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STUDY OF THE PROBLEM OF LATENT TUBERCULOSIS INFECTION IN HIV-INFECTED INDIVIDUALS

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ABSTRACT

Latent tuberculosis infection (LTBI) remains one of the most significant challenges in global tuberculosis (TB) control, particularly among people living with HIV (PLHIV). HIV infection dramatically increases the risk of reactivation of latent Mycobacterium tuberculosis infection, contributing to high morbidity and mortality rates worldwide. This article presents a comprehensive review and analytical assessment of the epidemiology, immunopathogenesis, diagnostic challenges, preventive therapy, and public health implications of LTBI in HIV-infected individuals. Special attention is given to immunological mechanisms underlying reactivation, limitations of tuberculin skin testing (TST) and interferon-gamma release assays (IGRAs) in immunocompromised populations, and current WHO recommendations for tuberculosis preventive therapy (TPT). The study highlights the urgent need for improved diagnostic tools, integrated TB-HIV programs, and personalized preventive approaches to reduce TB incidence among PLHIV. Strengthening LTBI screening and preventive treatment strategies remains critical to achieving global TB elimination goals.

Tuberculosis (TB) remains one of the leading infectious causes of death globally. According to the World Health Organization (WHO), approximately one-quarter of the world's population is infected with Mycobacterium tuberculosis, most of whom harbor latent tuberculosis infection (LTBI). While immunocompetent individuals have a 5–10% lifetime risk of developing active TB, people living with HIV (PLHIV) face an annual risk of up to 10%.

The synergy between HIV and TB represents a major public health crisis. HIV-induced immunosuppression significantly impairs host immune control over latent infection, increasing the likelihood of reactivation and progression to active disease. In many high-burden countries, TB remains the leading cause of death among PLHIV.

This article explores the pathogenesis, epidemiology, diagnosis, management, and prevention of LTBI in HIV-infected individuals, emphasizing current evidence-based recommendations and future directions.

Epidemiology of LTBI in HIV-Infected Individuals

Globally, approximately 38 million people are living with HIV. Among them, LTBI prevalence varies widely depending on geographic region and TB endemicity. In high TB burden countries, LTBI prevalence among PLHIV may exceed 50%.

Key epidemiological observations include:

- Increased TB incidence in HIV-positive individuals
- Higher rates of extrapulmonary TB
- Increased mortality associated with co-infection
- Greater burden in sub-Saharan Africa and parts of Asia

The risk of progression from LTBI to active TB is strongly correlated with CD4+ T-cell depletion. Patients with CD4 counts below 200 cells/mm^3 are particularly vulnerable.

Immunopathogenesis of Latent TB in HIV Infection

Mechanisms of Latency

After primary infection, M. tuberculosis may persist in a dormant state within granulomas. Effective immune containment depends on:

- CD4+ T lymphocytes
- Macrophage activation
- Interferon-gamma (IFN-γ) production
- Tumor necrosis factor-alpha (TNF-α)

Impact of HIV on TB Immunity

HIV infection disrupts TB immune control through:

- Progressive CD4+ T-cell depletion
- Impaired cytokine signaling
- Dysfunctional macrophage activity
- Reduced granuloma integrity

This immunological breakdown facilitates reactivation of latent bacilli and dissemination of infection.

Diagnostic Challenges of LTBI in HIV

Diagnosing LTBI in HIV-positive individuals presents significant limitations.

Tuberculin Skin Test (TST)

Limitations:

- Reduced sensitivity in advanced immunosuppression
- False-negative results with low CD4 counts
- Cross-reactivity with BCG vaccination

Interferon-Gamma Release Assays (IGRAs)

Advantages:

- Higher specificity
- No cross-reactivity with BCG

Limitations:

- Reduced sensitivity in severe immunosuppression
- Indeterminate results common in advanced HIV

Emerging Diagnostic Approaches

Research focuses on:

- Biomarkers predicting progression risk
- Transcriptomic signatures
- Novel antigen-based assays

However, no current test reliably predicts reactivation in HIV-positive patients.

Risk Factors for Reactivation

Several factors increase LTBI reactivation risk among PLHIV:

- CD4 count <200 cells/mm^3
- High viral load
- Malnutrition
- Diabetes mellitus
- Substance abuse
- Delayed antiretroviral therapy (ART)
- High TB exposure environments

Early ART significantly reduces TB risk but does not eliminate it entirely.

Tuberculosis Preventive Therapy (TPT)

WHO Recommendations

WHO recommends TB preventive therapy for all PLHIV without active TB, regardless of CD4 count.

Recommended regimens include:

- Isoniazid for 6–9 months (6H or 9H)
- 3 months of weekly isoniazid plus rifapentine (3HP)
- 1 month of daily rifapentine plus isoniazid (1HP)
- 3 months of daily isoniazid plus rifampicin (3HR)

Effectiveness of TPT

Preventive therapy reduces active TB incidence by 33–67% among PLHIV. When combined with ART, the protective effect is synergistic.

Safety Considerations

Potential adverse effects:

- Hepatotoxicity
- Peripheral neuropathy
- Drug-drug interactions with ART

Careful monitoring is required.

Integration of TB-HIV Services

Integrated service delivery improves outcomes:

- Routine LTBI screening in HIV clinics
- Co-located TB-HIV treatment centers
- Coordinated ART and TPT initiation
- Strengthened infection control measures

Integration reduces diagnostic delays and mortality.

Public Health Implications

LTBI management in HIV populations is essential for:

- Reducing TB incidence
- Lowering transmission
- Achieving End TB Strategy goals
- Decreasing HIV-related mortality

Challenges include:

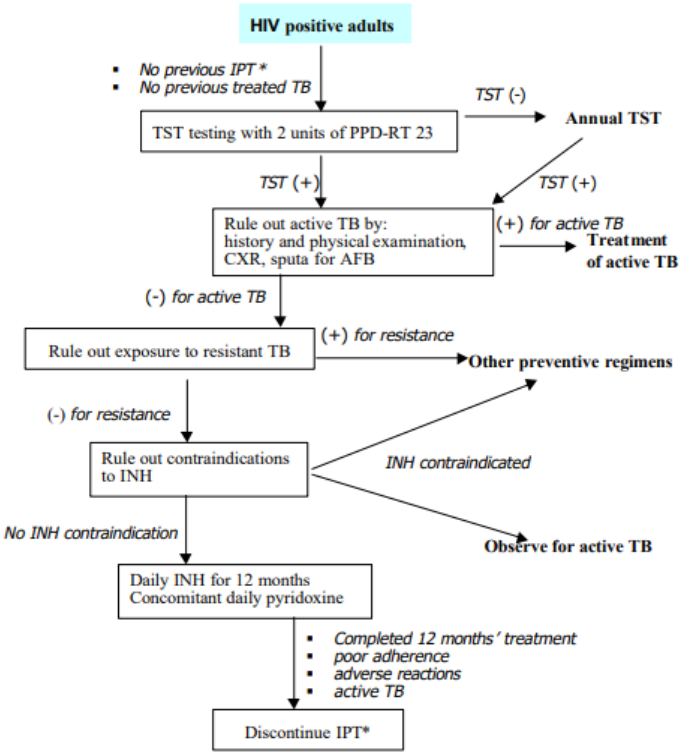
- Limited diagnostic tools
- Resource constraints
- Patient adherence
- Drug resistance concerns

Future Directions

Research priorities include:

- Development of predictive biomarkers
- Shorter, safer preventive regimens
- Host-directed therapies
- Vaccines effective in HIV-positive populations
- Personalized risk stratification models

Figure 1: Algorithm on the Treatment of LTBI in HIV infection



* IPT: INH preventive treatment

Implementation science approaches are also needed to improve coverage and adherence.

12 trials were included with a total of 8578 randomized participants. TB preventive therapy (any anti-TB drug) versus placebo was associated with a lower incidence of active TB (RR 0.68, 95% CI 0.54 to 0.85). This benefit was more pronounced in individuals with a positive tuberculin skin test (RR 0.38, 95% CI 0.25 to 0.57) than in those who had a negative test (RR 0.89, 95% CI 0.64 to 1.24). Efficacy was similar for all regimens (regardless of drug type, frequency or duration of treatment). However, compared to INH monotherapy, short-course multi-drug regimens were much more likely to require discontinuation of treatment due to adverse effects. Although there was reduction in mortality with INH monotherapy versus placebo among individuals with a positive tuberculin skin test (RR 0.74, 95% CI 0.55 to 1.00) and with INH plus rifampicin versus placebo regardless of tuberculin skin test status (RR 0.69, 95% CI 0.50 to 0.95), overall, there was no evidence that TB preventive therapy versus placebo reduced all-cause mortality (RR 0.94, 95% CI 0.85 to 1.05).

Most people infected with tuberculosis (TB) never get TB symptoms. This is called latent TB. People infected with HIV/AIDS are at increased risk of getting TB and about 30% of people with HIV who have latent TB will eventually get active TB. This results in an increase in the risk of earlier death. This update of the review of available clinical trials found that the risk of developing active TB was reduced when people infected with both HIV and TB used isoniazid. Isoniazid for latent TB is usually taken for six to 12 months, but

more research is still needed to show optimal duration of treatment, the best treatment regime for people with HIV, and especially the best regimen in combination with HIV drugs.

Although the availability of antiretroviral therapy (ART) has transformed human immunodeficiency virus (HIV) infection into a chronic and manageable disease in those who are able to access treatment; the successes recorded can easily be destroyed by the high burden of tuberculosis (TB) co-infection in the HIV-infected population. Even after the initiation of ART, the incidence of HIV-related TB remains unacceptably high.

According to the WHO Global TB Control report of 2008, worldwide, about 9.2 million new cases and 1.7 million deaths from TB occurred in 2006 and of these around 709,000 (7.7%) new cases and 200,000 deaths were estimated to have occurred in HIV-positive individuals (WHO 2008 (1)).

Therefore, prevention of TB is one of the most important measures that may help in reducing the morbidity and mortality associated with HIV infection particularly in countries with high burden of both infections.

Latent TB (LTB) infection is the presence of *Mycobacterium tuberculosis* (*M. tuberculosis*), the organism that causes TB, in an individual in a non-active phase and without producing clinical symptoms. Although, one third of the world's population is believed to be latently infected with *M. tuberculosis,* most of those infected will never have symptoms. Whereas in the general population the lifetime risk of progression from latent TB infection to active disease is about 10%, HIV positive persons who are infected with *M. tuberculosis* have a 5-8% annual risk and a 30% lifetime risk of developing active tuberculosis and this risk increases as immune deficiency worsens. HIV infection by impairing cell-mediated immunity is the most potent known risk factor for the reactivation of latent *M. tuberculosis* infection.

The tuberculin skin test (TST) is the primary screening test for the diagnosis of latent TB. Although this test is over 100 years old, it represents the second longest standing test in use for TB after sputum microscopy. In this test, purified protein derivative (PPD), a material derived from *M. tuberculosis* is injected into the skin of an individual and the reaction on the skin as indicated by the degree of induration is evaluated after about 48-72 hours.

A person is said to be positive to the TST (PPD positive) if there is a strong skin reaction. In HIV infected persons, a reaction greater than 5mm is considered positive while a reaction of less than 5mm is said to be a negative reaction. An individual without a reaction to TST and other common antigens such as mumps and candida is said to be anergic. PPD positive individuals are at a greater risk of progressing to active TB disease than people not infected with *M. tuberculosis*. Despite being an imperfect test, with both false positive and false negative results, TST remains a very useful and indeed a critical tool, both for epidemiologic research and the control and prevention of clinical tuberculosis.

HIV infection also has implications for the diagnosis and clinical presentation of TB. The proportion of

PPD negative individuals with tuberculosis infection seems to be higher in HIV positive populations than in those who are not infected with HIV (Daniel 2000). Similarly, the percentage of sputum smear negative patients with active tuberculosis is higher in HIV infected populations compared with HIV negative populations raising concerns for TB detection. Furthermore, extra-pulmonary tuberculosis is more common in patients with HIV infection than those who are not HIV-infected.

The treatment of LTB (also known as TB preventive therapy or chemoprophylaxis) is the administration of one or combination of anti-TB drugs to people with latent infection with *M. tuberculosis* with the aim of eradicating latent infection before it develops into active disease. The use of isoniazid preventive therapy (IPT) is one of the strategies recommended by the World Health Organization (WHO) to decrease the burden of TB in people living with HIV in addition to establishing intensified TB case finding and ensuring the control of TB infection in health-care and congregate settings (WHO 2004).

Several placebo-controlled trials in HIV negative people infected with *M. tuberculosis* have shown that daily isoniazid given for 6-12 months substantially reduces the subsequent risk of active tuberculosis. Similarly, several placebo-controlled trials have shown that treatment of latent TB is effective in HIV-infected individuals. Following the publication of these trials, a systematic review that included 10 trials was published in 2004 and the results showed that treatment of LTB infection reduces the risk of active TB in HIV positive individuals especially those with a positive TST. We hereby report an update of this review.

Table 1. Dosage adjustment of Rifampicin (RIF) in combination with common antiretroviral regimens (daily dosage in mg)

	NVP 200 bid	EFV 600 qd	RTV/SQV combination 400/400 bid	RTV 600 bid
RIF	**600 qd** +	**600 qd** +	**600 qd** +	**600 qd** +

Table 2. Dosage adjustment of Rifabutin (RFB) in combination with common antiretroviral regimens (daily dosage in mg unless otherwise specified))

	NVP 200 bid	EFV 600 qd	SGC-SQV 1200 tid	APV 1200 bid	IDV 1000 q8h, or 1200 q8h	NFV 750 tid, or 1000 tid, or 1250 bid	RTV 600 bid
RFB qd	**300 qd** +	**450 qd** +	**300 qd** +	**150 qd** +	**150 qd** +	**150 qd** +	**Daily RFB contra-indicated; 150 mg biw - tiw** +

ABBREVIATIONS: APV – amprenavir; EFV – effavirenz; IDV – indinavir; NFV – nelfinavir; NVP – nevirapine; RTV – ritonavir; SQV – saquinavir; SGC-SQV – soft gel capsule saquinavir.

Conclusion

Latent tuberculosis infection in HIV-infected individuals represents a major global health concern. HIV significantly increases the risk of LTBI reactivation through immunosuppression and disruption of granuloma integrity. Current diagnostic methods have limitations, particularly in advanced immunodeficiency. Tuberculosis preventive therapy, especially when combined with early ART initiation, remains the cornerstone of prevention. Strengthened TB-HIV integration, improved diagnostics, and innovative preventive strategies are essential to reduce the dual burden of TB and HIV worldwide.

Treatment of latent tuberculosis infection reduces the risk of active TB in HIV positive individuals especially in those with a positive tuberculin skin test. The choice of regimen will depend on factors such as availability, cost, adverse effects, adherence and drug resistance. Future studies should assess these aspects. In addition, trials evaluating the long-term effects of anti-tuberculosis chemoprophylaxis, the optimal duration of TB preventive therapy, the influence of level of immunocompromise on effectiveness and combination of anti-tuberculosis chemoprophylaxis with antiretroviral therapy are needed.

Addressing LTBI in PLHIV is not only a clinical priority but also a critical public health intervention necessary to achieve global TB elimination goals.

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