

# WHO consolidated guidelines on tuberculosis

Module 6: Tuberculosis and  
comorbidities



World Health  
Organization



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and comorbidities

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# Introduction to the consolidated guidelines on tuberculosis – Module 6

Globally, tuberculosis (TB) remains a significant cause of ill health and is a leading cause of death due to an infectious agent (1). Five main health-related risk factors, namely, diabetes mellitus (diabetes), HIV, smoking, undernutrition and disorders due to alcohol use, account collectively for just under half of all new TB episodes globally. The contribution of these risk factors to the global TB burden is reported annually in the WHO's *Global tuberculosis report* (1). For the purpose of these consolidated guidelines, a health-related risk factor is defined as a condition or action that increases the risk of TB disease (2). Other significant health-related risk factors for TB disease include silicosis and disorders due to drug use. When they occur in people with TB, health-related risk factors are also considered comorbidities, and may lead to poor TB treatment outcomes, lower health-related quality of life, or other suboptimal health or social outcomes, such as increased out-of-pocket costs or TB-associated disabilities. The impact of these risk factors for TB differs between and even within countries.

People with TB also frequently experience other comorbidities, including pulmonary and mental health conditions, and viral hepatitis (2). Moreover, people with TB may develop chronic lung disease or other impairments (for example musculoskeletal or neurological impairments), all of which require specialized care or rehabilitation during TB treatment and after TB treatment completion. Health-related risk factors and TB comorbidities require holistic people-centred care in the context of universal health coverage.

Addressing individual comorbidities, multimorbidity, TB-associated disabilities and health-related risk factors for TB are key elements of the WHO *End TB strategy*, which focuses on integrated patient-centred care and prevention (3). The *End TB strategy* emphasizes that relevant comorbidities and health-related risk factors should be routinely assessed and managed for improved TB treatment and general health outcomes.

The political declaration of the 2023 United Nations (UN) High-Level Meeting on the fight against TB (4) reaffirmed the commitment to ending the TB epidemic globally by 2030, in line with the Sustainable Development Goals. In the declaration, Member States committed to integrating services for TB, HIV and other comorbidities within primary health care, and to strengthening coordination and collaboration between programmes, to ensure universal access to integrated prevention, diagnosis, treatment and care for TB, HIV and other comorbidities. Member States also committed to three key targets by 2027: a) at least 90% of the estimated number of people who develop TB are reached with quality assured diagnosis and treatment; b) at least 90% of all people at high-risk of developing TB are provided with preventive treatment, including approximately 15 million people living with HIV, and c) all people with TB have access to a health and social benefits package so they do not have to endure financial hardship because of their illness (4). In the latest UN High-Level Meeting declarations on HIV (5) and on Universal Health Coverage (6) in 2021 and 2023, respectively, Member States also committed to assuring integrated people-centred services for TB, HIV, noncommunicable diseases and mental health.

Although global guidance on interventions to address TB and key comorbidities exists in different publications, its uptake has been variable. The *WHO consolidated guidelines on tuberculosis. Module 6: tuberculosis and comorbidities* consolidate the latest evidence-based recommendations and provide a one-stop shop for countries to scale up people-centred care and prevention of TB and comorbidities. They include the latest recommendations developed by various guideline development groups (GDGs) convened by WHO, which used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to summarize the evidence and formulate recommendations (see Annex 1 for the current approach). The GRADE approach was used to rate the certainty in the estimate of effect (that is, the quality of evidence) as high, moderate, low or very low; it was also used to determine the strength of the recommendations, rating them as strong or conditional. The GDGs used the version of the WHO Handbook for guideline development that applied at the time. For more details, please refer to the original guidelines.

These guidelines are accompanied by an operational handbook (7) and are aligned with WHO's *Framework for collaborative action on tuberculosis and comorbidities* (2). The consolidated guidelines summarize WHO recommendations on TB and comorbidities and the evidence and processes behind them, while the operational handbook provides practical guidance to aid in the implementation of these recommendations by country programmes. The Framework document provides a structure and mechanisms for establishing and strengthening collaborative action across disease programmes and with relevant sectors outside the health system for the delivery of people-centred care for TB and comorbidities. To further strengthen a comprehensive response to TB and comorbidities, it is critical to ensure linkages with the national coordination platforms and mechanisms for the Multisectoral accountability framework for TB (MAF-TB) (8).

## Objectives

The objectives of the consolidated guidelines are to:

- consolidate existing recommendations to address TB and comorbidities;
- support Member States in implementing effective people-centred interventions to address TB and comorbidities and contribute to reducing disease burden, morbidity and mortality, as well as costs and financial hardship for people affected by TB and comorbidities; and
- contribute to reducing the disease burden of TB and comorbidities.

## Structure and evolution

The consolidated guidelines are a living document and will include a separate section for each of the key TB comorbidities or health-related risk factors. The first edition of the consolidated guidelines on TB comorbidities focuses entirely on HIV-associated TB. In the second edition a section on nutrition will be added. Content for each section will be progressively updated and added.

**HIV**





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## HIV

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# Abbreviations and acronyms

<b>ART</b>	antiretroviral therapy
<b>CAD</b>	computer-aided detection of TB-related abnormalities on chest radiography
<b>CI</b>	confidence interval
<b>CRP</b>	C-reactive protein
<b>CXR</b>	chest X-ray
<b>DTG</b>	dolutegravir
<b>GDG</b>	Guideline Development Group
<b>GRADE</b>	Grading of Recommendations Assessment, Development and Evaluation
<b>IGRA</b>	interferon-gamma release assay
<b>IPD</b>	individual participant data
<b>IPT</b>	isoniazid preventive treatment
<b>IRIS</b>	immune reconstitution inflammatory syndrome
<b>LF-LAM</b>	lateral flow lipoarabinomannan
<b>LMIC</b>	low- and middle-income countries
<b>LTBI</b>	latent tuberculosis infection
<b>MDR-TB</b>	multidrug-resistant tuberculosis
<b>mWRD</b>	molecular WHO-recommended rapid diagnostic test
<b>OR</b>	odds ratio
<b>RCT</b>	randomized controlled trial
<b>RR</b>	risk ratio
<b>TB</b>	tuberculosis
<b>TPT</b>	TB preventive treatment
<b>TST</b>	tuberculin skin test
<b>W4SS</b>	WHO-recommended four symptom screen
<b>WHO</b>	World Health Organization

# Definitions

*Note:* The definitions listed below apply to the terms as used in these guidelines. They may have different meanings in other contexts.

**Adolescent:** a person aged 10–19 years.

**Adult:** a person over 19 years of age.

**Advanced HIV disease:** for adults, adolescents, and children aged 5 years or more, “advanced HIV disease” is defined as a CD4 cell count of less than 200 cells/mm<sup>3</sup> or a WHO clinical stage 3 or 4 event at presentation for care. All children with HIV aged under 5 years should be considered as having advanced disease at presentation.

**Bacteriologically confirmed TB:** a person from whom a biological specimen is positive by a WHO-recommended rapid diagnostic test, culture or smear microscopy.

**Child:** a person under 10 years of age.

**Clinically diagnosed:** when a person who does not fulfil the criteria for bacteriological confirmation has been diagnosed with TB disease by a medical practitioner who has decided to give the person a full course of TB treatment.

**Computer-aided detection (CAD):** the use of specialized software to interpret abnormalities on chest radiographs that are suggestive of TB. The results are expressed as abnormality scores. CAD may be used for screening or triage.

**Drug-resistant TB:** TB disease caused by a strain of *Mycobacterium tuberculosis* (*M. tuberculosis*) complex that is resistant to any TB medicines.

**Drug-susceptibility testing (DST):** in vitro testing using either molecular or genotypic techniques to detect resistance-conferring mutations, or phenotypic methods to determine susceptibility to a medicine.

**Extensively drug-resistant TB (XDR-TB):** TB disease caused by a strain of *M. tuberculosis* complex that is resistant to rifampicin (and may also be resistant to isoniazid), and that is also resistant to at least one fluoroquinolone (levofloxacin or moxifloxacin) and to at least one other “Group A” drug (bedaquiline or linezolid).

**Extrapulmonary TB (EPTB) (classification):** any bacteriologically confirmed or clinically diagnosed episode of TB involving organs other than the lungs (e.g. pleura, peripheral lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges).

**Inpatient healthcare setting:** a healthcare facility where patients are admitted and assigned a bed while undergoing diagnosis and receiving treatment and care, for at least one overnight stay.

**Integrated services:** health services that are managed and delivered in a way that ensures that people receive a continuum of health promotion, disease prevention, diagnosis, treatment, disease management, rehabilitation and palliative care services at the different levels and sites of care within the health system and according to their needs throughout the life-course.

**High TB transmission setting:** a setting with a high frequency of individuals with undetected or undiagnosed TB disease, or where infectious TB patients are present and there is a high risk of TB transmission. People with TB are most infectious when they are untreated or inadequately treated. Spread is increased by aerosol-generating procedures and by the presence of highly susceptible individuals.

**HIV-associated TB:** the disease state due to *M. tuberculosis* in an individual who is living with HIV.

**Household contact:** a person who shared the same enclosed living space as the individual diagnosed with TB for one or more nights or for frequent or extended daytime periods during the three months before the start of current treatment.

**Multidrug-resistant TB (MDR-TB):** TB caused by *M. tuberculosis* strains that are resistant to at least both rifampicin and isoniazid.

**Outpatient healthcare setting:** a healthcare facility where patients are undergoing diagnosis and receiving treatment and care but are not admitted for an overnight stay (e.g. an ambulatory clinic or a dispensary).

**People-centred services:** a human rights-based approach to care that consciously adopts individuals', carers', families' and communities' perspectives as participants in, and beneficiaries of, trusted health systems that are organized around the comprehensive needs of people rather than individual diseases, and respects social preferences.

**People who use drugs:** people who use psychoactive substances through any route of administration, including injection, oral, inhalation, transmucosal or transdermal. For the purposes of this document this definition does not include the use of widely used substances such as tobacco or alcoholic and caffeine-containing beverages and foods.

**Person with presumptive TB:** a person with symptoms or signs suggestive of TB disease (previously known as a TB suspect).

**TB disease:** the disease state due to *M. tuberculosis*. In this document, it is commonly referred to as TB "disease" (or "active" TB) in order to distinguish it from TB infection.

**TB infection:** a state of persistent immune response to stimulation by *M. tuberculosis* antigens with no evidence of clinically manifest active TB disease. Most infected people have no signs or symptoms of TB but are at risk for TB disease. This was previously referred to as latent TB infection (LTBI) but given that infection cannot always be considered latent the term TB infection (TBI) is being used instead. There is no gold standard test for direct identification of *M. tuberculosis* infection in humans.

**TB preventive treatment (TPT):** treatment offered to individuals who are considered at risk of TB disease in order to reduce that risk. Also referred to as treatment of TB infection, LTBI treatment or TB preventive therapy.

**Universal health coverage:** under universal health coverage, individuals and communities have access to high-quality promotive, preventive, curative, rehabilitative and palliative essential health services without experiencing financial hardship.

**Women (breastfeeding, pregnant, postpartum):** the terms breastfeeding, pregnant or postpartum women are used here given that the majority of data are disaggregated by sex and do not specify gender identity. However, the term “woman” is intended to be inclusive of all those who identify as women and/or who give birth. While the majority of persons who are or can give birth are cisgender women (who were born and identify as female), WHO acknowledges the importance of the experiences of transgender men and other gender diverse people who have the reproductive capacity to give birth.

# Executive summary

People living with HIV are about 14 times more likely to develop TB disease, have poorer treatment outcomes and more than two-fold higher mortality during TB treatment, compared to all people diagnosed with TB (7). Addressing HIV-associated TB through integrated patient-centred care and prevention is a key component of the WHO *End TB strategy* (3).

For several decades, WHO has developed and issued recommendations on screening, diagnosis, treatment, care and prevention of HIV-associated TB. To support countries to reduce the burden of HIV-associated TB in populations at risk of or affected by both diseases, WHO published an *Interim policy on collaborative TB/HIV activities* in 2004, which was updated in 2012 (9, 10). The TB/HIV policy has served as a vehicle for a robust global response, advocating for further investment and scale-up of collaborative TB/HIV activities, and has provided guidance to Member States and partners on effectively addressing HIV-associated TB. It is estimated that scale-up of these interventions between 2005–2022 has saved 9.2 million lives (7). Yet, despite impressive scale-up of collaborative TB/HIV activities and the advances in the prevention, diagnosis and treatment of TB disease, TB remains the leading cause of death among people living with HIV worldwide and gaps still remain in the implementation of TB/HIV collaborative activities. Since 2012, several recommendations have been updated and additional recommendations formulated as the evidence has evolved.

The guidance provided in this section of the *WHO consolidated guidelines on tuberculosis* (hereafter referred to as the TB/HIV guidelines) outlines specific WHO recommendations on screening, diagnosis, treatment, care and prevention of HIV-associated TB.

The TB/HIV guidelines contain a set of 31 recommendations on HIV-associated TB, which have been consolidated from WHO guidelines on TB and on HIV, as summarized below. The recommendations are accompanied by operational guidance and implementation considerations in the *WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities* (7).

## Summary of WHO recommendations on HIV-associated TB

These consolidated guidelines summarize the rationale and evidence behind all WHO recommendations that address HIV-associated TB for adults living with HIV although some recommendations will also be relevant for children and adolescents.<sup>1</sup> Recommendations specifically related to HIV-associated TB in children and adolescents can be found in the *WHO consolidated guidelines on tuberculosis. Module 5: management of tuberculosis in children and adolescents* (11). Other WHO recommendations on TB screening, diagnosis, treatment and care for all people with TB regardless of HIV status are available in the respective modules of the *WHO consolidated guidelines on tuberculosis* that can be found on the WHO TB Knowledge Sharing Platform (12–19). The WHO recommendations to reduce the burden of TB among people living with HIV and conversely, to reduce the burden of HIV among people with TB, are listed below. A summary of changes to recommendations published in the 2012 *WHO policy on collaborative TB/HIV activities* (10) is provided in Annex 2.

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<sup>1</sup> Updates to recommendations can be found on the TB knowledge sharing platform (<https://tbksp.org/>) and on the WHO HIV/AIDS knowledge sharing platform (<https://www.who.int/health-topics/hiv-aids>).

## Reduce the burden of TB among people with HIV

### Screening for TB among people living with HIV

1. People living with HIV should be systematically screened for TB disease at each visit to a health facility (*strong recommendation, very low certainty of evidence*) (12).
2. Among adults and adolescents living with HIV, systematic screening for TB disease should be conducted using the WHO-recommended four symptom screen and those who report any one of the symptoms of current cough, fever, weight loss or night sweats may have TB and should be evaluated for TB and other diseases (*strong recommendation, moderate certainty of evidence*) (12).
3. Among adults and adolescents living with HIV, C-reactive protein using a cut-off of > 5 mg/L may be used to screen for TB disease (*conditional recommendation, low certainty of evidence*) (12).
4. Among adults and adolescents living with HIV, chest X-ray may be used to screen for TB disease (*conditional recommendation, moderate certainty of evidence*) (12).
5. Among individuals aged 15 years and older in populations in which TB screening is recommended, computer-aided detection software programmes may be used in place of human readers for interpreting digital chest X-rays for screening and triage for TB disease (*conditional recommendation, low certainty of evidence*) (12).
6. Among adults and adolescents living with HIV, molecular WHO-recommended rapid diagnostic tests may be used to screen for TB disease (*conditional recommendation, moderate certainty of evidence*) (12).
7. Adult and adolescent inpatients with HIV in medical wards where the TB prevalence is > 10% should be tested systematically for TB disease with a molecular WHO-recommended rapid diagnostic test (*strong recommendation, moderate certainty of evidence*) (12).

### Diagnosis of TB in people living with HIV

#### Use of molecular WHO-approved rapid diagnostic tests in blood in the diagnosis of disseminated TB

8. In HIV-positive adults and children with signs and symptoms of disseminated TB, Xpert MTB/RIF may be used in blood, as an initial diagnostic test for disseminated TB (*conditional recommendation, very low certainty of evidence*) (14).

#### Use of lateral flow lipoarabinomannan (LF-LAM) in the diagnosis of TB in people living with HIV

##### In inpatient settings

9. WHO strongly recommends using LF-LAM to assist in the diagnosis of active TB in HIV-positive adults, adolescents and children:
  - with signs and symptoms of TB (pulmonary and/or extrapulmonary) (*strong recommendation, moderate certainty in the evidence about the intervention effects*); or
  - with advanced HIV disease or who are seriously ill (*strong recommendation, moderate certainty in the evidence about the intervention effects*); or
  - irrespective of signs and symptoms of TB and with a CD4 cell count of less than 200 cells/mm<sup>3</sup> (*strong recommendation, moderate certainty in the evidence about the intervention effects*) (14).

##### In outpatient settings

10. WHO suggests using LF-LAM to assist in the diagnosis of active TB in HIV-positive adults, adolescents and children:
  - with signs and symptoms of TB (pulmonary and/or extrapulmonary) or seriously ill (*conditional recommendation, low certainty in the evidence about test accuracy*); and
  - irrespective of signs and symptoms of TB and with a CD4 cell count of less than 100 cells/mm<sup>3</sup> (*conditional recommendation, very low certainty in the evidence about test accuracy*) (14).

##### In outpatient settings

11. WHO recommends against using LF-LAM to assist in the diagnosis of active TB in HIV-positive adults, adolescents and children:
  - without assessing TB symptoms (*strong recommendation, very low certainty in the evidence about test accuracy*);
  - without TB symptoms and unknown CD4 cell count or without TB symptoms and CD4 cell count greater than or equal to 200 cells/mm<sup>3</sup> (*strong recommendation, very low certainty in the evidence about test accuracy*); and
  - without TB symptoms and with a CD4 cell count of 100–200 cells/mm<sup>3</sup> (*conditional recommendation, very low certainty in the evidence about test accuracy*) (14).



## TB treatment in people living with HIV

12. It is recommended that TB patients who are living with HIV should receive at least the same duration of daily TB treatment as HIV-negative TB patients (*strong recommendation, high certainty of evidence*) (17).

13. People living with HIV with TB and histoplasmosis coinfection should receive TB therapy according to WHO treatment guidelines (*conditional recommendation, very low-certainty evidence*) (20).

## Integrated delivery of care for HIV-associated TB

14. In settings with a high burden of HIV and TB, TB treatment may be provided for people living with HIV in HIV care settings where a TB diagnosis has also been made (*strong recommendation, very low-certainty evidence*) (21).

## Eligibility for TB preventive treatment

15. Adults and adolescents living with HIV who are unlikely to have active TB should receive TB preventive treatment as part of a comprehensive package of HIV care. Treatment should be given to those on antiretroviral treatment, to pregnant women and to those who have previously been treated for TB, irrespective of the degree of immunosuppression and even if LTBI testing is unavailable (*strong recommendation, high certainty in the estimates of effect*) (22).

## Algorithms to rule out TB disease prior to offering TB preventive treatment

16. Adults and adolescents living with HIV who are screened for TB according to a clinical algorithm and who report any of the symptoms of current cough, fever, weight loss or night sweats may have active TB and should be evaluated for TB and other diseases and offered preventive treatment if active TB is excluded (*strong recommendation, moderate certainty in the estimates of effect*) (22).

17. Chest radiography may be offered to people living with HIV on ART, and preventive treatment be given to those with no abnormal radiographic findings (*conditional recommendation, low certainty in the estimates of effect*) (22).

## Testing for TB infection

18. Either the tuberculin skin test (TST) or interferon-gamma release assays (IGRAs) can be used to test for TB infection (*strong recommendation, very low certainty of the evidence*) (15).

19. Mycobacterium tuberculosis antigen-based skin tests (TBSTs) may be used to test for TB infection (*conditional recommendation for the intervention, very low certainty of evidence*) (15).

## TB preventive treatment regimens

20. The following options are recommended for the treatment of LTBI regardless of HIV status: 6 or 9 months of daily isoniazid, or a 3-month regimen of weekly rifapentine plus isoniazid, or a 3-month regimen of daily isoniazid plus rifampicin (*strong recommendation, moderate to high certainty in the estimates of effect*). A 1-month regimen of daily rifapentine plus isoniazid or 4 months of daily rifampicin alone may also be offered as alternatives (*conditional recommendation, low to moderate certainty in the estimates of effect*) (22).

21. In settings with high TB transmission, adults and adolescents living with HIV who have an unknown or a positive LTBI test and are unlikely to have active TB disease should receive at least 36 months of daily isoniazid preventive treatment (IPT). Daily IPT for 36 months should be given whether or not the person is on ART, and irrespective of the degree of immunosuppression, history of previous TB treatment and pregnancy in settings considered to have a high TB transmission as defined by national authorities (*conditional recommendation, low certainty in the estimates of effect*) (22).

## Reduce the burden of HIV among people with TB

### Routine HIV testing for people with presumptive and diagnosed TB

22. HIV testing services should be offered to all individuals with presumptive and diagnosed TB (*strong recommendation, low quality of evidence*) (10).

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23. All household contacts of a person with HIV-associated TB should be offered HIV testing services (*strong recommendation, very low-quality evidence*) (19).

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24. In settings of high HIV burden, all household and close contacts of people with TB should be offered HIV testing services (*strong recommendation, very low-quality evidence*) (19).

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25. In settings of low HIV burden, all household members and close contacts of people with TB who have symptoms compatible with TB disease may be offered HIV testing services as part of their clinical evaluation (*conditional recommendation, very low-quality evidence*) (19).

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26. Partner services should be offered to people with HIV-associated TB (*strong recommendation, moderate-quality evidence*) (23).

### HIV treatment and care for people with TB

27. A package of interventions including screening, treatment and/or prophylaxis for major opportunistic infections, rapid ART initiation and intensified adherence support interventions should be offered to everyone presenting with advanced HIV disease (*strong recommendation, moderate-quality evidence*) (24).

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28. ART should be started as soon as possible within two weeks of initiating TB treatment, regardless of CD4 cell count, among people living with HIV (25).<sup>a</sup>  
Adults and adolescents (*strong recommendation, low- to moderate-certainty evidence*)  
<sup>a</sup> Except when signs and symptoms of meningitis are present.

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29. Antiretroviral therapy is recommended for all patients with HIV and drug-resistant tuberculosis requiring second-line antituberculosis drugs, irrespective of CD4 cell count, as early as possible (within the first 8 weeks) following initiation of antituberculosis treatment (*strong recommendation, very low-certainty evidence*) (16, 21).

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30. Routine co-trimoxazole prophylaxis should be given to all people living with HIV with active TB disease regardless of CD4 cell count (*strong recommendation, high-certainty evidence*) (21).

### Integrated delivery of care for HIV-associated TB

31. In settings with a high burden of HIV and TB, ART should be initiated in TB treatment settings, with linkage to ongoing HIV care and ART (*strong recommendation, very-low-certainty evidence*) (21).

# 1. HIV: introduction

## 1.1 Background

People living with HIV are about 14 times more likely to develop TB disease, have poorer TB treatment outcomes and have more than two-fold higher mortality during TB treatment, compared to all people diagnosed with TB (7).

The WHO *End TB strategy* (3), endorsed by the World Health Assembly in May 2014, provides the strategic direction for the achievement of TB targets within the UN Sustainable Development Goals (5), including the provision of universal health coverage to all people affected by TB. Integrated patient-centred care and prevention of HIV-associated TB are key components of the *End TB strategy*, which outlines a range of medical and socioeconomic interventions to prevent TB and address TB morbidity and mortality. The importance of integrated people-centred services was reiterated in the political declarations of the respective UN high-level meetings on the fight against TB (4) and on HIV and AIDS (5).

To support countries to reduce the burden of HIV-associated TB in populations at risk of or affected by both diseases, WHO published an *Interim policy on collaborative TB/HIV activities* in 2004 (9), which was updated in 2012 (10). The WHO-recommended collaborative TB/HIV activities outlined within the 2012 policy are listed in Fig. 1.

**Fig. 1. 2012 WHO policy on collaborative TB/HIV activities (10)**

**WHO-recommended 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

The TB/HIV policy has served as a vehicle for a robust global response, advocating for further investment and scale-up of collaborative TB/HIV activities, and has provided guidance to Member States and other partners on effectively addressing HIV-associated TB. It is estimated that scale-up of these interventions between 2005-2022 has saved 9.2 million lives (7).<sup>2</sup> Yet, despite impressive uptake of collaborative TB/HIV activities and despite the advances in the prevention, diagnosis and treatment of TB disease, TB remains the leading cause of death among people living with HIV worldwide, accounting for 167 000 (27%) of global HIV-related deaths in 2022 (7). In addition, gaps in TB/HIV collaborative activities remain. In 2022, only 64% of new TB episodes among people living with HIV were diagnosed and notified, and the treatment success rate among people with HIV who started TB treatment in 2021 was 79%, lower than for all people with TB (7).

## 1.2 Rationale

Since the *WHO policy on collaborative TB/HIV activities (10)* was published in 2012, there have been remarkable scientific advances and consequently, updated WHO recommendations on screening, diagnosis, treatment and prevention of HIV-associated TB. These include:

- evidence on the overwhelming benefit of a combination of early ART and TPT in preventing TB and reducing morbidity and mortality among people living with HIV;
- the development of shorter rifamycin-based TPT regimens;
- C-reactive protein (CRP), chest X-ray (CXR) (including CAD software to interpret digital X-ray) and molecular WHO-recommended rapid diagnostic tests (mWRD) for TB screening among people living with HIV, in addition to the WHO-recommended four symptom screen (W4SS);
- the scale-up of molecular diagnostic tests to diagnose TB using a range of specimens, including non-sputum-based specimens such as urine or blood, recommended by WHO for the detection of both pulmonary and extra-pulmonary TB;
- LF-LAM to support in TB diagnosis;
- new antiretroviral therapy (ART) regimens as well as earlier start of ART after TB treatment initiation;
- new strategies for HIV testing;
- shorter TB treatment regimens;
- treatment support interventions and models of care that aim to make prevention and treatment more people-centred; and
- diagnosis and management of the most common infections in people with advanced HIV disease.

Based on this evidence, new WHO recommendations have been formulated, updated and published in WHO guidelines on TB (10, 11, 13-17, 21) and on HIV (21). The TB/HIV guidelines consolidate all WHO recommendations related to reducing the burden of TB among people living with HIV and to reducing the burden of HIV in people with TB.<sup>3</sup>

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<sup>2</sup> To estimate the number of deaths averted by collaborative TB/HIV activities, the actual numbers of TB deaths can be compared with the number of TB deaths that would have occurred in the absence of antiretroviral therapy (ART) provided alongside TB treatment for people with HIV-associated TB. This number can be estimated conservatively as the number of estimated incident cases multiplied by the relevant estimated case fatality ratio for untreated HIV-associated TB. The estimates are conservative because they do not account for the impact of TB services or availability of ART or TB preventive treatment on the level of TB incidence; they also do not account for the indirect, downstream impact of these interventions on future levels of infections, cases and deaths.

<sup>3</sup> Recommendations are consolidated in the existing language of the source guideline. Since these recommendations were published, the use of language in relation to HIV and TB has evolved to ensure that the terminology used is non-stigmatizing, people-centred and human rights-based. The wording of recommendations will be updated appropriately during the next respective guideline development process.

## 1.3 Scope

The TB/HIV guidelines summarize the recommendations and related evidence on interventions to reduce the burden of TB among people living with HIV and on interventions to reduce the burden of HIV among people with presumed or diagnosed TB, updating the recommendations outlined within objectives B and C from the TB/HIV policy as depicted in Fig. 1. They provide a single comprehensive source for evidence-informed recommendations to address HIV-associated TB and will allow policy makers in ministries of health and others providing services for people with TB and HIV to make decisions about implementation. The guidelines compile all current WHO recommendations for adults on screening, diagnosis, treatment, care and prevention of HIV-associated TB (11-18, 20-22, 26). For more information on each recommendation including the remarks, source of evidence, justification, subgroup, implementation and monitoring and evaluation considerations, the source guidelines or the WHO TB Knowledge Sharing Platform should be consulted.<sup>4</sup> Recommendations to address HIV-associated TB in children and adolescents have been compiled separately, in the *WHO consolidated guidelines on tuberculosis. Module 5: management of tuberculosis in children and adolescents* (11).

The TB/HIV guidelines are accompanied by a corresponding section within the *WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities* hereafter referred to as the TB/HIV operational handbook (7). The handbook contains guidance on actions to establish and strengthen mechanisms for effective collaboration between and within sectors to deliver people-centred TB and HIV services as well as guidance on implementation considerations for collaborative TB/HIV activities, updating activities outlined under objective A from the 2012 TB/HIV policy as shown in Fig. 1. WHO's *Framework for collaborative action on TB and comorbidities* (2) provides further guidance for establishing and strengthening mechanisms for effective collaboration to deliver people-centred services for TB and comorbidities, including HIV. Fig. 2 summarizes the updated collaborative TB/HIV activities.

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<sup>4</sup> The TB knowledge sharing platform is available at: <https://tbksp.org/>.

**Fig. 2. Updated 2024 collaborative TB/HIV activities**

### WHO-recommended collaborative TB/HIV activities

**Establish and strengthen the mechanisms for delivering integrated TB and HIV services<sup>a</sup>**

- Strengthen governance and accountability for TB/HIV collaborative activities
- Conduct an analysis of access to quality services for TB and HIV
- Coordinate planning and resource mobilization for collaborative action
- Implement and scale up people-centred services for HIV-associated TB
- Strengthen monitoring, evaluation and research

**Reduce the burden of TB among people living with HIV**

- Find and treat TB among people living with HIV
- Prevent TB among people living with HIV

**Reduce the burden of HIV among people with presumptive and diagnosed TB**

- Find and treat HIV among people with presumptive and diagnosed TB
- Prevent HIV among people with presumptive and diagnosed TB

<sup>a</sup> Details on these recommended actions are found within the TB/HIV operational handbook (7) and the *Framework for collaborative action on TB and co-morbidities* (2).

## 1.4 Objectives

The overall goal of the TB/HIV guidelines is to reduce suffering and death due to TB and HIV, in alignment with the WHO *End TB strategy* (3), the *Global health sector strategies on, respectively, HIV, viral hepatitis and sexually transmitted infections for the period 2022–2030* (27), the *Global AIDS Strategy 2021–2026* (28), the political declaration of the UN High-Level meeting on the fight against TB 2023 (29) and the UN High-Level Meeting on AIDS 2021 (5).

The specific objectives of the TB/HIV guidelines are to:

1. reduce the burden of TB among people living with HIV, by facilitating the uptake of WHO recommendations on TB prevention, screening, diagnosis, treatment and care; and
2. reduce the burden of HIV among people with TB, by facilitating the uptake of WHO recommendations on HIV prevention, screening, diagnosis, treatment and care.

## 1.5 Target audience

The TB/HIV guidelines are intended for managers of national TB and HIV programmes at all levels of the health system, managers in the private-for-profit sector, and other decision-makers in the health system. They are also a useful resource for clinicians and other healthcare providers, including community-based and primary care, harm-reduction services and maternal and child health programmes, as well as for relevant line ministries working on HIV-associated TB, such as ministries responsible for prisons or mining services. The TB/HIV guidelines are also of value to communities, civil society organisations and people with or at risk of TB and HIV.

## 1.6 Process of consolidating the guidelines

To develop the TB/HIV guidelines, WHO mapped the WHO publications containing recommendations on HIV-associated TB, which had been formulated by the respective GDGs and approved by the WHO Guidelines Review Committee (GRC). All the recommendations included in these guidelines were developed in accordance with the WHO guideline development process, as outlined in the source guidelines. A full list of the source guidelines that were used to consolidate all WHO recommendations and inform the TB/HIV guidelines is provided in Box 1.1.

### Box 1.1. List of guidelines used to develop the 2023 TB/HIV guidelines

#### WHO guidelines on HIV

- *Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring (21)*
- *Consolidated guidelines on HIV, viral hepatitis and STI prevention, diagnosis, treatment and care for key populations (30)*
- *Guidelines for diagnosing, preventing and managing cryptococcal disease among adults, adolescents and children living with HIV (31)*
- *Guidelines for diagnosing and managing disseminated histoplasmosis among people living with HIV (20)*
- *Consolidated guidelines on HIV testing services (23)*

#### WHO guidelines on TB

- *WHO consolidated guidelines on tuberculosis. Module 1: prevention – tuberculosis preventive treatment (22)*
- *WHO consolidated guidelines on tuberculosis. Module 1: prevention – infection prevention and control (13)*
- *WHO consolidated guidelines on tuberculosis. Module 2: screening – systematic screening for tuberculosis disease (12)*
- *WHO consolidated guidelines on tuberculosis. Module 3: diagnosis – rapid diagnostics for tuberculosis detection, 2021 update (14)*
- *WHO consolidated guidelines on tuberculosis. Module 3: diagnosis – tests for tuberculosis infection (15)*
- *WHO consolidated guidelines on tuberculosis. Module 4: treatment – drug-resistant tuberculosis treatment, 2022 update (16)*
- *WHO consolidated guidelines on tuberculosis. Module 4: treatment – drug-susceptible tuberculosis treatment (17)*
- *WHO consolidated guidelines on tuberculosis. Module 4: treatment – tuberculosis care and support (18)*
- *Guidance for national tuberculosis programmes on the management of tuberculosis in children, 2nd ed (19)*

#### WHO guidelines on HIV-associated TB

- *WHO policy on collaborative TB/HIV activities (10)*

## 1.7 Publication, dissemination, implementation, evaluation and expiry

These guidelines are published on the WHO website and can also be freely downloaded from the WHO TB Knowledge Sharing Platform.<sup>5</sup> Implementation considerations are also reflected in the TB/HIV operational handbook (7).

Following consolidation of the guidelines, WHO will review and update individual recommendations if new evidence becomes available. WHO works closely with Member States, as well as with technical and funding agencies and partners, to ensure wide communication of the updated guidance in technical meetings and training activities. WHO collaborates with technical partners to support national TB and HIV programmes in adopting new recommendations in national policies and guidelines.

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<sup>5</sup> The TB Knowledge Sharing Platform is available at: <https://tbksp.org/>.



## 2. Reduce the burden of TB among people living with HIV

Tuberculosis remains the primary cause of HIV-related morbidity and mortality worldwide, despite impressive scale-up of ART. In 2022, an estimated 671 000 (uncertainty interval (UI): 600 000–746 000) people living with HIV developed TB disease, among whom only 426 958 (64%) were diagnosed and notified (7). In the same year, an estimated 167 000 (UI: 139 000–198 000) people living with HIV died from TB, representing 27% of all HIV-related deaths (7). A systematic review and meta-analysis of post-mortem studies of global HIV-related deaths found that TB was the primary cause of death in 37.2% of individuals (95% confidence interval (CI): 25.7–48.7%), and that TB remained undiagnosed prior to death in 45.8% of individuals (95% CI: 32.6–59.1%) (32).

### 2.1 TB screening

#### WHO recommendations

##### Screening for TB among people living with HIV

1. People living with HIV should be systematically screened for TB disease at each visit to a health facility (*strong recommendation, very low certainty of evidence*). (12)
2. Among adults and adolescents living with HIV, systematic screening for TB disease should be conducted using the WHO-recommended four symptom screen, and those who report any one of the symptoms of current cough, fever, weight loss or night sweats may have TB and should be evaluated for TB and other diseases (*strong recommendation, moderate certainty of evidence*). (12)
3. Among adults and adolescents living with HIV, C-reactive protein using a cut-off of >5 mg/L may be used to screen for TB disease (*conditional recommendation, low certainty of evidence for test accuracy*). (12)
4. Among adults and adolescents living with HIV, chest X-ray may be used to screen for TB disease (*conditional recommendation, moderate certainty of evidence for test accuracy*). (12)
5. Among individuals aged 15 years and older in populations in which TB screening is recommended, computer-aided detection software programmes may be used in place of human readers for interpreting digital chest X-rays for screening and triage for TB disease (*conditional recommendation, low certainty of evidence*). (12)
6. Among adults and adolescents living with HIV, molecular WHO-recommended rapid diagnostic tests may be used to screen for TB disease (*conditional recommendation, moderate certainty of evidence for test accuracy*). (12)
7. Adult and adolescent inpatients with HIV in medical wards where the TB prevalence is >10% should be tested systematically for TB disease with a molecular WHO-recommended rapid diagnostic test (*strong recommendation, moderate certainty of evidence for test accuracy*). (12)

#### 2.1.1 Background

Early detection and treatment for TB among people living with HIV is crucial for reducing morbidity and mortality. TB screening tools are designed to distinguish people with a higher probability of having TB disease, from those with a lower probability. Screening tests need to be followed by a diagnostic test, offered as part of a comprehensive clinical evaluation, to confirm or rule out TB disease (12). WHO recommends that people living with HIV are systematically screened for TB disease at each visit to a health facility. Initially, the four symptom screen was recommended by WHO for TB

screening among people living with HIV, as part of the *Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings*, published in 2011 (33). WHO recommendations on TB screening among people living with HIV using CRP, CXR, with the possibility to read the CXR using CAD, and mWRDs were first published in the 2021 *WHO consolidated guidelines on tuberculosis. Module 2: screening – systematic screening for tuberculosis disease* (12). Therefore, there are now four recommended approaches to TB screening among people living with HIV, namely the W4SS, CRP, CXR (with the possibility of CAD for reading) and mWRDs.

## 2.1.2 Summary of evidence and rationale

A systematic literature review and individual participant data (IPD) meta-analysis was conducted in 2020 to review the accuracy of tools for TB screening among adults and adolescents with HIV, including the W4SS, CRP, CXR and mWRDs. Data were analyzed for all study participants, as well as for five different subpopulations (inpatients, outpatients on ART, outpatients not on ART, people with CD4 count  $\leq 200$  cells/ $\mu$ l, and pregnant women living with HIV) where disaggregated data was available. Key findings are summarized below; further details are published in the TB screening guidelines (12).

### **Recommendation 1: Systematic screening for TB among people living with HIV at every visit**

This recommendation, which applies to people of all ages, was first published in 2011 in WHO's *Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings* (33), and it remains in place. The GDG for the development of the 2021 updated WHO guidelines on TB screening placed high value on ensuring that TB is diagnosed early in this risk group, who have a high likelihood of having undetected TB and a high risk of poor health outcomes in the absence of early diagnosis and treatment (12).

### **Recommendation 2: WHO-recommended four symptom screen**

The 2020 IPD meta-analysis included 23 studies of 16 269 participants living with HIV, all of which reviewed the accuracy of the W4SS. The studies primarily focused on pulmonary TB disease. The unweighted average TB prevalence among participants within these studies was 9.2%, ranging from 1% to 26%; and 52% of people living with HIV screened positive on the W4SS. The sensitivity of the W4SS among all people living with HIV was 83% (95% CI: 74–89) and specificity was 38% (95% CI: 25–53). Estimates of the accuracy of the W4SS in different subgroups of people living with HIV are shown in Table 2.1. When used alone, the W4SS was found to have its lowest sensitivity among outpatients on ART and among pregnant women, and it had markedly low specificity among medical inpatients.

While there may be real-life limitations to the W4SS in terms of consistency that might not be reflected in studies, it remains the simplest non-invasive tool to implement in any setting, requiring no infrastructure. However, the high proportion of W4SS positivity (94%) and very low specificity in medical inpatients living with HIV in settings where TB prevalence among study participants was  $> 10\%$  gives it limited utility as a screening tool to rule in TB prior to diagnostic confirmation by mWRD in this very ill population.

The IPD meta-analysis found no alternative screening tools or strategies that were significantly higher in both sensitivity and specificity than the W4SS or that met the WHO target product profile for a screening test on both parameters. In all cases, when sensitivity was higher and met the minimal requirements of the target product profile, specificity was compromised, and vice versa. Depending on a programme's decision to prioritize higher sensitivity or higher specificity, other tools or combinations of tools may be used to complement the W4SS.

**Table 2.1. Diagnostic accuracy of the WHO-recommended four symptom screen among different subpopulations of people living with HIV compared with culture as a reference standard**

Population	No. of studies (no. of participants)	Sensitivity (95% CI)	Specificity (95% CI)
WHO target product profile	NA	> 0.90	> 0.70
All people living with HIV	23 (16 269)	0.83 (0.74–0.89)	0.38 (0.25–0.53)
Inpatients	4 (672)	0.96 (0.92–0.98)	0.11 (0.08–0.14)
Outpatients on ART	9 (4309)	0.53 (0.36–0.69)	0.70 (0.50–0.85)
Outpatients not on ART	19 (11 159)	0.84 (0.75–0.90)	0.37 (0.25–0.50)
CD4 ≤ 200 cells/μL	22 (5956)	0.86 (0.77–0.92)	0.30 (0.18–0.45)
Pregnant women living with HIV	8 (1937)	0.61 (0.39–0.79)	0.58 (0.39–0.75)

ART: antiretroviral therapy; CI: confidence interval; NA: not applicable

### **Recommendation 3: C-reactive protein**

CRP is an indicator of general inflammation that can be measured using point-of-care tests performed on capillary blood collected via finger prick. The evidence reviewed for the performance of CRP included six studies from Kenya, South Africa and Uganda with a total of 3971 participants. The average unweighted prevalence of TB among participants in the studies was 14%, ranging from 1% to 26%.

Data on the accuracy of CRP using a cut-off value of > 5 mg/L and of > 10 mg/L as indicators of TB disease were reviewed and both cut-offs were considered to have similar or superior accuracy when compared with the W4SS. The cut-off of > 5 mg/L was recommended because it is the lowest threshold indicating abnormality in many clinical settings, and it has higher sensitivity than the cut-off of > 10 mg/L. The choice of cut-off will depend on the type of CRP technology available in a given setting, the prevalence of TB and of other conditions that may increase CRP and the preference for increased sensitivity or increased specificity.

The IPD meta-analysis on CRP using a cut-off of > 5 mg/L reported similar sensitivity to and higher or similar specificity to the W4SS in all subpopulations assessed (see Table 2.2). When combined with the W4SS and used in parallel, whereby a positive screen for either tool led to a diagnostic test, it was found to have similar or higher sensitivity and specificity to the W4SS for all populations, depending on the cut-off threshold used and the subpopulation assessed. CRP was found to be most accurate among outpatients who were not on ART, compared with the W4SS alone, which had a sensitivity of 0.84 (95% CI: 0.75–0.90) and specificity of 0.37 (95% CI: 0.25–0.50) in this subpopulation. When performed sequentially after a positive W4SS among people living with HIV not on ART, CRP with a cut-off of > 5 mg/L was found to be as sensitive (0.84; 95% CI: 0.73–0.90) as the W4SS alone but to have significantly higher specificity (0.64; 95% CI: 0.55–0.72). Similar to the W4SS, the specificity of CRP for TB screening among inpatients living with HIV was found to be extremely low, likely due to other comorbidities that would also result in raised CRP levels and the presence of symptoms.

**Table 2.2 Diagnostic accuracy of CRP using a cut-off of > 5 mg/L among different subpopulations of people living with HIV compared with culture as a reference standard**

Population	No. of studies (no. of participants)	Sensitivity (95% CI)	Specificity (95% CI)
WHO target product profile	NA	> 0.90	> 0.70
All people living with HIV	6 (3971)	0.90 (0.78–0.96)	0.50 (0.29–0.71)
Inpatients	1 (400)	0.98 (0.93–1.00)	0.12 (0.09–0.17)
Outpatients on ART	1 (381)	0.40 (0.10–0.80)	0.80 (0.75–0.84)
Outpatients not on ART	4 (3186)	0.89 (0.85–0.92)	0.54 (0.45–0.62)
CD4 ≤ 200 cells/μL	6 (1829)	0.93 (0.87–0.97)	0.40 (0.22–0.62)
Pregnant women living with HIV	2 (62)	0.70 (0.12–0.97)	0.41 (0.12–0.78)

ART: antiretroviral therapy; CI: confidence interval; NA: not applicable

As a point-of-care biomedical test, CRP represents an opportunity for enhancing TB screening among people living with HIV. Health staff and patients might be more motivated to pursue a confirmatory diagnostic test following a positive screen for CRP. The specificity and predictive value of the test for detecting TB, however, will likely be reduced in settings with a lower TB prevalence than in those included in the meta-analysis.

#### **Recommendation 4: Chest X-ray**

Where available, WHO recommends using CXR in parallel with the W4SS, to assist in ruling out TB disease prior to initiating TPT among people living with HIV who are on ART. The GDG agreed that, due to the increased sensitivity, the evidence supported using CXR in addition to the W4SS as a parallel screening strategy in which a positive or abnormal result on either screen would indicate a referral for diagnostic evaluation. Data on “any abnormality” and an “abnormality suggestive of TB” detected by CXR were reviewed and either approach is recommended, depending on the context, the availability of radiological expertise, resources and preference towards higher sensitivity or higher specificity.

The evidence reviewed for the performance of CXR and the W4SS for all people living with HIV came from eight studies conducted in Benin, Botswana, Brazil, Guinea, India, Kenya, Malawi, Myanmar, Peru, South Africa and Zimbabwe, with a total of 6238 participants. The average prevalence of TB in all people living with HIV in the studies was 7%, ranging from 3% to 18%. Among outpatients on ART, the average prevalence was 2.6%.

CXR alone was found to have similar sensitivity to and similar or higher specificity than the W4SS across all subpopulations. When combined in a sequence whereby CXR followed a positive W4SS screen, CXR had a lower or similar sensitivity with higher or similar specificity. When combined and used in parallel with the W4SS, whereby a positive screen from either tool indicates the need for a diagnostic test, it had a higher or similar sensitivity and similar specificity (see Table 2.3). The IPD meta-analysis found this strategy to have the highest sensitivity (0.85; 95% CI: 0.69–0.94) compared with the W4SS (0.53; 95% CI: 0.36–0.69) and the other tools and strategies assessed for TB screening in outpatients on ART. While the data were limited for inpatients living with HIV, the combined strategy of CXR and the W4SS had a very low specificity (0.07; 95% CI: 0.03–0.19), similar to findings for using CRP or the W4SS alone.

**Table 2.3 Diagnostic accuracy among different subpopulations of people living with HIV of the W4SS combined with CXR (any abnormality) compared with culture as the reference standard and using a positive or abnormal result on either screen or both**

Population	No. of studies (no. of participants)	Sensitivity (95% CI)	Specificity (95% CI)
WHO target product profile	NA	> 0.90	> 0.70
All people living with HIV	8 (6238)	0.93 (0.88–0.96)	0.20 (0.10–0.38)
Inpatients	1 (52)	0.90 (0.33–0.99)	0.07 (0.03–0.19)
Outpatients on ART	4 (2670)	0.85 (0.69–0.94)	0.33 (0.15–0.58)
Outpatients not on ART	8 (3516)	0.94 (0.89–0.96)	0.19 (0.09–0.34)
CD4 ≤ 200 cells/μL	8 (2232)	0.94 (0.90–0.97)	0.14 (0.07–0.25)
Pregnant women living with HIV	1 (8)	0.75 (0.11–0.99)	0.56 (0.24–0.84)

ART: antiretroviral therapy; CI: confidence interval; NA: not applicable

### **Recommendation 5: Computer-aided detection of chest X-ray**

In many settings, the use of CXR for TB screening and triage for TB disease is limited by the unavailability of trained health personnel to interpret radiography images and by substantial intra- and inter-reader variability in its accuracy to detect abnormalities associated with TB. Numerous software packages that provide CAD, or automated interpretation of digital CXR images for the express purpose of determining the likelihood of TB disease, have been developed and offer a potential technological answer to the numerous implementation challenges inherent in human interpretation of CXRs.

For the development of the 2021 TB screening guidelines the performance of three CAD software programmes was compared with the performance of human readers. Due to methodological challenges, the estimates of CAD diagnostic accuracy were not able to be pooled across software programmes or across evaluations. Thus, the performances of CAD programmes and human readers from the included evaluations were presented as ranges (see Table 2.4).

**Table 2.4 Sensitivity and specificity ranges of computer-aided detection software and human readers interpreting digital chest radiographs for detection of bacteriologically confirmed TB across three software programmes, from three independent evaluations of the software in a range of populations and settings**

Type of case and type of reader	Accuracy estimate range	
	Sensitivity	Specificity
WHO target product profile	> 0.90	> 0.70
<b>Screening use case</b>		
CAD software	0.90–0.92	0.23–0.66
CXR with human reader	0.82–0.93	0.14–0.63
<b>Triage use case</b>		
CAD software	0.90–0.91	0.25–0.79
CXR with human reader	0.89–0.96	0.36–0.63

CAD: computer-aided detection; CXR: chest X-ray

The results of the evaluation showed the variability of both human readers and CAD software programmes across different settings and populations. In comparing the range of accuracy of CAD to that of human readers interpreting CXRs and noting the variability of readers and the substantial overlap between the two ranges, the data suggested there is little difference between the two. Therefore, the GDG considered that CAD software programmes can be considered accurate when compared with human readers.

The recommendation applies to software brands that upon external validation demonstrate a performance that is not inferior to the products reviewed by the GDG in 2020. The analysis for this recommendation was restricted to bacteriologically confirmed TB and, thus, the recommendation may not necessarily apply to other forms of TB (such as exclusively extrapulmonary TB or clinically diagnosed TB).

This recommendation is specific to adults and adolescents aged 15 years and older but applies regardless of HIV status. Limited data were available for comparing CAD to human interpretation of CXR among people living with HIV; further evidence is needed about the performance of CAD software among people living with HIV, to enable better setting-specific and patient-specific calibration of CAD software.

### ***Recommendation 6: Screening for TB using molecular WHO-recommended rapid diagnostic tests***

The systematic review of the performance of an mWRD used to screen for TB among people living with HIV included 14 studies with a total of 9209 participants. The Xpert MTB/RIF assay was the primary mWRD used in these studies. The prevalence of TB in the studies ranged from 1% to 26%. The average TB prevalence among participants attending outpatient facilities was 8.6%. Using an mWRD alone was found to have sensitivity of 0.69 (95% CI: 0.60–0.76) and specificity of 0.98 (95% CI: 0.97–0.99) compared with using the W4SS followed by an mWRD as a diagnostic test, which had sensitivity of 0.62 (95% CI: 0.56–0.69) and specificity of 0.99 (95% CI: 0.97–0.99) (see Table 2.5). There were no significant differences in the accuracy of the mWRD between the different subpopulations when compared with using the W4SS followed by the mWRD.

Due to the increased sensitivity of mWRDs, but also in consideration of the likely challenges relating to access, high costs and feasibility in many countries, mWRDs are recommended conditionally as an option for screening for TB disease among all adults and adolescents living with HIV, who are not medical inpatients in settings where the TB prevalence exceeds 10% (for whom there is a strong recommendation, see below). As with all screening tools, the GDG emphasized the importance in all settings of following up an mWRD screen with a diagnostic assessment (see Section 2.2) to prevent the potential harm of overtreatment. In addition, due consideration should be made to prioritizing mWRDs as a diagnostic test for all people with presumptive TB before scaling up mWRD as a screening test.

**Table 2.5 Diagnostic accuracy of mWRD for screening for TB among different subpopulations of people living with HIV compared with microbiological reference standard**

Population	No. of studies (no. of participants)	Sensitivity (95% CI)	Specificity (95% CI)
WHO target product profile	NA	> 0.90	> 0.70
All people living with HIV	14 (9209)	0.69 (0.60–0.76)	0.98 (0.97–0.99)
Inpatients	4 (639)	0.77 (0.69–0.84)	0.93 (0.89–0.96)
Outpatients on ART	4 (2645)	0.54 (0.20–0.84)	0.99 (0.97–1.00)
Outpatients not on ART	10 (5796)	0.72 (0.64–0.79)	0.98 (0.98–0.99)
CD4 ≤ 200 cells/μL	12 (3422)	0.76 (0.68–0.82)	0.97 (0.95–0.98)
Pregnant women living with HIV	4 (473)	0.55 (0.33–0.75)	0.99 (0.97–0.99)

ART: antiretroviral therapy; CI: confidence interval; NA: not applicable

***Recommendation 7: Screening for TB using molecular WHO-recommended rapid diagnostic tests among medical inpatients with HIV***

TB is the main cause of hospitalization and mortality among people living with HIV (12). Given the high mortality among people living with HIV who are medical in-patients in TB high burden settings, WHO strongly recommends the use of mWRDs for rapid work-up in this population, regardless of symptoms. The assessment of the performance of an mWRD used as a combined TB screening and diagnostic strategy for medical ward patients with HIV included four studies in Ghana, Myanmar and South Africa with a total of 639 participants. The prevalence of TB in the included studies was 23.8%, ranging from 7% to 26%. The mWRD test assessed in the IPD was primarily the Xpert MTB/RIF assay.

Using the W4SS alone had 96% sensitivity and 11% specificity in the IPD meta-analysis of medical ward inpatients living with HIV, 94% of whom were positive on the W4SS. Thus, the difference in accuracy was minimal between the full screening and diagnostic strategy of using W4SS followed by mWRD, and using mWRD alone. Therefore, the value of the W4SS was judged to have limited utility in screening for TB in this population prior to an mWRD test, and the GDG recommended that medical inpatients should be screened and tested with an mWRD, irrespective of symptoms, to inform a decision about whether to treat for TB. A 10% threshold TB prevalence among hospital inpatients living with HIV is recommended, taking into account the TB prevalence among the participants studied and striking a balance between ensuring rapid diagnosis in this critically ill population and the need to avoid overtreatment. In lower prevalence settings, a screening and diagnostic strategy with mWRD alone would give rise to higher numbers of false positives, with overtreatment and the related social and economic consequences, including potential delay in starting ART. This recommendation may not be applicable to settings with a lower pre-test probability of TB.



## 2.2 TB diagnosis

### WHO recommendations

#### Diagnosis of TB in people living with HIV

##### WHO standard on the use of molecular WHO-approved rapid diagnostic tests

- All individuals with TB have access to a WHO-recommended rapid diagnostic (WRD<sup>a</sup>) as the initial diagnostic test. (26)
- In all facilities in all districts, the TB diagnostic algorithm requires use of a WRD<sup>a</sup> as the initial diagnostic test for all patients with presumed TB, including children, people living with HIV (combined with lateral flow lipoarabinomannan [LF-LAM]) and extrapulmonary TB. (26)

<sup>a</sup> In the source document the term “WRD” refers to molecular WHO-recommended rapid diagnostic test

#### Use of molecular WHO-approved rapid diagnostic tests in blood in the diagnosis of disseminated TB

8. In HIV-positive adults and children with signs and symptoms of disseminated TB, Xpert MTB/RIF may be used in blood, as an initial diagnostic test for disseminated TB (*conditional recommendation, very low certainty of evidence*). (14)

##### Remarks:

Blood was only evaluated in people living with HIV and under particular processing specifications (9), using third-generation Xpert MTB/RIF cartridges, based on one study with a small number of participants. The recommendation applies only to a particular population (HIV-positive adults with signs and symptoms of disseminated TB). The GDG did not feel comfortable extrapolating this recommendation to other patient populations.

#### Use of LF-LAM in the diagnosis of TB in people living with HIV

##### In inpatient settings

9. WHO strongly recommends using LF-LAM to assist in the diagnosis of active TB in HIV-positive adults, adolescents and children:
- with signs and symptoms of TB (pulmonary and/or extrapulmonary) (*strong recommendation, moderate certainty in the evidence about the intervention effects*); or
  - with advanced HIV disease or who are seriously ill (*strong recommendation, moderate certainty in the evidence about the intervention effects*); or
  - irrespective of signs and symptoms of TB and with a CD4 cell count of less than 200 cells/mm<sup>3</sup> (*strong recommendation, moderate certainty in the evidence about the intervention effects*). (14)

##### In outpatient settings

10. WHO suggests using LF-LAM to assist in the diagnosis of active TB in HIV-positive adults, adolescents and children:
- with signs and symptoms of TB (pulmonary and/or extrapulmonary) or seriously ill (*conditional recommendation, low certainty in the evidence about test accuracy*); and
  - irrespective of signs and symptoms of TB and with a CD4 cell count of less than 100 cells/mm<sup>3</sup> (*conditional recommendation, very low certainty in the evidence about test accuracy*). (14)

##### In outpatient settings

11. WHO recommends against using LF-LAM to assist in the diagnosis of active TB in HIV-positive adults, adolescents and children:
- without assessing TB symptoms (*strong recommendation, very low certainty in the evidence about test accuracy*);
  - without TB symptoms and unknown CD4 cell count or without TB symptoms and CD4 cell count greater than or equal to 200 cells/mm<sup>3</sup> (*strong recommendation, very low certainty in the evidence about test accuracy*); and
  - without TB symptoms and with a CD4 cell count of 100–200 cells/mm<sup>3</sup> (*conditional recommendation, very low certainty in the evidence about test accuracy*). (14)

##### Remarks:

1. The reviewed evidence and recommendations apply to the use of AlereLAM only, because other in-house LAM-based assays have not been adequately validated or used outside limited research settings. Any new or generic LAM-based assay should be subject to adequate validation in the settings of intended use.
2. All patients with signs and symptoms of pulmonary TB who are capable of producing sputum should submit at least one sputum specimen for Xpert MTB/RIF (Ultra) assay, as their initial diagnostic test. This also includes children and adolescents living with HIV who are able to provide a sputum sample.
3. These recommendations also apply to adolescents and children living with HIV, based on generalization of data from adults, while acknowledging that there are very limited data for these population groups.
4. LF-LAM should be used as an add-on to clinical judgement in combination with other tests; it should not be used as a replacement or triage test.



## 2.2.1 Background

People living with HIV may have an atypical clinical picture, especially those with advanced HIV disease, complicating the diagnosis of pulmonary and extrapulmonary forms of TB disease. Access to a rapid and accurate diagnosis is essential to ensure that TB is effectively treated among people living with HIV.

Options for TB diagnosis recommended by WHO comprise two broad groups: i) initial tests for diagnosing TB, often including at least rifampicin resistance detection, and ii) follow-on tests used after TB confirmation to detect additional drug resistance. These guidelines focus on the first category. Table 2.6 summarizes the initial WHO-recommended rapid diagnostic tests for TB, which are applicable for everyone, except LF-LAM and the use of mWRD in blood which are specific to people living with HIV. Further details on the accuracy of all the tests as well as the follow-on tests to detect additional drug resistance can be found in *WHO consolidated guidelines on tuberculosis. Module 3: diagnosis – rapid diagnostics for tuberculosis detection, 2021 update (14)*.

**Table 2.6 WHO-recommended rapid diagnostic tests as initial tests for TB diagnosis**

Test	Specimen type	Resistance
	Adults	DST R/H
<b>Xpert® MTB/RIF</b>	Sputum	R
	Blood <sup>a</sup>	
	Cerebrospinal fluid	
	Lymph node aspirate	
	Lymph node biopsy	
	Pericardial	
	Peritoneal	
	Pleural	
	Synovial fluid	
	Urine	
<b>Xpert® MTB/RIF Ultra</b>	Sputum	R
	Cerebrospinal fluid	
	Lymph node aspirate	
	Lymph node biopsy	
<b>Truenat™ MTB, MTB Plus and MTB-RIF Dx tests<sup>b</sup></b>	Sputum	R
<b>TB-LAMP<sup>c</sup></b>	Sputum	-
<b>Moderate complexity automated NAATs<sup>d</sup></b>	Sputum	R and H
<b>LF-LAM<sup>a</sup></b>	Urine	-

DST: drug-susceptibility testing; R: rifampicin; H: isoniazid

<sup>a</sup> Specific to people living with HIV

<sup>b</sup> There is uncertainty about the use of Truenat™ MTB or MTB Plus in people living with HIV.

<sup>c</sup> Limited data on the performance of loop-mediated isothermal amplification (TB-LAMP) among people living with HIV were available at time of recommendation development.

<sup>d</sup> The currently recommended nucleic acid amplification tests (NAATs) in this class include: RealTime MTB (Abbott Molecular), BD MAX™ MDR-TB (Becton Dickinson), FluoroType® MTB/MTBDR (*Bruker-Hain Diagnostics*), and cobas® MTB-RIF/INH (Roche Diagnostics)

In many high TB burden settings, sputum-smear microscopy remains the primary diagnostic tool for evaluating individuals presenting with signs and symptoms of TB. However, sputum-smear microscopy has a low sensitivity up to approximately 50% among people living with HIV (34, 35), who often have difficulty in producing sputum or have paucibacillary sputum. The sensitivity will vary with the setting and as well as with the degree of immunosuppression of the individual. Furthermore, sputum-smear microscopy cannot distinguish drug-susceptible strains from drug-resistant strains. WHO recommends that TB programmes transition to replacing microscopy as the initial diagnostic test with mWRDs that detect *Mycobacterium tuberculosis* (*M. tuberculosis*) complex bacteria (MTBC). The *WHO standard: universal access to rapid tuberculosis diagnostics* includes two benchmarks relating to access to mWRDs as an initial diagnostic test, including one that requires the use of mWRD as an initial diagnostic test, combined with urinary LF-LAM, for people living with HIV (26).

## 2.2.2 Summary of evidence and rationale

### **Recommendation 8: use of molecular WHO-recommended rapid diagnostic tests**

mWRDs incorporate a growing number of different products that detect *M. tuberculosis* genetic material in samples. Most mWRDs detect rifampicin resistance, while some also detect isoniazid resistance. Table 2.7 summarizes the evidence on the accuracy of the different tests in the diagnosis of TB in people living with HIV.

**Table 2.7 Diagnostic accuracy of mWRDs for TB diagnosis in people living with HIV compared with microbiological reference standard**

mWRD test	No. of studies (no. of participants)	Sensitivity and specificity	Certainty of evidence
Xpert® MTB/RIF for pulmonary TB	14 (1159)	Se: 0.81 (95% CrI: 0.75–0.86)	High
	14 (3505)	Sp: 0.98 (95% CrI: 0.97–0.99)	High
Xpert Ultra for pulmonary TB	2 (149)	Se: 0.88 (95% CrI: 0.74–0.94)	Low
	2 (430)	Sp: 0.95 (95% CrI: 0.79–0.96)	High
TB-LAMP for pulmonary TB	5 (370)	Se: 0.64 (95% CI: 0.49–0.76) <sup>a</sup>	Very low
		Sp: 0.99 (95% CI: 0.85–0.999) <sup>a</sup>	Very low
Xpert® MTB/RIF blood	1 (9)	Se: 0.56 (95% CI: 0.21–0.86)	Very low
	1 (65)	Sp: 0.94 (95% CI: 0.85–0.98)	Very low

<sup>a</sup> TB loop-mediated isothermal amplification (TB-LAMP) in people living with HIV was assessed according to two mycobacterial culture reference standards. The pooled sensitivity ranged from 0.64 (0.49–0.76) to 0.73 (95% CI: 0.52–0.88) and the pooled specificity ranged from 0.95 (95% CI: 0.64–0.995) to 0.99 (0.8–0.999).

In 2011 WHO first recommended the use of Xpert MTB/RIF, as the initial diagnostic test using sputum for pulmonary TB in individuals suspected of MDR-TB or HIV-associated TB (36). This strong recommendation was updated in 2013, based on high-quality evidence and increased accuracy, recommending that Xpert MTB/RIF should be used rather than conventional microscopy, culture and drug-susceptibility testing, as the initial diagnostic test in adults suspected of having MDR-TB or HIV-associated TB (36). Since 2020, WHO has recommended a number of mWRDs for the initial diagnosis of TB, instead of smear microscopy, for all people being evaluated for pulmonary and extrapulmonary TB, regardless of HIV status (37).

WHO recommends that mWRDs can be used for testing the following non-respiratory specimens for people presenting with signs and symptoms of extrapulmonary TB: cerebrospinal fluid (strong recommendation), lymph node samples, pleural, peritoneal, pericardial, synovial fluid or urine (conditional recommendations). Of the total 65 studies that reviewed data on the diagnosis of extrapulmonary TB, 41 studies (63%) took place in high burden TB/HIV countries. Although data in the evaluation are not disaggregated by HIV status these recommendations also apply to people living with HIV.

The use of mWRD to test blood is recommended specifically for people living with HIV who present with signs and symptoms of disseminated TB. For the 2021 update of the *WHO consolidated guidelines on tuberculosis. Module 3: diagnosis – rapid diagnostics for tuberculosis detection, 2021 update (14)*, the use of mWRD in blood was only evaluated in people living with HIV and under particular processing specifications using third-generation Xpert MTB/RIF cartridges, based on one study with a small number of participants (38).

At the time of the guideline development for recommendations on loop-mediated isothermal amplification (TB-LAMP), the assay was found to have limited additional diagnostic value over sputum-smear microscopy for testing people living with HIV, however a further review is planned. It was also emphasized that TB-LAMP should not replace the use of rapid molecular tests that have a higher sensitivity for the detection of TB among people living with HIV who have signs and symptoms consistent with TB.

There is some uncertainty about the use of Truenat™ (MTB, MTBPlus and MTB-RIF) in people living with HIV, given that there were no HIV-specific data on accuracy of the version of Truenat™ that was assessed during the guideline development. The recommendation on the use of Truenat™ (MTB, MTBPlus and MTB-RIF) in people living with HIV is thus based on extrapolation of the data on test performance with smear-negative sputum specimens.

### **Recommendations 9–11: Lateral flow urine lipoarabinomannan assay**

LF-LAM is a point-of-care test to assist in the diagnosis of TB, specifically used among people living with HIV. It is performed on a urine sample, based on the detection of the lipoarabinomannan (LAM) antigen, and is suitable for use as part of the standard package of care for people with advanced HIV disease. At the time of writing, the Alere Determine TB LAM Ag (AlereLAM) is the only commercially available urine LF-LAM test endorsed by WHO. Details on the use of LF-LAM are provided in the TB diagnostic guidelines (14) and accompanying handbook (39).

As part of a WHO process to update guidelines for the use of the AlereLAM assay, WHO commissioned a systematic review to summarize the current scientific literature on the accuracy of AlereLAM for the diagnosis of TB in people living with HIV. The review identified 15 unique published studies that assessed the accuracy of AlereLAM in adults and integrated nine new studies identified since the original WHO and Cochrane reviews in 2015 and 2016, respectively (10, 11). All studies were performed in high TB/HIV burden countries that were classified as low-income or middle-income countries.

The 15 included studies involved 6814 participants, of whom 1761 (26%) had TB. Eight of the studies evaluated the accuracy of AlereLAM for TB diagnosis in participants with signs and symptoms suggestive of TB; these studies involved 3449 participants, of whom 1277 (37%) had TB. Seven studies evaluated the accuracy of AlereLAM for diagnosis of unselected participants who may or may not have had TB signs and symptoms at enrolment; these studies involved 3365 participants, of whom 439 (13%) had TB. Table 2.8 presents pooled sensitivity and specificity results for AlereLAM against a microbiological reference standard grouped by the study population, TB diagnosis among “symptomatic participants” and TB diagnosis among “unselected participants”.

Unlike traditional diagnostic methods, evidence demonstrates improved sensitivity in people living with HIV with low CD4 cell counts. In addition, the pooled risk ratio from two randomized trials on the impact of AlereLAM in reducing mortality associated with advanced HIV disease was 0.85 (0.76–0.94); and the absolute effect was 35 fewer deaths per 1000 (from 14 fewer to 55 fewer). Economic evidence for the implementation and scale-up of LF-LAM is limited. The studies that have been done show a consistent trend, suggesting that LF-LAM could be cost-effective in a population of African adults living with HIV (particularly among hospitalized patients). More details are given in [web annex 4.13](#) of the *WHO consolidated guidelines on tuberculosis. Module 3: diagnosis – rapid diagnostics for tuberculosis detection: “Economic evaluations of LF-LAM for the diagnosis of active tuberculosis in HIV-positive individuals: an updated systematic review”*.

**Table 2.8 Diagnostic accuracy of urine LF-LAM for diagnosis of TB among different subpopulations of people living with HIV compared to culture as a reference standard (14)**

	Symptomatic participants				Unselected participants			
	Studies (total participants)	Participants with TB	Pooled sensitivity (95% CrI)	Pooled specificity (95% CrI)	Studies (total participants)	Participants with TB	Pooled sensitivity (95% CrI)	Pooled specificity (95% CrI)
<b>Overall accuracy</b>	8 studies (3449)	1277 (37%)	42% (31–55%)	91% (85–95%)	7 studies (3365)	432 (13%)	35% (22–50%)	95% (89–98%)
<b>By setting</b>								
<b>Inpatient</b>	6 studies (2253)	868 (39%)	52% (40–64%)	87% (78–93%)	3 studies (537)	159 (30%)	62% (41–83%)	84% (48–96%)
<b>Outpatient</b>	4 studies (1196)	409 (34%)	29% (17–47%)	96% (91–99%)	6 studies (2828)	273 (10%)	31% (18–47%)	95% (87–99%)
<b>By CD4 cell count</b>								
<b>CD4 &gt; 200</b>	3 studies (738)	163 (22%)	16% (8–31%)	94% (81–97%)	1 study <sup>a</sup> (156)	11 (7%)	Not applicable	Not applicable
<b>CD4 ≤ 200</b>	4 studies (1825)	722 (40%)	45% (31–61%)	89% (77–94%)	2 studies (706)	82 (12%)	26% (9–56%)	96% (87–98%)
<b>CD4 &gt; 100</b>	4 studies (1519)	425 (28%)	17% (10–27%)	95% (89–98%)	4 studies (952)	115 (12%)	20% (10–35%)	98% (95–99%)
<b>CD4 ≤ 100</b>	4 studies (1239)	512 (41%)	54% (38–69%)	88% (77–94%)	3 studies (417)	130 (31%)	47% (40–64%)	90% (77–96%)
<b>CD4 101–200</b>	4 studies (586)	210 (36%)	24% (14–38%)	90% (77–96%)	1 study <sup>b</sup> (103)	13 (13%)	Not applicable	Not applicable
<b>By CD4 and setting</b>								
<b>CD4 ≤ 200 inpatient</b>	2 studies (1009)	348 (34%)	54% (34–73%)	80% (58–91%)	1 study <sup>c</sup> (54)	14 (26%)	Not applicable	Not applicable
<b>CD4 ≤ 100 inpatient</b>	2 studies (734)	270 (37%)	61% (40–78%)	81% (61–91%)	2 studies (200)	84 (42%)	57% (33–79%)	90% (69–97%)
<b>CD4 101–200 inpatient</b>	2 studies (275)	78 (28%)	32% (16–57%)	81% (55–92%)	1 study <sup>d</sup> (9)	4 (44%)	Not applicable	2 studies (275)
<b>CD4 ≤ 200 outpatient</b>	1 study <sup>e</sup> (249)	97 (39%)	Not applicable	Not applicable	2 studies (652)	68 (10%)	21% (8–48%)	96% (89–99%)
<b>CD4 ≤ 100 outpatient</b>	1 study <sup>f</sup> (121)	48 (40%)	Not applicable	Not applicable	2 studies (217)	46 (21%)	40% (20–64%)	87% (68–94%)
<b>CD4 101–200 outpatient</b>	1 study <sup>g</sup> (128)	51 (40%)	Not applicable	Not applicable	1 study <sup>h</sup> (94)	9 (10%)	Not applicable	Not applicable

CrI: credible interval; TB: tuberculosis.

<sup>a</sup> sensitivity 27% (6–61%); specificity 99% (96–100%).

<sup>b</sup> sensitivity 38% (14–68%); specificity 99% (94–100%).

<sup>c</sup> sensitivity 64% (35–87%); specificity 82% (67–93%).

<sup>d</sup> sensitivity 75% (19–99%); specificity 100% (48–100%).

<sup>e</sup> sensitivity 24% (16–33%); specificity 94% (89–97%).

<sup>f</sup> sensitivity 30% (18–46%); specificity 93% (85–98%).

<sup>g</sup> sensitivity 18% (8–31%); specificity 95% (87–99%).

<sup>h</sup> sensitivity 22% (3–60%); specificity 99% (94–100%).

## 2.3 High quality tuberculosis treatment for people living with HIV

### WHO recommendations

#### TB treatment for people living with HIV

12. It is recommended that TB patients who are living with HIV should receive at least the same duration of daily TB treatment as HIV-negative TB patients (*strong recommendation, high certainty of evidence*). (17)

13. People living with HIV with TB and histoplasmosis coinfection should receive TB therapy according to WHO treatment guidelines (*conditional recommendation; very-low-certainty evidence*). (20)

#### Integrated delivery of care for HIV-associated TB

14. In settings with a high burden of HIV and TB, TB treatment may be provided for people living with HIV in HIV care settings where a TB diagnosis has also been made (*strong recommendation, very-low-certainty evidence*). (21)

### 2.3.1 Background

Early initiation of TB treatment and ART among people with both TB and HIV is critical for reducing mortality and improving TB treatment outcomes. People living with HIV who receive a diagnosis of TB should receive a WHO-recommended TB treatment regimen. This section covers timing of TB treatment, as well as provision of integrated care. WHO recommendations on treatment regimens for people with drug-susceptible TB and MDR-TB can be found in *WHO consolidated guidelines on tuberculosis. Module 4: treatment – drug-susceptible tuberculosis treatment* (17) and in *WHO consolidated guidelines on tuberculosis. Module 4: treatment – drug-resistant tuberculosis treatment* (16). The timing of ART initiation in people with presumed or diagnosed TB is covered in Section 3.2.

### 2.3.2 Summary of evidence and rationale

#### **Recommendation 12: Duration of daily TB treatment for people living with HIV**

This recommendation was first put forward in 2010 and is considered valid in the guidelines update of 2017 and in the current consolidated guidelines on drug susceptible TB treatment. A systematic review and meta-analysis of six randomized controlled trials (RCTs) and 21 cohort studies provided pooled estimates of failure, relapse and death by duration of rifampicin, and daily intensive phase versus intermittent throughout (40). The systematic review revealed a marked and significant reduction in failure and relapse in the study arms in which some or all study participants received ART. In a regression model, treatment failure or relapse was 1.8–2.5 times more likely with intermittent rather than daily dosing in the intensive phase. Compared with 8 or more months of rifampicin, 2-month rifampicin regimens carried a 3-fold higher risk of relapse, and 6-month regimens carried a 2.2-fold higher risk. Extending treatment beyond 6 months is recommended by some expert groups in certain persons living with HIV and the meta-analysis showed that this is associated with significantly lower relapse rates. However, several other considerations were given greater weight. Separate regimens for people with TB living with or without HIV would be very challenging in operational terms and could create stigma. Other potential harms of extending treatment are acquired resistance to rifampicin, and a longer period during which ART options are limited (because of ART–rifampicin interactions).

### ***Recommendation 13: TB treatment for people living with HIV and histoplasmosis***

Histoplasmosis is highly endemic in some parts of the WHO Region of the Americas and is also reported in certain countries of Asia and Africa (20). Co-occurrence can lead to complex management, with drug-drug interactions that may affect HIV, TB, and histoplasmosis treatment (41). In particular, rifampicin results in reduced itraconazole levels, potentially leading to ineffective treatment for histoplasmosis (42).

A systematic review that informed the development of the Pan American Health Organization (PAHO) and WHO *Guidelines for diagnosing and managing disseminated histoplasmosis among people living with HIV* (20) found two studies (including one case report) reporting on treatment outcomes among people living with HIV, histoplasmosis and TB (42, 43). This recommendation therefore relies on the expertise of the GDG and considers existing guidance on managing HIV and TB disease. The recommendation balances the risk for acquisition of TB drug resistance and the risk of drug-drug interactions (rifampicin and itraconazole), leading to subtherapeutic itraconazole levels and potential ineffective treatment for histoplasmosis.

When histoplasmosis is not controlled because of interactions between rifampicin and itraconazole, clinicians may consider, depending on local context, extending the duration of amphotericin B induction therapy, once-weekly courses of amphotericin B, increasing the itraconazole dose and monitoring the blood level and toxicity and considering using other azole drugs (osaconazole, voriconazole, or fluconazole). Finally, clinicians can consider replacing rifampicin with rifabutin. Treatment may need to be revised for people experiencing toxicity, drug-drug interactions, or for those with resistance profiles requiring protease inhibitors or second-line TB drugs. When possible, antiretroviral resistance genotyping and TB drug susceptibility testing may assist clinical decisions. Itraconazole serum level testing may not be available in some areas.

### ***Recommendation 14: Providing TB treatment in HIV care settings***

A systematic review evaluating the effectiveness of delivering ART in TB treatment settings identified 19 observational studies, many of which showed increased uptake and timeliness of ART initiation. However, the data on mortality and TB treatment success were inconsistent. The same systematic review identified five observational studies evaluating the effectiveness of delivering TB treatment in HIV care settings. Two studies reported decreased mortality and another showed comparable mortality rates. The TB treatment success rates and ART uptake were comparable across studies (44).

## 2.4 Prevention of TB

### 2.4.1 TB preventive treatment

#### WHO recommendations

##### Eligibility for TB preventive treatment

15. Adults and adolescents living with HIV who are unlikely to have active TB should receive TB preventive treatment as part of a comprehensive package of HIV care. Treatment should be given to those on antiretroviral treatment, to pregnant women and to those who have previously been treated for TB, irrespective of the degree of immunosuppression and even if LTBI testing is unavailable (*strong recommendation, high certainty in the estimates of effect*). (22)

##### Algorithms to rule out TB disease prior to offering TB preventive treatment

16. Adults and adolescents living with HIV who are screened for TB according to a clinical algorithm and who report any of the symptoms of current cough, fever, weight loss or night sweats may have active TB and should be evaluated for TB and other diseases and offered preventive treatment if active TB is excluded (*strong recommendation, moderate certainty in the estimates of effect*). (22)

17. Chest radiography may be offered to people living with HIV on ART and preventive treatment be given to those with no abnormal radiographic findings (*conditional recommendation, low certainty in the estimates of effect*). (22)

##### Testing for TB infection

18. Either the tuberculin skin test or interferon-gamma release assays can be used to test for TB infection (*strong recommendation, very low certainty of the evidence*). (15)

19. *Mycobacterium tuberculosis* antigen-based skin tests (TBSTs) may be used to test for TB infection (*conditional recommendation for the intervention, very low certainty of evidence*). (15)

##### TB preventive treatment regimens

20. The following options are recommended for the treatment of LTBI regardless of HIV status: 6 or 22 months of daily isoniazid, or a 3-month regimen of weekly rifapentine plus isoniazid, or a 3-month regimen of daily isoniazid plus rifampicin (*strong recommendation, moderate to high certainty in the estimates of effect*). A 1-month regimen of daily rifapentine plus isoniazid or 4 months of daily rifampicin alone may also be offered as alternatives (*conditional recommendation, low to moderate certainty in the estimates of effect*). (22)

21. In settings with high TB transmission, adults and adolescents living with HIV who have an unknown or a positive LTBI test and are unlikely to have active TB disease should receive at least 36 months of daily isoniazid preventive treatment (IPT). Daily IPT for 36 months should be given whether or not the person is on ART, and irrespective of the degree of immunosuppression, history of previous TB treatment and pregnancy in settings considered to have a high TB transmission as defined by national authorities (*conditional recommendation, low certainty in the estimates of effect*). (22)

#### 2.4.1.1 Background

People living with HIV have a higher risk of developing TB disease compared to the general population, even when on ART and with high CD4 cell counts. The combined use of TPT and ART has been shown to reduce TB incidence and mortality among people living with HIV, including among those with higher CD4 cell counts (45-47). TPT also provides additional protection when given immediately after the successful completion of treatment for TB disease in people living with HIV (48). TPT should be a core component of the package of care for people living with HIV and should be primarily the responsibility of national HIV and AIDS programmes and HIV service providers (21).



### 2.4.1.2 Summary of evidence and rationale

#### **Recommendation 15: TPT for adults and adolescents living with HIV**

The recommendation of TPT for all people living with HIV was first published by WHO in 2011 (33). A systematic review of 12 RCTs, which included 8578 people living with HIV, found that preventive treatment reduced the overall risk for TB by 33% (relative risk (RR) 0.67; 95% CI: 0.51–0.87) (49). For those who were TST positive, the reduction increased to 64% (RR 0.36; 95% CI: 0.22–0.61). Although not statistically significant, the reduction was 14% among TST-negative people (RR 0.86; 95% CI: 0.59–1.26) and those of unknown TST status (RR 0.86; 95% CI: 0.48–1.52). Most of the studies in the review were, however, conducted before ART became available, and there is now increasing evidence from observational studies and RCTs of the efficacy of TPT in people receiving ART. TB incidence has been reported to be high among people living with HIV who did not receive IPT, including those with CD4 > 350 cells/mm<sup>3</sup> and who were TST negative (50). One double-blind RCT of 1329 people living with HIV receiving ART indicated that those on ART with negative TST or IGRA benefited more from IPT than those who were TST or IGRA positive (45). An RCT of 2056 people living with HIV showed additive benefits of TPT plus ART in reducing both TB incidence and overall mortality (47, 51). The protective effect lasted for more than 5 years.

The GDG reviewed the evidence from the systematic reviews and discussed each population risk group identified in detail for the prevalence of TB infection, risk of progression to TB disease and the incidence of TB disease as compared with the general population. They concluded that the evidence shows a clear benefit of systematic testing and treatment of TB infection for people living with HIV. The wording of the recommendation now refers to TB infection testing rather than TST given that IGRA is also an option (see Recommendation 18), in addition to the recently recommended *M. tuberculosis* antigen-based skin tests (TBST) (see Recommendation 19). Preventive treatment should be given to adults and adolescents living with HIV, regardless of their immune status and whether they are on ART, given the evidence of additional protective effect when provided with ART. A systematic review of studies conducted before ART became available showed the value of providing preventive treatment immediately after successful completion of TB treatment among people living with HIV in countries with a TB incidence > 100 per 100 000 population (33, 47). Therefore, preventive treatment is recommended for people who were previously treated for TB and for whom a new exposure to TB is confirmed. No evidence was found, however, for preventive treatment of people who had successfully completed treatment for MDR-TB or XDR-TB. The effect of repeated courses of preventive treatment is unclear and hence no recommendation on this is made in the present guidelines. One recent RCT showed that in settings with high TB transmission, a second round of preventive therapy did not provide additional benefit to persons receiving ART (52). In settings with high TB transmission, however, daily IPT for 36 months or longer is recommended conditionally (53) (see Recommendation 21). The relative risk of TB transmission is determined by the local authorities on the basis of risk of exposure (e.g. TB incidence, occurrence of undiagnosed or inadequately treated disease, population density, environmental factors) and host immune response (13).

Pregnant women living with HIV are at risk for TB, which can have severe consequences for both the mother and the fetus, with increased risk of maternal and infant death (54). Pregnancy should not disqualify women living with HIV from receiving preventive treatment with medicines commonly used to treat TB disease that are generally considered safe for use in pregnancy, such as isoniazid and rifampicin (classified as Pregnancy Category C by the United States Food and Drug Administration (FDA)) (55, 56).

### **Recommendations 16–17: Algorithms to rule out TB disease prior to giving TPT**

In 2011, WHO conducted a systematic review and IPD meta-analysis and recommended a symptom-screening rule of a combination of current cough, weight loss, night sweats and fever to exclude TB disease in adults and adolescents (57). The review showed that the rule had a sensitivity of 78.9% (95% CI: 58.3%–90.9%), a specificity of 49.6% (95% CI: 29.2%–70.1%) and a negative predictive value of 97.7% (95% CI: 97.4%–98.0%) at a TB prevalence of 5%. Most people living with HIV in studies included in the systematic review were not receiving ART.

During the 2018 update of the guidelines on TPT, a systematic review was undertaken to compare the performance of the four symptom screen in people living with HIV who were and were not receiving ART (58). Data from 17 studies were included in this analysis. The pooled sensitivity of the four symptom screen for people living with HIV on ART was 51.0% (95% CI: 28.4–73.2), and the specificity was 70.7% (95% CI: 47.7–86.4); in people living with HIV who were not receiving ART the pooled sensitivity was 89.3% (95% CI: 82.6–93.6), and the specificity was 27.2% (95% CI: 17.3–40.0). Two studies provided data on the addition of abnormal chest radiographic findings to the screening rule for people living with HIV on ART (59, 60). The pooled sensitivity was higher (84.6%, 95% CI: 69.7–92.9), but the specificity was lower (29.8%, 95% CI: 26.3–33.6) when compared with the symptom screen alone.

In all studies, the median prevalence of TB among people living with HIV on ART was 1.5% (interquartile range: 0.6–3.5%). At a 1% prevalence of TB, the negative predictive value of the symptom screening rule was 99.3%; addition of abnormal chest radiographic findings increased the negative predictive value by 0.2%. No studies of the addition of chest radiography to the symptom rule for pregnant women were found in the review.

During the development of the 2020 updated guidelines, the GDG agreed that in adults and adolescents living with HIV the four symptom screen – current cough, fever, weight loss or night sweats – is very useful for ruling out TB disease, regardless of ART use. Confirmation of TB infection would be desirable before starting TPT, although lack of access to TB infection testing should not be a barrier to TPT initiation. It noted the potential benefits of adding an abnormal chest radiographic finding to the rule, while recognizing that the improvement in performance was marginal. Moreover, increased use of chest radiography would add more false-positive results to the screening rule, which would require more investigations for TB and other illnesses. Therefore, the GDG reiterated that chest radiography may be added as an additional investigation only if it does not pose a barrier to the provision of preventive treatment for people living with HIV. It should not be a requirement for initiating preventive treatment. Although no study was found of the additive role of chest radiography in testing pregnant women, the GDG noted that pregnant women living with HIV could also benefit, as long as good practices are observed to prevent harmful radiation exposure to the fetus (61).

### **Recommendation 18: IGRA and TST for testing for TB infection**

In 2011, WHO issued recommendations on the use of IGRAs for the diagnosis of TB infection, including the blood-based QIAGEN QuantiFERON®-TB Gold (QFT-G), QIAGEN QuantiFERON-TB Gold In-Tube (QFT-GIT) and Oxford Immunotec T-SPOT®.TB (T-Spot) (62) assays. In 2018, WHO updated the recommendations to stipulate that the TST or IGRAs (or both) can be used to test for TB infection in LMICs. The recommendation on IGRA for use as a test for infection was first published in the 2018 WHO guidelines (63). A previous systematic review was updated to compare the predictive performance of IGRA and TST for identifying incident TB disease in countries with a TB incidence > 100 per 100 000 population (64). Only studies in which TST was compared with IGRA in the same population (“head-to-head” studies) were included. Relative risk ratios for TB for people who tested positive and those who tested negative with TST and IGRA were estimated.

Five prospective cohort studies were identified, with a total of 7769 participants; four were newly identified. Three of the studies were conducted in South Africa and two in India (45, 65–68). The studies included people living with HIV, pregnant women, adolescents, healthcare workers and household contacts. The pooled risk ratio estimate for TST was 1.49 (95% CI: 0.79–2.80), and that for IGRA was 2.03 (95% CI: 1.18–3.50). Although the estimate for IGRA was slightly higher than that for TST, the 95% CIs for the estimates for TST and IGRA overlapped and were imprecise. Furthermore, there was limited evidence for the predictive utility of the tests in specific at-risk populations.

The evidence reviewed and the recommendations apply only to the use of the two commercially available IGRAs (QuantiFERON®-TB Gold In-Tube and T-SPOT®.TB). The GDG concluded that the comparison of TST and IGRA in the same population does not provide strong evidence that one test should be preferred over the other for predicting progression to TB disease. TST may require significantly fewer resources than IGRA and may be more familiar to practitioners in resource-constrained settings; however, recurrent global shortages and stock-outs of TST reduce prospects for its scale-up in programmatic management of TPT.

The GDG cautioned that imperfect performance of these tests can lead to false-negative results, particularly for young children and immunocompromised individuals such as people living with HIV with low CD4 counts. Although some studies suggest otherwise (45, 50), the GDG maintained the past position that people living with HIV who have a positive test for TB infection benefit more from TPT than those who have a negative TB infection test (33, 63). TB infection testing can be used, where feasible, to identify such individuals. However, based upon evidence of moderate certainty, the GDG strongly emphasized that TB infection testing by TST or IGRA should not be a prerequisite to start TPT in people living with HIV and household contacts aged < 5 years, particularly in settings with a high TB incidence (e.g. > 100 TB cases per 100 000 population), given that benefits clearly outweigh the risks. A negative TB infection test in these two groups, as well as in HIV-negative infant household contacts, should be followed by a case-by-case assessment for the potential benefit and harms of TPT.

### **Recommendation 19: *Mycobacterium tuberculosis* antigen-based skin tests for testing for TB infection**

In 2022, WHO issued recommendations on the use of TBST for the diagnosis of TB infection. To inform these recommendations WHO commissioned a systematic review in 2021 of published and unpublished data on this new class of tests for TB infection not previously reviewed by WHO. The technologies that were included in the evaluation were Cy-Tb (Serum Institute of India, India), Diaskintest® (Generium, Russian Federation) and C-TST (formerly known as ESAT6-CFP10 test, Anhui Zhifei Longcom, China). This more recent class of TB infection tests is defined as in vivo skin tests for the detection of TB infection that use *M. tuberculosis*-specific antigens (ESAT-6 and CFP-10).

Based on available evidence, in 2022 the WHO GDG panel concluded that the diagnostic accuracy of TBSTs is similar to that of IGRAs and greater than that of the TST. The GDG panel expressed concerns about the certainty (quality) of evidence in many areas and the lack of longitudinal studies that include impact on people affected by important outcomes of TB. The risk of bias was primarily from non-blinded studies, and the quantity and quality of evidence varied among the different tests. For two of the three tests evaluated during the GDG meeting (Diaskintest® and C-TST), evidence on specificity was generated in high TB burden settings; therefore, additional analysis considered the concordance in specificity with existing WHO-recommended IGRAs. All three evaluated TBSTs have the potential to be used for the detection of TB infection and are recommended. No safety concerns were identified for the class of tests; however, evaluation and approval by the competent regulatory agencies for the individual products are essential before introduction of these in vivo tests. Although

the data were limited, based on the available evidence, the GDG members supported extrapolation of the recommendation for people living with HIV. Further details, including on safety, cost analysis and user perspective, can be found in the *WHO consolidated guidelines on tuberculosis. Module 3: diagnosis – tests for tuberculosis infection (15)*.

### **Recommendation 20: TPT regimens**

#### **Daily isoniazid monotherapy**

The efficacy of six months daily isoniazid monotherapy (6H) in different populations and settings has been shown in a number of systematic reviews (49, 69, 70). A systematic review of RCTs in people living with HIV showed isoniazid monotherapy reduces the overall risk for TB by 33% (RR 0.67; 95% CI: 0.51–0.87), and that the preventive efficacy reached 64% for people with a positive TST (RR 0.36; 95% CI: 0.22–0.61) (49). Furthermore, the efficacy of the 6-month regimen was not significantly different from that of 12 months' daily isoniazid monotherapy (RR 0.58; 95% CI: 0.3–1.12). A systematic review of RCTs also showed a significantly greater reduction in TB incidence among participants given the 6-month regimen than in those given a placebo (odds ratio (OR) 0.65; 95% CI: 0.50–0.83) (71). No controlled clinical trials were found of daily isoniazid monotherapy for 9 months (9H) versus 6H. Re-analysis and modelling of the United States Public Health Service trials of isoniazid conducted in the 1950s and 1960s, however, showed that the benefit of isoniazid increases progressively when it is given for up to 9–10 months and stabilizes thereafter (72). For this reason, 9H is retained as an alternative regimen to 6H in the recommended TPT options.

#### **Daily rifampicin plus isoniazid for 3 months (3HR)**

A systematic review updated in 2017 showed that the efficacy and the safety profile of 3–4 months' daily rifampicin plus isoniazid were similar to those of 6 months' isoniazid (71, 73). A previous GDG therefore strongly recommended that daily rifampicin plus isoniazid could be used as an alternative to isoniazid in settings with a TB incidence < 100 per 100 000 population (74).

#### **Daily rifampicin monotherapy for 4 months (4R)**

A previous systematic review conducted for the 2015 guidelines on TPT and updated in 2017, found similar efficacy for 3–4 months' daily rifampicin and 6H (OR 0.78; 95% CI: 0.41–1.46) (71, 73). The review also showed that individuals given rifampicin daily for 3–4 months had a lower risk for hepatotoxicity than those treated with isoniazid monotherapy (OR 0.03; 95% CI: 0.00–0.48).

In 2019, the GDG discussed the implications of using 4R in high TB burden settings based on findings from RCTs of 4R vs 9H that included adults and children from such countries (75–78). In study participants > 17 years, the difference in rate of confirmed TB between 4R and 9H (4R arm minus 9H arm) was < 0.01 cases per 100 person-years (95% CI: –0.14 to –0.16); the difference in treatment completion was 15.1% (95% CI: 12.7–17.4); the difference for Grade 3–5 adverse events was –1.1% (95% CI: –1.9 to –0.4). In individuals < 18 years, the difference in rate of TB disease between 4R and 9H was –0.37 cases per 100 person-years (95% CI: –0.88 to 0.14); the difference in treatment completion was 13.4% (95% CI: 7.5–19.3); the difference in risk for adverse events attributed to the medicine used and resulting in discontinuation was –0.0 (95% CI: –0.1 to 0.1).

#### **Daily rifapentine plus isoniazid for 1 month (1HP)**

In 2019, the GDG considered data from the only known published study of the 1HP regimen: a randomized, open-label, phase 3 non-inferiority trial comparing the efficacy and safety of 1HP with 9 months of isoniazid alone (9H) in people living with HIV in high TB prevalence settings or who had evidence of TB infection (78). Enrolment was restricted to individuals ≥ 13 years old who were not pregnant or breastfeeding. Non-inferiority would be shown if the upper limit of the 95% CI for the between-group difference in the number of events per 100 person-years was less than 1.25.

Among all study participants, the difference in incidence rate of TB (including deaths from any cause) between 1HP and 9H (1HP arm minus 9H arm) was  $-0.02$  per 100 person-years (95% CI:  $-0.35$  to  $0.30$ ); the relative risk (RR) for treatment completion of 1HP over 9H was  $1.04$  (95% CI:  $0.99$ – $1.10$ ); the RR for Grade 3–5 adverse events was  $0.86$  (95% CI:  $0.58$ – $1.27$ ); hazard ratio of death from any cause was  $0.75$  in favour of 1HP (95% CI:  $0.42$ – $1.31$ ); RR for emergence of resistance to isoniazid and rifampicin were, respectively,  $1.63$  (95% CI:  $0.17$ – $15.99$ ) and  $0.81$  (95% CI:  $0.06$ – $11.77$ ). Overall non-inferiority as defined by the study protocol was thus shown in the modified intention to treat (mITT) population. Non-inferiority was also shown for the sub-group with confirmed TB infection (incidence rate difference per 100 person-years was  $0.069$  ( $-0.830$  to  $0.690$ )), as well as in males and females, and among those on or without ART at start of study. The number of patients with  $CD4 < 250$  cells/ $mm^3$  was small, and neither inferiority nor non-inferiority of 1HP was shown in this stratum.

### **Weekly rifapentine plus isoniazid for 3 months (3HP)**

A systematic review was conducted for the 2018 guidelines update to compare the effectiveness of a 3-month weekly regimen of rifapentine plus isoniazid (3HP) with that of isoniazid monotherapy. The review covered four RCTs (79–82), which were analyzed for three subgroups, including adults living with HIV.

Two of the RCTs involved adults with HIV from South Africa, Peru and a number of countries with a TB incidence  $< 100$  per 100 000 population. No significant difference was found in the incidence of TB disease between participants given a 3HP and 6H or 9H (RR  $0.73$ ; 95% CI:  $0.23$ – $2.30$ ). Furthermore, the risk for hepatotoxicity was significantly lower with 3HP in adults living with HIV (RR  $0.26$ ; 95% CI:  $0.12$ – $0.55$ ). The 3HP regimen was also associated with a higher completion rate in all subgroups (adults with HIV: RR  $1.25$ ; 95% CI:  $1.01$ – $1.55$ ). One RCT included a comparison between 3HP and continuous isoniazid monotherapy in adult people living with HIV (79). No significant difference in TB incidence was found in an intention-to-treat analysis; however, a per-protocol analysis showed a lower rate of TB infection or death in participants given continuous isoniazid. In all the studies, 3HP was given under direct observation.

### ***Recommendation 21: 36 months of daily isoniazid monotherapy***

A systematic review and meta-analysis of three RCTs of people living with HIV in settings with high TB prevalence and transmission showed that continuous IPT can reduce the risk for TB disease by 38% more than 6 months' isoniazid (83). The effect was greater in people with a positive TST (49% for TB disease and 50% for death). In those with a negative TST, neither effect was significant, although the point estimate indicated a reduction in TB incidence of 27%. In two of the studies reviewed, ART was not used and in the third ART coverage was low at baseline but increased during the period of observation.

This recommendation is conditional and based on evidence that longer-term IPT significantly adds benefit to ART. The efficacy, safety and convenience of repeated treatment with shorter rifapentine regimens is being studied in people living with HIV in such settings. The definition of a high TB transmission setting should be established by the national authorities. Testing for TB infection is not a prerequisite for TPT in people living with HIV but its use is encouraged because people who are TST positive have a greater protective benefit from TPT. People living with HIV with a negative TST should not receive 36 months of daily IPT.

### **Special considerations**

Careful consideration should be given to the selection of TPT regimen for people living with HIV. Rifamycins induce certain cytochrome P-450 enzymes and may therefore accelerate the elimination of medicines that depend on this metabolic pathway, including several antiretroviral drugs (ARVs) (22).



These regimens should not be administered to people receiving protease inhibitors or nevirapine, including for HIV-exposed infants on TPT. Rifampicin can decrease the concentrations of other antiviral agents: atazanavir, darunavir, fosamprenavir, lopinavir, saquinavir and tipranavir. It should not be used with saquinavir/ritonavir. No dose adjustment is required when rifampicin is co-administered with efavirenz. The dose of dolutegravir (DTG) however needs to be increased to 50 mg twice daily when given together with rifampicin, a dose that is usually well tolerated and gives equivalent efficacy in viral suppression and recovery of CD4 cell count compared with efavirenz (22).

The 3HP regimen can be administered to individuals receiving efavirenz-based antiretroviral regimens without dose adjustment, according to a study of pharmacokinetics (84). Administration of rifapentine with raltegravir was found to be safe and well tolerated (85). A drug interaction study in healthy volunteers of DTG with once weekly HP reported toxicities in two of four participants (86). However results released more recently from a Phase 1/2 trial of 3HP and DTG in adults with HIV reported good tolerance and viral load suppression, no adverse events of Grade > 3 related to 3HP, and did not indicate that rifapentine reduced DTG levels sufficiently to require dose adjustment (87).

Pregnant women living with HIV are at risk for TB, which can have severe consequences for both the mother and the fetus, with increased risk of maternal and infant death (54). Pregnancy should not disqualify women living with HIV from receiving preventive treatment with medicines commonly used to treat TB that are generally considered safe for use in pregnancy, such as isoniazid and rifampicin (classified as Pregnancy Category C by the United States FDA (55, 56). There are limited data on the efficacy and safety of rifapentine during pregnancy. WHO currently recommends six months of isoniazid regimen as TPT for pregnant women living with HIV. A systematic review in 2019 identified one RCT and three non-randomized comparative observational studies that provided data on adverse pregnancy outcomes associated with the use of IPT among pregnant women living with HIV. While the RCT showed a higher risk of adverse pregnancy outcomes among those who initiated IPT during pregnancy (Mantel-Haenszel OR stratified by gestational age, 1.51; 95% CI: 1.09–2.10), all three other studies reported an overall OR < 1 suggesting the opposite (I<sup>2</sup>=80%, p=0.002). A meta-analysis from two observational studies that cited adjusted estimates and whose data could be pooled suggested lower risk for composite adverse pregnancy outcomes (OR 0.40; 95% CI: 0.20–0.74) (88). Based upon these findings the GDG concluded that there were insufficient grounds to change previous guidance or to develop a separate recommendation for the use of IPT in pregnant women living with HIV. The GDG considered that systematic deferral of IPT to the postpartum period would deprive people from its protective effect at a point when they are more vulnerable to TB.

Concurrent use of alcohol should be avoided with TPT.

Further details on drug-drug interactions for TPT and TB treatment regimens are provided in the *WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities* (7).

## 2.4.2 TB infection prevention and control

Comprehensive infection prevention and control (IPC) measures are essential to prevent TB transmission in clinical settings that provide services for people living with HIV (13). Whilst there are no recommendations specifically for TB IPC in HIV care settings, the general TB IPC recommendations are relevant and are listed in Box 2.1 below. Also of relevance are the WHO *Guidelines on core components of infection prevention and control programmes at the national and acute health care facility level* (89), which cover IPC measures preventing transmission of infectious diseases that apply to all healthcare settings.

## Box 2.1. WHO recommendations on TB infection prevention and control (13)

### Administrative controls

- Triage of people with TB signs and symptoms, or with TB disease, is recommended to reduce *M. tuberculosis* transmission to health workers (including community health workers), persons attending healthcare facilities or other persons in settings with a high risk of transmission (*conditional recommendation based on very low certainty in the estimates of effects*).
- Respiratory separation/isolation of people with presumed or demonstrated infectious TB is recommended to reduce *M. tuberculosis* transmission to health workers or other persons attending healthcare facilities (*conditional recommendation, based on very low certainty in the estimates of effects*).
- Prompt initiation of effective TB treatment of people with TB disease is recommended to reduce *M. tuberculosis* transmission to health workers, persons attending healthcare facilities or other persons in settings with a high risk of transmission (*strong recommendation, based on very low certainty in the estimates of effects*).
- Respiratory hygiene (including cough etiquette) in people with presumed or confirmed TB is recommended to reduce *M. tuberculosis* transmission to health workers, persons attending healthcare facilities or other persons in settings with a high risk of transmission (*strong recommendation, based on low certainty in the estimates of effects*).

### Environmental controls

- Upper-room germicidal ultraviolet (GUV) systems are recommended to reduce *M. tuberculosis* transmission to health workers, persons attending healthcare facilities or other persons in settings with a high risk of transmission (*conditional recommendation, based on moderate certainty in the estimates of effects*).
- Ventilation systems (including natural, mixed-mode, mechanical ventilation and recirculated air through high-efficiency particulate air [HEPA] filters) are recommended to reduce *M. tuberculosis* transmission to health workers, persons attending healthcare facilities or other persons in settings with a high risk of transmission (*conditional recommendation, based on very low certainty in the estimates of effects*).

### Respiratory protection

- Particulate respirators, within the framework of a respiratory protection programme, are recommended to reduce *M. tuberculosis* transmission to health workers, persons attending healthcare facilities or other persons in settings with a high risk of transmission (*conditional recommendation, based on very low-certainty in the estimates of effects*).

### 2.4.2.1 Summary of evidence and rationale

Healthcare facilities and congregate settings can present a high risk for acquiring TB (including MDR-TB) for people living with HIV as well as for healthcare workers. Evidence has shown an increased risk of TB due to HIV among healthcare workers as well as medical and nursing students with patient contact (90). Further, studies have highlighted the role of HIV in fuelling the TB epidemic among people in prison (91) and refugees and internally displaced people living in crowded camps or detention centres (92).

The *WHO consolidated guidelines on tuberculosis. Module 1: prevention – infection prevention and control (13)* comprises (i) a set of core components of IPC programmes, and (ii) a set of TB-specific interventions to reduce transmission of *M. tuberculosis* at the facility level. The core components include recommendations that should underpin all activities aimed at reducing healthcare-associated infections and antimicrobial resistance, including for TB, while the TB-specific interventions comprise recommendations on administrative controls, environmental controls and respiratory protection measures to reduce TB transmission in high-risk setting (13). Administrative controls aim to reduce the risk of exposure to persons with infectious TB; recommended interventions include triage of people with signs and symptoms of TB, respiratory isolation of people with presumed or demonstrated infectious TB, prompt initiation of effective treatment, and education on respiratory

hygiene including cough etiquette. Environmental controls aim to prevent the spread of infectious respiratory particles and reduce their concentration; recommended interventions include the use of upper-room germicidal ultraviolet (GUV) systems and maximizing ventilation. Respiratory protection measures comprise the use of personal protective equipment, including particulate respirators, in situations that pose a high risk of exposure to *M. tuberculosis*.

The *WHO consolidated guidelines on tuberculosis. Module 1: prevention – infection prevention and control (13)* provides recommendations and supporting evidence on preventing the transmission of TB in healthcare and other congregate settings, through administrative controls, environmental controls and respiratory protection measures, and the *WHO operational handbook on tuberculosis. Module 1: prevention – infection prevention and control (93)* provides implementation guidance. The *WHO Guidelines on core components of infection prevention and control programmes at the national and acute health care facility level (89)* provides additional detail on IPC measures preventing transmission of infectious diseases that apply to all healthcare settings.



# 3. Reduce the burden of HIV among people with presumptive or diagnosed TB

## 3.1 HIV testing services for people with presumptive and diagnosed TB

### WHO recommendations

#### Routine HIV testing services for people with presumptive and diagnosed TB

22. HIV testing services should be offered to all individuals with presumptive and diagnosed TB (*strong recommendation, low quality of evidence*). (10)

23. All household contacts of a person with HIV-associated TB should be offered HIV testing services (*strong recommendation, very low-quality evidence*). (19)

24. In settings of high HIV burden, all household and close contacts of people with TB should be offered HIV testing services (*strong recommendation, very low-quality evidence*). (19)

25. In settings of low HIV burden, all household members and close contacts of people with TB who have symptoms compatible with TB disease may be offered HIV testing services as part of their clinical evaluation (*conditional recommendation, very low-quality evidence*). (19)

26. Partner services should be offered to people with HIV-associated TB (*strong recommendation, moderate-quality evidence*). (23)

### 3.1.1 Background

Among people newly diagnosed with TB globally in 2022, 80% had a documented HIV test result (1). At the regional level, the highest percentages were achieved in the WHO African and European regions, at 89% and 93%, respectively, in 2022 (1). Globally 7.3% of people with a new episode of TB who had an HIV test result were living with HIV. HIV testing for people with diagnosed or presumptive TB offers a strategic entry point to a continuum of prevention, care, support and treatment of HIV and for TB. Offering HIV testing services along with TB contact tracing among close or family contacts of people with TB can help in the targeted scale-up of HIV testing, and in TB prevention due to early identification of those who do not know their HIV status, early initiation of ART and treatment of TB disease or TB infection when TB disease is ruled out.

### 3.1.2 Summary of evidence and rationale

#### ***Recommendations 22–26: HIV testing for people with presumptive and diagnosed TB and their contacts***

Evidence from a review of studies that informed these recommendations found that offering HIV testing, now referred to as “HIV testing services” (HTS) to people with presumptive and diagnosed TB and their contacts yields a high number of new diagnoses of HIV (70), also for those with presumptive TB who turn out not to have TB disease (94, 95). A systematic review of HIV prevalence among adults with signs and symptoms of TB, primarily among studies conducted in sub-Saharan Africa, showed substantial variability in the yield of HIV testing, with a median HIV prevalence from 19.2% (interquartile range: 8.3–40.4%) at the community level to 55.7% (interquartile range: 20.9–71.2%) at primary care level and 80.7% (73.8–84.6%) among hospital inpatients (96). Despite the low quality of evidence at the time of policy update in 2012, the GDG strongly recommended routine HIV testing and counselling to all people with presumptive and diagnosed TB as benefits of testing accrue to the individual, their partner, the family and the community at large.

The two recommendations on the provision of HIV testing services to household or close contacts of people with TB were based on a study in a concentrated HIV epidemic setting which showed a relatively high yield of HIV testing in contacts of people with TB, with a higher HIV prevalence rate (13.8%) among contacts of people with HIV-associated TB as compared with contacts of people who had TB but not HIV (2.5%). Furthermore, there was a 74% acceptance rate of HIV testing among contacts of people with TB (27).

HIV partner services is a process whereby a trained provider offers voluntary HTS to the partners and contacts of consenting HIV-positive individuals. WHO recommends a range of feasible and acceptable HIV partner service approaches to enable programmes to reach as many people with HIV as possible, which can be adapted according to setting, population, available resources and client preferences. Provider-assisted referral for HIV testing (also called assisted partner notification, index testing or family-based index case testing) is an effective method of delivering HIV partner services to people with TB living with HIV and is an important strategy for extending HIV testing, prevention and treatment services to their sexual partners and household members (27).

The provider can contact partner(s) by telephone or email or in person and offer them home-based HIV testing services or invite them to visit a facility to receive HIV testing services. Assistance in partner notification for sexual or drug-sharing partners, with shared disclosure and mutual support, may also improve the uptake of and adherence to ART, benefiting both the index individual and their partners regardless of HIV status (97). A strategic mix of facility-based, community-based, home-based and HIV self-testing options should be made available to ensure access to HIV testing services across these groups.

In all circumstances, HTS should be provided in accordance with WHO’s essential five Cs: consent, confidentiality, counselling, correct test results and connection or linkage to prevention, care and treatment. Age-appropriate algorithms should be in place for undertaking HIV testing in young children, and HIV testing should be family- and child-focused. All people diagnosed with HIV should be offered HIV prevention, diagnosis, treatment and care services, including ART. These services should be offered by TB programmes or through effective referral to HIV services.

## 3.2 HIV treatment and care for people living with HIV diagnosed with TB

### WHO recommendations

#### HIV treatment and care for people with TB

27. A package of interventions including screening, treatment and/or prophylaxis for major opportunistic infections, rapid ART initiation and intensified adherence support interventions should be offered to everyone presenting with advanced HIV disease (*strong recommendation, moderate-certainty evidence*). (24)

28. ART should be started as soon as possible within two weeks of initiating TB treatment, regardless of CD4 cell count, among people living with HIV.<sup>a</sup> (25)

Adults and adolescents (*strong recommendation, low- to moderate-certainty evidence*)

<sup>a</sup> Except when signs and symptoms of meningitis are present

29. Antiretroviral therapy is recommended for all patients with HIV and drug-resistant tuberculosis requiring second-line antituberculosis drugs, irrespective of CD4 cell count, as early as possible (within the first 8 weeks) following initiation of antituberculosis treatment (*strong recommendation, very-low-certainty evidence*). (16, 21)

30. Routine co-trimoxazole prophylaxis should be given to all people living with HIV with active TB disease regardless of CD4 cell count (*strong recommendation, high-certainty evidence*). (21)

#### Integrated delivery of care for HIV-associated TB

31. In settings with a high burden of HIV and TB, ART should be initiated in TB treatment settings, with linkage to ongoing HIV care and ART (*strong recommendation, very-low-certainty evidence*). (21)

### 3.2.1 Background

WHO defines advanced HIV disease for adults and adolescents (and children five years and older) as having a CD4 cell count of less than 200 cells/mm<sup>3</sup> or WHO clinical stage 3 or 4 disease (13). All children younger than five years living with HIV are considered to have advanced HIV disease. People presenting with advanced HIV disease are at high risk of death, even after starting ART, with the risk increasing with decreasing CD4 cell count, especially with CD4 cell count < 100 cells/mm<sup>3</sup> (98-101). Advanced HIV disease is also associated with increased healthcare costs (102), increased risk of opportunistic infections, immune reconstitution inflammatory syndrome (IRIS), incomplete immune reconstitution, higher viral reservoirs, higher inflammation, increased risk of HIV-related and non-HIV-related comorbidities, use of more healthcare services and more frequent monitoring needs (102).

To address the leading causes of morbidity and mortality among people with advanced HIV disease, WHO recommends that a package of interventions including screening, treatment and/or prophylaxis for major opportunistic infections, rapid ART initiation, and intensified adherence support interventions, be offered to everyone (all populations and age groups) living with HIV presenting with advanced HIV disease.

## 3.2.2 Summary of evidence and rationale

### **Recommendation 27: Package of interventions for people with advanced HIV disease**

Tuberculosis is a marker for advanced HIV disease and is well recognized as a leading cause of morbidity and mortality among people living with HIV. People with HIV and TB have a higher risk of mortality compared with people with TB who do not have HIV. Other causes of mortality among adults with advanced HIV disease globally include severe bacterial infections, cryptococcal disease, histoplasmosis, toxoplasmosis and *Pneumocystis jirovecii* pneumonia. Addressing these other comorbidities as part of an integrated package of care for people with HIV-associated TB can help to reduce mortality. TB and HIV programmes are therefore encouraged to work together to expand access to an integrated package of care for advanced HIV disease among people with TB.

This recommendation is based on two RCTs: REMSTART (103) and REALITY (104). REMSTART was conducted in the United Republic of Tanzania and Zambia, and randomized 1999 ART-naïve adults with HIV with CD4 count < 200 cells/mm<sup>3</sup> to either standard care or standard care plus enhanced clinic-based care with serum cryptococcal antigen (CrAg) screening, pre-emptive antifungal treatment for those who screened positive for CrAg, as well as additional community support (comprising a weekly home or community visit by trained and paid lay workers who delivered ART, provided adherence support and monitored participants for signs and symptoms of drug toxicity or new symptoms). The intervention group had 28% fewer people dying: mortality was 13% in the intervention group versus 18% in the group receiving standard care (103).

The REALITY study enrolled 1805 people living with HIV with CD4 counts < 100 cells/mm<sup>3</sup> in Kenya, Malawi, Uganda and Zimbabwe (104). Participants were mainly adults (72 were 5–17 years old). All underwent screening for TB disease at enrolment and were then randomized to the standard of care (co-trimoxazole) according to national guidelines or an enhanced prophylaxis package: 12 weeks of fluconazole (100 mg once daily), 12 weeks of a fixed-dose combination of co-trimoxazole (800 + 160 mg) + isoniazid (300 mg) + pyridoxine (25 mg) as a scored once-daily tablet, five days of 500 mg of azithromycin once daily and a single dose of 400 mg of albendazole. All drugs were started simultaneously, and ART was offered on the same day as the prophylaxis package. The enhanced prophylaxis package at the time of ART initiation reduced mortality by 27% (from 12.2% to 8.9%) over 24 weeks. Mortality from *Cryptococcus* species declined considerably, from 1.5% to 0.4%, and mortality from unascertained causes (most people died at home) declined from 6.0% to 3.8%. TB incidence was reduced by 28%, cryptococcal disease by 62% and hospitalization by 17% in the enhanced prophylaxis group versus the standard-of-care group. Most of the deaths in this study occurred within the first three weeks, highlighting the value of early prophylaxis for people with advanced disease (104).

### **Recommendations 28–29: Timing of ART initiation for HIV-associated TB**

Early initiation of ART for people living with HIV-associated TB is critical in reducing morbidity and mortality and preventing HIV transmission. HIV and TB programmes should ensure that people with TB who also have HIV are offered ART as early as possible, preferably within integrated services or within TB facilities (70). In 2010, WHO recommended that ART be started as soon as possible within eight weeks of initiating TB treatment, and in 2012, WHO recommended to initiate ART within two weeks among those with CD4 count ≤ 50 cells/mm<sup>3</sup>. Since 2021, WHO has recommended that ART should be started as soon as possible within two weeks of initiating TB treatment, regardless of CD4 cell count for people with drug-susceptible TB and in whom TB meningitis is excluded (27).

### **Timing of ART initiation for people living with HIV diagnosed with drug-susceptible TB**

This recommendation was informed by a systematic review and meta-analysis which identified nine trials that compared earlier ART to later ART initiation in people with HIV and TB. Four studies provided information on ART initiation within two weeks of starting TB treatment and between two and eight weeks from the commencement of TB treatment (105-108).

Moderate-certainty evidence indicates that mortality may be similar with ART initiated within two weeks of TB treatment versus ART initiated between two and eight weeks from the start of TB treatment (risk difference = -0.01; 95% CI: -0.06 to 0.04), which can be interpreted as one less death per 100 people, ranging from 6 fewer deaths to 4 more deaths per 100 people.

In a sub-analysis of people with a CD4 cell count less than or equal to 50 cells/mm<sup>3</sup>, low-certainty evidence indicated that mortality may not differ (3 fewer deaths per 100 people, 95% CI: from 10 fewer to 4 more, per 100 people) with ART initiated within two weeks of TB treatment versus between two weeks and eight weeks. Among the subgroup with CD4 cell count greater than 50 cells/mm<sup>3</sup>, low-certainty evidence indicated that mortality may be similar with earlier ART initiation (2 fewer deaths per 100, 95% CI: from 7 fewer to 4 more deaths per 100 people) with ART initiated within two weeks of TB treatment versus between two weeks and eight weeks.

Low-certainty evidence indicated that AIDS-defining events (for all CD4 cell counts) may be similar with ART initiation within two weeks of TB treatment initiation versus ART initiation between two and eight weeks from TB treatment initiation (2 fewer AIDS-defining events per 100 people, 95% CI: 6 fewer to 3 more per 100 people). Among people living with HIV with any CD4 cell count, low-certainty evidence indicated that viral load suppression also may not differ between people initiating ART within two weeks versus those initiating ART between two and eight weeks from TB treatment initiation (1 person with viral load suppression less per 100 people, 95% CI: from 3 fewer to 6 more per 100 people).

Very low-certainty evidence indicated that the incidence of IRIS events may be increased among people offered ART initiation within two weeks from TB treatment initiation versus those initiating ART between two and eight weeks from TB treatment initiation (7 more events per 100 people, 95% CI: 3 fewer events to 17 more events per 100 people). However, mortality related to IRIS was uncommon.

Therefore, based on the public health approach, and after weighing up the evidence on the potential harms of mortality, AIDS-defining events and IRIS against the benefits of early start of ART among all people living with HIV, WHO now recommends that people with HIV and drug-susceptible TB should start ART within two weeks of TB treatment initiation, regardless of CD4 cell-count.

Among people living with HIV with TB meningitis, immediate ART is associated with more severe adverse events compared with initiating ART two months after the start of TB treatment. The expert opinion of the GDG was that ART should be delayed by at least four weeks (and initiated within eight weeks) after TB treatment is initiated for TB meningitis, due to safety concerns.

Whilst there have been concerns about the possible increased risk of IRIS in DTG-based regimens, the INSPIRING trial (109) reported that the incidence of IRIS was similar between the DTG and efavirenz arms (in this small trial of safety and efficacy of rifampicin-based TB treatment and ART initiated within eight weeks). These findings were consistent with the 2019 network meta-analysis undertaken

to inform the 2019 WHO ARV drug guidelines update, with the safety of DTG examined among people with both TB and HIV. No deaths were reported in either arm (DTG versus efavirenz), and there were fewer severe adverse events in the DTG arm (odds ratio: 0.61, 95% CI: 0.17–2.24), with low-certainty evidence (110). The REALITY trial among people with advanced HIV disease included raltegravir as an additional option and also did not find any increased incidence of IRIS (104). However, close follow-up is advisable to monitor IRIS and other clinical events requiring prompt assessment and management, especially among children and pregnant or breastfeeding women. HIV programmes and service providers should establish mechanisms for adequate monitoring, including pharmacovigilance and surveillance for drug-drug interactions.

The review did not identify any studies that included pregnant and breastfeeding women. However, the GDG noted that earlier ART was unlikely to increase harm in this population, and the well-known and demonstrable benefits of earlier ART for both the mother's health and the child's health, with reduced vertical transmission of HIV, outweighed potential harm (21). Evidence was also limited regarding the timing of ART for those with drug-resistant TB and those receiving second- and third-line ART regimens.

### **Timing of ART initiation for people living with HIV diagnosed with drug-resistant TB**

Evidence was reviewed from 10 studies (111–120) to assess treatment outcomes when ART and second-line TB drugs were used together. None of the data were from RCTs. Individual participant data were available for 217 people with drug-resistant TB in total, of whom 127 received ART. The level of evidence in individual observational studies varied from a low- to a very low-certainty.

The pooled individual participant data from longitudinal cohort studies showed a lower risk of death and a higher likelihood of cure and resolution of TB signs and symptoms in individuals using ART compared with those not using ART (low-quality evidence). There is very low-quality evidence for other outcomes that were considered critical or important for decision-making (for example, severe adverse effects from second-line drugs for DR-TB, occurrence of sputum smear or culture conversion, interactions of ART with TB drugs and default from treatment). Available data did not allow assessment for a number of other outcomes of interest, namely, avoiding the acquisition of additional drug resistance, preventing TB transmission, sustaining relapse-free cure, establishing the optimal duration of MDR-TB treatment, avoiding unnecessary MDR-TB treatment, reducing cost and improving population access to appropriate care.

### **Recommendation 30: Co-trimoxazole prophylaxis for people living with HIV with diagnosed TB**

Co-trimoxazole is a fixed-dose combination of two broad-spectrum antimicrobial agents (sulfamethoxazole and trimethoprim) that prevents a range of secondary bacterial, fungal and protozoan infections. People living with HIV who also have TB disease should receive co-trimoxazole regardless of CD4 count. Evidence from RCTs, including areas with high levels of antibiotic resistance, has shown reduced mortality, morbidity and hospitalization with no significant increase in adverse events among people living with HIV who have smear-positive TB, regardless of their CD4 counts (121, 122). Other non-randomized and operational studies showed that co-trimoxazole preventive therapy is feasible (123, 124), safe and reduces mortality rates in people with TB (123, 125).

### **Recommendation 31: ART initiation in TB treatment settings and linkages to HIV care**

Coordination between TB and HIV programmes to deliver comprehensive and uninterrupted care for TB and HIV is important for the individual in need of care. It can also reduce out-of-pocket costs related to travelling to multiple appointments (126). Community engagement, patient education,



engagement of adherence counsellors and social workers and peer support for early recognition of adverse events and to support retention and adherence to co-treatment are also needed, as well as for continuation of ART after TB treatment completion.

A systematic review evaluating the effectiveness of delivering ART in TB treatment settings identified 19 observational studies, many of which showed increased uptake and timeliness of ART initiation. However, the data on mortality and TB treatment success were inconsistent. The same systematic review identified five observational studies evaluating the effectiveness of delivering TB treatment in HIV care settings. Two studies reported decreased mortality, and another showed comparable mortality rates. The TB treatment success rates and ART uptake were comparable across studies (44).

## 3.3 HIV prevention

### 3.3.1 Background

Whilst there are no recommendations on HIV prevention among people with presumptive and diagnosed TB that have been assessed using the GRADE methodology, programmatic guidance was developed as part of the development of the *WHO policy on collaborative TB/HIV activities (10)*, as listed below in Box 3.1.

#### **Box 3.1. Guidance on HIV prevention interventions for people with presumptive and diagnosed TB (10)**

- TB programmes should implement comprehensive HIV prevention strategies for people attending TB care and their partners, targeting sexual, parenteral or vertical transmission or should establish a referral linkage with HIV programmes to do so.
- HIV programmes and TB programmes should implement procedures to ensure access to voluntary, acceptable and confidential HIV testing services for healthcare providers and for reduction of occupational and nosocomial exposure to HIV infection in their services.
- All personnel working with people with presumptive and diagnosed TB, people living with HIV and people who use drugs should be able to assess risk factors for HIV infection and transmission and should provide comprehensive information and services to their clients to minimize their risks.
- HIV programmes and TB programmes should collaborate with harm reduction services to ensure universal access to comprehensive TB and HIV prevention, diagnosis, treatment and care as well as drug treatment services, including opioid agonist maintenance therapy for people who use drugs, in a holistic person-centred approach to maximize access and adherence within one setting as much as possible.
- TB programmes should ensure that all pregnant women living with HIV who attend TB services are referred to services for prevention of vertical transmission of HIV.

WHO's *Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, 2021 update (21)* recommend combination HIV prevention programmes, which use a mix of evidence-based biomedical, behavioural and structural interventions to have the greatest possible impact on reducing the number of people newly infected with HIV, designed according to the local HIV epidemiology and context. These approaches are also relevant for people with TB and their contacts who are at risk of, or living with, HIV. This section provides a brief overview of key HIV prevention considerations. Detailed guidance is published in

the *Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, 2021 update* (21).

### 3.3.2 Summary of evidence and rationale

ARV drugs play a key role in HIV prevention. People living with HIV who have an undetectable viral load and continue taking medication as prescribed have zero risk of transmitting HIV to their sexual partner(s). Furthermore, people living with HIV who have a suppressed but detectable (detected but  $\leq 1000$  copies/mL) viral load and are taking medication as prescribed have almost zero or negligible risk of transmitting HIV to their sexual partner(s) (127).

TB among pregnant women living with HIV is associated with a 2.5-fold increased risk of vertical transmission of HIV (128). ART during pregnancy and breastfeeding can effectively prevent mother-to-child transmission of HIV. ARV drugs taken by people without HIV as pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP) are also highly effective in preventing HIV acquisition. Other key biomedical measures to prevent HIV transmission include provision of male and female condoms; voluntary medical male circumcision; and harm reduction services, such as needle and syringe programmes and opioid agonist maintenance therapy, for people who inject drugs (21, 97). Behavioural interventions to prevent HIV include approaches to delivering targeted information and education about HIV prevention. Structural interventions aim to remove structural barriers to accessing services by addressing the social, legal and political environment that contribute to HIV transmission, for example by reducing stigma and discrimination, promoting gender equality and supporting economic and social empowerment.

It is essential to prevent transmission of HIV in healthcare settings through primary prevention measures such as standard precautions, injection safety, blood safety and safe waste disposal including of infectious and sharps waste, as well as through secondary prevention measures such as occupational PEP following needle stick injuries (10). Facility management in each healthcare facility should ensure that there is a suitable segregation, transport and storage system for waste management in place and that all staff adhere to these procedures, in accordance with standardized national systems for healthcare waste management (129). Details on safe management of healthcare waste are outlined in *Safe management of wastes from health-care activities: a summary* (129).

WHO has defined five key populations who are at higher risk of acquiring HIV: men who have sex with men, sex workers, people in prisons and other closed settings, people who inject drugs and trans and gender diverse people (30). Members of these populations are often at elevated risk of also acquiring TB, depending on the context, regardless of HIV status. Guidance specific to these key populations can be found in the WHO *Consolidated guidelines on HIV, viral hepatitis and STI prevention, diagnosis, treatment and care for key populations* (30), as well as the consolidated guidelines on *Integrating collaborative TB and HIV services within a comprehensive package of care for people who inject drugs* (97).



## 4. Monitoring and evaluation

Monitoring, evaluation and review provide the means to assess the quality, effectiveness, coverage and delivery of collaborative TB/HIV activities. It promotes a learning culture within and across programmes and ensures continuous improvement of interventions. Evidence from operational research (130, 131) has shown the importance of standardized monitoring and evaluation of collaborative TB/HIV activities to determine the impact of the activities and to ensure implementation and effective programme management. This section provides a brief overview of the monitoring and evaluation actions to support the implementation of collaborative TB/HIV activities. The section on HIV-associated TB within the accompanying operational handbook on TB and comorbidities provides further details, including a list of currently recommended core indicators to monitor collaborative TB/HIV activities (7). These indicators are drawn from WHO's guidance on TB surveillance ([*WHO Consolidated guidance on tuberculosis data generation and use. Module 1 – tuberculosis surveillance*], [WHO], in press [2023]) and from the WHO guidance on HIV strategic information (132). Further indicators can be found in *A guide to monitoring and evaluation for collaborative TB/HIV activities - 2015 revision* (133).

The monitoring and evaluation system for collaborative TB/HIV activities should be based on a strategy that includes clear goals, targets and guidelines for implementation of activities, as well as specific indicators to measure progress. It should also include plans for data collection and management, analysis and dissemination, and use of results for programme improvement (133). Recording and reporting formats for HIV-associated TB should be standardized and aligned with existing monitoring and surveillance systems. Standardized indicators should be measured regularly, in both the private and public health sectors, to inform decision-making for programme implementation. Electronic health records and the use of unique identifiers can greatly enhance recording and reporting processes, facilitate analysis and minimize duplication (132).

The national TB/HIV coordination mechanism plays a vital role in coordinating monitoring and evaluation, as well as in convening stakeholders for regular review at all levels of the healthcare system. The review process should include steps to (i) convene a body of stakeholders to review data at specified intervals; (ii) develop simple, standard core analysis plans for routinely collected data; (iii) adjust service delivery, supervision and resource allocation according to review findings and conclusions; and (iv) track the effect of these adjustments by ongoing regular review. The frequency with which reviews are carried out will vary with level of the healthcare system; at facility level, reviews should be conducted at least monthly, while at national level, reviews may be conducted quarterly or annually (132).

# 5. Research gaps

Research gaps related to HIV-associated TB were identified during the respective GDG meetings and are listed below. Further research gaps, some of which may have already been addressed, can be found in *Priority research questions for TB/HIV in HIV-prevalent and resource-limited settings* (134).

## 5.1 Find and treat TB

### 5.1.1 Screening for TB among people living with HIV

Research gaps relating to TB screening among people living with HIV are listed below. A more comprehensive list of research priorities on TB screening can be found in the consolidated guidelines on TB screening (12).

- Well-designed clinical trials are needed on the accuracy, effectiveness (including the impact on patient-important outcomes such as mortality), feasibility and cost implications of using the W4SS, CRP, CXR and mWRD to screen for TB across all HIV subpopulations in settings with low, medium and high burdens of HIV and TB with and without high ART coverage.
- Sub-populations of people living with HIV for whom further investigation is required would include, but not be limited to, inpatients, acute care service attendees, people with ART treatment failure, people newly diagnosed with HIV and enrolling in ART clinics, people living with HIV who are clinically stable and established on ART, pregnant women, and children and adolescents living with HIV.
- Evaluation is needed of the accuracy and effectiveness of complete screening and diagnostic algorithms, including symptom screening, CXR, CRP and mWRDs used in various combinations with diagnostic evaluation. Research into their effectiveness should include measures of the impacts on patient-important outcomes, such as mortality and treatment success.
- More data are needed on the effectiveness, cost-effectiveness, feasibility and acceptability, frequency and optimal periodicity of routine, regular screening with the W4SS, CRP, CXR and mWRD among people living with HIV.
- Evaluation is needed of the accuracy and predictive value of measuring CRP above any cut-off higher than 5 mg/L for TB screening in settings with different TB prevalences, when it is used either alone or in combination with other screening tests.
- Studies that explore the optimal placement of mWRDs for screening in antenatal care settings versus within ART clinics are also needed.
- Assessments of the potential for screening of people living with HIV with mWRDs using specimens other than sputum are needed. Further evidence is also required about the performance of CAD software stratified according to the characteristics of the individual being evaluated (e.g. by smear status, HIV status, age cohort, history of TB, smoking status, sex) to allow for better setting-specific and patient-specific calibration of CAD software.

## 5.1.2 Diagnosis of TB among people living with HIV

Research gaps relating to the initial tests for TB diagnosis that may be more pertinent for TB diagnosis among people living with HIV are listed below. The more comprehensive lists of research priorities relating to TB diagnosis are highlighted within the *WHO consolidated guidelines on tuberculosis. Module 3: diagnosis – rapid diagnostics for tuberculosis detection, 2021 update (14)*.

### **Xpert MTB/RIF and Xpert Ultra**

- Identification of an improved reference standard that accurately defines TB disease in children and paucibacillary specimens is needed because the sensitivity of all available diagnostics is suboptimal.
- Comparisons of different tests should be made, including Xpert MTB/RIF and Xpert Ultra, to determine which tests (or strategies) yield superior diagnostic accuracy. The preferred study design is one in which all participants receive all available diagnostic tests or are randomly assigned to receive a particular test. Studies should include children and people living with HIV. Future research should acknowledge the concern associated with culture as a reference standard and consider ways to address this limitation.
- Development of rapid point-of-care diagnostic tests for extrapulmonary TB is also needed. Research groups should focus on developing diagnostic tests and strategies that use readily available clinical specimens such as urine rather than specimens that require invasive procedures for collection.

### **Truenat™ MTB, MTB Plus and MTB-RIF Dx assays**

- Evaluations should be conducted to assess the diagnostic accuracy of Truenat™ (MTB, MTB Plus and MTB-RIF) in specific populations such as people living with HIV, former TB patients for pulmonary TB and extrapulmonary TB in adults and children.

### **Loop-mediated isothermal amplification (TB-LAMP)**

- Evaluations are needed of diagnostic algorithms in different epidemiological and geographical settings and populations (including people living with HIV).
- More rigorous studies should be conducted with higher quality reference standards (including multiple specimen types and extrapulmonary specimens) to improve confidence in specificity estimates.

### **Moderate complexity automated nucleic acid amplification test (NAATs)**

- Studies are needed of the diagnostic accuracy in specific populations (e.g. children, people living with HIV, and people with signs and symptoms of extrapulmonary TB) and in non-sputum samples.
- The impact of diagnostic technologies on clinical decision-making and outcomes that are important to affected individuals (e.g. cure, mortality, time to diagnosis and time to start treatment) should be assessed in all populations.
- Studies are needed on the use, integration and optimization of diagnostic technologies in the overall landscape of testing and care, as well as diagnostic pathways and algorithms.
- The effect of moderate complexity automated NAATs in fostering collaboration and integration between disease programmes should also be evaluated.

### **LF-LAM assay**

- Development of simple, more accurate tests based on LAM detection is needed, with the potential to be used for HIV-negative populations.

- Studies should be conducted on the use of LF-LAM in people living with HIV without signs and symptoms of TB.
- Evaluation of the use of LF-LAM in children and adolescents with HIV should be undertaken.
- Studies should be conducted to assess the combination of parallel use of LF-LAM and rapid qualitative CD4 cell count systems.
- Undertaking implementation research into the acceptance, scale-up and impact of LF-LAM in routine clinical settings is also needed.
- Qualitative research should be carried out on user perspectives of LF-LAM for feasibility, accessibility and equity issues.
- Implementation research on LF-LAM integrated into HIV care packages should also be undertaken.
- Evaluations are required to assess the performance of LF-LAM as the HIV epidemic evolves and a higher proportion of people living with HIV who are hospitalized may be on treatment with viral load suppression.
- Studies of the cost-effectiveness of LF-LAM are needed.
- Evaluation of other rapid LAM-based tests such as FujiLAM is also required.

### 5.1.3 TB treatment for people living with HIV

Research gaps relating to the TB treatment that may be more relevant for TB diagnosis among people living with HIV are listed below. The more comprehensive lists of research priorities relating to TB diagnosis are highlighted within the respective WHO consolidated guidelines on drug-susceptible (17) and drug resistant TB (16).

#### Drug susceptible TB

- More evidence is needed on the use of the 4-month regimen of isoniazid, rifapentine, moxifloxacin and pyrazinamide for drug susceptible pulmonary TB among people living with HIV on non-efavirenz-based ART regimens, and with a CD4 cell count less than 100 cells/mm<sup>3</sup>, and people with diabetes mellitus and people with a body weight of less than 40 kg.
- Operational research is needed to define how best to provide high-quality integrated TB and HIV interventions at facility and community levels in order to inform global and national policy and strategy development.
- The optimal steroid dose for TB meningitis (including different drug formulations) should be studied.
- The optimal steroid duration for TB meningitis should also be assessed and whether this duration differs between different grades of meningitis.
- Studies should be conducted on the different effects of steroids on people living with or without HIV, or who are being treated (or not) with ART.
- Additional work is needed on fixed dose formulations for drug-susceptible TB to further decrease the pill burden, especially among people with comorbidities.

#### Drug-resistant TB

- The efficacy, safety and tolerability of the bedaquiline, pretomanid, linezolid and moxifloxacin regimen (BPaLM/BPaL) should be studied for subpopulations for whom current data are limited or missing; that is, children aged below 14 years, people with extrapulmonary TB, people living with HIV with CD4 counts below 100 cells/mm<sup>3</sup>, and pregnant and lactating women.
- Inclusion and separate reporting of outcomes for longer regimens for multidrug- or rifampicin-resistant TB (MDR/RR-TB) are needed in key subgroups in RCTs, especially children, pregnant and breastfeeding women, and people living with HIV on treatment.

- Better understanding is needed of the role of delamanid in MDR-TB regimens, including in children (pharmacokinetics and pharmacodynamics), people living with HIV and pregnant women; mechanisms of development of drug resistance; and optimization of the treatment duration in both adults and children.
- High-quality studies should be conducted on treatment prolongation among people living with HIV with regimens for rifampicin-susceptible and isoniazid-resistant TB (Hr-TB).

## 5.2 TB prevention

Research gaps relating to TPT that are more pertinent for people living with HIV are listed below. The more comprehensive lists of research priorities relating to TB diagnosis are highlighted within the *WHO consolidated guidelines on tuberculosis. Module 1: prevention – tuberculosis preventive treatment* (22).

- Diagnostic tests with improved performance and predictive value for progression to TB disease are needed.
- The performance of LTBI tests should be evaluated in various risk groups to assess reinfection and to understand how best to use available tools in each population (e.g. combination or sequential use of TST and IGRA).
- Research to find shorter, better-tolerated TPT regimens than those currently recommended remains a priority.
- Trial data on 1HP in people living with HIV with low CD4 counts is needed, under different settings.
- Research on the direct comparison of 1HP vs. 3HP for safety, effectiveness, and cost-effectiveness will be useful.
- Pharmacokinetics studies should be conducted to establish interactions between rifamycin-containing regimens and other medicines, particularly ART, in both adults and children.
- Studies should be undertaken to assess the durability of protection of different preventive treatment regimens including long-acting injectables, in settings in which TB is endemic, and should include the efficacy of repeated courses of preventive treatment. Studies of the preferences of different stakeholders for different regimen characteristics would be helpful.
- RCTs with adequate power are urgently needed to update the recommendation on preventive treatment for contacts of people with MDR/RR-TB. Trials should be performed with both adult and paediatric populations and with at-risk populations such as people living with HIV. The composition, dosage and duration of preventive treatment regimens for MDR-TB should be optimized, and the potential role of newer agents with good sterilization properties should be investigated. The effectiveness and safety of preventive treatment for contacts of people with MDR-TB should be evaluated under operational conditions. Further evidence on the risk of contacts of people with MDR-TB for progression to TB disease will be important to understand the benefits of preventive treatment.
- Prospective randomized studies should be undertaken to determine the incremental benefits of routine monitoring of liver enzyme levels over education and clinical observation alone for preventing severe clinical adverse events, with stratification of the evidence by at-risk population. Programmatic data on maternal and pregnancy outcomes, inclusive of post-natal follow-up of the child, could supplement current knowledge about the safety of different LTBI regimens when used in pregnancy.
- Carefully designed studies including RCTs should be conducted to generate evidence on the effectiveness of context-specific interventions to enhance adherence and completion of TPT. These studies should address questions about how to integrate TPT into differentiated models of HIV service delivery.

## 5.3 Find and treat HIV

A more comprehensive list of research gaps is outlined within the consolidated guidelines for HIV (21) and the guidelines on diagnosing and managing histoplasmosis in people living with HIV (20) but a selection of research gaps more relevant for reducing the burden of HIV in people with presumptive or diagnosed TB are listed below.

- Studies are needed to assess how initiating ART among people with TB symptoms (excluding those with signs and symptoms of meningitis) affects mortality, TB and HIV outcomes, adverse events, IRIS, retention in care and ART adherence.
- The role of prophylactic corticosteroids to reduce the incidence of IRIS among people with TB and HIV in public health settings should also be studied, as well as the timing of this prophylaxis.
- Safety and tolerability of earlier ART initiation should also be evaluated among children, pregnant and breastfeeding women living with HIV and TB, and for people living with HIV who have drug-resistant TB.
- Studies are also needed of the long-term safety and tolerability of newer ARV drugs used in first-, second- or third-line regimens in the context of TB and HIV coinfection.
- More data are needed on the use of corticosteroids for people living with HIV who have low CD4 cell counts, to prevent IRIS.
- Improved long-term information on suppression of viral loads among people using formulations containing efavirenz 400 mg is needed, especially among pregnant women and individuals requiring TB co-treatment, particularly including rifampicin.
- The pharmacokinetics and safety of alternative dosing of tenofovir alafenamide (TAF) when used during TB co-treatment need to be better understood.
- Finally, additional research is needed to determine the outcomes of treating TB and histoplasmosis coinfection.

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# Annex 1. Current methodology for WHO guideline development

The formulation of WHO recommendations is based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. Once evidence has been synthesized through a systematic review approach, evidence reviewers use the GRADE methodology to categorize the quality of the evidence into four levels: high, moderate, low or very low (see Table A1.1). The starting point for rating the quality of evidence is always the study design, whereby evidence from RCTs is rated as high quality, while evidence from non-randomized or observational studies is rated as low quality. This value is then adjusted based on additional considerations. Five factors may lower the quality of evidence, namely: limitations in study design and execution, indirectness, imprecision, inconsistency and publication bias. Three factors may increase the quality of evidence from observational studies: dose-response gradient, direction of plausible bias and magnitude of the effect (7).

**Table A1.1 Quality of evidence in GRADE (1)**

Quality level	Definition and rationale
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

A recommendation may be strong or conditional (see Table A1.2), reflecting the degree to which the GDG is confident in the balance between desirable and undesirable consequences of implementing the recommendation. The strength of a recommendation is primarily determined by four main factors, namely: the confidence in the estimates of effect of the evidence (that is, the quality of the evidence as assessed through GRADE); the values and preferences related to the outcomes of an intervention or exposure; the balance of benefits and harms; and resource implications. Other considerations that may affect the strength of a recommendation include priority of the problem, equity and human rights, acceptability and feasibility.



**Table A1.2 Interpretation of strong and conditional recommendations for an intervention (1)**

<b>Audience</b>	<b>Strong recommendation</b>	<b>Conditional recommendation</b>
<b>Patients</b>	Most individuals in this situation would want the recommended course of action; only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Most individuals in this situation would want the suggested course of action, but many would not.
<b>Clinicians</b>	Most individuals should receive the intervention. Adherence to the recommendation could be used as a quality criterion or performance indicator.	Different choices will be appropriate for individual patients, who will require assistance in arriving at a management decision consistent with their values and preferences. Decision aids may be useful in helping individuals make decisions consistent with their values and preferences.
<b>Policymakers</b>	The recommendation can be adopted as policy in most situations.	Policymaking will require substantial debate and involvement of various stakeholders.

### **Annex 1 References**

1. WHO handbook for guideline development – 2<sup>nd</sup> ed. Geneva: World Health Organization; 2014 (<https://iris.who.int/handle/10665/145714>, accessed 17 October 2023).

## Annex 2. Summary of changes to recommendations

Table A2.1 summarizes changes to recommendations published in the 2012 *WHO policy on collaborative TB/HIV activities (1)*. The 2012 policy contained (i) WHO recommendations, which were formulated using the GRADE approach, and (ii) operational recommendations not assessed using the GRADE methodology, which were developed during consultation with key stakeholders.

Definitions of actions for changes to recommendations developed using the GRADE approach are as follows.

- New recommendation adopted: this relates to recommendations that have been newly developed by a guideline development group (GDG) since the publication of the 2012 TB/HIV policy.
- Updated recommendation adopted: this relates to recommendations that have been rephrased since the publication of the 2012 TB/HIV policy, by a GDG.
- Removed: recommendation is redundant or no longer valid and has hence been removed.
- Edited: recommendation has been edited for language.

**Table A2.1 Summary of changes to recommendations on HIV-associated TB**

Original recommendation in WHO policy on collaborative TB/HIV activities, 2012 (1)	Recommendation in the TB/HIV guidelines, 2023	Source guideline for 2023 TB/HIV guidelines
<b>Establish and strengthen the mechanisms for delivering integrated TB and HIV services</b>		
<b>A.1.1. HIV programmes and TB-control programmes or their equivalents should create and strengthen a joint national TB/HIV coordinating body, functional at regional, district, local and facility levels (sensitive to country-specific factors), with equal or reasonable representation of the two programmes including of people at risk of or affected by both diseases, and other line ministries (e.g. working on harm reduction and prison or mining health services).</b>	Incorporated in the <i>WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)</i>	Not applicable, not in the 2023 TB/HIV guidelines
<b>A.1.2. The TB/HIV coordination bodies should be responsible for the governance, planning, coordination and implementation of collaborative TB/HIV activities as well as mobilization of financial resources.</b>	Incorporated in the <i>WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)</i>	Not applicable, not in the 2023 TB/HIV guidelines

Original recommendation in WHO policy on collaborative TB/HIV activities, 2012 (1)	Recommendation in the TB/HIV guidelines, 2023	Source guideline for 2023 TB/HIV guidelines
<b>A.2.1. Surveillance of HIV should be conducted among TB patients and surveillance of active TB disease among people living with HIV in all countries, irrespective of national adult HIV and TB prevalence rates, in order to inform programme planning and implementation.</b>	Incorporated in the <i>WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)</i>	Not applicable, not in the 2023 TB/HIV guidelines
<b>A.2.2. Countries with unknown HIV prevalence rates among TB patients should conduct a seroprevalence (periodic or sentinel) survey to assess the situation.</b>	Incorporated in the <i>WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)</i>	Not applicable, not in the 2023 TB/HIV guidelines
<b>A.2.3. In countries with a generalized epidemic state, HIV testing and counselling of all patients with presumptive or diagnosed TB should form the basis of surveillance. Where this is not yet in place, periodic surveys or sentinel surveys are suitable alternatives.</b>	Incorporated in the <i>WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)</i>	Not applicable, not in the 2023 TB/HIV guidelines
<b>A.2.4. In countries with a concentrated epidemic state where groups at high risk of HIV infection are localized in certain administrative areas, HIV testing and counselling of all patients with presumptive or diagnosed TB in those administrative areas should form the basis of surveillance. Where this is not yet in place, periodic (special) or sentinel surveys every 2–3 years are suitable alternatives.</b>	Incorporated in the <i>WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)</i>	Not applicable, not in the 2023 TB/HIV guidelines
<b>A.2.5. In countries with a low-level epidemic state, periodic (special) or sentinel surveys are recommended every 2–3 years.</b>	Incorporated in the <i>WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)</i>	Not applicable, not in the 2023 TB/HIV guidelines
<b>A.2.6. HIV testing should be an integral part of TB prevalence surveys and antituberculosis drug resistance surveillance.</b>	Incorporated in the <i>WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)</i>	Not applicable, not in the 2023 TB/HIV guidelines
<b>A.3.1. Joint planning should clearly define the roles and responsibilities of HIV and TB control programmes in implementing, scaling-up and monitoring and evaluating collaborative TB/HIV activities at all levels of the health system.</b>	Incorporated in the <i>WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)</i>	Not applicable, not in the 2023 TB/HIV guidelines

Original recommendation in WHO policy on collaborative TB/HIV activities, 2012 (1)	Recommendation in the TB/HIV guidelines, 2023	Source guideline for 2023 TB/HIV guidelines
<p><b>A.3.2. HIV programmes and TB-control programmes should describe models to deliver client- and family-centred integrated TB and HIV services at facility and community levels compatible with national and local contexts.</b></p>	<p>Incorporated in the <i>WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)</i></p>	<p>Not applicable, not in the 2023 TB/HIV guidelines</p>
<p><b>A.3.3. HIV programmes and TB-control programmes should ensure resource mobilization and adequate deployment of qualified human resources to implement and scale-up collaborative TB/HIV activities in accordance with country-specific situations.</b></p>	<p>Incorporated in the <i>WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)</i></p>	<p>Not applicable, not in the 2023 TB/HIV guidelines</p>
<p><b>A.3.4. HIV programmes and TB-control programmes should formulate a joint training plan to provide pre-service and in-service training, and continuing competency-based education on collaborative TB/HIV activities for all categories of healthcare workers. Job descriptions of health workers should be developed and/or adapted to include collaborative TB/HIV activities.</b></p>	<p>Incorporated in the <i>WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)</i></p>	<p>Not applicable, not in the 2023 TB/HIV guidelines</p>
<p><b>A.3.5. HIV programmes and TB-control programmes should ensure that there is sufficient capacity to deliver health care (e.g. adequate laboratories, supplies of medicines, referral capacity, private sector involvement, focus on key populations such as women, children, people who use drugs and prisoners) and effectively implement and scale up collaborative TB/HIV activities.</b></p>	<p>Incorporated in the <i>WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)</i></p>	<p>Not applicable, not in the 2023 TB/HIV guidelines</p>
<p><b>A.3.6. HIV programmes and TB-control programmes should develop specific strategies to enhance the involvement of nongovernmental and other civil society organizations and individuals affected by or at risk of both diseases in developing and implementing policy and programmes, and the monitoring and evaluation of collaborative TB/HIV activities at all levels.</b></p>	<p>Incorporated in the <i>WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)</i></p>	<p>Not applicable, not in the 2023 TB/HIV guidelines</p>
<p><b>A.3.7. Well-designed TB/HIV advocacy activities that are jointly planned to ensure coherence between their messages and targeted at key stakeholders and decision-makers, should be carried out at global, national, regional and local levels.</b></p>	<p>Incorporated in the <i>WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)</i></p>	<p>Not applicable, not in the 2023 TB/HIV guidelines</p>

Original recommendation in WHO policy on collaborative TB/HIV activities, 2012 (1)	Recommendation in the TB/HIV guidelines, 2023	Source guideline for 2023 TB/HIV guidelines
<b>A.3.8. The joint communication strategies should ensure the mainstreaming of HIV components in TB communication and of TB components in HIV communication.</b>	Incorporated in the <i>WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)</i>	Not applicable, not in the 2023 TB/HIV guidelines
<b>A.3.9. All stakeholders of collaborative TB/HIV activities, including HIV programmes and TB-control programmes, should support and encourage operational research on country-specific issues to develop the evidence base for efficient and effective implementation of collaborative TB/HIV activities.</b>	Incorporated in the <i>WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)</i>	Not applicable, not in the 2023 TB/HIV guidelines
<b>A.4.1. HIV programmes and TB-control programmes should establish harmonized indicators and standard reporting and recording templates to collect data for monitoring and evaluation of collaborative TB/ HIV activities.</b>	Incorporated in the <i>WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)</i>	Not applicable, not in the 2023 TB/HIV guidelines
<b>A.4.2. Organizations implementing collaborative TB/HIV activities should embrace harmonized indicators and establish a reporting mechanism to ensure that their data are captured by the national monitoring and evaluation system.</b>	Incorporated in the <i>WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)</i>	Not applicable, not in the 2023 TB/HIV guidelines
<b>A.4.3. The WHO guide to monitoring and evaluation of collaborative TB/HIV activities and the three interlinked patient monitoring systems for HIV care/ ART, maternal and child health (MCH)/prevention of mother-to-child transmission (PMTCT) and TB/HIV should be used as a basis to standardize country-specific monitoring and evaluation activities.</b>	Incorporated in the <i>WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)</i>	Not applicable, not in the 2023 TB/HIV guidelines
<b>Reduce the burden of TB in people living with HIV and initiate early antiretroviral therapy (ART) (the Three I's for HIV/TB)</b>		
<b>NA</b>	New recommendation adopted: 1. People living with HIV should be systematically screened for TB disease at each visit to a health facility ( <i>strong recommendation, very low certainty of evidence</i> ).	<i>WHO consolidated guidelines on tuberculosis. Module 2: screening – systematic screening for tuberculosis disease (3)</i>

Original recommendation in WHO policy on collaborative TB/HIV activities, 2012 (1)	Recommendation in the TB/HIV guidelines, 2023	Source guideline for 2023 TB/HIV guidelines
<b>B.1.1. Adults and adolescents living with HIV should be screened for TB with a clinical algorithm; those who report any one of the symptoms of current cough, fever, weight loss or night sweats may have active TB and should be evaluated for TB and other diseases (strong recommendation, moderate quality of evidence).</b>	Updated recommendation adopted: 2. Among adults and adolescents living with HIV, systematic screening for TB disease should be conducted using the WHO-recommended four symptom screen and those who report any one of the symptoms of current cough, fever, weight loss or night sweats may have TB and should be evaluated for TB and other diseases ( <i>strong recommendation, moderate certainty of evidence</i> ).	<i>WHO consolidated guidelines on tuberculosis. Module 2: screening – systematic screening for tuberculosis disease (3)</i>
NA	New recommendation adopted: 3. Among adults and adolescents living with HIV, C-reactive protein using a cut-off of > 5mg/L may be used to screen for TB disease ( <i>conditional recommendation, low certainty of evidence</i> ).	<i>WHO consolidated guidelines on tuberculosis. Module 2: screening – systematic screening for tuberculosis disease (3)</i>
NA	New recommendation adopted: 4. Among adults and adolescents living with HIV, chest X-ray may be used to screen for TB disease ( <i>conditional recommendation, moderate certainty of evidence</i> ).	<i>WHO consolidated guidelines on tuberculosis. Module 2: screening – systematic screening for tuberculosis disease (3)</i>
NA	New recommendation adopted: 5. Among individuals aged 15 years and older in populations in which TB screening is recommended, computer-aided detection software programmes may be used in place of human readers for interpreting digital chest X-rays for screening and triage for TB disease ( <i>conditional recommendation, low certainty of evidence</i> ).	<i>WHO consolidated guidelines on tuberculosis. Module 2: screening – systematic screening for tuberculosis disease (3)</i>
NA	New recommendation adopted: 6. Among adults and adolescents living with HIV, molecular WHO-recommended rapid diagnostic tests may be used to screen for TB disease ( <i>conditional recommendation, moderate certainty of evidence</i> ).	<i>WHO consolidated guidelines on tuberculosis. Module 2: screening – systematic screening for tuberculosis disease (3)</i>
NA	New recommendation adopted: 7. Adult and adolescent inpatients with HIV in medical wards where the TB prevalence is > 10% should be tested systematically for TB disease with a molecular WHO-recommended rapid diagnostic test ( <i>strong recommendation, moderate certainty of evidence</i> ).	<i>WHO consolidated guidelines on tuberculosis. Module 2: screening – systematic screening for tuberculosis disease (3)</i>

Original recommendation in WHO policy on collaborative TB/HIV activities, 2012 (1)	Recommendation in the TB/HIV guidelines, 2023	Source guideline for 2023 TB/HIV guidelines
NA	<p>New recommendation adopted:</p> <p>8. In HIV-positive adults and children with signs and symptoms of disseminated TB, Xpert MTB/RIF may be used in blood, as an initial diagnostic test for disseminated TB (<i>conditional recommendation, very low certainty of evidence</i>).</p>	<p><i>WHO consolidated guidelines on tuberculosis. Module 3: diagnosis – rapid diagnostics for tuberculosis detection, 2021 update (4)</i></p>
NA	<p>New recommendation adopted:</p> <p>9. In inpatient settings: WHO strongly recommends using LF-LAM to assist in the diagnosis of active TB in HIV-positive adults, adolescents and children:</p> <ul style="list-style-type: none"> <li>• with signs and symptoms of TB (<i>pulmonary and/or extrapulmonary</i>) (<i>strong recommendation, moderate certainty in the evidence about the intervention effects</i>); or</li> <li>• with advanced HIV disease or who are seriously ill (<i>strong recommendation, moderate certainty in the evidence about the intervention effects</i>); or</li> <li>• irrespective of signs and symptoms of TB and with a CD4 cell count of less than 200 cells/mm<sup>3</sup> (<i>strong recommendation, moderate certainty in the evidence about the intervention effects</i>).</li> </ul>	<p><i>WHO consolidated guidelines on tuberculosis. Module 3: diagnosis – rapid diagnostics for tuberculosis detection, 2021 update (4)</i></p>
NA	<p>New recommendation adopted:</p> <p>10. In outpatient settings: WHO suggests using LF-LAM to assist in the diagnosis of active TB in HIV-positive adults, adolescents and children:</p> <ul style="list-style-type: none"> <li>• with signs and symptoms of TB (<i>pulmonary and/or extrapulmonary</i>) or <i>seriously ill</i> (<i>conditional recommendation, low certainty in the evidence about test accuracy</i>); and</li> <li>• irrespective of signs and symptoms of TB and with a CD4 cell count of less than 100 cells/mm<sup>3</sup> (<i>conditional recommendation, very low certainty in the evidence about test accuracy</i>).</li> </ul>	<p><i>WHO consolidated guidelines on tuberculosis. Module 3: diagnosis – rapid diagnostics for tuberculosis detection, 2021 update (4)</i></p>



Original recommendation in WHO policy on collaborative TB/HIV activities, 2012 (1)	Recommendation in the TB/HIV guidelines, 2023	Source guideline for 2023 TB/HIV guidelines
NA	<p>New recommendation adopted:</p> <p>11. In outpatient settings: WHO recommends against using LF-LAM to assist in the diagnosis of active TB in HIV-positive adults, adolescents and children:</p> <ul style="list-style-type: none"> <li>• without assessing TB symptoms (<i>strong recommendation, very low certainty in the evidence about test accuracy</i>);</li> <li>• without TB symptoms and unknown CD4 cell count or without TB symptoms and CD4 cell count greater than or equal to 200 cells/mm<sup>3</sup> (<i>strong recommendation, very low certainty in the evidence about test accuracy</i>); and</li> <li>• without TB symptoms and with a CD4 cell count of 100–200 cells/mm<sup>3</sup> (<i>conditional recommendation, very low certainty in the evidence about test accuracy</i>).</li> </ul>	<p><i>WHO consolidated guidelines on tuberculosis. Module 3: diagnosis – rapid diagnostics for tuberculosis detection, 2021 update (4)</i></p>
NA	<p>New recommendation adopted:</p> <p>13. People living with HIV with TB and histoplasmosis coinfection should receive TB therapy according to WHO treatment guidelines (<i>conditional recommendation, very low-certainty evidence</i>).</p>	<p><i>Diagnosing and managing disseminated histoplasmosis among people living with HIV (6)</i></p>
NA	<p>New recommendation adopted:</p> <p>14. In settings with a high burden of HIV and TB, TB treatment may be provided for people living with HIV in HIV care settings where a TB diagnosis has also been made (<i>strong recommendation, very low-certainty evidence</i>).</p>	<p><i>Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach (7)</i></p>
<p><b>B.1.2. Children living with HIV who have any of the following symptoms – poor weight gain, fever or current cough or contact history with a TB case – may have TB and should be evaluated for TB and other conditions. If the evaluation shows no TB, children should be offered IPT regardless of their age (<i>strong recommendation, low quality of evidence</i>).</b></p>	<p>Outside scope (<i>children</i>)</p>	<p>Not applicable, not in the 2023 TB/HIV guidelines</p>
NA	<p>New recommendation adopted:</p> <p>17. Chest radiography may be offered to people living with HIV on ART and preventive treatment be given to those with no abnormal radiographic findings (<i>conditional recommendation, low certainty in the estimates of effect</i>).</p>	<p><i>WHO consolidated guidelines on tuberculosis. Module 1: prevention – tuberculosis preventive treatment (8)</i></p>

Original recommendation in WHO policy on collaborative TB/HIV activities, 2012 (1)	Recommendation in the TB/HIV guidelines, 2023	Source guideline for 2023 TB/HIV guidelines
<p><b>B.1.3. TB patients with known positive HIV status and TB patients living in HIV-prevalent settings should receive at least 6 months of rifampicin treatment regimen (strong recommendation, high quality of evidence). The optimal dosing frequency is daily during the intensive and continuation phases (strong recommendation, high quality of evidence).</b></p>	<p>Updated recommendation adopted: 12. It is recommended that TB patients who are living with HIV should receive at least the same duration of daily TB treatment as HIV-negative TB patients (<i>strong recommendation, high certainty of evidence</i>)</p>	<p><i>WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-susceptible tuberculosis treatment (5)</i></p>
<p><b>B.2.1. Adults and adolescents living with HIV should be screened with a clinical algorithm; those who do not report any one of the symptoms of current cough, fever, weight loss or night sweats are unlikely to have active TB and should be offered IPT (strong recommendation, moderate quality of evidence).</b></p>	<p>Updated recommendation adopted: 16. Adults and adolescents living with HIV who are screened for TB according to a clinical algorithm and who report any of the symptoms of current cough, fever, weight loss or night sweats may have active TB and should be evaluated for TB and other diseases and offered preventive treatment if active TB is excluded (<i>strong recommendation, moderate certainty in the estimates of effect</i>).</p>	<p><i>WHO consolidated guidelines on tuberculosis. Module 1: prevention – tuberculosis preventive treatment (8)</i></p>
<p><b>B.2.2. Adults and adolescents who are living with HIV, have unknown or positive tuberculin skin test (TST) status and are unlikely to have active TB should receive at least 6 months of IPT as part of a comprehensive package of HIV care. IPT should be given to such individuals irrespective of the degree of immunosuppression, and also to those on ART, those who have previously been treated for TB and pregnant women (strong recommendation, high quality of evidence).</b></p>	<p>Updated recommendation adopted: 15. Adults and adolescents living with HIV who are unlikely to have active TB should receive TB preventive treatment as part of a comprehensive package of HIV care. Treatment should be given to those on antiretroviral treatment, to pregnant women and to those who have previously been treated for TB, irrespective of the degree of immunosuppression and even if LTBI testing is unavailable (<i>strong recommendation, high certainty in the estimates of effect</i>).</p> <p>20. The following options are recommended for the treatment of LTBI regardless of HIV status: 6 or 9 months of daily isoniazid, or a 3-month regimen of weekly rifapentine plus isoniazid, or a 3-month regimen of daily isoniazid plus rifampicin (<i>strong recommendation, moderate to high certainty in the estimates of effect</i>). A 1-month regimen of daily rifapentine plus isoniazid or 4 months of daily rifampicin alone may also be offered as alternatives (<i>conditional recommendation, low to moderate certainty in the estimates of effect</i>).</p>	<p><i>WHO consolidated guidelines on tuberculosis. Module 1: prevention – tuberculosis preventive treatment (8)</i></p>

Original recommendation in WHO policy on collaborative TB/HIV activities, 2012 (1)	Recommendation in the TB/HIV guidelines, 2023	Source guideline for 2023 TB/HIV guidelines
<p><b>B.2.3. Adults and adolescents living with HIV who have an unknown or positive TST status and who are unlikely to have active TB should receive at least 36 months of IPT. IPT should be given to such individuals irrespective of the degree of immunosuppression, and also those on ART, those who have previously been treated for TB and pregnant women (conditional recommendation, moderate quality of evidence).</b></p>	<p>Updated recommendation adopted: 21. In settings with high TB transmission, adults and adolescents living with HIV who have an unknown or a positive LTBI test and are unlikely to have active TB disease should receive at least 36 months of daily isoniazid preventive treatment (IPT). Daily IPT for 36 months should be given whether or not the person is on ART, and irrespective of the degree of immunosuppression, history of previous TB treatment and pregnancy in settings considered to have a high TB transmission as defined by national authorities (<i>conditional recommendation, low certainty in the estimates of effect</i>).</p>	<p><i>WHO consolidated guidelines on tuberculosis. Module 1: prevention – tuberculosis preventive treatment (8)</i></p>
<p><b>B.2.4. Tuberculin skin test (TST) is not a requirement for initiating IPT in people living with HIV (strong recommendation, moderate quality of evidence). People living with HIV who have a positive TST benefit more from IPT; TST can be used where feasible to identify such individuals (strong recommendation, high quality of evidence).</b></p>	<p>Incorporated in the <i>WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)</i></p>	<p>Not applicable, not in the 2023 TB/HIV guidelines</p>
<p>NA</p>	<p>New recommendation adopted: 18. Either the tuberculin skin test (TST) or interferon-gamma release assays (IGRAs) can be used to test for TB infection (<i>strong recommendation, very low certainty of the evidence</i>).</p>	<p><i>WHO consolidated guidelines on tuberculosis. Module 3: diagnosis – tests for tuberculosis infection (9)</i></p>
<p>NA</p>	<p>New recommendation adopted: 19. Mycobacterium tuberculosis antigen-based skin tests (TBSTs) may be used to test for TB infection (<i>conditional recommendation for the intervention, very low certainty of evidence</i>).</p>	<p><i>WHO consolidated guidelines on tuberculosis. Module 3: diagnosis – tests for tuberculosis infection (9)</i></p>
<p><b>B.2.5. Providing IPT to people living with HIV does not increase the risk of developing isoniazid-resistant TB. Therefore, concerns regarding the development of INH resistance should not be a barrier to providing IPT (strong recommendation, moderate quality of evidence).</b></p>	<p>Incorporated in the <i>WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)</i></p>	<p>Not applicable, not in the 2023 TB/HIV guidelines</p>
<p><b>B.2.6. Children living with HIV who do not have poor weight gain, fever or current cough are unlikely to have active TB (strong recommendation, low quality of evidence).</b></p>	<p>Outside scope (children)</p>	<p>Not applicable, not in the 2023 TB/HIV guidelines</p>

Original recommendation in WHO policy on collaborative TB/HIV activities, 2012 (1)	Recommendation in the TB/HIV guidelines, 2023	Source guideline for 2023 TB/HIV guidelines
<p><b>B.2.7. Children living with HIV who are more than 12 months of age and who are unlikely to have active TB on symptom-based screening and have no contact with a TB case should receive six months of IPT (10 mg/kg per day) as part of a comprehensive package of HIV prevention and care services (<i>strong recommendation, moderate quality of evidence</i>).</b></p>	<p>Outside scope (children)</p>	<p>Not applicable, not in the 2023 TB/HIV guidelines</p>
<p><b>B.2.8. In children living with HIV who are less than 12 months of age, only those who have contact with a TB case and who are evaluated for TB (using investigations) should receive six months IPT if the evaluation shows no TB disease (<i>strong recommendation, low quality of evidence</i>).</b></p>	<p>Outside scope (children)</p>	<p>Not applicable, not in the 2023 TB/HIV guidelines</p>
<p><b>B.2.9. All children living with HIV after successful completion of treatment for TB disease should receive isoniazid for an additional 6 months (<i>conditional recommendation, low quality of evidence</i>).</b></p>	<p>Outside scope (children)</p>	<p>Not applicable, not in the 2023 TB/HIV guidelines</p>
<p><b>B.2.10. All people living with HIV with CD4 counts of <math>\leq 350</math> cells/mm<sup>3</sup> irrespective of the WHO clinical stage should start ART (<i>strong recommendation, moderate quality of evidence</i>).</b></p>	<p>Removed: Redundant. ART is now recommended for all people living with HIV regardless of CD4 cell count.</p>	<p>Not applicable, not in the 2023 TB/HIV guidelines</p>
<p><b>B.3.1. HIV programmes and TB-control programmes should provide managerial direction at national and subnational levels for the implementation of TB infection control in healthcare facilities and congregate settings.</b></p>	<p>Incorporated in the <i>WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)</i></p>	<p>Not applicable, not in the 2023 TB/HIV guidelines</p>
<p><b>B.3.2. Each healthcare and congregate setting should have a TB infection control plan of the facility, preferably included into a general infection control plan, supported by all stakeholders, which includes administrative, environmental and personal protection measures to reduce transmission of TB in healthcare and congregate settings, and surveillance of TB disease among workers.</b></p>	<p>Incorporated in the <i>WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)</i></p>	<p>Not applicable, not in the 2023 TB/HIV guidelines</p>

Original recommendation in WHO policy on collaborative TB/HIV activities, 2012 (1)	Recommendation in the TB/HIV guidelines, 2023	Source guideline for 2023 TB/HIV guidelines
<p><b>B.3.3. Health-care workers, community health workers and care providers living with HIV should be provided with ART and IPT if eligible. Furthermore, they should be offered an opportunity for transfer to work in clinical sites that have the least risk of TB transmission.</b></p>	<p>Incorporated in the <i>WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)</i></p>	<p>Not applicable, not in the 2023 TB/HIV guidelines</p>
<p><b>Reduce the burden of HIV in patients with presumptive and diagnosed TB</b></p>		
<p><b>C.1.1. Routine HIV testing should be offered to all patients with presumptive and diagnosed TB (strong recommendation, low quality of evidence).</b></p>	<p>Edited: 22. HIV testing services should be offered to all individuals with presumptive and diagnosed TB (strong recommendation, low quality of evidence).</p>	<p><i>WHO policy on collaborative TB/HIV activities: Guidelines for national programmes and other stakeholders (1)</i></p>
<p><b>C.1.2. Partners of known HIV-positive TB patients should be offered voluntary HIV testing and counselling with mutual disclosure (strong recommendation for all people with HIV in all general HIV epidemic settings).</b></p>	<p>Edited: 26. Partner services should be offered to people with HIV-associated TB (strong recommendation, moderate-quality evidence).</p>	<p><i>WHO policy on collaborative TB/HIV activities: Guidelines for national programmes and other stakeholders (1)</i></p>
<p>NA</p>	<p>New recommendation adopted and edited: 24. In settings of high HIV burden, all household and close contacts of people with TB should be offered HIV testing services (strong recommendation, very low-quality evidence).</p>	<p><i>Guidance for national tuberculosis programmes on the management of tuberculosis in children, 2nd ed (10)</i></p>
<p>NA</p>	<p>New recommendation adopted and edited: 25. In settings of low HIV burden, all household members and close contacts of people with TB who have symptoms compatible with TB disease may be offered HIV testing services as part of their clinical evaluation (conditional recommendation, very low-quality evidence).</p>	<p><i>Guidance for national tuberculosis programmes on the management of tuberculosis in children, 2nd ed (10)</i></p>
<p>NA</p>	<p>New recommendation adopted and edited: 23. All household contacts of a person with HIV-associated TB should be offered HIV testing services (strong recommendation, very low-quality evidence).</p>	<p><i>Guidance for national tuberculosis programmes on the management of tuberculosis in children, 2nd ed (10)</i></p>

Original recommendation in WHO policy on collaborative TB/HIV activities, 2012 (1)	Recommendation in the TB/HIV guidelines, 2023	Source guideline for 2023 TB/HIV guidelines
NA	New recommendation adopted: 27. A package of interventions including screening, treatment and/or prophylaxis for major opportunistic infections, rapid ART initiation and intensified adherence support interventions should be offered to everyone presenting with advanced HIV disease ( <i>strong recommendation, moderate-quality evidence</i> ).	<i>Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach (7)</i>
<b>C.1.3. TB-control programmes should mainstream provision of HIV testing and counselling in their operations and routine services.</b>	Incorporated in the <i>WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)</i>	Not applicable, not in the 2023 TB/HIV guidelines
<b>C.2.1. TB-control programmes should implement comprehensive HIV prevention strategies for their patients and their partners, targeting sexual, parenteral or vertical transmission or should establish a referral linkage with HIV programmes to do so.</b>	Edited for language and incorporated into Box 1 – Guidance on HIV prevention interventions for people with presumptive and diagnosed TB.	Not applicable, not in the 2023 TB/HIV guidelines
<b>C.2.2. HIV programmes and TB-control programmes should implement procedures for voluntary, acceptable and confidential HIV counselling and testing for healthcare providers and for reduction of occupational and nosocomial exposure to HIV infection in their services.</b>	Edited for language and incorporated into Box 1 – Guidance on HIV prevention interventions for people with presumptive and diagnosed TB.	Not applicable, not in the 2023 TB/HIV guidelines
<b>C.2.3. All personnel working with presumptive and confirmed TB cases, people living with HIV and people who use drugs should be able to assess risk factors for HIV infection and transmission and should provide comprehensive information and services to their clients to minimize their risks.</b>	Edited for language and incorporated into Box 1 – Guidance on HIV prevention interventions for people with presumptive and diagnosed TB.	Not applicable, not in the 2023 TB/HIV guidelines
<b>C.2.4. HIV programmes and TB-control programmes should collaborate with harm reduction services to ensure universal access to comprehensive TB and HIV prevention, diagnosis, treatment and care as well as drug treatment services, including opioid substitution therapy, for people who use drugs, in a holistic person-centred approach to maximize access and adherence within one setting as much as possible.</b>	Edited for language and incorporated into Box 1 – Guidance on HIV prevention interventions for people with presumptive and diagnosed TB.	Not applicable, not in the 2023 TB/HIV guidelines

Original recommendation in WHO policy on collaborative TB/HIV activities, 2012 (1)	Recommendation in the TB/HIV guidelines, 2023	Source guideline for 2023 TB/HIV guidelines
C.2.5. TB-control programmes should ensure that vertical transmission of HIV is prevented by referring all HIV-positive pregnant women attending TB services to providers of services for prevention of vertical transmission of HIV for ART or prophylaxis as needed.	Edited for language and incorporated into Box 1 – Guidance on HIV prevention interventions for people with presumptive and diagnosed TB.	Not applicable, not in the 2023 TB/HIV guidelines
C.3. Routine co-trimoxazole preventive therapy should be administered in all HIV-infected patients with active TB disease regardless of CD4 counts ( <i>strong recommendation, high quality of evidence</i> ).	Updated recommendation adopted: 30. Routine co-trimoxazole prophylaxis should be given to all people living with HIV with active TB disease regardless of CD4 cell count ( <i>strong recommendation, high-certainty evidence</i> ).	<i>Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach (7)</i>
C.4.1. All people living with HIV who are diagnosed with TB should receive integrated services for prevention, diagnosis, treatment and care of TB and HIV.	Incorporated in the <i>WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)</i>	Not applicable, not in the 2023 TB/HIV guidelines
C.4.2. HIV programmes and TB-control programmes should ensure access to a continuum of comprehensive and integrated prevention, care and treatment for people living with HIV who are receiving or who have completed their antituberculosis treatment.	Incorporated in the <i>WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)</i>	Not applicable, not in the 2023 TB/HIV guidelines
C.5.1. ART should be started in all TB patients living with HIV irrespective of their CD4 counts ( <i>strong recommendation, low quality of evidence</i> ).	Removed: Redundant. ART is now recommended for all people living with HIV, regardless of CD4 count or TB status.	Not applicable, not in the 2023 TB/HIV guidelines
C.5.2. Antituberculosis treatment should be initiated first, followed by ART as soon as possible within the first 8 weeks of treatment ( <i>strong recommendation, moderate quality of evidence</i> ). Those HIV-positive TB patients with profound immunosuppression (e.g. CD4 counts less than 50 cells/mm <sup>3</sup> ) should receive ART immediately within the first 2 weeks of initiating TB treatment.	Updated recommendation adopted: 28. ART should be started as soon as possible within two weeks of initiating TB treatment, regardless of CD4 cell count, among people living with HIV. <sup>a</sup> Adults and adolescents ( <i>strong recommendation, low- to moderate-certainty evidence</i> ). <sup>a</sup> Except when signs and symptoms of meningitis are present.	<i>Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach (7)</i>
NA	New recommendation adopted: 29. Antiretroviral therapy is recommended for all patients with HIV and drug-resistant tuberculosis requiring second-line antituberculosis drugs, irrespective of CD4 cell count, as early as possible (within the first 8 weeks) following initiation of antituberculosis treatment ( <i>strong recommendation, very low-certainty evidence</i> ).	<i>WHO consolidated guidelines on tuberculosis. Module 4: treatment – drug-resistant tuberculosis treatment, 2022 update (11)</i>



Original recommendation in WHO policy on collaborative TB/HIV activities, 2012 (1)	Recommendation in the TB/HIV guidelines, 2023	Source guideline for 2023 TB/HIV guidelines
<b>C.5.3. Efavirenz should be used as the preferred non-nucleoside reverse transcriptase inhibitor (NNRTI) in patients starting ART while on antituberculosis treatment (strong recommendation, high quality of evidence).</b>	Removed: No longer valid. Dolutegravir is currently recommended as the preferred NNRTI in people living with HIV initiating ART, including for people with TB.	Not applicable, not in the 2023 TB/HIV guidelines
NA	New recommendation adopted: 31. In settings with a high burden of HIV and TB, ART should be initiated in TB treatment settings, with linkage to ongoing HIV care and ART (strong recommendation, very low-certainty evidence).	<i>Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach (7)</i>

ART: antiretroviral therapy; IGRA: interferon-gamma release assay; INH: isoniazid; IPT: isoniazid preventive treatment; LF-LAM: lateral flow lipoarabinomannan; LMIC: low- and middle income countries; LTBI: latent tuberculosis infection; MCH: maternal and child health; NNRTI: non-nucleoside reverse transcriptase inhibitor; PMTCT: prevention of mother-to-child transmission; TB: tuberculosis; TBSTs: Mycobacterium tuberculosis antigen-based skin tests; TST: tuberculin skin test; WHO: World Health Organization

## Annex 2 References

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7. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, 2021 update. Geneva: World Health Organization; 2021 (<https://apps.who.int/iris/handle/10665/342899>, accessed 31 August 2023).
8. WHO consolidated guidelines on tuberculosis. Module 1: prevention – tuberculosis preventive treatment. Geneva: World Health Organization; 2020 (<https://apps.who.int/iris/handle/10665/331170>, accessed 31 August 2023).
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11. WHO consolidated guidelines on tuberculosis. Module 4: treatment – drug-resistant tuberculosis treatment, 2022 update. Geneva: World Health Organization; 2022 (<https://apps.who.int/iris/handle/10665/365308>, accessed 31 August 2023).





For further information, please contact:

Global Tuberculosis Programme  
World Health Organization  
20, Avenue Appia CH-1211 Geneva 27  
Switzerland

Web site: [www.who.int/tb](http://www.who.int/tb)

