REVIEW ARTICLE

LATENT TUBERCULOSIS TREATMENT IN HIV-POSITIVE PATIENTS: WHAT'S NEW? IS IT OVERTREATMENT? WHICH ONE IS PREFERRED?

Arya Marganda Simanjuntak1, Ellya Catharine Lumbantoruan2, Merlinda Veronica3, Heri Ginting4, Anwar Sholeh4, Dani Rosidana4
1 Research Intern, Department of Internal Medicine, Faculty of Medicine, Universitas Riau, Arifin Achmad General Hospital
2 Faculty of Medicine, Universitas Tanjungpura, Pontianak, Indonesia
3 Tropical Infection Division, Department of Internal Medicine, Faculty of Medicine, Universitas Riau, Arifin Achmad General Hospital, Pekanbaru, Riau, Indonesia
4 Pulmonary and Critical Medicine Division, Department of Internal Medicine, Faculty of Medicine, Universitas Riau, Arifin Achmad General Hospital, Pekanbaru, Riau, Indonesia

ABSTRACT

Latent Tuberculosis Infection (LTBI) is a focus especially in HIV-seropositive patients because immunocompromise increases the risk of reactivation of LTBI into active TB. Therefore, LTBI therapy was developed to prevent the TB from becoming active. However, several issues have been questioned regarding LTBI therapy in HIV patients as an overtreatment and potentially dangerous because both drugs in TB and HIV have the same profile of hepatotoxicity. This review comprehensively discusses existing regimens and current evidence on the management of LTBI in HIV patients. This should be taken into consideration, but we also see from recent studies that if a patient has TB activation in HIV, it will decrease treatment success and also increase morbidity and mortality. Therefore, LTBI therapy has been developed up to the latest prevention guideline in 2024 with fewer treatment regimens than Active TB with 3HP or 3 HR. While it can be argued that LTBI therapy in HIV patients is necessary and not overtreatment, measures have also been developed to reduce the rate of hepatotoxicity that may occur.

Keywords : HIV, Latent Tuberculosis, Pharmacotherapy, Tuberculosis, Treatment

Correspondence :
Arya Marganda Simanjuntak,
Dept of Internal Medicine, Faculty of Medicine,
Universitas Riau, Arifin Achmad General hospital.
Email : arya.marganda@gmail.com

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INTRODUCTION

An estimated ⅓ of people worldwide have mycobacterium tuberculosis infections, with 5% of cases occurring in the active phase and 95% in the latent phase. There are a number of elements that might activate the latent phase during this phase; about 5% of these factors will be active while the other 95% will remain in the latent phase. Latent tuberculosis infection (LTBI) is characterized by a state of ongoing immunological response to MTB antigen stimulation in the absence of clinically evident active tuberculosis.2. Ding et al.'s 2022 study looked at LTBI prevalence rates on a national, regional, and worldwide scale. Globally, the prevalence of LTBI decreased from 30.66% to 23.67% between 1990 and 2019.Despite a slight decline in LTBI infections, around 25% of people worldwide have a latent MTB infection in 2019, according to Ding et al.[2]

Human Immunodeficiency Virus (HIV) affects millions of individuals globally and can coexist with TB. HIV coinfection, which dramatically increases the likelihood of TB reactivation for patients with latent TB and increases vulnerability to primary infection or reinfection, is the most important risk factor for developing active TB in high-burden settings. M. tuberculosis infection adversely affects the immune response to HIV, speeding up the progression from HIV infection to AIDS.[3] According to Ajayi *et al*. (2022), the prevalence of LTBI condition was 10% in controls and 22.5% in HIV-positive patients, with a statistically significant difference (p 0.0001).[4] 41 (10.5%) of 390 HIV-seropositive individuals were found to be positive by the Interferon Gamma Release Assay (IGRA) in a cohort study conducted by White et al. in 2022.5. Given that there is a correlation between LTBI and HIV, patients who are HIV-positive may have LTBI reactivation leading to active tuberculosis.

In order to avoid the spread of HIV and TB, treatment is crucial for LTBI patients who are HIV-positive. It is preferable to stop TB before HIV patients get symptoms. This is due to the poor treatment outcome for active TB in individuals living with HIV. According to a meta-analysis conducted in Ethiopia in 2024 by Mekonen et al., the success rate of TB therapy among patients living with HIV was only 19.3%, and the probability of treatment failure was 2.6 times higher than that of individuals without HIV (OR 2.65 (2.1 - 3.3)).[6] This is also supported by several other studies that show more or less similar results.[7,8] Therefore, HIV-seropositive patients are at risk of reactivation of tuberculosis and if the tuberculosis becomes active, it will certainly increase the morbidity and mortality of the patient. The provision of chemoprophylaxis/treatment in patients with known latent TB infection plays an important role.

However, issues arise that treatment for latent tuberculosis patients could be overtreatment and actually harm patients in HIV patients. It happen due to the effect of Anti-Tuberculosis Drug (ATD) reported to be hepatotoxic[9] and potential liver injury due to ATD treatment reported in Network Meta-analysis by Akkahadsee *et al.,* in 2023.[10] This should be a consideration due to antiretroviral therapy itself also could affect liver due the profile for hepatotoxicity[11] and Liver injury.[12,13] Therefore the issue would be should Latent TB in HIV-Positive patients be treated? How the effect for hepatotoxicity and liver failure reported in latent TB treatment in HIV-Positive? Which ATD preferably in Latent TB Patients with HIV-Positive? This study objective to comprehensively review current evidence of latent TB in HIV-Positive patients and answering clinical issues.

HOW TO DIAGNOSE LATENT TUBERCULOSIS?

Based on the cellular immune system's reaction to mycobacterial antigens, latent tuberculosis infection (LTBI) is a subclinical mycobacterial infection. Currently, the interferon gamma release assay (IGRA) and the tuberculin skin test (TST) are employed to diagnose tuberculosis (LTB). Nevertheless, it is not possible to distinguish between latent and active TB using either IGRA or TST. Furthermore, it is impossible to determine from these tests whether a person with LTBI will go on to get active tuberculosis (TB) or if LTBI therapy will be helpful in lowering that risk.

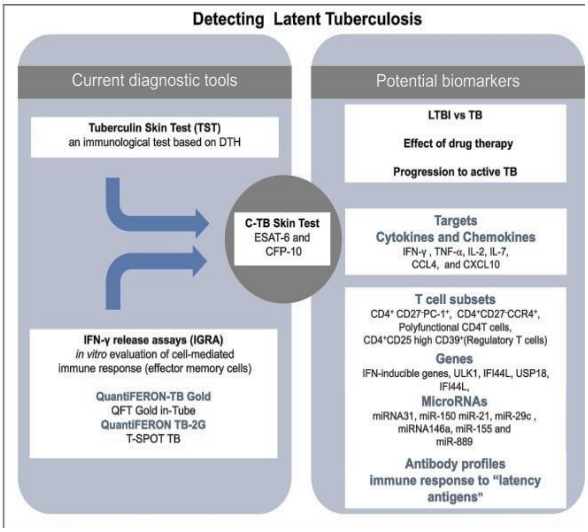

Figure 1. An overview of the available and possible diagnostic instruments for latent tuberculosis (LTBI).[14]

There is no gold standard test for LTBI. The diagnosis of LTBI is somewhat indirect since it relies on evidence of a cellular immune response to mycobacterial antigens. The IGRA and intradermal tuberculin test (TST) are the most often utilized tests for diagnosing LTBI.The TST, commonly known as the Mantoux test or "old tuberculin," was created more than a century ago by Robert Koch. TST has also been used in epidemiological studies to evaluate the prevalence of LTBI. TSTs are delivered intradermally to people' forearms using pure protein derivative (PPD) injections. When tested 48 or 72 hours later, an induration response of 15 mm or higher is considered indicative of a previous or present mycobacterial infection. The TST must be administered, read, and interpreted by qualified persons. TST relies on delayed-type hypersensitivity (DTH) skin reactivation to tuberculin PPD.[14]

People with latent tuberculosis (TB) usually have a positive TB blood test or skin test that indicates TB infection, but they also have normal chest radiographs, negative sputum smears, and culture findings. These people don't feel ill, but they might get sick if the germs in their systems become active. Patients with latent TB infection exhibit no symptoms. Thus, obtaining a patient's medical history has two functions: it helps rule out current TB illness and identifies people who may benefit from testing for latent tuberculosis infection. Patients at high risk of a new TB infection, patients at moderate-to-high risk of reactivation in a high-incidence area, and patients at high risk of reactivation in low-incidence countries are all candidates for latent tuberculosis infection testing. A history of solid organ or hematopoietic transplantation, dialysis, silicosis, anti-tumor necrosis factor treatment, and HIV coinfection are all risk factors for reactivation that must be properly investigated. Furthermore, persons of any age who come into contact with currently infected patients are far more likely to get a new TB infection.

A cough lasting more than two weeks, hemoptysis, shortness of breath, chest pain, fever, night sweats, and weight loss are all symptoms of active TB. Individuals who have migrated from high-incidence TB countries to low-incidence countries, as well as prisoners, healthcare workers, homeless people, drug addicts, silicosis patients, and others, are more likely to come into contact with cases of pulmonary tuberculosis. The physical examination should look for signs of active TB, including extrapulmonary and pulmonary.

Fever, diaphoresis, sputum jars of hemoptysis, and weight loss can all be symptoms of active TB. Extrapulmonary symptoms include anemia-related pallor, skin abnormalities such as erythema nodosum, panniculitis, as well as meningeal, peritoneal, and osteoarticular indications.[15] Examinable features, such as dialysis catheters or arteriovenous fistulas, reasons for organ donation and treatment, and steroid-related changes, may predispose the patient to reactivation risk.[15]

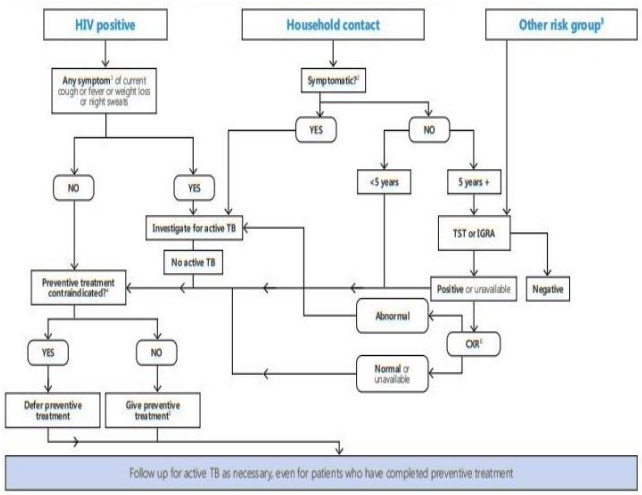

Figure 2. Algorithm for LTBI testing and TB Preventive Treatment in Individual at Risk.[16]

LTBI TREATMENT IN HIV-POSITIVE PATIENT: WHAT'S NEW?

For several reasons, including the following, LTBI can be treated in HIV-positive individuals: Two requirements must be fulfilled, regardless of the screening test's result: (1) a positive result on the latent or active tuberculin skin test (TST) or immunoglobulin-negative blood (IGRA) AND no indication of current tuberculosis (TB) illness without previous treatment; and (2) evidence of recent exposure to or close contact with a person who has infectious tuberculosis.17 People with HIV who have a negative TST or IGRA, have not recently interacted with someone who has infectious TB, and are unlikely to benefit from LTBI therapy.[17]

Three suggested and two alternative treatment regimens are included in the recommended treatment regimens (Table 1). Rifamycin-based regimens, which consist of 4 months of daily rifampin, 3 months of daily isoniazid plus rifampin, and 3 months of once-weekly isoniazid plus rifapentine, are the preferred suggested regimens because to their effectiveness, tolerability, and high rates of treatment completion. While effective, other recommended regimens, such as 6 or 9 months of daily isoniazid, have lower treatment completion rates and a higher risk of toxicity, which diminishes their efficacy.

Table 1. Recommendation for TB-Latent Treatment.[17]

Priority rank*	Regimen	Recommendation (strong or conditional)	Evidence (high, moderate, low, or very low)
Preferred	3 mos isoniazid plus rifapentine given once weekly	Strong	Moderate
Preferred	4 mos rifampin given daily	Strong	Moderate (HIV negative)†
Preferred	3 mos isoniazid plus rifampin given daily	Conditional	Very low (HIV negative)
		Conditional	Low (HIV positive)
Alternative	6 mos isoniazid given daily	Strong§	Moderate (HIV negative)
		Conditional	Moderate (HIV positive)
Alternative	9 mos isoniazid given daily	Conditional	Moderate

Abbreviation: HIV = human immunodeficiency virus.

Preferred Regimens:[17]

1. Three Months of Weekly Isoniazid Plus Rifapentine

For HIV-positive individuals, rifapentine with once-weekly isoniazid for three months is the recommended regimen (as long as medication interactions allow). When compared to the standard regimen of 9 months of daily isoniazid in HIV-positive individuals, this directly observed therapy regimen was equally effective and not more toxic. There was no discernible difference in the outcomes of isoniazid plus rifapentine when the regimen was given for 6 or 9 months.

2. Four Months of Daily Rifampin

For HIV-negative adults and children of all ages, a four-month daily rifampin regimen is recommended. In addition to having a lower incidence of treatment discontinuation due to side effects, a lower rate of hepatotoxicity, and a higher rate of treatment completion, four months of daily rifampin was found to be noninferior in its ability to prevent tuberculosis illness when compared to nine months of daily isoniazid. The multiple pharmaceutical interactions with rifamycin-based regimens, including those involving warfarin, oral contraceptives, azole antifungals, and HIV antiretroviral therapy, may be a disadvantage.

3. Alternative Regimens: Six or Nine Months of Daily Isoniazid

The benefit of isoniazid in low-TB incidence settings is unknown for HIV-positive individuals with negative TST results; however, for these individuals, there is a chance that isoniazid therapy will increase side effects while also decreasing the incidence of TB disease; six months of therapy is very effective. Nine months of daily isoniazid treatment may be more beneficial than six months and comparable to twelve months, according to the research. Nevertheless, there are no clinical trial results that directly contrast isoniazid administered for nine months with that administered for six months or for twelve months. Isoniazid is used in conjunction with antiretroviral treatment to prevent tuberculosis in HIV-positive individuals residing in regions with a high TB prevalence. Isoniazid with antiretroviral therapy lowers the incidence of tuberculosis illness more than isoniazid or antiretroviral therapy alone, according to two randomized controlled studies.[18]

Treatment for long-term brain injury (LTBI) has recently advanced with an emphasis on creating shorter, more efficient regimens to improve adherence and lower toxicity. The 12-week, once-weekly isoniazid and rifapentine (3HP) regimen is one of the most noteworthy advancements. It has demonstrated effectiveness comparable to the conventional 6 – 9 months isoniazid monotherapy, but with far higher adherence rates and a reduced incidence of hepatotoxicity. Furthermore, the accuracy of LTBI identification in HIV-positive patients has increased with the advent of sophisticated diagnostic technologies such interferon-gamma release assays (IGRAs), allowing for more prompt and accurate therapeutic approaches.[19] In addition to considering the drugs to be selected in LTBI therapy, the use of ARV drugs also needs to be a concern so that the effects of hepatotoxicity can be suppressed and Table.2 has summarized the choice of ATDs and ARV combinations and the latest recommended doses to date.

Table 2. Dosing Recommendation for Use of ARV and ATD When Treating LTBI.[17]

ATD	ARV	Dose of TB Drug
Isoniazid (INH)	All ARV's Note : For information on coadministration of ARV with Rifampin or Rifapentine, see entries below	Use INH with Pyridoxine 25 - 50mg PO daily (50mg once weekly if used with 3HP) For 3HP (weekly INH + Rifapentine x 12 weeks) 15mg/kg PO once weekly (900mg maximum) For 3HR (daily INH + Rifampin x 3 months, or 1HP (daily INH x Rifampentine

		x 4 months, or INH alone (daily INH 6 - 9 months) 300mg PO daily
Rifampin	NRTIs (TAF with cautionb) EFV 600 mg DTG, RAL (twice daily), and MVC without a strong CYP3A4 inhibitor (**note:** doses of these ARV drugs need to be adjusted when used with rifampin) IBA, T-20	For 3HR (daily rifampin + INH x 3 months), or 4R (daily rifampin x 4 months) 600 mg PO daily
	All others ARVs	**Not Recommended**
Rifapentine[a] 3HP *Weekly rifapentine + INH x 12 weeks*	EFV 600 mg, RAL or once daily DTG NRTIs (TAF with caution[b]) IBA, T-20	Weighing 32.1–49.9 kg: 750 mg PO weekly `Weighing ≥50.0 kg: 900 mg PO weekly`
	All others ARVs	**Not Recommended**
Rifapentinea 1HP *Daily rifapentine + INH x 4 weeks*	NRTIs (TAF with cautionb) EFV 600 mg IBA, T-20	Weighing <35 kg: 300 mg PO daily Weighing 35–45 kg: 450 mg PO daily Weighing >45 kg: 600 mg PO daily
	All others ARVs	**Not Recommended**

COMPARISON BETWEEN ALL POTENTIAL THERAPY THAT EXIST FOR LTBI TREATMENT

In 2017, a research by Sterling compared the 3HP regimen to the 9H regimen for LTBI in HIV-seropositive patients. The study found that the 3HP regimen resulted in greater treatment completion (89% vs 64%, p<0.001) and equivalent medication discontinuation owing to adverse events (3% vs 4%, p=0.79).[20] Semitala et al.'s 2021 RCT using the 3HP regimen found that patients accepted therapy well and completed treatment (92.9%), with just 8 patients (1.7%) reporting side effects. Only one of these eight instances was classified as acute liver injury, with the others being non-hepatotoxic medication interactions.[21] Assefa et al.,22 2023 found that 3HP has the ability to lower the incidence of active tuberculosis by 36% among those who have had contact with tuberculosis patients. According to the Network, the regimen most likely to cause hepatotoxicity of concern (Degrees 3 and 4) was the 9H regimen, followed by the 1HP and the 6H. The study discovered that utilizing 3HP produces good outcomes, although information on acute liver damage patients was limited.[22]

A network meta-analysis by Yoopetch *et al.*[23], in 2023 The effectiveness of ATD on LTBI was also investigated; the 3HR regime showed a favorable association with high likelihood in active TB prevention (SUCRA 0.7), followed by 3HP (SUCRA 0.6). In addition to the 3HP regimen, the study found that 3HR is related with satisfactory treatment completion. In terms of side effects, the 6H regimen has a greater risk (0.3%) than the 3HR. Indeed, in terms of TB prevention, there is no difference between 6H, 9H, 4R, 3HR, and 3HP.[23]

IS IT OKAY TO EARLY TREATMENT FOR TB PREVENTION IN HIV-POSITIVE PATIENT?

The overtreatment concerns about LTBI cases with HIV-seropositive need to be reconsidered. The risk for HIV-positive patients when tuberculosis becomes active will

be greater from the decrease in treatment success and also the morbidity and mortality that can be higher. During TB therapy, 44 (5.31%) out of 828 co-infected patients with HIV died; the crude death rate was 7.76 per 1000 person-months. The first three months of TB therapy accounted for more than half of the fatalities (n = 23). The overall chances of survival were 97.20%, 95.16%, and 91.75% in the third, sixth, and twelve months, respectively.[24] Further studies have evolved to this day until network meta-analysis has shown success preventive active TB in HIV-positive patients who are well using the recommended regimes.[22,23] Therefore the treatment of LTBI patients is assessed appropriately to reduce the risk of active tuberculosis.

The concerns about the possible emergence of resistance as a result of us giving therapy as soon as possible to LTBI patients also need to be reassessed. Giving LTBI therapy to HIV-positive patients as indicated will have an effect that will lower the risk of morbidity and mortality in patients. Therefore, not all HIV patients need direct LTBI therapy. The right therapy strategy and timing must play a role as a clinic providing treatment to reduce the risk of future resistance. There are reports of cases that found acquired resistance in patients who had previously undergone LTBI therapy.[25] However, it should be noted that this occurred in cases of isoniazid monotherapy therapy that took longer than the current new regimes. The newly followed regimes with clinical proficiency in determining therapies as well as patient compliance in medication are key in reducing the risk of resistance during LTBI treatment in HIV-patients.

CONCLUSION

LTBI therapy in HIV-Seropositive patients plays an important role in preventing active tuberculosis, reducing morbidity and mortality of HIV patients. Indicated, dosed, and combined ATD and ARV therapy is the key to success in treatment completion, therapeutic integrity, reduced risk of resistance, and patient safety.

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CONFLICT OF INTEREST

All authors claimed that there is no conflict of interest.

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ETHICAL APPROVAL AND INFORMED CONSENT

Ethical approval and informed consent were not required for this study

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