



Modern Approaches to the Diagnosis, Prevention, and Management of Tuberculosis in People Living with Human Immunodeficiency Virus Infection

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Abstract. Tuberculosis and human immunodeficiency virus infection remain among the leading causes of infectious morbidity and mortality worldwide. The coexistence of these diseases is associated with a markedly increased risk of developing active tuberculosis, difficulties in timely diagnosis, the emergence of drug-resistant *Mycobacterium tuberculosis*, and considerable challenges in patient management, highlighting the need to improve current approaches to diagnosis, prevention, and treatment. Objective of the study: to summarize current scientific evidence regarding the epidemiology, pathogenesis, modern diagnostic methods, prevention, and treatment of tuberculosis in people living with human immunodeficiency virus infection. A comprehensive review of contemporary scientific publications and World Health Organization recommendations addressing the epidemiology, diagnosis, prevention, and management of tuberculosis in people living with human immunodeficiency virus infection was conducted. The analysis of current evidence demonstrated that human immunodeficiency virus infection substantially increases the risk of active tuberculosis through progressive impairment of cellular immune responses, whereas tuberculosis accelerates the progression of immunodeficiency. The highest diagnostic accuracy is achieved through the combined use of clinical screening, radiological examination, molecular diagnostic techniques, and bacteriological methods. Timely identification of latent tuberculosis infection and the initiation of preventive treatment after exclusion of active tuberculosis significantly reduce the incidence of active disease and tuberculosis-related mortality. Short-course rifamycin-containing preventive regimens have demonstrated high effectiveness and improved treatment adherence. Effective patient management requires an individualized therapeutic approach that considers clinically significant drug interactions between antituberculosis and antiretroviral medications. The synthesis of current evidence supports the implementation of comprehensive diagnostic algorithms, systematic screening for latent tuberculosis infection,

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timely preventive treatment, and individualized therapeutic strategies. These approaches may improve the quality of healthcare, optimize patient management, enhance treatment outcomes, and reduce mortality among people living with human immunodeficiency virus infection.

Keywords: tuberculosis; human immunodeficiency virus infection; tuberculosis/human immunodeficiency virus coinfection; latent tuberculosis infection; antiretroviral therapy; molecular diagnostics; drug resistance; tuberculosis preventive treatment.

Introduction

Early detection of tuberculosis (TB), followed by the timely initiation of effective treatment, remains a cornerstone of global efforts to control the disease. It is estimated that approximately 3 million cases of TB remain undiagnosed each year. Timely diagnosis and effective patient management can prevent the progression of severe disease, reduce mortality, and limit transmission of infection [1, 2].

Both naturally occurring (intrinsic) and acquired drug resistance in *Mycobacterium tuberculosis* (MTB) substantially limit the therapeutic options available for TB treatment. This underscores the need to develop and implement effective public health policies aimed at the rational use of new anti-TB drugs and the prevention of further emergence and spread of drug resistance [3].

Furthermore, tuberculosis and human immunodeficiency virus (HIV) infection mutually accelerate disease progression, with each condition exacerbating the adverse effects of the other. Thus, TB/HIV coinfection is characterized by an unfavorable bidirectional interaction. People living with HIV have an approximately 22-fold higher risk of developing active TB than individuals with intact immune function [1].

Analysis of contemporary challenges in TB control is essential for achieving the objectives of the global End TB Strategy. Such an analysis may provide new opportunities to strengthen global TB control and identify a comprehensive set of measures required to accelerate progress toward TB elimination. This review examines the major challenges in the current era of TB control, including drug resistance, TB/HIV coinfection, diagnostic limitations, and treatment-related challenges [1, 3].

The aim of the study: to summarize current scientific evidence regarding the epidemiology, pathogenesis, modern diagnostic methods, prevention, and treatment of tuberculosis in people living with human immunodeficiency virus infection.

Materials and Methods

A comprehensive review of contemporary scientific publications and World Health Organization recommendations addressing the epidemiology, diagnosis, prevention, and management of tuberculosis in people living with human immunodeficiency virus infection was conducted.

Results

Tuberculosis (TB) and human immunodeficiency virus (HIV) infection remain among the most serious global public health threats. Although HIV-related mortality has declined substantially in recent years, progress in reducing TB-related mortality remains insufficient. In 2014, TB ranked alongside HIV as one of the leading causes of death from infectious diseases worldwide [1, 2].

During the 1990 s, the HIV epidemic became one of the major drivers of the resurgence of TB, and TB continues to disproportionately affect people living with HIV (PLHIV). TB remains a leading cause of death among PLHIV. HIV infection substantially increases the risk of progression from latent tuberculosis infection (LTBI) to active TB disease. According to WHO estimates, PLHIV have a markedly higher risk of developing active TB than people without HIV infection [1, 4].

Thus, HIV infection and TB demonstrate a pronounced lethal synergy: HIV-associated immunosuppression substantially increases susceptibility to TB, while TB, in turn, may accelerate HIV disease progression, thereby contributing to increased morbidity and mortality among affected individuals [1, 4].

Among HIV-negative individuals with LTBI, the lifetime risk of developing active TB is generally estimated at approximately 5–10%. In contrast, the risk among PLHIV is substantially higher, reflecting the impaired immune control of *Mycobacterium tuberculosis* infection.

Importantly, the increased risk of TB develops soon after HIV acquisition, even when CD4⁺ T-cell counts remain relatively preserved. Some of the most compelling evidence for the early increase in TB risk following HIV infection comes from studies of South African gold miners who worked and lived in conditions of close communal contact, experienced substantial exposure to *Mycobacterium tuberculosis*, and were under regular medical surveillance that included repeated HIV testing [5].

In one such study, the incidence of TB doubled during the first year after HIV seroconversion compared with HIV-negative individuals. Although an increased risk of TB was observed even among individuals with recently acquired HIV infection and relatively preserved immune function, the risk increased further with longer duration of HIV infection [5].

Timely diagnosis of TB among PLHIV remains challenging because of the high prevalence of smear-negative disease and extrapulmonary TB. Clinical screening alone has limited sensitivity in this population and may fail to identify a substantial proportion of laboratory-confirmed TB cases, particularly among pregnant women living with HIV. Important opportunities for improving early diagnosis are associated with the use of highly sensitive molecular diagnostic methods and lateral flow assays, which may provide improved diagnostic performance in people living with HIV [6–8].

Treatment of TB in people living with HIV (PLHIV) is also challenging because of multiple drug–drug interactions between anti-TB drugs and antiretroviral therapy (ART), as well as overlapping drug toxicities. Nevertheless, findings from a large international cohort study involving children demonstrated that initiation of ART within the first eight weeks after starting anti-TB treatment was associated with more favourable clinical outcomes [9].

TB prevention in PLHIV is likewise associated with several challenges. Although isoniazid preventive therapy has demonstrated substantial efficacy, concerns have been raised that its widespread use could contribute to the emergence and transmission of *Mycobacterium tuberculosis* strains resistant to isoniazid. However, available evidence indicates that, in settings with a controlled or declining TB epidemic, the benefits of preventive treatment in PLHIV in terms of reducing TB incidence and mortality outweigh the potential risk of selection for drug resistance [10–13].

PLHIV should be systematically assessed for TB disease and, where indicated, for TB infection. The timing and approach to testing for TB infection should be determined according to the epidemiological and clinical context, national policies, and individual risk factors. In individuals with a negative test for TB infection who remain at substantial risk of exposure to *Mycobacterium tuberculosis*, including healthcare workers and persons with ongoing close contact with individuals with TB, repeat testing may be considered according to the level and persistence of individual risk [14, 15].

When a test for TB infection is positive, the priority is to exclude active TB disease before initiating TB preventive treatment (TPT). This assessment should include clinical evaluation and, where indicated, chest radiography and microbiological testing using rapid molecular or other appropriate diagnostic methods.

Both the tuberculin skin test (TST) and interferon-gamma release assays (IGRAs) can be used to detect TB infection. WHO recommendations recognize both approaches, with the choice depending on availability, laboratory capacity, cost, programmatic considerations and the epidemiological context. WHO's updated

diagnostic guidance also includes newer TB infection testing technologies based on *M. tuberculosis*-specific antigens [14, 15].

In PLHIV, a TST induration of ≥ 5 mm, assessed 48–72 hours after administration of tuberculin, is generally considered positive in clinical guidelines. Important limitations of TST include the requirement for a second visit to assess the result, reduced specificity in BCG-vaccinated populations, and reduced sensitivity in individuals with advanced immunosuppression [14].

IGRAs generally have higher specificity than TST because they use antigens specific to the *M. tuberculosis* complex that are absent from BCG vaccine strains and most non-tuberculous mycobacteria. This reduces the likelihood of false-positive results associated with prior BCG vaccination. However, IGRA performance may also be affected by immunosuppression, and indeterminate results may occur more frequently in individuals with advanced HIV-associated immunodeficiency.

Current recommendations do not establish a universal preference for either TST or IGRA in PLHIV. The choice should be guided by the clinical and epidemiological context, test availability, laboratory capacity and programmatic resources. When serial testing is performed, variability in IGRA results and the potential booster phenomenon associated with repeated TST should be taken into account.

Although discordance between TST and IGRA results is relatively common, a positive result with either test is associated with an increased risk of subsequent TB disease. Nevertheless, neither test has sufficient predictive accuracy to determine at the individual level which person with TB infection will subsequently develop active disease.

Current WHO recommendations emphasize that the decision to provide TPT to PLHIV should not be based exclusively on the result of a TST or IGRA. After active TB disease has been excluded, TPT may be offered to PLHIV according to epidemiological risk, national policy and the individual's clinical circumstances. In high TB-burden settings, TPT may be provided to PLHIV regardless of the result of TB infection testing, provided that active TB has been excluded. In lower-incidence settings, TST or IGRA may be used as part of the assessment for eligibility for preventive treatment. WHO currently recommends several short-course preventive regimens, including 3HP, 1HP and 3HR, with the choice depending on drug availability, potential drug–drug interactions and individual clinical circumstances [10–13].

Adding chest radiography to symptom-based screening can increase the detection of TB disease, but its specificity may be limited and its implementation can increase the cost and logistical complexity of screening programmes. Moreover, chest radiography may fail to identify a proportion of subclinical or

atypical TB cases, particularly among PLHIV with advanced immunosuppression. A normal chest radiograph therefore does not exclude TB in PLHIV, especially in individuals with a low CD4⁺ T-cell count or extrapulmonary disease. In such cases, laboratory-based diagnostic methods, particularly rapid molecular testing and culture, are essential [14, 15].

Historically, sputum smear microscopy for acid-fast bacilli (AFB) was one of the most widely used methods for laboratory confirmation of pulmonary TB. Its advantages include technical simplicity, relatively low cost, rapid availability of results and high specificity in many clinical settings. However, its sensitivity is limited because a relatively high bacillary burden is required for reliable microscopic detection, making the method particularly insensitive in paucibacillary disease [14, 15].

In PLHIV, the sensitivity of sputum smear microscopy is substantially lower than in people without HIV because smear-negative disease is more common and the bacillary burden in clinical specimens is often lower. Consequently, smear microscopy alone is insufficient for the initial diagnosis of TB in PLHIV when WHO-recommended rapid diagnostic tests (WRDs) are available. Current WHO guidance prioritizes rapid molecular testing over smear microscopy as the initial diagnostic approach.

WHO-recommended rapid diagnostic tests (WRDs) are now prioritized for the initial diagnosis of TB. These include rapid molecular tests capable of detecting *M. tuberculosis* and, depending on the test, resistance to rifampicin. Xpert MTB/RIF Ultra is one of the widely used molecular assays in this category and provides improved analytical sensitivity compared with earlier Xpert MTB/RIF technology, which is particularly relevant in paucibacillary disease, including TB in PLHIV, smear-negative TB and paediatric TB [14–16].

The 2025 WHO diagnostic framework further consolidates Xpert MTB/RIF Ultra and Truenat MTB Plus with appropriate rifampicin-resistance testing within the low-complexity automated nucleic acid amplification test (LC-aNAAT) class. The updated guidance also emphasizes the use of concurrent testing of respiratory and non-respiratory specimens in PLHIV in appropriate clinical circumstances, thereby increasing the likelihood of detecting TB when disease is extrapulmonary, disseminated or paucibacillary [14–16].

Culture of *M. tuberculosis* using liquid or solid media remains an important reference method for microbiological confirmation and phenotypic drug susceptibility testing (DST). Culture generally provides higher analytical sensitivity than smear microscopy and allows isolates to undergo further phenotypic susceptibility testing. However, the relatively long turnaround time limits its role as the sole initial

diagnostic method, and it is therefore increasingly complemented by rapid molecular diagnostics.

Although sputum-processing procedures such as concentration, centrifugation and fluorescence microscopy can improve the yield of smear microscopy, their diagnostic performance remains inferior to that of rapid molecular tests. Accordingly, smear microscopy is now primarily considered an adjunctive or alternative diagnostic method in settings where rapid molecular testing is unavailable or inaccessible.

According to current WHO recommendations, PLHIV should undergo systematic screening for TB disease at appropriate intervals and whenever clinically indicated. After TB disease has been excluded, PLHIV at increased risk of progression from TB infection to disease should be considered for TPT as part of a comprehensive TB prevention strategy [10,11,13].

Results from randomized clinical trials and systematic reviews have demonstrated that TPT reduces the risk of developing active TB among PLHIV and can contribute to reductions in mortality, particularly when combined with effective ART [10–12].

In contrast to earlier strategies in which six months of isoniazid monotherapy (6H) was widely used, current WHO recommendations favour shorter preventive regimens when they are appropriate and available. These include 3HP (isoniazid plus rifapentine administered once weekly for three months), 1HP (daily isoniazid plus rifapentine for one month), and 3HR (daily isoniazid plus rifampicin for three months). Longer isoniazid-containing regimens, such as 6H or 9H, remain options when rifamycin-based regimens cannot be used because of drug–drug interactions, contraindications or lack of availability.

TPT should only be initiated after active TB disease has been appropriately excluded. Depending on the clinical context, this may require symptom-based screening, chest radiography and rapid molecular testing of appropriate clinical specimens. Reliance on symptom assessment alone may be insufficient in individuals with advanced immunosuppression or atypical and extrapulmonary disease [14, 15].

Concerns that TPT could promote the emergence of isoniazid resistance have not been consistently supported by available evidence. When active TB is appropriately excluded before treatment, TPT has not been associated with a clinically significant increase in the risk of developing drug-resistant TB. Ensuring adequate diagnostic assessment before initiation of preventive treatment remains essential.

The effectiveness of TB prevention is further enhanced by timely initiation of ART, which substantially reduces the risk of TB among PLHIV. TPT and ART should therefore be regarded as complementary components of comprehensive TB prevention and HIV care.

Overall, contemporary TB diagnostic strategies in PLHIV rely on the integrated use of systematic clinical screening, chest radiography when indicated, WHO-recommended rapid molecular diagnostics, culture-based testing and drug susceptibility testing. This multimodal approach is particularly important for detecting paucibacillary, subclinical, disseminated and extrapulmonary TB in individuals with advanced HIV-associated immunosuppression [14–16].

The development and implementation of accessible, rapid and highly sensitive molecular diagnostic technologies remain key components of the WHO End TB Strategy, particularly for improving early TB detection among PLHIV. Timely diagnosis is especially important in this population because TB frequently presents with atypical clinical and radiological features, a low bacillary burden, extrapulmonary involvement and subclinical disease.

According to current WHO recommendations, WRDs should be used as initial diagnostic tests in individuals with suspected TB, including PLHIV. Xpert MTB/RIF Ultra and Truenat-based technologies are among the established rapid molecular platforms, while the updated WHO diagnostic framework also recognizes new diagnostic classes that may expand access to rapid testing. The use of these technologies facilitates the simultaneous detection of *M. tuberculosis* and, where applicable, molecular markers of rifampicin resistance, thereby shortening the time to diagnosis and initiation of appropriate treatment [14–16].

For more comprehensive assessment of drug resistance, molecular tests and line probe assays (LPAs) can provide rapid information on resistance-associated genetic mutations. First-line LPAs can detect mutations associated with resistance to rifampicin and isoniazid, whereas second-line LPAs can be used for detection of resistance to selected fluoroquinolones and second-line injectable agents. Their use should be integrated into diagnostic algorithms according to WHO recommendations and local laboratory capacity [14, 15].

Targeted next-generation sequencing (NGS) represents an increasingly important approach to rapid detection of drug resistance. These technologies can identify resistance-associated mutations across multiple anti-TB drugs and may provide more comprehensive information than individual targeted molecular assays. WHO has incorporated targeted NGS into its diagnostic framework as an approach for detecting resistance to a range of anti-TB drugs. Whole-genome sequencing (WGS) also has an important role in molecular epidemiology, surveillance and investigation of transmission patterns and may assist, in selected settings, in distinguishing relapse from reinfection. However, its routine clinical implementation remains dependent on laboratory infrastructure, sequencing capacity and bioinformatic expertise [14, 17, 18].

An important area of ongoing development is the use of biomarker-based diagnostic approaches. Urine lipoarabinomannan (LAM) testing has particular clinical relevance for PLHIV with advanced immunosuppression or severe illness. WHO recommends lateral flow LAM (LF-LAM) testing as an adjunct to the diagnosis of active TB in specific groups of PLHIV, including hospitalized patients with signs and symptoms suggestive of TB and individuals with advanced HIV disease or severe illness, according to the applicable clinical criteria [8, 19, 20]. The use of urine as a diagnostic specimen is particularly valuable in patients who are unable to produce an adequate sputum sample and may facilitate earlier diagnosis in severely ill patients.

Research is also ongoing into transcriptomic biomarkers, protein signatures and metabolomic profiles for the early detection of active TB and prediction of progression from TB infection to disease. Although these approaches are promising, most remain under clinical validation and are not yet recommended for widespread routine use [21].

Despite substantial advances in TB diagnostic technologies, their widespread implementation remains constrained by the cost of equipment, the need for appropriate laboratory infrastructure and trained personnel, and reliable supply chains for consumables. Ensuring equitable access to rapid and accurate diagnostic technologies therefore remains a major priority of global TB control programmes, particularly in countries with a high burden of TB and HIV-associated TB.

Thus, contemporary laboratory diagnosis of TB in PLHIV is based on the preferential use of rapid molecular diagnostics, complemented by culture-based testing, drug susceptibility testing, targeted sequencing technologies and selected biomarker-based approaches. The integrated use of these diagnostic modalities can facilitate earlier detection of TB, more rapid identification of drug resistance and timely initiation of effective treatment, thereby contributing to reduced morbidity and mortality among people with TB/HIV coinfection [14–21].

Discussion

An analysis of recommendations from international professional organizations indicates that the diagnostic strategy for TB in people living with HIV has changed substantially over recent years. Whereas sputum smear microscopy was historically the principal laboratory method for confirming TB, current practice prioritizes rapid molecular diagnostic technologies, which enable earlier detection of *M. tuberculosis* and, in appropriate assays, simultaneous identification of drug-resistance markers. The 2025 WHO diagnostic framework further expands this approach by consolidating recommendations for TB infection, TB disease and

drug-resistance testing and by introducing new diagnostic technology classes and updated testing algorithms [14–19].

At the same time, implementation of modern diagnostic technologies remains constrained by their cost, laboratory infrastructure requirements, availability of trained personnel and unequal access across health systems, particularly in high-burden settings. Consequently, alongside the introduction of innovative diagnostic methods, systematic clinical screening, appropriate TB preventive treatment and timely initiation of ART remain essential components of comprehensive TB/HIV care. Together, these measures can improve early case detection, reduce progression to active TB and contribute to lower morbidity and mortality among PLHIV.

Conclusions

1. Human immunodeficiency virus (HIV) infection substantially increases the risk of developing active tuberculosis (TB), complicates its diagnosis, and is associated with poorer clinical outcomes.

2. WHO-recommended rapid molecular diagnostic tests should be prioritized for the early detection of TB, as they provide high diagnostic sensitivity and, depending on the assay, enable simultaneous detection of molecular markers of drug resistance.

3. The integrated use of systematic clinical screening, rapid molecular diagnostics, culture-based methods, drug susceptibility testing, and emerging molecular technologies facilitates timely diagnosis and supports the selection of appropriate treatment strategies.

4. TB preventive treatment following appropriate exclusion of active TB disease, together with timely initiation of antiretroviral therapy (ART), remains a key component of TB prevention among people living with HIV (PLHIV).

5. Further expansion of equitable access to modern diagnostic technologies, particularly rapid molecular and drug-resistance testing, represents a major priority for improving TB control and reducing morbidity and mortality among people with TB/HIV coinfection.

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Conflict of interest

The authors declare no conflict of interest.

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Сучасні підходи до діагностики, профілактики та лікування туберкульозу в осіб, які живуть з вірусом імунодефіциту людини

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Анотація. Туберкульоз та інфекція, спричинена вірусом імунодефіциту людини (ВІЛ), залишаються одними з провідних причин інфекційної захворюваності та смертності у світі. Поєднання цих хвороб асоціюється зі значним підвищенням ризику розвитку активного туберкульозу, труднощами у своєчасній діагностиці, виникненням лікарсько-стійких форм *Mycobacterium tuberculosis* та значними труднощами у веденні пацієнтів, що зумовлює необхідність удосконалення сучасних підходів до діагностики, профілактики та лікування. Метою дослідження було узагальнити сучасні наукові дані щодо епідеміології, патогенезу, сучасних методів діагностики, профілактики та лікування туберкульозу в осіб, які живуть з ВІЛ-інфекцією. Проведено комплексний огляд сучасних наукових публікацій, рекомендацій Всесвітньої організації охорони здоров'я, настанов міжнародних професійних товариств та національних клінічних рекомендацій, присвячених питанням діагностики, профілактики та

лікування туберкульозу в осіб, які живуть з ВІЛ-інфекцією. Аналіз сучасних даних продемонстрував, що інфекція, спричинена вірусом імунодефіциту людини, суттєво підвищує ризик розвитку активного туберкульозу внаслідок прогресуючого порушення клітинної імунної відповіді, тоді як туберкульоз пришвидшує прогресування імунодефіциту. Найвища діагностична точність досягається завдяки комплексному застосуванню клінічного скринінгу, променевих методів дослідження, молекулярно-генетичних та бактеріологічних методів діагностики. Своєчасне виявлення латентної туберкульозної інфекції та призначення профілактичного лікування після виключення активного туберкульозу суттєво знижують частоту розвитку активного захворювання та смертність, пов'язану з туберкульозом. Короткострокові схеми профілактичного лікування, що містять рифаміцини, продемонстрували високу ефективність та сприяють кращій прихильності до лікування. Ефективне ведення пацієнтів потребує індивідуалізованого терапевтичного підходу з урахуванням клінічно значущих лікарських взаємодій між протитуберкульозними та антиретровірусними препаратами. Узагальнення сучасних наукових даних підтверджує доцільність впровадження комплексних діагностичних алгоритмів, систематичного скринінгу на латентну туберкульозну інфекцію, своєчасного призначення профілактичного лікування та застосування індивідуалізованих терапевтичних стратегій. Реалізація цих підходів може сприяти підвищенню якості медичної допомоги, оптимізації ведення пацієнтів, покращенню результатів лікування та зниженню смертності серед людей, які живуть з ВІЛ-інфекцією.

Ключові слова: туберкульоз; інфекція, спричинена вірусом імунодефіциту людини; коінфекція туберкульоз / ВІЛ; латентна туберкульозна інфекція; антиретровірусна терапія; молекулярна діагностика; лікарська стійкість; профілактичне лікування туберкульозу.