

A Comprehensive Review On -Tuberculosis and Hiv Co-Infection: Diagnostic Andtherapeutic Challenges

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ABSTRACT:

Tuberculosis (TB) and Human Immunodeficiency Virus (HIV) together represent a global syndemic with profound clinical and public health implications. HIV increases the risk of active TB by 16–27 times due to immune suppression, while TB accelerates HIV progression and mortality. Co-infection poses diagnostic and therapeutic challenges, including atypical disease presentations, drug–drug interactions, overlapping toxicities, and adherence issues. Despite advances in antiretroviral therapy (ART) and molecular diagnostics, TB remains the leading cause of death among people living with HIV, especially in sub-Saharan Africa. Preventive strategies—such as Isoniazid Preventive Therapy (IPT), early ART initiation, and infection control—are vital to reducing morbidity and mortality. Future priorities include developing rapid diagnostics, shorter and safer drug regimens, novel vaccines, and host-directed therapies. Strengthening integrated TB–HIV services and health systems is essential to achieving global TB elimination and HIV control goals.

Keywords: Tuberculosis, HIV, Co-infection, ART, IPT, Diagnosis, Prevention.

I. INTRODUCTION:

Tuberculosis (TB) and Human Immunodeficiency Virus (HIV) remain two of the most significant infectious diseases globally, accounting for millions of deaths annually, particularly in low- and middle-income countries. Individually, each disease poses a major public health challenge; however, their convergence has created a devastating syndemic with far-reaching clinical and epidemiological consequences. TB is one of the oldest known infectious diseases, caused by *Mycobacterium tuberculosis*, and continues to be a leading cause of morbidity and mortality worldwide. HIV, on the other hand, progressively weakens the immune system, increasing susceptibility to opportunistic infections, with TB

being the most common and life-threatening of these infections.

The interaction between TB and HIV is bidirectional and synergistic. HIV infection increases the risk of progression from latent TB infection to active disease by approximately 16–27 times compared to HIV-negative individuals, as reported by the World Health Organization (WHO). This is due to the profound immunosuppression caused by the depletion of CD4+ T lymphocytes, which play a crucial role in containing TB infection. Conversely, TB infection accelerates the progression of HIV disease by increasing viral replication and further compromising immune function, leading to faster clinical deterioration and higher mortality rates.

The burden of TB–HIV co-infection is disproportionately high in regions with generalized HIV epidemics, particularly in sub-Saharan Africa and parts of Asia. Co-infection presents substantial diagnostic and therapeutic challenges, as TB may manifest atypically in HIV-infected individuals, often leading to delayed diagnosis and treatment. Furthermore, overlapping drug toxicities, complex drug–drug interactions, and the risk of immune reconstitution inflammatory syndrome (IRIS) complicate management strategies. These factors collectively hinder efforts to achieve global TB elimination goals and highlight the urgent need for integrated approaches to prevention, diagnosis, and treatment of both diseases.

EPIDEMIOLOGY OF TB-HIV CO-INFECTION:

The dual epidemics of tuberculosis (TB) and Human Immunodeficiency Virus (HIV) continue to pose a significant global public health challenge, particularly in low- and middle-income countries. According to the World Health Organization (WHO), in 2023 there were an estimated 10.6 million new TB cases worldwide, of which approximately 6–7% occurred in people living with HIV. Sub-Saharan Africa remains the epicenter of the TB–HIV Syndemic, accounting for the majority of global co-infections due to the high

prevalence of both diseases in the region. Countries such as South Africa, Mozambique, Zimbabwe, and Kenya have some of the highest rates of TB–HIV co-infection globally, with prevalence exceeding 50% in certain populations.

TB is the leading cause of death among people living with HIV, responsible for nearly one-third of all AIDS-related deaths. Immunosuppression caused by HIV significantly increases susceptibility to TB infection and progression to active disease, while TB accelerates HIV disease progression and mortality. The highest burden of TB–HIV co-infection is observed among adults of reproductive age, which further impacts economic productivity and healthcare systems in high-burden regions.

Despite significant advancements in early HIV diagnosis and expanded antiretroviral therapy (ART) coverage, major gaps remain in TB detection and treatment among HIV-infected individuals. Many cases are missed due to atypical presentations and the limited sensitivity of conventional diagnostic tools in immunocompromised patients. Delays in TB diagnosis and initiation of appropriate treatment contribute to ongoing transmission and higher mortality rates.

Globally, the scale-up of integrated TB–HIV services has led to improved outcomes, with declining incidence and mortality trends in some high-burden countries. However, regional disparities persist. High TB–HIV co-infection rates in resource-limited settings are compounded by challenges such as limited access to molecular diagnostics, weak health systems, stigma, and socioeconomic barriers to care. Achieving global TB elimination targets will therefore require intensified efforts to address the intertwined epidemiology of TB and HIV through strengthened surveillance, targeted screening, preventive interventions, and integrated treatment programs.

DIAGNOSTIC CHALLENGES:

The diagnosis of tuberculosis (TB) in individuals infected with Human Immunodeficiency Virus (HIV) remains one of the most significant clinical and public health challenges in TB control. Co-infection alters the classical clinical and radiological features of TB and affects the performance of standard diagnostic tools. This frequently leads to delayed diagnosis, missed cases, and increased morbidity and mortality in HIV-infected populations.

a. Atypical Clinical Presentation:

In immunocompetent individuals, pulmonary TB typically presents with classical symptoms such as persistent cough, hemoptysis, weight loss, night sweats, and radiographic evidence of upper lobe cavitation. However, in HIV-positive individuals, especially those with advanced immunosuppression, TB often presents atypically. Extrapulmonary and disseminated forms of TB are significantly more common, involving lymph nodes, pleura, meninges, abdomen, or multiple organ systems simultaneously.

Clinical symptoms are frequently non-specific and may include only fever, malaise, or weight loss, without the hallmark respiratory symptoms. Cough may be absent or minimal, and chest signs may be subtle or entirely lacking. These atypical features make clinical suspicion more difficult and can result in delayed presentation, misdiagnosis, or empirical treatment for other conditions such as bacterial pneumonia or malignancies.

b. Limitations of Conventional Tests:

Traditional diagnostic methods such as sputum smear microscopy and chest radiography have reduced diagnostic yield in HIV-positive patients.

Sputum smear microscopy, while inexpensive and widely used, has low sensitivity in people living with HIV, particularly in those with low CD4 counts. The paucibacillary nature of disease in immunosuppressed individuals leads to a higher rate of smear-negative TB, making reliance on microscopy alone inadequate.

Chest radiography often shows non-classical patterns in HIV-infected individuals. Instead of the typical upper lobe cavitory lesions, findings may include lower lobe infiltrates, interstitial patterns, or even normal chest X-rays despite active disease. As a result, radiographic interpretation becomes less specific, increasing the risk of both underdiagnosis and overdiagnosis.

These limitations underline the inadequacy of conventional methods as sole diagnostic tools in high HIV prevalence settings.

c. Role of Molecular and Immunological Tests:

The development of rapid molecular diagnostic tools has significantly improved TB detection, especially in HIV-infected populations.

GeneXpert MTB/RIF, a nucleic acid amplification test, offers higher sensitivity compared to smear microscopy and can detect Mycobacterium tuberculosis as well as rifampicin resistance within

two hours. Its performance is particularly beneficial in smear-negative and extrapulmonary TB cases, which are common in HIV patients.

Urine Lipoarabinomannan (LAM) assay has emerged as a valuable point-of-care tool for TB diagnosis in patients with advanced HIV disease (CD4 count <100 cells/mm³). It is simple, rapid, and useful for diagnosing disseminated TB in hospitalized patients, especially when sputum samples are unavailable or inadequate. WHO now recommends its use to improve early detection and reduce mortality in this high-risk group.

Culture remains the gold standard for TB diagnosis due to its high sensitivity and ability to perform drug susceptibility testing. However, culture methods are time-consuming (taking 2–8 weeks), require specialized laboratory facilities, and are often unavailable in resource-limited settings, leading to delays in initiating treatment.

THERAPEUTIC CHALLENGES:

Management of tuberculosis (TB) in individuals co-infected with Human Immunodeficiency Virus (HIV) is complex due to several interrelated therapeutic issues. These include determining the optimal timing for initiation of antiretroviral therapy (ART), managing significant drug–drug interactions, addressing overlapping drug toxicities, and ensuring adherence in the context of high pill burden. Each of these factors has direct implications for treatment outcomes and patient survival.

a. Timing of ART Initiation

The decision regarding when to start ART in TB–HIV co-infected patients is critical. Initiating ART too early can lead to immune reconstitution inflammatory syndrome (IRIS), a paradoxical worsening of TB symptoms due to immune recovery. However, delaying ART increases the risk of HIV-related morbidity and mortality.

Clinical trials have demonstrated that early ART initiation, within 2–8 weeks after starting anti-TB therapy, significantly improves survival, particularly among patients with low CD4 counts. In individuals with CD4 counts below 50 cells/mm³, ART should be commenced within two weeks of TB treatment initiation to maximize survival benefits.

For patients with higher CD4 counts (>50 cells/mm³), ART can be safely delayed until after the intensive phase of TB therapy (around 8 weeks), which may help reduce IRIS risk. The timing must also consider factors such as drug tolerance, adherence capability, and clinical stability.

b. Drug–Drug Interactions

A major therapeutic obstacle in TB–HIV co-management arises from pharmacokinetic interactions between anti-TB and antiretroviral medications. Rifampicin, a cornerstone of TB treatment, is a potent inducer of cytochrome P450 (CYP450) enzymes, which accelerates the metabolism of many antiretrovirals, particularly protease inhibitors (PIs) and some non-nucleoside reverse transcriptase inhibitors (NNRTIs).

This interaction can result in subtherapeutic ART levels, risking virologic failure and drug resistance. To mitigate this, clinicians may use rifabutin (a less potent enzyme inducer) as a substitute for rifampicin, or adjust ART regimens to include drugs less affected by enzyme induction, such as efavirenz or dolutegravir at modified doses.

Ongoing monitoring of therapeutic efficacy, liver function, and adherence is vital to manage these interactions effectively.

c. Overlapping Toxicities

Both anti-TB and antiretroviral drugs can cause similar adverse effects, which complicates the identification of the offending agent and increases the likelihood of treatment discontinuation. Common overlapping toxicities include:

Hepatotoxicity: Seen with isoniazid, rifampicin, pyrazinamide, and several ART agents such as nevirapine.

Peripheral neuropathy: Caused by isoniazid and certain nucleoside reverse transcriptase inhibitors (e.g., stavudine, didanosine).

Gastrointestinal intolerance: Nausea, vomiting, and abdominal pain are frequent with both regimens.

Cutaneous reactions and rash: May occur with both ART and TB drugs.

Close clinical and laboratory monitoring, along with appropriate supportive management (e.g., pyridoxine supplementation to prevent neuropathy), is essential to minimize toxicity-related interruptions. When severe reactions occur, sequential reintroduction of medications under supervision helps identify the culprit drug.

d. Adherence and Pill Burden

Co-treatment of TB and HIV often requires patients to take multiple medications daily for prolonged periods, leading to a high pill burden and potential adherence challenges. Poor adherence increases the risk of drug resistance, treatment failure, and disease relapse.

Factors contributing to non-adherence include adverse effects, socioeconomic constraints, stigma, depression, and limited access to healthcare services. Integrated TB–HIV care, patient education,

psychosocial support, and simplified fixed-dose combination therapies can help improve adherence. Furthermore, directly observed therapy (DOT) and community-based support programs have shown success in ensuring treatment completion and reducing default rates.

PREVENTIVE STRATEGIES:

Prevention of tuberculosis (TB) among individuals living with Human Immunodeficiency Virus (HIV) is a critical component of global TB control programs. Since HIV infection significantly increases the risk of developing active TB, preventive measures are essential to reduce morbidity, mortality, and transmission. The cornerstone strategies include Isoniazid Preventive Therapy (IPT), early initiation of antiretroviral therapy (ART), and infection control practices in healthcare and community settings.

a. Isoniazid Preventive Therapy (IPT)

Isoniazid Preventive Therapy is one of the most effective interventions for preventing progression from latent TB infection (LTBI) to active TB disease in people living with HIV. Isoniazid, when administered daily for 6 to 9 months, significantly reduces TB incidence, particularly in individuals with a positive tuberculin skin test (TST) or interferon-gamma release assay (IGRA) result.

The World Health Organization (WHO) recommends IPT for all HIV-infected individuals who do not have active TB, irrespective of TST status, especially in high TB-burden countries. IPT works synergistically with ART to provide dual protection against TB.

Implementation challenges include concerns about hepatotoxicity, poor adherence, and the potential for drug resistance if active TB is not adequately ruled out prior to initiation. To overcome these barriers, screening protocols (using symptom-based algorithms and molecular tests) and patient counseling are crucial. In some settings, continuous or extended IPT (beyond 36 months) has been shown to provide sustained protection against TB in high-transmission environments.

b. Early Initiation of Antiretroviral Therapy (ART)

Early initiation of antiretroviral therapy (ART) plays a vital preventive role in TB–HIV co-infection. ART strengthens immune function by increasing CD4 T-cell counts, thereby reducing the risk of reactivation of latent TB infection and new TB acquisition.

Studies have shown that starting ART regardless of CD4 count substantially decreases TB incidence and TB-related deaths. The “test and treat” approach—initiating ART immediately upon HIV diagnosis—

has become a cornerstone of integrated HIV–TB prevention programs.

In addition, combining ART with IPT provides additive benefits, with greater TB risk reduction compared to either intervention alone. However, successful implementation requires adherence support, routine TB screening at ART initiation, and monitoring for drug-related toxicity.

c. Infection Control Measures in Healthcare and Community Settings

Healthcare facilities are major points of exposure for TB transmission, particularly among immunocompromised HIV patients. Effective infection prevention and control (IPC) strategies are therefore essential to reduce nosocomial (healthcare-associated) transmission.

Key measures include:

Administrative controls: Early triage and separation of patients with suspected TB, prompt diagnosis, and initiation of treatment.

Environmental controls: Adequate natural ventilation, use of exhaust fans, and ultraviolet germicidal irradiation (UVGI) systems in high-risk areas.

Personal protective measures: Use of N95 respirators by healthcare workers and surgical masks for patients with suspected or confirmed TB.

Community-based infection control also involves improving living conditions, reducing overcrowding, and ensuring community TB awareness and screening campaigns. Strengthening infection control not only protects patients but also reduces occupational risk among healthcare workers and caregivers.

PROGRAMMATIC AND PUBLIC HEALTH CHALLENGES:

Despite advances in diagnosis and treatment, the effective management of TB–HIV co-infection continues to face significant programmatic and public health barriers. These challenges are deeply rooted in health system limitations, socio-economic inequities, and the complexity of coordinating dual disease programs. Strengthening the integration of TB and HIV services, improving accessibility, and addressing stigma and structural barriers are critical to achieving the goals of TB and HIV control programs.

a. Inadequate Coordination Between TB and HIV Programs

One of the most persistent obstacles is the fragmentation of TB and HIV control programs. Historically, TB and HIV services have operated as

separate vertical programs, each with its own infrastructure, funding sources, and monitoring systems. This lack of coordination often leads to missed opportunities for early diagnosis, delayed initiation of therapy, and suboptimal patient outcomes.

Integrated TB–HIV care requires collaboration at all levels of the healthcare system—from policy planning to frontline service delivery. Effective coordination involves:

Harmonizing policies and treatment guidelines.

Conducting joint training for healthcare providers.

Sharing data between TB and HIV registries to ensure comprehensive surveillance.

Countries that have implemented “one-stop” service models—where TB and HIV diagnosis and treatment are provided under the same roof—have demonstrated improved case detection, treatment adherence, and patient retention.

b. Integration of Services and Joint Surveillance

Integration of services is essential to streamline care and improve efficiency. Co-location of testing and treatment services allows simultaneous screening for both infections, reducing diagnostic delays and loss to follow-up. For example, offering HIV testing to all TB patients and TB screening to all people living with HIV are WHO-recommended collaborative activities.

Joint surveillance systems help track co-infection trends, monitor treatment outcomes, and allocate resources effectively. However, challenges such as limited digital infrastructure, inconsistent data collection, and lack of interdepartmental communication hinder progress. Strengthening electronic medical record systems and ensuring real-time data sharing between TB and HIV programs can significantly enhance public health response and resource utilization.

c. Stigma and Discrimination

Social stigma remains a powerful barrier to TB and HIV control. Both diseases are associated with fear, misinformation, and discrimination, which discourage individuals from seeking testing and treatment. HIV-related stigma is often compounded by TB stigma, especially in communities where TB is perceived as a marker of advanced HIV infection. Patients facing stigma may hide their illness, discontinue treatment, or avoid health facilities altogether. Addressing stigma requires community education campaigns, peer support networks, and the involvement of civil society organizations to promote acceptance and understanding. Healthcare providers must also receive sensitivity training to ensure non-discriminatory, patient-centered care.

d. Limited Access to Healthcare and Socioeconomic Barriers

In many low- and middle-income countries, poverty, geographic isolation, and weak health infrastructure impede access to quality TB and HIV services. Patients often face long travel distances, high transportation costs, and loss of income during treatment. Inadequate human resources, frequent drug stock-outs, and limited laboratory capacity further exacerbate these challenges.

Socioeconomic factors—such as malnutrition, unemployment, and poor living conditions—also increase vulnerability to both infections and hinder recovery. Addressing these determinants requires multi-sectoral collaboration beyond the health system, involving education, housing, and social welfare sectors. Expanding community-based care, mobile health clinics, and telemedicine initiatives can help bridge access gaps in underserved regions.

e. Funding and Sustainability Issues

Sustained financial investment is crucial for the success of TB–HIV programs. However, reliance on donor-driven funding (e.g., from the Global Fund or PEPFAR) can threaten long-term sustainability, especially when domestic resource mobilization is limited. Integrating TB and HIV services under universal health coverage (UHC) frameworks and ensuring domestic budget allocation for essential interventions are key strategies for program continuity.

Transparent monitoring, efficient resource use, and accountability mechanisms are essential to maintain funding and build trust among stakeholders.

II. FUTURE DIRECTIONS:

The dual epidemic of tuberculosis (TB) and Human Immunodeficiency Virus (HIV) continues to pose a formidable challenge to global public health. Despite significant advances in diagnostics, therapeutics, and preventive interventions, TB–HIV co-infection remains a major cause of morbidity and mortality, particularly in low-resource settings. Future progress will depend on the development of innovative diagnostic tools, safer and more compatible drug regimens, novel preventive approaches such as vaccines and host-directed therapies, and strengthened health systems to support integrated care delivery.

a. Development of Rapid, Point-of-Care Diagnostics
Early and accurate diagnosis is the cornerstone of effective TB–HIV management. However, diagnostic challenges persist due to atypical disease presentations and reduced test sensitivity in

immunocompromised individuals. The future lies in rapid, point-of-care (POC) diagnostic technologies that are affordable, accurate, and suitable for decentralized healthcare settings.

Emerging molecular platforms such as GeneXpert MTB/RIF Ultra and Truenat assays have already improved sensitivity, but further innovations are needed for detecting extrapulmonary and paucibacillary TB. Development of multi-disease diagnostic tools capable of simultaneously detecting TB, HIV, and drug resistance markers would significantly streamline patient management.

Moreover, biomarker-based tests, such as those detecting host immune responses (e.g., transcriptomic or proteomic signatures), hold promise for identifying latent TB infection and predicting progression to active disease. Investments in digital health technologies and portable diagnostic devices can enhance early case detection, particularly in rural or resource-limited areas.

b. Novel TB Drug Regimens with Fewer Interactions with ART

The emergence of drug-resistant TB and the complexity of drug–drug interactions with antiretroviral therapy (ART) underscore the urgent need for new TB treatment regimens. Future research is focused on developing shorter, more tolerable, and less toxic regimens that are compatible with ART and effective against both drug-susceptible and resistant TB strains.

Promising new agents such as bedaquiline, delamanid, pretomanid, and linezolid are being incorporated into shorter multidrug regimens that show encouraging outcomes even in multidrug-resistant TB (MDR-TB). The goal is to achieve universal regimens that can be safely co-administered with ART without significant pharmacokinetic interference.

In parallel, efforts are underway to develop long-acting or injectable formulations that reduce pill burden and improve adherence. Ongoing pharmacogenomic research may also enable personalized therapy, optimizing drug selection and dosing based on genetic variability in metabolism and drug response.

c. Vaccines and Host-Directed Therapies

While the Bacillus Calmette–Guérin (BCG) vaccine offers partial protection against severe childhood TB, it provides limited efficacy in preventing adult pulmonary disease, particularly among HIV-infected populations. Therefore, novel TB vaccines are a major research priority.

Several vaccine candidates are in advanced stages of clinical trials, including M72/AS01E, which has demonstrated about 50% efficacy in preventing progression from latent to active TB in adults. Future vaccines aim to provide broader, longer-lasting immunity and improved safety for immunocompromised individuals.

Beyond vaccines, host-directed therapies (HDTs) represent a transformative approach. These therapies focus on modulating the host immune response rather than directly

targeting the pathogen. HDTs such as metformin, vitamin D supplementation, and anti-inflammatory agents have shown potential to enhance immune-mediated bacterial clearance, reduce inflammation, and prevent tissue damage. Combining HDTs with standard antimicrobial regimens could improve outcomes and limit the development of drug resistance.

d. Strengthening Health Systems for Integrated TB–HIV Care

Sustainable progress in TB–HIV control requires robust and resilient health systems capable of delivering integrated, patient-centered care. Integration ensures that patients receive simultaneous screening, treatment, and follow-up for both diseases under a single framework.

Future strategies should focus on:

Health workforce strengthening through capacity building and continuous training services.

Digital health innovations, such as electronic health records, mobile apps, and teleconsultation systems to support case tracking and adherence monitoring. Community-based interventions to improve awareness, reduce stigma, and enhance access to care.

Furthermore, policy harmonization between TB and HIV programs, increased domestic funding, and research investment are essential to ensure sustainability. Collaborative efforts between governments, non-governmental organizations, and international partners will be pivotal in achieving the WHO End TB Strategy and UNAIDS 95–95–95 goals.

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