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Original Article

Interferon-gamma release assay versus tuberculin skin test for latent tuberculosis infection among HIV patients in Brazil

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ABSTRACT

Setting: Patients HIV+ attending in a reference clinic, Southern Brazil.
Objective: To compare the interferon-gamma-release assay (IGRA – QuantiFERON® TB Gold In-Tube) with the tuberculin skin test (TST – PPD-Rt 23) for latent tuberculosis infection (LTBI) in patients with HIV.
Design: Cohort study. Patients were simultaneously submitted to the TST and blood collection for the IGRA.
Results: A total of 140 subjects were included. Nine (6.4%) were IGRA+/TST+, 12 (8.6%) were IGRA+/TST−, 4 (3%) were IGRA−/TST+, and 115 (82%) IGRA−/TST−. There was poor agreement between tests (kappa = 0.2), and no correlation between these results and CD4+ T lymphocyte counts. During follow-up, one patient with negative results on both tests died from sepsis, and another with discordant results (IGRA+/TST−) exhibited TST seroconversion. Compared to the TST, IGRA showed a sensitivity and specificity of 69% and 90%, respectively. The IGRA detected 8% more positive results than the TST. All patients were followed up for 2 years.
Conclusion: The higher accuracy of the IGRA would result in LTBI treatments being administered to patients who would have otherwise been overlooked, decreasing the number of active tuberculosis cases. The long-term survival of HIV carriers requires further evaluation.

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Introduction

In 2012, approximately 8.6 million people worldwide developed tuberculosis (TB),[1–3] with the majority occurring in Asia (55%) and Africa (30%).[4,5] Brazil is among the 22 countries with high TB burden; in 2012, 70,000 new cases of TB were detected in Brazil and approximately 4600 patients died of the disease. In Paraná State the incidence of tuberculosis is 22 for every 100,000 inhabitants. In addition, HIV/TB co-infection is the main cause of death with defined etiology among AIDS patients.[4–6] Preliminary data from the Brazilian Ministry of Health show an average of 9.7% of HIV/TB co-infection; the rate is highest in the state of Rio Grande do Sul in Southern Brazil at approximately 19%.[7,8]

One of the main tasks of the Stop TB Partnership project, which aims to control the worldwide impact of TB, is more rapid detection and treatment of latent TB infection (LTBI), particularly in HIV-positive patients.[5] Latent infection occurs through initial first contact with *Mycobacterium tuberculosis* and has no signs of active infection. At this stage, the tuberculin skin test (TST) can detect an immune response against the microorganisms that may persist throughout a person's lifetime.[6] However, there is a risk of disease reactivation, which occurs in 2–23% of immunocompetent patients and at a rate of least 10% per year in immunocompromised individuals.[6,9] LTBI treatment with isoniazid monotherapy can reduce the possibility of active disease progression and is recommended for patients with risk factors such as HIV and immunosuppressive drug treatment.[10,11]

The TST is a widely used immunodiagnostic test for LTBI detection.[9] However, this technique has several disadvantages such as false-positive results in vaccinated individuals[9,12–15]; many lost readings[14–16]; false-negative results in individuals with recent active TB, malnutrition, congenital immunodeficiency, malignant neoplasms, disseminated TB, systemic viral diseases, live-virus vaccines, and immunosuppression (e.g., patients with HIV with CD4+ T lymphocyte counts <400 cells/mm^3)[12,17]; and errors in technical implementation and/or reading of the results.[16,18,19]

In vitro interferon-gamma (IFN-γ) release assays (IGRAs) are an alternative for detecting LTBI that have become a widespread mainly in developed countries, which have low TB prevalence.[9,20,21] IGRAs are based on measuring IFN-γ released from CD4+ T lymphocytes upon stimulation by *M. tuberculosis*-specific antigens.[21] Two commercial IGRAs are currently available: QuantiFERON® TB Gold In-Tube (Cellestis Limited, Victoria, Australia), which is based on an enzyme immunoassay, and the T-SPOT®.*TB* test (T-Spot; Oxford Immunotec, Abingdon, UK), which detects the numbers of IFN-γ-producing cells represented as spot-forming units.[22] IFN-γ release indicates the presence of TB infection either latent or disease.[2] Unlike the TST, neither Bacillus Calmette-Guérin vaccine nor infection by non-TB mycobacteria interferes with IGRA results.[23]

Despite the importance of the detection and treatment of LTBI to control TB in developing countries, few studies have evaluated the performance of IGRA testing in HIV-infected patients in countries with high TB incidence. Therefore, this study compared the ability of the IGRA with the TST to detect LTBI in a cohort of patients with HIV and determined the correlations between test results and outcomes.

Materials and methods

Study population

This was a prospective non-randomized cohort study conducted from August 2012 to August 2014 in a tertiary care academic center, Hospital de Clínicas/Universidade Federal do Paraná (HC/UFPR) in Curitiba, Southern Brazil. The Institutional Review Board approved this study (IRB: #02239612.4.0000.0096), and all included patients provided written informed consent.

Sample size calculation was based on an α error of 0.05 and β error of 0.10 (90% power). For these calculations, the discordance rate between the TST and IGRA was arbitrarily set at 30%. Considering that there were approximately 1400 HIV-positive patients treated at this hospital, a finite population correction factor was used to reduce the standard error. Incorporating these estimates into the equation yielded a sample size of 100. A total of 154 patients were enrolled.

Outpatients aged >18 years who attended the HIV reference clinics at HC/UFPR were invited to participate in this study. Patients currently undergoing chemoprophylaxis or treatment for TB and those with recent TST results were excluded. A standardized form was created for data collection, which included patient demographic, laboratory, and clinical information.

Participants were simultaneously submitted first to the venous blood collection for the IGRA and then to the TST. To exclude active TB, all HIV-positive patients with a positive TST result (>5 mm) underwent chest radiography and sputum specimen analysis by acid-fast bacilli smear and culture. In excluded active disease cases, isoniazid was administered for 6 months.[11,24] Chemoprophylaxis was not recommended for patients with negative TST results regardless of IGRA results according to the Brazilian guideline at the time of the study.[4] CD4+ T lymphocyte counts were determined in all patients by flow cytometry with FACScalibur™ (Becton Dickinson Inc., San Jose, CA, USA) and the Point-Of-Care CD4 Alere Pima™ (Alere, Germany).

IGRA

QuantiFERON® TB Gold In-Tube (Cellestis Limited, Victoria, Australia) was used according to the manufacturer's instructions. The results were interpreted using specific software provided by the manufacturer. A result was considered positive if there was IFN-γ production in the test tube indicated by an optical density ≥0.35 IU/mL and ≥25% of that in the negative control tube. An indeterminate result was defined as low mitogen response (<0.5 IU/mL), if the negative control tube showed an optical density >8 IU/mL, or if the test tube optical density was <0.35 IU/mL or <25% of that of the negative control tube.