

Access and adherence to isoniazid preventive therapy and occurrence of active TB in a cohort of people living with HIV: a retrospective cohort study in Sao Paulo, Brazil

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ABSTRACT

Tuberculosis (TB) is still a leading cause of morbidity and mortality among people living with HIV (PLHIV). The diagnosis of latent TB is required for the implementation of prophylactic therapy with isoniazid (PTI). However, low access to diagnosis of latent TB and non-adherence to PTI may hinder potential benefits of this essential intervention. In this study, we addressed the access and adherence to PTI in a cohort of PLHIV with positive tuberculin skin test (TST) in a reference HIV clinic in Sao Paulo, Brazil. We have also analyzed the occurrence of active TB over a median of 131 months after a positive TST among study participants. Our findings revealed that 88.3% of the 238 TST-positive patients had access to PTI, and 196 (93.3%) of those with access adhered to PTI. Active tuberculosis was diagnosed in three of the 196 TST-positive patients who adhered to PTI (1.5%; 95% confidence interval [CI] 0.3–4.4%), whereas seven cases were detected among 42 patients without access or who did not adhere to PTI (16.6%; 95% CI 7.0–31.3%). The apparent beneficial effect of PTI in our cohort is consistent with previous studies including PLHIV, and highlights the importance of reliably delivering each of the steps between screening for latent TB and provision of PTI.

KEYWORDS: Active tuberculosis. Adherence. HIV. Isoniazid preventive therapy. Prophylactic therapy. Tuberculin skin test. Tuberculin test. Tuberculosis.

INTRODUCTION

According to the World Health Organization (WHO) Global tuberculosis report 2019, tuberculosis (TB) is the leading cause of death from a single infectious agent, with estimated 1.2 million deaths among HIV-negative people and additional 251,000 deaths among people living with HIV (PLHIV) in 2018 alone. HIV infection is a consistent risk factor for active TB, and PLHIV represent 8.6% of all TB cases¹.

Brazil is one of the 30 countries with high TB burden listed by WHO, which collectively represent 87% of the global occurrence of the disease. In 2015, 69,000 TB cases and 4,500 TB-related deaths were registered in Brazil, of which 1,700 occurred among PLHIV. Sao Paulo State recorded more than 17,000 TB cases in the same year, of which 1,474 occurred among PLHIV².

Asymptomatic or latent infection with *Mycobacterium tuberculosis* precedes the development of active TB. Prophylactic therapy with isoniazid (PTI) is a safe and effective intervention to prevent the development of active TB among patients with latent infection^{3,4}. A positive tuberculin skin test (TST) and/or positive interferon- γ

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release assay are the currently available tools for latent TB diagnosis in clinical settings⁵.

Although previous studies have documented the beneficial impact of PTI among PLHIV⁶⁻¹⁰, barriers in the diagnosis of latent TB infection, in the implementation of PTI, and non-adherence to PTI may hinder potential benefits of this essential intervention¹¹⁻¹⁴.

In this retrospective cohort study, we addressed the access and adherence to PTI in a cohort of PLHIV with positive TST. We have also analyzed the occurrence of active tuberculosis over a median 131 months after a positive TST, according to PTI uptake among study participants.

METHODS

Around 3,500 adult patients attending the HIV outpatient clinic at Hospital das Clinicas da Faculdade de Medicina da Universidade de Sao Paulo were screened to participate in the study.

We included all patients undergoing a TST between February 2005 and December 2009 as part of routine care. Local guidelines recommend yearly TST to all PLHIV without a previously positive TST and without previous or current active TB¹⁵, regardless of CD4+ counts. The test was performed with an intradermal injection of 0.1 mL of the purified protein derivative (PPD-Rt-23, Statens Serum Institut, Copenhagen)¹⁶ on the anterior part of the left arm. A trained nurse measured the local reaction 72 h after TST administration¹⁷⁻¹⁹. All patients with reactions ≥ 5 mm were considered to have a positive TST result.

We addressed the access to PTI among patients who had a positive TST using isoniazid prescription records as well as medical chart records of isoniazid use. PTI regimen prescribed in our institution consisted of 300 mg of isoniazid daily, for 180 days. Adherence to PTI was characterized using pharmacy records of isoniazid monthly dispensations and data from medical charts. Directly observed treatment is not used for PTI in our clinic. PTI was considered complete for the all patients receiving treatment for at least 180 consecutive days.

Retrospective follow-up of clinical outcomes was performed for a median of 131 months (range 107-154) to identify cases of active TB. We used data from medical charts, pharmacy records for dispensation of active TB regimen, laboratory results, histopathology and radiology reports, and the TB surveillance system from Sao Paulo State; the adjudication of active TB was carried out by two independent infectious diseases specialists. Different data sources were linked using either the unique identifier assigned for each patient in the hospital system, or the patient's name and date of birth in the case of the TB surveillance system.

We used descriptive statistics to present patients' characteristics. To compare patients with or without access to PTI we used chi-squared test for categorical variables and the Wilcoxon Rank-Sum test for numerical variables. For all analyses, we used Stata 15.1 (StataCorp. College Station, TX: StataCorp LP) with a 0.05 significance level.

The Ethics Committee of Hospital das Clinicas da Faculdade de Medicina da Universidade de Sao Paulo approved the study (approval N° 2.624.521) with exemption of the informed consent due to the retrospective design and data collection of the study. All the participants' identifiable information were maintained confidential throughout the study.

RESULTS

Between February 2005 and December 2009, 3,260 TST were performed in 1,983 patients. Of those, 72 h reaction measurement was carried out for 2,878 tests, with an overall percentage of missing TST measurement appointment of 11.7%. TST was positive (≥ 5 mm) in 246 participants, representing 8.5% of the patients with available TST measurement. After the exclusion of six patients lost to follow-up, one patient transferred to another clinic and one patient who died due to TB-unrelated causes, 238 TST-positive patients were retrieved for evaluation of PTI access and adherence.

Access and adherence to PTI

Demographic and clinical characteristics of the 238 TST-positive patients according to access to PTI are shown in [Table 1](#). Access to PTI was identified in 210 of 238 TST-positive patients (88.2%). Groups were similar in regard to sex, age, race, education, proportion under antiretroviral treatment, proportion with undetectable HIV viral load and regarding CD4+ lymphocyte counts; however, patients with access to PTI had higher median CD4+ nadir (215 vs. 153, $p=0.031$) and were more likely to have a TST ≥ 10 mm (71 vs. 32%, $p<0.001$).

Among the 28 TST-positive patients for whom no PTI was prescribed (11.8%), 21 (75.0%) had no clear justification for the missed prescription in medical charts. The remaining seven TST-positive patients without access to PTI had medical chart notes listing depression (two patients) and chronic liver disease (three patients) as reasons for the absence of PTI; in two additional cases the healthcare provider questioned the accuracy of the TST result.

Among the 210 TST-positive patients who had access to PTI, 196 (93.3%) were considered adherent to PTI ([Figure 1](#)). Of the 14 patients who were non-adherent, eight

Table 1 - Demographic and clinical characteristics of the 238 tuberculin skin test-positive patients, according to access to prophylactic therapy with isoniazid.

	Access to prophylactic isoniazid		p-value
	Yes N=210	No N=28	
Male sex (%)	147 (70.0)	21 (75.0)	0.585
Age at TST (years)	42	46	0.196
Ethnicity (%)			
White/Caucasian	166 (79.0)	25 (89.3)	0.434
Non-white/caucasian	40 (19.0)	3 (10.7)	
Not informed	4 (1.9)	-	
Education (years)			
0	3 (1.4)	0	0.864
≤ 7	22 (10.5)	2 (7.1)	
8 - 11	134 (63.8)	20 (71.4)	
≥ 12	29 (13.8)	5 (17.9)	
Missing	22 (10.5)	1 (3.6)	
Under antiretroviral therapy (%)	185 (88.1)	26 (92.9)	0.455
CD4+ count at TST (cells/mm ³)	653	514	0.140
Nadir CD4+ count (cells/mm ³)	215	153	0.031
Undetectable HIV viral load (%)	150 (71.4)	23 (82.1)	0.359
Coexisting comorbidity (%)	106 (50.5)	12 (42.9)	0.449
Concurrent medications (%)	110 (52.4)	18 (64.3)	0.235
Tuberculin skin test ≥ 10 mm (%)	150 (71.4)	9 (32.1)	< 0.001

Numeric variables are presented as medians. Undetectable HIV viral load is defined as < 400 copies/mL.

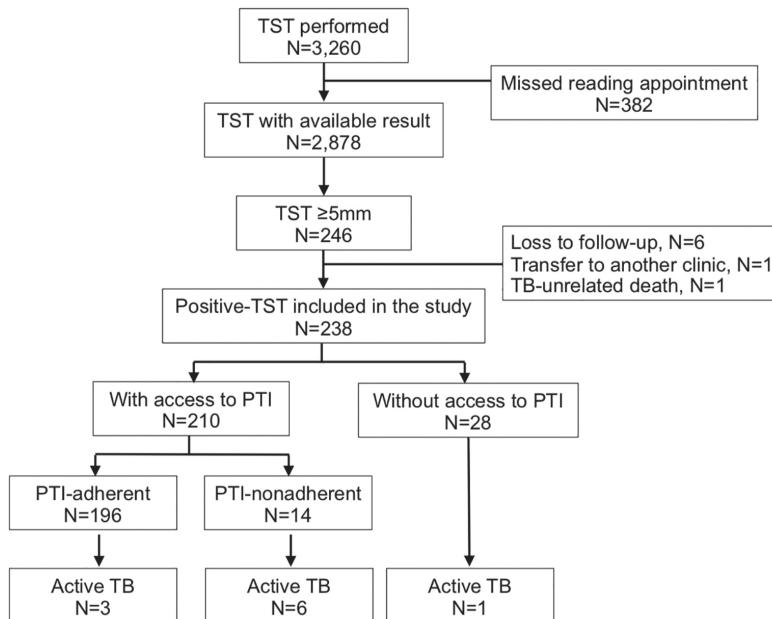


Figure 1 - Overview of the study participants and their outcomes.

remained free of active TB during the follow-up period. The median time on PTI was 75 days (41.7% of total PTI treatment) for the eight non-adherent patients without active TB. Information on the reasons for PTI withdrawal was available for two patients: one reported gastrointestinal side-effects and the other simply refused PTI.

Active TB diagnosis during follow-up

We detected active TB in three of the 196 PTI-adherent patients (1.5%) after a median follow-up of 114 months. In contrast, six of the 14 patients who were non-adherent to PTI developed active TB after a median follow-up of

106 months post positive TST (42.9%). Of the 28 patients who failed to access PTI, one (3.6%) developed active TB after 59 months.

A complete description of the access and adherence to PTI, as well as active TB development is presented in [Figure 1](#), and a detailed description of active TB cases is provided in [Table 2](#). All patients with active TB were under antiretroviral therapy, although only six of them had undetectable HIV viral load (< 400 copies/mL). In six patients, CD4 count was < 350/mm³. Respiratory tract was the single site of TB in only three cases; disseminated TB, affecting two or more organs was diagnosed in five cases; TB restricted to eyes and lymph nodes accounted for one case each.

All except for one patient had access to PTI, however non-adherence was detected in six cases, including four patients with CD4 count < 350/mm³. Among the three patients adherent to PTI, two had very low CD4+ counts (147 and 42 cells/mm³), which may have predisposed to active TB despite PTI. Poor retention in TB treatment was observed for two patients. One patient with pulmonary and meningeal TB died three months after TB diagnosis, and the remaining seven patients were considered cured after TB treatment.

Effect of prophylactic therapy with isoniazid on the development of active tuberculosis among PLHIV with a positive TST

Overall, only three TB cases were diagnosed among 196 TST-positive patients who adhered to PTI (1.5%; 95% confidence interval [CI] 0.3-4.4%), whereas seven cases were detected among 42 patients without access or non-adherent to PTI (16.6%; 95% CI 7.0-31.3%; $p < 0.001$).

DISCUSSION

In this retrospective cohort, we showed that more than 10% of PLHIV who had positive TST as part of routine care, failed to receive PTI in an academic HIV outpatient clinic in Sao Paulo, Brazil. Interestingly, participants with access to PTI had higher median CD4+ nadir (215 vs. 153, $p = 0.031$). Access to PTI may have been facilitated for patients with better overall access to healthcare, who underwent HIV testing earlier in the course of infection. We have also found that participants with access to PTI were more likely to have a TST ≥ 10 mm (71 vs. 32%, $p < 0.001$). It is plausible that providers were more persuaded to prescribe PTI for patients

Table 2 - Detailed description of the 10 active tuberculosis cases identified in the cohort.

Case	Age, Sex	Ethnicity	ART	CD4+ count (cells/mm ³)	Undetectable HIV viral load under ART	TST (mm)	PTI access	PTI adherence	Time on PTI (days)	Time to TB (months)	TB presentation and clinical outcome
1	41, F	Mixed	Yes	511	Yes	15	Yes	Yes	180	16	Pulmonary and urinary tract TB, treatment completed; cure
2	49, M	Caucasian	Yes	42	No	9	Yes	Yes	180	114	Pulmonary and bone TB, poor retention, did not complete treatment
3	38, F	Caucasian	Yes	147	Yes	19	Yes	Yes	180	132	Pulmonary TB, treatment completed; cure
4	58, M	Caucasian	Yes	271	No	6	Yes	No	90	23	Pulmonary TB, treatment completed; cure
5	25, M	Caucasian	Yes	119	No	18	Yes	No	90	53	Lymph node TB, poor retention, did not complete treatment
6	32, F	Caucasian	Yes	609	Yes	21	Yes	No	30	95	Meningeal and urinary tract TB, treatment completed; cure
7	24, F	Caucasian	Yes	339	Yes	20	Yes	No	90	117	Pulmonary and meningeal TB, treatment completed; death
8	71, M	Black	Yes	37	No	9	Yes	No	60	121	Pulmonary TB, treatment completed; cure
9	42, M	Caucasian	Yes	447	Yes	19	Yes	No	150	129	Miliary TB, treatment completed; cure
10	57, M	Black	Yes	550	Yes	15	No	Not applicable	0	59	Ocular TB, treatment completed; cure

M = male; F = female; ART = antiretroviral therapy; TST = tuberculin skin test; PTI = prophylactic therapy with isoniazid; TB = tuberculosis; HIV viral load was considered undetectable when < 400 copies/mL

with a TST ≥ 10 mm given that lower measurements might be due to previous BCG vaccination, routinely performed in Brazil.

Adherence to PTI was high (93.3%) among patients who received PTI. Although active TB was diagnosed in only 10 cases (4.2%) after a median follow-up of 105 months, patients with access and adherence to PTI had lower occurrence of active TB when compared to patients without access or non-adherent to PTI (1.5%, 95% CI 0.3-4.4 vs. 16.6%, 95% CI 7.0-31.3, respectively).

Yearly screening of latent TB infection is recommended by the Brazilian Ministry of Health^{20,21}, and PTI is recommended for all PLHIV with a TST ≥ 5 mm. In settings with scarcity of TST, PTI is recommended for all PLHIV with CD4+ counts < 350 , those with virological failure or who are not on antiretroviral therapy, and those with increased risk based on epidemiological characteristics^{15,22}. It is also important to mention that antiretroviral treatment is available in the Brazilian public healthcare system for all PLHIV, and HIV clinics offer joint, free of charge care for patients with latent or active TB. The Brazilian Ministry of Health issues comprehensive and updated guidelines for TB management among PLHIV²².

TST has important limitations. The yearly frequency of TST performance may fail to detect TB exposure between the measurements. Moreover, the measurement of TST result requires an additional consultation at the healthcare service, increasing the cost, complexity, and incurring in a higher percentage of missing results. In our cohort, 382 (11.7%) of 3,260 TST performed missed the return visit and could not be included in the study^{23,24}. Finally, the shortage of supplies required to perform TST has been documented in several states of Brazil and have also been reported in a few studies²⁵⁻²⁷. One alternative diagnostic test to identify latent TB is the interferon- γ release assay, which detects the patient's lymphocyte response to TB-specific antigens using a single blood sample. Cost-effectiveness studies are currently underway in Brazil to investigate the feasibility of implementation of this test.

Our study had a few limitations. Only 1,983 patients underwent TST during the study period. The remaining 1,500 PLHIV regularly followed in our clinic failed to perform TST because: i) They had a positive test in the past, with or without prior PTI; ii) They had previous or current TB; iii) They had contraindications to PTI; iv) The healthcare provider failed to request the test; v) The patient failed to perform the test despite a medical indication.

Considering that the nursing providers in our institution routinely screen patients who are eligible for TST, we believe that failure of TST requesting was a rare event.

In addition, most patients have been followed for several years and, in an endemic country such as Brazil, are likely to have had a positive TST in the past.

One strength of our study is the use of prospectively collected data from a large reference clinic in the Sao Paulo State, allowing the linkage of data from different sources.

Previous studies conducted in Africa and in Brazil showed lower rates of access and adherence to PTI compared to our study^{12,28,29}. In the study conducted by Saraceni *et al.*³⁰ in Rio de Janeiro, only 17 of 67 eligible PLHIV (25.4%) had access to PTI; adherence to PTI was 53% among Brazilian patients enrolled in general healthcare facilities³¹. Santos *et al.*³² showed that 53 out of 66 eligible PLHIV had access to PTI (80.3%), but only 26 completed PTI (49.1%). In our own institution, a cross-sectional study conducted in 2005 showed that only 59% of eligible PLHIV had access to TST and only 55% of eligible patients had access to PTI¹¹. This study prompted the initiation of a training and education program along with the establishment of routine screening of patients during every pre-consultation evaluation and consequently, the access and adherence to PTI have increased substantially in our institution.

Although the overall access and adherence to PTI were high in our cohort (88.2 and 93.3% respectively), only seven out of 28 patients (25%) included in our study who failed to access PTI had medical charts notes describing the reason why PTI was not prescribed. This highlights the need for continuous training among healthcare providers, even in an academic institution.

Other studies including PLHIV have addressed predictors of adherence to PTI among PLHIV. In a study conducted in urban Malawi, Thindwa *et al.*³³ showed that lower CD4+ counts, PTI side effects and HIV WHO stages 3 and 4 were associated with lower adherence to PTI. In Brazil, treatment intolerance and distance to the healthcare facility were identified as predictors of non-adherence to PTI among household contacts of TB patients³⁴. In our study, since most patients were adherent to PTI, we could not explore the risk factors for PTI non-adherence.

The apparent beneficial effect of PTI in our cohort is consistent with previous studies including PLHIV and underscores the importance of a reliable delivery of each step between screening of latent TB and provision of PTI. In a recent review, Alsdurf *et al.*³⁵ described significant flaws at several steps in the cascade of latent TB diagnosis and treatment, including completion of testing, medical evaluation after testing, referral for treatment and completion of treatment. The high access and adherence to PTI observed in our clinic was achieved after education and treatment interventions that must be periodically repeated so as to attain the highest impact. However, 11.7% of

our patients missed the TST measurement appointment, revealing potential pitfalls in the cascade of latent TB diagnosis and treatment. Strategies to further improve access and adherence to PTI have been explored by several authors, including shorter duration regimens, use of digital technologies to improve adherence and retention in care, use of simplified treatment regimens or use of regimens with better tolerance³⁶⁻³⁸. In addition, access to PTI could be improved with the implementation of the interferon- γ release assay testing in settings with scarcity of TST or whenever an additional visit to the clinic to assess the TST result is not feasible³⁹. The burden of TB-associated morbidity and mortality among PLHIV highlights the need for a comprehensive management of latent TB diagnosis and treatment.

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