WHO operational handbook 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)*. The TB epidemic is attributable to five main health-related risk factors globally, namely, diabetes mellitus (diabetes), HIV, smoking, undernutrition, and disorders due to alcohol use. The contribution of these risk factors to the global TB burden is reported annually in the *WHO global tuberculosis report (1)*. For this operational handbook, a health-related risk factor is defined as a condition or action that increases the risk of TB disease *(2)*. When they occur in people with TB, health-related risk factors are also considered comorbidities, and may lead to poor TB treatment outcomes, lower health-related quality of life, or other suboptimal health or social outcomes, such as increased out-of-pocket costs or TB-associated disabilities.

The impact of these risk factors for TB differs between and even within countries. Collectively, they account for just under half of the new TB episodes globally *(1)*. Other significant health-related risk factors for TB disease include silicosis and disorders due to drug use. 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 (such as musculoskeletal or neurological), all of which require specialized care or rehabilitation during TB treatment and after TB treatment completion. People with TB may also have multiple comorbidities or health-related risk factors which require holistic people-centred care in the context of universal health coverage.

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

The political declaration of the 2023 United Nations High Level Meeting on the fight against TB reaffirmed the commitment to ending the TB epidemic globally by 2030, in line with the Sustainable Development Goals *(4, 5)*. In the declaration, Member States committed to a comprehensive response that addresses TB and comorbidities, as well as social and economic determinants of the epidemic, and that protects and fulfils all people's human rights and dignity *(4)*. This commitment was echoed in the latest United Nations High Level Meeting declarations on noncommunicable diseases and on HIV in 2018 *(6)* and 2021 *(7)*, respectively, in which Member States committed to assuring integrated people-centred services for TB, HIV, noncommunicable diseases and mental health.

Although global guidance on interventions to address TB and key comorbidities exists, its uptake has been variable. This operational handbook aims to support countries in scaling up people-centred care, based on the latest WHO recommendations on TB and key comorbidities, and drawing upon additional evidence, best practices and advice from experts, garnered through WHO processes.

This operational handbook is complementary to and should be used in conjunction with the *WHO consolidated guidelines on tuberculosis. Module 6: tuberculosis and comorbidities* (in press) and it also aligns with WHO's *Framework for collaborative action on tuberculosis and comorbidities (2)*. While the consolidated guidelines summarize WHO recommendations on TB and comorbidities and the evidence and processes behind them, this 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. It focuses on actions in five key areas and is underpinned by six principles that are fundamental to implementation *(2)*.

Objectives

The objectives of the operational handbook are to:

- support Member States to implement and scale up WHO recommendations on TB, comorbidities and health-related risk factors for TB;
- inform the development of national TB strategic plans and other relevant health strategies, guidelines and tools on integrated people-centred care for people with TB and comorbidities; and
- contribute to high quality people-centred care for people at risk of TB or with TB disease, and for people with comorbidities and health-related risk factors, contributing to improved health, social and economic outcomes over the longer term.

Structure and evolution

The first edition of the operational handbook on TB comorbidities focused entirely on mental health. In the second edition a section on HIV-associated TB has been added. Subsequent editions will include sections on diabetes and on undernutrition, respectively.

Target audience

This operational handbook is intended for use by people working in ministries of health, particularly TB programmes and the relevant departments or programmes responsible for comorbidities and health-related risk factors such as HIV, diabetes mellitus and other noncommunicable diseases, mental health, lung health, undernutrition, substance use and tobacco use. The operational handbook is also targeted at relevant line-ministries, policymakers, international technical and funding organizations, researchers, nongovernmental and civil society organizations, as well as healthcare workers, including specialists and community health workers who support the response to TB and comorbidities in both the public and private sectors.

References for the introduction

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Mental health conditions and substance use disorders

Contents

Mental health conditions and substance use disorders

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Abbreviations

ASSIST	Alcohol, Smoking and Substance Involvement Screening Test
AUDIT	Alcohol Use Disorders Identification Test
GAD	generalized anxiety disorder
GAD-7	Generalized Anxiety Disorder Assessment-7
HIV	human immunodeficiency virus
MDR-TB	multidrug-resistant TB
mhGAP	Mental Health Gap Action Programme
PHQ-9	Patient Health Questionnaire-9
PM+	Problem Management Plus
PWID	people who inject drugs
SH+	Self-Help Plus
SSRIs	selective serotonin reuptake inhibitors
TB	tuberculosis
UNODC	United Nations Office for Drugs and Crime
WHO	World Health Organization

Definitions

Comorbidity: A concurrent disease or health condition in a person with TB.

Disorders due to substance use: According to the International Classification of Diseases (ICD)-11 *(8)*, the term "disorders due to substance use" refers to a group of disorders that arise from a single or repeated use of substances that have psychoactive properties, including certain medications. For the purposes of this operational handbook, "disorders due to substance use" is divided into "disorders due to alcohol use" (or "alcohol use disorders"), which refers specifically to the use of alcohol, and "disorders due to drug use" (or "drug use disorders"), which refers to the use of psychoactive substances other than alcohol and nicotine.

Mental disorder: As defined by the International Classification of Diseases 11th Revision (ICD-11) *(8)*, a mental disorder is a syndrome characterized by clinically significant disturbance in an individual's cognition, emotional regulation, or behaviour that reflects a dysfunction in the psychological, biological or developmental processes that underlie mental and behavioural functioning. These disturbances are usually associated with stress or impairment in personal, family, social, educational, occupational or other important areas of functioning.

Mental health condition: A broad term covering mental disorders and psychosocial disabilities. It also covers other mental states associated with significant distress, impairment in functioning or risk of self-harm.

People-centred services: A human rights-based approach to care that consciously adopts the perspectives of individuals, carers, families and communities as participants in, and beneficiaries of, trusted health systems that respect social preferences and are organized around the comprehensive needs of people rather than individual diseases *(9)*.

Psychosocial disability: Aligned with the Convention on the Rights of Persons with Disabilities, psychosocial disability is disability that rises when someone with a long-term mental impairment interacts with various barriers that may hinder their full and effective participation in society on an equal basis with others.

Tuberculosis (TB): The disease state due to *Mycobacterium tuberculosis (10)*. It is commonly referred to as "TB disease" to distinguish it from TB infection.

Tuberculosis (TB) infection: state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens with no evidence of clinically manifest active TB *(10)*.

1. Mental health conditions and substance use disorders: background and rationale

Mental disorders[1] are prevalent in all countries *(8)*. Nearly 1 billion people worldwide are living with a mental disorder, which has become the leading cause of years of living with disability. The risk factors for developing a mental disorder are multi-faceted and may include any combination of individual factors (psychological or biological), family or community factors (such as poverty or violence), and structural factors (such as inequality or environmental emergencies) *(11)*.

People affected by TB have a higher risk for mental health conditions and substance use disorders *(12, 13)*. This comorbidity negatively impacts a person's capacity to adhere to their medication and infection control practices. It can also worsen morbidity and increase risk of poor TB treatment outcomes and poor overall health-related quality of life *(14, 15)*. Studies suggest that depression may independently increase the risk for TB *(16, 17)*. Several of the anti-TB medications are associated with depression, anxiety and/or psychoses *(12, 18, 19)*, which may require either temporary or complete suspension of the suspected agent and/or initiation of adjunct psychopharmacological medication. There is an increased risk of depression, anxiety or psychoses in people with multidrug resistant TB (MDR-TB) *(20, 21)*. Disorders due to alcohol use significantly increase the risk for developing TB *(22)*. Psychological stress associated with stigma and discrimination may also trigger or aggravate mental health conditions or substance use disorders in affected individuals. Individuals with drug-resistant TB *(23)* and/or co-infected with HIV are at an even higher risk for mental health conditions including substance use disorders *(24)*.

Many individuals with TB – and particularly those affected with drug-resistant TB – experience some degree of mental distress related to the illness, its treatment and complications, and/or TB-related stigma *(25)*. In some cases, distress, which is not always a pathological issue, can be alleviated through preventive interventions such as health education or by providing access to social and financial resources, as described below.

[1] A mental disorder - as defined by the International Classification of Diseases 11th Revision (ICD-11), is a syndrome characterized by clinically significant disturbance in an individual's cognition, emotional regulation, or behaviour that reflects a dysfunction in the psychological, biological or developmental processes that underlie mental and behavioural functioning. These disturbances are usually associated with stress or impairment in personal, family, social, educational, occupational or other important areas of functioning. This section will use 'mental disorder' when explicitly referring to data that rely on defined categories of mental disorder. A mental health condition is a broad term covering mental disorders and psychosocial disabilities. It also covers other mental states associated with significant distress, impairment in functioning or risk of self-harm. The term 'mental health conditions' will be used throughout this section except when describing data which rely on defined mental disorder categories.

For some people, however, the distress can become severe and persistent, leading to significant functional impairment or disability (such as inability to work, study or take care of family members, interpersonal strain and withdrawal from social connections) and a diagnosis of a mental disorder may be appropriate *(26)*. In addition, people already living with mental health conditions may experience a worsening of their symptoms upon diagnosis of TB. Sustained autonomic and neuroendocrine responses associated with chronic psychological distress can weaken the immune system, as well as influence health behaviours that can jeopardize TB treatment *(17)*. Since TB often affects people who are already socially vulnerable, TB-related stigma can intersect with and exacerbate other social stigmas related to poverty, mental health conditions and/or HIV co-infection, substance use, incarceration or use of social protection services. Issues created by diagnosis or treatment, such as loss of regular income, can worsen a person's mental health. TB-related stigma and discrimination can have significant deleterious impact on the physical and mental health of individuals with drug-resistant TB and may trigger mental health conditions in individuals without a history of mental health conditions *(17, 25)*. Prevention, early identification, monitoring and treatment of mental health conditions and substance use disorders are essential to ensure both alleviation of mental health conditions and positive TB treatment outcomes *(27)*.

2. People-centred care for mental health conditions and substance use disorders in people affected by TB

TB disproportionately affects people living in poverty and other socially vulnerable populations, which amplifies their risk for mental health conditions. Providers of TB care can undertake various actions to influence both the impact of disease-specific triggers on poor mental health and social determinants of mental health. In particular, social support, including education and facilitating access to psychological and material support, is critical to mitigate the impact of poverty, TB, its treatment, and the related stigma and discrimination, on people's mental health *(28)*. For individuals experiencing significant financial strain and/or food insecurity *(29)*, among other vulnerabilities, social protection interventions may mitigate stress and help prevent mental health conditions or substance use disorders *(28)*. Effective interventions to prevent and mitigate TB stigma and discrimination at the community level can help people to understand and cope with the impact of the disease.

3. Identifying and managing care for mental health conditions and substance use disorders in people affected by TB

Mental health care is one of the health services to be integrated with TB services as outlined in the End TB Strategy and the WHO *Framework for collaborative action on tuberculosis and comorbidities (2, 30)*. Within healthcare services, this integration includes identifying people with TB who are experiencing comorbid mental health or substance use conditions, and upon identification, managing the needs of the person – which can be achieved through referral to existing mental health or substance use services, or through task shifting to primary care health workers who have been trained in the assessment and management of mental disorders.

Key mental health conditions affecting individuals with TB are depression, anxiety, psychosis, substance use disorders and suicidal behaviours. TB diagnosis, illness course, treatment and/or stigma and discrimination, inflate the likelihood of each of these. Table 1 shows the common presentations of these conditions, and that many symptoms of mental health conditions overlap with those of TB or the side effects of TB treatment. The annex lists WHO guidance available to address these conditions.

Ideally, everyone with TB should be assessed for the above-mentioned mental health conditions or substance use disorders prior to or upon initiating treatment for TB, and at routine assessments. However, the availability of services for mental health and substance use in most countries remains largely inadequate – in some countries the treatment gap for severe mental health conditions is up to 90% *(11)*. For this reason, opportunistic identification may be a prudent use of existing resources: health workers can initiate identification when a person accessing TB care appears with signs of the common presentations of mental disorders (see Table 1). Identification can be achieved through use of screening tools for mental health and substance use.

Several standardized instruments (discussed in more detail within this guidance) are available in many languages, are easy and fast to administer, and have been widely used across diverse settings (see Table 1). As screening instruments offer information on the severity of a person's symptoms, rather than whether or not they meet diagnostic status, they can be used to identify people in need of further assessment (by a person trained in assessment of mental disorders) and/or detect changes in symptoms over time. Additionally, people at the end of anti-TB treatment may also be assessed for mental health conditions or substance use disorders. If mental health conditions or substance use disorders are present, linking people to mental health care may be important to prevent loss to follow-up during treatment, or to continue care after being discharged from the TB programme.

Ensuring TB services have referral pathways to available mental health services is an essential aspect of integrating services. Yet, task-sharing with primary healthcare providers has been shown to help reduce the treatment gap and increase coverage for priority mental health conditions. WHO has developed a series of guidelines and materials to inform the management of mental disorders in non-

specialized primary care settings *(31-34)*. Under the WHO Mental Health Gap Action Programme (mhGAP), the WHO *mhGAP Intervention Guide for mental, neurological and substance use disorders (32)* provides evidence-based guidance and capacity building tools for health professionals and settings not specialized in providing mental health care. Non-specialist health workers (such as those serving TB populations) can be trained in the identification, assessment, management and follow-up of priority mental health conditions. Table 1 presents an overview of priority mental health conditions and their common presentations. Additional guidance is also available for specific conditions or situations, such as the WHO/UNODC *International Standards for the Treatment of Drug Use Disorders (35)*, WHO *Guidelines for identification and management of substance use and substance use disorders in pregnancy (36)*, and the WHO guidelines on *Community management of opioid overdose (37)*.

Table 1. Overview of priority mental health conditions

Adapted from WHO mhGAP *Intervention Guide 2.0 (32)*	
• These common presentations indicate the need for assessment by persons trained in assessment, management and follow-up of these conditions, such as health workers trained in mhGAP. • If people present with features of more than one condition, then all relevant conditions need to be assessed. • All conditions apply to all ages, unless otherwise specified. • For emergency presentations (such as, but not limited to: imminent risk of self-harm/suicide, agitated or aggressive behaviour, acute alcohol intoxication), see page 18: Emergency Presentations of Priority Mental, Neurological and Substance Use Conditions in WHO *mhGAP Intervention Guide 2.0 (32)*. • For full mental health assessment, management and follow up protocols, see WHO *mhGAP Intervention Guide 2.0 (32)*. • For potential drug-drug interactions between mental health and TB treatment, see WHO *Guidelines for the management of physical health conditions in adults with severe mental disorders (38)*.	
Common presentation	**Priority condition**
• Multiple persistent physical symptoms with no clear cause • Low energy, fatigue, sleep problems • Persistent sadness or depressed mood, anxiety • Loss of interest or pleasure in activities that are normally pleasurable	**Depression**
• Multiple persistent physical symptoms with no clear cause • Persistent and excessive anxiety or worry • Muscle tension • Difficulty controlling worries • Difficulty concentrating and making decisions	**Anxiety**[a]
• Marked behavioural changes; neglecting usual responsibilities related to work, school, domestic or social activities • Agitated, aggressive behaviour, decreased or increased activity • Fixed false beliefs not shared by others in the person's culture • Hearing voices or seeing things that are not there • Lack of realization that one is having mental health problems	**Psychoses**

Adapted from WHO mhGAP *Intervention Guide 2.0 (32)*	
• Appearing affected by alcohol or other substance (e.g. smell of alcohol, slurred speech, sedated, erratic behaviour) • Signs and symptoms of acute behavioural effects, withdrawal features or effects of prolonged use • Deterioration of social functioning (e.g. difficulties at work or home, unkempt appearance) • Signs of chronic liver disease (abnormal liver enzymes), jaundiced (yellow) skin and eyes, palpable and tender liver edge (in early liver disease), ascites (distended abdomen is filled with fluid), spider naevi (spider-like blood vessels visible on the surface of the skin), and altered mental status (hepatic encephalopathy) • Problems with balance, walking, coordinated movements and nystagmus • Incidental findings: macrocytic anaemia, low platelet count, elevated mean corpuscular volume • Emergency presentation due to substance withdrawal, overdose, or intoxication. Person may appear sedated, overstimulated, agitated, anxious or confused • Recurrent requests for psychoactive medications including analgesics • Injuries • Infections associated with intravenous drug use (HIV/AIDS, Hepatitis C)	**Substance use disorders**
• Extreme hopelessness and despair • Current thoughts, plan or act of self-harm/suicide, or history thereof • Any of the other priority conditions, chronic pain or extreme emotional distress	**Self-harm/suicide**

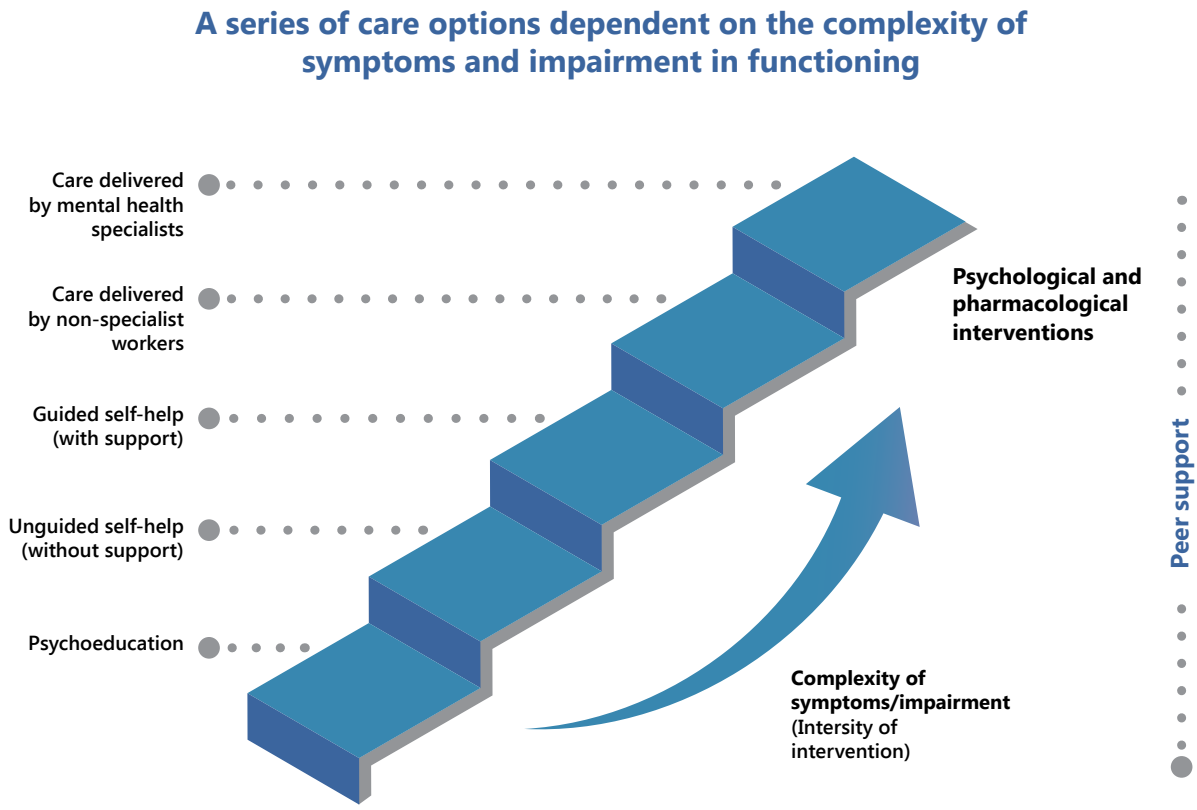
[a] Note that there are many overlapping symptoms between depression and anxiety – both of which are also referred to as common mental health conditions. The overlapping symptoms include reduced interest or pleasure in activities; significant change in appetite or weight even when food is available (decrease or increase); observable physical restlessness or retardation; irritability; unexplained physical complaints (aches, pains, muscle tension); insomnia or hypersomnia nearly every day; easily fatigued or loss of energy; difficulty concentrating or indecisiveness.

Models of delivery such as collaborative care *(39)* are also a promising approach for providing integrated evidence-based, person-centred care for mental health in physical healthcare settings. Collaborative care employs systematic identification of affected people, close monitoring of individual outcomes, treatment by care managers who may be trained to deliver brief educational, psychological and social interventions, and organized caseload consultations with mental health specialists, where available. Similarly, the 2022 *Framework for collaborative action on tuberculosis and comorbidities* provides guidance on how to develop and scale up collaborative action on TB and comorbidities, complementing the clinical aspects considered in this guidance *(2)*.

At the systems level, and echoing the guidance outlined within the WHO Framework for collaborative action, the WHO implementation guidance on *Integrating the prevention and control of noncommunicable diseases in HIV/AIDS, tuberculosis and sexual and reproductive health programmes* to strengthen health systems *(40)*, outlines action at multiple domain levels to benefit integration:

1. people and community, e.g. people with lived experience of the health condition must be included in planning and design of services;
2. policy and leadership, e.g. ensuring policies or legislation are in place to provide the mandate for integrated service delivery;
3. financing, e.g. health financing should support and incentivize the delivery and use of integrated care;
4. capacity and infrastructure, e.g. health workers have the necessary capacity and competencies to deliver integrated services; and
5. models of delivering integrated care give due consideration to how services should be delivered, the processes of care, and how providers and management of services are organized.

Fig. 1. Continuum of options in mental health care



At the services level, establishing person-centred, integrated TB and mental health services involves several steps. First, is the identification of opportunities for mental health support options within the local geography serving the TB community. This can include opportunities to strengthen family support and community support through, for example, a religious organization. Other opportunities might include the delivery of psychoeducation by care providers, peer supporters, trained providers of brief psychological interventions, and available mental health specialists.

One key element of people-centred care is the tailoring of interventions to the needs of individuals. In mental health care, a continuum of options is available, depending on the complexity of symptoms and associated functional impairment, as illustrated in Fig. 1. Some individuals experiencing mental health symptoms will benefit from basic psychoeducation and self-help strategies. Others may require additional support such as brief psychological interventions, which can be delivered by trained and

supervised non-specialist workers. Others may require the support of mental health specialists who deliver psychological interventions and/or pharmacological care and in the rarest circumstance they are needed, acute-care options should be available.

Next, it is necessary to strengthen linkages between the existing mental health support options and services to ensure close coordination of care. Further, TB services must establish clear protocols for identification and management of people with mental health conditions by employing screening tools, for example, or building the capacity of TB health workers to assess and manage mental disorders through WHO mhGAP *(32)*. Referral pathways can also be established with existing mental health support systems and services. Finally, robust monitoring and evaluation are needed for ongoing quality improvement.

3.1 Depression

Depression is a common and treatable mental health condition, associated with immunosuppression, which is often unrecognized and undiagnosed in individuals with TB and results in poor treatment outcomes, including treatment failure, loss to follow-up and death *(17)*.

People with depression experience a range of symptoms, including persistent depressed (or low) mood or loss of interest and pleasure, for at least two weeks, and also have considerable difficulty with daily functioning in personal, familial, social, educational, occupational or other areas *(32)*. When considering whether a person with TB has depression, it is essential to assess not only the symptoms of depression, but also difficulties in day-to-day functioning due to the symptoms, beyond those that can be attributed to TB and/or its treatment (see Table 1 and WHO *mhGAP Intervention Guide 2.0* protocol for Depression) *(32)*.

Identifying depression among individuals with TB can be difficult since some symptoms, such as marked change in appetite or weight (even when food is available), fatigue or loss of energy, and disturbed sleep, may also be commonly present in TB, thus making identification difficult. Identifying symptoms of depression can be done using screening tools such as the Patient Health Questionnaire (PHQ-9) *(41)*. Such tools do not establish a diagnosis of a mental disorder but provide an indication of the severity of symptoms. They remain a useful tool as people with symptoms of depression can be supported by lower intensity, non-pharmacological approaches, as described below. If a health worker suspects depression, a person can be referred to a health worker trained in the assessment of mental health conditions, where available, such as a mental health specialist or health worker trained in WHO mhGAP *(32)*.

Several symptoms of depression (depressed mood, diminished interest or pleasure in activities, beliefs of worthlessness or guilt and hopelessness) may be perceived as part of common reactions to TB diagnosis, stigma and discrimination, and/or worries about the likelihood of being cured. People exposed to such severe stressors often experience psychological difficulties consistent with symptoms of depression that may not necessarily meet the criteria for a diagnosis of depression *(31)*. Even so, such common reactions may cause distress, which can be mitigated through lower intensity approaches such as education or guided or unguided self-help for stress management. Initial support can also include social support to address stressors, such as for finance or housing.

In circumstances in which people demonstrate symptoms of significant distress, provision of brief psychological interventions in a stepped care approach, including guided self-help, may be warranted. If trained and supervised psychological-intervention providers are available, approaches may include

WHO Problem Management Plus (PM+) – a brief psychological intervention delivered in individual or group format for people with high distress and impaired functioning *(42)*; or WHO Self-Help Plus (SH+) – a brief guided self-help package *(43, 44)*. If symptoms of depression persist even after TB symptoms improve and external stressors have been effectively addressed through social support and social protection interventions, a referral to mental health specialists may be indicated.

Another method for identifying depression is through assessment conducted by a mental health specialist or health worker trained in such an assessment, for example following the depression protocol in the *mhGAP Intervention Guide 2.0 (32)*. This type of assessment can also be conducted following positive identification via a screening tool.

People living with depression should be regularly monitored. Management of depression should be initiated through psychosocial interventions such as psychoeducation, stress reduction, strengthening social support and promotion of daily activity functioning. Management of depression also includes offering brief evidence-based psychological interventions such as interpersonal psychotherapy, cognitive behavioural therapy, behavioural activation and problem-solving counselling, where these are available *(45)*. WHO Problem Management Plus *(42)* is a brief psychological intervention which can be delivered by trained non-mental health specialists under adequate supervision. For people with moderate to severe depression, pharmacological interventions can also be considered in the management of depression. Two recommended interventions include selective serotonin reuptake inhibitors (SSRIs), like fluoxetine, and tricyclic antidepressants like amitriptyline *(46)*. While generally safe to use among people receiving treatment for drug-susceptible TB, evidence suggests that their combination with rifampin can lead to reduced efficacy of these drugs and therefore dosing should be monitored closely. For people receiving treatment for drug-resistant TB, moderate drug-drug interactions have also been observed with levofloxacin, bedaquiline and delamanid, specifically an increased risk for QT-prolongation and/or arrhythmias *(38)*. People who experience these moderate drug interactions may use SSRIs and tricyclic antidepressants but require closer monitoring.

3.2 Anxiety

Many individuals experience symptoms of anxiety (not necessarily an anxiety disorder) as a common reaction to a TB diagnosis and the required treatment, which can often be mitigated by social support *(28, 32)*. Symptoms of anxiety in TB may present as fear of infecting others or mortality, or because of stigma and discrimination. Acute anxiety may also be an adverse reaction to a particular anti-TB agent. People with TB and symptoms of anxiety can benefit from more social support than they have in their own personal or community networks, such as peer support among other TB-affected individuals. A person-centred approach in which health workers build trust and professional rapport and increase a person's knowledge of TB and its treatment, contributes to providing a supportive environment *(47)*. As with the PHQ-9 other screening tools are available to identify whether significant symptoms of anxiety are being experienced, such as the Generalized Anxiety Disorder Assessment-7 (GAD-7) *(48)*.

If a person appears to be experiencing symptoms of anxiety that are not explained by their circumstances, and that are causing impairment in important areas of functioning, and/or that persist despite marked improvement in their physical or social environment (for example, reduced physical symptoms or increased social support), it may indicate an anxiety disorder that requires further assessment (see Table 1).

Many different anxiety- or fear-related disorders exist, such as social anxiety or panic disorders. Generalized anxiety disorder (GAD) is one type of anxiety disorder which is characterized by a generalized and persistent anxiety usually accompanied by physical symptoms such as motor tension and/or autonomic overactivity *(26)*. Anxiety symptoms in GAD must persist for more days than not, over a 6-month period, and may be focused on multiple external factors, situations or triggers.

Depending on the onset, severity, and duration of symptoms, the provider may consider (i) suspending all TB medications temporarily or (ii) suspending the suspected drug for a brief period according to the principles described in the *WHO operational handbook on tuberculosis, Module 4: Treatment - Drug-resistant tuberculosis treatment, 2022 update (49)*, and/or (iii) providing brief psychoeducation on anxiety, associated symptoms and relations to TB; offering brief training in stress management skills (e.g. mindfulness or relaxation training); offering advice on engaging in physical exercise, which can reduce symptoms of anxiety; providing brief psychological interventions based on the principles of cognitive behavioral therapy, such as PM+ or SH+, where possible and; prescribing a psychotropic medication, such as an SSRI[2] *(38)*; and offering models of collaborative care in physical disease programmes to treat comorbid TB and anxiety disorders *(50)*.

If the anxiety is associated with a drug that is part of the TB treatment regimen, any adjustment to the regimen should be done according to the principles for treatment regimen design (see *WHO operational handbook on tuberculosis, Module 4: Treatment - Drug-resistant tuberculosis treatment, 2022 update*) *(49)*. WHO is developing guidelines on the clinical management of anxiety disorders (GAD and panic disorder), as well as guidance via mhGAP for anxiety disorders.

3.3 Psychoses

People with mental disorders (such as schizophrenia, which is characterized by symptoms of psychoses) are at greater risk than the general population for exposure to infectious diseases, including TB *(51)*. Psychosis is characterized by distorted thoughts and perceptions, disturbed emotions and behaviours, and the possibility of incoherent or irrelevant speech (see Table 1). Delusions, which are fixed false beliefs not shared by others in the person's culture, are another psychosis symptom, as is hallucination – a severe alteration in the way a person perceives reality, typically exhibited as sensory experiences that do not correspond to reality, such as seeing or hearing things in the absence of an external stimulus.

In the case of drug-resistant TB, symptoms of psychoses can be triggered as a side effect of some anti-TB medications, including cycloserine, high-dose isoniazid and fluoroquinolones. Side effects resulting from anti-TB medications may include visual or auditory hallucinations, with or without delusional elaboration *(26)*. Sometimes it may present with clouding of consciousness, intellectual decline, predominant disturbance of mood, or marked delusions. In case of these presentations, it is best to refer to a mental health specialist for assessment *(26)*. In general, psychosis is best managed either by or under the supervision of a mental health specialist. Where resources are available, a baseline assessment for psychosis may be considered prior to the initiation of treatment with cycloserine, high-dose isoniazid and fluoroquinolones. This may aid providers in determining whether onset of symptoms of psychoses is associated with an anti-TB agent; and for individuals screening positive for symptoms of psychoses at baseline, close coordination between TB and mental health services is required to manage potential exacerbation of symptoms. Since the onset of psychosis as a reaction to

[2] For potential drug-drug interactions, see *WHO guidelines for management of physical health conditions in adults with severe mental disorders (38)*.

anti-TB medications is often very rapid, having a baseline assessment can help providers determine whether the symptoms may be related to a specific anti-TB agent or a mental disorder. For people with psychotic symptoms at baseline, very careful monitoring is required to ensure that these symptoms are not exacerbated by these anti-TB medications. For additional guidance, refer to the WHO *Guidelines for the management of physical health conditions in adults with severe mental disorders (38)*.

If the symptoms of psychoses do not improve after the suspected anti-TB medication has been stopped for 1–2 weeks, anti-psychotic pharmacological intervention should be considered, in consultation with a mental health specialist (see Table 1 for management of psychotic symptoms). Any adjustment to the regimen should be made according to the principles for treatment regimen design (see *WHO operational handbook on tuberculosis, Module 4: Treatment - Drug-resistant tuberculosis treatment, 2022 update*) *(49)*.

3.4 Substance use disorders

Substance use disorders (both alcohol and drug use disorders) comprise two major health conditions: "harmful substance use" and "dependence". Harmful substance use is defined as a pattern of continuous, recurrent or sporadic use of a psychoactive substance that has caused clinically significant damage to a person's physical or mental health. Dependence is defined as a disorder of regulation of psychoactive substance use arising from repeated or continuous use. The characteristic feature of dependence is a strong internal drive to use substances, which manifests itself by: (a) impaired ability to control substance use; (b) increasing priority given to substance use over other activities; and (c) persistence of use despite the occurrence of harm or negative consequences. Physiological features of dependence may also be present, including (1) increased tolerance to the effects of the substance or a need to use increasing amounts of the substance to achieve the same effect; (2) withdrawal symptoms following cessation of or reduction in the use of that substance; or (3) repeated use of the substance or pharmacologically similar substances to prevent or alleviate withdrawal symptoms.

Individuals with alcohol and other substance use disorders have a significantly higher risk for acquiring TB, TB reinfection and worse treatment outcomes *(52–54)*. According to WHO estimations, alcohol is attributable to about 20% of deaths due to TB *(55)* and according to the World Drug Report *(56)*, about 8% of people who inject drugs (PWID) have TB. Some research reports suggest even higher figures of TB prevalence among PWID, with about 17–52% testing positive on tuberculin skin testing, 60% of community-recruited PWID testing positive with interferon-gamma-release assays, and up to 68% of PWID with active TB having multidrug resistant TB *(57)*. Worse TB treatment outcomes among people with substance use and substance use disorders are often due to associated HIV infection, or viral hepatitis B and/or C, but there are other factors as well, such as worse access to treatment, stigma and discrimination, delays in seeking care, poor treatment adherence (including to HIV and TB medication), worse treatment engagement and effectiveness, compromised immune response, malnutrition, and drug-drug interactions *(52, 54)*. For potential drug-drug interactions, see WHO *Guidelines for the management of physical health conditions in adults with severe mental disorders (38)*.

Targeting substance use (both alcohol and drugs) and substance use disorders is a key strategy to prevent and treat TB *(58)*. There is evidence that treatment of substance use disorders (especially opioid agonists maintenance treatment) is associated with better initiation of and adherence to antiretroviral therapy *(59, 60)* improvements in TB treatment completion, and adherence to TB medication *(61, 62)*. However, management of substance use and substance use disorders are rarely integrated into TB and HIV care.

Due to the high comorbidity between substance use disorders and TB, it is essential to ensure access to prevention, treatment and care for both conditions. People-centred care with adequate support should be available to people with comorbid TB and substance use disorders. Health professionals providing treatment of TB should be informed and capacitated to provide basic elements of care for people with substance use disorders, including screening, providing brief intervention, recognizing and managing acute and life-threatening substance use-related conditions, and referring for specialized care when needed. Professionals working in services for mental and substance use disorders should be vigilant about comorbid TB and know how to provide care for people with both conditions.

All health professionals providing TB treatment should be able to assess and manage life-threatening conditions related to substance use, including alcohol withdrawal (complicated and not complicated with delirium and/or seizures), drug overdose and substance intoxication. Health professionals should also be able to perform screening using standardized screening tools and linked brief interventions, such as the Alcohol Use Disorders Identification Test (AUDIT) *(63)* and the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) *(33)*. For those who have difficulties in stabilizing substance use disorders while receiving treatment for TB, coordinated referral, follow-up and consultation with specialized services for mental health and substance use disorders is needed. Understanding interventions for the treatment of substance use disorders (such as harm reduction, psychosocial and pharmacological interventions, and recovery management) will help improve coordination between services and increase the effectiveness of people-centred treatment and care for people with TB and substance use disorders.

3.5 Suicidal behaviours

Over 700 000 people a year die by suicide worldwide *(64)*. One of the four key interventions in WHO's *LIVE LIFE: An implementation guide for suicide prevention in countries (65)* is the early identification of anyone affected by suicidal behaviours, and their assessment, management and follow-up. Suicidal behaviours include suicidal thoughts (or ideation), plans of suicide, suicide attempts and suicide. Individuals should be assessed for risk of self-harm/suicide prior to initiating or during TB treatment if any of the following applies: extreme hopelessness and despair, current thoughts, plan or act of self-harm/suicide or history of suicidal behaviours (e.g. thoughts, plans, acts); if a person has a comorbid mental, neurological or substance use condition (such as depression, substance use disorder, anxiety or psychosis), chronic pain or extreme emotional distress; or where cycloserine is part of the treatment regimen.

It is important to manage self-harm/suicide, including follow-up, according to the WHO mhGAP Intervention Guide 2.0, Self-Harm/Suicide protocol) *(32)*.

4. Special considerations

4.1 Stigma

Stigma refers to negative attitudes that involve discriminatory actions towards, for example, people who are receiving treatment for TB or towards those living with mental health conditions. Unfortunately, this is very common, and this stigma can result in serious violations of human rights *(66)*. Since TB and mental health conditions can affect people who are socially vulnerable, health-related stigma and discrimination can exacerbate other social stigmas which can adversely affect a person's personal, social, health and financial well-being. Health-related stigma and discrimination can have significant negative impacts on physical and mental health. Staff providing TB care should therefore be trained to avoid the use of stigmatizing language and practices related to both TB and mental health conditions. WHO's QualityRights initiative includes e-training[3] which promotes the rights of people with psychosocial, intellectual and cognitive disabilities (including mental health conditions), to address stigma, discrimination and abuse. It promotes improved quality of care in mental health and related services using a person-centred, rights-based recovery approach. The training is designed for a wide audience, including health workers.

4.2 Palliative care

Psychological support is a critical element of palliative care where the overall goal is to relieve pain and distress and sustain a person's well-being. Psychological support needs to be tailored to local settings with a culturally sensitive approach and respect for individual values and beliefs. Moreover, caregivers and healthcare providers providing palliative care frequently experience psychological distress themselves, for which psychological support can be beneficial *(67)*.

4.3 Homelessness

Individuals who are homeless or in temporary housing have a significantly greater risk of exposure to TB, developing active TB and acquiring drug resistance *(68)*; as well as an increased likelihood of having a mental health condition *(69)*. Assessment of their situation and related socioeconomic risk factors is required (such as poor quality or no housing, low or no income), followed by referral to the necessary support (such as social care or financial, housing or employment support). Ongoing close monitoring then is needed to provide people-centred services. Assessment for mental health conditions is also beneficial to ensure that people have access to the care they may need. These actions are important to ensure that people have improved quality of life, which can also have a positive effect on treatment outcomes.

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[3] https://www.who.int/teams/mental-health-and-substance-use/policy-law-rights/qr-e-training

4.4 Multimorbidity and TB-associated disabilities

TB often occurs along with other illnesses – not only mental disorders but also HIV, diabetes, hypertension and other conditions *(70)*. These comorbidities are also independently associated with a higher risk of mental health problems *(71)*. Health workers in TB and mental health services should endeavor to understand each person's main priorities and concerns and support the treatment of both TB and mental disorders in order to comprehensively address the person's needs. This underscores the importance of integrating mental health care and social protection in physical health care for many conditions, including TB and mental disorders.

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Annex. WHO resources for mental and substance use disorders

Mental health guidelines

- Management of physical health conditions in adults with severe mental disorders: WHO guidelines *(1)*
- WHO Website: WHO Mental Health Gap Action Programme (mhGAP) *(2)*
- mhGAP Intervention Guide for mental, neurological and substance use disorders in non-specialized health settings: mental health Gap Action Programme - Version 2.0 *(3)*

Brief biological interventions

- Problem Management Plus (PM+): Individual psychological help for adults impaired by distress in communities exposed to adversity, WHO generic field-trial version 1.0. *(4)*
- Group Problem Management Plus (Group PM+): group psychological help for adults impaired by distress in communities exposed to adversity, Generic field-trial version 1.0. *(5)*
- Self-Help Plus (SH+): A group-based stress management course for adults, Generic field-trial version 1.0. *(6)*
- Group interpersonal therapy (IPT) for depression *(7)*
- Thinking healthy: A manual for psychological management of perinatal depression *(8)*

Substance use disorders

- mhGAP Intervention Guide for mental, neurological and substance use disorders in non-specialized health settings – Version 2.0 *(3)*
- The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST): manual for use in primary care *(9)*
- The ASSIST-linked brief intervention for hazardous and harmful substance use: Manual for use in primary care *(10)*
- Self-help strategies for cutting down or stopping substance use: a guide *(11)*
- International standards for the treatment of drug use disorders: revised edition incorporating results of field-testing *(12)*
- Guidelines for identification and management of substance use and substance use disorders in pregnancy *(13)*
- WHO guidelines on Community management of opioid overdose *(14)*
- Integrating collaborative TB and HIV services within a comprehensive package of care for people who inject drugs: consolidated guidelines *(15)*

Mental health integration

- Integrating the response to mental health disorders and other chronic diseases in healthcare systems *(16)*
- Framework for collaborative action on tuberculosis and comorbidities *(17)*

Suicide prevention

- mhGAP Intervention Guide for mental, neurological and substance use disorders in non-specialized health settings – Version 2.0 *(3)*
- LIVE LIFE: An implementation guide for suicide prevention in countries *(18)*
- Preventing suicide: A global imperative *(19)*

Mental health in emergency settings

- mhGAP humanitarian intervention guide (mhGAP-HIG): clinical management of mental, neurological and substance use conditions in humanitarian emergencies *(20)*
- Building back better: sustainable mental health care after emergencies *(21)*
- Psychological first aid: Guide for field workers *(22)*
- Mental Health and Psychosocial Support in Humanitarian Emergencies: What Should Humanitarian Health Actors Know? *(23)*
- Assessing mental health and psychosocial needs and resources: toolkit for humanitarian settings *(24)*

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HIV

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Experts consulted during stakeholder consultation and external review

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WHO headquarters

Annabel Baddeley (Global Tuberculosis Programme), Rachael Baggaley (Global HIV, Hepatitis and STIs Programmes), Magdalena Barr-DiChiara (Global HIV, Hepatitis and STIs Programmes), Delia Boccia (Global Tuberculosis Programme), Anna Carlqvist (Global Tuberculosis Programme), Fabrizia del Greco (Global HIV, Hepatitis and STIs Programmes), Meg Doherty (Global HIV, Hepatitis and STIs Programmes), Dennis Falzon (Global Tuberculosis Programme), Nathan Ford (Global HIV, Hepatitis and STIs Programmes), Nazir Ismail (Global Tuberculosis Programme), Ernesto Jaramillo (Global Tuberculosis Programme), Cheryl Johnson (Global HIV, Hepatitis and STIs Programmes), Avinash Kanchar (Global Tuberculosis Programme), Alexei Korobitsyn (Global Tuberculosis Programme), Celine Lastrucci (Global HIV, Hepatitis and STIs Programmes), Irwin Law (Global Tuberculosis Programme), Farai Mavhunga (Global Tuberculosis Programme), Cecily Miller (Global Tuberculosis Programme), Fuad Mirzayev (Global Tuberculosis Programme), Carl-Michael Nathanson (Global Tuberculosis Programme), Morkor Newman (Global HIV, Hepatitis and STIs Programmes), Ajay Rangaraj (Global HIV, Hepatitis and STIs Programmes), Lana Syed (Global Tuberculosis Programme), Sabine Verkuijl (Global Tuberculosis Programme), Kerri Viney (Global Tuberculosis Programme), Lara Vojnov (Global HIV, Hepatitis and STIs Programmes), Elena Vovc (Global HIV, Hepatitis and STIs Programmes), Matteo Zignol (Global Tuberculosis Programme).

WHO regional and country offices staff

Omoniyi Amos (Country Office for Nigeria), Kleydson Andrade (Country Office for Brazil), Pedro Avedillo (Regional Office for the Americas), Vineet Bhatia (Regional Office for South-East Asia), Lastone Chitembo (Country Office for Zambia), Maria Regina Christian (Country Office for Indonesia), Marcelo Freitas (Country Office for Brazil), Michel Gasana (Regional Office for Africa), Aman Gupta (Country Office for India), Clarissa Halum (Country Office for Philippines), Joumana Hermez (Regional Office for the Eastern Mediterranean), Kaliya Kasymbekova (Country Office for Kyrgyzstan), Laeeq Khawaja (Country Office for Pakistan), Frank Lule (Regional Office for Africa), Nkateko Mkhondo (Country Office for South Africa), Halima Momodu (Country Office for Nigeria), Ilesanmi Oluwafunke (Country Office for Nigeria), Malik Parmar (Country Office for India), Muhammad Pasha (Country Office for Pakistan), Patrobas Dashi Philip (Country Office for Nigeria), Busisiwe Radebe (Country Office for South Africa), Kalpeshsinh Rahevar (Regional Office for the Western Pacific), BB Rewari (Regional Office for South-East Asia), Md Kamar Rezwan (Regional Office for South-East Asia), Nicole Seguy (Regional Office for Europe), Nympha Elisa Sia (Country Office for Philippines), Omar Sued (Regional Office for the Americas), Martin van den Boom (Regional Office for the Eastern Mediterranean), Askar Yedilbayev (Regional Office for Europe).

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Abbreviations and acronyms

AFB	acid-fast bacilli
AHD	advanced HIV disease
AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
CAD	computer-aided detection
CFP-10	culture filtrate protein 10
CI	confidence interval
CRP	C-reactive protein
CSF	cerebrospinal fluid
CXR	chest X-ray
DR-TB	drug-resistant tuberculosis
DS-TB	drug-susceptible tuberculosis
ESAT-6	early secretory antigenic target 6 kDa protein
FDC	fixed-dose combination
GDF	Global Drug Facility
GI	gastrointestinal
HIV	human immunodeficiency virus
HIVST	HIV self-testing
HMIS	health management information system
HTS	HIV testing services
IGRA	interferon-gamma release assay
IPT	isoniazid preventive treatment
IRIS	immune reconstitution inflammatory syndrome
LF-LAM	lateral flow lipoarabinomannan
LFT	liver function test

LTBI	latent tuberculosis infection
MDR-TB	multidrug-resistant tuberculosis
MTB	Mycobacterium tuberculosis
mWRD	molecular WHO-recommended rapid diagnostic test
NNRTI	non-nucleoside reverse transcriptase inhibitor
OAMT	opioid agonist maintenance therapy
PI	protease inhibitor
PLHIV	people living with HIV
PrEP	pre-exposure prophylaxis
PWUD	people who use drugs
QA	quality assurance
RR-TB	rifampacin-resistant tuberculosis
SOP	standard operating procedure
TB	tuberculosis
TBST	Mycobacterium tuberculosis antigen-based skin test
TPT	tuberculosis preventive treatment
TST	tuberculin skin test
W4SS	WHO-recommended four symptom screen
WHO	World Health Organization
XDR-TB	extensively drug-resistant tuberculosis

HIV medicines

3TC	lamivudine
ABC	abacavir
ATV	atazanavir
AZT	zidovudine
CPT	co-trimoxazole prophylactic therapy
DTG	dolutegravir
DRV	darunavir
EFV	efavirenz
FTC	emtricitabine
LPV	lopinavir
NVP	nevirapine
RAL	raltegravir
RTV	ritonavir
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate

Tuberculosis medicines

B	bedaquiline
B6	pyridoxine
E	ethambutol
H	isoniazid
L	linezolid
M	moxifloxacin
P	rifapentine
Pa	pretomanid
R	rifampicin
Z	pyrazinamide

Definitions

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 (DR-TB): TB disease caused by a strain of *Mycobacterium 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 tuberculosis (EPTB) (classification): any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs (e.g. pleura, peripheral lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges).

High TB transmission setting: a setting with a high frequency of individuals with undetected or undiagnosed active TB, 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.

Household contact: a person who shared the same enclosed living space as the index case for one or more nights or for frequent or extended daytime periods during the 3 months before the start of current treatment.

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

Index patient (index case) of TB: The initially identified person of any age with new or recurrent TB in a specific household or other comparable setting in which others may have been exposed. An index patient is the person on which a contact investigation is centred but is not necessarily the source case.

Inpatient health-care setting: a health-care 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: integrated health services are 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.

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

Number needed to screen (NNS): the number of persons that need to undergo screening in order to diagnose one person with TB disease.

Outpatient health-care setting: a health-care 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 substances such as tobacco or alcoholic and caffeine-containing beverages and foods.

Presumptive tuberculosis (TB): presumptive TB refers to a patient who presents with symptoms or signs suggestive of TB (prfeviously known as a TB suspect).

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.

Tuberculosis (TB) disease: the disease state due to *M. tuberculosis*, commonly referred to as TB.

Tuberculosis (TB) infection: a state of persistent immune response to stimulation by *M. tuberculosis* antigens with no evidence of clinically manifest active TB. There is no gold standard test for direct identification of *M. tuberculosis* infection in humans. Most infected people have no signs or symptoms of TB but are at risk of active TB disease.

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.

WHO-recommended rapid diagnostic test: A test approved by WHO that employs molecular (e.g. Xpert Ultra®) or biomarker-based techniques (e.g. urinary lipoarabinomannan assays (U-LAM)) for the diagnosis of TB. Throughout this publication, the term "WRD" refers to molecular WRDs unless otherwise specified.

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.

1. Background and rationale

1.1 Background and burden of HIV-associated TB

People with HIV are 12–16 times more likely to develop tuberculosis (TB) disease. They also have poorer TB treatment outcomes and have more than two-fold higher mortality during TB treatment compared to people without HIV *(1)*. Despite advances in the prevention, diagnosis and treatment of TB disease, TB remains the leading cause of death among people with HIV worldwide, accounting for 167 000 (27%) of global AIDS-related deaths in 2022 *(1)*. In 2022, only 64% of TB episodes among people 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)*. A global review of autopsy studies, among people who had died from HIV, found 40% prevalence of TB among adults, with only 46% of TB diagnosed before death *(2)*.

The World Health Organization (WHO) *End TB strategy*, endorsed by the World Health Assembly in May 2014, provides strategic direction for the achievement of the TB targets within the United Nations (UN) Sustainable Development Goals (SDGs). Integrated patient-centred prevention, care and social protection for people with HIV-associated TB are key components of the *End TB strategy*. The Strategy outlines a range of medical and socioeconomic interventions to address TB morbidity and mortality and the social determinants of TB *(3)*. The importance of protecting human rights with integrated people-centred services is reiterated by the political declarations of the respective United Nations high-level meetings on the fight against TB *(4)* and on HIV and AIDS *(5)*.

To help countries mitigate the burden of HIV-associated TB in populations at risk of or affected by both diseases, WHO published the *Interim policy on collaborative TB/HIV activities* in 2004 *(6)* which was updated in 2012 *(7)*. The policy has served as a vehicle for a robust global response, advocating for further investment and scale-up of collaborative TB/HIV activities, and provided guidance to Member States and other partners on effectively addressing HIV-associated TB. Collaborative TB/HIV activities include the establishment and strengthening of mechanisms for delivering services for TB and HIV, reducing the burden of TB among people living with HIV, and reducing the burden of HIV in people with presumptive and diagnosed TB. Scale-up of these interventions between 2005 and 2022 is estimated to have saved 9.2 million lives according to modelling for the *Global tuberculosis report 2023*[1]. However, although there has been widespread rollout and uptake of antiretroviral therapy, HIV testing in TB services and TB screening in HIV services, in 2022 an estimated 671 000 (uncertainty interval: 600 000–746 000) people living with HIV developed TB disease *(1)*. To reach the *End TB strategy* target of ending TB, sustained efforts to implement and scale up collaborative TB/HIV activities are essential.

This section of the operational handbook aims to support the implementation of recommendations outlined within the TB/HIV section of the *WHO consolidated guidelines on tuberculosis. Module 6: tuberculosis and comorbidities* (in press) (hereinafter referred to as the *TB/HIV guidelines*). Whilst the focus of the handbook is primarily on adults, guidance on programmatic aspects is applicable to collaborative TB/HIV activities for all age groups.

[1] 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.

1.2 Development of the document

The development of the section on HIV-associated TB (hereinafter referred to as the *TB/HIV section*) was coordinated by the WHO Global Tuberculosis Programme in collaboration with the Department of Global HIV, Hepatitis and Sexually Transmitted Infections Programmes. A WHO steering group was set up in 2022 to guide the development of the *TB/HIV section*, and a stakeholder consultation with a broad array of experts was convened in September 2022, to inform the drafting process. This consultation included participants with expertise in research, clinical practice and programmatic implementation, as well as civil society organizations and people with lived experience of HIV-associated TB, all contributing towards a people-centred perspective.

1.3 Summary of recommendations

Table 1.1 summarizes all existing WHO recommendations[2] that relate to HIV-associated TB in adults, as published in the *WHO consolidated guidelines on tuberculosis. Module 6: tuberculosis and comorbidities. HIV-associated TB* (in press). Some recommendations will however also be relevant for children and adolescents. A full summary of recommendations on HIV-associated TB for children and adolescents specifically, can be found in the *WHO consolidated guidelines on tuberculosis. Module 5: management of TB in children and adolescents (8)*. Other recommendations for TB screening, diagnosis, treatment and care for people regardless of HIV status are also applicable and have been published in the respective modules of the *WHO consolidated guidelines on tuberculosis (8-15)*.

Table 1.1. Recommendations in the *WHO consolidated guidelines on tuberculosis. Module 6: TB and comorbidities. HIV-associated TB*

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). (11)*
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*). *(11)*
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). (11)*
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). (11)*
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). (11)*
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). (11)*
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). (11)*

[2] Updates to recommendations will be found on the WHO TB knowledge sharing platform (https://tbksp.org/) and on the WHO HIV/AIDS page (https://www.who.int/health-topics/hiv-aids).

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). (12)*

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). (12)*

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). (12)*

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). (12)*

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). (14)*

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). (16)*

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). (17)*

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). (9)*

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). (9)*

17. Chest radiography may be offered to people living with HIV on antiretroviral therapy (ART) and preventive treatment be given to those with no abnormal radiographic findings *(conditional recommendation, low certainty in the estimates of effect). (9)*

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). (13)*

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 the evidence). (13)*

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*). *(9)*

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*). *(9)*

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). (7)*

23. All household contacts of a person with HIV-associated TB should be offered HIV testing services *(strong recommendation, very low-quality evidence). (18)*

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). (18)*

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). (18)*

26. Partner services should be offered to people with HIV-associated TB *(strong recommendation, moderate-quality evidence). (19)*

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). (20)*

28. ART should be started as soon as possible within 2 weeks of initiating TB treatment, regardless of CD4 cell count, among people living with HIV.[a] *(21)*

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). (10, 17)*

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). (17)*

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). (17)*

2. Establish and strengthen collaboration across health programmes and across sectors for delivering people-centred services for HIV-associated TB

To support countries in the introduction and scale-up of collaborative action on TB and comorbidities, including for HIV-associated TB, WHO developed the *Framework for collaborative action on tuberculosis and comorbidities (22)*. This document focuses on five key areas that are central to delivering people-centred care for TB and comorbidities: (A) Strengthen governance and accountability for collaborative action; (B) Conduct an analysis of access to quality services for TB and comorbidities; (C) Coordinate planning and resource mobilization for collaborative action; (D) Implement and scale up people-centred services for TB and comorbidities; and (E) Strengthen monitoring, evaluation and research. Recommended actions are summarized in Table 2.1.

The Framework for collaborative action on TB and comorbidities has been adapted in this chaper, to include specific considerations for assuring human rights-based person-centred services to address HIV-associated TB. Depending on the context, people with HIV and TB may also experience other comorbidities such as diabetes, pulmonary disorders other than TB, mental health disorders, smoking and substance use disorders, undernutrition and viral hepatitis. Collaboration between TB and HIV programmes as well as with other programmes is therefore critical to provide comprehensive and holistic people-centred services using a human rights-based approach that supports integrated quality care *(22)*.

Table 2.1. Summary of the *Framework for collaborative action on TB and comorbidities*

Strengthen governance and accountability for collaborative action

A.1 Strengthen political commitment, coordination and accountability for collaborative action on TB and comorbidities
A.2 Support financing and legislation that promote people-centred care
A.3 Ensure meaningful engagement of civil society and affected communities at all stages of planning, implementation, monitoring and evaluation

Conduct an analysis of access to quality services for TB and comorbidities

B.1 Assess the joint burden of TB and comorbidities
B.2 Determine access to services and the financial burden for people with TB and comorbidities
B.3 Map health service delivery for TB and comorbidities
B.4 Identify gaps in services and conduct root cause analysis

Coordinate planning and resource mobilization for collaborative action

C.1 Identify priority comorbidities and interventions
C.2 Define and reorient models of care for TB and comorbidities towards people-centred services, primary health care and universal health coverage
C.3 Conduct collaborative planning and budgeting to scale up people-centred services for TB and comorbidities
C.4 Align advocacy and communication across health programmes

Implement and scale up people-centred services for TB and comorbidities

D.1 Jointly develop policies, guidelines and procedures for collaborative action on TB and comorbidities
D.2 Mobilize a qualified multidisciplinary workforce, including among private providers and non-health sectors for collaborative action
D.3 Ensure access to essential medicines, vaccines, diagnostics and health technologies for TB and comorbidities
D.4 Engage civil society and communities affected by TB and comorbidities in refining and delivering people-centred services
D.5 Optimize access to social protection to prevent financial hardship due to TB and comorbidities
D.6 Facilitate uptake of digital technologies to deliver health and social protection services across programmes
D.7 Introduce phased scale-up of people-centred services for TB and comorbidities

Strengthen monitoring, evaluation and research

E.1 Adopt indicators and set targets for collaborative action on TB and comorbidities
E.2 Strengthen surveillance for comorbidities among people with TB, and surveillance for TB among people with comorbidities and health-related risk factors in accordance with WHO recommendations
E.3 Introduce and scale up monitoring and evaluation of collaborative action on TB and comorbidities at all levels
E.4 Conduct joint reviews of quality and coverage of services to inform programming
E.5 Conduct operational and implementation research to inform policy, programming and service delivery

Source: Framework for collaborative action on tuberculosis and comorbidities. Geneva: World Health Organization; 2022 (22)

2.1 Strengthen governance and accountability for TB/HIV collaborative activities

2.1.1 Strengthen political commitment, coordination and accountability for collaborative action on TB and HIV

HIV programmes and TB programmes, including their counterparts in other line ministries (for example, in ministries responsible for prison or mining health services), the private-for-profit sector, communities and civil society organizations should work together to provide access to integrated services, preferably at the same time and location. To address other comorbidities and to enhance integrated delivery of health and social protection services, representatives from other programmes within and beyond the health sector may also be considered, for example departments overseeing primary health care, mental health, noncommunicable diseases, nutrition, reproductive, mother, child and adolescent health, smoking and substance use disorders, social support services, and gender.

National coordinating bodies are needed at all levels of the health system to ensure strong and effective collaboration between HIV programmes and national TB programmes and to offer a platform for coordination and synergy among stakeholders within and beyond the health sector. Evidence has shown that coordinating bodies for HIV-associated TB that operate at all levels of the health system with active participation of all relevant stakeholders – including affected people and communities, civil society, and the respective health and social protection programmes – are feasible. Coordinating bodies can also effectively establish political commitment and ownership of collaborative activities at the country level *(23, 24)*. Representation of people at risk of, or affected by, both diseases is essential to ensure effective implementation of integrated services and programme success. In countries where a national multisectoral mechanism for TB has already been established (e.g. as part of the *Multisectoral accountability framework for TB (25)*), the coordinating platforms for TB and HIV should have clear linkages with this mechanism to optimize synergies including, for example, for financing, social protection and housing. There should also be clear linkages with the national AIDS commissions, which coordinate the multisectoral response to HIV.

A national coordinating body for collaborative TB/HIV activities should have clear and consensus-based terms of reference, including the roles and responsibilities of the national TB and HIV programmes, and of other health programmes and relevant sectors in implementing, scaling up, monitoring and evaluating TB/HIV collaborative activities at all levels. The important areas of responsibility are:

- coordination of collaborative TB/HIV activities throughout the programme management cycle from assessment, planning and resource mobilization, to scale-up and monitoring and evaluation;
- liaison with and reporting to the multisectoral coordination mechanism for TB and the national AIDS commissions; and other coordinating mechanism(s) that may exist on human rights, social protection, and gender, among others;

- facilitation of the involvement of communities and their organizations, civil society, nongovernmental organizations, and individuals; and
- ensuring alignment of advocacy and communication on TB and HIV and other comorbidities.

2.1.2 Support financing and legislation that protect human rights and promote people-centred care

Programmes should work together to ensure financing and legislation to support the delivery of integrated care. This might include:

- scaling up financing models that incentivize the provision of comprehensive services as part of national health financing strategies;
- advocating for change in legislation and financing to allow task shifting and the engagement of peer supporters to deliver human rights-based people-centred care, for example for differentiated service delivery;
- building capacity among civil society organizations to monitor and strengthen implementation of laws to address stigma and discrimination and other forms of social exclusion; and
- advocating for decriminalization of drug use and strengthening linkages with prison services to ensure fulfilment of the human right to equitable access to care for HIV-associated TB and other related comorbidities for prisoners.

Since legislation and financing often lie outside the purview of the TB and HIV programmes, it is essential to develop strong partnerships with stakeholders from outside the health system, including funding agencies, to advocate for and assist in addressing these areas. This may include, for example, advocating for legislation that allows prescription of opioid agonist maintenance therapy (OAMT), or advocating for financing that allows implementation of social protection. Moreover, the coordinating platforms for TB and HIV should also liaise with the coordinating platform for the *Multisectoral accountability framework for TB (25)* and with the National AIDS Council to optimize synergies.

2.1.3 Ensure meaningful engagement of civil society and affected communities at all stages of planning, implementation, monitoring and evaluation

Expanding collaborative TB/HIV activities beyond the health sector is crucial, through meaningful involvement of communities, civil society organizations and individuals in the governance and decision-making, planning, implementation and monitoring of TB/HIV activities at all levels. People at risk of, or affected by, TB and HIV, as well as community stakeholders (e.g. opinion and religious leaders), community-led and community-based organizations working on advocacy, treatment literacy and community mobilization are key actors in generating demand for people-centred services at all levels of care. Engagement and support, including financial support, for civil society and affected communities is therefore critical. Advocacy targeted at influencing policy and sustaining political commitment, programme implementation and resource mobilization is needed to accelerate the implementation of collaborative TB/HIV activities. Programmes and stakeholders should work together to empower affected people and communities, and civil society, to ensure they are a continuum of the health system and can be actively, formally and regularly engaged in shaping the agenda on HIV-associated TB. This includes from governance, decision-making and planning, to monitoring and evaluation, as well as in advocacy for scale-up of non-discriminatory, high-quality care for HIV-associated TB and other comorbidities, and for availability of related resources through domestic and external sources.

2.2 Conduct an analysis of access to quality services for TB and HIV

2.2.1 Assess the joint burden of TB and HIV

Routine surveillance is essential for understanding the characteristics of the TB and HIV epidemics in the country and to inform programme planning and implementation. The surveillance of TB disease among people with HIV can be based on the analysis of routine programme data collected for people with HIV who are newly initiated on ART. Surveillance of HIV among people with TB can be performed through: (i) periodic cross-sectional HIV seroprevalence surveys among a representative sample of people with TB in a country; (ii) sentinel surveys using people with TB as a sentinel group within the general HIV sentinel surveillance system; and (iii) using data from routine HIV testing of people with presumptive or diagnosed TB. The surveillance method depends on the state of the underlying HIV epidemic, the overall TB epidemiology, and the level of integration and decentralization of services for HIV-associated TB. Inclusion of surveillance of other comorbidities and social determinants, common to TB and HIV, may also be considered as part of this assessment. These might include undernutrition, pulmonary disorders other than TB, mental health disorders, smoking and substance use disorders (alcohol and drugs), viral hepatitis and diabetes. If the collection of data on comorbidities and social determinants is not integrated into routine TB surveillance, then these data may be shared by other programmes responsible for their surveillance or can be collected through population- or facility-based surveys. Key considerations for assessing the joint burden of TB and HIV are summarized in Box 2.1.

Incorporating HIV testing within TB prevalence surveys and antituberculosis drug resistance surveys provides an opportunity to optimize HIV testing coverage and improve knowledge among national TB and HIV programmes on the relationship between HIV, TB and drug-resistant TB at the population level *(26, 27)*. It also provides critically important benefits to individuals living with HIV, including better access to testing, early detection and rapid initiation of treatment *(7)*.

In the context of a TB prevalence survey, HIV testing may be offered according to the following strategies: in settings with a generalized HIV epidemic or where HIV care is more decentralized, HIV screening and testing should be offered for all participants in a TB prevalence survey; in settings where the HIV epidemic is concentrated or where HIV care is more centralized, HIV testing should be offered to all participants diagnosed with TB and to participants presenting with symptoms and/or chest X-ray findings suggestive of TB, in accordance with WHO recommendations. The minimum acceptable standard would be to offer HIV testing to all participants found to have TB.

Further guidance on inclusion of HIV and other comorbidities within TB prevalence surveys is published in *WHO consolidated guidelines on tuberculosis data generation and use. Module 3: national tuberculosis prevalence surveys guidance, tuberculosis data generation and use* (in press) *(28)*.

Box 2.1 Guidance for assessment of the joint burden of TB and HIV

1. Surveillance of HIV should be conducted among people with TB and surveillance of 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.
2. Countries where HIV services are not yet scaled up, with unknown HIV prevalence rates among people with TB, should conduct an HIV seroprevalence (periodic or sentinel) survey to assess the situation.
3. In countries with a generalized HIV epidemic state,[a] HIV testing services for all people 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.
4. In countries with a low-level HIV epidemic state,[b] where HIV services are not yet scaled up, periodic (special) or sentinel surveys among people with TB are recommended every 2–3 years.
5. In countries with a concentrated HIV epidemic state,[c] where groups at high risk of HIV infection are localized in certain administrative areas, HIV testing services for all people with presumptive or diagnosed TB in those administrative areas should form the basis of surveillance. In administrative areas with a low-level HIV epidemic state, where HIV services are not yet scaled up, periodic (special) or sentinel surveys every 2–3 years are suitable alternatives.
6. HIV testing should be an integral part of TB prevalence surveys and antituberculosis drug resistance surveillance.

[a] Generalized epidemic state: HIV prevalence is consistently >1% in pregnant women.
[b] Low-level epidemic state: HIV prevalence has not consistently exceeded 5% in any defined subpopulation.
[c] Concentrated epidemic state: HIV prevalence is consistently >5% in at least one defined subpopulation and is <1% in pregnant women in urban areas.

Source: WHO policy on collaborative TB/HIV activities. Guidelines for national programmes and other stakeholders. Geneva: World Health Organization; 2012 (7)

Whatever strategy is selected, HIV surveillance among people with TB should follow nationally recommended guidelines related to HIV testing, in terms of who to test, the testing strategy and in accordance with the 5 Cs: Consent, Confidentiality, Counselling, Correct test results and Connection or linkage to prevention, care and treatment *(17, 26)*. Unlinked anonymous testing for HIV is not recommended because results cannot be traced back to individuals who need HIV care and treatment *(26)*. For HIV testing to be offered, HIV care and ART provision need to be in place so that those individuals newly diagnosed with HIV during the surveillance can immediately receive TB and HIV treatment and services based on national guidelines.

Evidence from descriptive studies has shown HIV surveillance among people with TB to be a critical activity in understanding the trends of the HIV epidemic and in the development of sound strategies to address the dual TB/HIV epidemic *(7)*. Mortality audits may also highlight other causes of death, such as undernutrition, that need to be addressed during care for HIV-associated TB *(29)*. These data can be consolidated and analysed as part of overall country review and planning processes for TB and HIV as well as other relevant comorbidities. Gaps in evidence identified during this process can inform further data collection.

2.2.2 Determine access to services and the financial burden for people with TB and HIV

To deliver human rights-based people-centred services, it is crucial to understand the factors that affect general access to services for HIV-associated TB, with attention to barriers experienced by subpopulations, including people with other comorbidities, barriers specific to certain geographic locations, and the socioeconomic impact of HIV-associated TB *(30)*. Access to TB/HIV services can be determined through patient pathway analyses, or operational research. Understanding the root causes to the barriers is essential in planning for improving access to TB/HIV services for those in need. The financial burden may be assessed through analysis of data from TB patient cost surveys which include disaggregation by HIV status, national demographic and health surveys and health expenditure and utilization surveys. When assessing the socioeconomic impact of HIV-associated TB, access to existing social protection schemes that mitigate the financial impact of HIV-associated TB and enable affected people to adhere to treatment should also be considered.

2.2.3 Map health service delivery for TB and HIV

Data on the current capacity, performance, limitations and distribution of health and social protection services for HIV-associated TB and other comorbidities can be gathered from sources including health system reviews or readiness assessment mapping such as the Harmonized Health Facility Assessment *(31)*. The mapping of service delivery for TB, HIV and HIV-associated TB should assess public and private sectors and nongovernmental stakeholders, including an assessment of access to services among the key populations for HIV and other vulnerable or at-risk populations. Guidance on public-private mix is published in *Guide to develop a national action plan on public-private mix for tuberculosis prevention and care (32)*. Availability of, or proximity to, equipment and consumables to screen for and diagnose TB and HIV should be assessed in the respective services. For diagnostics, it is also important to understand the connection with the laboratory and sample transportation network, including factors such as frequency of sample collection and speed of turnaround of results. It is also important to determine the availability, deployment, qualifications and training needs of the health workforce for the detection, prevention, treatment and care of HIV-associated TB, including community health workers and social workers.

2.2.4 Identify gaps in services and conduct root cause analysis

Data collected on epidemiology, access to services from the user perspective, the health system and service delivery, as described above, should be analysed to identify gaps and opportunities. Root cause analysis *(33)* can help understanding of the reasons for gaps in services and inform strategies to address these.

2.3 Coordinate planning and resource mobilization for collaborative action

2.3.1 Identify priority comorbidities and interventions

WHO has recommended collaborative TB/HIV activities in all contexts since 2004 and as such, HIV should be a prioritized TB comorbidity for all countries. Collaborative TB/HIV activities have been scaled up in most high TB/HIV burden settings. However, there will likely be gaps in access and quality across the cascade of care.

As part of the planning process, countries should identify priority gaps and related interventions to scale up and strengthen access to TB/HIV services, based on the analysis of access to quality services for TB and HIV, which should also include other comorbidities. Criteria for prioritization should be agreed using the coordination platform or related technical working group. The criteria for prioritization may include, but should not be limited to, the causes and distribution of morbidity and mortality, cost implications, ethical, equity and human rights considerations and acceptability. During the data review, another comorbidity such as undernutrition may be identified as important among people dying from TB and HIV, and so priority may be given to assessment of and management of undernutrition in all people with TB and HIV.

Some countries have a concentrated HIV epidemic and a high burden of TB, with a limited coverage of collaborative TB/HIV activities. In such a context they should prioritize, in the short term, activities to reduce the burden of TB among people with HIV (TB screening, TB preventive treatment, diagnosis, treatment and care) among all people attending HIV care. In parallel, HIV testing and ART within TB services may be scaled up strategically starting with urban centres, high HIV burden provinces or populations more at risk of HIV.

2.3.2 Define and reorient models of care for HIV-associated TB and other comorbidities towards people-centred services, primary health care and universal health coverage

Where feasible, programmes should aspire to decentralize and integrate services for TB and HIV down to the primary care and community levels, so that people with HIV-associated TB can access care on an ambulatory basis where possible *(34)*. Services for TB and HIV should be tailored to the needs and preferences of affected persons and should aim to minimize the time and financial costs incurred while accessing care. To this end, programmes should work together to shape models of care and social protection that assure the provision of integrated services, preferably at the same time and location, and as close as possible to people who need them. Integrated models of care

are feasible, acceptable, cost-effective and may have high rates of TB treatment success *(35-39)*. A concern with any model of integration is the risk of nosocomial spread of TB. Thus, implementation of proper infection prevention and control measures (see Chapter 3.5) is crucial throughout health facilities in high burden settings to minimize the risk of nosocomial spread of TB to immunosuppressed people living with HIV. On the other hand, integrated care supports early detection and treatment of undiagnosed infectious TB and may result in a reduction of TB risk compared with separate services. Box 2.2 and Fig. 2.1 describe models of service delivery for TB, HIV and other comorbidities, according to where a person first seeks care, and according to the degree of integration *(22)*.

Box 2.2 Models of service delivery for HIV-associated TB

Models of service delivery for HIV-associated TB range from disease-specific separate service providers for TB and for HIV, to "one-stop-shop" services where integrated care for TB and HIV is provided at the same time and location by the same trained healthcare provider. Within these models, care may be provided by separate specialist healthcare workers who refer clients to different services according to established pathways. Alternatively, multidisciplinary teams comprising professionals with a mix of skills, including medical and non-medical, required to meet the needs of the end user, may provide coordinated care *(40)*. Care can also be provided by one healthcare worker for both TB and comorbidities, where the expertise is available *(41)*. In most settings, the engagement of community health workers, outreach teams and peer supporters will help strengthen all models of care.

Integrated services for HIV-associated TB have been associated with higher notification of smear-negative pulmonary and extrapulmonary TB, improved treatment success rates and lower TB mortality, as well as timely initiation of ART *(42-45)*. Models of care for HIV-associated TB can be categorized according to where a person first seeks care, and according to the degree of integration (Fig. 2.1) *(22, 41)*. These models are not exhaustive nor prescriptive; national programmes should define the models that best enable the provision of quality-assured comprehensive services as close as possible to the end user.

Separate service delivery

Entry via TB services: in this model, TB services may offer HIV testing on site and refer people with a positive HIV test to HIV services for ART initiation and HIV care. Alternatively, TB services may offer HIV self-testing, and referral for further HIV test confirmation, and ART as required, within HIV services. Regardless of test results, people should be provided with HIV prevention information. This model may require training of healthcare workers on HIV testing tools, recording and reporting and referral pathways.

Entry via HIV services: in this model, HIV services screen for TB using available screening tools. Where indicated, HIV services may also test for TB using the point-of-care LF-LAM test and take an appropriate sample for diagnostic testing. As for models with entry via TB services, this model requires training of healthcare workers on the relevant TB screening tools and LF-LAM, TB diagnostic sample collection, as well as recording and reporting and referral pathways.

Co-located services

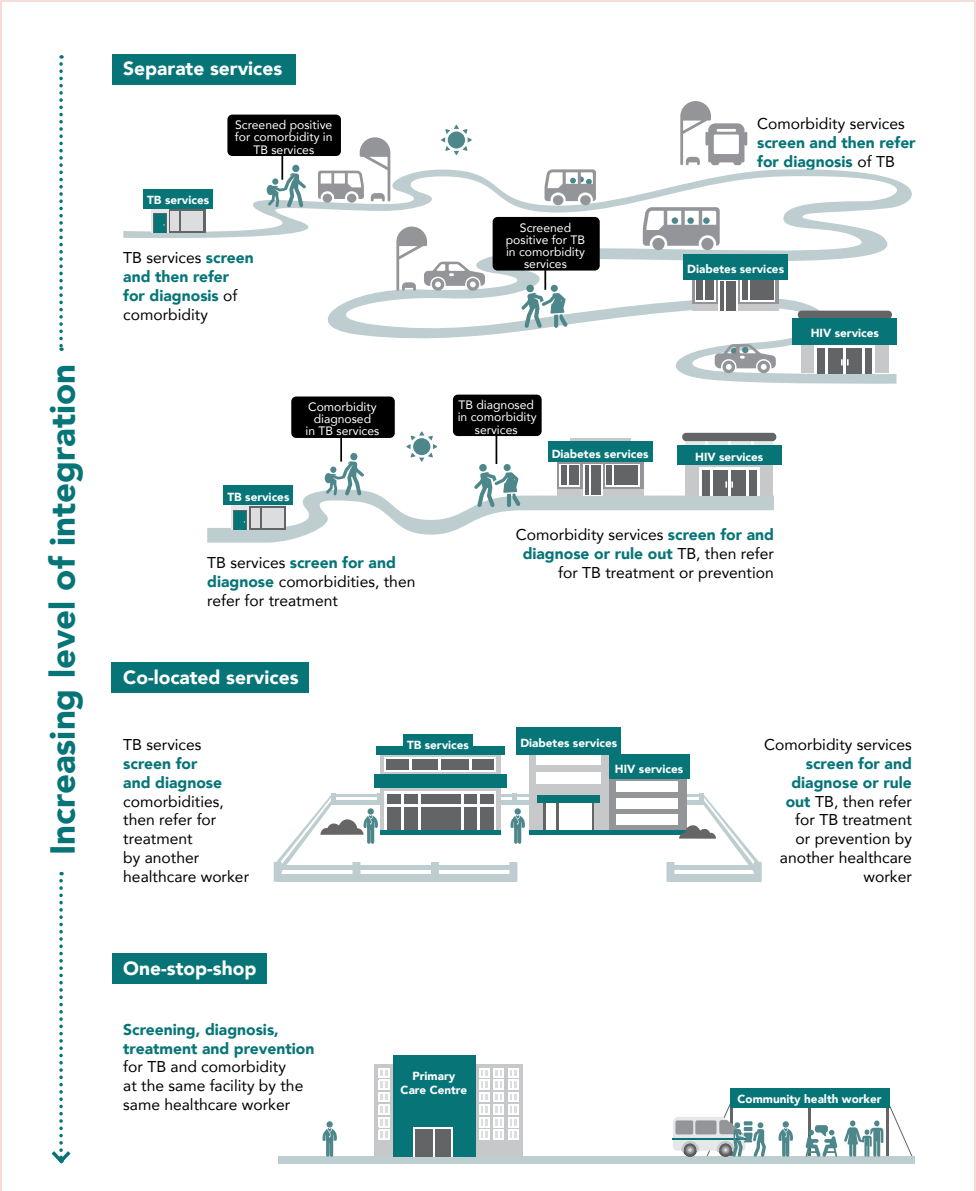
Co-location refers to separate service providers located in the same or adjacent premises. Co-located models of care may further reduce the need to travel to multiple distant facilities and enable a higher degree of integration between TB and HIV services. However, while services are provided on the same premises, it is important to highlight the need for close collaboration in order to minimize the waiting time between appointments, for example, as well as reduce the number of times a person needs to attend to receive care for TB and for HIV, and enable integrated patient health records. This model of care facilitates

linkage to care and promotes closer collaboration between providers but may be more time-consuming and costly to the end user and their family compared to one-stop-shop services.

One-stop-shop services

This model provides people-centred care for TB and HIV through a spectrum of activities including screening, diagnosis, treatment and care by the same healthcare worker in the respective specialist services or in primary healthcare services, in the same visit. Services may be provided in primary care settings or through community outreach initiatives that are adapted to the needs of service users and are available close to where they live. Integrated models of care may improve health outcomes; reduce transport costs, income loss and other costs associated with attending appointments; simplify recording and reporting; and can be more time efficient.

Fig. 2.1. Models of integrated care for people with TB, HIV and other comorbidities



Source: Framework for collaborative action on tuberculosis and comorbidities. Geneva: World Health Organization; 2022 (22)

2.3.3 Conduct collaborative planning and budgeting to scale up people-centred services for TB and HIV

Joint planning and budgeting for integrated services may contribute to efficiency of resource use and improved health outcomes. To ensure sustainability, planning should be harmonized with the country's national health strategic plans, health system-strengthening agenda and overall efforts towards achieving universal health coverage (UHC) and social protection. Key areas for joint planning include quality-assured health services; health workforce; information systems and sharing of data with relevant agencies; equitable access to essential medicines, vaccines and technologies; health financing and social protection; and leadership and governance. Joint proposals should be prepared for mobilizing domestic and external resources for collaborative TB/HIV activities. These should be prepared within the framework of the joint coordinating body, building on the comparative strengths of both programmes and the specific needs of the country. Alternatively, both HIV and TB funding proposals should include resources to address collaborative TB/HIV activities in each proposal with clear division of labour to avoid duplication of efforts *(7)*.

2.3.4 Align advocacy and communication across health programmes

Advocacy targeted at influencing policy, programme implementation, and resource and community mobilization is important to accelerate implementation of collaborative TB/HIV activities at all levels. Two-way communication between the programmes and the public and with affected populations, can inform and create awareness about both diseases and is crucial for ensuring that people actively seek and demand services. Effective communication measures focus on communities rather than individuals and combine a series of elements from the use of data, science, research, policy and advocacy. This can inform the public, shape perceptions and attitudes, mitigate stigma and enhance the protection of human rights. It can also create demand for services, form stronger links with health services and systems, and improve provider–client relationships. Joint communication strategies for HIV-associated TB should ensure the mainstreaming of HIV messaging in TB communications and of TB messaging in HIV communications *(7)*.

2.4 Implement and scale up people-centred services for HIV-associated TB

2.4.1 Jointly develop policies, guidelines and procedures for collaborative TB/HIV activities

To implement and scale up people-centred services for TB and HIV, programmes should jointly develop policies, guidelines and procedures for collaborative action and mainstream collaborative TB/HIV activities within national guidelines and standard operating procedures. Consideration should also be given to assessing and addressing other common comorbidities and risk factors such as under-nutrition, pulmonary disorders other than TB, mental illness, tobacco use, substance use disorders and diabetes.

2.4.2 Mobilize a qualified multidisciplinary workforce, including among private providers and non-health sectors for collaborative action

An adequately trained multidisciplinary workforce should be mobilized according to needs identified. Joint capacity-building for collaborative activities should include training of TB, HIV and primary healthcare workers in issues related to HIV-associated TB. Consideration should also be given to the role of the private sector and medical associations in increasing capacity and resources *(32)*. Ensuring continued competency-based education of healthcare workers through clinical mentoring, regular supportive supervision and the availability of standard operating procedures and job aids, reference materials and up-to-date national guidelines is important *(7)*.

2.4.3 Ensure access to essential medicines, vaccines, diagnostics and health technologies for TB and HIV

Countries should ensure access to essential medicines, vaccines, diagnostics and health technologies as required in the respective services, according to the models of care for delivering integrated services for HIV-associated TB. Capacity should also be enhanced in the healthcare system, for example in the laboratory, supply management, health information, referral and integrated service delivery systems, to enable them to deliver collaborative TB/HIV activities *(46)*. Box 2.3 outlines key considerations to ensure delivery of integrated services for HIV-associated TB.

Box 2.3 Key actions to ensure access to essential medicines, vaccines, diagnostics and health technologies:

- Advocate for inclusion of prevention measures, screening tools, diagnostic tests including point-of-care tests, medication and care for TB and HIV within the essential package of care under UHC, to eliminate out-of-pocket costs.
- Ensure all commodities are registered and quality assured.
- Collaborate with international organizations, such as the World Food Programme, and nongovernmental organizations working on food security and nutrition to facilitate access to nutritional support.
- Strengthen capacity in procurement and supply management, including training, storage and management information systems to reduce stockouts.
- Where possible, stock medications for key comorbidities in TB services, and vice versa, to minimize the need for referral for diagnosis and treatment.
- Develop adequate laboratory network capacity or strong linkages to existing laboratory networks (e.g. expand sputum transportation networks to where relevant comorbidity services are delivered; invest in expanded use of common diagnostic platforms for TB, HIV, viral hepatitis, SARS-CoV-2).

2.4.4 Engage civil society and communities affected by TB and HIV in refining and delivering people-centred services

Persons affected by or at risk of HIV-associated TB, their communities and civil society should be actively engaged in decision-making, defining needs, prioritizing actions, designing and implementing interventions to address HIV-associated TB and comorbidities, in research as well as in monitoring, evaluating and reviewing their impact *(22)*. They are also important partners in generating demand for integrated services, monitoring and addressing stigma and discrimination and other forms of social exclusion, as well as in delivering health education, advocacy and peer support for those undergoing treatment, for key populations and for the wider community *(3)*. Community health workers should be remunerated according to the scope of their engagement, in line with local employment rules and regulations *(47)*. Advocacy targeted at influencing policy and sustaining political commitment, programme implementation and resource mobilization is very important to accelerate the implementation of collaborative TB/HIV activities *(7)*.

Services for TB prevention, diagnosis, treatment and care can be integrated with those for HIV, and vice versa, through community-based organizations such as TB care or home-based HIV care, and community-based social support. Trained home-based care and community health workers as well as nongovernmental organizations have been successful in providing TB and HIV services in various countries, including for key populations *(48-53)*. Community-based TB *(54, 55)* and HIV care services *(56)* are cost effective. While implementing collaborative TB/HIV activities, it is imperative that civil society organizations, including nongovernmental and community-based organizations, advocate, promote and follow national TB and HIV guidelines, including monitoring and evaluation of TB/HIV activities using nationally recommended indicators.

2.4.5 Address the needs of key, vulnerable and at-risk populations

Box 2.4 Good practice and guidance statements on critical enablers for key populations

Removing punitive laws, policies and practices

- Laws, legal policies and practices should be reviewed and, where necessary, revised by policy-makers and government leaders, with meaningful engagement of stakeholders from key population groups to allow and support increased access to services for key populations
- Countries should work towards decriminalization of drug use/injecting, drug possession, sex work, same-sex activity and nonconforming gender identities, and towards elimination of the unjust application of civil law and regulations against people who use/inject drugs, sex workers, men who have sex with men and trans and gender diverse people

Reducing stigma and discrimination

- Health services should be made available, accessible and acceptable to people from key populations, based on the principles of medical ethics, avoidance of stigma, non-discrimination and the right to health
- Countries should work towards implementing and enforcing anti-discrimination and protective laws derived from human rights standards, to eliminate stigma, discrimination and violence against people from key populations
- Policy-makers, parliamentarians and other public health leaders should work together with civil society organizations in their efforts to monitor stigma, confront discrimination against key populations and change punitive legal and social norms

Community empowerment

- Key population-led groups and organizations should be made essential partners and leaders in designing, planning, implementing, monitoring and evaluating health services
- Programmes should implement a package of interventions to enhance community empowerment among key populations

Addressing violence

- Violence against people from key populations should be prevented and addressed in partnership with key population-led organizations. All violence against people from key population groups should be monitored and reported, and redress mechanisms should be established to provide justice

Key populations for HIV are defined groups who are at increased risk of HIV, irrespective of the epidemic type or local context *(57)*. The five key populations as defined by WHO are 1) men who have sex with men; 2) people who inject drugs; 3) people in prisons and other closed settings; 4) sex workers; and 5) trans and gender diverse people *(57)*. Due to the increased risk of HIV, members of key population groups are also at significant risk of HIV-associated TB. In addition, members of some key populations, in particular people who use drugs and people in prisons and other closed settings, are also at elevated risk of TB, regardless of HIV status *(58, 59)*. However, whilst the evidence

is limited, men who have sex with men, sex workers and trans and gender diverse people may also be at elevated risk of TB disease, depending on the setting. This would be due to the overlapping social vulnerabilities that drive the TB epidemic.

Multiple social, legal and structural factors both increase vulnerability to HIV and TB, and impede access to health and other essential services. These structural barriers include laws and policies that criminalize drug use or possession, sex work and diverse forms of gender expression and sexuality; stigma and discrimination; lack of community empowerment; and violence. WHO's *Consolidated guidelines on HIV, viral hepatitis and STI prevention, diagnosis, treatment and care for key populations (57)* outlines critical enablers that are central to addressing structural barriers and implementing comprehensive services for HIV care for key populations in all epidemic contexts, as shown in Box 2.4. These are also pertinent to populations at risk of TB, regardless of HIV status.

2.4.6 Facilitate access to social protection to prevent financial hardship due to TB and HIV

Although TB and HIV services are generally free of charge, services for TB and HIV often incur costs at the point-of-care *(60-62)*. In addition, there may be high costs related to accessing services for TB and HIV, such as transport costs and income loss, particularly if these services are not delivered at the same time and place *(63)*. Access to social protection interventions, including nutritional support, may help prevent financial hardship across the cascade of care, and prevention of HIV-associated TB. This would also contribute to reducing the impact of social determinants on the TB and HIV epidemics.

2.4.7 Facilitate uptake of digital technologies to deliver health and social protection services across programmes

Countries should harness digital technologies to support the scale-up of TB/HIV collaborative activities. Such technologies may include telemedicine appointments, remote adherence support, video-supported TB treatment and digital data collection tools. Box 2.5 describes the use of a mobile application to support scale-up of tuberculosis preventive treatment (TPT).

Box 2.5 Prevent TB: a prototype mobile application to support programmatic management of TPT and screening

The WHO Global Tuberculosis Programme has developed a mobile application (app) to facilitate monitoring and evaluation of programmatic management of TPT *(64)*. The Prevent TB App was built using the District Health Information Software 2 (DHIS2; https://www.dhis2.org/) and is compatible with several electronic data systems currently in use in countries. It is designed to help healthcare workers collect person-specific data across the cascade of care for TB screening and TPT, including recording and reporting of adverse events, monitoring of adherence to TPT, and to visualize them on an online dashboard for real-time monitoring. The app can be adapted to meet country programme needs. WHO conducted field testing of this application in several high-burden countries and has now upgraded the original tool released in 2017, with more user-friendly features and utilities to link up more easily to other information systems available to the programmes. The platform provides a smart setup that enables country programmes to design and modify the app depending on the country context. The app can be adapted and deployed across all types of HIV care settings.

2.4.8 Scale up people-centred services for TB and HIV

In many countries, collaborative TB/HIV activities are scaled up nationally. However, in some countries, for example with a concentrated HIV epidemic, access to integrated services for HIV-associated TB can be limited at subnational level. Countries should strive to ensure national coverage of collaborative TB/HIV activities. Scale-up should be informed by ongoing monitoring, review and prioritization. Approaches to scale-up include, for example, by geographical region, such as starting in one or two districts with phased nationwide decentralization at the community level, or through the various stages of care such as starting with screening in the respective services, then gradually scaling up to provide the full cascade of care for TB and HIV in the same facility.

2.5 Strengthen monitoring, evaluation and research

2.5.1 Adopt indicators and set targets for collaborative TB/HIV activities

TB and HIV programmes should jointly identify harmonized indicators to avoid duplication of effort *(65)*. Clear definitions of indicators can drive progress and accountability, especially if linked with established accountability mechanisms such as the *Multisectoral accountability framework for TB (25)*. Recommended core indicators can be found in Annex 1. Additional indicators that may be adopted at the national level are included in the WHO's *A guide to monitoring and evaluation for collaborative TB/HIV activities (65)* and the *Consolidated HIV strategic information guidelines: driving impact through programme monitoring and management (66)*. Countries should also set time-bound targets to scale up people-centred collaborative TB/HIV activities, which can strengthen collaboration between programmes, promote involvement across sectors and help to mobilize political commitment *(7)*.

2.5.2 Strengthen surveillance for HIV among people with TB, and surveillance for TB among people with HIV in accordance with WHO recommendations

Surveillance and regular assessment are essential to inform budgeting, planning and implementation of services for HIV-associated TB. To this end, countries should strengthen their surveillance in accordance with the epidemiological context, build staff capacity to record and use data, and scale up interoperable electronic recording and reporting systems. Data from a range of non-health sectors may also be utilized to promote multisectoral action and accountability. The sources may include, inter alia, the prison sector, mining sector and social services *(67)*. The checklist in Box 2.6 may be used to support implementation and scale-up of systems for the surveillance of TB and HIV prevalence.

Box 2.6 Guidance for strengthening surveillance of HIV-associated TB

- Select appropriate method for surveillance depending on the epidemiological and health systems context, as outlined in 2.2.1
- Adapt standardized paper-based recording and reporting systems to collect data on TB, HIV and other comorbidities, where digital recording and reporting is not yet feasible
- Collaborate in the design, implementation and scale-up of a single integrated system or interoperable digital recording and reporting systems, that are aligned with the overall health management information system (HMIS) digital health information strategy
- Introduce unique identifiers to facilitate information sharing and minimize duplication across systems, while maintaining patient confidentiality
- Establish data sharing agreements and data harmonization practices across disease programmes, particularly where digital recording and reporting is not integrated, not interoperable across systems or is absent
- Establish mechanisms to ensure that data captured by private, nongovernmental and non-health sectors are aligned with national monitoring and evaluation guidelines, and are shared with relevant programmes as per data sharing agreements
- Establish collaborative data quality standard operating procedures across disease programmes to ensure that data collected and shared are complete, accurate and consistent
- Ensure availability and maintenance of the infrastructure upon which a digital system can be built
- Build the required technical capacity among healthcare workers to document and access patient health information on electronic health records
- Train staff at all levels to collect, report, analyse and use data

2.5.3 Introduce and scale up monitoring and evaluation of collaborative TB/HIV activities at all levels

Joint monitoring and evaluation activities provide the means to assess the quality, effectiveness, coverage and delivery of collaborative TB/HIV activities. They promote a learning culture within and across the programmes and ensure continuous improvement of individual and joint programme performance. Monitoring and evaluation involves collaboration between the TB and HIV programmes and the general health system (public and private), the development of referral linkages between different services and organizations, and joint supervision.

As part of scale-up, recording and reporting tools should be co-developed by the TB and HIV programmes, and standardized and updated to capture and strengthen data on the continuum of care for TB and HIV. The rapid development of digital technology provides novel opportunities for collecting and analysing data, including among subpopulations *(67-69)*. During the introduction of digital systems, programmes should strive to implement either an integrated digital recording and reporting system or one that is interoperable with other systems used by other programmes, such as DHIS2 *(70)*, which can facilitate the co-management, referral and follow-up of people in care. Similarly, digital systems should be designed to facilitate the visualization of data in real-time for rapid analysis of emerging trends in TB/HIV epidemiology. It is important that all digital systems safeguard the confidentiality of patient data throughout implementation *(69, 71)*.

2.5.4 Conduct joint reviews of quality and coverage of services to inform programming

To ensure quality, the national TB and HIV programmes at the different levels should conduct joint reviews as part of regular quarterly supervision activities. Results from joint supervision should be used to mentor, adapt and adjust the response to HIV-associated TB, in order to drive performance improvement.

To assess progress of implementation of the respective TB and HIV national strategic plans in generalized HIV epidemic settings, countries may choose to conduct one joint TB and HIV programme review. Alternatively, countries may choose to keep to disease-specific reviews with active participation by staff from the other programme. Other TB and HIV stakeholders, healthcare and social-protection providers, and affected communities should also be engaged during programme reviews and to appraise the evidence. WHO has recently developed guidance on TB programme reviews, which includes checklists for HIV and other comorbidities.

2.5.5 Conduct operational and implementation research to inform policy, programming and service delivery

All stakeholders of collaborative TB/HIV activities, including HIV programmes and national TB 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 *(7)*. Operational research is needed to define how best to provide high-quality integrated TB and HIV interventions at facility and community levels to inform global and national policy and strategy development, and fine-tune programming and human rights-based people-centred service delivery *(72)*. Consolidated research priorities are summarized in the *WHO consolidated guidelines on tuberculosis. Module 6: tuberculosis and comorbidities TB* (in press).

3. Reduce the burden of TB among people living with HIV

Close to half of people estimated to have HIV-associated TB are not diagnosed and reported *(1)*. Post-mortem studies have found very high prevalence of undiagnosed TB among people with HIV who have died in healthcare facilities in high TB burden settings *(2)*. Early identification of signs and symptoms of TB followed by diagnosis and prompt initiation of treatment in people living with HIV reduces mortality, improves health-related quality of life and reduces transmission of TB. Close collaboration between TB and HIV programmes is essential for minimizing loss to follow-up during the TB screening and diagnostic cascade and for ensuring appropriate treatment of TB infection or TB disease. Close coordination between health providers is also required to ensure household members and close contacts are followed up for TB screening and HIV testing, as well as treatment and prevention, as necessary.

3.1 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). (11)*
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*). *(11)*
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). (11)*
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). (11)*
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). (11)*
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). (11)*
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). (11)*

3.1.1 Frequency of screening

WHO recommends that people living with HIV should be screened for TB disease at each visit to a health facility *(73)*. In addition to the WHO-recommended four symptom screen (W4SS), three more TB screening tools are now recommended for people living with HIV, namely, chest X-ray (CXR), C-reactive protein and molecular WHO-recommended diagnostic tests. These may be used alone or in combination with the W4SS, depending on the resources available. At a minimum, a W4SS should be conducted and this may be supplemented with additional screening tools, for instance at the time of initial HIV diagnosis or during the first antenatal care visit for pregnant women, and then annually thereafter.

3.1.2 Screening tools

All the screening tests described here identify adults and adolescents with HIV with a higher probability of TB disease and who should be referred for diagnostic evaluation. When TB disease is ruled out, the individual should be referred for evaluation for TB preventive treatment.

WHO-recommended four symptom screen

The W4SS comprises the following symptoms: current cough, fever, night sweats or weight loss. It was first recommended in 2011, with an initial recommendation for systematic screening of all people living with HIV at every visit to a healthcare facility, primarily for ruling out TB disease, due to its high negative predictive value. However, if adults and adolescents with HIV screen positive for any one of these symptoms, further diagnostic workup is recommended. W4SS is a simple screening approach that is non-invasive and is feasible to implement repeatedly in any setting, by any level of healthcare provider. The results of a symptom screen may be subjective and depend on the end user's level of understanding and willingness to share their physical experience of symptoms, as well as on the provider's interpretation of the reported symptoms. Thus, the quality and consistency of the W4SS is likely to vary between clinical settings.

An individual participant data meta-analysis that informed the 2021 WHO screening guideline revision found that 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%). When used alone, the sensitivity of the W4SS was lowest among outpatients on ART and among pregnant women, and it had markedly low specificity among medical inpatients and individuals not receiving ART (ART naïve or interrupted treatment) *(11)*. The W4SS has an important role in ruling out TB disease due to its high negative predictive value in most settings. This is important in the preventive TB care pathway of people living with HIV who would benefit from receiving TPT in the absence of TB disease.

While there may be real-life limitations to the W4SS in terms of consistency and quality of delivery that might not be reflected in studies, the W4SS is an essential part of the clinical examination of most subpopulations and is the most accessible screening tool at all levels of the health system. It can be repeated as often as necessary, while more intense screening strategies with additional screening technologies might be used less frequently, such as at initial HIV diagnosis and at annual check-ups such as for viral load monitoring. Familiarity with W4SS is already widespread in many HIV services, as a result of capacity-building efforts and supervision.

It is however important to continuously monitor and enhance the quality of delivery of the W4SS in all settings, including within differentiated service delivery. This can be done through training of healthcare workers and peer workers, and through operational research. Studies to monitor quality may include tracking screening positivity rates, the use of auditing tools and exit interviews among people attending HIV care as well as studies to monitor the cascade of screening, diagnosis and care *(74, 75)*. Indicators listed in Annex 1 can assist programmes in assessing the gaps in the cascade, from screening through to diagnosis and initiation of TB treatment and TB preventive treatment.

C-reactive protein

C-reactive protein (CRP) is an indicator of systemic inflammation that can be measured with a blood test. CRP offers an improvement in accuracy over the W4SS among outpatients with HIV who are not yet on ART (CRP, sensitivity 89% and specificity 54%; W4SS, sensitivity 84% and specificity 37%). CRP at cut-off values of either >5 mg/L or >10 mg/L is similar to or more accurate than W4SS, depending on the subpopulation tested *(76)*. The cut-off of >5 mg/L is recommended because it is the lowest threshold that indicates abnormality in many clinical settings and is more sensitive. At this cut-off, CRP has a similar sensitivity and higher or similar specificity to symptom screening in all subpopulations of adults and adolescents with HIV. The choice of cut-off value will, however, depend on the type of CRP technology available, the prevalence of other conditions that may increase CRP values and a preference for increased sensitivity or increased specificity.

CRP can be used on its own or in combination with the W4SS. The parallel use of two screening tools, whereby a positive screen for either tool leads to a diagnostic test, will have resource implications because of the higher sensitivity and lower specificity. However, data reviewed for the 2021 guideline revision supports the sequential combination of a positive W4SS followed by CRP (with a pre-specified cut-off of >5 mg/L), particularly for people living with HIV not yet on ART, for whom it has a sensitivity of 84% (95% CI: 73–90%) and a significantly higher specificity of 64% (95% CI: 55–72%). CRP can play an important role in ruling out TB disease before initiation of TPT. Screening with the W4SS followed by CRP increases the number of true negatives compared with the W4SS alone, thus increasing the number of people eligible for TPT. An additional potential benefit of CRP is that it can alert clinicians to the presence of other infectious or non-infectious conditions. Health staff and individuals being screened may be more confident in the results of a biochemical test than of a more subjective symptom screen *(76)*.

Currently, many analysers are available for measuring CRP, with different levels of detection, although all can be used for TB screening with a CRP cut-off between 5 and 10 mg/L. The results obtained with most quantitative point-of-care analysers to measure CRP, correlate strongly with those of laboratory analysers. Point-of-care CRP tests provide rapid (≤5 min) quantitative results from a capillary blood sample. Hence, they do not require phlebotomy, are simple enough to be performed by front-line healthcare workers after minimal training and do not require connection to a laboratory transportation network for analysis. Some semi-quantitative test strips are available with operational characteristics, ideal for use in remote settings (inexpensive, no analyser required); however, the agreement of results with those of laboratory analysers is moderate and may decrease further if time-to-test strip interpretation exceeds 5 min.

Containers for safe disposal of needles and lancets must be available, and other infection control measures in the collection of blood must be followed. The overall laboratory requirements are minimal; however, most analysers require a continuous electricity source, and most CRP assays require cold storage and refrigeration (+2 to +8 °C). If point-of-care testing for CRP is not available, blood samples will have to be sent to the nearest laboratory, which will significantly undermine the utility of the test for on-the-spot decision-making and render it less useful for screening in outpatient settings.

Chest radiography

Chest X-ray is currently recommended by WHO for use in parallel with the W4SS for ruling out TB disease before initiating TPT. Similarly, CXR can be used in parallel with the W4SS to screen for TB disease, a positive or abnormal result on either screen indicating referral for diagnostic evaluation. Reading modalities of "any abnormality" or "abnormality suggestive of TB" can be used, depending on the context, the availability of radiological expertise, resources and a preference for higher sensitivity or higher specificity.

CXR alone was found to have similar sensitivity to and similar or higher specificity than the W4SS across all subpopulations of people living with HIV. A combined parallel screening strategy of the W4SS and CXR offers a significant improvement in sensitivity (93% for W4SS only vs 53% for W4SS and CXR in parallel), particularly for screening outpatients enrolled in ART care, over the W4SS alone, although with lower specificity. However, in some subgroups like inpatients and people with advanced HIV disease, the specificity is very low.

CXR requires interpretation by a radiologist, other trained health personnel or computer-aided detection (CAD) software. CAD products, which were first recommended by WHO in 2021 *(11)*, use artificial intelligence to analyse CXR images for the presence of abnormalities suggestive of pulmonary TB, producing an abnormality score that can be used to determine the need for follow-on diagnostic testing for TB relative to a selected threshold. Access to and scale-up of CAD has been facilitated by the advent of digital radiography. CAD technology can improve the feasibility and performance of CXR for screening and triage for TB disease by enhancing capacity for TB screening. Such technology can replace or augment human expert interpretation of plain CXR when screening for TB and can avoid inter-reader variability and reduce delays in reading radiographs when skilled personnel are scarce *(77)*.

Further information on CAD for the interpretation of CXR can be found in the consolidated guidelines and operational handbook on TB screening *(11, 76)*. CXR findings may differ widely in people living with HIV-associated TB, from a completely normal picture to multiple radiological abnormalities typically associated with advanced TB disease *(78)*.

Although no data are available on the optimal periodicity of CXR screening, a pragmatic approach would be to perform CXR annually among outpatients with HIV at the time of viral load testing or other investigations, in addition to W4SS at every encounter with a health worker between annual screens. A baseline CXR and access to imaging taken previously are useful for comparing subsequent radiological changes.

Although CXR is the preferred screening tool when combined in parallel with the W4SS, from the viewpoint of test sensitivity, it is important to consider how costs can be mitigated. Programmes should consider eliminating out-of-pocket costs for CXR or using vouchers to further reduce barriers to accessing this critical tool for TB control. Where HIV services are not co-located with TB and radiography services, programmes should consider providing funding for people to travel for CXR or using mobile screening to improve access to CXR screening *(79)*.

As with all TB screening, it is essential to engage with and provide information to local civil society organizations and primary care providers to enhance screening uptake and performance. Chest X-ray is most relevant for people living with HIV who are clinically stable on ART, in care, are immunocompetent and likely to be supported in the community. The risks of exposure to ionizing radiation might be a greater concern for this group, particularly if they undergo CXR regularly and may also receive radiography to evaluate health problems between screenings. Direct CXR is a safe technology using a radiation dose of 0.1 mSv, which corresponds to 1/10 of the annual accepted dose of ionizing radiation for the general public (1 mSv) *(80)*. Therefore, exposure to the low radiation doses delivered during a chest X-ray poses a minimal risk of inducing tissue reactions or cancer in the years or decades following the examination *(81)*. Furthermore, CXR does not pose any significant risk for pregnant women or the fetus, provided that good practices are observed, with the primary beam targeted away from the pelvis.

Molecular WHO-recommended rapid TB diagnostic tests

There is now a conditional recommendation for the use of molecular WHO-recommended rapid TB diagnostic tests (mWRDs) in TB screening among people living with HIV. Implementation of an mWRD as a screening tool will require significant resources, including increased capacity and expansion of diagnostic and sample transportation networks. There has been limited experience in widescale use of mWRDs for screening under programmatic conditions. However, depending on feasibility and available resources, countries may choose to adopt a targeted approach to TB screening with mWRDs in certain subpopulations such as people with advanced HIV disease, or pregnant women living with HIV. Priority should be given to ensuring universal access to mWRDs as a diagnostic test for TB and drug-resistant TB before extending its use to screening. The accuracy of mWRDs in most subpopulations is not significantly different from that of a W4SS followed by an mWRD. Screening with an mWRD in lower prevalence settings may result in higher false positives should the diagnosis not be confirmed, with the associated overtreatment and related social and economic consequences, including potential delays in starting ART.

People who screen positive for TB with an mWRD should always receive a thorough clinical evaluation, including symptom screening and further tests, such as CXR or repeat mWRDs on additional sputum samples, to establish a definitive diagnosis of TB *(76)*. Among medical inpatients in settings where the prevalence of TB is ≥10%, mWRDs are strongly recommended as part of rapid diagnostic workup, because of the severity of illness in this population. As rapid diagnosis and care are required in this particular subpopulation, a positive mWRD result can be considered an indication for treatment and need not be followed by a separate diagnostic evaluation. It is also essential to ensure proper monitoring of treatment response and evaluation for alternative diagnoses.

Several considerations apply to the use of mWRDs as a screening tool. mWRDs perform differently when used for screening than when used for diagnosis. Because of the differences in accuracy and the lower TB prevalence typically found in a population undergoing screening rather than diagnostic evaluation, the positive and negative predictive values of mWRDs also differ. For example, despite a high estimated specificity of 99%, over one half of positive screening tests will be false-positive when mWRDs are used to screen a population with a 1% prevalence of TB. Thus, the different implications for clinical

interpretation and programmatic use of mWRDs for screening and for diagnosis must be understood. In addition, clinicians may wish to exercise their clinical judgement when interpreting mWRD results in light of the findings of a clinical examination, patient history, as well as results from other tests.

For people who have had TB in the previous 5 years, a positive mWRD result may be due to the detection of DNA persisting from the earlier TB episode. Therefore, a positive test in such cases should be investigated with phenotypic methods to exclude a false-positive result *(12)*. A negative mWRD for a single sputum sample does not exclude TB, as individuals with TB may test mWRD-negative because they cannot produce an adequate quantity of sputum or any at all, have a very low bacillary burden in the sample or have extrapulmonary disease. If a person is unable to provide sputum, other TB screening strategies should be considered.

If use of mWRDs for screening requires decentralization of the technology, there may be significant implications in terms of the purchase of machines, cartridges and other consumables, the need for an uninterrupted supply of electric power, and maintenance. If mWRD technology does not reach most health centres, samples will have to be transferred; in this instance, shifting from mWRDs for diagnosis to screening would substantially increase the workload for sample transport systems. Diagnostic connectivity platforms that automate the transmission, storage and retrieval of test results will improve the utility of mWRDs for decision-making.

3.2 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. *(82)*
- 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. *(82)*

[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). (12)*

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). (12)*

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). (12)*

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). (12)*

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.

People living with HIV may have an atypical clinical picture, with higher rates of extrapulmonary and disseminated TB, especially those with advanced disease, see Box 3.1. Up to one third of people with HIV-associated TB are unable to produce sputum *(83)*. HIV-associated TB is disseminated in up to 88% of post-mortem cases, likely due to its non-specific clinical presentation and a high proportion of bacteriologically negative and radiographically non-specific disease *(2)*. Given the challenges in diagnosing TB in people living with HIV and the high risk of mortality, a diagnostic strategy that has high sensitivity is critical.

The TB diagnostic tests recommended by WHO *(12)* belong to two broad groups: (i) initial tests for diagnosing TB, with or without at least rifampicin resistance detection, and (ii) follow-on tests aimed at detecting additional drug resistance once a TB diagnosis is made. Table 3.1 describes initial tests for diagnosing TB which are applicable to everyone, with LF-LAM and the use of mWRDs in blood being specific to people living with HIV. Follow-on tests are not included in this chapter but covered in the relevant TB guidelines *(12)* and operational handbook *(84)*. Further details on each of these tests can be found in *WHO consolidated guidelines on tuberculosis. Module 3: diagnosis. Rapid diagnostic tests for TB detection (12)*.

In many high TB burden settings, sputum-smear microscopy remains the primary diagnostic technique for evaluating individuals presenting with signs and symptoms of TB. However, sputum-smear microscopy has a low sensitivity, particularly in people living with HIV and among people who have difficulty in producing sputum or have paucibacillary sputum. 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 complex (MTBC). The initial diagnostic test for TB among people living with HIV should therefore be an mWRD for testing sputum or another sample, as indicated *(84)*. In addition, a urine LF-LAM test can be used in parallel with an mWRD to assist in the diagnosis of TB disease in eligible people living with HIV *(84)*, alongside other clinical, radiological or laboratory procedures for detecting pulmonary and extrapulmonary TB.

Table 3.1. WHO-recommended rapid diagnostic tests as initial tests for TB diagnosis

	Specimen type	Resistance
Test	**Adults**	**DST R/H[b]**
Xpert® MTB/RIF	Sputum Urine Blood[a] Cerebrospinal fluid Lymph node samples Pleural, peritoneal, pericardial or synovial fluid	R
Xpert® MTB/RIF Ultra	Sputum Cerebrospinal fluid Lymph node samples	R
Truenat™ MTB, MTB Plus and MTB-RIF Dx tests[c]	Sputum	R
TB-LAMP (Eiken)[d]	Sputum	-
Moderate complexity automated NAATs[e]	Sputum	R and H
LF-LAM[a]	Urine	–

[a] Specific to people living with HIV.
[b] DST: drug-susceptibility testing; R: rifampicin; H: isoniazid.
[c] There is uncertainty about the use of Truenat MTB or MTB Plus in people living with HIV.
[d] Limited data on the performance of loop-mediated isothermal amplification (TB-LAMP) among people living with HIV were available at time of recommendation development.
[e] The currently recommended tests in this class (nucleic acid amplification tests, NAAT) include: RealTime MTB (Abbott Molecular), BD MAX™ MDR-TB (Becton Dickinson), FluoroType® MTBDR (Bruker-Hain Diagnostics), and cobas® MTB-RIF/INH (Roche Diagnostics).

3.2.1 Initial diagnostic tests for diagnosis of TB with drug-resistance detection

The *WHO standard: universal access to rapid tuberculosis diagnostics* includes two benchmarks that require that all individuals have access to an mWRD as an initial diagnostic test and that all facilities use an algorithm that includes an mWRD as an initial diagnostic test, alongside urinary lateral flow lipoarabinomannan, for people living with HIV for both pulmonary and extrapulmonary TB *(82)*.

In 2011, WHO first recommended Xpert MTB/RIF as a replacement for smear microscopy for people being assessed for multidrug-resistant TB (MDR-TB) or HIV-associated TB. Since 2020, WHO has recommended mWRDs for the initial diagnosis of TB, instead of smear microscopy, for all people being evaluated for TB disease, regardless of HIV status *(85)*. Molecular WHO-recommended rapid diagnostic tests are also prescribed for diagnosis of most forms of extrapulmonary TB. In addition, for people living with HIV who have signs and symptoms of disseminated TB, WHO recommends that Xpert MTB/RIF may be used in blood, as an initial diagnostic test for disseminated TB. It is still critical that people living with HIV have access to mWRDs as early as possible in the diagnostic cascade.

Programmes should ensure that when TB samples cannot be tested at the same location where they are collected, the TB sample transportation network has good links with health facilities providing HIV care, to ensure fast turnaround from presentation to initiation of TB treatment.

The use of multi-disease diagnostic platforms presents an opportunity for increasing access to mWRDs. Several of the molecular diagnostic platforms for diagnosing TB are also widely used in early infant diagnosis of HIV and viral load monitoring for people living with HIV, as well as, for example, for diagnosis of SARS-CoV-2, viral hepatitis, and for antimicrobial resistance detection of

bacterial pathogens. Countries may also consider integrating sample transport systems for TB and HIV. Multi-disease testing and integrated sample transportation can have the advantage of shared financial costs and functionality, and improved efficiencies. Turnaround time from initial presentation with presumptive TB to treatment initiation should not, however, be compromised.

Multi-disease testing is mainly useful where the number of tests by individual programmes is small, relative to the testing capacity within a particular setting. In contrast, scenarios where there are large TB and HIV testing needs, and infrastructure is installed to meet the demand to match the requirements of each disease, multi-disease testing may be less relevant. Nonetheless, the burden of disease and testing volumes change over time; hence, the use of equipment should be monitored, and programmes may need to adapt.

Box 3.1 Extrapulmonary and disseminated TB

Extrapulmonary TB refers to any bacteriologically confirmed or clinically diagnosed TB involving organs other than the lungs, e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones or meninges *(86)*. The risk of extrapulmonary TB is higher among people living with HIV, especially those with lower CD4 cell counts. Studies have found extrapulmonary TB occurring in up to 70% of people living with HIV-associated TB with CD4 counts of <100 cells/mm^3 and in about 30% of people with CD4 counts of >300 cells/mm^3 *(87, 88)*. People living with HIV with extrapulmonary TB often have disseminated disease and are at high risk of rapid clinical deterioration and death *(89)*.

The diagnosis of some forms of extrapulmonary TB is complex, especially in peripheral health facilities with limited support and diagnostic infrastructure. Given the high rates of extrapulmonary TB in people living with HIV, particularly among individuals with advanced disease, there should be a high index of suspicion for extrapulmonary TB among those presenting with signs and symptoms of TB. Lack of radiographic changes suggestive of pulmonary TB is not uncommon among people living with HIV with advanced immunosuppression, and disseminated TB can manifest as a non-specific febrile illness. Further, symptoms suggesting specific organ involvement, such as breathlessness (for example due to pleural effusion or pericarditis), enlarged cervical or axillary lymph nodes and chronic headache or altered mental status (for example due to meningitis) should prompt further investigation for extrapulmonary and disseminated TB. Bacterial confirmation is often difficult because of technical complexity in obtaining samples from selected extrapulmonary sites and the paucibacillary nature of many types of extrapulmonary TB. Diagnostics are particularly challenging in settings which only have smear microscopy.

If indicated and if possible, extrapulmonary specimens should be obtained. WHO recommends using urinary LF-LAM for people with signs and symptoms of both pulmonary and extrapulmonary TB disease. WHO also recommends that mWRDs can be used on samples including urine, lymph node aspirate, lymph node biopsy, pleural fluid, peritoneal fluid, pericardial fluid or synovial fluid. In people living with HIV who have signs and symptoms of disseminated TB, WHO recommends that Xpert MTB/RIF may be used in blood as an initial diagnostic test.

3.2.2 Urine LF-LAM

Urine LF-LAM is an immunocapture assay based on the detection of the mycobacterial LAM antigen in urine, which can be used as a point-of-care test for people living with HIV being evaluated for TB. Although the assay has low sensitivity, it can be used as a fast (test time <15 min) rule-in test for TB among people living with HIV, especially where a rapid TB diagnosis is critical for survival. Bedside LF-LAM guided initiation of TB treatment in hospital inpatients with HIV, with presumptive TB, was associated with reduced 8-week mortality *(90)*. Including LF-LAM in TB diagnostic algorithms for people living with HIV who are severely ill has been shown to be cost-effective *(90)*. The Alere/Abbot Determine TB LAM Ag is currently the only commercially available urine LF-LAM test endorsed by WHO, since this was the only LAM-based assay that had been adequately validated or used outside limited research settings at the time of updating the *WHO consolidated guidelines on tuberculosis. Module 3: diagnosis – rapid diagnostics for tuberculosis detection, 2021 update (84)*. This test can be used in any setting, unlike other diagnostics which have specific infrastructure requirements.

Due to its low sensitivity, LF-LAM should not be used as a screening test, and a negative LF-LAM test result does not rule out TB. Furthermore, the detection of mycobacterial LAM antigen in the urine does not provide any information on drug resistance, and people living with HIV are particularly at risk of dying from multidrug-resistant TB *(91, 92)*. Therefore, testing with an mWRD is critical for ensuring TB is not missed and the correct treatment is provided. For their initial diagnostic test, all people with signs and symptoms of pulmonary TB who are able to produce sputum should have at least one sputum specimen submitted for an mWRD assay. For people who are unable to produce sputum, alternative specimens should be submitted for an mWRD, as appropriate. LF-LAM results (test time <15 min) are likely to be available before mWRD results; hence, treatment decisions should be based on the LF-LAM result while awaiting the results of other diagnostic tests. Box 3.2 below outlines key steps to consider for the introduction of all new diagnostic tests, including LF-LAM. For further details, see the *WHO operational handbook on tuberculosis. Module 3: diagnosis – rapid diagnostics for tuberculosis detection, 2021 update (84)*.

Box 3.2 Steps and processes for introducing and scaling up a new diagnostic test

Key steps that countries should take when implementing a new diagnostic test include:

- register and validate the diagnostic test;
- establish a technical working group to lead the process;
- define the intended use and placement of the new test, and update diagnostic algorithms;
- develop a realistic costed implementation plan and budget for ongoing costs;
- procure and install equipment (if equipment is required) in safe, functional testing sites;
- ensure a reliable supply of quality-assured reagents and consumables;
- develop clinical protocols and standard operating procedures, including on preparing non-sputum samples;
- implement a comprehensive quality-assurance programme;
- implement training, mentoring and competency assessment programmes; and
- monitor and evaluate the implementation and impact of the new test.

3.2.3 Clinical diagnosis of TB

The decision to carry out treatment based on a clinical diagnosis of TB, also referred to as presumptive TB treatment or empirical treatment, is of relevance among seriously ill people living with HIV who are at high risk of mortality and among whom establishing a TB diagnosis may be difficult. The rationale for empirical treatment is to prevent the death of people living with HIV in situations when expedited diagnosis of TB is not possible or feasible because of the person's clinical condition, and there is limited access to TB diagnostic services *(84)*. WHO algorithms include initiating TB treatment for people living with HIV based on the judgement of the clinician *(84, 89)*. If results from LF-LAM and mWRD are negative, or if an mWRD is unavailable, further assessments and investigations may include the assessment of risk factors such as malnourishment, poor living conditions, a clinical symptoms assessment, chest X-ray, and referral for mWRD testing or culture. In line with WHO's recommended package of care for advanced HIV disease, empirical treatment of pneumocystis or bacterial pneumonia should be considered for people with severe respiratory distress. If after 3–5 days of antibiotic treatment there is clinical worsening or no improvement and the person is seriously ill with danger signs, empirical TB treatment is indicated.

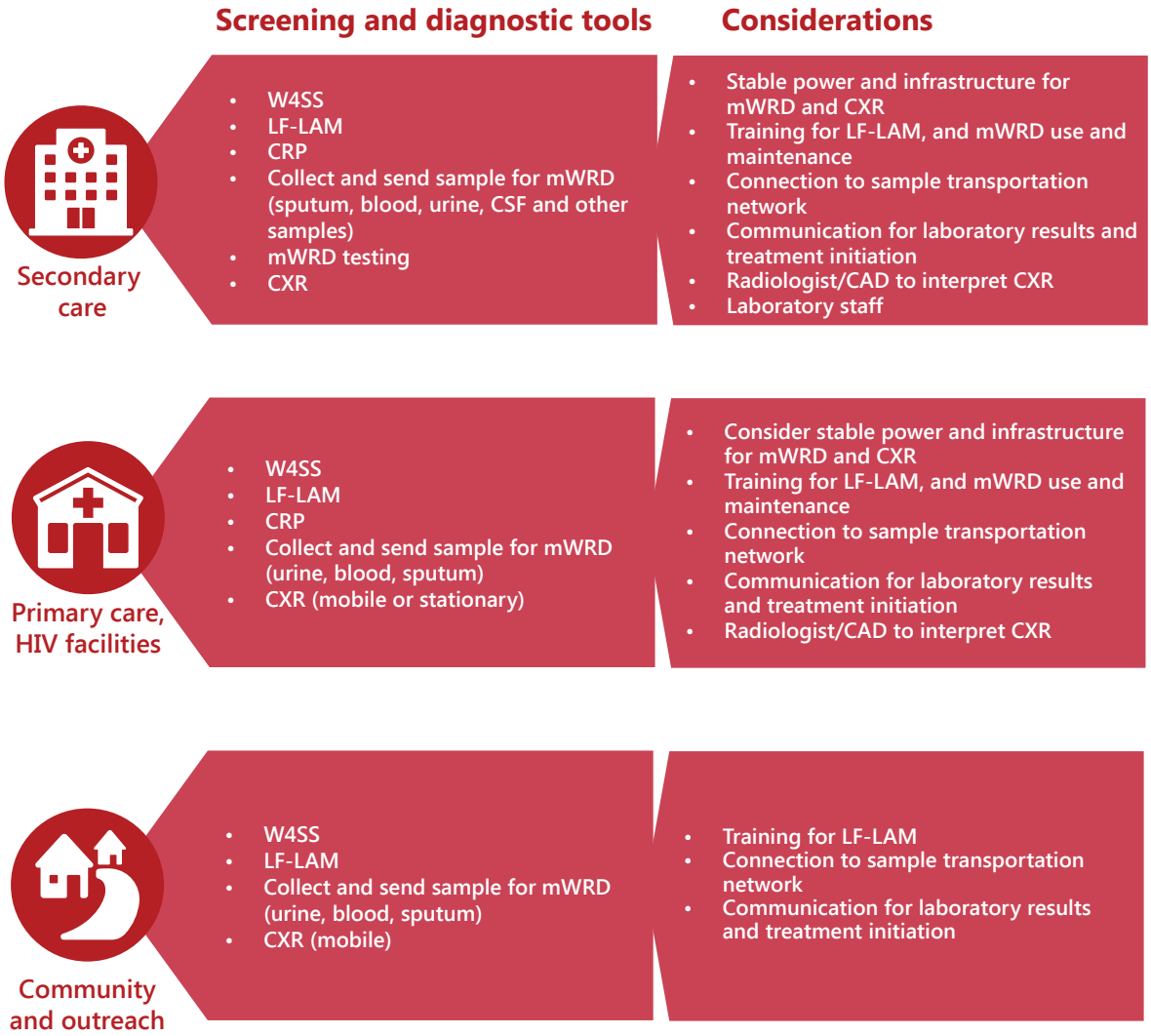
It should be emphasized that every effort should be made to confirm the diagnosis of TB after initiating empirical treatment and that treatment should be stopped only if bacteriological, histological or strong clinical evidence indicates an alternative diagnosis.

3.3 Algorithms for informing the decision to treat TB infection or TB disease among people living with HIV

For people living with HIV, screening and diagnostic algorithms should serve both to include TB disease to identify those requiring treatment and to exclude TB disease to determine eligibility for TPT. Lack of access to any of the tools described here should not be a barrier to TB screening or ruling out TB to allow initiation of TPT. Here we present five practical algorithms that combine WHO-recommended TB screening tools (W4SS, CRP, CXR and mWRD) with diagnostic tools (LF-LAM and mWRD) for people living with HIV. The algorithms may be adapted to the local context according to factors including, but not limited to, epidemiology, feasibility, the level of the health facility where they are being implemented, resources and equity concerns.

Fig. 3.1 outlines the suggested placement of screening tools and initial diagnostic tests at the community level, the primary health care level and secondary care. Programmes should ensure that health facilities are connected to reliable and rapid sample transportation networks to facilitate collection and delivery of samples, and to ensure an efficient turnaround time and communication of results to the clinician. TB and HIV programmes should also collaborate to ensure that different cadres of healthcare workers, including lay health workers, are trained to collect samples for screening and diagnosis of TB, the use of the relevant tools and recording and reporting.

Fig. 3.1. Placement of screening tools and initial diagnostic tests



CAD: computer-aided detection; CRP: C-reactive protein; CSF: cerebrospinal fluid; CXR: chest X-ray; LF-LAM: lateral flow lipoarabinomannan; mWRD: molecular WHO-recommended rapid diagnostic test; W4SS: WHO-recommended four symptom screen

The *WHO operational handbook on tuberculosis. Module 2: Screening: systematic screening for tuberculosis disease (76)* details key considerations for the choice of screening and diagnostic algorithms. These include: the specific objectives of screening; the accuracy and yield of screening and diagnostic tests; the profile of prioritized risk groups; the TB prevalence in the risk groups; the costs, availability and feasibility of different tests; and the ability to engage the population to be screened. In practice, when implementing an algorithm, its performance will also be influenced by external factors such as connection to and reliability of the sample transportation network, loss to follow-up between screening tests and diagnostic evaluation, and availability of tools and equipment.

Each of the five screening and diagnostic algorithms presented below is accompanied by data on their sensitivity, specificity, diagnostic yield, and cost per TB diagnosis in given sub-populations. This is to help guide programmes in algorithm selection, according to the strengths and weaknesses of the different algorithms in different populations. Table 3.2 provides a summary of which algorithms may be best used for which population. Selection of algorithms should be informed by clinical presentation, availability of the screening and diagnostic tests, and connection to the required sample transportation networks.

Table 3.2. Summary of algorithms for screening and diagnosing TB among people living with HIV

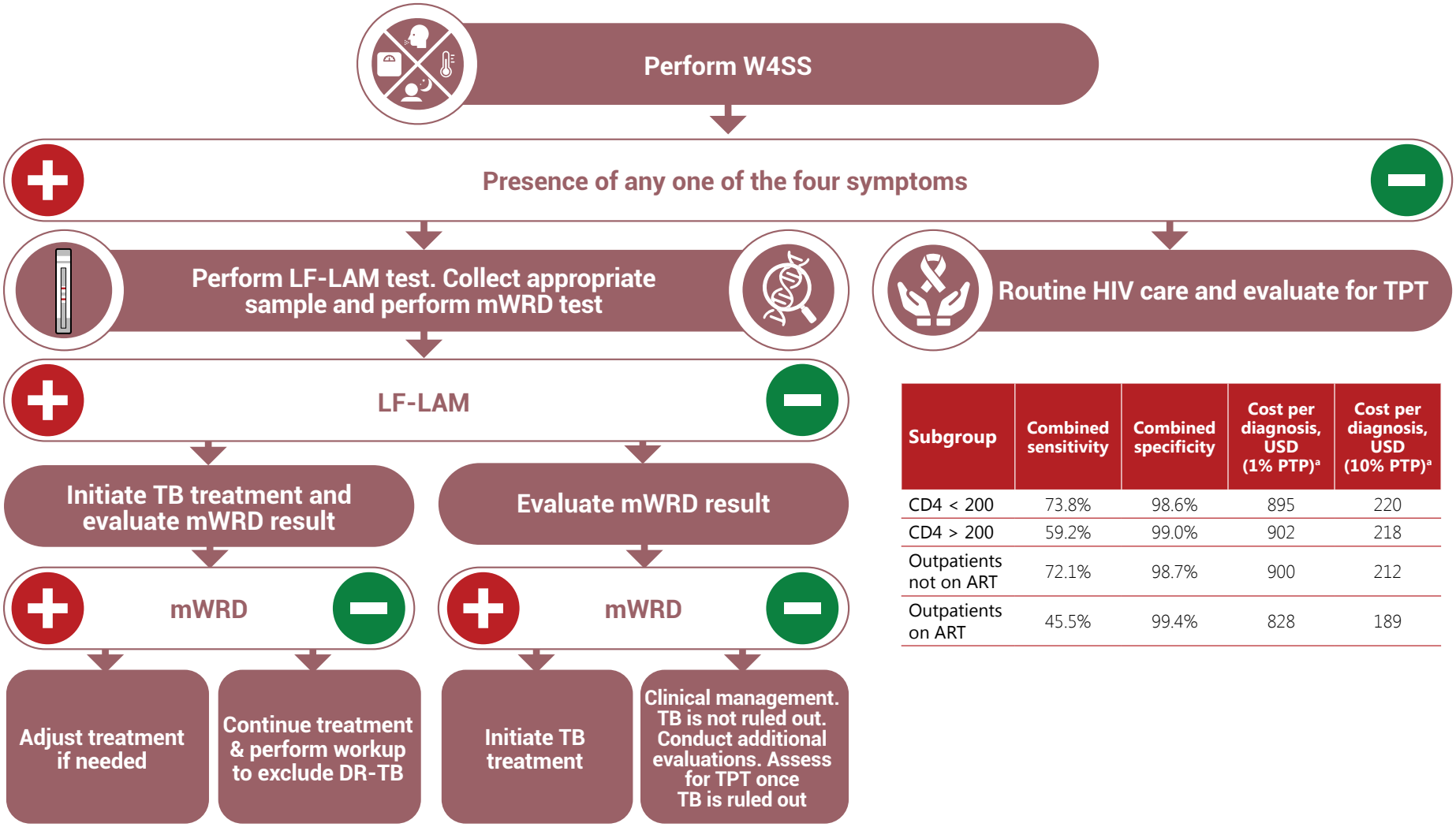
Algorithm	Who?	When?	Where?	Why?
Algorithm 1: W4SS followed by LF-LAM and mWRD	All populations, but reduced accuracy in some populations (reduced sensitivity for people who are clinically stable on ART, reduced specificity for people not on ART [ART-naïve or interrupted treatment])	At every encounter with a healthcare worker or peer supporter	Anywhere. When access to tools such as CD4 cell count, CXR, or CRP is limited	This algorithm is feasible to implement in all settings: rapid, and low resource and infrastructure requirements
Algorithm 2: W4SS and CXR followed by LF-LAM and mWRD	For people who are clinically stable on ART or with a higher CD4 cell count	When resources allow; at baseline investigation and annually thereafter, aligned with viral load testing	Where there is access to CXR. For people who are asymptomatic, access to CD4 cell count is required to determine eligibility for LF-LAM	The inclusion of CXR in this algorithm increases the sensitivity over symptom screening alone, identifying more people with prevalent TB disease
Algorithm 3: W4SS followed by CRP followed by LF-LAM and mWRD	For people not yet on ART (ART naïve or interrupted treatment) or with CD4 cell count of less than 200	When HIV is first diagnosed, during initial HIV investigation or when someone has returned after ART interruption	Where there is access to point-of-care CRP	The inclusion of CRP in this algorithm increases the specificity over symptom screening alone. It can save costs on diagnostic tests and may allow more people without TB disease to initiate TPT immediately
Algorithm 4: LF-LAM and mWRD in facilities where TB prevalence is >10%	For people living with HIV who are medical inpatients or who are seriously ill and require hospitalization	When people living with HIV present to a health facility in need of hospitalization, with danger signs indicating serious illness	In facilities where TB prevalence is >10% and where there is quick turnaround time for diagnostic test results	In this population, rapid action is necessary to reduce mortality, therefore a single mWRD test alongside LF-LAM can indicate immediate treatment initiation
Algorithm 5: Clinical diagnosis for people living with HIV who are seriously ill	For people living with HIV who present with any one of the following danger signs: • respiratory rate >30 per minute • heart rate >120 beats per minute • unable to walk unaided • temperature >39 °C	When diagnostic tests are not immediately available or initial diagnostic test results are negative and there is a strong possibility of TB	In peripheral health facilities where immediate referral to a higher-level facility is not possible	May prevent the death of people with HIV in situations when expedited bacteriologically confirmed diagnosis of TB is not possible or feasible because of the person's clinical condition and limited access to TB diagnostic services

ART: antiretroviral therapy; CRP: C-reactive protein; CXR: chest X-ray; LF-LAM: lateral flow lipoarabinomannan; mWRD: molecular WHO-recommended rapid diagnostic test; TPT: tuberculosis preventive treatment; W4SS: WHO-recommended four symptom screen

It is important to note the assumptions made when developing these model estimates, which include the fact that all people undergoing screening can produce sputum, that tools are available and used, that there is no loss to follow-up between the screening and diagnostic pathway, and that timely results are received for each test that is undertaken. Costs to implement an algorithm will vary widely between settings, depending on factors such as TB prevalence, availability and cost of tools and equipment, existing infrastructure, personnel costs and healthcare worker training needs. The estimated costs for each algorithm are global cost estimates based on a prevalence of 1% and 10% and may be a guide to comparing relevant costs for the different algorithms, while considering that the actual costs will vary between settings. Details on methods for development of the algorithms, yields, and calculation of algorithm performance and costs, including assumptions, can be found in Annex 2. For country-specific costs, please refer to the ScreenTB web-based tool (https://screentb.org/).

Algorithms for screening and diagnosis of TB among people living with HIV

Algorithm 1: W4SS followed by LF-LAM and mWRD



Subgroup	Combined sensitivity	Combined specificity	Cost per diagnosis, USD (1% PTP)[a]	Cost per diagnosis, USD (10% PTP)[a]
CD4 < 200	73.8%	98.6%	895	220
CD4 > 200	59.2%	99.0%	902	218
Outpatients not on ART	72.1%	98.7%	900	212
Outpatients on ART	45.5%	99.4%	828	189

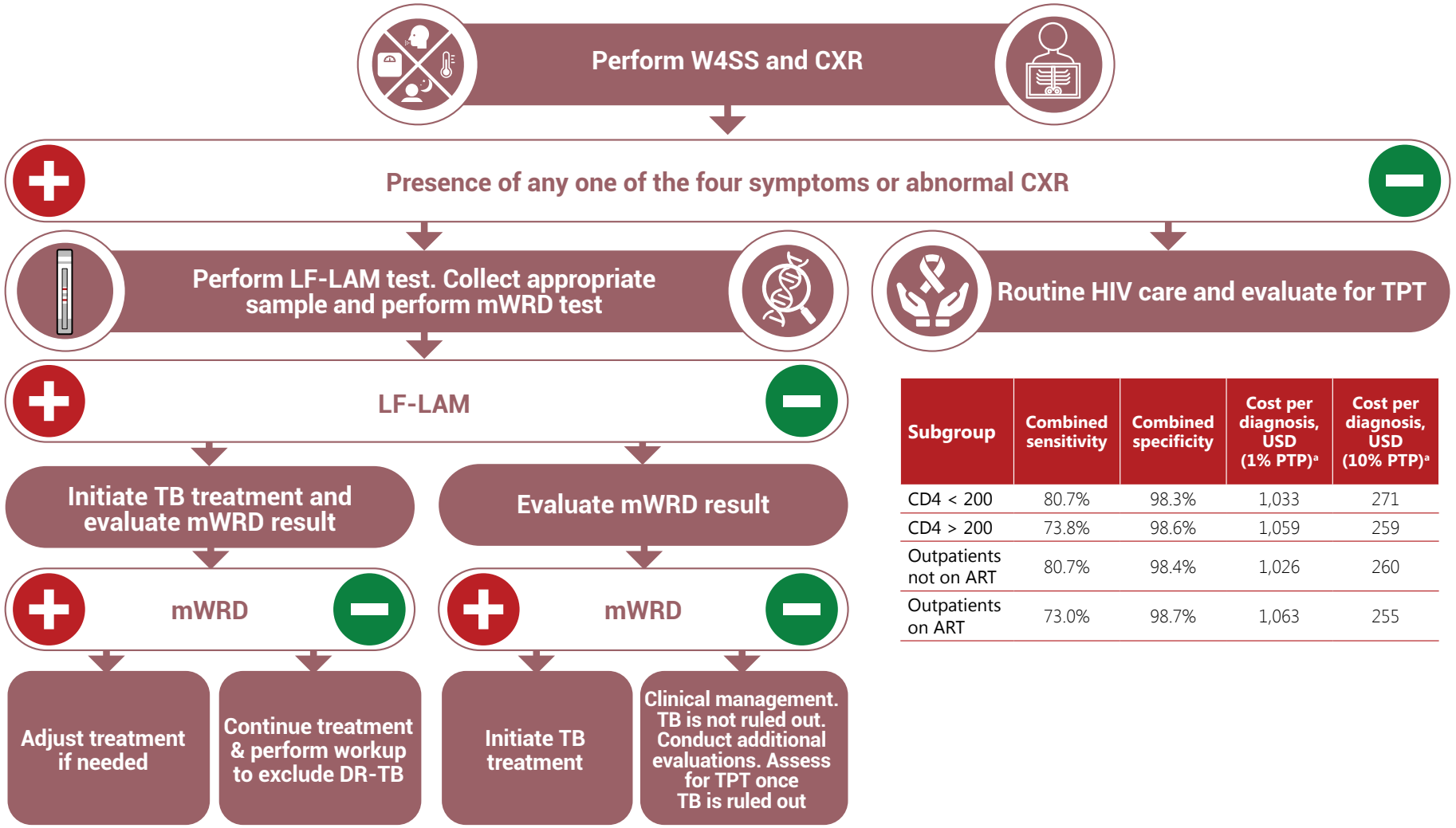
Considerations for Algorithm 1:

- Applicable to all populations but reduced accuracy in some populations: very reduced sensitivity for people who are clinically stable on ART and for people with higher CD4 cell counts leading to a high number of missed diagnoses; reduced specificity for people not on ART (ART-naïve or interrupted treatment) and for people who are seriously ill.
- At every encounter with a healthcare worker or peer supporter.
- Where access to tools such as CD4 cell count, CXR, or CRP is limited.

[a] For methodology, please see Annex 2.

ART:antiretroviraltherapy;CRP:C-reactiveprotein;CXR:chestX-ray;DR-TB:drug-resistanttuberculosis;LF-LAM:lateralflowlipoarabinomannan;mWRD:molecularWHO-recommendedrapiddiagnostictest;PTP:pre-testprobability;TB:tuberculosis; TPT: tuberculosis preventive treatment; W4SS: WHO-recommended four- symptom screen.

Algorithm 2: W4SS and CXR followed by LF-LAM and mWRD



Subgroup	Combined sensitivity	Combined specificity	Cost per diagnosis, USD (1% PTP)[a]	Cost per diagnosis, USD (10% PTP)[a]
CD4 < 200	80.7%	98.3%	1,033	271
CD4 > 200	73.8%	98.6%	1,059	259
Outpatients not on ART	80.7%	98.4%	1,026	260
Outpatients on ART	73.0%	98.7%	1,063	255

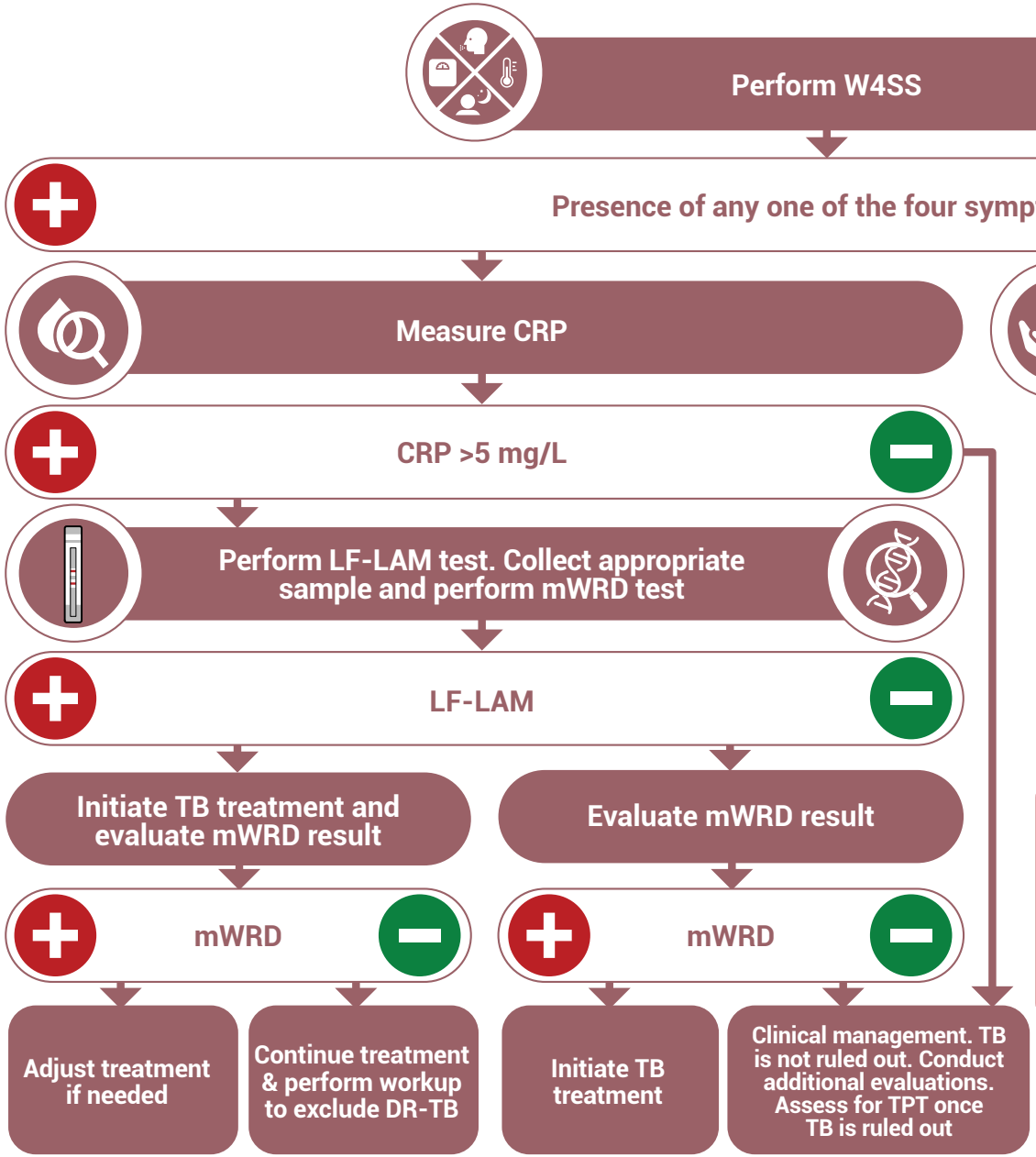
Considerations for Algorithm 2:

- For people who are clinically stable on ART or with a higher CD4 cell count.
- Recommended during catch-up campaigns to rule out TB disease among people with HIV on ART who have not previously received TPT.
- Increases sensitivity in outpatients on ART (by 27.5%) and among people with CD4 >200 (by 14.6%) compared to Algorithm 1.
- LF-LAM should not be used in asymptomatic individuals who do not have signs of advanced HIV disease or serious illness and who have a CD4 count >100 (outpatients) or >200 (inpatients).
- If resources allow, could be used for a baseline screen and annual screening thereafter to be aligned with visits for viral load monitoring.

[a] For methodology, please see Annex 2.

ART: antiretroviral therapy; CXR: chest X-ray; DR-TB: drug-resistant tuberculosis; LF-LAM: lateral flow lipoarabinomannan; mWRD: molecular WHO- recommended rapid diagnostic test; PTP: pre-test probability; TB: tuberculosis; TPT: tuberculosis preventive treatment; W4SS: WHO-recommended four symptom screen.

Algorithm 3: W4SS followed by CRP followed by LF-LAM and mWRD



Subgroup	Combined sensitivity	Combined specificity	Cost per diagnosis, USD (1% PTP)[a]	Cost per diagnosis, USD (10% PTP)[a]
CD4 < 200	73.8%	99.1%	987	204
CD4 > 200	60.1%	99.5%	971	179
Outpatients not on ART	72.1%	99.3%	955	185
Outpatients on ART	6.9%	99.9%	2,062	528

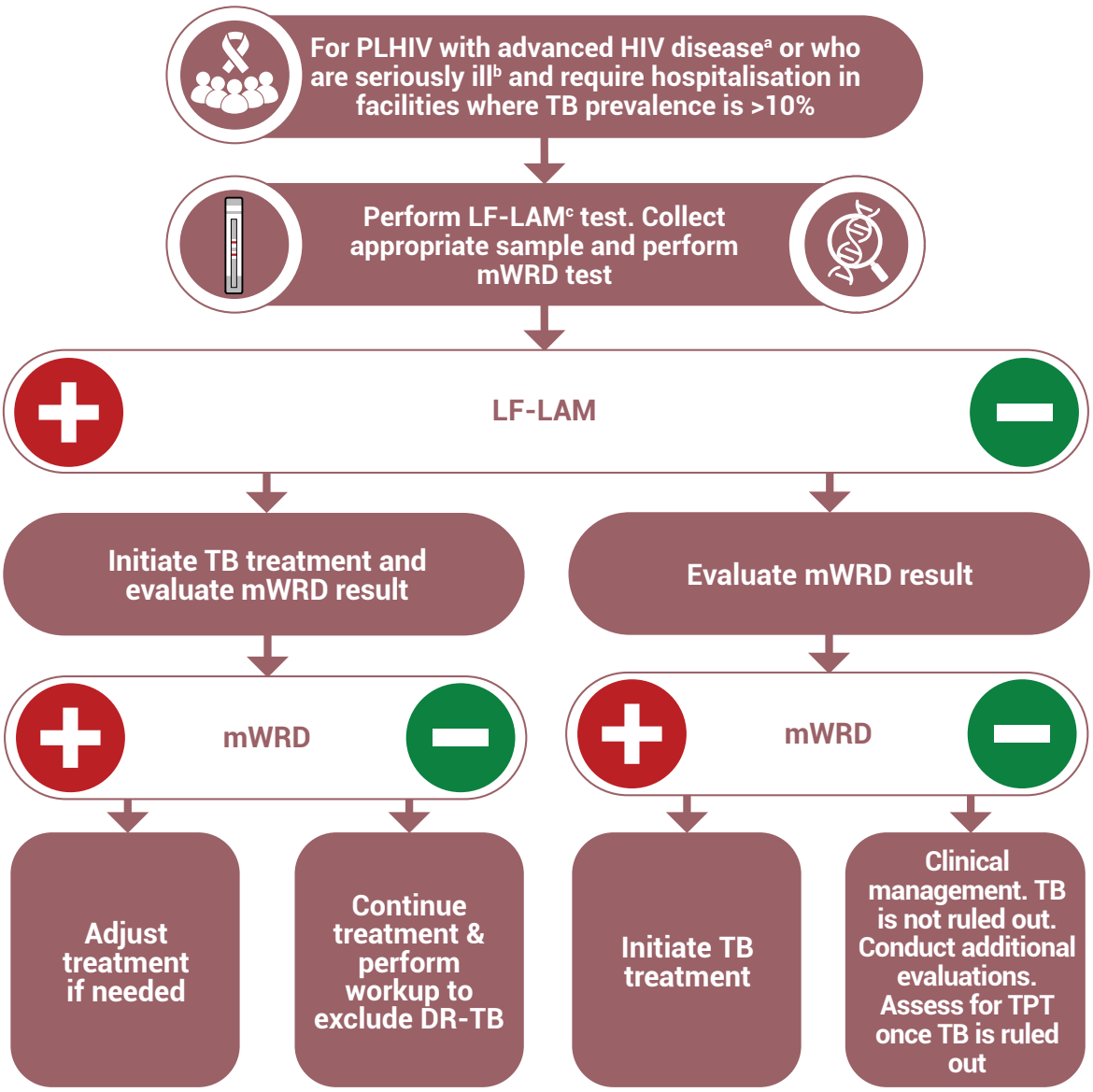
Considerations for Algorithm 3:

- Performs better among people not yet on ART (ART naïve or interrupted treatment) and among people with CD4 cell count <200.
- Increases specificity without compromising sensitivity, when compared to W4SS alone.
- Higher number of people found immediately eligible for TPT at the stage of screening.
- Cost per diagnosis lower compared to W4SS alone.
- Depending on type of technology available (laboratory-based or point-of-care CRP), may require additional infrastructure.

[a] For methodology, please see Annex 2

ART: antiretroviral therapy; CRP: C-reactive protein; DR-TB: drug-resistant tuberculosis; LF-LAM: lateral flow lipoarabinomannan; mWRD: molecular WHO- recommended rapid diagnostic test; PTP: pre-test probability; TB: tuberculosis; TPT: tuberculosis preventive treatment; W4SS: WHO-recommended four symptom screen.

Algorithm 4: LF-LAM and mWRD for medical inpatients living with HIV or people living with HIV who are seriously ill and require hospitalization in facilities where TB prevalence is >10%



Sub-group	Combined sensitivity	Combined specificity	Cost per diagnosis, USD (10% PTP)[d]
CD4 < 200[e]	80.7%	97.0%	224
Inpatients	82.7%	93.0%	166

Considerations for Algorithm 4:

- For people living with HIV who are medical inpatients or who are seriously ill and require hospitalization in facilities where TB prevalence is >10%.
- Requires immediate access to both diagnostic tests, to expedite diagnosis and treatment initiation.
- People with advanced HIV disease should receive all components of the package of care for advanced HIV disease.

[a] Advanced HIV disease is defined based on a CD4 cell count <200 cells/mm^3 or WHO stage 3 or 4 in adults and adolescents

[b] Seriously ill is defined based on four danger signs: respiratory rate of more than 30/minute, temperature of more than 39 °C, heart rate of more than 120/minute and unable to walk unaided

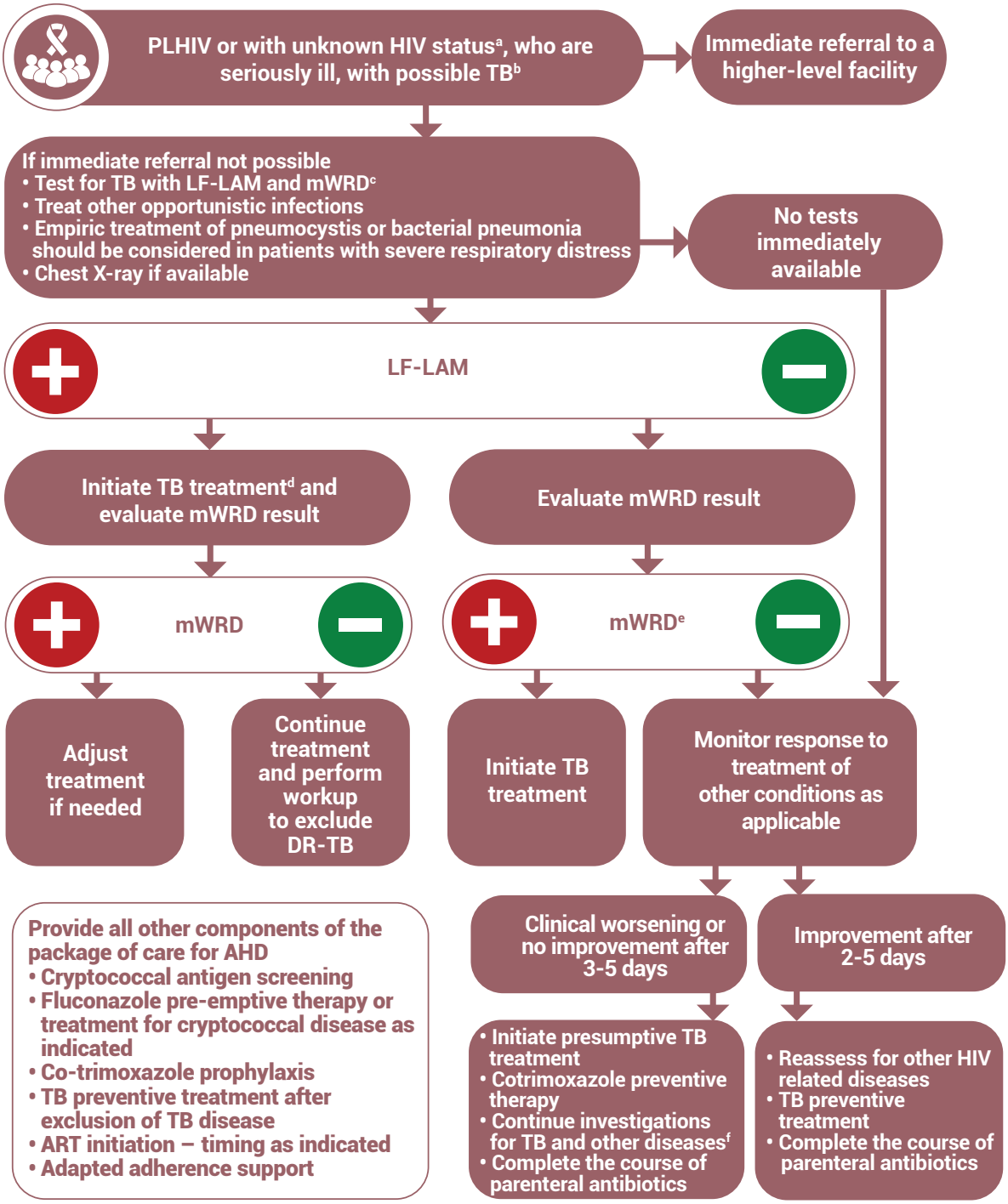
[c] Asymptomatic outpatients with a CD4 cell count <100 are eligible for LF-LAM

[d] For methodology, please see Annex 2.

[e] In the absence of data on sensitivity and specificity for people with advanced HIV disease who are seriously ill, CD4 cell count of <200 has been used as a proxy for this subgroup.

DR-TB: drug-resistant tuberculosis; LF-LAM: lateral flow lipoarabinomannan; mWRD: molecular WHO- recommended rapid diagnostic test; PLHIV: people living with HIV; PTP: pre-test probability; TB: tuberculosis; TPT: tuberculosis preventive treatment.

Algorithm 5: Clinical diagnosis of TB in people living with HIV who are seriously ill



[a] For all people with unknown HIV status, HIV testing should be performed according to national guidelines.

[b] Possible TB is defined by the presence of any one of the following symptoms: current cough, fever, weight loss or night sweats. Danger signs are defined as any one of the following: respiratory rate > 30 per minute, heart rate >120 beats per minute, unable to walk unaided, temperature >39 °.

[c] For people with possible extrapulmonary TB, extrapulmonary specimens should be obtained for mWRD (cerebrospinal fluid, lymph nodes and other tissues: mWRD has low sensitivity for pleural fluid and data are limited for stool, urine or blood). If mWRD is not available, conduct other available TB diagnostic tests and refer appopriate specimens for testing with mWRD and TB culture where feasible.

[d] If mWRD shows rifampicin resistance, treatment for multidrug-resistant TB should be initiated. If the person is considered at low risk for rifampicin resistance, a second mWRD test should be performed on a fresh specimen. Collect and refer a sample for culture and additional drug sensitivity testing.

[e] If mWRD shows negative results, the test can be repeated using a fresh specimen.

[f] Further investigations for TB include chest X-ray, clinical assessment, a repeat mWRD using a fresh specimen and culture. If extrapulmonary TB is suspected, extrapulmonary specimens should be obtained and sent for culture and abdominal ultrasound may be performed.

AHD: advanced HIV disease; ART: antiretroviral therapy; DR-TB: drug-resistant tuberculosis; LF-LAM: lateral flow lipoarabinomannan; mWRD: molecular WHO- recommended rapid diagnostic test; PLHIV: people living with HIV; TB: tuberculosis.

3.4 TB treatment

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). (14)*
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*). (16)*
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). (17)*

3.4.1 WHO-recommended treatment regimens for adults with drug-susceptible TB

WHO currently recommends two treatment regimens for adults with drug-susceptible TB (DS-TB): a 6-month regimen composed of 2 months of isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E), followed by 4 months of isoniazid and rifampicin (2HRZE/4HR) and a 4-month regimen composed of 8 weeks of isoniazid, rifapentine (P), moxifloxacin (M) and pyrazinamide, followed by 9 weeks of daily isoniazid, rifapentine, and moxifloxacin (2HPMZ/2HPM). Both the 6-month and 4-month regimens are applicable to people living with HIV except for certain subpopulations as indicated. Aligned to the recommendation on the 6-month regimen, WHO has published four additional recommendations on dosing frequency, the use of fixed dose combination tablets and extension of the intensive phase. Recommendations on treatment regimens for DS-TB are outlined in full in the *WHO consolidated guidelines on tuberculosis. Module 4: treatment – drug-susceptible tuberculosis treatment (14)* as well as the *WHO consolidated guidelines on tuberculosis. Module 5: management of tuberculosis in children and adolescents (8)*. Two additional recommendations on the use of corticosteroids for the treatment of TB meningitis or TB pericarditis are also included in the *WHO consolidated guidelines on tuberculosis. Module 4: treatment – drug-susceptible tuberculosis treatment (14)*. Treatment regimens for drug-susceptible TB are summarized in Table 3.3.

3.4.1.1 Six-month TB treatment regimen for adults living with HIV

The 6-month regimen can be used in all subgroups, including people living with HIV. This regimen can also be used for people with extrapulmonary TB, except those with TB affecting the central nervous system or with osteoarticular forms of TB, for whom expert groups suggest a longer duration of therapy. Despite its familiarity, safety and efficacy, many people find the 6-month regimen difficult to complete due to its length. The 6-month regimen is available in fixed-dose combination tablets which helps decrease the pill burden; an important consideration for people living with HIV and other comorbidities *(93)*.

The interactions of rifampicin (the mainstay of TB treatment) with ART are of concern in HIV-associated TB. When the 6-month regimen is used, these drug interactions may result in decreased concentrations of antiretroviral drugs. Rifampicin is known to lower plasma concentrations of the first-line antiretroviral drug dolutegravir. This has led to concerns about efficacy of dolutegravir when co-administered with rifampicin, and the subsequent development of HIV drug resistance due to lower levels of dolutegravir. In such cases, WHO guidelines recommend adjusting the dose by offering 50 mg of dolutegravir twice per day (instead of a single daily dose of 50 mg) *(17)*. These

recommendations are still in place, although evidence that doubling the dose of dolutegravir might not be necessary is emerging. A study from Botswana demonstrated the efficacy and safety of a standard dose dolutegravir-based regimen compatible with an efavirenz-based regimen for people living with HIV-associated TB who received rifampicin *(94)*.

Standard, rifampicin-containing anti-TB treatment is recommended in combination with efavirenz-based ART, without the need for dose adjustment. Conversely, rifampicin is contraindicated in combination with nevirapine and protease inhibitors. Rifabutin is a less potent inducer of the cytochrome P450 system which may be considered in people on some ART regimens that include nevirapine or a protease inhibitor, with close monitoring for safety and tolerability *(7, 95)*. Rifabutin is also the preferred rifamycin to be administered alongside OAMT *(96)*.

3.4.1.2 Four-month TB treatment regimen for adults living with HIV

Study 31 provided the evidence that informed the WHO recommendation on the 4-month moxifloxacin-based regimen *(10)*. This study included some people living with HIV (8%), most of whom were on ART (efavirenz-based regimens). However, people with a CD4 count of less than 100 cells/mm^3 were excluded from the trial *(97)*. Thus, sufficient evidence is available to support the use of the 4-month regimen when the CD4 count is above 100 cells/mm^3. Additional studies are needed to inform the use of the 4-month regimen in people living with HIV who are taking non-efavirenz-based ART regimens, and for people who have a CD4 count less than 100 cells/mm^3 *(98)*. In settings with a high background prevalence of fluoroquinolone resistance, fluoroquinolone drug susceptibility testing is recommended, which might pose a further barrier to scale-up in certain settings.

There may be challenges to implementation of the 4-month regimen initially, until rifapentine becomes more widely and readily available at costs comparable with rifampicin, and a fixed-dose combination (FDC) tablet is developed. At present, the overall pill burden will be higher for people who receive this 4-month regimen[1] because no FDC tablet currently exists for the regimen and the dose of rifapentine is high (1200 mg). This may affect acceptability; however, this situation may change in future as uptake of this regimen improves, creating a demand for the regimen and its component medicines. Wider availability of the rifapentine formulation of 300 mg[2] may decrease the pill burden and facilitate the implementation of this new regimen until the FDC tablet becomes available.

[1] Based on estimates by the Global Drug Facility for an average weight of 55–70 kg: 1358 tablets versus 728 for whole course of treatment.

[2] Rifapentine 150 mg and 300 mg are both included in the WHO model list of essential medicines: 23rd list (2023) (https://apps.who.int/iris/handle/10665/371090

Table 3.3. Treatment regimens for drug-susceptible TB

TB treatment regimens	Eligibility	Comments
6-month rifampicin-based regimen: 2HRZE/4HR	Individuals with a new episode of pulmonary TB and extrapulmonary TB except for people with TB meningitis and osteoarticular TB	Some expert groups suggest 9–12 months therapy for TB meningitis, and 9 months for osteoarticular TB
4-month moxifloxacin-based regimen: 2HPMZ/2HPM	People aged 12 years or older with drug-susceptible pulmonary TB and extrapulmonary TB	Recommended for people living with HIV, except for the following groups (due to limited evidence): PLHIV on non-efavirenz-based regimens,[a] PLHIV with a CD4 count <100 cells/mm^3, people weighing <40 kg, people with TB meningitis, disseminated TB, osteoarticular TB, abdominal TB, adolescents and children less than 12 years of age, pregnant, breastfeeding and postpartum women

E: ethambutol; H: isoniazid; M: moxifloxacin; P: rifapentine; PLHIV: people living with HIV; R: rifampicin; Z: pyrazinamide

[a] Study 31 that informed the 4-month recommendation included efavirenz-based ART which was, at the time, the globally preferred regimen; however, dolutegravir in combination with a nucleoside reverse-transcriptase inhibitor backbone is now recommended as the preferred first-line regimen *(99)* (see Chapter 4 for more details).

3.4.2 WHO-recommended treatment regimens for drug-resistant TB

People with both HIV and multidrug-resistant TB face complicated clinical management, fewer treatment options and poorer treatment outcomes *(100)*. Systematic reviews have shown an association between HIV and MDR-TB *(101, 102)*. Outbreaks of multidrug-resistant TB among people living with HIV have been documented in hospital and other settings, especially in eastern Europe and central Asia and in southern African countries with a high HIV prevalence *(103)*.

Table 3.4 below provides a brief overview of treatment regimens for drug-resistant TB; detailed guidance is published in the *WHO consolidated guidelines on tuberculosis. Module 4: treatment – drug-resistant tuberculosis treatment, 2022 update (10)* and the accompanying *operational handbook (104)*. People living with HIV and drug-resistant TB are generally eligible for all the currently available TB treatment regimens, but due care should be taken to monitor for adverse events and drug–drug interactions. Detailed guidance on caution when administering treatment for drug-resistant TB together with ART is available in the *WHO consolidated guidelines on tuberculosis. Module 4: treatment – drug-resistant tuberculosis treatment, 2022 update (104)*, and in the University of Liverpool's HIV Drug Interactions resource[3] (www.hiv-druginteractions.org).

[3] The Liverpool Drug Interactions resources receive support from the pharmaceutical industry, the British HIV Association, the European AIDS Clinical Society, and the HIV Glasgow Congress. Editorial content is independent of financial support and is overseen by an independent international editorial board. For details, please see www.hiv-druginteractions.org. The evaluation methodology is published in Seden et al. PLoS One. 2017 Mar 23;12(3):e0173509.

Table 3.4. Treatment regimens for drug-resistant TB

TB treatment regimens	Eligibility	Comments
6-month BPaLM/BPaL[a] regimen for MDR/RR-TB and pre-XDR-TB	All people, regardless of HIV status, except for people with TB involving the central nervous system, and osteoarticular and disseminated (miliary) TB	Caution should be used when enrolling individuals with CD4 counts less than 100 cells/mm^3 Efavirenz may induce the metabolism of bedaquiline; hence, an alternative antiretroviral agent should be used (potentially dolutegravir, although there is currently insufficient evidence for this)
9-month all-oral regimen for MDR/RR-TB[b]	People with drug-resistant TB, regardless of HIV status, and: No documented resistance to drugs included in regimen No exposure to previous treatment with bedaquiline, fluoroquinolones, clofazimine, or ethionamide or linezolid for >1 month No extensive or severe TB disease and no severe extrapulmonary disease	Efavirenz can reduce the concentration of bedaquiline; therefore, this antiretroviral drug should be avoided in individuals receiving the 9-month all-oral regimen There are no overlapping toxicities or drug–drug interactions with dolutegravir in individuals receiving the shorter regimen with either linezolid or ethionamide
Individualized longer regimen designed using the priority grouping of medicines recommended in current WHO guidelines	People with extensive forms of DR-TB (e.g. XDR-TB) or those who are not eligible for or have had no response to shorter treatment regimens	Drug–drug interactions and adverse events need to be carefully considered and monitored, depending on the TB treatment and ART regimens prescribed

ART: antiretroviral therapy; BPaLM/BPaL: bedaquiline, pretomanid, linezolid and moxifloxacin/bedaquiline, pretomanid, linezolid; DR-TB: drug-resistant TB; MDR-TB: multidrug-resistant TB; RR-TB: rifampicin-resistant TB; XDR-TB: extensively drug-resistant tuberculosis

[a] With or without moxifloxacin depending on drug susceptibility.

[b] The 9-month all-oral regimen for MDR/RR-TB contains bedaquiline (used for 6 months), in combination with levofloxacin/moxifloxacin, ethionamide, ethambutol, isoniazid (high dose), pyrazinamide and clofazimine (for 4 months, with the possibility of extending to 6 months if the individual remains sputum–smear positive at the end of 4 months), followed by treatment with levofloxacin/moxifloxacin, clofazimine, ethambutol and pyrazinamide (for 5 months). Ethionamide can be replaced by 2 months of linezolid (600 mg daily).

3.4.3 TB treatment for people with HIV-associated TB 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 *(16)*. People with HIV-associated TB who also have histoplasmosis should receive prompt treatment after diagnosis according to WHO treatment guidelines. Joint management of TB, HIV and histoplasmosis can be complex, with drug–drug interactions that may affect treatment. Rifampicin, in particular, results in reduced itraconazole levels, potentially leading to ineffective treatment for histoplasmosis *(105)*. Clinicians may consider replacing rifampicin with rifabutin. More information on histoplasmosis can be found in Chapter 4, and in the Pan American Health Organization and WHO *Guidelines for diagnosing and managing disseminated histoplasmosis among people living with HIV (16)*.

3.4.4 TB care and support

TB and HIV programmes should aim to deliver integrated TB and HIV care, preferably at the same time and location, with due consideration for the prevention of TB transmission. Early ambulatory care is recommended, including for the management of drug-resistant TB (DR-TB) using the latest recommended DR-TB regimens, because it complements the person-centred approach to the management of TB *(10)*. Therefore, countries are encouraged to move towards a decentralized and ambulatory model of care. However, some people with HIV-associated TB may need to stay in hospital to receive treatment for TB. This would be the case, for instance, if the individual is seriously ill with HIV, develops severe immune reconstitution inflammatory syndrome (IRIS), has a severe form of DS-TB or DR-TB disease (e.g. meningitis, vertebral bone infection, pericarditis, miliary TB or severe TB lung disease with signs of respiratory distress/failure or sepsis), has other serious comorbidities (such as severe malnutrition or uncontrolled diabetes mellitus), is either very young or elderly or has serious adverse reactions to medication *(106)*. In such situations, these individuals may need to be hospitalized until their condition stabilizes. Long hospitalization should not be routinely required for people on DR-TB treatment unless it is absolutely necessary from a medical standpoint. The treatment regimen should rarely require a person with DR-TB to be hospitalized because every attempt should be made to put the person on an all-oral regimen that they can receive as an outpatient. Furthermore, the individual should be kept in isolation while hospitalized only when no other options remain.

Social determinants of health are not only driving the HIV and TB epidemics but are also a challenge for affected people to adhere to treatment for any form of TB – particularly for people living with HIV. Persons with TB and HIV often experience stigma and discrimination in many areas of life, including work, social activities and family life. Social, economic, cultural and legal issues may pose additional barriers in accessing health care and being able to consistently follow medical advice. Consequently, it is important that the healthcare services are aware of all the barriers faced by people affected by TB and provide appropriate and comprehensive social support; furthermore, social protection measures to enable adherence and reduce economic hardship should be provided. Treatment adherence interventions that may be offered for people on TB treatment include material support (e.g. food, financial enablers, transport fees), psychological support, tracers such as home visits or digital health communication (e.g. SMS, telephone call) and medicine monitoring *(14, 15)*. Interventions should be selected based on the assessment of the individual's barriers to access, needs and preferences as well as available resources. Education and counselling on TB and its treatment should also be provided to all people with TB.

3.5 Prevention of TB

3.5.1 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). (9)*
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). (9)*
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). (9)*
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). (13)*
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). (13)*
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*). *(9)*
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*). *(9)*

It is estimated that a quarter of the world's population has been infected with TB bacilli. TB infection, previously called latent TB infection (LTBI), is defined as a state of persistent immune response to stimulation by *M. tuberculosis* antigens with no evidence of clinically manifest TB disease *(107, 108)*. People living with HIV have a higher risk of developing TB disease compared to the general population, even when on ART and with a high CD4 cell count *(109, 110)*. Among people living with HIV, TB preventive treatment provides an added benefit to ART alone in reducing both TB incidence and overall mortality, regardless of CD4 count *(111, 112)*. TB preventive treatment for people living with HIV should be a core component of the HIV package of care and should primarily be the responsibility of national HIV and AIDS programmes and HIV service providers *(17)*.

3.5.1.1 Eligibility for TB preventive treatment

WHO recommends that all adults and adolescents with HIV who are unlikely to have TB disease should receive TPT as part of a comprehensive package of HIV care. This includes those receiving ART, pregnant women and those who have previously been treated for TB; it applies irrespective of the degree of immunosuppression and even if TB infection testing is unavailable *(9)*. Whilst there is no evidence to date on the utility of repeated courses of TPT, and WHO does not have any recommendations on this approach, a repeat course of TPT should be considered among people living with HIV who have previously completed a course of TPT and have been thereafter a household or close contact of a person with TB *(113)*.

3.5.1.2 Ruling out TB disease prior to offering TB preventive treatment

Offering TPT to someone who has TB disease can delay the resolution of disease and may favour the emergence of drug resistance. Thus, excluding TB disease before initiating TPT is one of the critical steps in the TPT care pathway. Table 3.5 summarizes the key steps in ruling out TB disease prior to starting TPT in people living with HIV.

Screening for TB using a standard set of signs and symptoms has multiple advantages. The W4SS – current cough, fever, weight loss or night sweats – is useful for ruling out TB disease among people living with HIV, regardless of ART use. In many settings, it has high sensitivity and a high negative predictive value, and it is a straightforward intervention; it can be implemented during any clinical encounter and repeated as often as necessary, without the need for special equipment. Where available, additional tests such as chest radiography, CRP or mWRD may also be used to improve screening accuracy *(76)*. These tests are described in more detail in Section 3.1.

WHO specifically recommends that chest radiography may be offered, if available, for people who are receiving ART. If there are no TB symptoms or abnormal radiographic findings, TPT should be considered. The use of chest radiography together with the W4SS is likely to increase the confidence of health providers given the very high sensitivity of the combination (with less chance of missing TB disease). This may reduce potential provider concerns around the development of drug resistant-TB resulting from inadvertent treatment of TB disease with a TPT regimen. However, chest radiography provides only a marginal gain in accuracy for ruling out TB disease, as compared with the W4SS alone, and will result in more screen positive results, which would require more investigations for TB and other illnesses. The addition of chest radiography to symptom screening may also present logistical difficulties and increase the cost to programmes and individuals, leading to missed opportunities to give TPT to people who could benefit from it *(113)*. Chest radiography should only be added as an additional investigation if it does not pose a barrier to the provision of preventive treatment for people living with HIV *(113)*.

If a person living with HIV has a positive screening test for TB with any of the WHO-recommended screening tools, but TB disease is ruled out after subsequent diagnostic investigations, the individual should also receive TPT. Thus, collaboration between TB and HIV services is critical to minimize attrition across the diagnostic and prevention cascades of care, and to close the gap in TPT coverage.

Algorithm 6: Algorithm to rule out TB disease in people living with HIV

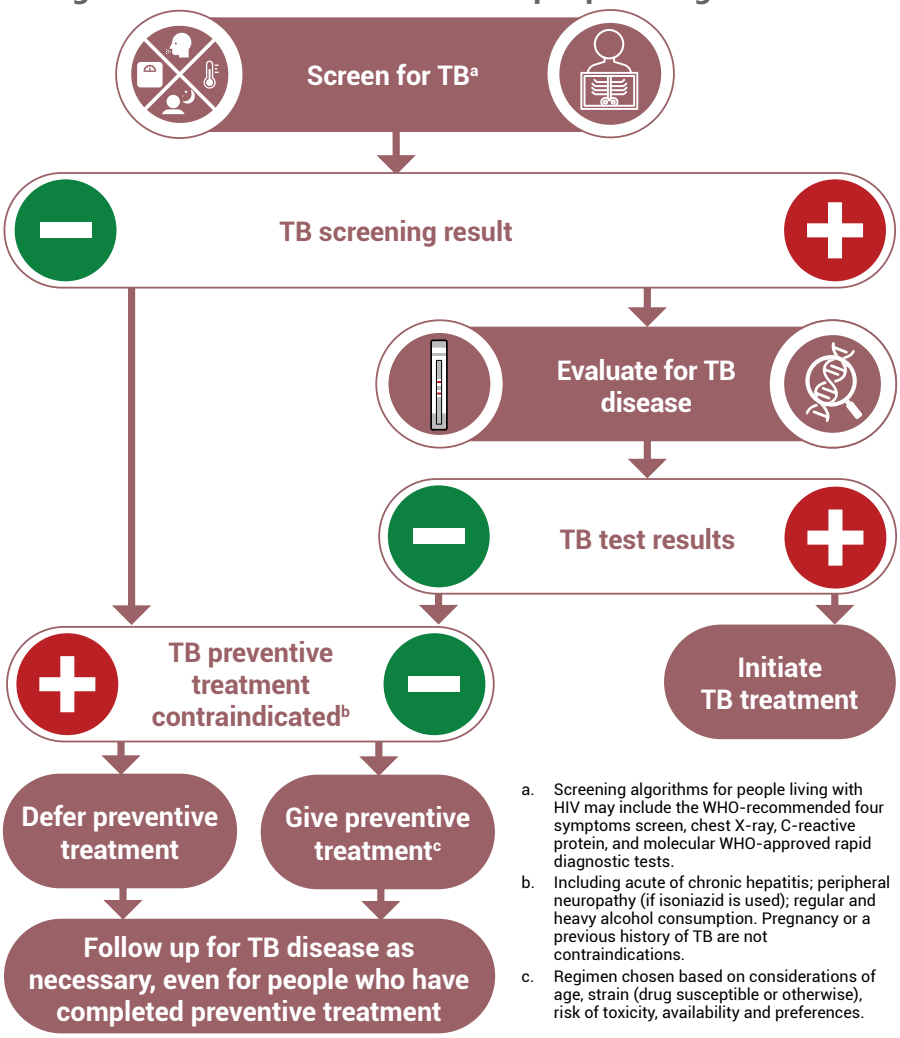


Table 3.5. Key considerations for assessment of eligibility for TPT in people living with HIV *(113)*

Clinical symptom-based screening (W4SS)	Screen for any one of current cough, fever, weight loss or night sweats
Frequency of symptom screening	At every visit to a health facility or contact with a health worker
Chest radiography	Not mandatory although desirable. May be considered where facilities are available and human resources and health system capacity permits
Diagnostic testing for TB if screen test is positive	WHO recommends rapid diagnostics such as Xpert® MTB/RIF, LF-LAM assay among seriously ill PLHIV (see Section 3.2 on diagnostics) or as per national guidelines
Test for TB infection (TST, IGRA or TBSTs)	Not required among people living with HIV. Unavailability of tests should not be a barrier to provision of TPT to those in need
Contraindications to TPT	• Acute hepatitis, regular and heavy alcohol consumption or symptoms of peripheral neuropathy • Concurrent use of other hepatotoxic medications (such as nevirapine) • History of hypersensitivity to TPT
Counselling	Information on TB infection, need for TPT, schedule of medication collection, medication adherence support and follow-up visits, benefits from completing the course, adverse events, awareness about and actions on development of TB symptoms or adverse events

3.5.1.3 Testing for TB infection

Testing for TB infection prior to initiating TPT is not required for people living with HIV. People living with HIV who are on ART benefit from TPT regardless of whether they test positive or negative for TB infection *(114)*. People living with HIV who are not on ART and who test positive for TB infection are shown to benefit more from TPT than those with a negative test *(73)*; however, testing for TB infection should not be a requirement for initiating TPT among people living with HIV, particularly in countries with high TB incidence, given that the benefits of treatment (even without testing) clearly outweigh the risks *(9)*. Similarly, unavailability of TB infection testing should not constitute a barrier to providing TPT for people living with HIV.

There is no gold standard to diagnose TB infection, however, WHO recommendations have been formulated for three types of tests for TB infection: the tuberculin skin test (TST), the interferon-gamma release assay, and newer *M. tuberculosis* antigen-based skin tests *(9, 12, 13)*. The TST is a point-of-care test that involves intradermal injection of purified protein derivative (PPD), a crude mixture of mycobacterial antigens, which stimulates a hypersensitivity reaction that causes an induration at the injection site within 48 to 72 hours but has low specificity among people living with HIV. Recurrent global shortages and stockouts of PPD reduce prospects for the scale-up of this test and may pose a further barrier to the programmatic management of TPT in people living with HIV.

In contrast, IGRAs are in vitro tests that measure the release of interferon-gamma (IFN-γ) following stimulation with two *M. tuberculosis*-specific antigens: the early secretory antigenic target 6 kDa protein (ESAT-6) and culture filtrate protein 10 (CFP-10). IGRAs are more expensive than TSTs and require specialized facilities and trained personnel *(115)*. Both TST and IGRA require the person to mount an immune response to *M. tuberculosis* to work properly, thus a negative result does not rule out TB infection, especially among people living with HIV who may not mount an immune response to *M. tuberculosis* antigens. TST and IGRA could remain positive even after successful completion of TPT. Therefore, results of TST and IGRA should not be used to assess the efficacy of TPT. Since 2022, WHO also recommends the use of newer TBSTs, including Cy-Tb, Diaskintest® and C-TST (formerly known as ESAT6-CFP10 test). The TBSTs are point-of-care skin tests that measure the response to the ESAT-6 and CFP-10 antigens, combining the simple, point-of-care based platform of the TST with the specificity of IGRAs *(13)*.

3.5.1.4 TB preventive treatment regimens

TB preventive treatment for an infection with strains presumed to be drug-susceptible broadly falls into two categories: (i) isoniazid monotherapy for at least 6 months, and (ii) rifamycin-based shorter preventive treatment regimens. Isoniazid preventive therapy has been the most widely used type of TB preventive treatment, but the shorter duration of rifamycin regimens presents a clear advantage *(9)*. The *WHO consolidated guidelines on tuberculosis. Module 1: prevention – tuberculosis preventive treatment* outlines 9H, 6H, 4R, 3HP, 3HR, 1HP and 36H as TPT options for use across all disease burden settings and target populations including people living with HIV, as summarized in Table 3.6 *(9)*. However, a potential challenge with rifamycin-based TPT regimens among people living with HIV is drug–drug interactions. The choice of TPT regimen will depend on availability of appropriate formulations and considerations for age, safety, drug–drug interactions and adherence. Preventive treatment for people who have been in close contact with a person with MDR-TB requires a different regimen using a fluoroquinolone or other second-line agents *(9)*. Further guidance on MDR-TB preventive treatment is due to come out in 2024.

Table 3.6. TB preventive treatment regimens

Regimen	6H	3HP	3HR	4R	1HP	H + B6 + CPT (Q-TIB)
Medicines	Isoniazid	Isoniazid + rifapentine	Isoniazid + rifampicin	Rifampicin	Isoniazid + rifapentine	Isoniazid+ pyridoxine+ co-trimoxazole
Duration (months)	6	3	3	4	1	6
Interval	Daily	Weekly	Daily	Daily	Daily	Daily
Doses	182	12	84	120	28	182
Dosing for adults (average individual weighing 60 kg)	300 mg	900 mg/ 900 mg	300 mg/ 600 mg	600 mg	300 mg/ 600 mg	300 mg/ 25 mg/800 mg/160 mg
Pill burden per dose (total number of pills for average adult)[a]	1 (182)	6 singles (72) or 3 with FDC (36)	3 singles (252) or 4 with FDC (336)	2 (240)	5 (140)	1 (182)
Cost for a full treatment (unless otherwise specified)[b] (116)	US$ 3.11–3.58	Rifapentine: US$ 12.21 Isoniazid: US$ 0.62–0.71 FDC: US$ 14.25	Isoniazid: US$ 1.44–1.65 Rifampicin: US$ 32.47 FDC: US$ 15.89–17.54	US$ 46.4	Isoniazid: US$ 0.48–0.55 Rifapentine: US$ 19.00 FDC + rifapentine single: US$ 20.58	FDC: US$ 14.44
Pregnant women	Safe for use[d]	Not known	Safe for use[d, e]	May be safe, although no safety or efficacy data available specifically in this population[e]	Not known	Safe for use; preferred option – in PLHIV[d]
Dose adjustments when co-administered with ART[c]	No dose adjustment required	Contraindicated: all PIs, NVP/NNRTIs, TAF Use: TDF, EFV (600 mg), DTG,[f] RAL[f]	Contraindicated: all PIs, NVP/most NNRTIs Use with caution: TAF Adjust dose: DTG, RAL Use: TDF, EFV (600 mg)	Contraindicated: All PIs, NVP/most NNRTIs, TAF Adjust dose: DTG, RAL Use: TDF, EFV (600 mg)	Contraindicated: all PIs, NVP/most NNRTIs, TAF Use: TDF, EFV (600 mg), DTG,[f] RAL[f]	No dose adjustment required
Toxicity	Hepatotoxicity (more), peripheral neuropathy, rash, gastrointestinal (GI) upset	Flu-like syndrome, hypersensitivity reactions, GI upset, orange discolouration of body fluids, rash, hepatotoxicity (less)	Hypersensitivity reactions, hepatotoxicity (less), rash, GI upset, hypoprothrombinaemia, orange discolouration of body fluids	Rash, GI upset, hepatotoxicity (less), hypoprothrombinaemia, orange discolouration of body fluids	Hepatotoxicity (more), hypersensitivity reaction, rash, GI upset, orange discolouration of body fluids	Hepatotoxicity, rash, GI upset
Absorption	Best absorbed on an empty stomach; up to 50% reduction in peak concentration with a fatty meal	Oral rifapentine bioavailability is 70% (not HP); peak concentration increased if given with a meal	Rifampicin absorption is rapid but may be delayed or decreased by high-fat meals	Rifampicin absorption is rapid but may be delayed or decreased by high-fat meals	Same as 3HP	Same as 6H

Footnotes for Table 3.6

Note: B6 = pyridoxine, CPT = co-trimoxazole, DTG = dolutegravir, EFV = efavirenz, FDC: fixed dose combination, H = isoniazid, LPV/RTV = lopinavir + ritonavir, NNRTI = non-nucleoside reverse transcriptase inhibitor, NVP = nevirapine, P = rifapentine, PIs = protease inhibitors, R = rifampicin, RAL = raltegravir, TAF = tenofovir alafenamide, TDF = tenofovir disoproxil fumarate

[a] Average available adult formulations: H-300 mg, R-300 mg/150 mg, P-300 mg.

[b] Prices as per the *Global Drug Facility Medicines Catalog*, March 2023 *(116)*. Advice on planning orders, including details on the cost of regimens, can also be found on the GDF website: https://www.stoptb.org/buyers/plan-order.

[c] For women living with HIV (as well as HIV-negative) receiving rifamycin-based TPT and oral contraceptives, consider additional barrier contraception methods to prevent pregnancy.

[d] One randomized trial has shown increased risk of poor birth outcomes for mothers taking isoniazid during pregnancy; however, several other studies have shown benefits of IPT, hence caution is required.

[e] Bleeding attributed to hypoprothrombinaemia has been reported in infants and mothers following the use of rifampicin in late pregnancy. Vitamin K is recommended for both the mother and the infant postpartum if rifampicin is used in the last few weeks of pregnancy (US Food and Drug Administration).

[f] Indicates that drug interaction has been studied in adults and not children; applies to adults taking DTG or RAL only.

The efficacy, safety and convenience of repeated treatment with shorter rifapentine regimens is being studied in people living with HIV in such settings. Findings from one study have shown that a second round of TPT did not provide additional benefit to persons receiving antiretroviral therapy *(117)*. The definition of a high TB transmission setting should be established by the national authorities[4] (see also Definitions).

Long-term treatment with high-dose isoniazid may cause peripheral neuropathy, which develops secondary to a deficiency of vitamin B6 (pyridoxine) during therapy. Individuals at risk of peripheral neuropathy include people living with HIV as well as those with chronic malnutrition, renal failure or diabetes, or those who are pregnant or breastfeeding. All people living with HIV should receive pyridoxine while taking isoniazid, to prevent peripheral neuropathy. Preventive and therapeutic doses of pyridoxine are available through the Stop TB Partnership Global Drug Facility (GDF). National programmes may consider the use of a triple pill combination of isoniazid, co-trimoxazole and pyridoxine for people living with HIV, instead of an isoniazid-only regimen, available at a discounted price through the GDF *(116)*.

TPT regimens and antiretrovirals

The 3HP regimen can be administered to individuals receiving efavirenz-based antiretroviral regimens without dose adjustment, according to a study of pharmacokinetics *(118)*. The 1HP or 3HP regimens for TPT are not recommended for people receiving PIs or NVP because of the risk of HIV virological failure. Administration of rifapentine with raltegravir was found to be safe and well tolerated *(119)*. Results from a Phase 1/2 trial of 3HP and dolutegravir in adults with HIV reported good tolerance and viral load suppression, no adverse events of Grade ≥3 related to 3HP, and it did not indicate that rifapentine reduced dolutegravir levels sufficiently to require dose adjustment *(120)*. There is a continued need for studies of the pharmacokinetics of 3HP concomitantly with other medicines, particularly ART.

In terms of timing of TPT start, preliminary evidence from another Phase 1/2 trial (DOLPHIN TOO) supports the immediate start of TPT among ART-naïve people starting a dolutegravir based regimen. 3HP administered to 50 persons with HIV who were ART-naïve and started on dolutegravir-containing ART showed high rates of viral suppression comparable with 6H and no difference in GRADE 3 or 4 adverse events ([Ethel Weld], [Johns Hopkins University], DOLPHIN-TOO: Oral abstract presented at The Union World Conference on Lung Health, [2023]).

[4] A setting with a high frequency of individuals with undetected or undiagnosed active TB, or where individuals with infectious TB are present and there is a high risk of TB transmission. TB is most infectious when it is untreated or inadequately treated. Spread is increased by aerosol-generating procedures and by the presence of highly susceptible individuals.

Preventive treatment for MDR-TB

The capacity of programmes to provide preventive treatment for MDR-TB should be carefully planned for. Providing preventive treatment for MDR-TB requires that all the necessary resources are in place. Considerations should include the ability to identify people who may benefit from MDR-TB preventive treatment, the capacity to rule out TB disease, to perform quality-assured testing for drug susceptibility (in the presumed index patient), to deliver the necessary medications and to monitor closely for adverse events and for the emergence of active disease. The choice of preventive treatment for MDR-TB is discussed further in the *WHO consolidated guidelines on tuberculosis. Module 1: prevention – tuberculosis preventive treatment (9)* and the accompanying operational handbook *(113)*.

Liver function tests

There is insufficient evidence to support mandatory or routine liver function tests (LFTs) at baseline *(121)*, and perhaps the benefit of TPT without LFTs would likely outweigh harm, particularly with a less hepatotoxic regimen. However, where feasible, baseline testing is strongly encouraged for individuals with risk factors – such as a history of liver disease, regular use of alcohol, chronic liver disease, HIV infection, age over 35 years and in pregnancy or immediate postpartum period (within 3 months of delivery). In individuals having abnormal baseline LFT results, sound clinical judgement is required to determine if the benefit of TPT outweighs the risk of adverse events. These individuals should be tested routinely at subsequent visits.

Subpopulation considerations

TPT among pregnant women living with HIV: pregnant women living with HIV are at higher risk of TB during pregnancy and postpartum, which can have severe consequences for both the mother and the infant *(122, 123)*. Pregnancy should not prevent women living with HIV from receiving TPT. Preventive treatment should be started during the antenatal and postnatal periods, provided it is given with due care. There are limited data on the efficacy and safety of rifapentine during pregnancy. WHO currently recommends 6 months of isoniazid regimen as TB preventive treatment for pregnant women living with HIV. The triple pill combination of isoniazid + co-trimoxazole + B6 may be the preferred option for TPT among pregnant and postpartum women living with HIV until more safety data on the use of rifapentine-based shorter regimens are available.

TPT among people who use drugs: people who use drugs (PWUD) have a higher prevalence of TB infection and incidence of TB disease, regardless of HIV status, when compared to people who do not use drugs *(124)*. Isoniazid preventive therapy is safe to use among PWUD, if acute hepatitis or heavy alcohol consumption are ruled out, whilst careful monitoring for liver toxicity is important *(125)*. WHO recommends methadone or buprenorphine for treating opioid dependence *(126)*. Rifampicin is known to reduce exposure to OAMT such as methadone and buprenorphine *(127)*, which may result in opiate withdrawal syndrome. Rifapentine has not been systematically studied among PWUD. People taking 1HP, 3HP, 3HR or 4R with ART and OAMT should be closely monitored for signs of opiate withdrawal and other adverse events, and doses of methadone or buprenorphine may need to be increased accordingly, to lessen the risk of withdrawal. Drug use should not be a reason to deny someone access to TPT, and healthcare providers should proactively manage drug–drug interactions for PWUD safely, as well as provide treatment and adherence support *(128)*.

Scale-up of TB preventive treatment

In recent years, as part of efforts to meeting the commitments made at the first UN High-level Meeting on the Fight Against Tuberculosis, there has been considerable scale-up of TPT among people living with HIV. Previously, countries prioritized TPT among individuals newly enrolled on ART. However, given that all people living with HIV are eligible for TPT, countries are now beginning to conduct catch-up TPT campaigns or TPT surge initiatives to include people already on ART who have not yet received TPT. Whilst there is need for careful resource planning for such initiatives, these actions have proven to be effective in gaining political support and engaging stakeholders across multiple sectors *(129)*. Fig. 3.2 draws experience from countries in scaling up TPT and outlines the enablers for scale-up in line with health system building blocks.

Fig. 3.2 Key enablers to scaling up TPT among people living with HIV

LEADERSHIP & GOVERNANCE

- Enhance political commitment and political buy-in, for instance set and report on a national target.
- Establish a TPT task force within the TB/HIV coordinating platform with defined roles and responsibilities of key stakeholders, including private sector, correctional facilities, mining groups.
- Review quality and coverage of services as part of national TB and HIV programme reviews.
- Set targets on TPT for people living with HIV (both newly and currently on ART) and assure alignment of indicators among stakeholders.
- Create demand through community engagement.

FINANCING

- **Develop a budget for the TPT scale-up plan. Items to consider include the following:**
  - **human resources, task shifting, training, mentoring and capacity-building;**
  - **procurement of TPT medications and pyridoxine;**
  - **workshops for developing standard operating procedures (SOPs), updating policies and guidelines, and aligning monitoring and evaluation;**
  - **updating of digital recording and reporting tools;**
  - **information, education and communication materials; and**
  - **additional resources for TPT surge initiative, including catch-up for people previously started on ART but who have never received TPT.**
- **Advocate for extra resources for accelerated scale-up and post-acceleration period.**

HEALTH WORKFORCE

- **Define the roles and responsibilities of health providers, community health workers and other allied professionals in health facilities and related services (e.g. prisons and other places of detention, refugee camps, and mining communities) in evaluation of eligibility and initiation of TPT.**
- **Evaluate capacity and availability of healthcare workers, community health workers and other networks, such as TB survivors, and assess additional needs for nationwide scale-up of TPT services.**
- **Build workforce capacity for TPT among staff including community health workers, on history taking, symptom screening and referral for investigations, assessment of eligibility for TPT and starting TPT:**
  - **develop TPT training packages and SOPs; and**
  - **conduct training of trainers for TPT, sensitization and capacity-building of staff.**

MEDICAL PRODUCTS AND TECHNOLOGIES

- Review and strengthen the mechanism for quantification, ordering and uninterrupted supply of commodities (such as TPT medications, pyridoxine).
- Undertake phase-in/phase-out planning for TPT medications (from a procurement perspective) as the national programme transitions to shorter TPT regimens. This is important during the introduction of the new regimen.
- Supply chain commodity management:
  - assess facility and national stock status;
  - conduct quantification and forecasting using set targets; ensure adequate and steady supply of commodities; and
  - plan procurement to fill gap (actual status vs new TPT targets) – buffer stock.
- Ensure access to TPT commodities and TB diagnostics:
  - distribute and ensure adequate stock of all TPT regimens and pyridoxine at facility level;
  - strengthen access to diagnostic tools (CXR, mWRD) to rule out TB disease; and
  - monitor consumption on weekly basis and report back to central level.

INFORMATION & RESEARCH

- Identify and address challenges and gaps in monitoring and evaluation tools (paper-based and/or electronic).
- Integrate key data variables on TPT initiation and completion into the HMIS (paper-based and/or electronic).
- Quantify the backlog of people currently in care who have never received TPT, for example through review of records.
- Adopt digital tools to facilitate data capture and reporting to national HMIS by all stakeholders.
- Train and mentor staff and stakeholders on data capture, review and assessment.
- Conduct district and provincial data review and report to central level.
- Use data for ongoing identification of gaps and challenges to be addressed.
- Promote operational research, such as retrospective analysis of the data or prospective studies.

SERVICE DELIVERY

- Identify levels of healthcare system where TPT can be started and medicines refilled for continuation.
- Establish TPT services in all relevant service delivery sites (such as ART centres, maternal and child health service centres, community health centres, differentiated service delivery platforms, mines, prisons).
- Leverage on existing HIV services to provide specialized care as needed for people receiving TPT (such as management of adverse events, drug–drug interactions, special situations, pregnancy).
- Decentralize initiation and continuation of TPT to HIV services closest to person's residence to minimize travel time to receive TPT.
- Jointly develop policies, guidelines and standard operating procedures for TPT initiation and follow-up to:
  - maintain flow of persons considered for TPT in various health facilities and across different service points within those facilities;
  - provide adherence support for TPT;
  - manage TPT interruptions; and
  - identify, document and manage adverse drug events.
- Create demand for TPT by people living with HIV through awareness campaigns on availability and benefits, through national communication campaigns, community engagement activities, and dissemination of information, education and communication materials.
- Engage civil society and communities affected by TB and HIV in refining and delivering people-centred services by:
  - involving civil society in all stages of the planning and implementation of TPT;
  - using HIV structure for strengthening of support groups; and
  - developing adapted models that address stigma, fears and barriers for a specific population.

3.5.2 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 *(130)*. There are no separate infection prevention and control measures that are specific to HIV-associated TB. The *WHO consolidated guidelines on tuberculosis. Module 1: prevention – infection prevention and control (130)* provide recommendations on preventing the transmission of TB in health care and other congregate settings, through administrative controls, environmental controls and respiratory protection measures. The WHO *Guidelines on core components of infection prevention and control programmes at the national and acute health care facility level (131)* provide additional detail on IPC measures to prevent transmission of infectious diseases that apply to all healthcare settings. Box 3.3 summarizes WHO recommendations on TB infection prevention and control.

Box 3.3 WHO recommendations on TB infection prevention and control

To reduce *M. tuberculosis* transmission to health workers, persons attending healthcare facilities, or other persons in settings with a high risk of transmission, the following measures are recommended:

- Administrative controls:
  - triage of people with TB signs and symptoms, or with TB disease;
  - respiratory separation or isolation of people with presumed or demonstrated infectious TB;
  - prompt initiation of effective TB treatment of people with TB disease; and
  - respiratory hygiene (including cough etiquette) in people with presumed or confirmed TB.
- Environmental controls:
  - upper-room germicidal ultraviolet systems;
  - ventilation systems (including natural, mixed-mode, mechanical ventilation); and
  - recirculated air through high-efficiency particulate air filters.
- Respiratory protection:
  - particulate respirators, within the framework of a respiratory protection programme.

Source: WHO consolidated guidelines on tuberculosis. Module 1: prevention – infection prevention and control. Geneva: World Health Organization; 2022 (130)

Healthcare facilities and congregate settings can present a risk for acquiring TB (including MDR-TB) for people living with HIV, as well as for healthcare workers. At facility level, measures to reduce TB transmission include administrative controls, environmental controls and respiratory protection, which are aimed at generally reducing exposure to *M. tuberculosis* for clients, healthcare workers, prison staff, police and any other persons visiting or working in congregate settings *(132)*.

To minimize time spent in healthcare facilities, community-based or home-based treatment support is recommended over health facility-based treatment support or unsupervised treatment *(15)*. People with HIV and TB and their communities should be trained on TB transmission, infection prevention and control, and cough etiquette to reduce the risk of TB transmission in healthcare facilities, in congregate settings and within their own homes.

All measures should be taken to ensure that people working in healthcare facilities and congregate settings have access to prevention measures, including HIV prevention interventions, and ART and TPT for workers who are living with HIV. Healthcare workers should have access to acceptable, confidential and quality-assured HIV testing services. Even when they are on ART, healthcare workers with HIV will remain at higher risk of developing TB, and transfer of their clinical responsibilities to sites that have the least risk of TB transmission, as well as regular TB screening, should be considered to mitigate this risk. Similarly, healthcare workers with TB disease should be temporarily relocated from HIV care facilities.

Implementation of TB infection prevention and control measures requires managerial oversight at national, subnational and facility levels, which includes establishing TB infection prevention and control committees at all levels; developing a plan preferably incorporated into a broader infection prevention and control plan; appropriate health facility design and use; surveillance of TB disease among healthcare workers; an advocacy and communication strategy; monitoring and evaluation; and operational research *(130)*. Periodic evaluation of infection prevention and control practices is essential to ensure that appropriate measures are in place. Facility-level assessment of TB infection prevention and control should be incorporated into the routine supervisory activities of all health facilities which provide care for people living with HIV. A standardized checklist for periodic evaluation of infection prevention and control practices can serve as a tool for such an assessment and can help measure progress over time. An example of a checklist that can be adapted by countries to suit the context can be found in Annex 3. To reduce the transmission of TB to the family and the community, key information, education and counselling should also be provided to the individual and family members. This should include advice on cough etiquette, sleeping alone, avoiding congregate settings and spending as much time as possible outdoors where feasible, until no longer infectious *(130)*.

4. Reduce the burden of HIV among people with TB

4.1 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*). *(7)*
23. All household contacts of a person with HIV-associated TB should be offered HIV testing services *(strong recommendation, very low-quality evidence). (18)*
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). (18)*
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). (18)*
26. Partner services should be offered to people with HIV-associated TB *(strong recommendation, moderate-quality evidence). (19)*

WHO recommends that all people with presumptive and diagnosed TB should be offered an HIV test as part of the essential package of TB care *(17)*. Countries should offer HIV testing services (HTS) to 100% of people with new or relapse TB episodes, as part of the implementation of the End TB Strategy, by 2025 at the latest *(133)*. Since the publication of the *Interim policy on collaborative TB/HIV activities* in 2004 *(6)*, there has been considerable scale-up of HIV testing in people with TB, including in concentrated HIV-epidemic settings where the network of TB facilities has been leveraged to expand and decentralize HIV testing and ART services *(134)*. However, there are still countries where there is limited coverage of HTS among people with TB, and, in many settings, offering testing services to people with presumptive TB along with household contacts of people diagnosed with TB provides a missed opportunity for targeted scale-up. Key considerations for scale-up of HTS among people with presumptive and diagnosed TB are listed in Box 4.1.

HIV testing services for people with diagnosed or presumptive TB can offer a strategic entry point for both HIV and TB prevention, care, support and treatment. HIV testing among household contacts also identifies a high number of new diagnoses of HIV infection, as the prevalence of HIV is higher than among the general adult population *(7, 135)*. Household contacts with HIV, with unknown HIV status who are not receiving treatment, are at increased risk for rapid progression to TB disease, and at increased risk of mortality from TB.

Box 4.1 Summary of key considerations for scaling up HIV testing services among people with TB

To ensure greater access to and uptake of testing among people with diagnosed and presumptive TB, programmes should consider the following:

- ➔ Strengthen collaboration across service delivery sites and in programme planning and monitoring, including through the development of joint SOPs and job aides, and in quantification and supply chain management of HIV test kits.
- ➔ Ensure access to essential HIV testing products on site, such as HIV rapid diagnostic tests as part of the national algorithm, as well as HIV self-test kits.
- ➔ Train and capacitate staff and provide supportive supervision for healthcare workers, nurses, lay providers, community health workers and peers to deliver HIV testing services alongside TB services.
- ➔ Strengthen service delivery site capacity and facility infrastructure to enable HIV testing services to be delivered in accordance with the 5Cs: Consent, Confidentiality, Counselling, Correct results and Connection (linkage to prevention, treatment and care).

HIV partner services is a process whereby a trained provider offers voluntary testing services 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 services (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. It is also an approach for extending HIV services to drug-injecting partners. A strategic mix of facility-based, community-based, home-based and HIV self-testing (HIVST) options should be made available to ensure access to testing services across these groups.

People living with HIV who are household contacts or close contacts of someone with TB disease and who, after an appropriate clinical evaluation, are found not to have TB disease should be evaluated for TPT, even if they have previously completed a course of TPT *(113)*. It is also important to assess eligibility for TB preventive treatment in those contacts for whom TB disease is ruled out, regardless of HIV status.

4.1.1 HIV testing service delivery approaches

WHO recommends differentiated HIV testing service delivery approaches that address the needs of a variety of population groups, geographies, contexts and epidemic settings. This includes facility-based HTS within TB services, which is associated with improved uptake of HIV testing and HIV diagnoses among people with TB *(136)*. There are also non-facility-based approaches to HTS, such as community-based testing, which may complement facility-based testing for people with diagnosed or presumptive TB, help address barriers to HIV testing service access, and provide an opportunity to expand HIV testing *(17)*. Community-based HTS could be integrated as part of multi-disease testing outreach and/or conducted together with TB screening as part of efforts to roll out TPT for household contacts *(17)*. HIV testing services should never be mandatory. Policies and practices to protect vulnerable populations from mandatory or compulsory testing are needed, as well as monitoring and accountability for policies already in place. It is critical to ensure that HTS are delivered within a human rights framework. Some jurisdictions mandate HIV testing among specific groups such as immigrants. This requirement is not justified, and it can jeopardize voluntary access to health services in general and to HTS. In all circumstances, testing services should be provided in accordance with WHO's essential 5 Cs: Consent, Confidentiality, Counselling, Correct test results and Connection (linkage to prevention, care and treatment), as outlined in Box 4.2 *(137)*.

Box 4.2 WHO 5 Cs for HIV testing services:

- **Consent.** People receiving HTS must give informed consent to be tested and counselled (verbal consent is sufficient; written consent is not required). They should be informed of the process for HIV testing and counselling and of their right to decline testing. It should not be assumed that people who request or report self-testing for HIV are providing or have implicitly provided consent. It is important that all people who self-test are informed that mandatory or coercive testing is never warranted. Provider-assisted referral and social network-based approaches, which offer HTS to their clients' sexual partners, drug injecting partners and social contacts, are voluntary and implemented only with the consent of clients and contacts.
- **Confidentiality.** HTS must be confidential, meaning that what the HTS provider and the client discuss will not be disclosed to anyone else without the express consent of the person being tested. Although confidentiality should be respected, it should not be allowed to reinforce secrecy, stigma or shame. Counsellors should discuss, among other issues, who they may wish to inform and how they would like this to be done. Shared confidentiality with a partner or family members – i.e. trusted others – and healthcare providers is often highly beneficial.
- **Counselling.** Concise pre-test information and post-test counselling can be provided in a group setting if appropriate, but all persons should have the opportunity to ask questions in a private setting if they request it. All HTS must be accompanied by appropriate post-test counselling, based on the HIV test result. Quality assurance (QA) mechanisms as well as supportive supervision and mentoring systems should be in place to ensure the provision of high-quality counselling. Various channels and tools can be used to deliver messages, information and counselling, including peer providers and innovative digital approaches such as videos, social media and other mobile phone applications or services.

- **Correct.** Providers of HTS should strive to offer high-quality testing services, and QA mechanisms should ensure that people receive a correct diagnosis. QA may cover both internal and external measures and should include support from the national reference laboratory. All people who receive a positive HIV diagnosis should be retested to verify their diagnosis before initiation of ART or engagement in HIV care.
- **Connection.** Linkage to prevention, care and treatment services should include the provision of effective and appropriate follow-up as indicated, including long-term prevention and treatment support. Providing HTS where there is no access or poor linkage to care, including ART, has limited benefit for those with HIV. Linkage is the responsibility of providers and testers delivering HTS.

Source: Consolidated guidelines on HIV testing services, 2019. Geneva: World Health Organization; 2020 (19)

To enable greater access to HIV testing services, WHO also recommends lay provider-delivered HTS in healthcare facilities and in the community *(137)*. Community health workers and lay providers such as TB champions can be trained to deliver all HTS. These include pre-test information, HIV rapid testing, interpreting HIV test results and reporting HIV status, providing post-test counselling, referrals and support to facilitate the linkage to prevention, treatment and care services.

Additional approaches and testing modalities, such as HIV partner services and HIV self-testing, can also be beneficial when delivered in facilities or in community settings. HIVST is a process in which people collect their own specimen (oral fluid or blood), perform a test using a simple rapid HIV test and interpret their results, often in a private setting, either alone or with someone they trust. Because of their flexible nature, these rapid HIV tests enable providers to offer HIV testing services wherever they are most needed, including door-to-door distribution and in different types of health facilities. A recent WHO systematic review found that in sub-Saharan Africa, offering self-testing in health facilities increased uptake of HIV testing, the number of people diagnosed with HIV and linkage to care. People with diagnosed or presumptive TB, presenting for care in private clinics or sites with limited staff and testing capacity, could benefit from accessing HIV self-test kits. Additionally, providing HIV self-test kits to people with HIV-associated TB so that they can share them with their partners and close contacts can also be a way to reach more people with HIV testing, prevention and care services.

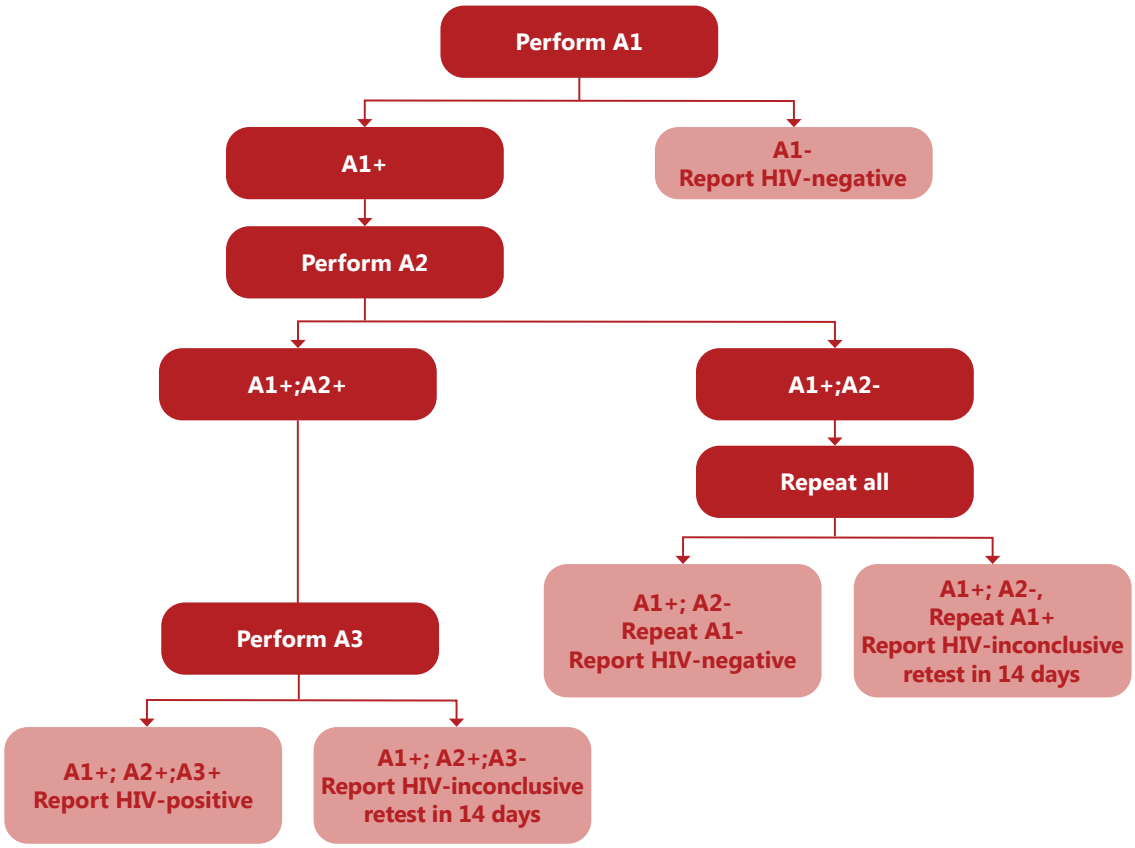
4.1.2 Algorithms for HIV testing

Providing a correct HIV diagnosis, as quickly as possible, is critical for all HIV testing services. Accurate diagnosis enables newly identified people living with HIV to start ART sooner, which has immediate benefits for their health and, through provider-assisted referral (index testing), for the health of their partners and the community *(19)*. Most people testing for HIV will be negative and will likely require only one test. However, no single test can be used to provide a definitive positive HIV diagnosis. To achieve accurate results, WHO recommends that countries use a three-assay HIV testing strategy where three consecutive reactive test results are required to give an HIV-positive diagnosis (see Fig. 4.1). This strategy is considered to be the WHO standard HIV testing strategy. The HIV testing strategy can combine rapid diagnostic tests (RDTs) and/or enzyme immunoassays (EIAs) that, when used together, achieve a positive predictive value (PPV) of at least 99%. The positive predictive value indicates the probability that an HIV-positive diagnosis is correct.

The testing strategy does not stipulate the specific products to be used at each step, rather, it provides guidance on the characteristics of the test used at each step. Countries should populate the testing strategy with different products for each step, considering products that are WHO prequalified; see https://extranet.who.int/pqweb/vitro-diagnostics/vitro-diagnostics-lists. The WHO HIV testing algorithms toolkit also provides guidance to help countries optimize product selection and ensure the products selected work well together: https://www.who.int/tools/optimizing-hiv-testing-algorithms-toolkit.

To achieve a PPV of at least 99%, it is critical that Assay 1 provides the best chance to rule in all HIV-positive individuals and has the highest sensitivity, while Assay 2 and Assay 3 must be able to rule out any false HIV-reactive test results, and thus should have very high specificity – higher than Assay 1.

Fig. 4.1. WHO standard testing strategy for HIV-1[a] diagnosis (among children or adults ≥18 months of age)

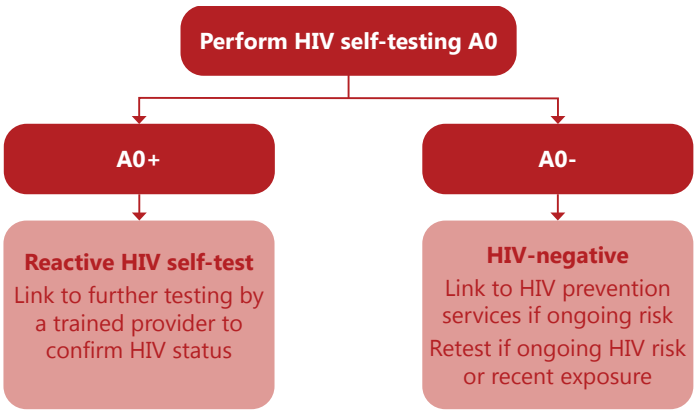


A1: Assay 1 (first test); A2: Assay 2 (second test); A3: Assay 3 (third test).
Assay (tests) are rapid diagonistic tests (RDTs) or enzyme immunoassays (EIAs)

a To provide an HIV-2 diagnosis, serological tests which discriminate between HIV-1 and HIV-2 antibodies can be used. However, these should be followed by appropriate supplemental testing including serological or virological tests that are specific to HIV-1 and HIV-2. It is important to conduct supplemental testing specific to HIV-2 because there is substantial risk of cross-reactivity, and dual infection of HIV-1 and HIV-2 is exceedingly rare.

HIV self-testing can be used as a test for triage but does not provide a definitive HIV-positive diagnosis and people with reactive results need to be linked to provider-delivered testing services for HIV diagnosis. A test for triage may reduce the potential for stigma, as all individuals are tested with the same number of tests, whereas with the standard testing strategy, further testing identifies those with a reactive result on A1. Assay 0 for self-testing is not intended to replace Assay 1 of the WHO testing strategy for diagnosis. Instead, all reactive HIVST results need to be followed by further testing by a trained provider to confirm HIV status, starting with the first test in the national testing algorithm. Non-reactive self-testing results should be considered negative, with no need for further testing except for those starting pre-exposure prophylaxis (PrEP). For further details see Fig. 4.2 below and for the WHO standard HIV testing strategy and population of an HIV testing algorithm, see the WHO *Consolidated guidelines on HIV testing services, 2019 (19)*.

Fig. 4.2. Algorithm for self-testing for HIV



A0 = Assay 0 (test for triage)

4.1.3 Retesting for HIV among people with TB

Retesting for HIV is advised for people with TB for the following reasons:

1. **Retesting to verify a positive diagnosis before initiating lifelong ART.** To ensure that individuals are not incorrectly started on lifelong ART, WHO recommends that all people newly diagnosed with HIV should be retested to verify their HIV status before starting ART, using the same testing strategy (Fig. 4.1). Misdiagnosis is difficult to detect after ART is initiated. Retesting for this purpose is a quality assessment measure that aims to detect misdiagnosis by ruling out errors related to the lot, testing site or testing provider. It may detect clerical errors, such as transcription errors during result interpretation and reporting, and specimen mix-ups. Modelling estimates indicate that retesting to identify a person incorrectly classified as HIV-positive is cost-effective and will likely cost less than unnecessary lifelong ART and virological monitoring *(138)*.

2. **Retesting to provide an HIV diagnosis following inconclusive results.** While most people testing for HIV will receive a diagnosis the same day, a small number of individuals will receive inconclusive results. Inconclusive results are rare but occur when (1) cross-reactivity exists between kits or patient-related factors; (2) the tester or test kit makes an error; and/or (3) individuals are seroconverting and in the window period, when infection cannot be determined. When this occurs, it is important that providers deliver messages to explain the results to clients and support them to come for retesting in 14 days. Retesting at this time will enable the provider to rule in or rule out HIV seroconversion and provide a definitive diagnosis. Retesting to resolve an HIV-inconclusive status must be conducted with the same testing strategy or algorithm and preferably at the same site.

3. **Retesting people with diagnosed or presumptive TB with ongoing risk of acquiring HIV, including PrEP users.** While most people who test HIV-negative do not require retesting, certain population groups may need annual or more frequent retesting. In low HIV burden settings, one lifetime HIV test is sufficient for most people when there is no ongoing risk. Retesting people who are HIV-negative is only for people with ongoing HIV-related risk. In most settings, key populations require retesting at least annually. More frequent retesting every 3–6 months may be cost effective in some settings. In certain conditions and situations, individuals who have tested negative for HIV in the past can also be advised to retest. This includes, inter alia, people with presumptive or diagnosed TB and individuals with recent HIV risk exposure. Individuals from specific groups such as those receiving pre-exposure prophylaxis and pregnant women in high HIV burden settings are also encouraged to be retested. For example, people taking PrEP should receive quarterly testing, and pregnant women in high HIV burden settings should be tested at the first antenatal care visit and in the third trimester.

4. **Retesting to re-engage in treatment and care.** In some situations, people with known HIV status may retest to check or come to terms with their diagnosis. For others, this is a way to initiate or re-engage in care. In all these situations it is important that providers offer support and deliver messages that will address concerns about their diagnosis, build trust, and encourage their successful linkage to treatment. Retesting to re-engage in treatment and care follows the same testing strategy as shown in Fig. 4.1.

4.1.4 CD4 testing

All people with HIV who enter or re-enter care should receive a CD4 cell count test at treatment baseline and as indicated for people who are clinically unstable or have advanced HIV disease (AHD)[5] *(17)*. CD4 cell count is the best predictor for HIV disease status, clinical staging, and immediate risk of death and should thus be used to identify those who have AHD. If viral load testing is not routinely available, CD4 count and clinical monitoring should be used to diagnose treatment failure *(17)*. Further guidance on monitoring the response to ART and treatment failure can be found in the *Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach (17)*.

Where possible, people living with HIV admitted to hospital or presenting to care due to serious illness should have their CD4 cell count measured. CD4 cell counts are useful to identify people who could benefit from testing for cryptococcal infection, and to help guide diagnosis and clinical management. CD4 cell counts can also help determine how likely it is that illness is due to IRIS. For people established on ART, a low CD4 cell count can be an indicator of treatment failure (which should be confirmed by viral load monitoring) and is also useful to determine whether prophylaxis for opportunistic infections is needed. Point-of-care CD4 technologies based on flow cytometry can provide results within a few minutes. Several rapid tests based on a lateral flow assay to identify patients with <200 cells/mm^3 are WHO prequalified *(139)*.

Viral load testing, where available, is indicated in any patient who is established on ART in order to identify treatment failure *(17)*. It is recommended that routine viral load monitoring be conducted after 6 months, 12 months and then every 12 months thereafter if the person is established on ART, to synchronize with routine monitoring and evaluation reporting.

[5] For adults and adolescent, advanced HIV disease is defined as CD4 cell count <200 cells/mm^3 or WHO stage 3 or 4 event. See: Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy, July 2017 (https://apps.who.int/iris/handle/10665/255884, accessed 31 August).

4.2 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). (20)*
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] *(21)* **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). (10, 17)*
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). (17)*
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). (17)*

WHO recommends that all people with AHD should receive a package of interventions including screening, treatment and/or prophylaxis for major opportunistic infections, rapid ART initiation and intensified adherence support interventions, as listed in Annex 4. Several of these interventions are outlined in other parts of this operational handbook, such as the use of TB screening and diagnosis, including with LF-LAM, the provision of TPT, initiation of ART, and provision of co-trimoxazole prophylaxis. Yet, there are further elements of the AHD package of care that could be integrated within services for HIV-associated TB, including interventions to address cryptococcal disease, as well as histoplasmosis where the epidemiology indicates.

Antiretroviral therapy greatly improves the survival rate and the quality of life of people with HIV-associated TB, prevents HIV transmission and is central to HIV and TB treatment and prevention. ART is recommended for all people living with HIV regardless of WHO clinical stage and CD4 cell count. This section relates to specific considerations for ART initiation among people with diagnosed or presumptive TB. For details on ART regimens, see the latest WHO guidance on ART: WHO *Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach (17)*.

4.2.1 Rapid ART initiation, including among people with HIV and TB symptoms

WHO guidelines recommend initiating ART within 7 days after HIV diagnosis and that people with advanced HIV disease are given priority for assessment and ART initiation. The guidelines further recommend offering ART initiation on the same day to people who are ready to start *(17)*. However, immediate ART initiation is contraindicated among people living with HIV who may have central nervous system infections with risk of life-threatening IRIS, such as TB meningitis or cryptococcal meningitis (see Box 4.3).

People presenting with HIV for the first time or those returning to HIV care should have their history taken and undergo clinical examination to evaluate for TB and other opportunistic infections before rapid ART is offered. Tuberculosis symptoms are common among people with HIV. This should not be a reason to delay start of ART *(17)*. Evidence from a systematic review which included four randomized controlled trials, found that 7–47% of people living with HIV presenting for same-day ART had TB symptoms *(140-144)*. Very little information is available on the potential harm of same-day ART initiation in the presence of TB symptoms; however, the review supported the feasibility of this approach. Experience in implementing rapid ART initiation among people living with HIV with TB symptoms (except for TB meningitis) in countries such as Malawi, also suggests that this approach is feasible *(145)*. Therefore, countries may consider initiating ART among people living with HIV who present signs and symptoms suggestive of TB, except for those with symptoms suggestive of meningitis,[6] while rapidly investigating for TB, with close follow-up within 7 days to initiate TB treatment if TB is confirmed *(17)*. The approach to rapid ART initiation must include an assessment for and related clinical management of advanced HIV disease.

4.2.2 ART initiation in people with HIV-associated TB

Since 2021, WHO has recommended that ART is initiated as soon as possible and within 2 weeks of starting TB treatment for all people with HIV-associated TB who are not on ART, regardless of CD4 cell count, with the exception of people with signs and symptoms of meningitis *(17)*. Caution is needed with people living with HIV with TB meningitis, as detailed in Box 4.3, as evidence shows that earlier ART is associated with more severe adverse events when compared with initiation of antiretroviral therapy 2 months after the start of TB treatment among people with HIV-associated TB meningitis *(146)*. ART should therefore be delayed for at least 4 weeks (and initiated within 8 weeks) after treatment for TB meningitis is initiated. Corticosteroids should be provided as an adjuvant treatment for TB meningitis. Furthermore, data are limited on the provision of ART to people with MDR-TB within 2 weeks, but initiation of ART in this population is recommended as soon as possible, and at most within 8 weeks. Fig. 4.3 summarizes the time frame for ART initiation among people with TB.

Box 4.3 ART initiation among people with signs and symptoms of meningitis

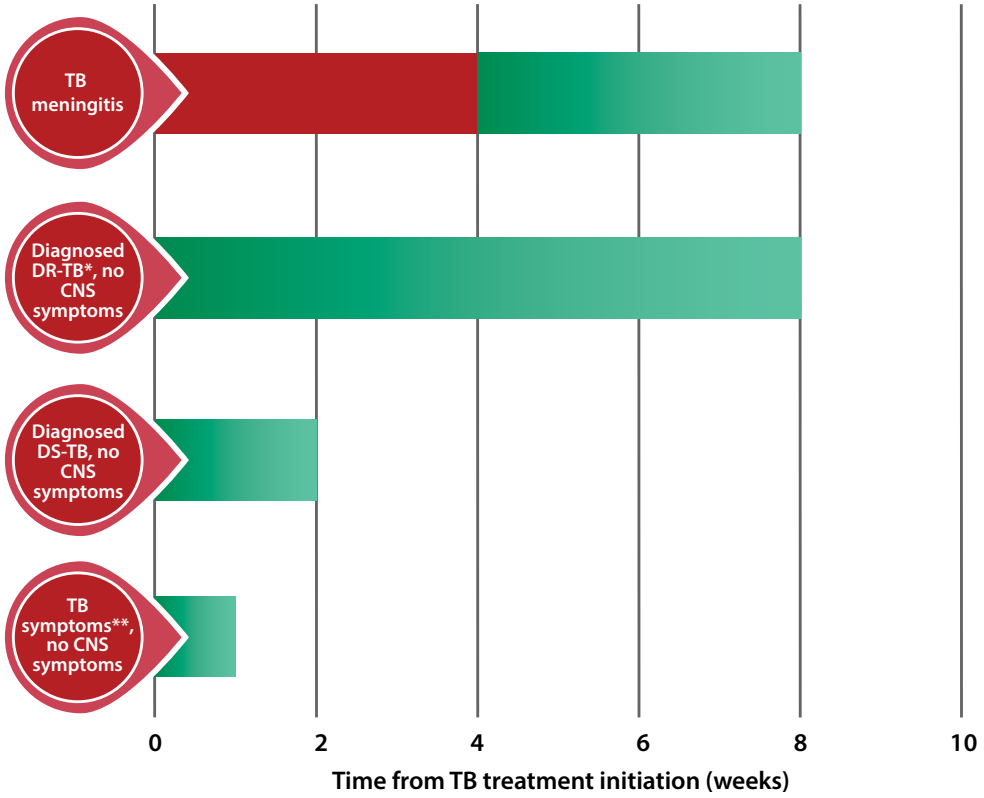
People living with HIV with TB meningitis, who start ART within 7 days of initiating TB treatment, experience a higher rate of more severe adverse events than those initiating antiretroviral therapy 2 months after the start of TB treatment. Furthermore, earlier ART is associated with increased mortality for people with cryptococcal meningitis.

- ➔ Based on expert opinion, ART should be delayed by at least 4 weeks (and initiated within 8 weeks) after TB treatment is initiated for TB meningitis, due to safety concerns *(21)*.
- ➔ Corticosteroids should be considered for adjuvant treatment of TB meningitis.[a]
- ➔ ART should be delayed 4–6 weeks following initiation of treatment for cryptococcal meningitis. Use of steroids is not recommended.[b]

Sources: [a] *WHO consolidated guidelines on tuberculosis. Module 4: Treatment. Drug-susceptible tuberculosis treatment (14)*
[b] *Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy (20)*

[6] Common signs and symptoms of meningitis include stiff neck, high fever, sensitivity to light, confusion, headaches and vomiting (https://www.who.int/news-room/fact-sheets/detail/meningitis).

Fig. 4.3. Time frame for ART initiation



ART: antiretroviral therapy; CNS: central nervous system; DR-TB: drug-resistant tuberculosis; DS-TB: drug-susceptible tuberculosis; TB: tuberculosis

* Currently, there are limited data to support ART start for people with DR-TB within 2 weeks. However, ART should be started as soon as possible.

** ART initiation may proceed while rapidly investigating for TB, with close follow-up within seven days to initiate TB treatment if a diagnosis of TB is made.

Tables 4.1 and 4.2 summarize current WHO recommendations for first-line and second-line ART regimens. For further details, see the latest WHO guidelines (currently the *Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach) (17)*.

Table 4.1. First-line ART regimens for adults and adolescents *(17)*

Population	Preferred	Alternative
Adults and adolescents	TDF + 3TC (or FTC) + DTG[a,b]	TDF + 3TC + EFV 400 mg[b]

[a] WHO *Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, 2021 update* discusses toxicity considerations for pregnant and breastfeeding women.

[b] EFV-based ART should not be used in settings with national estimates of pretreatment resistance to NNRTIs of 10% or higher. In settings with high HIV drug resistance prevalence and where DTG is unavailable or unsuitable due to toxicity, a boosted PI-based regimen (PI/r) should be used. The choice of PI/r will depend on clinical and programmatic characteristics. Among PI/r options, only LPV/r with adjusted dosage is suitable for people using TB regimens containing rifampicin. Alternatively, HIV drug resistance testing should be considered, where feasible, to guide first-line regimen selection.

Table 4.2. Second-line ART regimens for adults and adolescents *(17)*

Population	Failing first-line regimen	Preferred second-line regimen	Alternative second-line regimen
Adults and adolescents[a]	TDF[b] + 3TC (or FTC) + DTG[c]	AZT + 3TC + ATV/r (or LPV/r)	AZT + 3TC + DRV/r[d]
	TDF + 3TC (or FTC) + EFV (or NVP)	AZT + 3TC + DTG[c]	AZT + 3TC + ATV/r (or LPV/r or DRV/r)[d]
	AZT + 3TC + EFV (or NVP)	TDF[b] + 3TC (or FTC) + DTG[c]	TDF[b] + 3TC (or FTC) + ATV/r (or LPV/r or DRV/r)[d]

3TC: lamivudine; ATV/r: atazanavir/ritonavir; AZT: zidovudine; DRV/r: darunavir/ritonavir; DTG: dolutegravir; EFV: efavirenz; FTC: emtricitabine; LPV/r: lopinavir/ritonavir; NVP: nevirapine; TDF: tenofovir disoproxil fumarate

[a] Sequencing if a PI is used in first-line ART: TDF + 3TC (or FTC) + ATV/r (or LPV/r, or DRV/r, depending on programmatic considerations) in first-line ART should be sequenced to AZT + 3TC + DTG in second-line ART.

[b] See WHO *Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, 2021 update* for HIV drug resistance considerations when using TDF + 3TC + DTG in second-line ART following failure of TDF + 3TC (or FTC) + EFV.

[c] TAF can be used as an alternative NRTI for children and in special situations for adults (see section on TAF in first-line ART, in WHO *Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, 2021 update*).

[d] RAL + LPV/r can be used as an alternative second-line regimen for adults and adolescents.

People with HIV-associated TB should be closely followed up to monitor for adverse events related to co-treatment. IRIS and other adverse events require prompt assessment and management, especially among children and pregnant or breastfeeding women. IRIS is more common in people with TB who have started on ART, with lower CD4 cell counts, but with the exception of central nervous system IRIS (see Box 4.3), it is usually mild, self-limited and should normally not be a reason to interrupt ART *(147, 148)*.

Drug–drug interactions may occur in people with HIV-associated TB and people with HIV who receive TPT, in particular when rifampicin-based regimens are used. As an example, rifampicin is known to lower plasma concentrations of the first-line antiretroviral drug dolutegravir. WHO therefore recommends adjusting the dose by offering 50 mg of dolutegravir twice per day (instead of a single daily dose of 50 mg). Key considerations for drug–drug interactions are described in Section 3.4 (TB treatment), whilst Section 3.5 (TB prevention) also gives an overview of drug–drug interactions between HIV and medicines used for TB treatment or prevention. To check for drug–drug interactions from a comprehensive list of antiretrovirals and co-medications the reader is directed to the University of Liverpool's HIV Drug Interactions Group resource (www.hiv-druginteractions.org/) and the associated Android and iOS apps (search "HIV iChart").

HIV programmes and TB programmes should ensure that people with TB who receive a new diagnosis of HIV are offered ART as early as possible, preferably within integrated services or within TB health facilities in settings with a high burden of HIV and TB. Referral to HIV services remains an alternative but relies on sound referral systems and the patient's ability to afford other costs such as transport and the loss of wages. HIV programmes and TB programmes should work together to guarantee ART to all people with HIV-associated TB in as decentralized a manner as possible *(7)*.

A comprehensive package of prevention, diagnosis, treatment and care interventions should be provided to all people living with HIV. A continuum of care should also be provided to people living with HIV who are receiving or who have completed their antituberculosis treatment through integrated services or strengthened referral systems. Evidence has shown that linking TB and HIV prevention, diagnosis, treatment and care services may generate synergies, strengthen both programmes and scale up the delivery of these interventions to people with HIV-associated TB *(41)*.

Programmes should establish mechanisms for adequate monitoring, including pharmacovigilance and surveillance, for drug–drug interactions. For further guidance on this, please refer to the *Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach (17)*. Key considerations include adequate training of healthcare personnel and programme managers to deliver integrated TB and HIV services (cross-training), and HIV and maternal, newborn and child health services, including for children, adolescents and pregnant women; co-location of services and establishing an integrated supply chain, laboratory and information systems. Coordination between TB and HIV programmes to deliver these services is critical. Also needed are community engagement, patient education, engagement of adherence counsellors and social workers, and peer support for early recognition of IRIS and adverse events, and to support the retention of and adherence to co-treatment.

4.2.3 Co-trimoxazole prophylaxis

Co-trimoxazole is a fixed-dose combination of two antimicrobial agents (sulfamethoxazole and trimethoprim) used to treat or prevent a variety of bacterial, fungal and protozoan infections, including *Pneumocystis jirovecii* pneumonia, toxoplasmosis and malaria. Co-trimoxazole prophylaxis is a feasible, well-tolerated and inexpensive intervention to reduce HIV-related morbidity and mortality among people living with HIV and can be administered concomitantly with ART and TB treatments. Although co-trimoxazole has low rates of toxicity, skin rash (including Stevens-Johnson syndrome), reactions of the blood and blood-forming organs, and liver toxicity, have been reported *(149)*. WHO guidelines recommend providing lifelong co-trimoxazole prophylaxis to everyone living with HIV, regardless of CD4 cell count, in settings where severe bacterial infections or malaria are highly prevalent. This is an important consideration for linkage to ongoing treatment and care following completion of TB treatment.

Co-trimoxazole prophylaxis should be provided for people with HIV-associated TB, regardless of their CD4 cell count, as an integral component of the HIV care package. HIV programmes and TB programmes should establish a system to provide co-trimoxazole prophylaxis to all people living with HIV who have TB disease. Co-trimoxazole is an off-patent drug and is widely available in resource-limited settings *(17)*.

Given the importance of co-trimoxazole, TB and HIV programmes should work together to overcome any barriers to its provision, which may include supply chain and management issues leading to stockouts; imposing user charges for medication and/or monitoring; inadequate training, supervision and/or mentoring of healthcare workers; low coverage of HIV testing services; and lack of coordination across programmes.

4.2.4 Other opportunistic infections: cryptococcal disease and histoplasmosis

4.2.4.1 Cryptococcal disease

Cryptococcal disease causes severe morbidity among people living with advanced HIV disease and is a major contributor to disability and mortality *(20, 150-153)*. Up to 90% of HIV-related cryptococcal disease is cryptococcal meningitis *(151)*. A systematic review found a TB prevalence of 19% among people living with HIV testing positive for the cryptococcal antigen *(154)*. Early diagnosis and pre-emptive treatment of cryptococcal disease is key to reducing mortality among people living with HIV. Core aspects of testing and treatment for cryptococcal disease are summarized in Table 4.3.

Table 4.3. Testing and treatment for cryptococcal disease

	Population	Clinical considerations
Serum cryptococcal antigen test	Serum cryptococcal antigen test is recommended for adults and adolescents with signs and symptoms of cryptococcal meningitis or with a CD4 count <100 cells/mm^3; it should also be considered for persons with CD4 count <200 cells/mm^3	If serum cryptococcal antigen is positive, proceed to lumbar puncture and CSF cryptococcal antigen testing where available
CSF cryptococcal antigen test	Adults, adolescents with signs and symptoms of cryptococcal meningitis, or who have a positive serum cryptococcal antigen	If lumbar puncture is available and no contraindication to lumbar puncture For alternative diagnostic algorithms where rapid cryptococcal antigen test and/or lumbar puncture are not available, see the cryptococcal disease guidelines *(155)*
Cryptococcosis pre-emptive treatment	Adults and adolescents with serum cryptococcal antigen test positive but CSF cryptococcal antigen test negative	Maintenance treatment should continue until person is stable on ART with CD4 cell count >200 cells/mm^3
Cryptococcal disease treatment	Adults and adolescents with serum cryptococcal antigen test positive and CSF cryptococcal antigen test positive	The preferred induction regimen for adults, adolescents and children is a single high dose (10 mg/kg) of liposomal amphotericin B with 14 days of flucytosine (100 mg/kg per day divided into four doses per day) and fluconazole (1200 mg/daily for adults; 12 mg/kg per day for children and adolescents up to a maximum of 800 mg daily). Alternative regimens for settings where first-line induction regimen is unavailable are provided in the cryptococcal disease guidelines *(155)*

CSF: cerebrospinal fluid

Cryptococcal antigen screening

Adults and adolescents with advanced HIV disease should be screened for cryptococcal disease using serum, plasma or whole blood cryptococcal antigen testing. Everyone testing positive for cryptococcal antigen during screening should be carefully evaluated for signs and symptoms of meningitis; those presenting with signs or symptoms should have a lumbar puncture. Where feasible, those who test positive for serum cryptococcal antigen but who do not have signs or symptoms of meningitis should also have lumbar puncture, with CSF examination and cryptococcal antigen assay (or India ink if cryptococcal antigen assay is not available) to exclude cryptococcal meningitis *(33)*. When performing a lumbar puncture to assess for cryptococcal meningitis in people with presumed or diagnosed TB, samples may also be taken to assess other causes of meningitis, including TB meningitis.

Rapid cryptococcal antigen assay in CSF, serum, plasma or whole blood (depending on access to lumbar puncture) is preferred, based on the much higher diagnostic accuracy of these rapid cryptococcal antigen assays versus the India ink test and the fact that these rapid assays depend less on the healthcare provider's skills. Advantages of the lateral-flow assay over the latex agglutination assay include its rapid (<10 min) turnaround time, cost-effectiveness, minimal training requirements and laboratory infrastructure, no need for refrigerated storage and higher clinical and analytical sensitivity *(33)*.

Detailed guidance on screening and diagnostic algorithms for cryptococcal disease, depending on the availability of rapid cryptococcal antigen test and lumbar puncture, is outlined in the WHO *Guidelines for diagnosing, preventing and managing cryptococcal disease among adults, adolescents and children living with HIV (34)*.

Pre-emptive treatment of cryptococcal disease

All individuals who screen positive for serum cryptococcal antigen, but have a negative CSF cryptococcal antigen test, should receive pre-emptive antifungal therapy, consisting of fluconazole 800–1200 mg/day for adults and 12 mg/kg per day for adolescents for 2 weeks, followed by consolidation and maintenance fluconazole therapy, as per the treatment regimen *(33)*. When cryptococcal antigen screening is not available, fluconazole primary prophylaxis should be given to adults and adolescents living with HIV who have a CD4 count <100 cells/mm^3. This may also be considered at a higher CD4 cell count threshold of <200 cells/mm^3 *(33)*.

Treatment of cryptococcal meningitis

Treatment of cryptococcal meningitis consists of a 2-week induction phase, followed by an 8-week consolidation phase, and a maintenance phase to continue until immune reconstitution (CD4 >200 cells/mm^3) and suppression of viral load on ART. Steroids should not routinely be used for people with cryptococcal meningitis due to an increase in adverse events and delayed clearance of fungus from CSF *(156)*. Further guidance on treatment regimens is provided in the WHO *Guidelines for diagnosing, preventing and managing cryptococcal disease among adults, adolescents and children living with HIV (155)*.

Service delivery

Given its high morbidity among people with HIV, and the high rate of TB among people screening positive for cryptococcal antigen, it is important to address cryptococcal disease in people presenting with advanced HIV disease. Depending on the infrastructure and resources available, TB services offer an opportunity to expand access to screening, diagnosis, treatment and prevention of cryptococcal disease in both inpatient and outpatient settings.

The relative advantage of various approaches to screening for cryptococcal disease should be considered according to context. In resource-limited settings with limited laboratory infrastructure, task sharing has been found to overcome human resource limitations. A study in Lesotho found that cryptococcal antigen screening by lay counsellors followed by pre-emptive fluconazole treatment for asymptomatic people with a positive cryptococcal antigen screening test, or referral to hospital for those with symptomatic cryptococcal disease, was feasible *(157)*. This suggests that integration of screening and pre-emptive treatment for cryptococcal disease within TB services may also be feasible, and may be the preferred approach, especially when point-of-care CD4 cell count is available, enabling same-day initiation of fluconazole among those who screen cryptococcal antigen-positive.

4.2.4.2 Histoplasmosis

Histoplasmosis has a high endemicity in certain areas of the Americas, where it is most frequently encountered *(16)*. It is also diagnosed in certain countries of Asia (China, India, Indonesia, Japan, Malaysia, Singapore, Thailand, and Viet Nam) and Africa (Central African Republic, Congo, Côte d'Ivoire, Democratic Republic of the Congo, Gambia, Guinea-Bissau, Liberia, Senegal, South Africa, and Uganda) *(16)*. Among people living with HIV, the most frequent clinical presentation of this disease is disseminated histoplasmosis. Symptoms of disseminated histoplasmosis are nonspecific and may be indistinguishable from those of other infectious diseases, especially TB, thus complicating diagnosis and treatment *(158)*.

Lack of access to appropriate antifungal therapies, in vitro diagnostics for rapid detection of histoplasmosis and co-occurrence with TB, may affect clinical outcomes and contribute to the high mortality of people living with HIV *(159, 160)*. If histoplasmosis is clinically suspected, WHO recommends diagnostic testing using antigen detection assays *(16)*.

It is important to review potential ART options for people with TB and histoplasmosis and to make necessary adjustments as recommended in the *Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach (17)*. Because of the potential decrease in itraconazole levels related to some types of antiretroviral therapy, itraconazole drug levels should be monitored if possible *(161)*. When histoplasmosis is not controlled because of interactions with rifampicin and itraconazole, clinicians may consider extending the duration of amphotericin B induction therapy, depending on the local context; other options include once-weekly courses of amphotericin B, increasing the itraconazole dose and monitoring the blood level and toxicity, as well as considering using other azole drugs (posaconazole, voriconazole, or fluconazole).

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 anti-TB drugs. When possible, antiretroviral resistance genotyping may assist clinical decisions. Itraconazole serum level testing may not be available in some areas.

4.3 HIV prevention

4.3.1 Combination HIV prevention for people with diagnosed or presumed TB

National TB programmes should implement comprehensive HIV prevention strategies for their clients and their partners, or they should establish community and referral linkages as necessary. HIV preventive interventions by TB programmes or effective referral of people with TB to HIV programmes has been successfully implemented in many countries *(162-164)*.

Combination prevention programmes use a mix of evidence-based biomedical, behavioural and structural interventions to meet the current HIV prevention needs of individuals and communities, to have the greatest possible impact on reducing the number of people newly infected. Well-designed combination prevention programmes need to reflect the local HIV epidemiology and context. They should focus resources to reach populations at greatest HIV risk with effective, acceptable prevention to address both immediate risks and underlying vulnerabilities. Combination prevention mobilizes communities, civil society, the private sector, governments, and global resources in a collective undertaking. It requires and benefits from enhanced partnership and coordination and should incorporate mechanisms for learning, capacity-building and flexibility, to permit continual improvement and adaptation to the changing epidemiological environment. This section summarizes key aspects of HIV prevention, which will also benefit people with presumed and diagnosed TB. A comprehensive overview of HIV prevention interventions is provided in the *Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach (17)*.

To maximize HIV prevention for people with diagnosed TB and their partners, TB programmes should collaborate with HIV programmes and affected communities. Key considerations are listed in Box 4.4.

Box 4.4 Key considerations for expanding access to HIV prevention for people with TB and their partners:

1. include HIV prevention for people with TB, and related services, products, and within joint planning, monitoring and resource mobilization;
2. build the capacity of personnel working with people with TB, people living with HIV and key populations, to assess risk factors for HIV infection and transmission and to provide comprehensive information and services to their clients to minimize their risks;
3. build capacity and put in place measures to ensure access in the same facility or through referral, to combination HIV prevention strategies for people with TB and their partners, including for marginalized populations such as prisoners, people who use drugs, and migrants;
4. provide recurrent training and sensitization in collaboration with affected communities, to ensure that healthcare workers have the skills and understanding to provide services for people from key populations based on all persons' right to health, confidentiality and non-discrimination; and
5. put in place mechanisms and build capacity to assure fidelity and accountability to the 5 Cs for HIV testing services, including for healthcare providers and for the reduction of occupational and nosocomial exposure to HIV infection in their services.

Source: WHO policy on collaborative TB/HIV activities. Guidelines for national programmes and other stakeholders. Geneva: World Health Organization; 2012 (7)

4.3.1.1 Biomedical interventions for HIV prevention

Antiretroviral drugs play a key role in HIV prevention. People taking ART who achieve viral suppression (<200 copies/mL) do not transmit HIV to sexual partners. ART also plays a key role in the prevention of vertical (mother to child) transmission of HIV during pregnancy, delivery and breastfeeding. Antiretroviral drugs taken by people without HIV as PrEP and post-exposure prophylaxis are both highly effective in preventing HIV acquisition.

Harm reduction for people who inject drugs is provided through a range of interventions and services that can critically reduce transmission of HIV as well as other blood-borne viruses such as hepatitis C. Needle and syringe programmes are highly effective in reducing HIV and hepatitis C transmission through injecting drug use *(165)*. Opioid agonist maintenance therapy with methadone or buprenorphine is the most effective form of treatment for opioid dependence and has the additional benefit of effectively reducing HIV transmission through injecting drug use. OAMT is also effective in improving ART uptake and adherence for people dependent on opioids *(126, 166)*. Individuals receiving methadone or buprenorphine together with rifampicin should, however, be monitored closely, and those who experience opioid withdrawal should have their methadone or buprenorphine dose adjusted according to their needs. Rifabutin can be used as an alternative to rifampicin; rifabutin has not been documented to significantly affect buprenorphine or methadone levels *(96)*. For people who inject drugs during sex ("chemsex"), integrated sexual health, mental health and substance use services, with linkages to evidence-based prevention interventions, should be provided. National TB programmes should coordinate closely with HIV services and harm reduction services to ensure continued access to HIV prevention during and after TB treatment. Such linkages can be facilitated with the help of NGOs and community-led organizations.

Other biomedical interventions that reduce HIV risk practices and/or the probability of HIV transmission per contact event include male and female condoms and condom-compatible lubricant *(167-169)*, as well as voluntary medical male circumcision *(170)*. In healthcare settings, transmission of HIV can be prevented through primary prevention measures such as standard precautions, injection safety, blood safety and safe waste disposal, as well as secondary prevention measures such as occupational post-exposure prophylaxis *(7)*.

4.3.1.2 Behavioural and structural interventions for HIV prevention

Behavioural interventions can reduce the frequency of potential transmission events. Targeted information and education programmes use various communication approaches, such as school-based comprehensive sexuality education, peer counselling and community-level and interpersonal counselling (including brief interventions) to disseminate messages. Recognition is growing that social media and mobile technology are important tools that can be integrated in HIV prevention programmes and can be particularly critical in providing information and prevention services to key populations.

Enabling interventions to address structural barriers to accessing services may increase access to, uptake of and adherence to prevention, as well as testing and treatment services. Such interventions address the critical social, legal, political and enabling environment that contribute to HIV transmission, including legal and policy reform towards decriminalizing behaviour (such as drug use and same-sex sex) and sex work to reduce stigma and discrimination (including in the health sector), promoting gender equality and preventing gender-based violence and violence towards key populations, economic and social empowerment, access to schooling and supportive interventions designed to enhance referrals, adherence, retention and community mobilization.

WHO recommends a comprehensive package of evidence-based HIV-related interventions and services for all key populations. The package comprises health interventions and a set of critical enablers required for successful implementation of programmes and access for the five key populations, as outlined in Table 2.2 (Chapter 2).

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Annex 1. Monitoring and evaluation of collaborative TB/HIV activities

Ongoing monitoring of collaborative TB/HIV activities and evaluation of their impact is critically important for driving scale-up and for monitoring progress and identifying gaps in implementation. This requires an effective and efficient monitoring and evaluation system.

Table A1.1 summarizes the core indicators recommended for monitoring and evaluating collaborative TB/HIV activities. The indicators are categorized as core indicators for global and national monitoring and reporting, and core indicators for national-level monitoring and reporting only.

Table A1.1 Summary of indicators for monitoring and evaluating collaborative TB/HIV activities

A. Core global and national indicators	
These are essential indicators to monitor and report progress at both global and national level.	
Source (indicator reference)	**Indicator description**
Global Tuberculosis Programme[a]	1. Percentage of people diagnosed with a new episode of TB whose HIV status was documented
Global Tuberculosis Programme[a]	2. Percentage of people living with HIV diagnosed with a new episode of TB who were on or newly enrolled on antiretroviral treatment
Global Tuberculosis Programme[a]	3. Percentage of people living with HIV diagnosed with TB (rifampicin-susceptible or unknown) who were started on a TB treatment regimen designed to treat rifampicin-susceptible TB.
Global Tuberculosis Programme[a]	4. Percentage of people living with HIV diagnosed with TB (rifampicin-susceptible or unknown) with a treatment outcome in each of the following categories out of those diagnosed with TB (rifampicin-susceptible or unknown): success (cured + treatment completed); treatment failed; died: lost to follow-up; not evaluated
UNAIDS[b] (GAM 7.7)	5. Percentage of people living with HIV estimated to have incident tuberculosis (TB) that received treatment for both TB and HIV
WHO HIV[c] (TBH.4); UNAIDS[b] (GAM 7.8)	6. Percentage of people living with HIV newly enrolled on HIV treatment diagnosed with tuberculosis (TB) disease during the reporting period
WHO HIV[c] (TBH.1); UNAIDS[b] (GAM 7.9)	7. Percentage of people living with HIV (currently enrolled and newly enrolled) on ART who started TB preventive treatment during the reporting period 8. Percentage of people living with HIV currently enrolled on ART who have started TB preventive treatment prior to the reporting period
WHO HIV[c] (TBH.2); UNAIDS[b] (GAM 7.10)	9. Percentage of people living with HIV currently on ART initiating tuberculosis (TB) preventive treatment who completed a course of TB preventive treatment

B. Core national indicators

In addition to the core indicators in section A, the following are also core indicators essential for national-level monitoring and reporting. The indicators DFT.1–DFT.5 are recommended for use in countries with a high TB/HIV burden but may be adopted in any country.

Source (indicator reference)	Indicator description
WHO HIV[c] (TBH.3)	10. Percentage of people living with HIV with TB symptoms who receive a rapid molecular test, for example, Xpert MTB/RIF, as a first test for diagnosis of TB
WHO HIV[c] (DFT.1)	11. Percentage of people living with HIV newly initiated on ART who were screened for TB
WHO HIV[c] (DFT.2)	12. Percentage of people living with HIV newly initiated on ART who were screened for TB symptoms[d] and who screened positive
WHO HIV[c] (DFT.3)	13. Percentage of people living with HIV newly initiated on ART and screened positive for TB symptoms[d] who then are tested for TB
WHO HIV[c] (DFT.4)	14. Percentage of people living with HIV newly initiated on ART and tested for TB who are diagnosed with TB disease
WHO HIV[c] (DFT.5)	15. Percentage of people living with HIV newly initiated on ART and diagnosed with TB who initiated TB treatment

[a] Global Tuberculosis Programme online data collection system, and Consolidated guidance on tuberculosis data generation and use. Module 1: Tuberculosis surveillance. Geneva: World Health Organization; 2023.
[b] UNAIDS Global AIDS Monitoring Online Reporting Tool.
[c] Consolidated HIV strategic information guidelines: driving impact through programme monitoring and management. Geneva: World Health Organization; 2023.
[d] Countries may choose to alter the wording of this indicator to allow data capture on other TB screening tools

Core indicators for global and national monitoring and reporting

These indicators measure the efforts made by countries towards prevention, early detection and prompt treatment of HIV-associated TB along with its impact on mortality. Systematic measurement and reporting of these indicators is critical for monitoring the coverage of services and impact of collaborative TB/HIV activities nationally, and also provides insights into global progress. This information can be used in the process of global and national strategy development, programme planning, and resource mobilization and allocation. The data elements required for documentation of these indicators should be routinely captured in the national health management information system or the management information system of the national TB programme (NTP) or national AIDS control programme (NACP). They should be periodically reported at national and subnational level and consolidated annually for global- and national-level reporting.

Core indicators for national-level monitoring and reporting

In addition to the indicators mentioned above, a set of core indicators is required for routine monitoring of implementation of collaborative TB/HIV activities at national level, particularly the quality of care provided. Ongoing monitoring of these indicators is necessary for effective programme management at national, subnational and facility level, as they help in identification of weaknesses in programme implementation and thus facilitate improvement. Data required to measure these indicators should be captured systematically on a regular basis and should be an integral part of the national health management information system or the management information system of the NTP and NACP. The indicators referenced DFT.1–DFT.5 help to measure the cascade of TB diagnosis and care and are recommended for the 30 high TB/HIV burden countries as identified by WHO. However, these indicators may also be used by other countries.

Other indicators to support quality delivery of TB/HIV programme and services can be found in *A guide to monitoring and evaluation for collaborative TB/HIV activities – 2015 revision*.

Annex 2. Methods for algorithms for diagnosis of TB in people living with HIV

Algorithms

We modelled the accuracy of four algorithms for the diagnosis of TB in people living with HIV, using WHO-recommended screening and diagnostic tests. Each algorithm was composed of one or more screening tools and one or more confirmatory (diagnostic) tests. Algorithms with more than one screening tool could use parallel screening, in which a positive screen via either tool would prompt confirmatory testing; or sequential screening, in which individuals must screen positive by both tools in order to undergo confirmatory testing. The following assumptions were used for each algorithm:

- All persons in the population will undergo screening and receive a screening result.
- Persons who screen negative will not undergo further evaluation for TB.
- Persons who screen positive will undergo confirmatory testing and receive a test result.
- Persons with a positive confirmatory test result will receive a diagnosis of TB.
- Persons with a negative confirmatory test result will not receive a diagnosis of TB.
- Populations of people with HIV who undergo TB screening

We considered five populations with HIV who would undergo TB screening: 1) people with advanced HIV disease (CD4 cell count <200 cells/μL); 2) people without advanced HIV disease (CD4 cell count >200 cells/μL); 3) outpatients not on ART; 4) outpatients on ART; and 5) inpatients.

Tuberculosis screening tools

We considered the WHO-recommended TB screening tools for people living with HIV *(1, 2)* comprising the WHO four symptom screen, chest radiography for any abnormality, C-reactive protein with a cut off of >5 mg/L, and molecular WHO-recommended rapid diagnostic tests, drawing from data on Xpert MTB/RIF. Sensitivity and specificity estimates for each screening tool were obtained from two systematic reviews and meta-analyses of TB screening in outpatients *(3)* and inpatients *(4)* living with HIV that used data from a WHO-commissioned individual participant data analysis. These reviews informed the *WHO consolidated guidelines on tuberculosis. Module 2: screening – systematic screening for tuberculosis disease*.

Tuberculosis diagnostic tests

We considered two WHO-recommended TB diagnostic tests for people living with HIV *(5, 6)*, namely, mWRD tests and LF-LAM assays. Although neither test has 100% sensitivity, clinical diagnosis was not considered for those testing negative. Sensitivity and specificity estimates for mWRD were obtained from a systematic review and meta-analysis of the accuracy of Xpert MTB/RIF in people living with HIV *(7)* that informed the *WHO consolidated guidelines on tuberculosis. Module 3: diagnosis – rapid diagnostics for tuberculosis detection*. The incremental yield of LF-

LAM over mWRD was estimated based on a literature review *(8-11)* and was used to estimate the combined sensitivity of LF-LAM and mWRD.

Accuracy of algorithms

Diagnostic accuracy was calculated for each algorithm considering a hypothetical population of 1000 people living with HIV who were screened for TB. The algorithms referenced a range of pre-test probabilities of TB from 1% to 30%, taking into account the specifics of each subpopulation. For each algorithm, we calculated the number of true positives, false positives, false negatives, and true negatives detected; the number requiring secondary screening (if applicable); and the number requiring confirmatory (diagnostic) testing. We calculated the net sensitivity and specificity of each algorithm as follows:

- **Net sensitivity:** the number of true positives detected through confirmatory testing divided by the number of persons with TB disease undergoing screening.
- **Net specificity:** the number of true negatives detected through confirmatory testing divided by the number of persons without TB disease undergoing screening.

Tables A2.1–A2.4 show the accuracy of the algorithms for the different subgroups within the range of pre-test probabilities.

Costing of the algorithms

Costing was also calculated using a hypothetical population of 1000 people living with HIV who were screened for TB, with a 10% pre-test probability for all algorithms and a 1% pre-test probability of TB for all algorithms, with the exception of Algorithm 4 for medical inpatients with HIV and for people with advanced HIV disease who are seriously ill. Five cost parameters were estimated for each algorithm and population:

- **Cost of screening:** calculated as the number screened multiplied by the unit cost of the screening tool(s).
- **Cost of testing:** calculated as the number tested multiplied by the unit cost of mWRD plus the unit costs of LF-LAM.
- **Total cost:** calculated as the cost of screening plus the cost of testing.
- **Cost per TB diagnosis:** calculated as the total cost divided by the number of diagnoses of TB disease (true positives and false positives).
- **Cost per true TB diagnosis:** calculated as the total cost divided by the number of true positive diagnoses of TB disease.
- **Cost difference:** calculated as the difference in cost for each algorithm, with reference to Algorithm 1.

Unit cost estimates were obtained from the Value TB project, which collected data on costs of TB interventions per episode from 78 health facilities across five countries (Ethiopia, Georgia, India, Kenya and Philippines) *(12-16)*. For these analyses, we utilized median, low, and high unit cost estimates from the countries surveyed. The median cost estimates for the different algorithms to be used among the different subgroups of people living with HIV are provided in Tables A2.5 and A2.6.

Limitations

This analysis has several limitations. First, algorithm accuracy estimates were based on diagnostic accuracy estimates used to inform WHO TB screening and diagnostic guidelines *(3, 4, 7)*. Estimates for the accuracy of mWRD were not available for every population or screening tool, and therefore results may be less precise for some populations. Furthermore, estimates of the incremental yield of LF-LAM over mWRD were limited. Additional systematic reviews of accuracy of mWRD in different HIV populations and the incremental yield of LF-LAM over mWRD would help improve algorithm estimates.

Second, algorithm estimates assumed that all individuals who screen positive will undergo mWRD testing and receive a result. However, in practice, many individuals do not receive a test result, for a variety of reasons. Providers may not refer all individuals who screen positive for confirmatory testing, and some individuals who are referred may not present for testing due to barriers to seeking care. Furthermore, many individuals living with HIV have challenges producing sputum, substantially affecting the yield of sputum-based tests; in addition, the accuracy and yield of sputum-reliant tests is affected by sputum quality. Given these limitations, the true yield of the algorithms is likely lower than the estimates presented here. Importantly, the incremental yield of urine LF-LAM will be higher in populations with low sputum mWRD diagnostic yield *(17)*. Future analyses using diagnostic yield estimates rather than diagnostic accuracy estimates may be useful for TB and HIV programmes developing recommendations for TB screening and diagnostic algorithms for people living with HIV.

Third, costing estimates are based on data from a survey of five countries. Unit costs vary widely globally, and the costs used for analyses here may not be representative of costs in many settings. However, estimates presented here are useful to compare relative differences across algorithms and populations. In addition, cost estimates do not include costs associated with missed episodes of TB, treatment-associated costs or broader health system costs. In practice, algorithms with lower sensitivity may incur costs associated with management of missed TB, while algorithms with higher sensitivity may be associated with higher costs related to treatment of those diagnosed with TB.

Conclusion

Screening and diagnosis of TB in people with HIV is a global health priority, yet there are notable challenges in implementing effective, high-yield, and cost-effective screening and diagnostic algorithms in health-care settings worldwide. In this analysis, we estimated the accuracy and costs of four algorithms for TB screening and diagnosis in people with HIV. Accuracy estimates varied across algorithms, and within algorithms between the populations undergoing screening. In addition, costs varied substantially, and were affected by both cost and accuracy of the screening tool used in each algorithm. HIV and TB programmes should consider the populations being targeted for screening, level of health-care system where screening will be conducted, and resource availability when making local recommendations for TB screening and diagnosis for people with HIV.

RESULTS TABLES

Table A2.1. Algorithm 1

Subgroup	Alg. Sens	Alg. Spec	% Cases missed	PTP	Screening						N tested	Testing						NNS	NNT
					TP	FP	TN	FN	PPV	NPV		TP	FP	TN	FN	PPV	NPV		
CD4 <200	73.8%	98.6%	26.2%	5%	43	285	665	7	6.1	97.6	708	37	652	13	6	73.5	99.1	28	20
				10%	86	270	630	14	12.0	95.1	716	74	617	13	12	85.4	98.1	14	10
				15%	129	255	595	21	17.8	92.4	724	111	583	12	18	90.3	97.0	10	7
				20%	172	240	560	28	23.5	89.6	732	148	549	11	24	93.0	95.8	7	5
				30%	258	210	490	42	34.5	83.3	748	222	480	10	36	95.8	92.9	5	4
CD4 >200	59.2%	99.0%	40.8%	1%	7	475	515	3	1.3	99.4	522	6	505	10	1	36.5	99.8	169	89
				5%	35	456	494	16	6.5	96.7	529	30	484	10	5	75.0	99.0	34	18
				10%	69	432	468	31	12.8	93.3	537	59	459	9	10	86.4	97.9	17	10
Outpatients not on ART	72.1%	98.7%	27.9%	1%	8	366	624	2	1.3	99.6	632	7	611	12	1	36.6	99.8	139	88
				5%	42	352	599	8	6.6	97.8	641	36	587	12	6	75.1	99.0	28	18
				10%	84	333	567	16	12.9	95.4	651	72	556	11	12	86.4	97.9	14	10
Outpatients on ART	45.5%	99.4%	54.5%	1%	5	693	297	5	1.8	99.3	302	5	291	6	1	43.4	99.7	220	67
				5%	27	665	285	24	8.5	96.6	312	23	279	6	4	80.0	98.7	44	14
				10%	53	630	270	47	16.4	93.1	323	46	265	5	7	89.4	97.2	22	8
Inpatients	82.4%	98.2%	17.6%	5%	48	105	846	2	5.4	98.1	894	41	829	17	7	70.9	99.2	25	22
				10%	96	99	801	4	10.7	96.1	897	82	785	16	14	83.7	98.3	13	11
				15%	144	94	757	6	16.0	94.0	901	124	741	15	20	89.1	97.3	9	8
				20%	192	88	712	8	21.2	91.7	904	165	698	14	27	92.0	96.3	7	6
				30%	288	77	623	12	31.6	86.5	911	247	611	12	41	95.2	93.7	5	4

PTP: pre-test probability; TP: true positive; FP: false positive; TN: true negative; FN: false negative; PPV: positive predictive value; NPV: negative predictive value; NNS: number needed to screen; NNT: number needed to treat

Table A2.2 Algorithm 2

Subgroup	Alg. Sens	Alg. Spec	% Cases missed	PTP	Screening						N tested	Testing						NNS	NNT
					TP	FP	TN	FN	PPV	NPV		TP	FP	TN	FN	PPV	NPV		
CD4 <200	80.7%	98.3%	19.3%	5%	47	133	817	3	5.4	97.8	864	40	801	16	7	71.2	99.2	25	22
				10%	94	126	774	6	10.8	95.5	868	81	759	15	13	83.9	98.3	13	11
				15%	141	119	731	9	16.2	93.0	872	121	716	15	20	89.2	97.3	9	8
				20%	188	112	688	12	21.5	90.3	876	161	674	14	27	92.1	96.2	7	6
				30%	282	98	602	18	31.9	84.5	884	242	590	12	40	95.3	93.7	5	4
CD4 >200	73.8%	98.6%	26.2%	1%	9	287	703	1	1.2	99.5	712	7	689	14	1	34.4	99.8	136	97
				5%	43	276	675	7	6.0	97.5	718	37	661	13	6	73.2	99.1	28	20
				10%	86	261	639	14	11.9	94.9	725	74	626	13	12	85.2	98.1	14	10
Outpatients not on ART	80.7%	98.4%	19.3%	1%	9	188	802	1	1.2	99.7	811	8	786	16	1	33.5	99.8	124	101
				5%	47	181	770	3	5.8	98.4	817	40	754	15	7	72.4	99.1	25	21
				10%	94	171	729	6	11.4	96.6	823	81	714	15	13	84.7	98.2	13	11
Outpatients on ART	73.0%	98.7%	27.0%	1%	9	327	663	2	1.3	99.5	672	7	650	13	1	35.5	99.8	138	93
				5%	43	314	637	8	6.3	97.7	679	36	624	13	6	74.1	99.0	28	19
				10%	85	297	603	15	12.4	95.2	688	73	591	12	12	85.8	98.0	14	10
Inpatients	77.3%	98.1%	22.7%	5%	45	67	884	5	4.8	93.0	929	39	866	18	6	68.6	99.3	26	25
				10%	90	63	837	10	9.7	86.3	927	77	820	17	13	82.2	98.5	13	12
				15%	135	60	791	15	14.6	79.9	926	116	775	16	19	88.0	97.6	9	8
				20%	180	56	744	20	19.5	73.7	924	155	729	15	25	91.2	96.6	7	6
				30%	270	49	651	30	29.3	62.0	921	232	638	13	38	94.7	94.4	5	4

PTP: pre-test probability; TP: true positive; FP: false positive; TN: true negative; FN: false negative; PPV: positive predictive value; NPV: negative predictive value; NNS: number needed to screen; NNT: number needed to treat

Table A2.3 Algorithm 3

Subgroup	Alg. Sens	Alg. Spec	% Cases missed	PTP	Screening						N tested	Testing						NNS	NNT
					TP	FP	TN	FN	PPV	NPV		TP	FP	TN	FN	PPV	NPV		
CD4 <200	73.8%	99.1%	26.2%	5%	43	523	428	7	9.1	98.7	471	37	419	9	6	81.2	98.6	28	13
				10%	86	495	405	14	17.5	97.2	491	74	397	8	12	90.1	97.0	14	7
				15%	129	468	383	21	25.2	95.7	512	111	375	8	18	93.5	95.4	10	5
				20%	172	440	360	28	32.3	94.0	532	148	353	7	24	95.4	93.6	7	4
				30%	258	385	315	42	45.0	90.2	573	222	309	6	36	97.2	89.4	5	3
CD4 >200	60.1%	99.5%	39.9%	1%	7	723	267	3	2.6	99.6	274	6	262	5	1	52.9	99.6	167	46
				5%	35	694	257	15	12.0	97.9	292	30	251	5	5	85.4	98.1	34	10
				10%	70	657	243	30	22.4	95.6	313	60	238	5	10	92.5	96.0	17	6
Outpatients not on ART	72.1%	99.3%	27.9%	1%	8	634	356	2	2.3	99.7	365	7	349	7	1	50.3	99.7	139	51
				5%	42	608	342	8	10.9	98.7	384	36	335	7	6	84.1	98.3	28	11
				10%	84	576	324	16	20.6	97.3	408	72	318	6	12	91.8	96.4	14	6
Outpatients on ART	6.9%	99.9%	93.1%	1%	1	950	40	9	2.0	99.0	40	1	39	1	0	46.4	99.7	1456	59
				5%	4	912	38	46	9.5	95.2	42	3	37	1	1	81.9	98.5	292	13
				10%	8	864	36	92	18.2	90.4	44	7	35	1	1	90.5	96.9	146	7
Inpatients	81.6%	98.4%	18.4%	5%	48	190	760	3	5.9	98.7	808	41	745	15	7	72.8	99.1	25	20
				10%	95	180	720	5	11.7	97.3	815	82	706	14	13	85.0	98.1	13	10
				15%	143	170	680	8	17.3	95.8	823	122	666	14	20	90.0	97.1	9	7
				20%	190	160	640	10	22.9	94.1	830	163	627	13	27	92.7	95.9	7	6
				30%	285	140	560	15	33.7	90.3	845	245	549	11	40	95.6	93.2	5	4

PTP: pre-test probability; TP: true positive; FP: false positive; TN: true negative; FN: false negative; PPV: positive predictive value; NPV: negative predictive value; NNS: number needed to screen; NNT: number needed to treat

Table A2.4 Algorithm 4

Subgroup	Alg. Sens	Alg. Spec	% Cases missed	PTP	N tested	Testing						NNT
						TP	FP	TN	FN	PPV	NPV	
CD4 <200	80.7%	97.0%	19.3%	10%	1000	81	873	27	19	0.75	0.98	13
				20%	1000	161	776	24	39	0.87	0.95	7
				30%	1000	242	679	21	58	0.92	0.92	5
Inpatients	82.7%	93.0%	17.3%	10%	1000	83	837	63	17	0.57	0.98	13
				20%	1000	165	744	56	35	0.75	0.96	7
				30%	1000	248	651	49	52	0.84	0.93	5

PTP: pre-test probability; TP: true positive; FP: false positive; TN: true negative; FN: false negative; PPV: positive predictive value; NPV: negative predictive value; NNT: number needed to treat

Table A2.5 Cost estimates (median costs)

Costs associated with screening 1000 people with HIV (PTP 1%)

Subgroup	Algorithm	Cost of screening (USD)	Cost of testing	Total cost (screening + testing)	Cost per TB diagnosis (TP + FP)	Cost per true TB diagnosis	Difference from Alg. 1 per true TB diagnosis
CD4 <200	Alg. 1	1 800.00	16 988.40	18 788.40	894.69	2 684.06	—
	Alg. 2	5 000.00	20 836.20	25 836.20	1 033.45	3 229.53	545.47
	Alg. 3	4 807.20	10 986.80	15 794.00	987.13	2 256.29	–427.77
	Alg. 4	NA	NA	NA	NA	NA	NA
CD4 >200	Alg. 1	1 800.00	12 632.40	14 432.40	902.03	2 405.40	—
	Alg. 2	5 000.00	17 230.40	22 230.40	1 058.59	3 175.77	770.37
	Alg. 3	4 055.40	6 630.80	10 686.20	971.47	1 781.03	–624.37
Outpatients not on ART	Alg. 1	1 800.00	15 294.40	17 094.40	899.71	2 442.06	—
	Alg. 2	5 000.00	19 626.20	24 626.20	1 026.09	3 078.28	636.22
	Alg. 3	4 534.20	8 833.00	13 367.20	954.80	1 909.60	–532.46
Outpatients on ART	Alg. 1	1 800.00	7 308.40	9 108.40	828.04	1 821.68	—
	Alg. 2	5 000.00	16 262.40	21 262.40	1 063.12	3 037.49	1 215.81
	Alg. 3	3 156.60	968.00	4 124.60	2 062.30	4 124.60	2 302.92
Inpatients	Alg. 1	1 800.00	21 562.20	23 362.20	898.55	2 920.28	—
	Alg. 2	5 000.00	22 506.00	27 506.00	1 057.92	3 438.25	517.98
	Alg. 3	5 567.40	19 408.40	24 975.80	1 040.66	3 121.98	201.70
	Alg. 4	NA	NA	NA	NA	NA	NA

PTP: pre-test probability; TP: true positive; FP: false positive

Table A2.6 Cost estimates (median costs)

Costs associated with screening 1000 people with HIV (PTP 10%)

Subgroup	Algorithm	Cost of screening	Cost of testing	Total cost (screening + testing)	Cost per TB diagnosis (TP + FP)	Cost per true TB diagnosis	Difference from Alg. 1 per true TB diagnosis
CD4 <200	Alg. 1	1 800.00	17 327.20	19 127.20	219.85	258.48	—
	Alg. 2	5 000.00	21 005.60	26 005.60	270.89	321.06	62.58
	Alg. 3	4 807.20	11 882.20	16 689.40	203.53	225.53	–32.94
	Alg. 4	0.00	24 200.00	24 200.00	224.07	298.77	40.29
CD4 >200	Alg. 1	1 800.00	12 995.40	14 795.40	217.58	250.77	—
	Alg. 2	5 000.00	17 545.00	22 545.00	259.14	304.66	53.89
	Alg. 3	4 055.40	7 574.60	11 630.00	178.92	193.83	–56.94
Outpatients not on ART	Alg. 1	1 800.00	15 754.20	17 554.20	211.50	243.81	—
	Alg. 2	5 000.00	19 916.60	24 916.60	259.55	307.61	63.80
	Alg. 3	4 534.20	9 873.60	14 407.80	184.72	200.11	–43.70
Outpatients on ART	Alg. 1	1 800.00	7 816.60	9 616.60	188.56	209.06	—
	Alg. 2	5 000.00	16 649.60	21 649.60	254.70	296.57	87.51
	Alg. 3	3 156.60	1 064.80	4 221.40	527.68	603.06	394.00
Inpatients	Alg. 1	1 800.00	21 707.40	23 507.40	239.87	286.68	—
	Alg. 2	5 000.00	22 433.40	27 433.40	291.84	356.28	69.60
	Alg. 3	5 567.40	19 723.00	25 290.40	263.44	308.42	21.74
	Alg. 4	0.00	24 200.00	24 200.00	165.75	291.57	4.89

PTP: pre-test probability; TP: true positive; FP: false positive

References for Annex 2

1. World Health Organization. WHO operational handbook on tuberculosis. Module 2: screening - systematic screening for tuberculosis disease. Geneva; 2020 (9789240001503; https://apps.who.int/iris/handle/10665/340256.
2. World Health Organization. WHO consolidated guidelines on tuberculosis Module 2: Screening – Systematic screening for tuberculosis disease. Geneva 2021 (https://iris.who.int/handle/10665/340255.
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Annex 3. Checklist for TB infection prevention and control

This annex is based on a tool produced by Médecins Sans Frontières (MSF) and Partners in Health. *(1)*

Instructions: This tool helps to give an idea of the risk of transmission of *Mycobacterium tuberculosis* in health-care facility or congregate settings. The results should be completed by the infection prevention and control (IPC) focal person and interpreted by the IPC committee. For the Yes/No questions, a Yes answer indicates good tuberculosis IPC practices. Any pertinent information on No answers is noted in the Comments section below each table.

Overview of the facility (interview with the health facility manager)

Name, address and telephone number of the facility	
Name of assessor	
Name of facility manager	
Date of current TB IPC assessment	
Date of last TB IPC assessment	
Type of facility (e.g. primary health care or prison)	
Medical services offered (e.g. OPD consultation, VCT or antenatal care)	
Size of the population served by this facility	
Facility TB case notification rate per 100 000 per year	
National TB case notification rate per 100 000 per year	
Number of DR-TB patients in care	
Number of people living with HIV in care	
Average number of cases of TB reported per month in the facility	
Is there a functional IPC committee in the facility or a committee at which TB IPC is discussed?	
Is there a written facility-specific infection prevention and control plan (that includes TB IPC)? [a]	
Is there a budget allocated for TB IPC activities?	
Is there a person in charge or a focal person for TB?	
Is the TB focal person a member of the facility IPC committee?	
How often does the IPC committee meet? [a]	
Did all the clinical staff receive documented TB IPC training or refresher training within the past 2 years? [b]	

[a] If possible, obtain a copy of the minutes of the last IPC meeting and TB IPC plan.

[b] Review and note number (%).

Comments_____

Administrative measures

Risk identification and segregation

	Yes	No
Are high-risk areas (e.g. TB ward, ART centre or sputum collection corner) properly identified?		
If yes, is there a SOP to be followed in high-risk areas (e.g. wear respirators)?		
Are presumptive TB cases separated from other patients?		
Are persons segregated based on bacteriological status (positive/negative)?		
If treating DR-TB patients, is segregation by resistance pattern implemented?		
Is ambulatory treatment for patients with DR-TB encouraged in the intensive phase?		
Is access to high-risk areas limited or restricted for visitors?		

Comments_____

Waiting areas (observe behaviour for 1 hour, ideally in the main (or in the specific TB) waiting area during the busy early morning hours

	Yes	No
Are patients given health education on TB through talks or use of audiovisual aids while they wait?		
Is there educational content on display regarding TB and cough hygiene?		
Are visitors told to cover their nose and mouth when they cough or sneeze?		
Are presumptive TB cases separated in any way from other patients?		

Comments_____

Management of persons with presumptive or confirmed TB (interview health-care workers)

	Yes	No
Is fast tracking or accompanied referral implemented to minimize waiting time in crowded spaces?		
Are symptomatic individuals offered medical masks?		
Are results of sputum smear microscopy available in less than 48 hours?		
Is TB treatment started immediately after TB diagnosis? (Note the average duration between date of diagnosis and date of starting TB treatment)		

Comments_____

Sputum specimen collection and preparation (witness a sputum sample collection and preparation)

	Yes	No
Is sputum collection performed in a designated, well-ventilated area?		
Is sputum collected in labelled, screw-top sterile plastic containers?		
If sputum is induced, are the mask and tube replaced or decontaminated between patients?		

Comments_____

Staff measures (interview facility manager)

	Yes	No
Are educational sessions on TB risk for health-care workers conducted annually?		
Do staff members involved in patient care receive annual TB evaluation?		
Do staff members involved in patient care receive annual chest X-ray?		
Have staff members received TPT at least once?		
Number of employees notified with TB disease in the past 12–24 months		
Are staff aware of national occupational health and safety regulations when diagnosed with TB?		

Comments_____

Environmental measures (If possible, make rough estimates of ventilation using a vaneometer and smoke tube or incense stick)

	Yes	No
Is natural ventilation possible?		
If yes, are windows open during busy hours?		
Are health-care workers positioned "up-wind" from patients during consultation and counselling?		
Are waiting areas in outdoor or open areas?		
Is measurement of ACH possible?		
Are there at least 12 ACH in all waiting areas?		
Are there at least 12 ACH in consultation rooms and wards?		
Are there at least 20 ACH in the sputum collection area (or in open air)?		
Is a mechanical ventilation system used? [a]		
Are GUV fixtures used in areas frequented by patients with infectious TB? [a]		

[a] If a mechanical system or GUV fixtures are used, explain their functioning and maintenance in detail on a separate sheet

Obtain a scale drawing of the floor plan of the whole facility including doors and windows (if this is not available, make a sketch). Shade the different areas according to the level of risk based on the observations on environmental measures:

- high risk of TB transmission – dark grey
- limited risk of TB transmission – grey
- low risk of TB transmission – white

Include patients and staff flow, and environmental measures (e.g. ventilation fans and GUV fixtures).

Comments_____

Personal protective measures (walk unannounced around the facility and observe, then discuss with staff)

	Yes	No
Are medical masks for patients with presumptive TB available in sufficient quantities?		
Are respirators that meet FFP2 or N95 standards available for staff?		
Are respirators available in sufficient quantities for all health-care workers?		
Are respirators of more than one size, model or brand available?		
Are respirators available in sufficient quantities for care providers of patients with bacteriologically confirmed TB?		
Do health-care workers use respirators when assisting sputum collection or induction?		
Do health-care workers wear respirators before entering the room of a person with presumed TB or a patient with bacteriologically confirmed TB?		
Do health-care workers perform a seal check before wearing a respirator?		
Does the facility have a fit-test programme for health-care workers using respirators?		
Do health-care workers who use respirators undergo fit-testing at least once?		

Comments_____

ACH: air changes per hour; ART: antiretroviral therapy; DR-TB: drug-resistant TB; GUV: germicidal ultraviolet light; HIV: human immunodeficiency virus; IPC: infection prevention and control; OPD: outpatient department; SOP: standard operating procedure; TB: tuberculosis; TPT: TB preventive treatment; VCT: voluntary counselling and testing

Conclusions (debrief health facility manager after completing assessment)

According to the assessor and the facility manager, what are the current main issues and barriers in the implementation of TB IPC?

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_____

According to the assessor and the facility manager, what are the priority actions for the implementation of TB IPC in this facility for the next 6–12 months?

Reference for Annex 3

1 Varaine F, Rich ML. Appendix 16. Basic TB infection control risk assessment tool. In: Tuberculosis: Médecins Sans Frontières, Partners In Health; 2023: https://medicalguidelines.msf.org/sites/default/files/TB-Appendix%2B16.pdf.

Annex 4. Package of care for advanced HIV disease

Table A4.1 summarizes the specific components of the package of interventions that should be offered to people presenting with advancsed HIV disease. For detailed guidance on the package of interventions for advanced HIV disease, including for children, see *Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy (1)* and *WHO consolidated guidelines on tuberculosis: Module 5. management of tuberculosis in children and adolescents (2).*

Table A4.1. Components of the package of care for people with advanced HIV disease

	Intervention	CD4 cell count	Adults	Adoles-cents	Children <10 years
Screening and diagnosis	Screening tools for TB disease for adults and adolescents: W4SS, CXR, CRP, mWRDs, alone or in combination Screening tools for TB disease among children: symptom screening for children with HIV	Any	Yes	Yes	Yes (symptom screen only)
	mWRDs as the first test for pulmonary TB diagnosis among those who screen positive for TB and investigations for extrapulmonary TB as applicable; CXR may also be used to support investigations	Any	Yes	Yes	Yes
	LF-LAM to assist TB diagnosis among people with symptoms and signs of TB	≤200 cells/mm^3 (inpatient) ≤100 cells/mm^3 (outpatient) Or any CD4 count with symptoms or if seriously ill	Yes	Yes	Yes
	Cryptococcal antigen screening	Recommended for <100 cells/mm^3 and considered for <200 cells/mm^3	Yes	Yes	No

	Intervention	CD4 cell count	Adults	Adolescents	Children <10 years
Prophylaxis and pre-emptive treatment	Co-trimoxazole prophylaxis	<350 cells/mm^3 or clinical stage 3 or 4 Any CD4 count in settings with high prevalence of malaria or severe bacterial infections	Yes	Yes	Yes[a]
	TB preventive treatment[b]	Any	Yes	Yes	Yes
	Fluconazole pre-emptive therapy for cryptococcal antigen–positive people without evidence of meningitis	<100 cells/mm^3	Yes	Yes	Not applicable (screening not advised)
ART initiation	Rapid ART initiation[c]	Any	Yes	Yes	Yes
	Defer initiation if clinical symptoms suggest meningitis (TB or cryptococcal)	Any	Yes	Yes	Yes
Adapted adherence support	Tailored counselling to ensure optimal adherence to the advanced HIV disease package, including home visits if feasible	<200 cells/mm^3	Yes	Yes	Yes

ART: antiretroviral therapy; CRP: C-reactive protein; CXR: chest X-ray; LF-LAM: lateral flow lipoarabinomannan; mWRDs: molecular WHO-recommended rapid diagnostic test; W4SS: WHO-recommended four symptom screen

[a] Screening not advised in this age group

[b] TB preventive treatment should be provided in accordance with current WHO guidance.

[c] People receiving a positive WHO four symptom screen should initiate ART while being evaluated for TB if clinical signs and symptoms of meningitis are absent.

References for Annex 4

1. Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy, July 2017. Geneva: World Health Organization; 2017 (https://apps.who.int/iris/handle/10665/255884, accessed 31 August 2023).
2. WHO consolidated guidelines on tuberculosis. Module 5: management of tuberculosis in children and adolescents. Geneva: World Health Organization; 2022 (https://apps.who.int/iris/handle/10665/352522, accessed 31 August 2023).

For further information, please contact:
Global Tuberculosis Programme
World Health Organization
20, Avenue Appia CH-1211 Geneva 27
Switzerland
Web site: www.who.int/tb

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