

# Latent tuberculosis infection in HIV-infected adults of Kinshasa, DR Congo

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## Research article

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# Abstract

## Background

The World Health Organization (WHO) End Tuberculosis Strategy calls for a 90% reduction in tuberculosis (TB) deaths and an 80% reduction in the incidence rate between 2015 and 2035. The 2018 WHO guidelines recognize the need for high-burden countries to implement outreach and treatment for the most vulnerable patients with latent TB infection (LTBI) in addition to treating patients with the active disease. The Democratic Republic of Congo (DR Congo) is among the countries bearing the highest burden of TB. However, additional data on LTBI is required for effective policy and strategy against the disease. Accordingly, the aim of this study is to estimate the prevalence of LTBI in HIV-infected adults in Kinshasa, DR Congo.

## Methods

Over two hundred HIV-infected adult residents of Kinshasa were screened using both TUBERTEST®, which is a tuberculin skin test (TST), and QuantiFERON-TB Gold Plus® (QFT-Plus), which is an interferon gamma release assay. LTBI was screened using TST, QFT-Plus, and a combination of the two tests. The agreement between TST and QFT-Plus was calculated using Cohen's Kappa coefficient.

## Results

A total of 248 HIV-infected persons were enrolled in the study. Seventy-six patients (30.7% IC 95%: 25.2-36.7) had a positive TST result. Sixty-four (25.8% IC 95%: 20.7-31.6) had a positive QFT-Plus test result. The Kappa coefficient between TST and QFT-Plus was 0.225.

## Conclusions

The prevalence of LTBI among HIV positive adults in Kinshasa was high considering either the positive TST or the positive QFT-Plus. However, the two tests had poor agreement.

## Background

The diagnosis and treatment of latent tuberculosis infection (LTBI) is part of the World Health Organization's End Tuberculosis Strategy to control and eliminate tuberculosis (TB) worldwide [1]. The goal of this strategy is to reduce the incidence of tuberculosis worldwide to less than 10 per 100,000 by 2035 [1, 2]. The World Health Organization (WHO) guidelines for 2018 highlight the need for high-burden countries to implement awareness-raising and treatment activities for the most vulnerable patients with latent TB infection in addition to treating patients with active TB [3].

The World Health Organization estimates that 10 million new cases and 1.3 million deaths from TB occurred in 2017 [4]. Of the 10 million cases of TB, 9% were co-infected with the human immunodeficiency virus (HIV) [4]. In 2015, an estimated 10.4 million new TB cases and 1.8 million deaths

worldwide were recorded [5], and people living with HIV accounted for 1.2 million (11%) of all new TB cases [5]. Tuberculosis remains the leading cause of death in people living with HIV, particularly in sub-Saharan Africa (SSA), where it accounts for 50% of HIV-related deaths [6], [7]. It is estimated that about one third of the population worldwide is estimated to be latently infected with *Mycobacterium tuberculosis* [8, 9] and thus have the potential of developing active TB. Latent TB infection is highly widespread in developing countries and constitutes a major obstacle to global TB control [10]. Identifying individuals with LTBI will increase screening rates and assist TB control [11].

Several factors increase the risk of active TB by facilitating the reactivation of remote LTBI or by promoting the progression of an infection recently contracted due to active disease [12]. These factors include HIV infection, recent contact with an infectious patient, initiation of anti-tumor necrosis factor (TNF) treatment, receiving dialysis, receiving an organ or hematologic transplantation, silicosis, incarceration, homelessness, drug addiction, and malnutrition [6, 7]. In 1998, WHO recommended the detection of LTBI in HIV-infected individuals in order to institute prophylactic treatment [13].

Two tests available for the identification of LTBI are the tuberculin skin test (TST) and the gamma interferon (IFN- $\gamma$ ) release assay (IGRA) [14]. These tests are acceptable but imperfect [14]. They represent indirect markers of *M. tuberculosis* exposure and indicate a cellular immune response to *M. tuberculosis* [14]. There is no diagnostic gold standard for LTBI. Both the TST and the IGRA have reduced sensitivity in immune-compromised patients and low predictive value for progression to active TB [14]. The TST has several known limitations. False-positive and false-negative results can occur [14]. There are two important causes of false-positive results: (a) nontuberculosis mycobacterium (NTM) infection and (b) prior Bacillus Calmette-Guérin (BCG) vaccination [15]. False-negative TST results may occur because of limited sensitivity in particular patient subgroups such as immunosuppressed individuals due to medical conditions such as HIV infection and malnutrition or due to the ingestion of immunosuppressive medications [16]. Comparatively, IGRAs are more specific than the TST (Purified Protein Derivative (PPD) for *M. tuberculosis* because they are not encoded in the genomes of any BCG vaccine strains or in most species of NTM other than *Mycobacterium marinum*, *Mycobacterium kansasii*, *Mycobacterium szulgai*, and *Mycobacterium flavescens* [17]. Thus, IGRAs appear to be unaffected by most infections with NTMs, which can cause false positives in TSTs [17]. Consequently, infection with *M. marinum* or *M. kansasii*, which express ESAT-6 or CFP-10, has been shown to produce positive results in IGRAs, as with the TST [18], [19]. There is some evidence of cross-reactivity between ESAT-6 and CFP-10 of *M. tuberculosis* and *M. leprae*, but the clinical significance of this in settings where leprosy and TB are endemic (e.g., India and Brazil) is poorly characterized [20],[21].

In the DR Congo, as in most SSA countries, the high burden imposed by TB infection contrasts with the paucity of data on the prevalence of LTBI, which is increasingly considered a key step for TB control. This situation highlights the need to conduct studies in SSA countries in order to provide information for efficient TB control.

The aim of the present study is to determine the prevalence of LTBI in HIV-infected adults in Kinshasa, DR Congo, and to assess the concordance between the QuantiFERON TB Gold Plus<sup>®</sup> (QFT-Plus<sup>®</sup>) interferon gamma release assay and the TUBERTEST<sup>®</sup> skin test.

## Methods

### Study population, design, and inclusion criteria

This was a cross-sectional study conducted in nine HIV centers (Boyambi, Kimia, Libondi, Makala, Ngaba, St. Gabriel, St. Alphonse, Baudouin King, and 2<sup>ème</sup> Rue Limete) in Kinshasa, DR Congo, from March 2016 to March 2017. The eligibility criteria were: documented HIV-infection, age >18 years, no previous treatment for TB, no active TB at the beginning of the study, no TST test done in the previous three months, and ability to sign an informed consent form.

People with a previous history of TB disease and treatment were excluded from this study. Also, those who reported any of the symptoms of current cough, fever, weight loss, or night sweats were excluded as well as individuals who were too ill to consent or unable to understand or comply with the study protocol.

### Data collection

A detailed standard questionnaire was used to gather socio-demographic and clinical information and to record previous laboratory results. The information included date of birth, history of exposure to TB, history of TST test, BCG vaccination history, presence of a BCG scar, and symptoms suggestive of TB. Information on HIV infection was obtained from patient files.

### Collection of samples

A qualified phlebotomist collected one ml of blood from each patient for laboratory tests. The blood was collected aseptically by venipuncture directly into each of the four QFT-Plus blood collection tubes.

### Laboratory methods

#### *Tuberculin Skin Test (TST)*

The standardized TST was performed using TUBERTEST<sup>®</sup> (Sanofi, Paris, France), which consists of 0.1 ml to 5 IU of TST. The test results were read 72 hours later. A positive TST was defined as an induration of more than 5 mm in horizontal diameter on the forearm. A negative TST was defined as an induration of less than 5 mm. Anergy is defined as the absence of skin reaction with delayed hypersensitivity following the injection of an antigen to which an individual is known to have developed a cell-mediated immune response [22].

### *Interferon gamma release assay (IGRA)*

The QFT-Plus test was performed according to the manufacturer's instructions (Qiagen, Hilden, Germany) using the four-tube version comprising a negative control, a positive control, and two different TB antigen tubes.

### *Data management and statistical analysis*

The data was entered into an Excel spreadsheet (Microsoft, Redmond, WA) and analyzed using Excel Microsoft and STATA software (Stata Statistical Software, Version 11, College Station, TX, Stata Corp LP, 2009). For the TST, we used the standard 5 mm cut-off points, while for QFT-Plus, we used the QFT-Plus algorithm (Table 4). All individuals who had positive QFT-Plus and/or positive TST results were considered to have LTBI. The prevalence of LTBI was calculated as the number of positives by either the TST or QFT-Plus test divided by the total number of HIV positive adults tested [23]. The indeterminate results of QFT-Plus were considered negative results. Active TB was ruled out using the WHO symptom screen [3].

The concordances were estimated using Kappa coefficient ( $\kappa$ ), where  $\kappa > 0.75$  represents an excellent agreement,  $\kappa$  values from 0.4–0.75 represent a fair to good agreement, and  $\kappa < 0.4$  represents a poor agreement.

## **Ethics**

Ethical approval for the study was granted by the Senate Research and Publications Committee of Muhimbili University of Health and Allied Sciences (Ref. No 2016–04–21/AEC/Vol. X/218) and the Ethical committee of Public Health School of University of Kinshasa (Ref. No ESP/CE/057/2015, ESP/CE/057B/2016 and ESP/CE/057C/2017).

## **Results**

### **Baseline study population**

In total, 248 HIV-infected adults under antiretroviral therapy during a mean of 4 years were tested with both the TST and QFT-Plus. Seventy-five of the participants were females, 63% were aged between 30–49 years, 27% had close contact with patients who had active TB, and 2% were diabetics. The main characteristics of the study participants are summarized in Table 1.

*Table 1. Characteristics of the Study Population (N = 248)*

### **Prevalence of LTBI**

Valid TST and QFT-Plus results were both available for the 248 HIV positive adults. Seventy-six patients (30.7%) had a positive TST result, while 64 patients (25.8%) had a positive QFT-Plus test result (Table 2). Twenty-four percent positive TST results were female while twenty percent of positive QFT Plus results were also female.

*Table 2. TST and QFT results and estimated prevalence of LTBI*

## **Degree of concordance of different test diagnoses**

Thirty-two patients tested positive with both the TST and QFT-Plus, and 140 patients had a negative result on both the TST and QFT-Plus. Seventy-six patients had discordant results between the two tests. The Kappa coefficient has been estimated to 0.225.

## **Proportions by CD4 and sex classes of positive and negative immune responses in HIV infected adults**

HIV infected adults were stratified according to CD4+ T+ cells counts of  $\geq 200$  and  $< 200$  cell/ $\mu$ l in two groups. The first group with CD4  $\geq 200$  cell/ $\mu$ l had 132 patients while the second group with CD4+ T+ cells counts of  $< 200$  had 116 patients. The proportions of positive results for QFT Plus ( $p < 0,000$ ) went up from the lowest level to the highest level of CD4, while with the TST ( $p < 1$ ), more positive responses went up from a high CD4 level to the lowest level (Table 3). Furthermore, 21% of the positive results were from females while 5% from men. (Table 4).

*Table 3. Frequencies by CD4 classes of positive and negative TST and QFT Plus responses in HIV infected adults*

*Table 4. Frequencies by sex classes of positive and negative TST and QFT Plus responses in HIV infected adults*

## **Discussion**

This was a pilot study conducted in the DR Congo to estimate the prevalence of LTBI in HIV-infected adults. A larger study will be conducted all over the country.

Using the IGRA alone to diagnose LTBI, the prevalence of LTBI was found to be 25.8%. While using positivity by the TST, as requested by the guidelines of the WHO and suggested by some authors [24, 25], the prevalence of LTBI rose to 30.7%.

Our results are lower than those of the meta-analysis done by Ayubi et al. [26] who found the prevalence of LTBI among HIV infected adults to be 59% (95% CI: 49, 69).

The prevalence of LTBI estimated by the TST was greater than that estimated by QFT-Plus, which is similar to other observations [27]. The higher prevalence of LTBI seen in the TST is likely due to false-positive results attributed by nontuberculous mycobacterium (NTM) infection and prior BCG vaccination [15, 28–30]. In Sub-Saharan Africa, where the Bacillus Calmette-Guérin vaccine is administered at birth, the TST will be affected by vaccination, which is not the case with IGRAs [31, 32].

There are currently two tests for diagnosing latent tuberculosis infection (LTBI): the TST and the IGRA. We found the results of the TST and QFT-Plus tests to be in poor agreement (0.225), which is similar to what others have found [31, 33–38]. The accuracy measures of the TST are often confounded by BCG vaccination and non-tuberculous mycobacterial (NTM) infections [39], [14]. The IGRA tests, which are based on the early secreted antigenic target 6 (ESAT-6) and culture filtrate protein 10 (CFP-10) located in the region of difference 1 (RD1) of the *M. tuberculosis* genome [14, 40, 41], are more specific than PPD, since they are not encoded in the genomes of any BCG vaccine strains or most species of NTM [17].

Proportions of positive results for QFT Plus went up from the lowest level to the highest level of CD4, while with the TST; more positive responses went up from the high CD4 level to the lowest level. Latorre et al. found that the percentages of positive results obtained by T-SPOT.TB and QFN-G-IT in HIV positive patients were higher for patients with a CD4 count >350 cells/ $\mu$ l than <350 cells/ $\mu$ l (28%, 68% and 39%, which is 3% versus 20% and 10%, respectively) [32]. We believe the reason for this is that gamma interferon in the IGRA is produced after stimulation of CD4 and CD8. The TST is less influenced by the change of CD4 ( $p < 1$ ), while the IGRA is more influenced ( $p < 0,000$ ). Furthermore, even in the case of CD4 less than 200, the TST detects positive cases while the QFT Plus gives indeterminate results [32], [42].

It would be interesting to follow up patients with either TST or IGRA positive results to find out the potential of the tests in predicting active TB. Ethically though, we do recommend Isoniazid prophylaxis, especially in those individuals with positive results. We further recommend active TB screening in facilities providing HIV services to minimize the burden of TB in HIV-infected individuals.

## Conclusion

The prevalence of LTBI in HIV infected adults in Kinshasa is high. Therefore, active TB screening in health facilities providing HIV-related services is required urgently.

## Declarations

### List of abbreviations

BCG = Bacillus Calmette-Guérin

CI = Confidence interval

HIV = Human immunodeficiency virus

LTBI = Latent tuberculosis infection

SD = Standard deviation

TB = Tuberculosis

TST = Tuberculin skin test

WHO = World Health Organization

QFT-Plus = QuantiFERON-TB Gold Plus assay

(0) = Negative tests results

(1) = Positive test results

CRS = Composite reference standard

## **Ethics approval and consent to participate**

The protocol of the study received the approval of the Ethical Committee of the University of Kinshasa and the assent of the Senate Research and Publications Committee (SRPC) of Muhimbili University of Health and Allied Sciences. All study participants signed an informed consent form.

## **Consent for publication**

(Not applicable)

## **Availability of data and material**

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

## **Competing interests**

We declare that we have no conflict of interest.

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## Authors' contributions

JK, PL, and MM conceived and designed the experiments. JK performed the experiments, analyzed the data, and contributed reagents/materials/analysis tools. JK, PL, MK, VM, JM, and MM wrote the paper. All authors read and approved the final manuscript.

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## Tables

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