A Literature Review on the Adherence to Screening Guidelines for Latent Tuberculosis Infection Among Persons Living With HIV

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Abstract

Human immunodeficiency virus (HIV) infection increases the risk of reactivation of latent tuberculosis infection (LTBI). Although antiretroviral therapy decreases the progression of LTBI to tuberculosis disease (TBD), persons living with HIV (PLHIV) still have higher risk of TBD compared to the general population. LTBI screening is recommended for all newly diagnosed PLHIV to prevent TBD. However, several studies from low TBD incidence countries have reported sub-optimal implementation of these guidelines. This review aims to assess published studies on adherence to LTBI screening among PLHIV by identifying factors and determinants that affect the implementation of LTBI screening among PLHIV in low TBD incidence countries. Electronic databases were used to search for articles describing the adherence to LTBI screening guidelines. Fourteen studies were included in the final review. Ten studies assessed the frequency of PLHIV getting LTBI screening, and 4 studies assessed the compliance of health care providers in implementing the guidelines. PLHIV who were screened for LTBI ranged from 22.4% to 85%, of which 0.8% to 25.6% had positive results. Only 20% to 57.4% of surveyed physicians implemented the guidelines. Country of birth was an independent predictor of receiving LTBI screening. LTBI screening guidelines are inconsistently performed resulting in missed opportunities for TBD prevention. A comprehensive screening policy involving testing all PLHIV may be the best approach, rather than a targeted approach testing foreign-born individuals only. This will minimize missing domestic cases that can worsen disparity in HIV and tuberculosis infection among minority groups, including Asians, Native Hawaiians, and Pacific Islanders.

Keywords

Tuberculosis disease, tuberculosis infection, low TBD incidence countries, Human Immunodeficiency Virus (HIV) infection, Native Hawaiians, and Pacific Islanders

Abbreviations

ART = Antiretroviral therapy
BCG = Bacillus Calmette-Guerin
BHIVA = British HIV Association
CDC = Centers for Disease Control and Prevention
HIV = Human Immunodeficiency Virus
IDSA = Infectious Diseases Society of America
IGRA = Interferon-gamma release assay
LTBI = Latent tuberculosis infection
MSM = Men having sex with men
Mtb = Mycobacterium tuberculosis
NHPI = Native Hawaiians and Pacific Islanders
PLHIV = Persons living with HIV
TST = Tuberculin skin testing
TB = Tuberculosis
TBD = Tuberculosis disease
TBI = Tuberculosis infection
WHO = World Health Organization

Introduction

Tuberculosis disease (TBD), or active disease due to Mycobacterium tuberculosis (Mtb), predominantly presents as an infection in the lungs and is a leading cause of mortality and morbidity among persons living with Human Immunodeficiency Virus (PLHIV). Latent tuberculosis infection (LTBI), is a state of persistent immune response to Mtb with no evidence of active disease. TB infection encompasses both LTBI and TBD. Compared with individuals without HIV, PLHIV have a 3-16% annual risk and 30% lifetime risk of LTBI progressing to TBD. In 2019, an estimated 2 billion people worldwide had LTBI, and approximately 10 million were diagnosed with TBD. Of individuals with TBD, 8.2% were also living with HIV. TBD is the most common opportunistic infection among PLHIV and often leads to death.

In 2019, the US, a country with low TBD incidence, had 8 920 cases of TBD, and 13 million reported cases of LTBI. The prevalence of LTBI among PLHIV was 7.6%. Seventy percent of TBD cases occurred among persons born outside the US, and the majority of cases were Asian immigrants with an incidence rate of 25.7 per 100 000 persons followed by Native Hawaiians and Pacific islanders (NHPI) with an incidence rate of 25.1 per 100 000 persons. In the same year, there were 198 new cases of HIV-TBD coinfection in the country, including 2 cases in Hawai‘i. In 2021, Hawai‘i reported 107 TBD cases with an incidence of 7.35 cases per 100 000 persons. Although the incidence of TB infection in PLHIV overall is declining, new cases of foreign-born PLHIV and TBD have remained stable.

TBD and HIV have disproportionately impacted NHPI in the US. Among those who were born in the US, TBD were highest among NHPI population. From 2010-2019, the annual incidence rates of TBD among NHPI born in the US and US Affiliated Pacific Islands (USAPI) were 6.5 cases and 150.7 cases per 100 000 persons, respectively, in comparison to the nationwide incidence rate of 2.2 cases per 100 000 persons. The US populations consists of 0.4 percent of the NHPI race and 0.1% PLHIV. NHPI are also 2.4 times more likely to have TBD compared to the White population. Moreover, NHPI are also 2.4 times more likely to have HIV compared to the White population. Tuberculin skin test (TST) and interferon gamma release assay (IGRA) are 2 methods currently used to identify LTBI and TBD. Both screening tools have a sensitivity greater than 90% when tested on the general population, but their sensitivities are decreased when used among PLHIV, particularly in subjects...
with advanced immunosuppression.13,14 Even with lower test sensitivities among PLHIV, use of the 2 screening methods is highly recommended by different LTBI screening guidelines.15-18 LTBI treatment among PLHIV who have a positive TST reduces the risk of developing TBD by 62%.19

Clinical practice guidelines from the American Thoracic Society, the Infectious Diseases Society of America (IDSA), and Centers for Disease Control and Prevention (CDC) recommend screening populations who have increased risk of infection with Mtb, including PLHIV and immigrants from countries with high burden of TBD.15 The US Preventive Services Task Force recommends LTBI testing of asymptomatic adults who were born in or previously lived-in countries with increased TBD prevalence or who live in or have lived in high-risk congregate settings, but no recommendations are given for PLHIV.16 The Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-infected Adults and Adolescents developed by the CDC, the National Institutes of Health (NIH), and the HIV Medicine Association (HIVMA) of the IDSA recommend that all PLHIV should be tested for LTBI at the time of HIV diagnosis regardless of the risk of TBD exposure; persons with negative diagnostic tests for LTBI, advanced HIV infection (CD4 count <200 cells/mm³), and without indications for initiating empiric LTBI treatment should be retested for LTBI once they start antiretroviral therapy (ART) and attain a CD4 count ≥200 cells/mm³.17 In addition, annual testing for LTBI using TST is recommended for PLHIV who are at high risk of repeated or ongoing exposure to persons with TBD.17

LTBI screening guidelines are based on evidence-based medicine, but several studies from low TBD incidence countries, where there are fewer than 10 TBD cases per million population, reported sub-optimal implementation of these guidelines.20-34 The objective of this article is to review published studies on adherence to LTBI screening on PLHIV and to identify factors and determinants that affect the implementation of LTBI screening in low TBD incidence countries.

Methods

The online databases used for this study were OneSearch, the search engine of John A. Burns School of Medicine Library, PubMed, and PubMed Central. The keywords used for all 3 search engines was “LTBI screening” AND “HIV.” Hand searching of studies that were not indexed in the online databases was also done. Google search was performed for grey literature to extract data from CDC and World Health Organization (WHO) websites to compliment the literature. Peer-reviewed studies published in English between 1990 to 2021 were included in the study. Studies that assessed the adherence and implementation of LTBI screening among newly diagnosed PLHIV in low TBD incidence countries based on WHO’s criteria (<10 TBD cases per million population) were included in the study.20 Studies that merely reported on knowledge and perception of LTBI screening in HIV patients were not included. Studies that measured the predictive value, sensitivity, and specificity of LTBI screening tools used in PLHIV were also excluded from this study.

Titles and abstracts of all references were all screened by 1 reviewer. The title of the article was important for initial impressions of relevancy based on keywords and topic of interests. If the study seemed significant for the review, then the abstract was read to confirm the information within the article. Full text versions of potentially relevant articles were examined for eligibility. In order to prevent excluding relevant articles, results of the database searches were screened 3 times. The articles that were of interest for this study were organized using the Zotero version 6.0.20 (Corporation for Digital Scholarship, Vienna, VA).55

Results

A total of 471 articles were compiled through Zotero, of which 38 articles were duplicates. Three hundred seventy-six articles were excluded based on the relevance of their titles. Fifty-seven articles were then included for abstract and article review. Forty-five articles were excluded based on the exclusion criteria. Two articles cited by 1 study were hand-searched and included after reviewing the articles. A total of 14 articles were included in the final review (Figure 1). These studies were published from 1998 to 2019 and were conducted in low TBD incidence countries: USA, Switzerland, Canada, Belgium, the Netherlands, the United Kingdom (UK), New Zealand, and Italy.21-34 These studies either focused mainly on implementation and adherence to LTBI screening among newly diagnosed PLHIV or included LTBI screening adherence as 1 of the objectives of the study. Ten studies assessed the implementation of LTBI screening among HIV patients through retrospective medical chart review (Table 1). They assessed the frequency of HIV patients getting LTBI screening, of which, 9 studies measured the positivity rate of HIV patients who were tested for LTBI. Nine studies reviewed protocol adherence to LTBI screening guidelines performed within the first 6 months or 12 months of HIV diagnosis. The LTBI screening method used by 6 studies was TST alone whereas 4 studies used IGRA and TST in their studies. Four studies assessed the compliance of physicians in implementing the LTBI screening guidelines through survey of medical practitioners (Table 2).

PLHIV who were screened for LTBI ranged from 22.4% to 85% of the screening population. It is important to note that while the study by Schulte et al in the US reported the highest adherence to LTBI screening with 85% adherence, the population used for the study was limited only to pregnant women.23 On the other hand, the study by Kaplan et al reported an adherence percentage of 80%, but analyzed the general PLHIV population in Ryan White HIV/AIDS facilities.22 Gow et al in New Zealand reported improvement of LTBI guideline adherence from 55% in 2011 to 93% in 2014.29 TST and IGRA were both used as
the screening tools in 2011, but the significant improvement in 2014 was noted when IGRA was used as the sole screening tool. Similar results were noted by Adams et al in the US, where an improvement from 28% to 37% was noted as the facility transitioned from TST to IGRA-based screening.28

Nine studies reported positive results ranging from 0.8% to 25.6% of PLHIV screened for LTBI.21,23-30 The study by Schulte showed a 25.6% positive result in HIV-infected pregnant women, and the study by Brassard et al in Canada showed 14.1% positive results in all PLHIV.23,25 LTBI treatment was initiated in 36.9% to 100% positive patients, but only 5 studies showed treatment completion that ranged between 22.6% to 74.3%.21,25,26,29,30 Schulte reported that while LTBI treatment was initiated in all positive patients, completion and compliance among patients were not documented.23 In the study by Elzi et al, among the 246 LTBI positive participants who did not receive preventive treatment, 16 (6.5%) developed TBD.25 Missed opportunities to prevent TBD were also noted by Brassard et al in Canada where 4 (6%) subjects who tested positive but did not received treatment progressed to TBD.26

Seven studies assessed if CD4 count level was considered a factor in performing LTBI screening, and contrasting results...
### Table 1. Characteristics of Studies on Adherence to Guidelines for Screening LTBI Among PLHIV Based on Medical Chart Review

<table>
<thead>
<tr>
<th>Source</th>
<th>Year/ Country</th>
<th>Method of Screening and Adherence</th>
<th>Predictors of Having TST and/or IGRA Performed/Reasons of Low Adherence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sackoff, et al</td>
<td>1998/USA</td>
<td>TST: 865/1342 (64%); Screened within 6 months of diagnosis; Positive: 48 (6%)</td>
<td>Numbers of visit, same sex behavior with men, &gt;200 CD4 count</td>
</tr>
<tr>
<td>Kaplan, et al</td>
<td>1999/Ryan White Title III facilities USA</td>
<td>TST: 1129/1411 (80%); Screened within 12 months of diagnosis</td>
<td>Male sex, injecting drug users, patients from urban area, more than 1 year at the facility, who had had &gt; 1 CD4 count in the past year.</td>
</tr>
<tr>
<td>Schulte, et al</td>
<td>2002/ Miami, FL USA</td>
<td>TST: 176/207 (85%); Positive: 45 (25.6%)</td>
<td>Foreign born, unknown HIV status at the first prenatal visit, history of drug use</td>
</tr>
<tr>
<td>Lee, et al</td>
<td>2005/USA</td>
<td>TST: 436/841 (51.8%); Screened within 6 months of diagnosis; Positive: 27 (6.7%)</td>
<td>Additional risk factors for TB, history of HIV related preventive treatment, higher number of clinic visits, and attendance at facilities with a written policy to provide TST for all PLHIV</td>
</tr>
<tr>
<td>Elzi, et al</td>
<td>2007/ Switzerland</td>
<td>TST: 4158/6018 (69%); Screened within 12 months of diagnosis; Positive: 390 (9.4%)</td>
<td>&lt;200 CD4 count, patients not on HAART, female sex, country of birth</td>
</tr>
<tr>
<td>Brassard, et al</td>
<td>2009/ Canada</td>
<td>TST: 476/2123 (22.4%); Screened within 6 months of diagnosis; Positive: 67 (14.1%)</td>
<td>Foreign born, having a first clinic visit during the HAART era, time between HIV diagnosis and first visit, and previous antiretroviral exposure.</td>
</tr>
<tr>
<td>Reaves, et al</td>
<td>2017/USA</td>
<td>TST and IGRA: 1907/2772 (68.8%); Screened within 12 months of diagnosis; Positive: 131 (6.9%)</td>
<td>Reasons of low adherence: physicians were not aware of the standards of care for preventing tuberculosis among PLHIV even in a geographic area with a high prevalence of M. tuberculosis and HIV.</td>
</tr>
<tr>
<td>Adams, et al</td>
<td>2017/Pennsylvania USA</td>
<td>TST: 61/158 (27.9%); IGRA: 57/96 (37.3%); Screened within 12 months of diagnosis; Positive: 1 (8.8%)</td>
<td>Reasons of low adherence: physicians were not aware of the standards of care for preventing tuberculosis among PLHIV even in a geographic area with a high prevalence of M. tuberculosis and HIV.</td>
</tr>
<tr>
<td>Gow, et al</td>
<td>2017 New Zealand</td>
<td>TST and IGRA: Screened within 12 or more months of diagnosis 2011: 416/752 (55%); Positive: 74 (10%); 2014: 68/73 (93%); Positive: 2 (2%)</td>
<td>Foreign born, older population, and CD4 &lt;100</td>
</tr>
</tbody>
</table>

Abbreviations: ART: antiretroviral therapy; HAART: highly active antiretroviral therapy; IGRA: interferon-gamma release assay; LTBI: latent tuberculosis infection; PLHIV: people living with HIV; TB: tuberculosis; TST: tuberculin skin testing.

### Table 2. Characteristics of Studies on Adherence to Guidelines for Screening LTBI Among PLHIV Based on Health Care Provider Surveys

<table>
<thead>
<tr>
<th>Source</th>
<th>Year/ Country</th>
<th>Adherence</th>
<th>Predictors of Having TST Performed/Reasons of Low Adherence</th>
</tr>
</thead>
<tbody>
<tr>
<td>DeRiemer et al</td>
<td>1999/San Francisco, CA USA</td>
<td>139/350 (39.4%) physicians provide annual PPD testing</td>
<td>Reasons of low adherence: physicians were not aware of the standards of care for preventing tuberculosis among PLHIV even in a geographic area with a high prevalence of M. tuberculosis and HIV. Physicians with the least experience with PLHIV are the least familiar with current guidelines and standards of care for preventing tuberculosis.</td>
</tr>
<tr>
<td>Verbon, et al</td>
<td>2016/ Netherland</td>
<td>12/51 (25%) physicians intended to screen patients as the guideline stipulate</td>
<td>Predictors of having TST/IGRA performed: foreign born (Liberians vs Dutch), alcohol intake, higher CD4 count</td>
</tr>
<tr>
<td>White, et al</td>
<td>2017/UK</td>
<td>93/162 (57.4%) offered LTBI screening</td>
<td>Predictors of having TST/IGRA performed: CD4 count&lt; 200 cells/million and patients from high TB incidence countries</td>
</tr>
</tbody>
</table>

Abbreviations: ART: antiretroviral therapy; HAART: highly active antiretroviral therapy; IGRA: interferon-gamma release assay; LTBI: latent tuberculosis infection; PLHIV: people living with HIV; TB: tuberculosis; TST: tuberculin skin testing.
were noted. In Swiss and Italian studies, LTBI screening was performed more frequently among patients with CD4 <200 cells/mm³ at registration.25,36 In a study conducted by Sackoff et al in New York and by Adams et al in Philadelphia, CD4 level >200 cells/mm³ was associated with likelihood of getting screened with TST.21,28 In Canada, TST screening was done regardless of CD4 count level.26

Four survey studies among health care providers in the Netherlands, Belgium, USA, and UK were included in this review (Table 2).31-34 These studies showed only 20% to 57.4% of health care providers and representatives adhere to and implement LTBI screening guidelines. The study by White et al in the UK showed that 57.4% of health care representatives from 162 UK geographical areas, consisting of English, Welsh, Irish, and Scottish HIV healthcare provider organizations, reported offering LTBI screening, but adherence to British HIV Association (BHIVA) and National Institute for Health Care Excellence guidelines was only 35.5% and 6.5%, respectively.34 A study by Verbon et al in the Netherlands revealed that only 24% of physicians had the intention to screen PLHIV for LTBI; however, the Netherlands HIV-TB guidelines stipulate screening regardless of birth place, sex, and CD4 count.33 Barriers noted for low implementation include lack of sensitivity of screening tools, lack of confidence in the existing guidelines, and belief of cohorts having low risk of LTBI.31-34 Experience was a noted factor as physicians with the most encounters with HIV or TBD were more likely to adhere and implement the guideline.33

Thirteen studies assessed predictors of having TST and/or IGRA performed. Seven studies identified that PLHIV who were born from high TBD incidence countries were more likely to get screened for LTBI ranging from 40.4% to 82% compared to non-foreign-born patients, 15.3% to 68.9%.23,25-27,30,33,34 Other noted factors for increased likelihood of being screened include male sex, men having sex with men (MSM), and multiple clinic visits. Determinants of having a positive LTBI screening included, foreign birth, higher than 100 cells/mm³ CD 4 count baseline, and MSM.

**Discussion**

LTBI screening guidelines for PLHIV are developed to identify patients who should be evaluated for LTBI to reduce the morbidity and mortality of subsequent TBD and to prevent TBD transmission. However, LTBI screening guidelines among PLHIV in low TBD incidence countries are often not adhered to. Testing by TST involves a multistep process that requires 2 clinical encounters for administration and interpretation of TST reaction after 48 to 72 hours.3 This creates an opportunity for both the health care provider and the patient to fail to complete the screening process. Failure to follow-up and noncompliance of patients may result in missed opportunities in preventing TBD, hence, strategies should be considered to improve the compliance of these patients, such as requiring counseling and advising for those who refused to be screened and treated. Another strategy that could improve the adherence to LTBI screening is the implementation of LTBI screening policy in HIV care facilities. High adherence as a result of having a TST implementation policy in HIV care clinics is supported by studies from Schulte and Lee who reported that PLHIV were more likely to get screened for LTBI if they were seen in a facility with a written policy or TST programs to provide LTBI screening for all PLHIV.21,24 This approach may help reduce disparities in HIV and TBD among NHPI who are less likely to be screened for sexually transmitted diseases and opportunistic infections, including HIV and LTBI screening.36-38

A barrier identified for poor physician adherence to LTBI screening is the lack of sensitivity of the 2 recommended screening tools when used in PLHIV.39 Anergic reaction and bacillus Calmette-Guerin (BCG) vaccination may induce false-positive screening test results in PLHIV, which may discourage healthcare providers from adhering to the LTBI screening guideline. In addition, both screening tests are inadequate to predict the progression of LTBI to TBD.39,40 IGRA and TST have sensitivity of more than 90% when tested in non-HIV infected individuals, but sensitivity decreases in PLHIV to 72% and 61% for IGRA (TSPOT and QFT-GIT tests, respectively) and 64.3% and 71.2% for TST (at cut-off value of 10 mm and 5 mm, respectively).41,42 However, IGRA has higher specificity and less cross-reactivity with BCG vaccination than TST in low TBD prevalence settings.43-46 Therefore, testing by IGRA should be recommended as the diagnostic test of choice for patients who were born from high TBD incidence countries and those who received the BCG vaccination.

PLHIV who are on ART have significantly reduced hazard ratio (HR) of incident TBD (HR=.44), but their risk still remains higher than in general population.24,47 Hence, TBD preventive therapy should be offered for its beneficial effects in reducing the reactivation of LTBI in PLHIV on ART. However, poor initiation and completion of LTBI treatment was noted in this review. The treatment was initiated in 36.9% to 100% positive patients, but only 22.6% to 74.3% completed the treatment.21,23,26-29,30,36 Some of the low treatment initiation results may be attributed to physician decision making. Despite evidence of low isoniazid toxicity and the efficacy of isoniazid preventive therapy for 6 to 12 months in reducing TBD, some physicians are hesitant to follow the treatment guidelines due to fear and concerns of isoniazid toxicity and risks of polypharmacy treatment.32,34,48-50 Continued training in LTBI care in PLHIV is needed to implement evidence-based therapeutic guidelines. Other possible reasons for incomplete LTBI treatment were noncompliance of patients, refusal to be treated, loss to follow-up, and adverse reaction to treatment. One factor that results in noncompliance of patients is the length of preventive treatment of LTBI. A 1-month regimen of rifapentine and isoniazid therapeutic regimen for prevention of LTBI in PLHIV was recently proposed, and implementing this therapeutic regimen could result in
better patient compliance and higher completion rate of LTBI treatment.\cite{31,52} Shorter duration of treatment could also result in fewer adverse reactions. NHPI and Asians are less adherent to medications compared to other races, and a shorter treatment regimen will be beneficial in reducing health disparities among this group.\cite{33,54}

An observational prospective study by Capocci in the UK showed that it is not cost-effective to screen for LTBI in PLHIV with high ART usage from countries with medium and high TBD incidence settings.\cite{55} In this review, 6 studies advocated targeted LTBI screening among PLHIV who are born outside of low TBD incidence countries. All the European studies suggested adopting the BHIVA guidelines which recommends targeted screening of PLHIV who have the highest risk of developing TBD based on the country of origin, CD4 level, and length of time on ART. The BHIVA guideline also recommends screening PLHIV from low TBD incidence countries if they have additional TBD risk factors, including recent travel to high TBD incidence countries or close exposure to a known TBD case.\cite{56}

Although a targeted LTBI screening guideline among PLHIV in the US may be cost-effective, this approach will likely result in missed opportunities to detect both LTBI and TBD cases among PLHIV who were born in the US. The Canadian study by Brassard et al found that 55.6% cases of TBD in individuals who were not TST screened were born in Canada.\cite{26}

In 2021, Asians and NHPI constitute two-thirds of population in Hawai‘i and include groups who experience notable health disparities in TBD and HIV infection due to social and demographic risk factors contributing to poorer health outcomes.\cite{57,58}

Some Asian ethnic groups and NHPI are less likely to be screened and tested for HIV compared to other racial groups resulting to late TBD diagnosis and having opportunistic infection at the time of diagnosis.\cite{56,57,58} A targeted screening program, as advocated by several European countries, may miss domestic cases and create racial stereotypes. Triaging NHPI and Asians by country of birth could worsen the disparity in health care access and the prevalence of HIV infection and LTBI.

In conclusion, in a low-burden TBD country, such as the US, prevention among PLHIV is best accomplished through strict adherence to LTBI screening guidelines regardless of racial group and country of birth. Early detection and treatment of LTBI in high-risk populations can improve TBD control and decrease morbidity and mortality. As the US seeks to achieve the WHO TBD elimination goal, improving LTBI screening among PLHIV will be an important element of a comprehensive national strategy in TBD prevention.

**Conflict of Interest**

None of the authors identify a conflict of interest.

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