction)	TDF	Discontinue TDF Support treatment Replace
Peripheral neuropathy	ddI	Symptomatic treatment Consider substituting with AZT, TDF, or ABC

In a patient receiving ART, it also is important to consider alternative explanations for the adverse reaction, such as:

- Concomitant disease (viral hepatitis, malaria, etc.)
- Reaction to non-ARV drugs (isoniazid-induced hepatitis, anemia caused by trimethoprim/sulfamethoxazole [cotrimoxazole], etc.)

5.2.2 Interactions between ARV and TB drugs

Potential drug interactions can:

- render ARVs ineffective
- Increase drug-induced toxicity risk.

Drug interactions produce adverse effects, most commonly among first line ARVs and TB drugs (Table 18).

Table 18. Common adverse reactions associated with the use of the first-line ARVs and TB drugs

Adverse reaction	First-line ARV drug	TB drug
Exanthema	NVP EFV ABC (part of the hypersensitivity reaction)	Streptomycin (more common) Ethambutol Pyrazinamide Rifampicin Isoniazid (less common)
Peripheral neuropathy	ddl	Isoniazid
Renal failure	TDF	Streptomycin Rifampicin Ethambutol
Hepatitis	NVP	Isoniazid Rifampicin Pyrazinamide

Rifampicin increases the activity of cytochrome P450, a liver enzyme system that metabolizes PIs and INSTIs, significantly decreasing their serum levels and compromising the effectiveness of the ART. NNRTIs are metabolized to a lesser extent. Both PIs and NNRTIs can also affect this same enzyme system and raise rifampicin levels, increasing the risk of hepatotoxicity. Rifampicin is a powerful catalyst of the cytochrome P 450 system and reduces plasma concentrations of the standard doses of PI/r and INSTIs by 75-90%. Thus, simultaneous use of rifampicin and PI/r or INSTI at standard doses is contraindicated.

One option is to replace rifampicin with rifabutin, if available. The dose of rifabutin in the presence of PI/r is 150 mg once a day. Use of etravirine and rifabutin is contraindicated (their concomitant use reduces etravirine plasma concentrations by 37%). There are no significant interactions between rifabutin and INSTIs. The most common adverse effects associated with rifabutin are neutropenia, leukopenia, elevated liver enzymes, cutaneous eruptions, gastrointestinal symptoms and, less frequently, uveitis. The administration of rifabutin with ARVs must be done under strict supervision.

Table 19 summarizes the therapeutic options for ART regimens for coinfecting patients in receiving anti-TB treatment with rifabutin or rifampicin and with contraindication, toxicity, or intolerance to EFV, or who are receiving or need to begin second-line ART (1, 4, 5).²

² For more information on pharmacological interactions between TB drugs and ARVs, visit: www.hiv-druginteractions.org or www.interaccionesshiv.com

Table 19. Second-line regimens of choice for patients with TB/HIV coinfection

TB treatment	Recommended ARV dose	Remarks
TB treatment with rifampicin ¹	Use the same NRTI base recommended for adults, associated with: - RAL 800 mg q. 12h ^{2,3} - LPV/r 400 mg/400 mg q. 12h - LPV/r 800 mg/200 mg q. 12h	Rifampicin significantly reduces PI and INSTI levels, which limits the options.
TB treatment with rifabutin	Same regimens recommended for adults without coinfection (Table 14)	There is no difference in the efficacy of rifabutin and rifampicin. Rifabutin has fewer interactions with PIs boosted with low doses of RTV, permitting standard doses of the latter.

¹ DTG (50 mg q. 12h) can be another therapeutic option; however, sufficient evidence from clinical trials about its safety and efficacy in TB/HIV coinfecting patients in treatment with rifampicin is still unavailable.

² Reference: https://www.cdc.gov/tb/publications/guidelines/tb_hiv_drugs/recommendations02.htm

³ In the ANRS 12 180 Reflate TB clinical study, a statistically significant difference in safety and efficacy has not been observed between the use of regimens with RAL 800 mg q. 12h and RAL 400 mg q. 12h in TB/HIV coinfecting patients in treatment with rifampicin. In: Grinsztejn et al. *Lancet Infect Dis.* 2014 ;14(6):459-67).

Isoniazid can cause peripheral neuropathy. Though no longer recommended for ART, the NRTIs stavudine (d4T) and didanosine (ddI) can also cause this condition. Thus, there is the potential for concomitant toxicity if isoniazid is added to an ARV regimen with any of those NRTIs.

When considering changes in TB treatment due to toxicity, it should be recalled that TB treatment is the short-term priority above ART; furthermore, it has more limited options.

5.3 Immune reconstitution inflammatory syndrome

Immune reconstitution inflammatory syndrome (IRIS) is an inflammatory reaction that can occur when the immune system of an HIV-positive patient improves with ART. It can appear several weeks after treatment start, with signs and symptoms of an opportunistic infection (fever, inflammation, flushing, or secretions at lesion or infection site) that was previously not recognized by a weakened immune system and is now the target of a stronger immune response. These events can be misinterpreted as ART failure. Due to CD4 lymphocytes increase, the clinical

manifestations of IRIS depend on the immune reaction to the antigenic load of an associated opportunistic infection. The most common opportunistic infections associated with IRIS are mycobacterial infections (*M. tuberculosis* or *M. avium* complex infections) and cryptococcosis, which account for a large portion of all IRIS cases in developing countries. In patients with *C. neoformans* meningitis who have not begun ART, it should be deferred at least until the conclusion of induction (2 weeks) or until the complete course of antifungal treatment (10 weeks) has ended. This is because IRIS can be particularly severe and potentially fatal in patients with cryptococcal meningitis.

IRIS typically occurs two to twelve weeks from the start of antiretroviral therapy, although it can appear later. The estimated incidence of IRIS is 10% among all patients who start ART and up to 25% in those who begin ART with CD4 lymphocyte counts of < 50/mm³.

IRIS occurs in up to one-third of patients with HIV and tuberculosis who begin ART, and it generally does so within three months of treatment start. TB-associated IRIS presents with fever, increased size of preexisting adenopathy, appearance of new adenopathies, and pain or respiratory symptoms. Severe reactions can occur, such as tracheal compression caused by massive adenopathy or respiratory failure, which will require support and corticosteroids.

The conditions most commonly associated with IRIS are:

- Beginning ART close to the time of opportunistic infection diagnosis
- No previous exposure to ARVs when opportunistic infection is diagnosed
- Beginning ART with a CD4 lymphocyte count of < 50/mm³
- Rapid reduction in HIV-1 RNA levels in response to ART
- A rapid increase in CD4 lymphocytes

IRIS management includes

- Treatment of the opportunistic infection to reduce the antigenic load
- Continuation of ART
- Use of anti-inflammatory drugs or corticosteroids.

Ibuprofen (maximum dose 400 mg q. 8hours) is recommended for symptomatic treatment of IRIS. In severe cases (central nervous system compromise, general compromise, etc.), corticosteroids are indicated. Corticosteroid treatment dosage and length has not been established, but prednisolone (or prednisone) at a dose of 0.5 mg/kg/day for five to ten days can be suggested for severe cases.

5.4 Integrated care for patients with TB/HIV coinfection

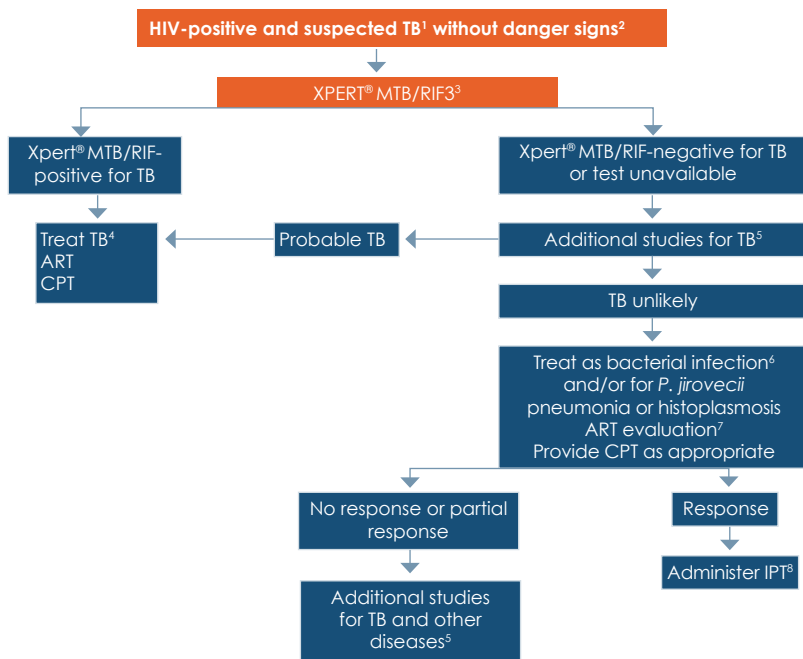
Due to the clinical complexities of TB/HIV coinfection and its multiple associated comorbidities, as well as the frequent social vulnerability of these patients, it is necessary to provide integrated, quality, compassionate, patient-centered

care, focused on patient's health needs and preferences, and to help people and their families make informed decisions, so that they can actively participate in their own care. Care for people with HIV, and especially TB/HIV coinfection, requires appropriate and acceptable multidisciplinary services, both clinical and nonclinical, to reduce morbidity and mortality, increase the effectiveness of the treatment, and improve their quality of life.

Figures 3 and 4 show the algorithm for HIV-positive patients with suspected TB management (ambulatory patients and those severely ill, respectively) (1).

Integrated management of HIV-positive people should include treatment for other sexually transmitted and opportunistic infections commonly associated with HIV (see Chapter 9), neoplastic diseases (AIDS-defining or not), cardiovascular diseases, and other chronic conditions (liver disease, kidney disease, diabetes, and other metabolic disorders, depression and other mental disorders).

Figure 3. Algorithm for managing ambulatory HIV-positive patients with suspected TB



¹ Suspected TB is defined as the presence of any of the following symptoms:

- For HIV-positive adults and adolescents: current cough, fever, weight loss, or night sweats.
- For HIV-positive children: limited weight gain, fever, current cough, or history of contact with a case of TB.

² Danger signs include any of the following: respiratory rate > 30/min, temperature > 39°C, heart rate > 120 bpm and inability to walk unassisted.

³ For people with suspected ETB, extrapulmonary specimens should be collected for Xpert[®] MTB/RIF (cerebrospinal fluid, lymph nodes, and other tissues. Xpert[®] MTB/RIF has low sensitivity for pleural fluid, and there is little information about stool, urine, or blood samples).

⁴ If Xpert[®] MTB/RIF shows rifampicin resistance, start treatment for MDR-TB. If the patient is considered to have a low risk of rifampicin resistance, a second Xpert[®] MTB/RIF test should be done on a fresh specimen. Collect a specimen for culture and DST.

⁵ Additional TB studies include chest x-ray, clinical assessment, and the repetition of Xpert[®] MTB/RIF using a fresh specimen. When possible, send a specimen for TB culture. If Xpert[®] MTB/RIF is not available, examine sputum. A positive result is defined as at least one positive smear, and a negative result, as two or more negative smears. If ETB is suspected, extrapulmonary specimens should be obtained and sent for culture, and an abdominal ultrasound can be done. These studies may require several visits.

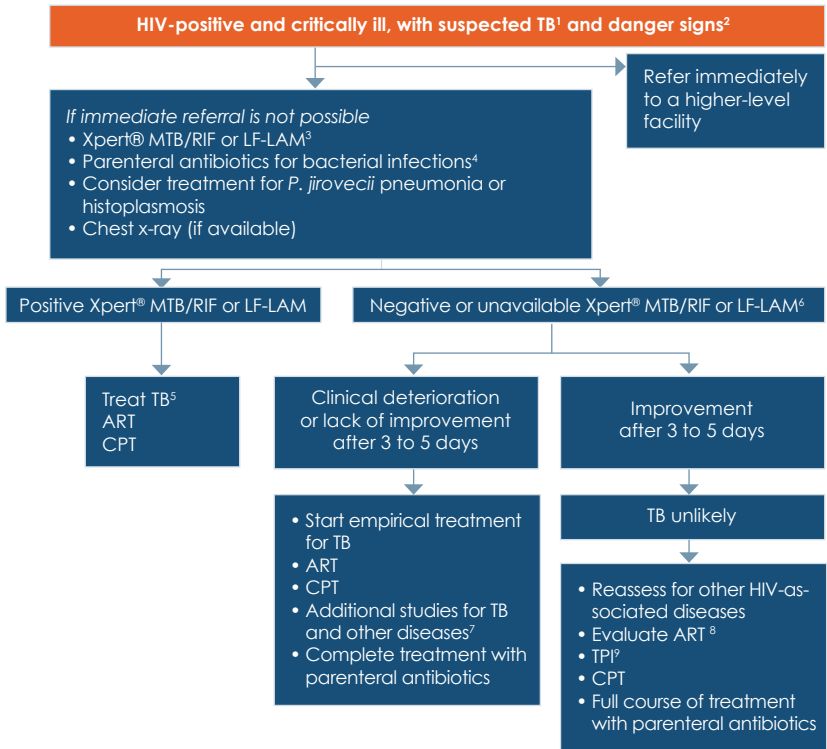
Urine LAM should not be performed for patients with no danger signs.

⁶ Broad-spectrum antibiotics (except for fluoroquinolones) should be used.

⁷ ART should be recommended for all adults, regardless of their CD4 count or clinical status.

⁸ Every HIV-positive person in whom active TB has been ruled out or latent TB infection has been detected should receive isoniazid preventive therapy (IPT), preferably for six months.

Figure 4. Algorithm for managing critically ill HIV-positive patients with suspected TB



¹ Suspected TB is defined as the presence of any of the following symptoms:

- For HIV-positive adults and adolescents: current cough, fever, weight loss, or night sweats.

- For HIV-positive children: limited weight gain, fever, current cough, or history of contact with a case of TB.

² Danger signs include any of the following: respiratory rate > 30/min, temperature >39°C, heart rate > 120 bpm and inability to walk unassisted.

³ For people with suspected ETB, extrapulmonary specimens should be obtained for Xpert® MTB/RIF (cerebrospinal fluid, lymph nodes, and other tissue. Xpert® MTB/RIF has low sensitivity for pleural fluid, and there is little information on stool, urine, or blood samples). Lateral flow urine liparabinomannan (LF-LAM) can be used to support the diagnosis of active TB in adults and critically ill children with HIV, regardless of their CD4 count. If Xpert® MTB/RIF or LF-LAM is unavailable, perform a sputum examination. A positive result is defined as at least one positive smear, and a negative one as two or more negative smears. When possible, send a specimen for TB culture.

⁴ Broad-spectrum antibiotics (except for fluoroquinolones) should be used.

⁵ If Xpert® MTB/RIF shows rifampicin resistance, treatment for MDR-TB should begin. If the patient is at low risk of rifampicin resistance, a second Xpert® MTB/RIF test should be performed on a fresh specimen. Collect a specimen for culture and DST.

⁶ If the result of the Xpert® MTB/RIF is negative, the test can be repeated using a fresh specimen.

⁷ Additional TB studies include chest x-ray, clinical assessment, repetition of the Xpert® MTB/RIF test using a fresh specimen, and culture. If ETB is suspected, extrapulmonary specimens should be collected for culture, and an abdominal ultrasound can be done.

⁸ ART should be recommended for all adults, regardless of their CD4 count or clinical stage.

⁹ Every HIV-positive person in whom active TB has been ruled out or latent TB infection has been detected should be administered isoniazid preventive therapy (IPT), preferably for six months.

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Chapter 6

TB and HIV prevention measures

KEY RECOMMENDATIONS

- Children with an established HIV diagnosis should not be vaccinated with BCG (1, 2).
- It is recommended that children whose HIV status is unknown and show with no signs of HIV infection, and whose mothers are HIV-positive, should receive the BCG vaccine, taking local factors into account (1, 2).
- Every HIV-positive person in whom active TB has been ruled out or latent TB infection has been detected should receive preventive therapy, preferably with isoniazid (IPT), for at least six months (Strong recommendation, high-quality evidence) (3, 4).
- Preventive treatment with trimethoprim/sulfamethoxazole (cotrimoxazole) should be systematically administered to all HIV-positive people with active TB, regardless of their CD4 count (Strong recommendation, high-quality evidence) (3, 5).
- Interventions for HIV prevention (e.g., the availability of information on HIV prevention and condoms) in health facilities that serve patients with a presumptive or confirmed TB diagnosis are basic prevention measures (6).
- Infection control measures based on the WHO guidelines should be implemented and sustained: administrative and managerial, environmental, and personal protection (3, 7, 8).

6.1 TB prevention in HIV-positive people

The best way to prevent TB is to provide effective treatment for patients with infectious TB to interrupt the chain of transmission. Cases of respiratory tract TB (pulmonary and laryngeal) are considered infectious. Patients with ETB are not considered infectious.

Administration of BCG (Calmette-Guérin bacillus) vaccine is a specific way of preventing TB in children. Chemoprophylaxis with isoniazid in HIV-positive people is another way of prevention, since the detection of latent TB infection in HIV-positive

people is essential for timely treatment and prevention of active TB. Likewise, infection control measures are key to preventing TB in HIV positive people.

6.1.1 Role of BCG in preventing TB in HIV-positive people

BCG is a vaccine with attenuated live microorganisms derived from *Mycobacterium bovis*. Route of administration is intradermal, and the usual dose is 0.1 mL. The BCG vaccine can protect children against severe and disseminated forms of TB, such as meningal or miliary tuberculosis. The BCG vaccine has little or no effect on PTB infection in adults. Table 20 presents the current recommendations for BCG immunization (1, 2).

Table 20. Recommendations for immunization with the BCG vaccine (1, 2)

Situation	Recommendation
Child whose mother's HIV status is unknown	Immunize with BCG Vaccination benefits outweigh risks
Asymptomatic child with unknown HIV status whose mother is HIV-positive	Immunize with BCG The benefits tend to outweigh risks
Child with an established HIV diagnosis, with or without signs or symptoms of HIV	DO NOT immunize with BCG Risks of BCG vaccination outweigh benefits
Child with unknown HIV status who has signs or symptoms suggestive of HIV and whose mother is HIV-positive	DO NOT immunize with BCG Risks of BCG vaccination outweigh benefits

6.1.2 Treatment of latent tuberculous infection

Treatment for HIV-positive people should begin once PPD or IGRA detect LTBI. This reduces the risk of their developing active TB. Treatment should be administered only when active TB has been ruled out, because use of only one or two drugs can lead to resistance. Every HIV-positive person in whom active TB has been ruled out or LTBI has been detected should be given preventive therapy, preferably with isoniazid (IPT), for at least six months (3, 4).

The risk reduction for developing active TB in HIV-positive people is even more significant when ITP is accompanied by ART. Although ITP can be self-administered, patients who receive it should be regularly assessed throughout treatment to document treatment adherence, absence of drug toxicity, or appearance of symptoms compatible with active TB.

In upper middle- or high-income countries, where the estimated TB incidence is less than 100 per 100,000 people, the following LTBI treatment options are recommended:

- Isoniazid for 9 months
- Rifapentine plus isoniazid weekly for 3 months
- Isoniazid plus rifampicin for 3 or 4 months
- Rifampicin for 3 or 4 months

Considering the potential pharmacological interactions between rifampicin, rifapentine and antiretroviral medicines, the preferred treatment option for LTBI is with isoniazid. In case the use of rifampicin or rifapentine should become necessary, refer to chapter 5.2 of this manual about adverse effects of antiretrovirals and interactions with anti-TB drugs.³

6.2 HIV prevention in TB patients

While it is important to prevent TB in people who are already infected with HIV, it is just as important to prevent HIV in people with an asymptomatic *M. tuberculosis* infection (LTBI), since HIV infection would substantially increase their risk of developing active TB (3-13% annually). Moreover, consistent condom use prevents HIV transmission from coinfecting people to their intimate partners and other sexual contacts (5).

HIV infection prevention in everyone, including people with TB, relies on taking precautions related to sexual practices, intravenous drug use, the screening of blood donors and blood products, prevention of mother-to-child transmission, and biosafety in health facilities.⁴

6.2.1 Prevention in sexual practices

Among HIV prevention measures, biomedical and behavioral measures to reduce the risk of sexual transmission are prioritized as part of TB-HIV program integration.

Although anal coitus is the sexual practice with the greatest risk of HIV transmission, followed by vaginal coitus, there is also a risk of transmission through oral sex involving penile stimulation with the mouth, such as fellatio. The risk is especially high for the receiving individual, whether man or woman, that is, the one who receives the penis and ejaculate in his or her anal, vaginal, or oral cavity.

A rough estimate of transmission risk can be made through mathematical models for each sexual practice, but not for every particular exposure, since it depends on many factors (the integrity of the mucous membranes, the presence of other sexually transmitted infections, recent infection, and viral load) (Table 21).

Everyone can benefit from counseling and agreeing to take an HIV test if they are not in a mutually faithful stable relationship with someone who has tested negative for HIV and has not recently engaged in risky sexual behavior or intravenous drug use.

³ For more information on pharmacological interactions between TB drugs and ARVs, visit: www.hiv-druginteractions.org or www.interaccionesshiv.com

⁴ For more information on combined HIV prevention measures, including preexposure prophylaxis (PrEP) with antiretroviral drugs, see the WHO *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection* (<http://www.who.int/hiv/pub/arv/arv-2016/en/>) and *Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations* (<http://www.who.int/hiv/pub/guidelines/keypopulations-2016/en/>).

Table 21. Risk of HIV transmission

Anal coitus	Vaginal coitus	Fellatio with ejaculation
Receptive 1:30 to 1:100 Insertive 1:1000	Receptive 1:1000 Insertive 1:10 000	Receptive 1:1000

People should know that, in addition to abstinence, the only way to protect themselves against sexual transmission of HIV is through the proper and consistent use of condoms. The effectiveness of condoms in preventing HIV transmission is approximately 95%, and people who use them should be counseled, especially about:

- Using them every time
- Putting them on when the penis is fully erect and before any genital contact
- Pinching the reservoir at the tip with the index finger and thumb so as not to leave air
- Holding it at the base before withdrawing the penis from the anus, vagina, or mouth
- Using only water-soluble lubricants
- Not reusing them

6.3 Prevention of opportunistic infections

6.3.1 Trimethoprim/sulfamethoxazole (cotrimoxazole) prophylaxis

Prophylaxis with trimethoprim/sulfamethoxazole (TMP/SMX), also known as cotrimoxazole, is recommended for all HIV-positive people, including pregnant women, throughout their treatment for tuberculosis. Cotrimoxazole preventive therapy (CPT) is especially useful in preventing *P. jirovecii* pneumonia and toxoplasmosis and reducing mortality in coinfecting patients. CPT has a significant impact in settings with a high prevalence of malaria and bacterial infections in HIV-positive people. The recommended dose of TMP/SMX is one 160/800 mg tablet/day p.o. (3, 5, 6).

6.3.2 Recommended primary and secondary prophylaxis

Primary and secondary prevention of opportunistic infections in TB/HIV patients is important, following the indications presented in Tables 22 and 23 (7).

Table 22. Primary prophylaxis recommended for TB/HIV patients

Disease or infection	Indication	Recommended regimen
<i>P. jirovecii</i> pneumonia	CD4 < 200 /mm ³ * Oral candidiasis (WHO stages 3 and 4)	First choice: Oral TMP/SMX 160/800 mg / day** Other options: Oral TMP/SMX 160/800 mg 3 times per week or Oral dapsone 100 mg /day
Toxoplasmosis	CD4 < 200 /mm ³ Oral candidiasis (WHO stages 3 and 4)	First choice: Oral TMP/SMX 160/800 mg /day Other options: Oral dapsone 50 mg /day + pyrimethamine 50 mg / week
Disseminated <i>M. avium</i> complex (MAC) infection	CD4 < 50 /mm ³ WHO stage 4	Oral azithromycin 1200 mg / week, or oral clarithromycin 500 mg q. 12h

* If the CD4 lymphocyte count for indicating prophylaxis is unavailable, use WHO stages 3 and 4

** Assess risk/benefit in pregnant women

Primary prophylaxis is not recommended for people with:

- Candidiasis
- Histoplasmosis
- *C. neoformans* meningitis

Secondary prophylaxis is not recommended for people with candidiasis.

Table 23. Recommended secondary prophylaxis in TB/HIV patients

Disease or infection	Therapeutic regimen	Duration*
<i>P. jirovecii</i> pneumonia	Oral TMP/SMX 160/800 mg /day	While the TB treatment lasts, regardless of CD4 count, and after it ends, until CD4 count is >200 /mm ³ with ART.
<i>C. neoformans</i> meningitis**	Oral fluconazole 200 mg /day	Discontinue in patients in ART and prophylaxis with fluconazole for at least one year in the presence of suppressed viral load and CD4 count ≥ 100/mm ³

Disease or infection	Therapeutic regimen	Duration*
Toxoplasmosis	Oral TMP/SMX 160/800 mg /day or Oral sulfadiazine 500 mg q. 6h + pyrimethamine 50 mg/day Add oral folic acid 10 mg /day	Until CD4 count is >200/mm ³ with ART
Histoplasmosis	Oral itraconazole 200 mg /day after breakfast	Until CD4 count is > 150/ mm ³ with ART
Disseminated <i>M. avium</i> complex (MAC) infection	Oral azithromycin 1200 mg/week or Oral clarithromycin 500 mg /12 h	Until CD4 count is > 100/ mm ³ with ART

* Suspension of secondary prophylaxis is indicated when, due to treatment with ARVs, the increase in the CD4 count above the established thresholds is sustained in successive monitoring over a 3-6-month period.

** In asymptomatic HIV-positive people with a CD4 count of < 100/mm³, the serum or plasma cryptococcal antigen test is recommended. If positive, treat with fluconazole 800 mg/day (or 12 mg/kg/day in patients under the age of 19) for 2 weeks, followed by fluconazole 400 mg/day (or 6 mg/kg/day up to 400-800 mg per day in patients under 19) for 8 weeks.

6.4 TB infection control (8, 9)

The recommendations on infection control are based on the 2014 regional guidelines for TB infection control in the Americas (7), which include recommendations from related documents.

Pulmonary and laryngeal TB patients can transmit the disease when they cough, talk, or sneeze through airborne microdroplet nuclei of less than 5 microns in diameter that contain the bacillus. These aerosols are also produced by such patients during therapeutic or invasive procedures, such as nebulization or bronchoscopy. The majority of TB patients are diagnosed in outpatient primary health care facilities. Hospitalization may sometimes be necessary, however – especially in case of people who have been weakened by HIV or other opportunistic infections.

HIV-positive people can be infected or reinfected and develop active TB within a few months if exposed to a TB patient. Health care workers and other health facility staff are also at particularly high risk of contracting TB due to their frequent exposure to patients with the disease. Health care workers can also be infected with HIV and be at greater risk of developing active TB if they are infected with *M. tuberculosis*. Infection control procedures must be followed, not only to prevent

transmission from the patient to health workers, but transmission from patient to patient, visitors, and, occasionally, from health care worker to patient.

Infection control measures fall under three categories, each operating at a different point in the transmission process. These categories are:

1. Administrative and managerial control measures
2. Environmental control measures
3. Respiratory protection measures

6.4.1 Administrative and managerial control measures

These are the first level of control, the first line of defense, and the most important measures, because they have the greatest impact on transmission, since they are designed to impede the production of microdroplet nuclei and, thus, reduce the exposure of health workers and patients to *M. tuberculosis*. At the outpatient level, these measures include:

- Prompt screening of all patients on arrival at the health facility to identify people with TB symptoms or who are being studied or treated for the disease.
- Instruct TB patients identified through screening in respiratory hygiene and cough etiquette, which includes covering the mouth and nose when coughing or sneezing; whenever possible, patients should be provided with surgical masks or paper towels to do so. Place patients with suspected or diagnosed TB in separate, well ventilated waiting areas, such as a covered open space with good air circulation.
- Prioritize care and management of these patients to minimize their time in the facility.
- Ensure rapid diagnosis of patients with suspected TB so that treatment can begin as soon as possible. This includes rapid referral, if necessary.
- Ensure directly observed treatment for TB patients.

Patients with pulmonary and laryngeal TB who require hospitalization should be placed in a well-ventilated isolated room, limiting their movement around other hospital areas and, on such occasions, always covering their mouth and nose with a surgical mask. The mask should be used only by one patient, and appropriate cleaning and disinfection procedures should be followed. Isolation measures should continue until a TB diagnosis is ruled out, or, if confirmed, until the patient has completed two weeks of effective treatment and/or has two consecutive negative sputum smears.

Patients diagnosed with MDR-TB require special management in a referral center, where isolation and ventilation procedures should be followed. Due to the high risk of morbidity and mortality in HIV-positive people, MDR-TB patients should receive care in different locations than those regularly used for HIV-positive people.

Another important administrative control measure is assessing the risk of transmission in the facility, and based on that assessment, preparing an infection control plan, providing adequate training for health care workers to implement

the plan, educating patients and the community about respiratory hygiene and cough etiquette, and ensuring coordination between the TB and HIV programs.

6.4.2 Environmental control measures

Environmental control measures are the second line of defense against *M. tuberculosis* transmission in health facilities. Since exposure to infectious droplet nuclei generally cannot be fully eliminated through administrative and managerial control measures, environmental control measures are designed to reduce the concentration of airborne droplet nuclei. It is important for health facilities to be aware that in the absence of adequate administrative control measures, environmental control measures will not eliminate the risk of transmission. Environmental control measures include:

- Ventilation (natural and mechanical)
- Filtration
- Ultraviolet germicidal radiation

The simplest and least expensive technique is to maximize natural ventilation to eliminate and dilute the airborne tubercle bacillus in areas where TB patients are kept, far from other patients. The areas where TB transmission in health facilities can occur include outpatient, emergency services; hospital rooms/wards, diagnostic imaging services, laboratory, operating rooms, and autopsy rooms.

Controlled natural ventilation helps reduce *M. tuberculosis* transmission ("controlled" meaning that windows are monitored to ensure that they remain open at all times to improve ventilation and air flow). Sputum collection for TB diagnosis should always be done in a well-ventilated area away from other people. It should never be done in a bathroom or small, poorly ventilated cubicles. To maximize natural ventilation patterns in hospitals, hospital wards, physician's offices, or rooms, the following steps should be taken, when possible:

- Keep waiting rooms, sputum collection areas, examination rooms, and hospital rooms open to the environment.
- Install windows or other openings in exterior walls so that air can move outside and not to other rooms or waiting areas.
- When ceiling fans are used, windows should remain open, since the objective is to dilute and change the air, rather than simply mix it.

As to mechanical ventilation, in resource-constrained countries, window fans are the least expensive and most feasible method for directing air flow outward. Other mechanisms, which are more expensive and require maintenance, include mechanical extraction ventilation systems that pump clean air from the outside into the building and channel the contaminated air to the outside, and closed filtration and recirculation systems.

Ideal isolation consists of a room where air flows from the outside in (negative pressure) with air changes of 6 (minimum) to 12 (ideal) volumes per hour and appropriate airflow to the outside. Negative pressure can be created with a fan that extracts air through the window to the outside. The door should remain

closed. When this is unfeasible, a service or wing could be designated for patients with probable or confirmed TB.

Sunlight is a safe and natural source of ultraviolet rays that can kill tuberculosis bacilli; thus, full advantage of this should be taken in the design and operation of areas for patient care. The use of ultraviolet germicidal lamps (UVGL) can be considered, but bearing in mind their potential adverse effects, such as chronic eye and skin problems due to overexposure. This is especially true when the equipment is not properly installed, monitored, and maintained.

6.4.3 Respiratory protection measures

Respiratory protection measures are the last line of defense against *M. tuberculosis* infection in health facilities and imply the use of particulate respirators by health workers, administrators, and visitors. These measures should be preceded by the aforementioned infection control measures.

Particulate respirators have tiny pores that block droplet nuclei and a seal that keeps air from entering through their edges, since they fit perfectly over the mouth and nose. They are not the same as surgical masks. Devices with a filtration efficiency of at least 95% for particles 0.3 microns in diameter are recommended. These are known as N95 respirators.

Cloth, paper, or plastic surgical masks have large pores and their edges are not sealed, which means they do not protect health care workers, other staff, patients, or visitors against infection. Surgical masks prevent the spread of microorganisms from the person who wears them (e.g., a surgeon or tuberculous patient) to others by capturing large particles near the nose and mouth. These are indicated for patients with suspected or diagnosed TB of the respiratory tract when they are transferred from place to place in a hospital or are in contact with other people.

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Chapter 7

Drug-resistant TB in HIV-positive people

New WHO policy guidelines on treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB) will be released by the end of 2018. Meanwhile refer to:

- Rapid Communication: Key changes to treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB): http://www.who.int/tb/publications/2018/rapid_communications_MDR/en/
- Frequently Asked Questions on the WHO Rapid Communication: key changes to the treatment of multidrug- and rifampicin-resistant TB: http://www.who.int/tb/publications/2018/MDR-TB_FAQs/en/

KEY RECOMMENDATIONS

- Xpert® MTB/RIF should be used as an initial diagnostic test in adults when TB associated with HIV infection or multidrug-resistant TB (MDR-TB) is suspected, instead of conventional sputum microscopy, culture, and DST. (Strong recommendation, high-quality evidence) (1).
- The use of microscopy and culture, instead of just conventional microscopy, is recommended for MDR-TB patient monitoring during treatment (Conditional recommendation, very low-quality evidence) (2).
- Antiretroviral therapy is recommended as soon as possible for all DR-TB/HIV patients requiring second line TB drugs, regardless of their CD4 count, within the first 8 weeks of the start of TB treatment (Conditional recommendation, very low-quality evidence) (1).

7.1 Context

Drug-resistant tuberculosis (DR-TB) (3) can be:

- Mono-resistant: resistant to one of the first-line drugs.
- Polydrug resistant: resistant to more than one first-line TB drug other than isoniazid and rifampicin at the same time.
- RR-TB: resistance to rifampicin, an essential TB drug.
- MDR-TB: multidrug-resistant, with resistance to at least isoniazid and rifampicin.
- XDR-TB: extensively resistant; this is MDR-TB with resistance to any fluoroquinolone (levofloxacin, moxifloxacin) and any of the injectable second-line TB drugs (capreomycin, kanamycin, and amikacin).

DR-TB/HIV coinfection poses a real challenge for the prevention, diagnosis, and treatment of both diseases. Studies show high mortality among the HIV-positive patients with DR-TB compared to HIV-negative patients and alarming mortality among HIV-positive patients with XDR-TB within a few weeks of diagnosis. Consequently, early diagnosis of DR-TB in HIV-positive people, rapid treatment with appropriate regimens, social support for patients, and infection control measures are essential components in managing RR/MDR/XDR-TB/HIV coinfection (1).

Recent data from global monitoring of TB drug resistance point to the existence of an association between HIV and DR-TB in certain parts of the world, with community or hospital-acquired transmission of resistant strains among HIV-positive people. This latter phenomenon appears to corroborate the multiple reports of DR-TB outbreaks in HIV positive people in hospitals where both diseases are treated. DR-TB is associated with higher mortality in HIV-positive than HIV-negative patients, and the use of ART with DR-TB treatment improves survival. Therefore, treatment administration for both diseases should be the norm (1).

7.2 General information for managing DR-TB/HIV coinfection

Early recognition of a TB patient's HIV status can determine the right diagnostic procedures and RR/MDR/XDR-TB treatment. Every TB patient found to be HIV-positive should undergo drug susceptibility testing (DST) to ensure early diagnosis of drug resistant TB and identify the prevalence of resistance among coinfecting patients. Likewise, every HIV-positive patient with a clinical symptom suggesting TB should have a rapid molecular assay (Xpert® MTB/RIF) done for rapid diagnosis TB and resistance to at least rifampicin. This will allow to provide appropriate treatment in a timely manner and, moreover, carry out a comparative analysis of HIV-positive and HIV-negative TB patients in terms of the presence or absence of TB drug resistance (1, 4).

Based on the collaborative TB/HIV activities mentioned in Section 1.3, the following adaptations have been made for the management of DR-TB/HIV coinfection (4):

- At the initiative of the health care provider, provide HIV testing and counseling for all patients with presumed or confirmed DR-TB
- Include HIV testing in TB drug resistance surveillance
- Use Xpert® MTB/RIF for people with suspected TB/HIV coinfection
- Do a mycobacteria culture for people with suspected TB/HIV coinfection
- Perform DST at the start of TB treatment
- Consider empirical treatment with second-line TB drugs
- Begin early ART in patients with DR-TB/HIV coinfection
- Administer cotrimoxazole preventive treatment to patients with active TB and HIV
- Set up a robust patient monitoring and follow-up system

- Provide additional nutritional, social, and financial support
- Provide integrated TB and HIV services
- Guarantee effective infection control measures
- Involve all key stakeholders in DR-TB and HIV activities

7.3 DR-TB diagnosis in HIV-positive people

Diagnosing DR-TB in HIV-positive people poses the same challenges as diagnosing drug susceptible TB. First, it requires a thorough knowledge of TB epidemiology in the location, the risk factors to which the HIV patient is exposed and the degree of immunosuppression and symptoms. In very low TB prevalence settings, it will also be necessary to consider other more prevalent pathologies without disregarding TB. If the patient has risk factors, such as having contact with a DR-TB case or with someone who died of TB or who has been treated for TB previously, DR TB must be considered. If immunosuppression is advanced, the patient most likely has extrapulmonary forms of TB with a very low bacillary load. It should be recalled that smear microscopy is not sufficient for an HIV-positive person with suspected TB, because environmental mycobacteria could be involved that will not respond adequately to treatment; thus, every specimen (pulmonary or extrapulmonary) must be sent for culture, species identification, and DST (4).

Because survival is directly related with early diagnosis and treatment, when pulmonary TB is suspected, Xpert® MTB/RIF, instead of conventional microscopy and culture, should be used as the initial diagnostic test in people with suspected HIV/TB or HIV/MDR TB. A negative result in a case with a positive sputum smear could signify mycobacteriosis. A positive result confirms TB and the presence or absence of rifampicin resistance. Another specimen should be sent for DST to determine sensitivity to isoniazid. If the patient has RR- and/or MDR-TB, DST for second line TB drugs (injectables and fluoroquinolones used in the country) should be ordered. These tests should not delay the start of treatment (1, 4).

If the patient has symptoms that suggest extrapulmonary TB, a specimen should be taken from the compromised area and processed as follows (1):

- Suspected meningitis: The use of Xpert® MTB/RIF instead of conventional microscopy and culture is preferred as the initial diagnostic test for the analysis of cerebrospinal fluid from patients with suspected TB meningitis; however, a negative result does not rule out the disease and should be correlated with clinical examination and the cytochemical results of the cerebrospinal fluid.
- Suspected TB of the lymph nodes or other tissues: Xpert® MTB/RIF can be used as a substitute for the usual practice (including conventional microscopy, culture, and/or histopathology) to analyze specific, non-respiratory specimens (lymph nodes and other tissues) from HIV-positive people with suspected extrapulmonary TB. It is not recommended for other fluids, such as pleural, peritoneal, blood, feces, or urine. In these cases, clinical examination, cytochemical studies, and culture with DST in fluid medium (e.g., MGIT) can support the diagnosis.

In addition to a culture and DST, a detailed history should be taken of every HIV-positive patient with suspected TB. This should cover the following (5, 6):

- Previous treatment with anti-TB drugs, especially for patients with a history of treatment failure.
- If the patient was previously treated, identify the provider (TB control program, private health service, social security, prison, other). Generally, treatments that do not follow national standards and are not provided free of charge can produce MDR TB.
- If the patient has no previous history of TB treatment, history of rifamycin derivatives use for opportunistic infections management should be investigated, since there is risk of rifampicin mono-resistance.
- Known contact with MDR-TB cases or with someone whose treatment failed or who died of TB while in treatment. These patients should be treated for MDR-TB until the DST results are in.
- A history of incarceration.
- A history of frequent visits to health facilities.

7.4 DR-TB treatment in HIV-positive patients

DR-TB treatment tends to be the same for both HIV-positive and HIV-negative patients. Table 24 shows the five groups of TB drugs (2).

Table 24. Classification of second-line TB drugs (2016 Revision)¹

Group	Name	Acronym	Dose	Maximum dose
A. Fluoroquinolones ²	Levofloxacin	Lfx	10-15 mg/kg /day	
	Moxifloxacin	Mfx	400 mg/ day	
	Gatifloxacin	Gfx	400 mg/ day	
B. Second-line injectables	Amikacin	Am	15 mg/kg /day	1 g
	Capreomycin	Cm	15 mg/kg /day	1 g
	Kanamycin	Km	15 mg/kg /day	1 g
	(Streptomycin) ³	(S)	15 mg/kg /day	1 g
C. Other key second-line drugs ²	Ethionamide/ prothionamide	Eto/ Pto	15-20 mg/kg / day	1 g 1 g
	Cycloserine/ terizidone	Cs/Trd	10-15 mg/kg/day	
	Linezolid	Lzd	600 mg/day	
	Clofazimine	Cfz**	100-200 mg/day	

Group	Name	Acro- nym	Dose	Maximum dose
D. Complementary drugs (not part of the core MDR-TB regimen)	D1 Pyrazinamide	Z	25 mg/kg/day	2 g
	Ethambutol	E	15-25 mg/kg/day	
	Isoniazid in high doses	H ^h	600-1500 mg/day	
	D2 Bedaquiline Delamanid	Bdq * Dlm***	200 mg/ day	
	D3 PAS	PAS	4 g q. 8-12h	
	Imipenem- cilastatin	lpm	1 g mg IV q. 12h	
	Meropenem ⁴	Mpm	1 g IV q. 8h	3 g
	Amoxicillin- clavulanate ⁴	Amx- Clv	80 mg/kg /day	
	(Thiacetazone) ⁵	(T)		

* 400 mg/day/14 days, followed by 200 mg/day 3 times per week for 22 weeks

** 200 mg/day for 2 months, followed by 100 mg/day

***100 mg twice a day for 24 weeks

¹ This regrouping of the previous classification is designed as a guide for the design of conventional regimens. For shorter regimens of 9-12 months, its composition tends to be standard (see Section A in reference 2).

² Group A and C drugs are shown in descending order of preference for use (subject to other considerations; see text).

³ See text for the conditions under which streptomycin could substitute other injectable drugs. Resistance to streptomycin only does not qualify as XDR-TB.

⁴ Carbapenems and clavulanate should be used in combination; clavulanate is only available in combined presentations with amoxicillin.

⁵ HIV infection should be ruled out before using thioacetazone.

The initial treatment for RR-TB diagnosed with Xpert® MTB/RIF in an HIV-positive patient is the same as that for MDR-TB, since it is assumed to be multidrug-resistant until culture and DST results are available. The treatment is tailored to test results (4).

MDR-TB treatment involves the prescription of pyrazinamide plus four of the main TB drugs (groups A, B, and C) that have never been administered before to the patient and is based on the following principles (2):

- Combine fluoroquinolone (group A: levofloxacin or moxifloxacin) with a second-line injectable drug (group B: kanamycin, amikacin or capreomycin)
- Add two drugs from group C.
- Combine first-line drugs from group D1 that can still be considered effective: ethambutol or isoniazid at high doses.
- Consider adding drugs from groups D2 or D3 if a regimen of 4 drugs from groups A, B, and C cannot be devised. This may be due to prior use, resistance, or adverse reactions.

The treatment includes two phases (4).

- The first phase includes the injectable drug and lasts up to 4 months after bacterial conversion. It usually takes 6 to 8 months.
- The second phase includes oral drugs. Its length depends on the patient's treatment response.

The total length of treatment will depend on the month of bacterial conversion. Bacterial conversion is defined as the negative result of two consecutive cultures done at least 30 days apart. The date of the first negative culture is the date taken as conversion. If conversion was at the second month of treatment, the length of treatment will be 20 months. All doses must be administered under strict supervision throughout the treatment, ideally on an outpatient basis. Some cases initially require hospitalization until the patient can tolerate the drugs or culture turns out negative (4).

XDR-TB management should be customized and conducted by an expert, especially if it is associated with HIV. The specific indications are outside the scope of this manual.

There are national and subnational expert committees on DR-TB in the Americas that define treatment regimens, monitor the management of difficult cases, evaluate results, and update national standards. These committees should include experts in HIV/AIDS management and develop diagnosis and treatment algorithms for HIV and DR/MDR/XDR-TB coinfection.

The following should be borne in mind in the treatment of DR-TB/HIV coinfection (4):

- ART is critical for preventing the extremely high mortality in patients who do not receive ARVs.
- When combined with ART, numerous drugs for the treatment of MDR-TB have a high incidence of adverse reactions. Some of them are common to both TB treatment and ART, and build-up.
- Surveillance of treatment response and adverse reactions should be more intense.
- Immune reconstitution inflammatory syndrome (IRIS) can complicate treatment.

ART should begin as soon as possible, within 8 weeks of the start of treatment for MDR TB, regardless of CD4 count. There is little information about the interaction between second-line TB drugs and ARVs, and overlapping toxicity is also a problem. The known interactions are (1, 4):

- Rifamycin derivatives: These drugs are not used in the treatment of MDR-TB; however, they are used in the treatment of mono- or polydrug-resistant TB and are sensitive to rifampicin.
- Bedaquiline: This drug is metabolized by cytochrome P450-3A4 and has multiple interactions with protease inhibitors and NNRTIs.
- Delamanid: This drug is metabolized by CYP3A1. Many drugs can induce or inhibit the CYP3A4 system, which causes drug interactions.

- Quinolones and didanosine: Buffered didanosine contains an aluminum- and magnesium-based antacid, and, if administered with fluoroquinolones, can result in diminished absorption of the latter. Its use should be avoided, but if it is necessary, it should be administered six hours before or two hours after administration of the fluoroquinolone. Enteric-coated didanosine can be used concomitantly without taking this precaution.
- Ethionamide and prothionamide: Based on the limited information available on the metabolism of these thioamides, this type of drugs can interact with ARVs. Ethionamide and prothionamide are metabolized by the CYP450 system, although which specific CYP enzymes is unknown. It is unknown whether the dosage of these drugs and/or certain ARVs should be modified during their concomitant use in the treatment of MDR-TB and HIV.

The definition of ART failure was provided in Section 5.1. When ART failure is diagnosed in a DR-TB patient, beginning a new treatment with ARVs at the same time is not recommended; instead, the treatment should be continued and a switch made to a second-line ARV two to eight weeks after the start of the DR-TB treatment.

In the case of monoresistance or polydrug-resistance (not MDR-TB), the indications in Chapter 6 of the WHO Manual for the management of DR-TB should be followed (4).

7.5 Monitoring and follow-up of DR-TB treatment in HIV-positive people

Treatment for these patients must be monitored by specialists in HIV and DR-TB management, with close surveillance of the following aspects:

- a. Risk of overlapping, or building up adverse reactions
- b. Nutritional status
- c. Regular monitoring of the therapeutic response of both infections. Treatment must be comprehensive (see Section 5.4).

Directly observed treatment of ART and DR-TB is recommended.

The complexity of ART and second-line TB treatment, each with its own adverse reactions (some of which are potentiated due to parallel treatment), calls for rigorous clinical and laboratory monitoring from treatment supervisors, infectious disease specialists, and lung specialists, who should be the ones in charge of monitoring the DR-TB treatment.

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Chapter 8

Diagnosis and treatment of TB/HIV in children

KEY RECOMMENDATIONS

- HIV-positive children with any of the following signs or symptoms—limited weight gain, fever, cough, or a history of contact with a TB case—may have TB and should be screened for TB and other illnesses. If TB is not detected, isoniazid prophylaxis should be started, regardless of the patient's age (Strong recommendation, medium-quality evidence) (1, 3).
- HIV-positive children over 12 months of age, who, according to the TB screening, do not show signs or symptoms of active TB and who have not had contact with a case of TB should receive IPT (10 mg/kg/day) for 6 months (Strong recommendation, medium-quality evidence) (1 - 3).
- HIV-positive children under 12 months of age, who, according to the TB screening, do not show signs or symptoms of active TB and have had contact with a case of TB, should receive IPT for 6 months (Strong recommendation, low-quality evidence) (1, 3).
- Xpert® MTB/RIF should be used as the initial diagnostic test when HIV-associated TB or MDR-TB is suspected. (Strong recommendation, very low-quality evidence) (2, 3).
- Children with suspected or confirmed pulmonary or peripheral TB living in areas with high HIV incidence or who are coinfecting with HIV should not be treated with intermittent treatment regimens. (Strong recommendation, low-medium-quality evidence) (2).
- All children with active TB should begin receiving ART as soon as possible, no more than 8 weeks from the start of TB treatment, regardless of their CD4 count and clinical stage (Strong recommendation, low-quality evidence) (3).
- For coinfecting children under 3 years of age, the recommended regimen for ART start is AZT + 3TC + ABC. Once TB treatment is completed, the ART regimen can be tailored to the child's age and switched to a PI- or NNRTI-based regimen (Strong recommendation, medium-quality evidence) (3).

- In coinfecting children aged 3 years and above, the recommended regimen for ART start is 2 NRTI + EFV or AZT + 3TC + ABC. Once TB treatment in children with 3 NRTIs is completed, the ART regimen can be tailored to the child's age and switched to an NNRTI-based regimen (EFV) (3).
- Once TB treatment is completed, all HIV-positive children should receive isoniazid for six additional months (Conditional recommendation, low-quality evidence) (3).
- TMP/SMX prophylaxis is recommended for HIV-positive children, regardless of their clinical or immune status, with emphasis on children under 5 and those with a clinically advanced stage of infection (Strong recommendation, high-quality evidence). (3, 4).

8.1 General information on TB/HIV coinfection in children ^(2, 5)

Pediatric tuberculosis tends to be primary. The age at which infection occurs determines the pattern of the primary disease. Unlike adults, who often have infiltrates or cavitations in the pulmonary vertices, children tend to have disease of the mediastinal lymph nodes, and younger children are particularly susceptible to disseminated forms of TB after primary infection.

In HIV-positive children, clinical manifestations of TB are highly influenced by the degree of immunosuppression. TB can be pulmonary and extrapulmonary:

- **Pulmonary TB:** TB/HIV-infected children with preserved immune function present in a manner similar to patients without HIV. Symptoms of pulmonary TB include fever, cough, weight loss, and malaise; night sweats can occasionally occur. Miliary TB is common in children under 2 years of age. It is important to rule out other HIV-related lung diseases, frequent in these children, including *P. jirovecii* pneumonia (PCP, formerly *Pneumocystis carinii* pneumonia), interstitial lymphoid pneumonitis, and other viral and bacterial pneumonias.
- **Extrapulmonary TB:** HIV-positive patients with advanced immunosuppression have a higher risk of extrapulmonary and disseminated TB. Frequent extrapulmonary affected areas are lymph nodes and pleura, but virtually any site can be involved. There is a greater probability of meningitis and, moreover, rapid progression from meningitis to mycobacterial sepsis may be observed without evident pulmonary involvement.

8.2 Diagnosis of TB and HIV in children

2.1 TB diagnosis in HIV-positive children (2, 5)

The diagnostic approach to TB in HIV-positive and HIV-negative children is essentially the same. The diagnosis is not easy, and the following parameters should be considered:

1. A history of contact with a TB case.
2. Signs and symptoms suggesting TB: cough, weight loss, or stunting.
3. Positive tuberculin skin test (PPD): ≥ 5 mm in diameter in HIV-positive children.
4. Chest x-ray with results suggesting TB signs.
5. Bacteriological confirmation by Xpert[®] MTB/RIF

Every child who is a contact of a TB case should be studied for TB, given the potential for contagion. This is even more important if the child is HIV-positive. Similarly, any child with a cough, weight loss, or stunting should be studied.

The PPD is the most useful method for diagnosing TB infection and a very valuable aid for TB diagnosis in children and adolescents. Nevertheless, the patient's immune status determines the test interpretation. A negative PPD in an AIDS patient does not rule out the diagnosis, due to the high prevalence of false negatives in patients with advanced immunosuppression. In an HIV-positive child with a relatively preserved CD4 count (for example, CD4 > 20%) a positive PPD in the presence of symptoms and signs compatible with TB is very suggestive of a diagnosis. However, there are false positive and negative PPDs, which should be considered.

False-positive PPDs can be caused by:

- Other non-tuberculous mycobacterial infections
- BCG vaccination
- Test misreading

BCG vaccine effect on the tuberculin skin test lasts up to 10 years and usually does not exceed 10 mm. In children who have received the BCG in the past 3 years and have a PPD of ≤ 10 mm, the result could be considered a post-vaccination effect; in children who have received the BCG and have a PPD of ≥ 15 mm, the result is always considered positive; and in children with the BCG and a tuberculin test of 11-14 mm, each case must be considered individually. In situations where there is a risk of developing tuberculosis, BCG history should be obviated.

False-negative PPDs can be caused by:

1. Patient-related factors:

- Window period between exposure and conversion: 4-12 weeks
- Disseminated TB or TB with serous involvement: miliary, tuberculous meningitis
- Advanced HIV infection
- Viral infections: measles, mumps, chickenpox, and flu

- Bacterial infections: typhoid fever, brucellosis, typhus, leprosy, whooping cough
- Intestinal parasitic infections in the past 2 months
- Vaccines with attenuated live viruses in the past 2 months: measles, rubella, mumps, oral polio, chickenpox, and yellow fever; oral typhoid vaccine.
- Immunosuppressive therapy (treatment with corticoids debatable)
- Lymphoid neoplasms.
- Primary immunodeficiencies
- Chronic renal failure
- Malnutrition, serious protein depletion
- Newborns

2. Technique-related factors

- Injection too deep
- Inadequate storage and conservation
- Expired antigen or contamination
- Incorrect dilutions
- Misreading
- Tuberculin > 30 min in the syringe

A chest x-ray can aid in the diagnosis of TB in HIV-positive children. As immunity declines, the radiologic image can show:

- Localized alveolar consolidation
- Pneumonitis
- Hilar and mediastinal adenopathies

Some relatively common atypical presentations are:

- Multilobar infiltrates
- Diffuse interstitial disease

A CT scan may be indicated for HIV-positive children who have contact with bacilliferous adult patients, especially if they are known to have drug-resistant TB and a normal chest x ray. In cases of coinfection and advanced immunosuppression, the chest x ray may be normal.

Bacteriological confirmation of TB in HIV-positive children is possible through Xpert® MTB/RIF and cultures of sputum, gastric aspirate, or other specimens, depending on the site of suspected TB. In younger children, sputum sample is usually obtained through gastric aspiration, taken early in the morning in a fasting state for 3 consecutive days. In older children and adolescents, a sputum sample, induced or not, can be obtained (see Section 2.1.2.2). Xpert® MTB/RIF should be used as the diagnostic test of choice in children with HIV or suspected MDR-TB. DST should also be performed, especially in contexts with a high rate of resistance to first-line TB drugs. In the case of suspected MDR TB, the child should be sent to a specialized center for study.

Differential diagnosis of TB in children, especially those coinfecting with HIV, should include both pulmonary diseases and pathologies with characteristics present in ETB. It should be based on symptoms and local epidemiological profile

8.2.2 HIV diagnosis in children

HIV diagnosis in children <18 months of age is done through virological tests (PCR-DNA, PCR-RNA, or antigen p24). In remote areas or lack of infrastructure to perform these tests, a dry blood spot (DBS) that can be easily transported can be obtained. Early HIV diagnosis in infants whose mother is HIV positive is a priority. After 18 months, when maternal antibodies have disappeared, diagnosis is made in the same way as for adults, through serological tests [2]

8.3 Treatment of TB and HIV in children

8.3.1 TB treatment in HIV-positive children (2, 3)

All children with active TB should immediately begin TB treatment and ART as soon as their tolerance to the TB treatment is verified. The current protocol is to start ART two weeks after and always within the first 8 weeks of TB treatment, regardless of the child's CD4 count and clinical stage. Overlapping both treatments increases the risk of toxicity; patients must therefore be closely monitored for early detection and treatment of adverse reactions.

The treatment regimen of choice for any form of TB in HIV-positive children is **daily** directly observed treatment (DOT) in an initial 2-month phase with:

isoniazid 10 mg/kg/day (range 7-15 mg/kg/day); maximum dose of 300 mg/day
+
rifampicin 15 mg/kg/day (range 10-20 mg/kg/day); maximum dose of 600 mg/day
+
pyrazinamide 35 mg/kg/day (range 30-40 mg/kg/day)
+
ethambutol 20 mg/kg/day (range 15 - 25 mg/kg/day)

This should be followed by a second, 4-month phase with isoniazid and rifampicin in the same dose. Treatment regimens of 2 or 3 times per week should not be used for these children, but daily doses instead.

In extrapulmonary TB cases (bone TB, miliary TB, and tuberculous meningitis), the first phase of treatment is the same, and the second phase with isoniazid and rifampicin should be extended to 10 months at the same dose, for a total of 12 months treatment.

Rifampicin interactions with some ARVs should always be watched for. Where available, rifabutin can be considered a substitute for rifampicin, as it involves less induction of cytochrome P450 3A4, although there is little data on its effects on children.

In MDR-TB cases, as in adults, a minimum of four TB drugs that have never been used before should be employed, including two or more bactericides to which the TB strain is sensitive (see Section 7.4). The regimen should be based on the resistance profile of the index case when the patient is a contact or on the DST results.

HIV-positive children already in treatment with ART at the time of the TB diagnosis should begin therapy immediately and continue with ART. ARV regimen adjustments should be made as needed to reduce toxicity potential and drug interactions. LPV/r concentrations fall substantially in presence of rifampicin. When LPV/r has been included in the child's regimen, consider dosage adjustment following national standards.

8.3.2 HIV treatment in children with TB (2, 3)

As previously mentioned, any child with TB and HIV should begin TB treatment and start ART within 8 weeks, as soon as TB treatment is tolerated, regardless of its CD4 count and clinical status. All children under 18 months with a presumptive clinical diagnosis of HIV should start ART.

For coinfecting children under 3 years of age, the recommended regimen to start ART is AZT + 3TC + ABC. Once the TB treatment is completed, the ART regimen can be tailored according to child's age and switched to a regimen based on PIs (LPV/r) or NNRTIs (NVP or EFV).

For coinfecting children aged 3 years and above, the recommended regimen to start ART is 2 NRTIs (ABC + 3TC or AZT + 3TC) + EFV or AZT + 3TC + ABC. Once pediatric anti-TB treatment with 3 NRTIs is completed, the ART regimen can be tailored to the child's age and switched to an NNRTI-based regimen (EFV).

8.4 Prophylactic treatments in children

8.4.1 Profilaxis para TB en niños con VIH (2)

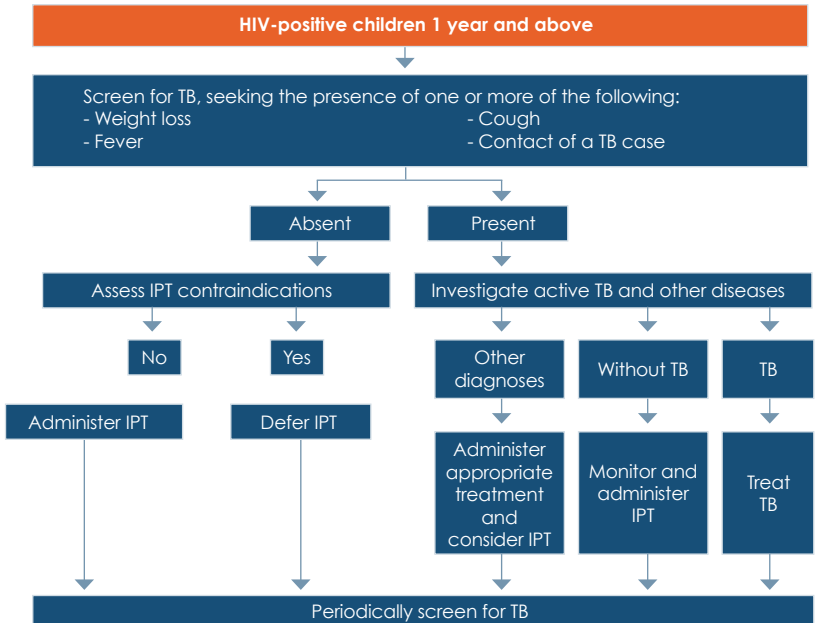
Parents and caregivers should be informed about HIV-positive children's risk of contracting serious and disseminated forms of TB and should be instructed about preventive measures. HIV-positive children exposed to a bacilliferous TB patient should be studied to rule out disease and receive prophylaxis or full treatment.

Any child under 5, with or without HIV, who is a contact of a TB case and in whom active TB has been ruled out should receive isoniazid 10 mg/kg/day (maximum 300 mg/day) for 6 months.

Similarly, any HIV-positive child aged 1 year or older without disease or who has had contact with a case of TB should receive IPT for 6 months at the aforementioned dose (Figure 5). Any HIV-positive child under 1 year of age should receive IPT only if it has contact with a bacilliferous TB patient.

Isoniazid prescribed to HIV-positive people does not increase their risk of developing isoniazid-resistant TB. Isoniazid does not have relevant interactions with ART.

Figure 5. Recommended algorithm for TB screening and IPT in HIV-positive children over 1 year



TB: tuberculosis; IPT: isoniazid preventive therapy; HIV: human immunodeficiency virus.

8.4.2 TMP/SMX prophylaxis in children with TB/HIV coinfection (3, 4)

P. jirovecii pneumonia is a major cause of death in HIV-positive children that do not receive TMP/SMX prophylaxis. There is evidence of the efficacy of this prophylaxis in reducing morbidity and mortality from all causes in HIV-positive children, including those with tuberculosis.

All children with perinatal exposure to HIV should receive TMP/SMX prophylaxis from the age of 4-6 weeks until HIV infection has been ruled out (Table 25). Children with a history of serious adverse reactions to TMP/SMX or other sulfa drugs, as well as those who suffer from glucose-6-phosphate dehydrogenase deficiency, should not be given TMP/SMX. Although TMP/SMX is a safe drug and adverse reactions are rare, clinical monitoring is important, with particular emphasis on cutaneous reactions and symptoms such as nausea, vomiting, and jaundice.

Table 25. Recommended dosages for TMP/SMX prophylaxis by age and weight

Age and/or weight	Daily dose of TMP/SMX
< 6 months or 5 kg	20/100 mg
6 months-5 years or 5-15 kg	40/200 mg
6-14 years or 15-30 kg	80/400 mg
> 14 years or 30 kg	160/800 mg

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Chapter 9

Management of other comorbidities

Patients with TB/HIV coinfection may develop other comorbidities that should be treated concomitantly. The sections below provide information on the management of the most common of these, including the specific treatments recommended.

The recommendations presented in this chapter are based on WHO and PAHO guidelines for treatment of infectious diseases (1-5).

9.1 Sexually transmitted infections

In most cases, HIV is acquired through sexual activity. Thus, it is important to remember that HIV-positive individuals often present other sexually transmitted infections (STI) that require treatment. Besides treatment, patient education, individual and couples counseling, as well as condoms, should be provided.

Etiological diagnosis and treatment of STIs is not always possible. A syndromic approach has therefore been developed, based on the recognition of a series of signs and symptoms (syndrome) (Table 26). The recommended treatment for each syndrome cures most of the causing infections (Table 27).

Table 26. Syndromic approach to the treatment of sexually transmitted infections

Sex	Syndrome	Treatment plan
Men	Urethral discharge	Treat as gonorrhea and chlamydia. Treat partner(s)
Women	Vaginal discharge	Treat as vaginitis (candidiasis/trichomoniasis/bacterial vaginosis) and evaluate treating as gonorrhea and chlamydia. Treat partner(s) for vaginitis only in if trichomoniasis is suspected. If treatment is provided for gonorrhea and chlamydia, treat partner(s) as well.
	Cervicitis	Treat as gonorrhea and chlamydia. Treat partner(s).
	Pelvic abdominal pain	Treat as pelvic inflammatory disease: gonorrhea, chlamydia, and anaerobes.

Sex	Syndrome	Treatment plan
Men and women	Genital ulcers	Treat as syphilis, chancroid, and herpes simplex. Treat the partner(s).
	Inguinal bubo with ulcers	Treat as syphilis and chancroid. Assess if lesions are compatible with herpes simplex.
	Inguinal bubo without ulcers	Treat as venereal lymphogranuloma.

Table 27. Treatment of sexually transmitted infections

STI	Treatment of choice	Other options
Gonorrhea (uncomplicated)	Cefixime 400 mg p.o. single dose and azitromycin 1g p.o. single dose or Ceftriaxone 250 mg IM single dose and azitromycin 1g p.o. single dose	* Cefixime 400 mg p.o. single dose or ceftriaxone 250 mg IM single dose or Spectinomycin 2g IM single dose
Chlamydia	Azithromycin 1g p.o. single dose, or doxycycline 100 mg p.o. q. 12h for 7 days In pregnant women: Azithromycin 1g p.o. single dose or Amoxicillin 500 mg p.o. q. 8h for 7 days or Erythromycin 500 mg p.o. q. 6h for 7 days	Tetracycline 500 mg p.o. q. 6h for 7 days or Erythromycin 500 mg p.o. q. 6h for 7 days Or Ofloxacin 200-400 mg p.o. q. 12h for 7 days
Trichomoniasis (<i>Trichomonas vaginalis</i>)	Metronidazole 2g p.o. single dose or Metronidazole 500 mg p.o. q. 12h for 7 days Pregnant women or infants: Metronidazole 250 mg p.o. q. 8h for 7 days or Metronidazole gel 0, 75%, 1 full applicator (5 g) vag. q. 12h for 5 days	Tinidazole 2g p.o. single dose Or Tinidazole 500 mg p.o. q. 12h for 5 days

STI	Treatment of choice	Other options
Bacterial vaginosis	<p>Metronidazole 2g p.o. single dose or Metronidazole 500 mg p.o. q. 12h for 7 days</p> <p>In pregnant women or infants: Metronidazole 250 mg p.o. q. 8h for 7 days or Metronidazole gel 0, 75% in a full applicator (5 g) vag. q. 12h for 5 days or Clindamycin 300 mg p.o. q. 12h for 7 days</p>	Clindamycin cream at 2% in 1 full applicator (5 g) vag. at bedtime for 7 days
Candidal vaginitis	<p>Miconazole 200 mg ovule vag. q. 24h for 3 days or Clotrimazole 100 mg ovule q. 12h for 3 days or Fluconazole 150 mg p.o. single dose</p> <p>In pregnant women or infants: Miconazole 200 mg vaginal suppository q. 24h for 3 days or Clotrimazole 100 mg, 1 ovule q. 12h for 3 days or Nystatin 100,000 U, 1 ovule q.24h for 14 days</p>	Nystatin 100,000 U, 1 ovule q. 24 h for 14 days
Syphilis (chancre)	<p>Penicillin benzathine 2.4 million units IM, single dose</p> <p>In pregnant women: Penicillin benzathine 2.4 million units IM or Erythromycin 500 mg p.o. q. 6h for 15 days</p>	Doxycycline 100 mg p.o. q. 12h for 14 days (do not use doxycycline in pregnant women)
Chancroid	<p>Ciprofloxacin 500 mg p.o. q. 12h for 3 days or Azithromycin 1g p.o. single dose or Erythromycin 500 mg p.o. q. 6h for 7 days</p>	Ceftriaxone 250 mg IM single dose

STI	Treatment of choice	Other options
Venereal lympho- granuloma	<p>Doxicycline 100 mg p.o. q. 12h for 21 days or Erythromycin 500 mg p.o. q. 6h for 21 days</p> <p>In pregnant women, infants, or children < 16: Azithromycin 1g p.o. once a week for 3 weeks or Erythromycin 500 mg p.o. q. 6h for 14 days</p>	Tetracycline 500 mg p.o. q. 6h for 21 days
Herpes simplex	<p>Primary infection: Acyclovir 400 mg p.o. q. 8h for 10 days or Acyclovir 200 mg p.o. 5 times per day for 10 days</p> <p>Recurrent infection: Acyclovir 400 mg p.o. q. 8h for 5 days or Acyclovir 800 mg p.o. q. 12h for 5 days Or Acyclovir 800 mg p.o. q. 8h for 2 days</p> <p>In pregnant women or infants ** primary infection: Acyclovir 400 mg p.o. q. 8h for 10 days Recurrent infection: Treat only when the benefit outweighs the risk of administering the treatment (equal dose and duration)</p>	<p>Primary infection: Famciclovir 250 mg p.o. q. 8h or Valacyclovir 500 mg p.o. q. 12h for 10 days***</p>

STI	Treatment of choice	Other options
Pelvic inflammatory disease (PID)	<p>Outpatient treatment (choose a drug for each etiologic agent)</p> <p><i>Neisseria gonorrhoeae</i> Cefixime 400 mg p.o. single dose and azitromycin 1g p.o. single dose or Ceftriaxone 250 mg IM single dose and azitromycin 1g p.o. single dose</p> <p><i>Chlamydia trachomatis</i> Doxycycline 100 mg p.o. q. 12h for 14 days or Tetracycline 500 mg p.o. q. 6h for 14 days or Azithromycin 1g p.o. daily for 7 days</p> <p>Anaerobes Metronidazole 500 mg p.o. q. 12h for 14 days</p> <p>Criteria for hospitalization:</p> <ul style="list-style-type: none"> • Suspected surgical abdomen • Pregnancy • No response to oral treatment • Intolerance to oral treatment • Salpingo-ovarian abscess <p>Choose a drug for each etiologic agent:</p> <p><i>Neisseria gonorrhoeae</i> Ceftriaxone 250 mg IM single dose or Ciprofloxacin * 500 mg p.o. single dose or Spectinomycin 2g IM single dose</p> <p><i>Chlamydia trachomatis</i> Doxycycline 100 mg p.o. or IV q. 12h or Tetracycline 500 mg p.o. q. 6h</p>	<p>Gentamicin 1.5 mg/kg IV q. 8h + clindamycin 900 mg IV q. 8h or Ampicillin 2g IV or IM, followed by 1g IV q. 6h + gentamicin 80 mg IM q. 8h + metronidazole 500 mg IV q. 8h</p>

STI	Treatment of choice	Other options
	<p>Anaerobes Metronidazole 500 mg p.o. or IV q. 12h or Chloramphenicol 500 mg p.o. or IV q. 6h</p> <p>All options above should be continued until 2 days after clinical improvement, after which Doxycycline 100 mg p.o. q. 12h or Tetracycline 500 mg p.o. q. 6h is indicated until 14 days of treatment are completed</p>	
Inguinal granuloma (continuous treatment until all lesions completely epithelize)	<p>Azithromycin 1g p.o. followed by 500 mg p.o. 1/day or Doxycycline 100 mg p.o. q. 12h</p> <p>In pregnant women, infants, or <16 years: Erythromycin 500 mg p.o. q. 6h for 7 days or Azithromycin 1g p.o. single dose</p>	<p>Erythromycin 500 mg p.o. q. 6h or Tetracycline 500 mg p.o. q. 6h or Trimethoprim/sulfamethoxazole 160/800 mg p.o. q. 12h</p>

STI: sexually transmitted infections; p.o.: by mouth; IM: intramuscularly, IV: intravenously.

* Given the increase in resistance in the Region of the Americas, ciprofloxacin is not recommended for the treatment of gonorrhea in the absence of susceptibility studies.

** The American College of Obstetricians and Gynecologists recommends treating all primary herpes infections.

***Evaluate the cost and availability of these drugs before prescribing them

Note 1. Do not use ciprofloxacin or tetracyclines during pregnancy.

Note 2. Avoid tetracyclines in children.

9.2 Skin problems

Condyloma acuminatum

Apply topical podophyllin 25% once a week for up to for 6 weeks; wash 1-4 hours after application. Or apply imiquimod cream 5% at night and remove in the morning for 3 consecutive nights, weekly for up to 16 weeks.

Seborrheal dermatitis

Hydrocortisone cream 1% twice daily.

Scabies

Permethrin lotion 5% or lindane (gamma benzene hexachloride) lotion 1%. Apply all over clean skin from the neck to the feet. Leave on 8-10 hours overnight. Repeat in 1 week. Wash all clothing in hot water and dry in the sun. Clip fingernails.

Herpes simplex

Mild infection: Acyclovir 400 mg p.o. q. 8h for 5-10 days or acyclovir 200 mg p.o. 5 times/day for 7-10 days or valacyclovir 1g p.o. q. 12h for 7-10 days
Severe infection: Acyclovir 5-10 mg/kg IV q. 8h for 5-10 days.

Herpes zoster

Mild infection: Acyclovir 800 mg p.o. 5 times/day for 7-10 days or valacyclovir 1g p.o. q. 8h for 7-10 days
Severe infection (compromise of the central nervous system, disseminated, ocular): Acyclovir 10-12 mg/kg IV for 14-21 days.

Molluscum contagiosum

Curettage, cryotherapy, or electrocauterization. Topical agents: podophyllin or trichloroacetic acid.

9.3 Problems of the oral and digestive cavity

Oral candidiasis

Nystatin, liquid or tablets 500,000 U p.o. q. 6-8h for 3-5 days or fluconazole 150 mg p.o. every day for 3-5 days

Candidal esophagitis

Fluconazole 200 mg IV every day until tolerated orally and then fluconazole 150 mg p.o. every day for 7 days; both with or without metronidazole 500 mg p.o. q. 8h for 10 days

Diarrhea of unknown etiology

TMP/SMX 160/800 mg p.o. q. 12h for 10 days or ciprofloxacin 500 mg p.o. q. 12h for 10 days with or without metronidazole 500 mg p.o. q. 8h for 10 days

Bacterial diarrhea

TMP/SMX 160/800 mg p.o. q. 12h for 10 days or ciprofloxacin 500 mg p.o. q. 12h for 10 days

***Entamoeba histolytica* diarrhea**

Metronidazole 500 mg p.o. q. 8h for 10 days (trophozoites) and/or diloxanide furoate 500 mg p.o. q. 8h for 10 days (cysts)

***Giardia lamblia* diarrhea**

Metronidazole 250 mg p.o. q. 8h for 5 days or nitazoxanide 500 mg p.o. q. 12h for 3 days

***Strongyloides stercoralis* diarrhea**

Ivermectin 200µg /kg/day p.o. every day for 2 days or albendazole 400 mg p.o. q. 12h for 7 days

***Cryptosporidium parvum* diarrhea**

Nitazoxanide 500 mg p.o. q. 12h for 3 days or paromomycin (aminosidine) 1g p.o. q. 12h for 1-4 weeks, depending on the response

9.4 Other respiratory problems

Histoplasmosis

Mild-to-moderate disease

Itraconazole 200 mg p.o. q. 8h (with meals) for 3 days, followed by 200 mg p.o. (with meals) for 12 months.

Severe or disseminated disease

Amphotericin B 1 mg/kg/day IV every day for 10-14 days, followed by itraconazole 200 mg p.o. (with meals) for 12 months.

***P. jirovecii* pneumonia**

Mild-to-moderate disease (PaO₂ > 70 mmHg or > 90% oxygen saturation or normal respiratory rate):

TMP/SMX 160/800 mg 2 tablets p.o. q. 8h for 21 days (15 mg/kg/day depending on TMP).

Severe disease (PaO₂ < 70 mmHg or < 90% oxygen saturation or RR > 30/min) 1 hour before TMP/SMX:

Prednisone 40 mg p.o. q. 12h for 5 days. Then: 40 mg p.o. every day for 5 days, and finally 20 mg p.o. every day for 11 days and TMP/SMX 160/800 mg, 2 tablets p.o. q. 8h for 21 days.

9.5 Neurological problems

Cryptococcal meningitis

Amphotericin B 0.7-1 mg/kg/day IV + fluconazole 800 mg/day p.o. or IV for 2 weeks, followed by fluconazole 400 mg p.o./day for 2 months.

Cerebral toxoplasmosis

Sulfadiazine 1.5g p.o. q. 6h and a single dose of pyrimethamine 100 mg p.o. for 1 day, followed by 25 mg p.o. q. 8h for 6 weeks. Add folinic acid 10 mg p.o. every day for the duration of the treatment or clindamycin 600 mg IV q. 6h and a single dose of pyrimethamine 100 mg p.o. for 1 day, followed by 25 mg p.o. q. 8h for 6 weeks. Add folinic acid 10 mg p.o. every day for the duration of the treatment or TMP/SMX 10/50 mg/kg/day p.o. q. 12h for 30 days.

9.6 Non-tuberculous mycobacteria

As their name indicates, these mycobacteria are not tuberculous, and they are also known as atypical or environmental mycobacteria. Although they share some characteristics (they are AFB), they should not be confused with resistant *M. tuberculosis* (MDR- or XDR TB). These mycobacteria are contracted from the environment (water and soil) and are associated with clinical manifestations in the lungs or skin; in HIV-positive people with CD4 levels of < 50/mm³, they can appear in disseminated forms that are hard to diagnose, especially in resource-constrained settings. They can also present asymptotically in HIV-positive people, colonizing their respiratory tracts; thus, every sputum with AFB reported should ideally be followed by a culture and DST. These mycobacteria are generally not susceptible to first-line TB drugs, and a specialist should always be consulted for their treatment (Table 28).

Table 28. Non-tuberculous mycobacteria in HIV-positive people

Mycobacteria species	Clinical form	Treatment of choice	Alternative treatment/Remarks
<i>M. avium</i> complex	Disseminated	Clarithromycin + ethambutol +/- rifabutin Time: Until immune recovery	Azithromycin + ethambutol +/- rifabutin + one or more: ciprofloxacin ofloxacin amikacin
	Pulmonary		
<i>M. kansasii</i>	Pulmonary	rifampicin + ethambutol + isoniazid Time: 15-18 months	isoniazid + ethambutol + sulfamethoxazole or clarithromycin + ethambutol + rifampicin
	Disseminated		
	Lymphadenitis	Surgical	
<i>M. fortuitum</i>	Cutaneous infections	Amikacin + cefoxitin + probenecid for a minimum of 3 months	Optimal treatment undefined
<i>M. chelonae</i>		Surgical For <i>M. chelonae</i> Clarithromycin	In serious cases of <i>M. chelonae</i> , add amikacin +imipenem or cefoxitin
<i>M. marinum</i>	Cutaneous	Rifampicin + ethambutol or doxycycline or minocycline or trimethoprim/ sulfamethoxazole or clarithromycin Surgical	

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Annexes

Annex 1. Fine-needle aspiration cytology (FNAC)

Indications

Investigation of lymphadenopathies

Contraindications

1. Dyspnea (cervical mass)
2. Hemorrhagic disorder
3. Uncooperative patient (disoriented, hostile)

Procedure (cervical mass)

1. Place patient in a position that allows optimal palpation of the mass.
2. Prepare the skin over the mass by moistening it with isopropyl alcohol 70%.
3. If right-handed, hold the mass down with the left hand to keep it in a fixed and stable position.
4. Insert a 21-gauge needle (needles with a larger gauge should be avoided to prevent bleeding and tumor seeding) connected to 20 ml syringe just under the surface of the skin. Apply negative pressure to the syringe, pulling the barrel up to the 10-ml mark.
5. Penetrate the mass repeatedly without withdrawing the needle from the surface of the skin.
6. When the neck and a cyst are involved, evacuate the latter completely and send the fluid and capsule for cytology.
7. Release syringe vacuum and withdraw the needle from the skin.
8. Place a small drop of the aspirate on a slide. Make a smear by placing another slide on the fluid and sliding the two slides in the opposite direction to spread it.
9. Apply Ziehl-Neelsen stain and keep the aspirated fluid to culture *M. tuberculosis* and, ideally, fungi.
10. When possible, place wet smears in 95% ethyl alcohol and apply the Pap technique and stains. These stains provide excellent cellular details and can indicate the cellular origin of a metastatic tumor.
11. Air-dry the specimens and prepare them for the Wright-Giemsa stain when the differential diagnosis includes salivary gland, lymphoproliferative, or fatty tumors.

In lymph node tuberculosis, FNAC can provide cytological evidence compatible with tuberculosis. FNAC histology can indicate the presence of granulomatous inflammation, caseous necrosis, or both. When FNAC does not yield a precise diagnosis, an excisional biopsy and cultures should be performed.

Complications

1. Large hematomas
2. Pneumothorax (lower cervical mass)
3. Salivary gland fistula
4. Subcutaneous emphysema

Annex 2. Thoracentesis

Indications

HIV-positive patient with pleural effusion

Contraindications

1. Thrombocytopenia
2. Hemorrhagic disorder
3. Uncooperative patient (disoriented, hostile)

Procedure

Site of the pleural effusion

This is established through physical examination (dull percussion) and chest auscultation (decreased breath sounds and egophony). Pleural effusion is easy to visualize in a posteroanterior chest x-ray, but a lateral decubitus x-ray is sometimes necessary to dispel any doubts.

Procedure

1. Seat patient in a position that provides support for arms and head (e.g., sitting backwards in a chair or on a bench, or leaning on a bed or an adjustable table).
2. Identify the site of the effusion through percussion and auscultation.
3. Disinfect the area with povidone-iodine and use an aseptic technique at all times.
4. Insert the needle in the posterior chest (approximately 5-10 cm lateral to the spine) in an intercostal space under the area where the dull percussion begins.
5. Inject the skin and subcutaneous tissue with 1-2% lidocaine.
6. Make sure that the needle is inserted above the superior border of the rib (the intercostal vessels and nerves are located near the inferior border of the rib).
7. Gently push the 20-21-gauge needle, anesthetize the pleura, and gently aspirate until the syringe contains pleural fluid; withdraw the needle and maintain the necessary depth for the thoracentesis needle.
8. At the infiltration site, insert a 17-gauge needle connected to a 30-ml syringe through a three-way valve connected to a drainage container.
9. Slowly insert the needle in the superior border of the rib and gently aspire as it advances.
10. When pleural fluid is obtained, place a clamp or hemostat on the needle to prevent it from inadvertently going deeper.
11. Aspirate the necessary amount of fluid (generally, 100 ml for diagnosis). It is not advisable to aspire more than 1,500 ml at a time due to the risk of causing acute pulmonary edema or hypotension. A pneumothorax from laceration of the visceral pleura is more common with attempts to aspire an effusion completely. Carefully withdraw the needle.
12. Ideally, serum glucose, protein, and DHL levels should be obtained.

13. Send the pleural fluid to the laboratory for cytochemical analysis, which will make it possible to distinguish an exudate from a transudate.

a. Tube 1: proteins and, ideally DHL.

b. Tubes 2, 3, and 4 for:

Gram Stain	Ziehl Neelsen stain and TB culture	Adenosine deaminase (ADA)
Cytology (malignancy)	Glucose	PH

Complications

1. Pneumothorax
2. Hemorrhage
3. Vasovagal episode
4. Infection
5. Unilateral pulmonary edema
6. Liver or spleen puncture
7. Subcutaneous emphysema
8. Embolism

Annex 3. Lumbar puncture

Indications

Suspected tuberculous meningitis

Contraindications

1. Infection at the site of the lumbar puncture
2. Increased intracranial pressure
3. Severe hemorrhagic disorder

Procedure

1. Careful fundoscopy. If increased intracranial pressure and/or a lesion occupying space in the CNS is suspected, a CT head scan should be performed prior to the lumbar puncture.
2. Place patient in lateral decubitus with his back flexed (shoulders forward and thighs against the abdomen).
3. Identify the L4-L5 space (an imaginary line between the ileac crests).
4. Disinfect the area with povidone-iodine solution.
5. Anesthetize the skin and subcutaneous tissue, injecting 1-2% lidocaine.
6. Gently insert the lumbar puncture needle with its stylet (bevel toward the head) in the L4-L5 space, horizontally and with a slight cephalic slant. Withdraw the stylet and, if CSF leakage is observed, measure the opening CSF pressure (normal is 100-200 mm H₂O).
 - a. If the pressure is increased, instruct the patient to relax and make sure there is no abdominal compression or breath holding (force and pressure against the abdominal wall increases CSF pressure).
 - b. If the pressure is markedly increased, extract only 5 ml of CSF and immediately withdraw the needle.
7. Collect 5-10 ml of cerebrospinal fluid in four tubes (2 ml/tube).
8. Measure the closing pressure, withdraw the manometer and valve, and place the stylet before withdrawing the lumbar puncture needle. Apply pressure at the puncture site with a sterile gauze for several minutes.
9. Instruct the patient to remain in dorsal decubitus for approximately 4 hours to minimize post-lumbar puncture headache (caused by the filtration of CSF through the puncture site).
10. Send the CSF for cytochemical analysis.
 - a. Tube 1: proteins, glucose
 - b. Tube 2: Gram stain
 - c. Tube 3: cell count (total and differential)
 - d. Tube 4: retain for other studies
11. Additional examinations
 - a. Ziehl-Neelsen stain (TB)
 - b. Lowenstein-Jensen culture (TB)
 - c. India ink (cryptococcosis)
 - d. ADA
 - e. VDRL test (syphilis)

If available:

 - f. Cryptococcal antigen
 - g. Culture for fungi (Sabouraud)
 - h. Cytology

Annex 4. Paracentesis

Indications

Suspected peritoneal tuberculosis

Contraindications

1. Hemorrhagic disorders
2. Abdominal distension
3. Infection or surgical scars at the needle insertion site

Procedure

1. Have the patient empty the bladder (catheter insertion may be necessary in some patients).
2. To identify paracentesis site, first locate the rectus muscle. A good place for the puncture is approximately 2-3 cm lateral to the border of the rectus muscle in the lower abdominal quadrants. Avoid the following:
 - a. Rectus muscle (greater risk of hemorrhage from the epigastric vessels).
 - b. Surgical scars (greater risk of perforation caused by intestinal adhesion to the peritoneal wall).
 - c. Areas of infected skin (greater risk of peritoneal infection).An alternative site is the linea alba, 3-4 cm below the navel.
3. Clean the area with povidone-iodine and cover the abdomen with sterile fields.
4. Anesthetize the puncture site with 1-2% lidocaine
5. Carefully insert the needle (connected to a syringe) perpendicular to the skin. A slight sound will be heard as the anterior and posterior muscular fascia yield; entry to the peritoneal cavity is indicated by the sudden disappearance of resistance to the needle. Push the needle gently to prevent it from going too deep.
6. Extract the necessary amount of fluid for diagnosis or treatment. Do not extract more than 1 liter of ascitic fluid in a patient who has little edema or is hemodynamically unstable.

Complications

1. Persistent leakage of ascitic fluid
2. Hypotension and shock
3. Hemorrhage
4. Intestinal perforation
5. Abscesses at the puncture site
6. Peritonitis



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