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A comparative study of two different methods for the detection of latent tuberculosis in HIV-positive individuals in Chile☆

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Summary
Objective: To compare the performance of two tests for diagnosing latent tuberculosis (TB) infection in the HIV-positive population in Chile, in order to better identify the subjects who might benefit from TB chemoprophylaxis.
Design: This was a cross-sectional study among individuals attending three HIV outpatient clinics in Santiago, tested with a 2-TU purified protein derivative, QuantiFERON®-TB Gold 'in-tube' (QFT-G), and a chest X-ray.
Results: A total of 116 subjects were enrolled in the study, having a mean CD4 count of 393 cells/μl (range 100—977). The tuberculin skin text (TST; 5 mm cutoff) and QFT-G results were positive in 10.9% and 14.8% of the individuals, respectively, with moderate agreement between both tests (kappa = 0.59). A history of both known TB exposure (odds ratio (OR) 3.46, 95% confidence interval (CI) 1.02—11.22) and past TB (OR 4.31, 95% CI 1.13—15.5) were associated with a positive QFT-G result. Only past TB was significantly associated with a positive TST result (OR 6.63, 95% CI 1.62—26.3). Among the subjects with TST $<$ 5 mm, 8.2% were positive by QFT-G test. These individuals had a lower mean CD4 cell count than those detected positive by both tests (328 cells/μl and 560 cells/μl, respectively, $p = 0.03$).
Conclusions: In this population of HIV-infected individuals, QFT-G and TST showed an acceptable level of agreement, although QFT-G appears less affected by more advanced immunosuppression.

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Introduction

Tuberculosis (TB) remains a major health problem worldwide. Despite enormous public health efforts, the World Health Organization (WHO) estimated 9.2 million new cases in 2006, of which 7.7% were co-infected with HIV.[1] The tuberculin skin test (TST) is still the most extensively used tool worldwide for the diagnosis of latent TB in HIV-positive individuals. A positive TST is considered a good predictor of the risk of developing clinical TB in HIV-positive individuals, and there is compelling evidence showing that these patients benefit from TB chemoprophylaxis.[2] However, there are several drawbacks when interpreting a TST result. The sensitivity of the test is reduced in HIV-positive patients, especially when the CD4 cell count is less than 100 cells/μl and the possibility of an anergic response impedes the correct interpretation of the test.[3] On the other hand, in countries where the bacille Calmette—Guérin (BCG) vaccine is still widely administered, the result of a positive TST is frequently ascribed to cross-reactivity with proteins present in the vaccine strain. In fact it has been shown that previous BCG vaccine increases the likelihood of a positive TST, especially if given within the last 15 years.[4] Furthermore, TST also cross-reacts with proteins present in *Mycobacterium avium* complex and other non-tuberculous mycobacteria.[5,6] These drawbacks result in low adherence to the testing of HIV-positive patients by clinicians and even to their not acting on a test result, as currently happens even in developed nations.[7]

In Chile, the incidence of active TB has been decreasing steadily over the last three decades from an annual incidence rate as high as 76/10^5 in the 1980s to a record rate of 13/10^5 in 2005.[8] However, among the HIV-positive population the number of TB cases is strikingly higher, with a prevalence of up to of 6.8 cases per 100 individuals according to the most recent survey.[9] This situation points to a need for greater awareness and better TB control in this group of patients. Regretfully, TST is locally disregarded for the above-mentioned reasons, with less than one third of individuals attending regular HIV programs being tested.[9]

Alternative methods have been developed as diagnostic tools for diagnosing latent TB infection. The whole-blood interferon-γ release assay QuantiFERON®-TB Gold (QFT-G) was approved by the US Food and Drug Administration for use in immunocompetent individuals in December 2005.[10] The test is based on exposing T-lymphocytes ex vivo to *Mycobacterium tuberculosis*-specific antigens (ESAT-6, CFP-10, and TB-7.7) and after a period of incubation measuring the interferon-γ elaborated in response to antigen recognition. These antigens are absent from the genome of *Mycobacterium bovis*, BCG, *M. avium*, and most other non-tuberculous mycobacteria, with the exception of *Mycobacterium kansasii*, *Mycobacterium szulgai*, and *Mycobacterium marinum*.[11—13]

The specificity of interferon-γ (IFN-γ) assays has been found to be as high as 98.1% in the immunocompetent population of BCG vaccinated individuals compared to only 68.1% for TST.[14,15] However the sensitivity of the test has been more difficult to determine and it has been extrapolated by active TB as the gold standard with results varying between 64% and 87%.[14,16]

A small number of studies have investigated the effectiveness of IFN-γ-based assays in diagnosing latent TB in HIV-positive individuals.[17,18] Recently, a comparative study conducted in a high TB prevalence setting found better agreement between TST and QFT-G in HIV-positive than in HIV-negative individuals.[19]

We aimed to compare the results of QFT-G and TST in a population of HIV-positive individuals from a low TB prevalence country, according to the level of immunosuppression. We hypothesized that QFT-G would correlate better than TST with the risk of TB infection in this group of patients, and also that more cases of latent TB would be detected with QFT-G than with the TST, this way helping to reduce the limitations of the TST.

Methods

Study population

Study participants were prospectively enrolled between January 2006 and May 2007 at three main HIV outpatient clinics in Santiago, Chile. These were either newly arrived patients with a confirmed diagnosis of HIV or patients under regular management in the clinics. The protocol was approved by the ethics review committee of the Pontificia Universidad Católica de Chile, and an informed consent was obtained from all the individuals in the study.

The inclusion criteria included age $>$18 years, a CD4 cell count higher than 100 cell/μl performed in the last three months, and no previous TST within the last two years. We included individuals who reported a history of past TB. We excluded pregnant women, individuals on steroid therapy or other immunosuppressants, and individuals presenting with cough, recent weight loss, or fever ongoing at the time of enrolment.

All the patients were interviewed following a structured questionnaire. The following variables were considered potential risk factors for latent TB infection: older age, history of previous TB disease, evidence of past TB in a chest X-ray, previous known exposure to a case of active pulmonary TB, healthcare workers or individuals working with homeless people, residence in prison, and long-duration stay in a country with a TB incidence higher than that in Chile. Previous BCG vaccine, previous TST, body mass index, previous *M. avium* complex disease, HIV viral load, and mean CD4 cell count were also recorded as possible confounders.

At each clinic, a physical examination was carried out by the infectious diseases specialist participating in the study.

Chest X-ray

A single-view chest X-ray was performed for all the subjects enrolled in the study within 2 weeks of enrolment. The radiologists, who were blind to the patient's medical history and test results, reviewed each chest X-ray looking for evidence of past TB. Evidence was defined as: (a) upper lobe pleural thickening, (b) upper lobe linear or nodular scarring images, (c) calcified nodules (granulomas), (d) reduction in the volume of upper lobes, (e) cranial retraction of the pulmonary helium, and (f) calcified mediastinal and hilar lymph nodes.