WHO consolidated guidelines on tuberculosis

Module 6: Tuberculosis and comorbidities

Second edition

World Health Organization

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Introduction

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 – 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 World Health Organization's (WHO's) global tuberculosis report *(1)*. In 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 considered comorbidities, and they may lead to poor TB treatment outcomes, lower health-related quality of life, or other suboptimal health or social outcomes (e.g. 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 (e.g. respiratory, musculoskeletal or neurological impairments), all of which require specialized care or rehabilitation during and after completion of TB treatment. Health-related risk factors and TB comorbidities require holistic people-centred care in the context of universal health coverage (UHC).

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 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. The aim is 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: at least 90% of the estimated number of people who develop TB are reached with quality-assured diagnosis and treatment; at least 90% of all people at high risk of developing TB are provided with preventive treatment, including about 15 million people living with HIV; and 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 UHC *(6)*, in 2021 and 2023, respectively, Member States also committed to assuring integrated people-centred services for TB, HIV, noncommunicable diseases and mental health.

Despite the provision of global guidance on interventions to address TB and key comorbidities, the uptake of such guidance has been variable. This publication – the *WHO consolidated guidelines on tuberculosis. Module 6: tuberculosis and comorbidities* – consolidates the latest evidence-based recommendations and provides a one-stop shop for countries to scale up people-centred care and prevention of TB and comorbidities. The guidelines 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 Web Annex A for the current approach). The GRADE approach was used to rate the certainty in the estimate of effect (i.e., the certainty 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 (7)* that applied at the time. For more details, please refer to the original guidelines.

These guidelines are accompanied by an operational handbook *(8)* 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; the operational handbook provides practical guidance to aid in the implementation of these recommendations by country programmes. The framework 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) *(9)*.

Objectives

The objectives of the consolidated guidelines are to:

- consolidate existing, updated and new 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 focused on HIV-associated TB. This second edition includes a section on undernutrition. Content for each section will be progressively updated and added.

References for the introduction[1]

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[1] All references were accessed on 15 April 2025.

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Abbreviations and acronyms

ART	antiretroviral therapy
CAD	computer-aided detection of TB-related abnormalities on chest radiography
CI	confidence interval
CRP	C-reactive protein
CXR	chest X-ray
DTG	dolutegravir
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
IGRA	interferon-gamma release assay
IPD	individual participant data
IPT	isoniazid preventive treatment
IRIS	immune reconstitution inflammatory syndrome
LF-LAM	lateral flow lipoarabinomannan
LMIC	low- and middle-income countries
LTBI	latent tuberculosis infection
MDR-TB	multidrug-resistant tuberculosis
mWRD	molecular WHO-recommended rapid diagnostic test
OR	odds ratio
RCT	randomized controlled trial
RR	risk ratio
TB	tuberculosis
TPT	TB preventive treatment
TST	tuberculin skin test
W4SS	WHO-recommended four symptom screen
WHO	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^3 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 *(1)*. 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 *(1)*. 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.[1] 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.

[1] 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^3 *(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^3 *(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^3 *(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^3 *(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).*

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).*

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).*

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).*[a]
Adults and adolescents *(strong recommendation, low- to moderate-certainty evidence)*
[a] 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).*

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 *(1)*.

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 *(1)*.[2] 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 *(1)*. 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 *(1)*.

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.[3]

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[2] 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.

[3] 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.

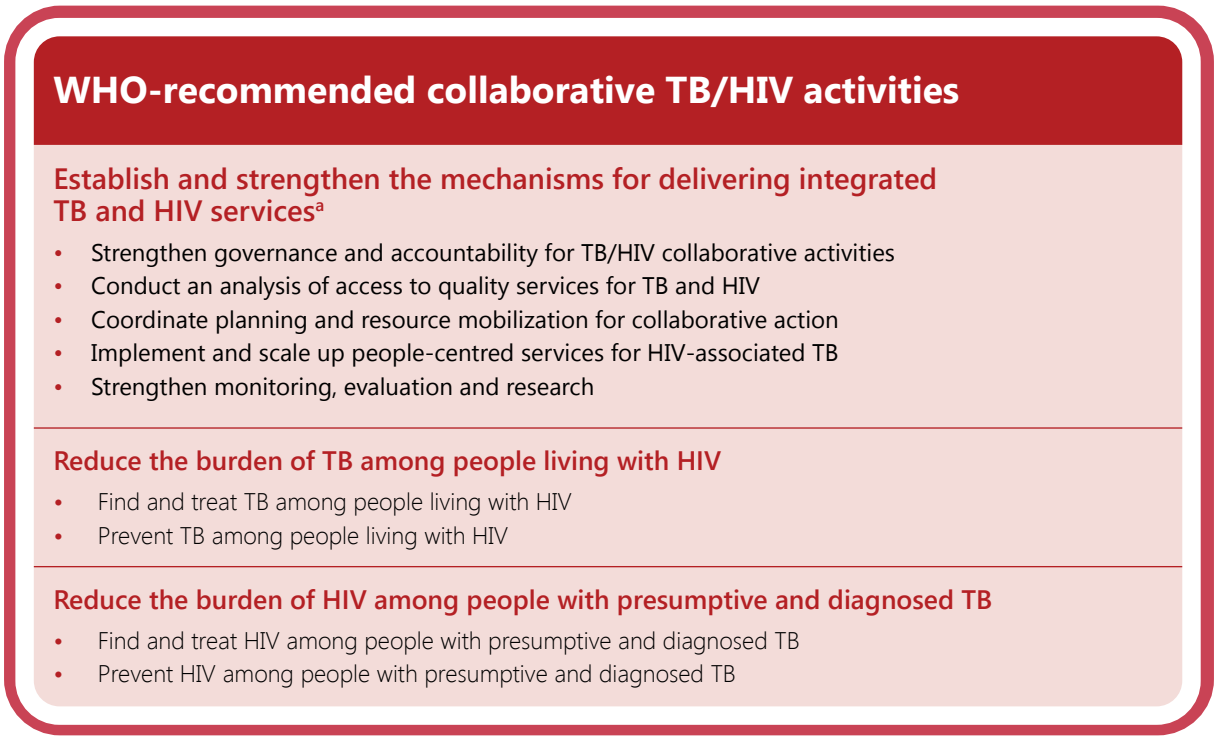
1.3 Scope

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.[4] 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.

[4] The TB knowledge sharing platform is available at: https://tbksp.org/.

Fig. 2. Updated 2024 collaborative TB/HIV activities



[a] 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.[5] 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.

[5] 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 *(1)*. 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 *(1)*. 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 ≤ 200 cells/μl, 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
Screening use case		
CAD software	0.90–0.92	0.23–0.66
CXR with human reader	0.82–0.93	0.14–0.63
Triage use case		
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[a]) as the initial diagnostic test. *(26)*
- In all facilities in all districts, the TB diagnostic algorithm requires use of a WRD[a] 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)*

[a] 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^3 *(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^3 *(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^3 *(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^3 *(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

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

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

[a] Specific to people living with HIV

[b] There is uncertainty about the use of Truenat™ MTB or MTB Plus in people living with HIV.

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

[d] 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) 14 (3505)	Se: 0.81 (95% CrI: 0.75–0.86) Sp: 0.98 (95% CrI: 0.97–0.99)	High High
Xpert Ultra for pulmonary TB	2 (149) 2 (430)	Se: 0.88 (95% CrI: 0.74–0.94) Sp: 0.95 (95% CrI: 0.79–0.96)	Low High
TB-LAMP for pulmonary TB	5 (370)	Se: 0.64 (95% CI: 0.49–0.76)[a] Sp: 0.99 (95% CI: 0.85–0.999)[a]	Very low Very low
Xpert® MTB/RIF blood	1 (9) 1 (65)	Se: 0.56 (95% CI: 0.21–0.86) Sp: 0.94 (95% CI: 0.85–0.98	Very low Very low

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

CrI: credible interval; TB: tuberculosis.
[a] sensitivity 27% (6–61%); specificity 99% (96–100%).
[b] sensitivity 38% (14–68%); specificity 99% (94–100%).
[c] sensitivity 64% (35–87%); specificity 82% (67–93%).
[d] sensitivity 75% (19–99%); specificity 100% (48–100%).
[e] sensitivity 24% (16–33%); specificity 94% (89–97%).
[f] sensitivity 30% (18–46%); specificity 93% (85–98%).
[g] sensitivity 18% (8–31%); specificity 95% (87–99%).
[h] 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^3 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 (I2=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 *(10)*, 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 *(21)*.

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 *(21)*.

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.[a] *(25)* Adults and adolescents *(strong recommendation, low- to moderate-certainty evidence)* [a] 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^3 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^3 *(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^3 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^3 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 *(10)*. 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^3. 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 *(21)*.

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^3, 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^3, 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 ≤ 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 TruenatTM (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^3, 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^3, 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 *(1)*.

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)*

Audience	Strong recommendation	Conditional recommendation
Patients	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.
Clinicians	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.
Policymakers	The recommendation can be adopted as policy in most situations.	Policymaking will require substantial debate and involvement of various stakeholders.

Annex 1 References

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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
Establish and strengthen the mechanisms for delivering integrated TB and HIV services		
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).	Incorporated in the *WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)*	Not applicable, not in the 2023 TB/HIV guidelines
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.	Incorporated in the *WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)*	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
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.	Incorporated in the *WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)*	Not applicable, not in the 2023 TB/HIV guidelines
A.2.2. Countries with unknown HIV prevalence rates among TB patients should conduct a seroprevalence (periodic or sentinel) survey to assess the situation.	Incorporated in the *WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)*	Not applicable, not in the 2023 TB/HIV guidelines
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.	Incorporated in the *WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)*	Not applicable, not in the 2023 TB/HIV guidelines
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.	Incorporated in the *WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)*	Not applicable, not in the 2023 TB/HIV guidelines
A.2.5. In countries with a low-level epidemic state, periodic (special) or sentinel surveys are recommended every 2–3 years.	Incorporated in the *WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)*	Not applicable, not in the 2023 TB/HIV guidelines
A.2.6. HIV testing should be an integral part of TB prevalence surveys and antituberculosis drug resistance surveillance.	Incorporated in the *WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)*	Not applicable, not in the 2023 TB/HIV guidelines
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.	Incorporated in the *WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)*	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
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.	Incorporated in the *WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)*	Not applicable, not in the 2023 TB/HIV guidelines
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.	Incorporated in the *WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)*	Not applicable, not in the 2023 TB/HIV guidelines
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.	Incorporated in the *WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)*	Not applicable, not in the 2023 TB/HIV guidelines
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.	Incorporated in the *WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)*	Not applicable, not in the 2023 TB/HIV guidelines
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.	Incorporated in the *WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)*	Not applicable, not in the 2023 TB/HIV guidelines
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.	Incorporated in the *WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)*	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
A.3.8. The joint communication strategies should ensure the mainstreaming of HIV components in TB communication and of TB components in HIV communication.	Incorporated in the *WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)*	Not applicable, not in the 2023 TB/ HIV guidelines
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.	Incorporated in the *WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)*	Not applicable, not in the 2023 TB/ HIV guidelines
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.	Incorporated in the *WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)*	Not applicable, not in the 2023 TB/ HIV guidelines
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.	Incorporated in the *WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)*	Not applicable, not in the 2023 TB/ HIV guidelines
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.	Incorporated in the *WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)*	Not applicable, not in the 2023 TB/ HIV guidelines
Reduce the burden of TB in people living with HIV and initiate early antiretroviral therapy (ART) (the Three I's for HIV/TB)		
NA	New recommendation adopted: 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).*	*WHO consolidated guidelines on tuberculosis. Module 2: screening – systematic screening for tuberculosis disease (3)*

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.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).	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 *(strong recommendation, moderate certainty of evidence).*	*WHO consolidated guidelines on tuberculosis. Module 2: screening – systematic screening for tuberculosis disease (3)*
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 *(conditional recommendation, low certainty of evidence).*	*WHO consolidated guidelines on tuberculosis. Module 2: screening – systematic screening for tuberculosis disease (3)*
NA	New recommendation adopted: 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).*	*WHO consolidated guidelines on tuberculosis. Module 2: screening – systematic screening for tuberculosis disease (3)*
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 *(conditional recommendation, low certainty of evidence).*	*WHO consolidated guidelines on tuberculosis. Module 2: screening – systematic screening for tuberculosis disease (3)*
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 *(conditional recommendation, moderate certainty of evidence).*	*WHO consolidated guidelines on tuberculosis. Module 2: screening – systematic screening for tuberculosis disease (3)*
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 *(strong recommendation, moderate certainty of evidence).*	*WHO consolidated guidelines on tuberculosis. Module 2: screening – systematic screening for tuberculosis disease (3)*

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: 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).*	*WHO consolidated guidelines on tuberculosis. Module 3: diagnosis – rapid diagnostics for tuberculosis detection, 2021 update (4)*
NA	New recommendation adopted: 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: • 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^3 *(strong recommendation, moderate certainty in the evidence about the intervention effects).*	*WHO consolidated guidelines on tuberculosis. Module 3: diagnosis – rapid diagnostics for tuberculosis detection, 2021 update (4)*
NA	New recommendation adopted: 10. In outpatient settings: 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^3 *(conditional recommendation, very low certainty in the evidence about test accuracy).*	*WHO consolidated guidelines on tuberculosis. Module 3: diagnosis – rapid diagnostics for tuberculosis detection, 2021 update (4)*

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: 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: • 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^3 *(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^3 *(conditional recommendation, very low certainty in the evidence about test accuracy).*	*WHO consolidated guidelines on tuberculosis. Module 3: diagnosis – rapid diagnostics for tuberculosis detection, 2021 update (4)*
NA	New recommendation adopted: 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).*	*Diagnosing and managing disseminated histoplasmosis among people living with HIV (6)*
NA	New recommendation adopted: 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).*	*Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach (7)*
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 *(strong recommendation, low quality of evidence).*	Outside scope *(children)*	Not applicable, not in the 2023 TB/HIV guidelines
NA	New recommendation adopted: 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).*	*WHO consolidated guidelines on tuberculosis. Module 1: prevention – tuberculosis preventive treatment (8)*

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.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)*.	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 *(strong recommendation, high certainty of evidence)*	*WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-susceptible tuberculosis treatment (5)*
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)*.	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 *(strong recommendation, moderate certainty in the estimates of effect).*	*WHO consolidated guidelines on tuberculosis. Module 1: prevention – tuberculosis preventive treatment (8)*
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).	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 *(strong recommendation, high certainty in the estimates of effect).* 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).*	*WHO consolidated guidelines on tuberculosis. Module 1: prevention – tuberculosis preventive treatment (8)*

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.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).	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 *(conditional recommendation, low certainty in the estimates of effect).*	*WHO consolidated guidelines on tuberculosis. Module 1: prevention – tuberculosis preventive treatment (8)*
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).	Incorporated in the *WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)*	Not applicable, not in the 2023 TB/HIV guidelines
NA	New recommendation adopted: 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).*	*WHO consolidated guidelines on tuberculosis. Module 3: diagnosis – tests for tuberculosis infection (9)*
NA	New recommendation adopted: 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).*	*WHO consolidated guidelines on tuberculosis. Module 3: diagnosis – tests for tuberculosis infection (9)*
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).*	Incorporated in the *WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)*	Not applicable, not in the 2023 TB/HIV guidelines
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).*	Outside scope (children)	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.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 *(strong recommendation, moderate quality of evidence)*.	Outside scope (children)	Not applicable, not in the 2023 TB/HIV guidelines
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 *(strong recommendation, low quality of evidence)*.	Outside scope (children)	Not applicable, not in the 2023 TB/HIV guidelines
B.2.9. All children living with HIV after successful completion of treatment for TB disease should receive isoniazid for an additional 6 months *(conditional recommendation, low quality of evidence)*.	Outside scope (children)	Not applicable, not in the 2023 TB/HIV guidelines
B.2.10. All people living with HIV with CD4 counts of ≤ 350 cells/mm³ irrespective of the WHO clinical stage should start ART *(strong recommendation, moderate quality of evidence)*.	Removed: Redundant. ART is now recommended for all people living with HIV regardless of CD4 cell count.	Not applicable, not in the 2023 TB/HIV guidelines
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.	Incorporated in the *WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)*	Not applicable, not in the 2023 TB/HIV guidelines
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.	Incorporated in the *WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)*	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.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.	Incorporated in the *WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)*	Not applicable, not in the 2023 TB/HIV guidelines
Reduce the burden of HIV in patients with presumptive and diagnosed TB		
C.1.1. Routine HIV testing should be offered to all patients with presumptive and diagnosed TB *(strong recommendation, low quality of evidence).*	Edited: 22. HIV testing services should be offered to all individuals with presumptive and diagnosed TB *(strong recommendation, low quality of evidence).*	*WHO policy on collaborative TB/HIV activities*: Guidelines for national programmes and other stakeholders *(1)*
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).*	Edited: 26. Partner services should be offered to people with HIV-associated TB *(strong recommendation, moderate-quality evidence).*	*WHO policy on collaborative TB/HIV activities*: Guidelines for national programmes and other stakeholders *(1)*
NA	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).*	*Guidance for national tuberculosis programmes on the management of tuberculosis in children, 2nd ed (10)*
NA	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).*	*Guidance for national tuberculosis programmes on the management of tuberculosis in children, 2nd ed (10)*
NA	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).*	*Guidance for national tuberculosis programmes on the management of tuberculosis in children, 2nd ed (10)*

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 *(strong recommendation, moderate-quality evidence)*.	*Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach (7)*
C.1.3. TB-control programmes should mainstream provision of HIV testing and counselling in their operations and routine services.	Incorporated in the *WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)*	Not applicable, not in the 2023 TB/HIV guidelines
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.	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.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.	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.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.	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.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.	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 *(strong recommendation, high quality of evidence).*	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 *(strong recommendation, high-certainty evidence).*	*Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach (7)*
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 *WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)*	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 *WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities (2)*	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 *(strong recommendation, low quality of evidence).*	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 *(strong recommendation, moderate quality of evidence).* Those HIV-positive TB patients with profound immunosuppression (e.g. CD4 counts less than 50 cells/mm^3) 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.[a] Adults and adolescents *(strong recommendation, low- to moderate-certainty evidence).* [a] Except when signs and symptoms of meningitis are present.	*Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach (7)*
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 *(strong recommendation, very low-certainty evidence).*	*WHO consolidated guidelines on tuberculosis. Module 4: treatment – drug-resistant tuberculosis treatment, 2022 update (11)*

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.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).*	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).*	*Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach (7)*

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

1. WHO policy on collaborative TB/HIV activities: guidelines for national programmes and other stakeholders. Geneva: World Health Organization; 2012 (https://apps.who.int/iris/handle/10665/44789, accessed 31 August 2023).
2. WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities. Geneva: World Health Organization; 2023.
3. WHO consolidated guidelines on tuberculosis. Module 2: screening – systematic screening for tuberculosis disease. Geneva: World Health Organization; 2021 (https://apps.who.int/iris/handle/10665/340255, accessed 31 August 2023).
4. WHO consolidated guidelines on tuberculosis. Module 3: diagnosis – rapid diagnostics for tuberculosis detection, 2021 update. Geneva: World Health Organization; 2021 (https://apps.who.int/iris/handle/10665/342331, accessed 31 August 2023).
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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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Undernutrition

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Abbreviations and acronyms

AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
BMI	body mass index
CI	confidence interval
DALY	disability-adjusted life year
FAO	Food and Agriculture Organization of the United Nations
FIES	Food Insecurity Experience Scale
GDG	guideline development group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HIV	human immunodeficiency virus
ICER	incremental cost–effectiveness ratio
IRR	incidence rate ratio
MD	mean difference
MDR-TB	multidrug-resistant tuberculosis
MoH	ministry of health
MUAC	mid-upper arm circumference
PICO	population, intervention, comparator, outcome
RATIONS	Reducing Activation of Tuberculosis by Improvement of Nutritional Status
RCT	randomized controlled trial
RR	risk ratio
SD	standard deviation
SDG	Sustainable Development Goal
TB	tuberculosis
TPT	tuberculosis preventive treatment
UI	uncertainty interval
UN	United Nations
WHO	World Health Organization

Definitions

Drug-susceptible TB: TB disease with no evidence of infection with a strain of *Mycobacterium tuberculosis* complex that is resistant to rifampicin or isoniazid *(1)*. This includes people for whom drug susceptibility testing was not done or for whom drug susceptibility testing shows a strain of *M. tuberculosis* complex that is susceptible to both rifampicin and isoniazid.

Extrapulmonary TB: TB disease involving organs other than the lung parenchyma or tracheobronchial tree (e.g. pleura, lymph nodes, digestive track, genitourinary tract, skin, joints and bones, or meninges) *(1)*.

Food assistance: A broad range of interventions that increase the options for households to access food, regardless of nutritional status. Examples include direct food provision, cash-based transfers, food vouchers and connection to broader social protection programmes.

Food insecurity: Lack of regular access to enough safe and nutritious food for normal growth and development, and an active and healthy life. This may be due to unavailability of food or lack of resources to obtain food *(2)*.

High energy–protein food: Food that aims to boost intake of energy and protein. This may include specially formulated food such as biscuits or shakes, or locally manufactured food.

Household contact: A person who shared the same enclosed living space as a person with TB for one or more nights or for frequent or extended daytime periods during the 3 months before the start of current treatment *(3)*.

Household of a person with TB: For the purposes of this guideline, a household where at least one member has been diagnosed with TB. This term also includes the person with TB.

Malnutrition: Deficiencies or excesses in nutrient intake, imbalance of essential nutrients or impaired use of nutrients. The double burden of malnutrition comprises both undernutrition and overweight and obesity, as well as micronutrient deficiencies and diet-related noncommunicable diseases *(4)*.

Micronutrients: Vitamins and minerals needed by the body in very small amounts. They enable the body to produce enzymes, hormones and other substances that are essential for proper growth and development *(5)*.

Mild undernutrition[1] (otherwise referred to as mild thinness in adults): Defined as a body mass index (BMI) of 17.00–18.49 kg/m^2 *(6)*. This term is not used for infants, children or adolescents.

[1] The word "undernutrition" has been used in the interest of uniformity of language across populations.

Moderate undernutrition[2] (commonly referred to as moderate acute malnutrition in children, and moderate thinness in adults):

- In infants and children aged below 5 years, this is defined as moderate wasting; that is, a weight-for-height Z-score or weight-for-length Z-score between –3 standard deviations (SD) and less than –2 SD (≥ –3 SD to < –2 SD) and/or a mid-upper arm circumference (MUAC) of between 115 mm and less than 125 mm (≥115 to <125 mm), and no nutritional oedema *(7)*.
- In children and adolescents aged 5–19 years, a BMI-for-age-and-sex Z-score between –3 SD and less than –2 SD (≥ –3 SD to < –2 SD) *(6)*.
- In adults aged over 19 years, a BMI of 16.00–16.99 kg/m^2 *(6)*.

Multidrug-resistant TB: TB disease caused by a strain of *M. tuberculosis* complex that is resistant to both rifampicin and isoniazid *(1)*.

Multiple micronutrients: In this document, a single administration of two or more micronutrients.

Nutritional assessment: An assessment that allows health care providers to systematically evaluate the overall nutritional status of individuals, diagnose malnutrition, identify underlying pathologies that lead to malnutrition and plan necessary interventions *(8)*.

Nutritional intervention: In this document, purposeful actions that are intended to increase macronutrient intake and improve the nutritional or clinical status of an individual. Examples include direct food provision, specially formulated foods, cash-based transfers and food vouchers. Although broadly recognized as a nutritional intervention, the provision of micronutrients is addressed separately in this guideline.

Pulmonary TB: TB disease involving the lung parenchyma or the tracheobronchial tree *(1)*. Note: A case with both pulmonary and extrapulmonary TB should be recorded and counted as a case of pulmonary TB for surveillance purposes.

Severe undernutrition[2] (commonly referred to as severe acute malnutrition in children and severe thinness in adults):

- In infants and children aged below 5 years, defined as nutritional oedema and/or severe wasting; that is, a weight-for-height Z-score or weight-for-length Z-score of less than –3 SD and/or a MUAC of less than 115 mm *(7)*.
- In children and adolescents aged 5–19 years, a BMI-for-age-and-sex Z-score of less than –3 SD *(6)*.
- In adults aged over 19 years, a BMI of less than 16 kg/m^2 *(6)*.

[2] The word "undernutrition" has been used in the interest of uniformity of language across populations.

Specially formulated foods: Foods that have been specifically designed, manufactured, distributed and used according to Codex Alimentarius for either special medical purposes *(9)* or special dietary uses *(10)* (e.g. ready to use therapeutic foods [RUTF], used to treat children with severe acute malnutrition; ready to use supplementary foods [RUSF], and fortified blended foods – used to supplement children with moderate acute malnutrition).

Stunting: Length-for-age or height-for-age Z-score of less than –2 SD according to the World Health Organization child growth standards *(11)*.

Tuberculosis (TB): The disease state caused by *M. tuberculosis* complex. Also referred to as TB "disease" to distinguish it from TB infection *(1)*. The term TB refers to all forms and includes pulmonary TB, extrapulmonary TB, drug-susceptible TB and drug-resistant TB.

Tuberculosis 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"; however, because infection cannot always be considered latent, the term TB infection is now used instead. There is no gold standard test for direct identification of *M. tuberculosis* infection in humans *(3)*.

Undernutrition: Includes wasting (low weight-for-height and/or nutritional oedema), stunting (low height-for-age) and underweight (low weight-for-age or low BMI-for-age or low BMI) and micronutrient deficiencies *(4, 7)*. In this document, "undernourished" refers to the state of undernutrition.

Underweight:

- In infants, children and adolescents aged up to 19 years, a weight-for-age Z-score of less than –2 SD *(4)*.
- In adults, a BMI of less than 18.5 kg/m^2 *(12)*.

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Executive summary

In 2023, an estimated 10.8 million people fell ill with tuberculosis (TB), among whom 1.25 million died from the disease *(1)*. Undernutrition is a key risk factor that drives the TB epidemic and each year it accounts for an estimated 0.96 million (95% uncertainty interval 0.4–1.1 million) episodes of TB *(1)*. The prevalence of undernutrition in people with TB is estimated to be 48% *(2)*. People with undernutrition are more than twice as likely to fall ill from TB *(3)*, and to have a higher risk of poor treatment outcomes such as death and loss to follow-up, compared with those who do not have undernutrition *(4, 5)*.

The World Health Organization's (WHO's) End TB Strategy includes targets to reduce TB incidence by 80% and TB deaths by 90% by the year 2030, relative to baseline levels in 2015 *(6)*. Addressing comorbidities and the determinants of TB, including undernutrition, is a central component of that strategy. In September 2023, in the political declaration of the United Nations (UN) high-level meeting on the fight against TB, Member States committed to strengthening comprehensive care and integrating within primary health care the systematic screening, prevention, treatment and care of TB and of related health conditions such as undernutrition *(7)*.

The 2013 WHO publication *Guideline: nutritional care and support for patients with tuberculosis (8)* included recommendations on nutritional assessment and counselling, management of moderate and severe acute malnutrition, micronutrient supplementation for people with TB, and nutritional assessment and support for household contacts of people with TB. Since 2013, there has been new evidence on the relationship between TB and undernutrition, on supplementation with macronutrients and micronutrients for people with TB, and on food assistance to prevent TB among household contacts of people with TB. In 2023, WHO commissioned a series of systematic reviews on nutritional interventions for people with TB and their household contacts, and in June–July 2024, WHO convened a guideline development group (GDG) to review WHO's recommendations on TB and undernutrition, in light of the available evidence.

The specific objectives of the undernutrition section of this document are to:

- reduce the burden of undernutrition among people with TB; and
- reduce the burden of TB among people with undernutrition and in food insecure settings.

The anticipated impacts are as follows: improved identification of undernutrition in people with TB and their household contacts; improved clinical outcomes in people with TB and undernutrition; reduced TB incidence in households of people with TB in food insecure settings; timely identification and management of TB in people with undernutrition or who experience food insecurity; and reduced out-of-pocket costs relating to nutrition for households of people with TB.

It is envisaged that implementation of these guidelines will contribute to the achievement of the End TB Strategy, to Sustainable Development Goal (SDG) 2 (zero hunger) and SDG 3 (good health and well-being).

The recommendations in this section replace those included in the 2013 guidelines. This document consolidates existing recommendations and new recommendations developed in 2024 on TB and undernutrition. The new, updated and retained recommendations on TB and undernutrition are summarized in Table A.

This section of the guidelines targets policy-makers in ministries of health and social affairs, as well as international technical and funding organizations, researchers, nongovernmental organizations and civil society organizations involved in nutrition, food assistance and social assistance. It is expected that these recommendations will also be used by health professionals, including doctors, nurses, community health workers and educators who provide TB and nutritional care and support in both public and private sectors.

Table A. Recommendations relating to undernutrition in the *WHO consolidated guidelines on tuberculosis. Module 6: tuberculosis and comorbidities*

Nutritional assessment and counselling in people with TB and their household contacts
1 At diagnosis and throughout treatment, all individuals with TB should be offered nutritional assessment and appropriate counselling based on their nutritional status. *(Existing recommendation with language edit: strong recommendation, no direct evidence available)*
2 Household contacts of people with TB should be offered nutritional assessment and counselling as part of contact tracing. If undernutrition is identified, it should be managed according to WHO guidance. **NEW** *(New recommendation: strong recommendation, low certainty of evidence)*
Nutritional interventions to improve clinical outcomes for people with TB
3 Nutritional interventions[a] should be offered to individuals with TB who have severe, moderate or mild undernutrition, as part of a comprehensive package of TB care. **NEW** *(New recommendation: strong recommendation, low–moderate certainty of evidence)*
4 A package of treatment adherence interventions[b] may be offered for patients on TB treatment in conjunction with the selection of a suitable treatment administration option. *(Existing recommendation: conditional recommendation, low certainty of evidence)*
5 One or more of the following treatment adherence interventions (complementary and not mutually exclusive) may be offered to patients on TB treatment or to health care providers: a) tracers or digital medication monitor *(conditional recommendation, very low certainty of evidence)*; b) material support to patient[c] *(conditional recommendation, moderate certainty of evidence)*; c) psychological support to patient *(conditional recommendation, low certainty of evidence)*; d) staff education (conditional recommendation, low certainty of evidence). *(Existing recommendation)*

a Examples of nutritional interventions are direct food provision, specially formulated foods and financial support.

b Treatment adherence interventions include social support such as: patient education and counselling; material support (e.g. food, financial incentive and transport fees); psychological support; tracers such as home visits or digital health communications (e.g. SMS, telephone calls); medication monitor; and staff education. The interventions should be selected on the basis of the assessment of the individual patient's needs, provider's resources and conditions for implementation.

c Material support can be food or financial support such as: meals, food baskets, food supplements, food vouchers, transport subsidies, living allowance, housing incentives, or financial bonus. This support addresses indirect costs incurred by patients or their attendants in order to access health services and, possibly, tries to mitigate consequences of income loss related to the disease.

Food assistance to prevent TB in household contacts

6 In settings of food insecurity, food baskets in combination with multiple micronutrient supplements should be offered to all households of people with TB.[d] **NEW**

(New recommendation: strong recommendation, moderate certainty of evidence)

Micronutrient supplementation in people with TB

7 Vitamin D supplementation may be provided to people with TB in the context of rigorous research. **NEW**

(New recommendation: conditional recommendation, low certainty of evidence)

TB screening for people with undernutrition and people with structural risk factors such as food insecurity

8 In settings where the TB prevalence in the general population is 100/100 000 population or higher, systematic screening for TB disease may be conducted among people with a risk factor[e] for TB who are either seeking health care or who are already in care.

(Existing recommendation: conditional recommendation, very low certainty of evidence)

9 Systematic screening for TB disease may be conducted among subpopulations with structural risk factors for TB.[f] These include urban poor communities, homeless communities, communities in remote or isolated areas, indigenous populations, migrants, refugees, internally displaced persons and other vulnerable or marginalized groups with limited access to health care.

(Existing recommendation: conditional recommendation, very low certainty of evidence)

d A household where at least one member has been diagnosed with TB; this term also includes the person with TB.

e The source guideline identifies undernutrition as a risk factor for TB.

f Structural risk factors for TB also include food insecurity.

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[4] All references were accessed on 7 May 2025.

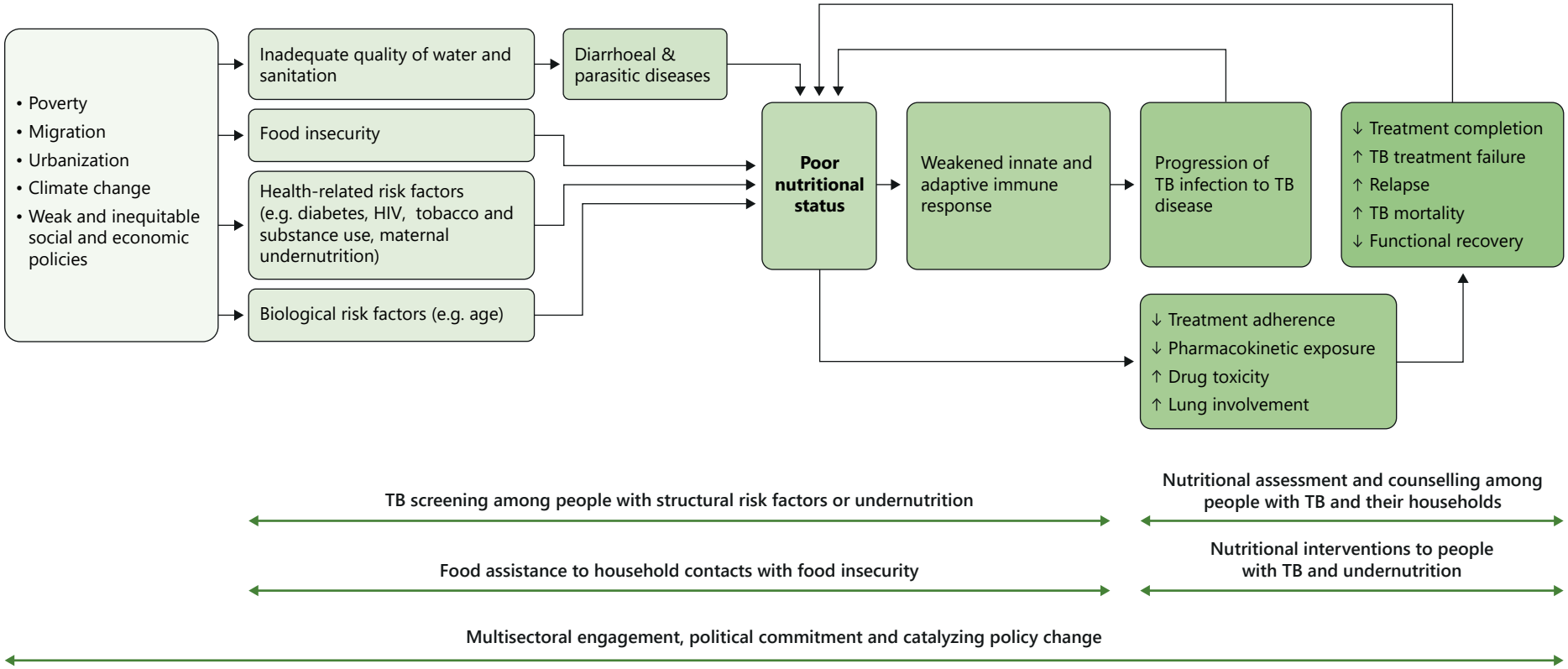
1. Undernutrition: introduction

1.1 Background

Tuberculosis (TB) is a leading cause of ill health and mortality from an infectious disease. In 2023, an estimated 10.8 million people fell ill with TB, among whom 1.25 million died from TB *(1)*. TB incidence is closely related to broader socioeconomic determinants such as poverty and food insecurity *(1)*, and undernutrition is one of the most important risk factors that drive the TB epidemic. A systematic review and meta-analysis estimated a 48% prevalence of undernutrition in people with TB *(2)*. People with undernutrition have a more than twofold increased risk of TB (hazard ratio 2.23; 95% confidence interval [CI]: 1.83–2.72) *(3)*, and often have more severe disease, delayed sputum culture conversion, and an elevated risk of death and loss to follow-up *(4, 5)*. TB also commonly causes undernutrition, due to TB-related changes in macronutrient and micronutrient status *(6)*. Thus, the management of TB and undernutrition requires careful attention to achieve adequate nutritional status and to optimize TB treatment outcomes. In addition, nutrition plays a critical role in TB prevention *(7)*. The relationship between undernutrition and TB, including potential points of intervention, is shown in Fig. 1.

Addressing comorbidities and the determinants of TB is a crucial component of World Health Organization's (WHO's) End TB Strategy *(8)*, which focuses on integrated people-centred TB care and prevention, including action on TB and comorbidities such as undernutrition. In September 2023, the political declaration of the United Nations (UN) high-level meeting on the fight against TB *(9)* reaffirmed the commitment to ending the TB epidemic globally by 2030. In the declaration, Member States committed to strengthening comprehensive care and integrating within primary health care the systematic screening, prevention, treatment and care of TB and of related health conditions such as undernutrition.

Fig. 1. Relationship between undernutrition and TB and points of intervention



TB: tuberculosis.
Adapted from Sinha et al. 2021 *(10)*.

1.2 Rationale for the guideline update

In 2013, WHO published the *Guideline: nutritional care and support for patients with tuberculosis (11)*. That document included recommendations on nutritional assessment and counselling, management of moderate and severe acute malnutrition, and micronutrient supplementation for people with TB disease. It also contained guidance on nutritional assessment and support for household contacts of people with TB. Since 2013, there has been new evidence on the relationship between TB and undernutrition, on nutritional interventions and micronutrient supplementation for people with TB, and on food assistance to prevent TB among household contacts of people with TB. In 2024, WHO convened a guideline development group (GDG) to examine the evidence, to update WHO's guidelines on TB and undernutrition.

1.3 Scope

This section of the guidelines consolidates existing recommendations on TB screening among people with undernutrition and in food insecure settings *(12)* with existing, updated and new recommendations on nutritional interventions for people with TB and their household contacts.

For the updated and new recommendations, three systematic reviews on the following questions worded in the PICO (population, intervention, comparator, outcome) format were conducted:

1. Among people with TB with or without undernutrition, who are receiving TB treatment, do nutritional interventions,[5] both alone and in combination with micronutrient supplementation, improve physical and mental health and well-being compared with TB treatment alone?

2. Among people with TB with or without undernutrition, who are receiving TB treatment, do micronutrient supplements improve physical and mental health and well-being compared with TB treatment alone?

3. Among household contacts of people with TB disease, do nutritional interventions,[5] both alone and in combination with micronutrient supplementation, reduce the incidence of TB disease, compared with not receiving nutritional interventions?

Background reviews were also conducted on the composition and duration of nutritional supplementation, and the cost–effectiveness, feasibility and acceptability of nutritional interventions for people with TB and their household contacts. In addition, WHO commissioned a survey among staff of national TB and nutrition programmes in high-burden countries, and interviews with people who had completed TB treatment (also known as TB survivors) and household contacts, to assess the feasibility and acceptability of nutritional interventions.

[5] For the purposes of PICOs 1 and 3, and as defined in the systematic review protocols, nutritional interventions include assessment, nutritional counselling and administration of macronutrients through different sources or initiatives (free food, nutrient-dense food, food vouchers or cash transfers).

The GDG reviewed the evidence from the three systematic reviews and associated studies, and formulated recommendations based on the evidence. When formulating recommendations, the GDG members considered the evidence for effectiveness and safety of the interventions, as well as the other dimensions important to both affected individuals and programmes; that is, values, preferences, resource requirements, costs, cost–effectiveness, impact on health equity, acceptability and feasibility, in alignment with the process outlined in the *WHO handbook for guideline development (13)*. The full methodology for the development of recommendations is described in Web Annex A. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) evidence profiles are published in Web Annex B, and the GRADE evidence-to-decision tables in Web Annex C. The wording of one previous recommendation was revised to improve clarity and to reflect current language use, while 10 recommendations were retired because they were considered redundant or no longer valid. The supplementary table summarizes all recommendations, including changes to a previous recommendation. The GDG reached consensus for all recommendations. The recommendations in this document supersede the recommendations in the 2013 guidelines.

These guidelines will be accompanied by a corresponding section on undernutrition in the latest edition of the *WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities*, which contains guidance on actions to establish and strengthen mechanisms for effective collaboration between and within sectors, as well as implementation considerations for delivering collaborative activities on TB and undernutrition. WHO's *Framework for collaborative action on TB and comorbidities (14)* provides further guidance for establishing and strengthening mechanisms for effective collaboration to deliver people-centred services for TB and comorbidities in general.

The guidelines and operational handbook will be found on the TB Knowledge Sharing Platform *(15)*. This platform also hosts all other WHO guidelines and operational handbooks on TB, including those on prevention, screening, diagnosis, treatment, childhood and adolescent TB, and TB and comorbidities.

1.4 Objectives

The specific objectives of the undernutrition section of this document are to:

- reduce the burden of undernutrition among people with TB; and
- reduce the burden of TB among people with undernutrition and in food insecure settings.

The anticipated impacts of the undernutrition section are:

- identification of undernutrition in people with TB and their household contacts through nutritional assessment;
- improvement in clinical outcomes in people with TB and undernutrition through counselling and nutritional interventions;
- reduction in TB incidence by addressing undernutrition and food insecurity in households of people with TB;
- timely identification and management of TB through screening of people with undernutrition or who experience food insecurity; and
- reduction in out-of-pocket costs relating to nutrition for households of people with TB.

It is envisaged that implementation of these guidelines will contribute to the achievement of the End TB Strategy, and Sustainable Development Goal (SDG) 2 (zero hunger) and SDG 3 (good health and well-being).

1.5 Target audience

This section of the guidelines is intended to support programmes in providing people-centred services for TB and undernutrition at all levels of the health system in all WHO Member States. The guidelines specifically target policy-makers in ministries of health (MoHs), particularly national programmes or relevant departments responsible for TB, undernutrition, primary health care and social protection; they are also aimed at international technical and funding organizations, researchers, and nongovernmental organizations and civil society organizations involved in TB, nutrition and food assistance. It is expected that these recommendations will also be used by health professionals, including doctors, nurses, nutritionists, community health workers and educators who provide TB and nutritional care and support in both the public and private sectors.

2. Recommendations

2.1 Nutritional assessment and counselling in people with TB and their household contacts

WHO recommendations	
1. At diagnosis and throughout treatment, all individuals with TB should be offered nutritional assessment and appropriate counselling based on their nutritional status. *(Existing recommendation with language edit: strong recommendation, no direct evidence available)*	
2. Household contacts of people with TB should be offered nutritional assessment and counselling as part of contact tracing. If undernutrition is identified, it should be managed according to WHO guidance. *(New recommendation: strong recommendation, low certainty of evidence)*	**NEW**

2.1.1 Justification and evidence

Undernutrition is a common condition among people with TB. A systematic review and meta-analysis of 53 studies involving 48 598 participants estimated that, globally, 48% of people with TB have undernutrition *(2)*. Nutritional assessment and counselling are recognized as critical interrelated interventions in the pathway of tailored nutritional care *(11, 16-18)*. Nutritional assessment is a prerequisite for identifying, preventing and managing undernutrition. Counselling is an interactive process, informed by the nutritional assessment; it informs the individual about the results of the nutritional assessment, helps to identify the individual's needs and barriers to optimizing nutrition, provides information to the individual to address any nutritional issues identified and helps in developing a plan to ensure a healthy diet is maintained *(17, 18)*.

In 2013, WHO recommended that all individuals with TB should receive nutritional assessment and counselling, and that their household contacts should receive nutritional screening and assessment in settings where household contact tracing is being conducted *(11)*. WHO also recommends that all household contacts are systematically screened for TB *(12)*. Assessing for unintended weight loss is already a part of symptom screening for household contacts of people with TB *(12)*.

Recommendation 1:
Nutritional assessment and counselling of people with TB

This strong recommendation was originally developed during the guideline development process for the 2013 publication *Guideline: nutritional care and support for patients with tuberculosis (11)*.

The systematic review conducted for PICO Question 1, on nutritional interventions for people with TB, also included assessment and counselling. The review did not identify any direct evidence on the effectiveness of assessment and counselling alone on improving outcomes in people with TB. However, it did identify studies that showed the benefit of nutritional interventions (e.g. high energy–protein food) to address undernutrition among people with TB, a large proportion of whom had undernutrition *(19-28)*. More details on this evidence are provided in Section 2.2.1.

Nutritional assessment is an essential prerequisite for identifying undernutrition and for informing an appropriate nutritional intervention. Most studies identified by the systematic review described the nutritional status of participants; hence, it can be assumed that nutritional assessment was conducted. However, the impact of nutritional assessment alone on the outcomes of participants with TB was not measured. Two of the studies identified by the systematic review that mentioned nutritional counselling provided it to participants in both the intervention and control arms, so were unable to measure the benefits of nutritional counselling *(25, 26)*. However, data from systematic reviews of nutritional counselling among other populations with undernutrition or at risk of undernutrition (e.g. people with cancer or older people) demonstrate that nutritional counselling may result in increased energy and protein intake, as well as an increase in body weight *(29-31)*. Thus, it seems that nutritional counselling, tailored to the individual's nutritional status, would also be of benefit to people with TB.

In a programmatic nested cohort study conducted as part of the Reducing Activation of Tuberculosis by Improvement of Nutritional Status (RATIONS) trial (described in Section 2.2.1), low baseline weight of people with TB was a predictor of TB mortality, whereas 5% weight gain in the first 2 months was protective against TB mortality *(32)*. Thus, assessment of nutritional status at baseline and throughout treatment is important for monitoring clinical and nutritional recovery in people with TB, and nutritional assessment and counselling can play an important role in reducing mortality. Identifying and addressing undernutrition in people with TB may save lives and would be unlikely to give rise to any significant adverse events.

Qualitative interviews with people who have been treated for TB conducted to inform these guidelines indicated that assessment and counselling throughout treatment, in combination with nutritional interventions, were well received and were motivating (Web Annex D). Participants who did not receive nutritional counselling in combination with food support frequently sought advice from other sources; for example, from their peers or online (Web Annex D).

The GDG highlighted that nutritional assessment and counselling are essential for the provision of appropriate nutritional care. However, GDG members observed the absence of direct evidence on the impact of nutritional assessment and counselling alone on clinical outcomes of people with TB. They also noted the challenge of measuring the effectiveness of nutritional assessment and counselling on outcomes, separate from any other intervention to address undernutrition. Members further highlighted the challenges of designing studies on the impact of nutritional assessment and counselling alone among people with TB, given that they are considered the standard of care and there has been a strong recommendation on nutritional assessment and counselling since 2013 (which might explain the absence of data). The GDG also noted that studies that include assessment and counselling will also include these activities in the control arm *(25, 26)*.

Based on the findings from the indirect evidence, the GDG agreed to retain the existing strong recommendation from the 2013 guidelines. The previous recommendation has been updated for clarity and to reflect the latest WHO-endorsed language.

Recommendation 2:
Nutritional assessment and counselling for household contacts of people with TB

The GDG noted that the recommendation from the 2013 guidelines on nutritional screening and assessment of household contacts should be replaced, primarily because it applied only to settings where contact tracing was being implemented. Given that there has been a strong recommendation for contact tracing since 2012, which is being scaled up in many countries, this conditionality was judged to be inappropriate *(1, 12, 33)*.

The systematic review conducted for PICO Question 3, on nutritional interventions for household contacts, also included assessment and counselling. The review did not identify any direct evidence that measured the effectiveness of nutritional assessment and counselling on reducing TB incidence among household contacts. However, it did identify one trial – the RATIONS trial – which provided a source of indirect evidence on nutritional assessment and counselling for the GDG to consider *(7)*.

The RATIONS trial (described in Section 2.2.1) was a cluster randomized controlled trial (RCT) that assessed the impact of food assistance on TB incidence among household contacts of people with TB. It estimated that the food assistance reduced the incidence of TB by 39%, regardless of baseline nutritional status. A high proportion (34%) of the household contacts had undernutrition. However, since all the household contacts in the intervention and the comparator arms received nutritional assessment as standard practice, the effect of assessment alone could not be determined. Similarly, all household contacts within the RATIONS trial were offered counselling as standard practice, so again the effect of counselling could not be determined. However, data from systematic reviews of nutritional counselling among other populations with undernutrition or at risk of undernutrition (e.g. people with cancer or older people) demonstrate that nutritional counselling may result in increased energy and protein intake, and an increase in body weight *(29-31)*.

Nutritional assessment is a critical step for identifying different types and severity of malnutrition (e.g. mild, moderate or severe undernutrition or obesity); it provides an entry to care for tailored nutritional interventions, and an opportunity for advice on a healthy balanced diet as part of counselling and TB prevention. Based on studies demonstrating the impact of nutritional counselling on other populations, it may be concluded that nutritional counselling tailored to the severity of nutritional status would also be of benefit to household contacts of people with TB *(29-31)*. The GDG noted that nutritional assessment and counselling of household contacts of people with TB are likely to be of more value to recipients if these initiatives are accompanied by nutritional interventions that are tailored according to degree of undernutrition. The GDG judged that if nutritional interventions appropriate to the severity of undernutrition are provided to household contacts who are identified as undernourished via the assessment, the benefits in terms of TB prevention could be moderate to large, as demonstrated by the RATIONS trial. It was also noted that nutritional assessment and counselling are not only critical for the provision of nutritional interventions but are also an important part of TB contact investigation and TB prevention activities. Identifying and addressing undernutrition, particularly severe undernutrition, in this high-risk population, may save lives and would be unlikely to give rise to any significant adverse events.

The overall certainty of evidence for nutritional assessment and counselling for household contacts of people with TB was downgraded twice, from high to low certainty, because of indirectness and because the RATIONS trial was a single trial in a single setting, with variability across subpopulations and with a population limited to household contacts of people with bacteriologically confirmed pulmonary TB.

As was the case for people with TB, it was noted that there might be challenges in designing trials to measure the effectiveness of nutritional assessment and counselling as standalone interventions to address undernutrition in household contacts of people with TB (which may explain the lack of evidence to support these interventions).

The review of background questions did not find any studies looking specifically at the resource implications, acceptability, feasibility or equity of assessment and counselling among household contacts of people with TB. However, interviews with TB survivors found that participants would have valued counselling conducted among their household members; they would also have valued receiving more information to clarify whom the nutritional support was for (Web Annex D). In the survey among representatives of MoHs, most participants responded that clinic staff would be supportive of providing nutritional interventions to household contacts (Web Annex D).[6] As countries are scaling up activities for TB screening and TB preventive treatment (TPT) among household contacts of people with TB, GDG members acknowledged that nutritional assessment and counselling were likely to be feasible (although this may vary according to the context), and that capacity-building would be necessary in terms of staff numbers, expertise and equipment, which would come at an additional cost if countries are not already implementing the existing recommendation. The GDG judged that the intervention would probably increase equity because it would identify those households in need of assistance and help to reduce costs incurred by the household due to TB.

Based on the indirect evidence reviewed on the balance of benefits and harms, and the evidence on acceptability and feasibility, cost implications and equity, the GDG agreed to develop a strong recommendation on the assessment and counselling of household contacts of people with TB.

2.1.2 Subgroup considerations for people with TB and household contacts

These recommendations apply to all people with TB, and household contacts, including the subpopulations described in this subsection.

People with comorbidities

People with TB and their household contacts may have other comorbidities or TB risk factors (e.g. HIV, diabetes, smoking, mental health conditions and alcohol or drug use), which may have their own nutritional implications and should be considered during nutritional assessment and counselling. Nutritional counselling, advice and support may need to be adjusted depending on the degree of undernutrition and the specific nutritional requirements of people with these comorbid conditions. Close collaboration between health care providers is also important to assure comprehensive care.

[6] Stephanie Law, McGill University, unpublished data, 5 June 2024.

Pregnant women, infants, children and older people

Nutritional assessment and counselling for pregnant women, infants, children and older people may require additional expertise. Coordination with specialist services (e.g. maternal, child health and nutrition services) may be advisable to optimize resource use, training and mentoring. In some low- and middle-income countries, mother and child health services are supported by international organizations such as the United Nations Children's Fund (UNICEF). Such organizations have specific expertise and can support policy change, provision of anthropometric supplies and capacity development of the government health workforce, including community health workers, for the assessment and provision of nutritional interventions for pregnant women, infants and children.

Guidance on nutritional assessment and management for infants and children below 5 years is found in the *WHO guideline on the prevention and management of wasting and nutritional oedema (acute malnutrition) in infants and children under 5 years (34)*. Guidance on nutritional assessment and management for pregnant women is found in *WHO recommendations on antenatal care for a positive pregnancy experience (35)*. Guidance on nutritional counselling for older people can be found in *Integrated care for older people: guidelines on community-level interventions to manage declines in intrinsic capacity (36)*.

2.1.3 Implementation considerations for people with TB and household contacts

Assessing nutritional status

WHO defines undernutrition according to anthropometric assessment, as described in Table 1, however, other methods of assessment include biochemical, clinical and dietary assessment which are also important for a comprehensive understanding of an individual's nutritional status at baseline and throughout TB treatment.

Anthropometric assessment can include:

- measurement of body mass index (BMI) in adults aged over 19 years;
- BMI-for-age Z-score in children and adolescents aged 5–19 years;
- weight-for-age Z-score in children aged below 5 years; and
- weight-for-length or weight-for-height Z-score, mid-upper arm circumference (MUAC) and/or a clinical assessment for the presence of nutritional oedema to identify children aged below 5 years with undernutrition.

To calculate BMI, weight and height need to be measured. Additional information on nutritional assessment, including accurate measurement of height and weight, on conversion to BMI and to WHO standardized Z-scores, and on the management of undernutrition will be available in the undernutrition section of the latest edition of the *WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities*, and is available in related WHO guidance *(34-40)*.

Definition of undernutrition

In the past, the term malnutrition (e.g. moderate acute malnutrition and severe acute malnutrition) has been used interchangeably with the term undernutrition. However, it is now recognized that malnutrition also incorporates excesses in nutrient intake and imbalance of essential nutrients or impaired use of nutrients. The term undernutrition is commonly referred to as mild, moderate or severe thinness in adults, and as wasting, oedema and stunting in children, and it can include micronutrient deficiency *(34, 41)*. In the interests of clarity and uniformity in language across the different populations, this document uses the term "undernutrition", rather than "thinness" or "malnutrition".

The anthropometric thresholds or markers for mild, moderate and severe undernutrition are defined in Table 1. More information on assessment of nutritional status will be available in the undernutrition section of the latest edition of the *WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities*.

Table 1. Definitions of mild, moderate and severe undernutrition by age group

Age group	Severe undernutrition	Moderate undernutrition	Mild undernutrition
0–59 months	Severe wasting: • Weight-for-height Z score < –3 SD, or • MUAC <115 mm for children aged 6–59 months, or • nutritional oedema	Moderate wasting: • Weight-for-height Z score ≥ –3 SD and < –2, or • MUAC ≥115 mm and <125 mm for children aged 6–59 months	Not applicable for children and adolescents
5–19 years	BMI-for-age Z score < –3 SD	BMI-for-age Z score ≥ –3 SD and < –2 SD	Not applicable for children and adolescents
>19 years	BMI <16 kg/m^2	BMI 16.0–16.99 kg/m^2	BMI 17.0–18.49 kg/m^2

BMI: body mass index; MUAC: mid-upper arm circumference; SD: standard deviation.

If undernutrition is identified, consideration should be given to any underlying physiological causes of undernutrition that might need to be addressed (e.g. HIV, diabetes, helminth infections or chronic diarrhoeal diseases). Wherever possible, assessment should also include questions to assess household food insecurity *(42)*.

Components of nutritional counselling

Nutritional counselling is a two-way interaction between a trained counsellor or health worker and one or more individuals (e.g. people with TB, household contacts, mothers or other caregivers of children). The process involves listening to concerns, discussing questions, sharing information about good nutrition practices and collaboratively identifying barriers to achieving food security and good nutrition, as well as supporting the identification of actions that individuals and families can take to address those barriers. Nutritional counselling should be sensitive to socioeconomic barriers experienced by the household. It may include advice on increasing daily energy and protein intake and on a healthy balanced diet, as well as meal plans composed of affordable, nutritious, locally available and culturally acceptable foods. Nutritional counselling should also emphasize the role of nutrition as a medical intervention in improving TB treatment outcomes and preventing TB among household contacts. Depending on the resources and time available, counselling may need to be simplified. Locally developed standardized nutritional counselling materials, for both the health worker and the people affected by TB, will help to simplify the delivery of nutritional counselling.

Equipment and human resources requirements

The costs of nutritional assessment and counselling will depend on the specific model of care deployed – in the health facility or in the community. If countries are not already implementing household contact tracing or other nutritional interventions, introducing and sustaining nutritional assessment and counselling services might require additional investment.

Additional staff or community health workers may be required to conduct nutritional assessment and provide nutritional counselling, and to ensure that TB case-finding activities are not compromised. Health workers will need to have access to standard equipment and charts to allow for anthropometric measurement according to age, as well as standard operating procedures and training to provide

nutritional assessment and counselling *(43)*. Health facilities are usually equipped with weighing scales (for infants, children and adults) and ideally should be equipped with a stadiometer and a tape measure for measuring MUAC. The development of standard nutritional counselling materials to improve health literacy may also be useful.

Delivery of nutritional assessment and counselling services

Nutritional assessment and counselling among household contacts can be included in the work-up for contact tracing and eligibility for TPT, just after TB disease is diagnosed in a person in the household. Nutritional assessment and counselling should be implemented in all settings, regardless of food insecurity.

Key considerations to maximize coverage are the provision of financial support to household contacts to enable travel to a health facility, or task shifting to community health workers to conduct nutritional assessment and counselling in the home *(44, 45)*. While carrying out nutritional assessment and counselling activities, all measures should be taken to minimize stigmatization; for example, protecting the confidentiality of personal data, maintaining privacy and receiving informed consent from the person with TB and the household members, according to programme guidelines.

2.2 Nutritional interventions and food assistance

WHO recommendations

Nutritional interventions to improve clinical outcomes for people with TB

3. Nutritional interventions[a] should be offered to individuals with TB who have severe, moderate or mild undernutrition, as part of a comprehensive package of TB care. **NEW**

   (New recommendation: strong recommendation, low–moderate certainty of evidence)

4. A package of treatment adherence interventions[b] may be offered for patients on TB treatment in conjunction with the selection of a suitable treatment administration option.

   (Existing recommendation: conditional recommendation, low certainty of evidence)

5. One or more of the following treatment adherence interventions (complementary and not mutually exclusive) may be offered to patients on TB treatment or to health care providers:

   a) tracers or digital medication monitor *(conditional recommendation, very low certainty of evidence)*;

   b) material support[c] to patient *(conditional recommendation, moderate certainty of evidence)*;

   c) psychological support to patient *(conditional recommendation, low certainty of evidence)*;

   d) staff education *(conditional recommendation, low certainty of evidence)*.

   (Existing recommendation)

Food assistance to prevent TB in household contacts

6. In settings of food insecurity, food baskets in combination with multiple micronutrient supplements should be offered to all households of people with TB.[d] **NEW**

   (New recommendation: strong recommendation, moderate certainty of evidence)

a Examples of nutritional interventions are direct food provision, specially formulated foods and financial support.

b Treatment adherence interventions include social support such as: patient education and counselling; material support (e.g. food, financial incentive and transport fees); psychological support; tracers such as home visits or digital health communications (e.g. SMS, telephone calls); medication monitor; and staff education. The interventions should be selected on the basis of the assessment of the individual patient's needs, provider's resources and conditions for implementation.

c Material support can be food or financial support such as: meals, food baskets, food supplements, food vouchers, transport subsidies, living allowance, housing incentives, or financial bonus. This support addresses indirect costs incurred by patients or their attendants in order to access health services and, possibly, tries to mitigate consequences of income loss related to the disease.

d A household where at least one member has been diagnosed with TB; this term also includes the person with TB.

2.2.1 Justification and evidence

People with TB who also have undernutrition have a higher risk of poor treatment outcomes, including an elevated risk of death and loss to follow-up *(4, 5)*. Household contacts, regardless of their age or TB infection status, are also at a substantially higher risk for progression to TB disease than the general population *(46)*. Adequate nutrients are required for regulating body processes, and building and repairing tissues, thereby promoting health and preventing disease *(11)*. In 2013, WHO published recommendations on the provision of nutritional support for people with TB and moderate or severe undernutrition *(11)*. In light of new evidence, systematic reviews were commissioned, to update the recommendations on food assistance and nutritional interventions for people with TB and their household contacts.

Recommendation 3:
Nutritional interventions for people with TB and undernutrition

Nutritional interventions are purposeful actions intended to increase macronutrient intake and improve the nutritional or clinical status of an individual. Such interventions may include direct food provision, specially formulated foods, cash-based transfers or food vouchers. The systematic review conducted for PICO Question 1 identified 17 RCTs, of nutritional interventions for people with TB which could be assessed according to GRADE, comprising a diverse range of dietary and non-dietary interventions *(19-26, 28, 47-54)*. Most of these studies focused on people with pulmonary TB but three studies included people with extrapulmonary TB *(23, 25, 53)*. One RCT included only people with multidrug-resistant TB (MDR-TB) *(47)*. The RCTs included the following eight groups of nutritional interventions: high energy–protein food (interventions aimed to boost energy and protein intake, which may include specially formulated food such as biscuits or shakes, or locally manufactured food) *(23-26, 28, 50)*, arginine-rich food *(19, 20, 52, 54)*, financial support with psychosocial counselling *(47)*, food vouchers *(53)*, green tea extract *(49)*, fish oil plus vitamin A and zinc *(22)*, channa striata extract *(21)*, "dietary nursing" *(48)* and cholesterol-rich diet *(51)*. The systematic review yielded information on the following outcomes rated critical by the GDG: death, TB cure, TB treatment completion, TB treatment success, loss to follow-up, TB treatment adherence, TB treatment failure, performance status (handgrip strength), change in weight or body mass, and anaemia. One study on a cholesterol-rich diet did not yield any evidence on any of the critical outcomes. The certainty of evidence for the different interventions and outcomes varied. There were no data on patient costs, adverse events, longer term survival and pregnancy outcomes.

The systematic review found that the evidence is very uncertain about the effect of fish oil plus vitamin A and zinc on BMI at 1 month among children with TB, compared with standard of care (mean difference [MD] 1.9 kg/m^2 [95% CI: 0.0, 3.8], very low certainty evidence) *(22)*. In addition, the studies that included green tea extract, channa striata and dietary nursing did not demonstrate any significant difference in the critical outcomes of treatment success, treatment failure, mortality, loss to follow-up or anaemia. The GDG therefore judged that, overall, the desirable effects for these interventions were trivial or unknown and the undesirable effects were trivial and thus the balance of effects was uncertain.

The systematic review found that high energy–protein food may improve TB treatment completion (1 trial, *n*=100, risk ratio [RR] 1.20 [95% CI: 1.04, 1.37], low certainty evidence) *(25)*, slightly increases percentage weight gain at 2 months (1 trial, *n*=265, MD 1.70% [95% CI: 0.19, 3.21], high certainty evidence) *(28)* and at 8 months (1 trial, *n*=265, MD 2.60% [95% CI: 0.51, 4.69], high certainty evidence) *(28)*, and probably increases handgrip strength at 3 months (2 trials, *n*=136, MD 1.51 [95% CI: 1.10, 1.92], moderate certainty evidence) *(25, 26)* compared with not giving high energy–protein food.

One trial reported reduced adherence to TB treatment at 2 months (1 trial, *n*=265, MD –4.7% [95% CI: –8.6, –0.8], moderate certainty evidence) among participants who received high energy–protein food *(28)*. This study required participants to attend the clinic daily at a specific time during the intensive phase of TB treatment to receive a cooked meal. Qualitative research conducted during this study and reported in the same publication *(28)* found that some participants expressed shyness about eating at the clinic, whereas others complained about time inflexibility relating to clinic attendance, which may have been a barrier to treatment adherence.

Arginine supplementation, compared with placebo, probably results in a slight reduction in the proportion of people with a BMI of less than 18.5 kg/m^2 at 1 month (1 trial, *n*=63, RR 0.35 [95% CI: 0.13, 0.99], moderate certainty evidence) *(19)*. An arginine-rich diet, compared with a low-arginine diet, may result in an increase in TB cure in people with HIV-associated TB (1 trial, *n*=69, RR 1.58 [95% CI: 1.11, 2.25], low certainty evidence) *(20)*.

Financial support with psychosocial counselling probably increases cure in people with MDR-TB (RR 1.21, 95% CI: 1.00, 1.46) *(47)*. The provision of food vouchers for specified foods to people receiving TB treatment probably increases cure slightly compared with the standard of care (1 trial, *n*=774, RR 1.08 [95% CI: 1.03, 1.13], moderate certainty evidence) *(53)*.

For the interventions of high energy–protein food, arginine-rich food, financial support with psychosocial counselling and food vouchers, the GDG judged the desirable effects as small to moderate, and the undesirable effects as trivial. The certainty of evidence for the studies investigating these interventions was judged to be low–moderate for high energy–protein food and moderate for the other three interventions. The GDG therefore judged that the overall certainty of evidence for these four groups of interventions was low–moderate. The GDG thus agreed to consider these four specific interventions during the process of making decisions based on the evidence before formulating a recommendation. Further information on these interventions and outcomes are given in Web Annex B (the GRADE summary of findings tables) and Web Annex C (the GRADE evidence-to-decision tables).

A high proportion of participants in the trials included in the systematic review had undernutrition. Two trials recruited only participants with undernutrition *(25, 26)*. In addition, seven trials recruited participants regardless of nutritional status, but the recruited participants had a mean or median BMI of less than 18.5 kg/m^2 *(20-24, 27, 28)*. One trial recruited participants regardless of nutritional status but reported a BMI of less than 18.5 kg/m^2 in 46% of participants *(19)*. Three trials reported a mean or median BMI of just above 18.5 kg/m^2 but less than 20 kg/m^2 *(50-52)*, and one trial reported a BMI of more than 20 kg/m^2 *(48)*. Four trials did not report on BMI in their inclusion criteria or among the included participants *(47, 49, 53, 54)*. A systematic review and meta-analysis of 53 studies conducted in 2023 involving 48 598 participants estimated that, globally, 48% of people with TB have undernutrition. Among the 53 studies, 51 defined undernutrition using the standard WHO-approved definitions. Thus, it might be assumed that a reasonable proportion of participants of the four trials that did not report nutritional status would have been undernourished *(2)*. A proportion of the participants may not have had undernutrition; however, the GDG members judged that the recommendation should only apply to people with TB who have undernutrition.

No data were identified that compared the effect of nutritional interventions for people with TB by undernutrition status at the beginning of TB treatment, by age group, for pregnant, postpartum or breastfeeding women, or for people with diabetes.

The GDG noted that the costs associated with providing nutritional interventions may vary with the context. Factors that might influence the costs include the number of people with TB, the nutritional status of people with TB, the cost of nutritional interventions in a given setting, and the background prevalence of undernutrition, food insecurity and poverty. The systematic review did not identify any data on the association between nutritional interventions for people with TB and costs to the household. However, findings from nationally representative TB household cost surveys, conducted according to the WHO methodology, highlight that a large proportion of indirect costs are for food and food supplements; these costs, which are already being paid by people with TB, often represent a high proportion of the household income *(55-57)*. Furthermore, people with TB incurred increased costs if they were living with HIV or if the TB treatment regimen was longer; this has been particularly relevant for people with MDR-TB *(55, 56, 58, 59)* (although the duration of regimens to treat people with MDR-TB is now as short as 6 months, reflected in WHO guidance first issued in 2022) *(60, 61)*. The GDG therefore concluded that the costs of providing nutritional interventions for programmes are highly likely to translate into savings for the person with TB.

The review did not identify any published evidence on cost–effectiveness of nutritional interventions for people with TB. Unpublished modelling studies presented to the GDG found that the provision of nutritional interventions for people with TB was cost effective. One modelling study presented at the GDG meeting and which was based in India found an incremental cost–effectiveness ratio (ICER) of nutritional interventions for people with TB of US$ 159 per disability-adjusted life year (DALY) averted (95% uncertainty interval [UI]: 65–316) (see Web Annex D).[7] Another modelling study, which was unpublished at the time of the GDG meeting, looked at scaling up the RATIONS intervention for people with TB (food rations of 1200 kcal and 52 g of protein per day, together with multiple micronutrient supplements *(32)*). It found that this was cost effective with an ICER of US$ 139 per DALY averted (95% UI: 113–167), with similar results from the societal perspective, for varying coverage, and for varying durations of protection *(62)*.

The review of background questions found that food baskets were broadly seen as acceptable and were frequently shared with all household members *(63)*. Interviews with TB survivors found that participants appreciated receiving nutritional interventions during TB treatment. Participants preferred receiving food or vouchers over cash or cooked meals (Web Annex D). However, financial support was also appreciated because it relieved other family members of the additional financial burden incurred on the household by TB *(64)*. The survey among MoH representatives found that nutritional interventions for people with TB were already being implemented in most of the high TB burden countries represented (Web Annex D). Although nutritional interventions were judged to be acceptable and feasible, GDG members recognized that feasibility might vary depending on the setting and the form of nutritional intervention delivered. There may also be issues around equity in settings of high food insecurity if it is only the households of people with TB that are receiving food support. The GDG noted that findings from qualitative research within the study that reported reduced adherence at 2 months underscored the importance of appropriate trial design and a people-centred approach in the delivery of nutritional interventions *(28)*.

After reviewing the evidence, the GDG agreed to develop a recommendation based on the four groups of interventions: high energy–protein food, arginine-rich food, financial support with psychosocial counselling and food vouchers. The GDG concluded that nutritional interventions should be offered to all people with pulmonary or extrapulmonary TB who have undernutrition, regardless of subpopulation, given the improved nutritional status observed, and the increased rates

[7] Julia Gallini, Boston University, unpublished data, 16 May 2024. Preprint: https://dx.doi.org/10.2139/ssrn.5217938. The ICER of US$ 159 per DALY averted was presented to the GDG during a preparatory webinar, whereas the preprint referenced here reports US$ 141 per DALY averted.

of TB cure and TB treatment completion. It was further underscored that it is an ethical imperative to address undernutrition, irrespective of a person's TB status. The new recommendation replaces the previous WHO recommendations on nutritional interventions for people with TB and moderate or severe undernutrition (see the Supplementary table).

Recommendations 4–5: Material support for people with TB, regardless of nutritional status

In 2022, WHO released two recommendations to enhance TB treatment adherence in people with TB, regardless of nutritional status *(61)*. The recommended interventions include material support, tracers or digital medication monitors, psychological support and staff education. Material support, as defined by the source guideline, includes the following: nutritional interventions such as meals, food baskets, food supplements and food vouchers; transport subsidies; living allowance; housing incentives; and financial incentives for reaching treatment targets. Details on the other forms of treatment adherence interventions can be found in the source guidelines, the WHO consolidated guidelines on tuberculosis. Module 4: treatment and care *(61)*.

The effects of material support were examined both with RCTs *(25, 28, 65, 66)* and observational studies *(67-75)*. There were higher rates of treatment success, completion and sputum conversion in individuals who received material support, and lower rates of treatment failure and loss to follow-up compared with individuals who did not receive material support. The studies in this review found that material support was usually given to the most vulnerable groups; hence, health equity was presumably improved by this intervention. However, if these incentives are not applied equitably, health disparities may be increased. The distribution of material support is likely to depend on the country context and its effect may differ, both within and between countries. Although this recommendation relates to treatment of TB disease, countries might also consider material support to enhance adherence among people receiving TPT *(46)*.

Recommendation 6: Food assistance to prevent TB in household contacts

The systematic review for PICO Question 3 – on the effect of assessment, counselling and food assistance in reducing the incidence of TB among household contacts – identified one field-based, open-label, cluster RCT from India: the RATIONS trial *(7)*. The RATIONS trial assessed the impact of food assistance (in this case, food baskets with multiple micronutrients) on TB incidence among household contacts. The trial also reported data on change in body weight and adverse events. It did not report data on household costs. The trial included 10 345 household contacts of people with bacteriologically confirmed pulmonary TB, 34% of whom had undernutrition at baseline, in a setting of food insecurity and multidimensional poverty in Jharkhand, India.

Household contacts in the intervention group received monthly food rations (750 kcal, 23 g of protein per day with multiple micronutrients[8]) for at least 6 months, and until improvement of nutritional status above age-specific BMI cut-offs pre-defined by the study team. The food basket for each household contact consisted of 5 kg rice, 1.5 kg split pigeon peas and micronutrient pills. Children aged below 10 years received 50% of this allocation *(7)*. In the comparator group, household contacts did not receive any food assistance. In accordance with national protocols, participants from both arms had access to the government-provided services including counselling for nutrition, advice on infection prevention and control, TB screening, and supplementary feeding and food rations

[8] Participants were given a multiple micronutrient pill to take every other day. The pill contained vitamin A 5000 international units (IU), vitamin D3 400 IU, vitamin E 15 mg, vitamin B1 5 mg, vitamin B2 5 mg, nicotinamide (vitamin B3) 45 mg, D-panthenol 5 mg, vitamin B6 2 mg, vitamin C 75 mg, folic acid 1000 mcg, vitamin B12 5 mcg, dibasic calcium phosphate 70 mg, copper sulfate 0.1 mg, manganese sulfate monohydrate 0.01 mg, zinc sulfate monohydrate 28.7 mg, potassium iodide 0.025 mg and magnesium oxide 0.15 mg.

if they were eligible. People with TB received a food basket in both the intervention and control groups (1200 kcal and 52 g of protein per day, and multiple micronutrient supplements) as well as the government-provided direct benefit transfer. The food baskets provided to adults with TB in the RATIONS trial consisted of 5 kg rice, 3 kg Bengal gram flour (chickpea flour), 1.5 kg milk powder and 500 mL vegetable oil *(32)*.

The RATIONS trial showed that there is probably a relative reduction in TB incidence of 39% among household contacts receiving food support, compared with the control group (1 trial, *n*=10 314, adjusted incidence rate ratio [IRR] of TB 0.61 [95% CI: 0.43, 0.85], moderate certainty evidence). The overall certainty of evidence was downgraded from high to moderate, owing to it being from a single trial in a single setting, with variability across subpopulations and with a population limited to household contacts of people with bacteriologically confirmed pulmonary TB.

There was some variation in overall effect reported in the subgroups analysed, and the GDG noted that the trial was randomized at the cluster level and not stratified by subgroup. Among adults, a lower TB incidence was reported in the intervention group (unadjusted IRR 0.55 [95% CI: 0.39, 0.77]), whereas no difference was reported for children and adolescents aged 6–17 years (unadjusted IRR 0.72 [95% CI: 0.32, 1.63]) or children aged 0–5 years (unadjusted IRR 2.15 [95% CI: 0.60, 7.77]). Among people with normal nutritional status at baseline, TB incidence was reported to be lower in the intervention group (unadjusted IRR 0.33 [95% CI: 0.17, 0.65]), with no reported difference among household contacts who were underweight[9] at baseline (unadjusted IRR 0.75 [95% CI: 0.51, 1.12]).

The GDG acknowledged that the study was adequately powered to detect differences in the primary outcome among household contacts overall, but not across any subgroup. The question of food sharing in the control group was raised as a potential issue by the GDG. The authors of the RATIONS trial highlighted that participants were counselled on the importance of consumption of food by the individuals with TB in both the intervention and control arms. However, it was emphasized that sharing of food by the person with TB with other household members could not be ruled out. The GDG noted that food sharing may thus result in a reduced estimate of effect, which may explain, in part, the limited difference in TB incidence among the household contacts who were children, adolescents or people with undernutrition. The GDG also hypothesized that the availability of existing government-provided supplementary feeding services for eligible participants in both arms might have affected the estimate of effect. No data were found on other subgroups, including people living with HIV, people with diabetes, elderly people, pregnant and postpartum women, or individuals with substance use disorders.

The RATIONS trial also reported on the costs associated with providing food assistance to household contacts: about US$ 13 per household contact per month inclusive of delivery charges (2019 prices). The GDG noted that the costs for providing food baskets to household contacts in the RATIONS trial in India were moderate, but that costs would vary considerably across countries and regions. Results from nationally representative TB household cost surveys, conducted according to WHO methodology, showed that a high proportion of the additional costs incurred in TB-affected households was due to nutritional supplementation *(76)*. The GDG highlighted that the provision of food assistance would represent a shift of costs from the household to the public sector, which might result in a cost saving due to reduced TB incidence.

[9] Underweight was defined in the RATIONS trial as weight-for-age Z-scores of less than –2 SD for those aged 5 years or below, BMI-for-age-and-sex Z-score of lower than –2 SD for those aged 6–17 years and a BMI of lower than 18.5 kg/m^2 for individuals aged at least 18 years.

One published modelling study included in the systematic review found that food baskets of 2600 kcal/day provided to undernourished household contacts in India over a period of 5 years was highly cost effective, with an ICER of US$ 360 per DALY averted *(77)*. Data from unpublished modelling work on the cost–effectiveness of the RATIONS trial intervention over the lifetime of recipients found the intervention was cost effective from both government (ICER: US$ 229 per DALY averted [95% UI: 133–387]) and societal perspectives (ICER: US$ 184 per DALY averted [95% UI: 83–344]).[10] Another modelling study, which was unpublished at the time, was presented to the GDG; it assessed the cost–effectiveness of scaling up the RATIONS trial intervention to the whole of India, and estimated that providing this intervention to the whole household, compared with providing it to just the person with TB, was cost effective at most willingness-to-pay thresholds, with an ICER of US$ 208 (95% UI: 181–234) per DALY averted,[11] with similar results from the societal perspective, for varying levels of coverage and for varying durations of protection *(62)*.

The findings from surveys with national TB and nutrition programmes, and interviews with TB survivors and household contacts, also highlighted that people with TB frequently shared food support with their household contacts, potentially reducing the positive impact of the nutritional intervention for the person with TB (Web Annex D) *(78)*. This practice underscores the importance of addressing household vulnerability as a whole and not just providing support to the person with TB.

The GDG determined that the RATIONS trial showed a large desirable effect in reducing TB incidence. Noting that the available evidence consisted of one trial conducted in an area with a high prevalence of food insecurity and undernutrition, the GDG agreed on a strong recommendation specifically for food insecure settings.

Although the evidence supporting this intervention relates to TB prevention among household contacts, the GDG agreed that the recommendation should apply to the entire household, including the individuals with TB, regardless of their nutritional status, to ensure equity in the household and in line with the trial's approach. Data from studies identified in the systematic review on micronutrients (Section 2.3.1) did not demonstrate a difference in TB treatment outcomes among people with TB who received multiple micronutrient supplements compared with those who received no multiple micronutrients or placebo. Countries might therefore consider whether they should provide food baskets with multiple micronutrient supplements or food baskets alone to the people with TB in such households.

2.2.2 Subgroup considerations for people with TB and household contacts

These recommendations apply to all people with TB and household contacts in food insecure settings, including the subpopulations described below.

People with comorbidities

People with TB and their household contacts may have comorbidities or health-related risk factors (e.g. HIV, diabetes, smoking, mental health conditions, and alcohol or drug use), which may have their own nutritional implications and should be addressed alongside nutritional interventions. Nutritional support may need to be adjusted depending on the degree of undernutrition and the specific nutritional requirements of people with these comorbid conditions. Close collaboration between health care providers is therefore important to assure comprehensive care.

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[10] Pranay Sinha, Boston University, unpublished data, 16 May 2024. Preprint: https://doi.org/10.1101/2023.12.30.23300673.

[11] The ICER of US$ 197 per DALY averted was presented to the GDG during a preparatory webinar, whereas the publication referenced here reports US$ 208 per DALY averted.

Pregnant women, infants, children and older people

WHO recommends that children aged 6–59 months with wasting and/or nutritional oedema and severe medical problems should be admitted for inpatient care and this may also be a consideration for other age groups *(34)*. Children with wasting but without medical problems that require inpatient admission can be managed in outpatient care. Recommendations relating to nutritional interventions for children aged below 5 years, pregnant or postpartum women and older people can be found in the related WHO guidance *(34-37)*. People who are aged 5 years and older and have severe undernutrition or wasting may also require treatment in an inpatient facility.

2.2.3 Implementation considerations for people with TB and household contacts

Eligibility for food assistance

The recommendation on food assistance for households is targeted at households in settings of food insecurity. These households may be eligible for support offered by other programmes or stakeholders. Depending on the context, a country may decide to apply this recommendation for all households of people with TB if there is a high level of food insecurity within the country, or they may choose to select geographical regions that experience high food insecurity. Alternatively, they may apply the recommendation to specific populations (e.g. nomadic populations, people experiencing homelessness, displaced populations or people living in informal settlements) that are food insecure, or they might assess food insecurity at the household level.

Food insecurity as defined by the Food and Agriculture Organization of the United Nations (FAO) is a situation when people lack regular access to enough safe and nutritious food for normal growth and development, and an active and healthy life *(79)*. Food insecurity is measured by the FAO using its Food Insecurity Experience Scale (FIES) *(42)*, which is the basis for SDG Indicator 2.1.1: the prevalence of moderate or severe food insecurity. National prevalence estimates (3-year averages) of moderate or severe food insecurity (combined), and severe food insecurity only, are available for most countries at the related FAO websites for Food Security Indicators (FAOSTAT) *(80)* and the FAO Hunger Map *(81)*. The FIES is generally not recommended to be used at the household level; however, some countries have adapted a subset of questions from the FIES or similar scales for use at the household level *(82, 83)*. In addition, the Integrated Food Security Phase Classification (IPC) regularly publishes national and subnational assessments of acute food insecurity for a set of countries and territories exposed to food crises *(84)*.

The RATIONS trial demonstrated the impact of food assistance in preventing TB in household contacts of a person with bacteriologically confirmed pulmonary TB. All people with presumptive TB should have access to a WHO-recommended rapid diagnostic test. However, bacteriological confirmation may be challenging in certain populations; for example, those who have difficulty producing sputum or who have paucibacillary sputum (e.g. people living with HIV and children). In addition, access to diagnostic tests for bacteriological confirmation can vary between populations and geographical locations *(85)*. Lack of bacteriological confirmation should not be a barrier to receiving food assistance for households in need; therefore, it is recommended that countries align their approach to food assistance with that of TB screening in household contacts.[12]

[12] WHO recommends that contact screening should always be done in the following circumstances: when a person with TB has bacteriologically confirmed pulmonary TB, has proven or presumed MDR-TB or extensively drug-resistant TB, is a person living with HIV or is a child aged below 5 years. Contact investigation may also be performed for TB patients with all other forms of disease.

Collaboration with key stakeholders

During planning and implementation, national TB programmes should work closely with nutrition and food assistance programmes, social protection services, maternal and child health services and national AIDS programmes to align synergies and maximize resources. UN agencies, international or civil society organizations and community-based organizations who are working on food assistance and nutritional interventions may provide support with logistics, transportation and human resources. Collaboration with national bodies and coordination platforms for food security is important to gain an understanding of food insecurity within a country.

People from households experiencing food insecurity should be referred for social support and social protection, where available. Given that TB is a marker of poverty, it is important to liaise with government departments and agencies working on food insecurity and poverty reduction to ensure that households of people with TB have access to existing food support and social protection programmes. Further guidance on social protection for people with TB can be found in the WHO and International Labour Organization publication *Guidance on social protection for people affected by tuberculosis (86)*.

Modalities of food assistance and nutritional interventions

In general, the same approaches to undernutrition management in people without TB should apply to people with TB, and the same established standards of care should be applied. Further guidance will be available in the undernutrition section of the latest edition of the *WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities*, and can be found in related WHO guidance *(34-38)*.

Programmes should work with stakeholders involved in addressing undernutrition and food insecurity to align approaches and modalities of delivering food assistance and nutritional interventions, and to optimize the use of resources. Appropriate nutritional interventions should include the use of specially formulated foods where indicated, and food baskets or financial support. The types of food assistance and nutritional interventions that might be considered are listed below.

Specially formulated foods: These are foods that have been specifically designed, manufactured, distributed and used according to Codex Alimentarius for either special medical purposes *(87)* or special dietary uses (e.g. ready-to-use therapeutic foods, used to treat children with severe undernutrition; and ready-to-use supplementary foods and fortified blended foods, used to supplement children with moderate undernutrition) *(88)*.

Direct food provision: This refers to the provision of free food or food baskets. Consideration should be given to infrastructure needs and storage requirements before distribution and at the household level. The content of the food baskets, the weight of the food support, and the frequency of collection or delivery should also be considered.

For the prevention of TB in household contacts, countries should aim to ensure that the nutritional composition of food baskets is aligned with that provided in the RATIONS trial (750 kcal, 23 g of protein per day with multiple micronutrients per person). The food basket in the RATIONS trial included split peas and rice; when combined, these foods provide all the essential amino acids of a high-quality protein. In settings where resources allow, other high-quality protein sources may be added to the food rations (e.g. milk powder or eggs).

For people with TB, consideration should be given to the extra calorific requirements and nutritional needs. The RATIONS trial provided 1200 kcal and 52 g of protein per day, and multiple micronutrients. The food baskets provided to adults with TB in the RATIONS trial consisted of 5 kg rice, 3 kg Bengal gram flour (chickpea flour), 1.5 kg milk powder and 500 mL vegetable oil.

Data on acceptability from the RATIONS trial presented to the GDG highlighted the need to ensure that food was culturally compatible and that households can appropriately store the foods provided (Web Annex D) *(78)*. Therefore, the composition of food baskets should be adapted to the local context and to the type of diet available locally. More practical food items that do not require refrigeration may also be a preferred option. For example, in emergency situations, the World Food Programme food baskets contain wheat flour or rice, lentils, chickpeas or other pulses, vegetable oil (fortified with vitamin A and D), sugar and iodized salt *(89)*. In situations where people have access to some but not enough food, or have mild undernutrition, a supplementary ration (consisting of a fortified blended food, sugar and vegetable oil) may be an alternative *(90)*. Four studies included in the systematic review provided arginine-rich food or supplementation. Arginine is an amino acid found in foods such as groundnuts, soy, beans, fish and dairy products *(20, 91)*.

Financial support: If financial support is the preferred intervention (rather than direct provision of food) for addressing undernutrition or food insecurity, that support should be sufficient to cover the cost of food baskets or supplementary food rations as appropriate, for at least the duration of TB treatment. Where financial support is provided for nutritional interventions or food assistance, it is important to ensure that there is enough food available in the market to buy. Financial support may be provided through, for example, cash transfer, bank transfer, post office payment, voucher, mobile money *(92)*, prepaid debit card or blockchain technology *(93)*. Whatever the modality of nutritional intervention, financial support should also be provided to mitigate income loss and to cover nonmedical costs, and affected households should always be linked to existing social protection programmes if they are eligible.

Psychosocial support: There is a high prevalence of mental health conditions among people with TB, which is further exacerbated by concerns about poverty and food insecurity *(94, 95)*. Psychosocial interventions can improve TB treatment outcomes *(47, 94, 96, 97)*. Such interventions, which focus on psychological, behavioural and social factors, can include psychoeducation, stress reduction, strengthening of social support and promotion of daily activity functioning *(96)*. Although not a standalone nutritional intervention, psychosocial support may be used to boost other forms of nutritional intervention and social protection *(86)*.

Human resource requirements

Increased human resources, capacity-building, task shifting and supportive supervision for health workers of all cadres will be needed for the delivery of nutritional interventions. Requirements will vary with the level of involvement of other stakeholders.

GDG members noted that – in settings where the health worker delivers the intervention to the affected household – health worker buy-in is key for the effective provision of nutritional interventions. Furthermore, in neighbourhoods of food insecurity, health workers and the individuals or households receiving nutritional interventions or food assistance might feel obliged to share the support with others in need. Sensitization and clear messaging should be provided to both health workers and household recipients about the therapeutic impact of food in preventing TB in the household and improving TB treatment outcomes. This may also help to increase buy-in from the health workers and reinforce the value of their work.

Delivery of nutritional interventions

Programmes should ensure that nutritional interventions are provided discreetly, in a way that does not give rise to stigmatization and discrimination, and does not advertise or inadvertently disclose the TB status of the household to the community.

If food support is to be provided, transportation should be factored into planning and budgeting. Household members may prefer to collect food rations rather than have them delivered. In such cases, reimbursement for additional transportation costs might need to be considered. Programmes should aim for flexibility in timing and frequency of collection or delivery.

The choice of delivery of financial interventions should ensure that the most vulnerable, including those without identity documents or mobile phones, can receive assistance.

2.3 Micronutrient supplementation in people with TB

WHO recommendation

7. Vitamin D supplementation may be provided to people with TB in the context of rigorous research. **NEW**
(New recommendation: conditional recommendation, low certainty of evidence)

2.3.1 Justification and evidence

Undernutrition is a common consequence of TB disease, due to TB-related changes in macronutrient and micronutrient status *(98)*. Micronutrients (vitamins and minerals) are required for metabolic processes. Low serum concentrations of micronutrients (e.g. vitamins A, E and D; and the minerals iron, zinc and selenium) have been reported from cohorts of patients starting treatment for TB disease *(99, 100)*. Macronutrients and micronutrients work together to contribute to tissue regeneration and cellular integrity.

2.3.1.1 Single micronutrients

The systematic review for PICO Question 2 identified 33 RCTs (36 publications) that provided data on the effect of single micronutrients (vitamin A, vitamin D, selenium or zinc) compared with no micronutrients or placebo, for people with TB *(52, 100-134)*. The overall certainty of evidence for each micronutrient intervention was rated as low. The provision of vitamin B6 (pyridoxine) alongside isoniazid-based treatment of TB infection and disease is already recommended and is an established practice for individuals at risk of peripheral neuropathy, including people living with HIV and people with undernutrition *(46, 135)*. Vitamin B6 was therefore not included in this systematic review.

Recommendation 7:
Vitamin D for people with TB in research settings

Vitamin D supplementation: Evidence from two trials suggests that vitamin D supplementation may result in an increase in TB cure (2 trials, *n*=570, RR 1.25 [95% CI: 1.09, 1.43], low certainty evidence) *(108, 128)*. The data from these two trials came from two different populations and used different approaches to participant selection and vitamin D administration. Participants (*n*=500) from one trial in Egypt came from a population with a high prevalence of vitamin D deficiency but their serum vitamin D levels were not measured *(108)*. Participants (*n*=70) from the other trial in China had recorded vitamin D deficiency *(128)*. The vitamin D dosing in the two studies also differed.

The evidence is very uncertain on the effect of vitamin D supplementation, compared with placebo or no vitamin D, for adverse events (4 trials, *n*=1246, RR 0.70 [95% CI: 0.50, 0.99], very low certainty evidence) *(104, 108, 124, 127)*, serious adverse events (4 trials, *n*=1577, RR 1.06 [95% CI: 0.38, 2.95], very low certainty evidence) *(52, 106, 116, 122)*, change in BMI (4 trials, *n*=1088, MD 0.09 [95% CI: –0.37, 0.55], very low certainty evidence) *(106, 120, 126)*, and change in serum vitamin D (4 trials, *n*=663, standardized MD 4.10 [95% CI: 2.64, 5.56], very low certainty evidence) *(101, 106, 111, 129)*. There was probably no difference in the risk of death during TB treatment between the intervention arm and the control arm (7 trials, *n*=2455, RR 1.20 [95% CI: 0.78,1.84], moderate certainty evidence) *(52, 104, 106, 116, 120, 127, 133)*.

The GDG noted the increase in TB cure and that the balance of desirable effects probably outweighed the undesirable effects. GDG members therefore agreed on a conditional recommendation in favour of the intervention. It was highlighted, however, that the data on TB cure were based on two trials that were rated low certainty evidence owing to a high risk of bias. The GDG noted that dosing differed between the two trials, and that one trial included participants with vitamin D deficiency only, whereas the other did not measure participants' serum vitamin D levels. There was no significant impact on other critical or important TB treatment outcomes. The GDG therefore agreed that vitamin D supplementation may be provided as part of TB treatment within the context of rigorous research, to answer outstanding questions such as dosage, the nutrient status of the target population and the impact of vitamin D on other TB treatment outcomes.

Other single micronutrients: The review found no association between vitamin A or zinc supplementation and the risk of death or TB treatment completion compared with the control group *(114, 115, 118, 130)*; there was also no association between zinc supplementation and TB cure or change in BMI *(113, 118)*. There were no data on the association of selenium with TB treatment outcomes, change in weight or BMI *(109)*. However, supplementation of vitamin A, selenium and zinc were each associated with increased serum levels of the respective micronutrients *(107, 109, 115, 118, 131)*. The certainty of evidence ranged from very low to moderate. Details of these outcomes are given in the GRADE summary of findings tables in Web Annex B.

The GDG observed that the data did not demonstrate any desirable effect of vitamin A, selenium and zinc on the critical and important TB treatment outcomes, or on any other critical outcomes other than micronutrient serum levels. After considering benefits, harms, resource implications, feasibility, acceptability and equity, the GDG agreed that an increase in micronutrient levels alone would not be sufficient to support a recommendation for or against the provision of these micronutrients to people with TB; therefore, they judged that no recommendations should be made.

2.3.1.2 Multiple micronutrients

The systematic review for PICO Question 2 identified 18 publications (17 trials) assessing the effect of multiple micronutrient supplements, defined as a single administration of two or more micronutrients, compared with no micronutrients or placebo in people with TB, on the outcomes rated as critical *(22, 98, 100, 102, 103, 107, 110, 112, 114, 115, 118, 119, 121, 125, 126, 134, 136, 137)*. The overall certainty of evidence was moderate.

The systematic review found that the provision of multiple micronutrients probably shows no difference in the critical outcomes of TB cure, treatment completion, mortality or change in weight or body mass (see Web Annex B). These findings were also consistent among studies that included only children *(22, 100, 115)*. In addition, no associated difference was found for death, TB treatment completion, and change in weight or body mass among people living with HIV (see Web Annex B) *(119, 121, 137)*. Multiple micronutrient supplements may result in an increased risk of blurred vision

(1 trial, *n*=373, RR 2.77 [95% CI: 1.11, 6.92], low certainty evidence) *(126)*, and probably increased serum levels of copper at 6 months (1 trial, *n*=403, standardized MD 1.81 [95% CI: 1.57, 2.04], moderate certainty evidence) *(115)*.

Multiple micronutrient supplements may result in a slight reduction in time to sputum culture conversion at 2 months (2 trials, *n*=385, MD –0.54 weeks [95% CI: –0.95, –0.13], low certainty evidence) *(114, 118)*. An important finding was that multiple micronutrients may result in a reduction in relapse among people living with HIV not on antiretroviral therapy (ART) (1 trial, *n*=241, RR 0.37 [95% CI: 0.15, 0.92], low certainty evidence). However, this evidence was not deemed to be sufficient to support any recommendation, given that ART is now recommended for all people living with HIV, regardless of CD4 cell count *(137)*.

After reviewing the data, and considering the desirable effects, harms, resource implications, feasibility and acceptability, the GDG agreed that the balance of desirable over undesirable effects did not favour the provision of multiple micronutrients as a nutritional intervention for people with TB, unless those micronutrients are otherwise indicated.

The GDG therefore agreed that the recommendation outlined in the 2013 guidelines on nutritional care and support for patients with TB *(11)* – "A daily multiple micronutrient supplement at 1× recommended nutrient intake should be provided in situations where fortified or supplementary foods should have been provided in accordance with standard management of moderate undernutrition" – should no longer apply as a standalone intervention to improve TB treatment outcomes.

In addition, it was agreed that the recommendations for pregnant and postpartum women outlined in the guidelines on nutritional care and support for patients with TB *(11)* should be retired. This decision was based on the fact that there were no data identified in the review that related specifically to pregnant and postpartum women with TB. Thus, for pregnant and postpartum women with TB, countries should refer to the updated guidelines on single and multiple micronutrient supplementation for the general population of pregnant and postpartum women *(35, 37, 138-140)*.

2.3.2 Subgroup considerations

In general, micronutrient supplementation is not recommended by WHO unless there is evidence of micronutrient deficiency or clear evidence to show a positive impact on a given condition compared with any undesirable effects. Hence, the only population for which WHO recommends vitamin D supplementation, outside the context of rigorous research, is very low birth weight infants aged below 6 months *(141)*. Vitamin D supplementation is not recommended for pregnant women unless they have documented vitamin D deficiency *(35, 139)*. A GDG that reviewed the evidence on vitamin D supplementation during pregnancy in 2019 concluded that there was insufficient evidence to assess the balance of desirable and undesirable effects of such supplementation during pregnancy *(139)*.

2.3.3 Implementation considerations

An intervention that is recommended only in the context of rigorous research indicates that there are important uncertainties about the intervention. In such instances, implementation should take the form of research that aims to address unanswered questions and uncertainties related both to the efficacy or effectiveness and the safety of the intervention, and to its acceptability and feasibility *(37)*. In addition to clinical trials, rigorous research includes implementation research using high-quality methods appropriate to the specific research questions *(138)*. Proposed research questions related to the use of vitamin D during TB treatment are listed in Chapter 4 (Research gaps).

As part of counselling, all people with TB should be encouraged and supported to be adequately nourished, which is best achieved through consumption of a healthy, balanced diet that contains the nutrients they require, including vitamin D, calcium and other micronutrients. People with TB should also be advised that sunlight is the most important source of vitamin D. Programmes may consider the inclusion of foods (e.g. oil or margarine) fortified with vitamin D as part of nutritional interventions provided to people with TB, particularly in settings with a high prevalence of vitamin D deficiency, according to the related WHO guidance *(142-144)*. In some countries with a high prevalence of vitamin D deficiency in the population, fortified foods may already be made available as part of a national public health strategy *(145, 146)*.

As part of updating national guidelines on TB and undernutrition, programmes will need to revise their guidance relating to micronutrients for people with TB. They will need to update health education materials to include clear messaging on the importance of a healthy balanced diet. Pregnant women with TB should receive nutritional care as per WHO guidelines for pregnant women who do not have TB *(35, 37, 138-140)*.

2.4 TB screening for people with undernutrition and people with structural risk factors such as food insecurity

WHO recommendations
8. In settings where the TB prevalence in the general population is 100/100 000 population or higher, systematic screening for TB disease may be conducted among people with a risk factor for TB[a] who are either seeking health care or who are already in care. *(Existing recommendation: conditional recommendation, very low certainty of evidence)*
9. Systematic screening for TB disease may be conducted among subpopulations with structural risk factors for TB.[b] These include urban poor communities, homeless communities, communities in remote or isolated areas, indigenous populations, migrants, refugees, internally displaced persons and other vulnerable or marginalized groups with limited access to health care. *(Existing recommendation: conditional recommendation, very low certainty of evidence)*

a Undernutrition is a recognized risk factor for TB, and malnourishment is listed as one of the key risk factors to consider for TB screening.

b Structural risk factors for TB also include food insecurity.

2.4.1 Justification and evidence

These recommendations are published in the 2021 *WHO consolidated guidelines on tuberculosis. Module 2: screening – systematic screening for tuberculosis disease (12)*. People with undernutrition are at higher risk of TB *(3)*. Populations with structural risk factors for TB are those who are at an increased risk of TB and of poor health outcomes from TB owing to structural determinants in their environment. Structural risk factors for TB include poverty; food insecurity; overcrowded and poorly ventilated conditions for living, working and gathering; and limited or no access to health care *(147, 148)*.

Recommendation 8:
TB screening among people with undernutrition

A systematic review found that lower BMI is associated with an increased risk of TB, with an increase in TB incidence of 13.8% (95% CI: 13.4–14.2) per unit decrease in BMI within the range 18.5–30 kg/m^2 *(6)*. There are multiple pathways by which undernutrition can increase the risk of TB, including cell-mediated immunity and micronutrient deficiency; also, other conditions (e.g. mental health and

substance use disorders) can increase the risk of malnourishment and TB. A full list of other risk factors to consider for TB screening in settings with a TB prevalence of 100 per 100 000 population or higher is given in the *WHO consolidated guidelines on tuberculosis. Module 2: screening – systematic screening for tuberculosis disease (12)*.

Recommendation 9:
TB screening among people with food insecurity
Observational studies conducted during 2013–2020 suggest that TB screening conducted among populations affected by structural risk factors may initially increase TB case notifications and decrease TB prevalence; however, all studies had a major risk of bias *(12)*.

2.4.2 Implementation considerations

Screening among people attending health services should be conducted in addition to passive case-finding (i.e. proper triaging and evaluation of people seeking care who report signs or symptoms of TB). Passive case-finding should be done in all settings, and is particularly important among people who have risk factors for TB.

WHO also recommends systematic screening in other groups who are at high risk of exposure to TB or of progression to TB disease, or who have limited access to TB services. The following risk groups should always be systematically screened for TB: household and close contacts of people with TB, people living with HIV, people exposed to silica (mainly some miners), and people in prisons and penitentiary institutions *(12)*.

Groups should be prioritized based on their risk of TB, the risk of poor treatment outcomes if diagnosis is delayed and the size of the risk group in a given setting. Although undernutrition and food insecurity are not an indication for TPT, some people in these populations (e.g. people with HIV and household contacts of people with TB) will be eligible for TPT. Details on eligibility for TPT are published in the *WHO consolidated guidelines on tuberculosis. Module 1: prevention – tuberculosis preventive treatment, second edition (46)*.

Due to the inherent lack of access to health care experienced by people with structural risk factors, screening interventions would need to be extended into the communities where members of these populations live and work, to achieve effective reach and coverage. The list of potential populations affected by structural risk factors included in this recommendation is not exhaustive; hence, this recommendation may apply to other groups that have a high risk of TB and poor access to health care, including poor access to high-quality TB services.

There is no evidence about the effectiveness of different screening intervals; in the absence of such evidence, the choice of screening interval should be guided by feasibility. As far as possible, community screening should be combined with screening for other diseases or risk factors, and with health-promotion or social support activities and provision of adequate referral pathways to ensure linkage to care when indicated. Additional operational considerations for TB screening in refugee camps and among displaced populations are outlined in *Tuberculosis prevention and care among refugees and other populations in humanitarian settings: an interagency field guide (149)*.

Further details on systematic screening for the different populations can be found in the *WHO consolidated guidelines on tuberculosis. Module 2: screening – systematic screening for tuberculosis disease (12)* and the accompanying operational handbook *(150)*.

3. Monitoring and evaluation

Evidence on the nutritional status of people with TB is important for understanding the nature of the TB epidemic at subnational and national levels. It can also be used to advocate for further support from other stakeholders within government and within nongovernmental sectors, in terms of both food assistance, and social protection and support.

Countries are encouraged to monitor and evaluate the impact of implementation of the new recommendations on TB and undernutrition on nutritional recovery and TB treatment outcomes in people with TB. They should also monitor and evaluate the impact on TB incidence within the households of people with TB. This can be achieved through periodic surveys or through routine monitoring.

On an individual basis, nutritional assessment of people with TB at the start of treatment and throughout its duration is important to understand the degree of clinical recovery or decline. If the data are not already captured, recording and reporting tools should be updated and health workers should be trained to capture data on the assessment and management of undernutrition in people with TB. Efforts should be made to ensure that the data from nutritional assessment and interventions for household contacts are captured within the appropriate health management information systems. Digital applications (apps) may be adapted to capture data on the nutritional status of people with TB and their household contacts.

A list of suggested indicators will be included in the latest edition of the accompanying operational handbook.

4. Research gaps

Similar to the approach recommended for TB treatment regimens, future research should be adequately powered and should report on a harmonized set of outcomes, aligned with WHO-defined TB treatment outcomes and measures of nutritional recovery, to maximize the possibility for future meta-analyses *(151)*. Examples of outcomes to measure include death during TB treatment, TB cure, TB treatment completion, TB treatment success, loss to follow-up from TB treatment, relapse, time to sputum conversion and nutritional outcomes (e.g. change in weight using anthropometric measurement and other outcomes) *(151)*.

Where feasible, research investigators should consider analyses of the following subpopulations: people with TB with mild, moderate or severe undernutrition (using WHO age-appropriate cut-off measurements); people without undernutrition; people with and without micronutrient deficiency; people living with HIV; people with diabetes; pregnant, postpartum and breastfeeding women; children; infants; elderly people; and people with substance use disorders.

Research gaps identified during the GDG meeting are listed below:

Nutritional assessment and counselling of people with TB and their household contacts

- Effective criteria and thresholds for weight change at different time points for monitoring nutritional and clinical recovery or deterioration in people with TB who have undernutrition.
- Effectiveness, feasibility and acceptability of different methodologies to simplify nutritional assessment of household contacts in the community.
- The best measure of nutritional status in pregnant women, with and without TB, considering both maternal and infant outcomes.
- The optimal BMI for healthy maternal and infant outcomes in pregnant women with TB.
- Effectiveness, feasibility and acceptability of different approaches and frequency of nutritional counselling that enhance the effectiveness and uptake of advice on nutritional outcomes.

Nutritional interventions (e.g. food baskets, ready-to-use therapeutic foods, food vouchers or cash transfers) for people with TB

- Ideal composition and duration of nutritional supplementation for people with TB, during TB treatment and afterwards.
- Comparison of the effectiveness, feasibility, acceptability and cost–effectiveness of different interventions such as food baskets, food vouchers and cash transfers, including in communities that experience food insecurity.
- Optimal nutritional management among people with TB and diabetes.

Micronutrient supplementation for people with TB

- The effectiveness of vitamin D supplementation as an additional component of nutritional interventions (e.g. food baskets) provided to people with TB and vitamin D deficiency, or in populations with high levels of vitamin D deficiency, compared with nutritional interventions only.
- The most effective, acceptable and feasible dose, frequency and duration (during and after treatment) of vitamin D supplementation.
- The most effective, acceptable and feasible method of administration of vitamin D (pills, sprays or fortified foods).
- The cost–effectiveness of vitamin D supplementation and fortified foods in different contexts, including the cost per additional cure for people with TB.
- The acceptability and feasibility among people with TB and care providers of testing vitamin D levels and the provision of vitamin D to people with TB.
- The association of undernutrition, measured by low BMI and weight-for-height, weight-for-age in people with TB and vitamin D deficiency in settings with high and low burden of vitamin D deficiency.
- The risk of micronutrient deficiencies in people with TB in relation to people without TB.
- The micronutrient requirements, including dosing and duration, of people with TB.
- The additional benefit of multiple micronutrient supplements and food baskets for people with TB, compared with food baskets alone.
- The cost–effectiveness of micronutrients and food baskets for people with TB with and without undernutrition, compared with food baskets alone.

Food assistance for household contacts of people with TB

- Comparison of the effectiveness, acceptability, feasibility and cost–effectiveness of different forms of interventions (e.g. food baskets, food vouchers or cash transfers) in preventing TB in household contacts in different settings.
- The effectiveness of multiple micronutrient supplements as an additional component of food baskets, compared with food baskets alone for household contacts in preventing TB.
- The optimal composition of nutritional supplementation for household contacts of people with TB, and people in prisons and other places of incarceration in preventing TB.
- The effectiveness of food assistance combined with TPT compared with TPT alone in preventing TB among household contacts in settings of food security.

Supplementary table: summary of changes to recommendations

Recommendation in the 2013 publication *Guideline: nutritional care and support for patients with tuberculosis*	**Recommendation in the 2025 nutrition section of *WHO consolidated guidelines on tuberculosis. Module 6: tuberculosis and comorbidities***
Nutritional assessment and counselling	
People with TB	
All individuals with active TB should receive (i) an assessment of their nutritional status and (ii) appropriate counselling based on their nutritional status at diagnosis and throughout treatment. *(Strong recommendation, no available evidence)*	At diagnosis and throughout treatment, all individuals with TB should be offered nutritional assessment and appropriate counselling based on their nutritional status. *(Existing recommendation with language edit: strong recommendation, no direct evidence available)*
Household contacts	
In settings where contact tracing is implemented, household contacts of people with active TB should have a nutrition screening and assessment as part of contact investigation. If malnutrition is identified, it should be managed according to WHO recommendations. *(Conditional recommendation, very low certainty of evidence)*	Household contacts of people with TB should be offered nutritional assessment and counselling as part of contact tracing. If undernutrition is identified, it should be managed according to WHO guidance. *(New recommendation: strong recommendation, low certainty of evidence)*
Nutritional interventions	
People with TB	
School-age children and adolescents (5 to 19 years), and adults, including pregnant and lactating women, with active TB and severe acute malnutrition should be treated in accordance with the WHO recommendations for management of severe acute malnutrition. *(Strong recommendation, very low certainty of evidence)*	Incorporated into a single new recommendation, applicable to all subpopulations: Nutritional interventions should be offered to individuals with TB who have severe, moderate or mild undernutrition, as part of a comprehensive package of TB care. *(New recommendation: strong recommendation, low–moderate certainty of evidence)*
Children who are less than 5 years of age with active TB and severe acute malnutrition should be treated in accordance with the WHO recommendations for the management of severe acute malnutrition in children who are less than 5 years of age. *(Strong recommendation, very low certainty of evidence)*	
School-age children and adolescents (5 to 19 years), and adults, including lactating women, with active TB and moderate undernutrition, who fail to regain normal body mass index after 2 months' TB treatment, as well as those who are losing weight during TB treatment, should be evaluated for adherence and comorbid conditions. They should also receive nutrition assessment and counselling and, if indicated, be provided with locally available nutrient-rich or fortified supplementary foods, as necessary to restore normal nutritional status. *(Conditional recommendation, low certainty of evidence)*	
Children who are less than 5 years of age with active TB and moderate undernutrition should be managed as any other children with moderate undernutrition. This includes provision of locally available nutrient-rich or fortified supplementary foods, in order to restore appropriate weight-for-height. *(Strong recommendation, very low certainty of evidence)*	

Recommendation in the 2013 publication *Guideline: nutritional care and support for patients with tuberculosis*	Recommendation in the 2025 nutrition section of *WHO consolidated guidelines on tuberculosis. Module 6: tuberculosis and comorbidities*
Pregnant women with active TB and moderate undernutrition, or with inadequate weight gain, should be provided with locally available nutrient-rich or fortified supplementary foods, as necessary to achieve an average weekly minimum weight gain of approximately 300 g in the second and third trimesters. *(Strong recommendation, very low certainty of evidence)*	
Patients with active multidrug-resistant TB and moderate undernutrition should be provided with locally available nutrient-rich or fortified supplementary foods, as necessary to restore normal nutritional status. *(Strong recommendation, very low certainty of evidence)*	
	A package of treatment adherence interventions may be offered for patients on TB treatment in conjunction with the selection of a suitable treatment administration option. *(Existing recommendation: conditional recommendation, low certainty of evidence)* Source: *WHO consolidated guidelines on tuberculosis. Module 4: treatment and care*
	One or more of the following treatment adherence interventions (complementary and not mutually exclusive) may be offered to patients on TB treatment or to health care providers: a) Tracers or digital medication monitor. *(Conditional recommendation, very low certainty of evidence)* b) Material support to patient. *(Conditional recommendation, moderate certainty of evidence)* c) Psychological support to patient. *(Conditional recommendation, low certainty of evidence)* d) Staff education. *(Conditional recommendation, low certainty of evidence)* *(Existing recommendation)* Source: *WHO consolidated guidelines on tuberculosis. Module 4: treatment and care*
Households of people with TB	
	In settings of food insecurity, food baskets in combination with multiple micronutrient supplements should be offered to all households of people with TB. *(New recommendation: strong recommendation, moderate certainty of evidence)*

Recommendation in the 2013 publication *Guideline: nutritional care and support for patients with tuberculosis*	Recommendation in the 2025 nutrition section of *WHO consolidated guidelines on tuberculosis. Module 6: tuberculosis and comorbidities*
Micronutrient supplementation	
People with TB	
A daily multiple micronutrient supplement at 1× recommended nutrient intake should be provided in situations where fortified or supplementary foods should have been provided in accordance with standard management of moderate undernutrition, but are unavailable. *(Conditional recommendation, very low certainty of evidence)*	Withdrawn.
All pregnant women with active TB should receive multiple micronutrient supplements that contain iron and folic acid and other vitamins and minerals, according to the United Nations Multiple Micronutrient Preparation, to complement their maternal micronutrient needs. *(Conditional recommendation, very low certainty of evidence)*	Redundant and replaced by WHO guidance on micronutrient supplementation during pregnancy, regardless of TB status: *WHO antenatal care recommendations for a positive pregnancy experience. Nutritional interventions update: multiple micronutrient supplements during pregnancy (138)* *WHO recommendations on antenatal care for a positive pregnancy experience (35)*
For pregnant women with active TB in settings where calcium intake is low, calcium supplementation as part of antenatal care is recommended for the prevention of pre-eclampsia, particularly among those pregnant women at higher risk of developing hypertension, in accordance with WHO recommendations. *(Strong recommendation, very low certainty of evidence)*	
All lactating women with active TB should be provided with iron and folic acid and other vitamins and minerals, according to the United Nations Multiple Micronutrient Preparation, to complement their maternal micronutrient needs. *(Conditional recommendation, very low certainty of evidence)*	Redundant and replaced by WHO guidance on micronutrient supplementation during the postpartum period, regardless of TB status: *WHO recommendations on maternal and newborn care for a positive postnatal experience (37)*
	Vitamin D supplementation may be provided to people with TB in the context of rigorous research. *(New recommendation: conditional recommendation, low certainty of evidence)*

Recommendation in the 2013 publication *Guideline: nutritional care and support for patients with tuberculosis*	Recommendation in the 2025 nutrition section of *WHO consolidated guidelines on tuberculosis. Module 6: tuberculosis and comorbidities*
TB screening	
	In settings where the TB prevalence in the general population is 100/100 000 population or higher, systematic screening for TB disease may be conducted among people with a risk factor for TB who are either seeking health care or who are already in care. *(Existing recommendation: conditional recommendation, very low certainty of evidence)* Source: *WHO consolidated guidelines on tuberculosis. Module 2: screening – systematic screening for tuberculosis disease*
	Systematic screening for TB disease may be conducted among subpopulations with structural risk factors for TB. These include urban poor communities, homeless communities, communities in remote or isolated areas, indigenous populations, migrants, refugees, internally displaced persons and other vulnerable or marginalized groups with limited access to health care. *(Existing recommendation: conditional recommendation, very low certainty of evidence)* Source: *WHO consolidated guidelines on tuberculosis. Module 2: screening – systematic screening for tuberculosis disease*

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