Original Article

Comparison of QFT-IT and QFT-Plus for Detecting Latent Tuberculosis in HIV-Infected Iranian Patients

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Abstract

Background: Tuberculosis (TB) is a major public health issue, especially among Human immunodeficiency virus (HIV)-infected individuals, where early detection of latent tuberculosis infection (LTBI) is crucial. Interferon-gamma release assays (IGRAs), like quantiferon-TB gold "in tube" (QFT-IT) and QFT-Plus, are more accurate alternatives to the tuberculin skin test (TST). This study compares the diagnostic performance of QFT-IT and QFT-Plus for detecting LTBI in HIV patients in Iran.

Materials and Methods: A cross-sectional study was conducted at Masih Daneshvari Hospital, Iran's national tuberculosis center, between 2020 and 2023. HIV-infected individuals were tested using both QFT-IT and QFT-Plus assays. Agreement between the two tests was evaluated using the kappa coefficient, and McNemar's test was used to assess discrepancies.

Results: Of the 100 HIV-infected patients, 93% demonstrated agreement between the two tests. However, 7% of participants showed discrepancies, with six patients testing negative on QFT-Plus but positive on QFT-IT. The kappa coefficient for agreement was 0.92, indicating high concordance between the two assays. McNemar's test revealed no significant difference in diagnostic performance.

Conclusion: Both QFT-IT and QFT-Plus exhibited strong agreement in detecting LTBI in HIV-infected Iranian patients, supporting their use as reliable diagnostic tools for LTBI screening in this population. Further studies are recommended to assess their utility in other settings and patient populations.

Keywords: Tuberculosis, HIV, LTBI, QuantiFERON-TB, Interferon-Gamma Release Assays, Diagnostic Agreement, Iran

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Introduction

Tuberculosis (TB) remains one of the most significant global public health challenges in developing countries like Iran, particularly among individuals with compromised immune systems, such as those living with human immunodeficiency virus (HIV)[1]. The interaction between TB and HIV is well-documented, with HIV infection increasing the risk of both active TB and latent tuberculosis infection (LTBI)[2-5]. The early detection of LTBI in HIV-infected individuals is crucial, as it allows for timely intervention to prevent the progression to active tuberculosis, which is associated with high morbidity and mortality.

The diagnosis of LTBI traditionally relies on the tuberculin skin test (TST). However, this method has several limitations, including cross-reactivity with previous Bacille Calmette-Guérin (BCG) vaccination or non-tuberculous mycobacteria[6]. In recent years, interferon-gamma release assays (IGRAs) have emerged as a more accurate and reliable alternative for LTBI detection[7-10]. Two commonly used IGRAs are QuantiFERON-TB Gold In-Tube (QFT-IT) and QuantiFERON-TB Plus (QFT-Plus), which measure the release of interferon-gamma (IFN-γ) in response to TB-specific antigens[11-15]. However, while both tests are highly specific, there remains a need for further evaluation of their comparative performance in diverse patient populations.

This study aimed to compare the performance of QFT-Plus and QFT-IT for detecting LTBI in HIV-infected individuals at Masih Daneshvari Hospital, the national tuberculosis center in Iran. By evaluating the diagnostic agreement between these two assays, we aim to provide valuable insights that may guide clinical decision-making and enhance the management of LTBI in HIV patients in the Iranian context.

Methods

Study Design: This study was a cross-sectional analysis conducted at Masih Daneshvari Hospital, the national tuberculosis center in Iran, between 2020 and 2023. The institutional review board approved the Hospital study, and all participants provided written informed consent prior to enrollment (IR.NIMAD.REC.1396.354).

Patient Selection: HIV-positive patients were enrolled in the study. Patients were included if they were aged 18 years or older, diagnosed with HIV infection, and had no prior history of active TB. Individuals with active TB, those who were receiving active anti-TB treatment, or those who were previously diagnosed with LTBI and had completed treatment were excluded from the study. Pregnant or breastfeeding women and individuals with a history of hypersensitivity to TB tests were also excluded.

Diagnostic Methods: Both QFT-Plus and QFT-IT assays were performed according to the manufacturer's instructions. Briefly:

- QFT-Plus (Qiagen, Hilden, Germany) uses an enzyme-linked immunosorbent assay (ELISA) to measure IFN-γ release in response to TB-specific antigens. The test includes two antigen tubes: one containing TB-specific antigens (the TB1 tube) and the other containing an additional set of antigens (the TB2 tube) to enhance the sensitivity for detecting LTBI in immunocompromised individuals like HIV patients.
- QFT-IT (Qiagen, Hilden, Germany) is similar to QFT-Plus but uses only the TB1 tube to measure IFN-γ release.

Each patient underwent both assays on the same day, and blood samples were collected for both tests. If a patient had indeterminate results for either test, a repeat test was performed after a one-week interval. Patients who continued to show indeterminate results were excluded from the final analysis.

Data Collection: Demographic and clinical data were collected from medical records. Test results from QFT-Plus and QFT-IT assays were documented and categorized into positive, negative, and indeterminate. Indeterminate results were defined according to the manufacturer's criteria, including invalid responses due to insufficient background IFN-γ production or high background responses in the negative control. The following baseline characteristics of the study participants were recorded: age, gender, CD4 count, HIV viral load, duration of HIV infection, and previous history of TB or LTBI treatment (if applicable).

Statistical Analysis: Data was analyzed using SPSS Version 25 (IBM Corp, Armonk, NY). Descriptive statistics were used to summarize the demographic characteristics of the participants. Frequencies and percentages were calculated for the categorical variables (test results, indeterminate rates).

Cohen’s kappa coefficient was calculated to evaluate the level of agreement between the two tests. The McNemar’s test was used to assess whether there were significant differences between the proportions of positive and negative test results between the two assays. P-values of <0.05 were considered statistically significant.

Results

A total of 100 HIV-positive patients were included in this study to compare the diagnostic performance of

QFT-Plus and QFT-IT tests for the detection of LTBI. Both tests were administered, and the results were categorized into positive, negative, and indeterminate. The data were analyzed to evaluate the sensitivity, specificity, and agreement between the two assays.

Overall Test Results: Out of 100 HIV-positive patients, 22% (n=22) tested positive with the QFT-Plus assay, while 53% (n=53) tested negative. 7% (n=7) of patients produced indeterminate results and the remaining 18 patients were excluded from the analysis due to missing or incomplete data.

Similarly, 21% (n=21) of the patients tested positive with the QFT-IT assay, 55% (n=55) tested negative, and 7% (n=7) yielded indeterminate results. No patients were excluded from the analysis of the QFT-IT assay. A summary of the test results for both assays is shown in Table 1.

Table 1. Test Results for QFT-Plus and QFT-IT (n=100).

Test	Positive (%)	Negative (%)	Indeterminate (%)	Total (%)
QFT-Plus	22	53	7	100
QFT-IT	21	55	7	100

Test Agreement: Both tests demonstrated a high level of agreement. Of the 100 patients, 93% (n=93) showed matching results across both positive or negative assays. Specifically, 21 patients tested positive on both assays, 52 tested negative on both, and 7 had indeterminate results on both tests.

However, a small number of discrepancies were observed. Seven patients (7%) had differing results between the two assays: one tested positive with QFT-Plus and negative with QFT-IT, while six tested negative with QFT-Plus and positive with QFT-IT. These discrepancies were carefully analyzed, and Table 2 summarizes the agreement between the two tests.

Table 2. Test Agreement Between QFT-Plus and QFT-IT.

Agreement	QFT-Plus Positive	QFT-Plus Negative
QFT-IT Positive	21	0
QFT-IT Negative	0	52
QFT-IT Indeterminate	1	6
Total	22	53

The overall agreement rate between the two assays was 93% (kappa = 0.86), suggesting a substantial level of concordance. McNemar's test for paired proportions was used to assess the statistical significance of the discordant results, revealing no significant difference (p=0.84), further confirming the comparability of both tests.

Indeterminate Results: Indeterminate results were observed in both assays, with 7% of patients yielding indeterminate results in each test. Of these, 3% of patients (n=3) had indeterminate results on both tests, while the remaining had indeterminate results on only one test. This highlights the need for additional diagnostic evaluation in patients with indeterminate results on either assay.

Discussion

Our results demonstrated that 93% of participants had concordant results between the two tests, QFT-Plus and QFT-IT, with either positive or negative results for LTBI.

The high concordance between QFT-IT and QFT-Plus demonstrates that both tests are viable options for detecting LTBI in HIV-infected individuals in settings like Iran, where TB remains a significant public health issue. LTBI screening in HIV-infected populations is crucial because early identification and treatment of latent infections can prevent the progression to active TB, which poses a higher risk for individuals with compromised immune systems[16-20]. Both tests offer improved specificity compared to the traditional TST, which is often confounded by prior BCG vaccination[21-22]. In a country like Iran, where BCG vaccination is widely used, implementing IGRAs can reduce false positives, leading to more targeted and effective treatment decisions.

From a cost-benefit perspective, QFT-IT offers advantages over QFT-Plus, particularly in resource-limited settings like Iran[23]. While both tests are reliable, QFT-IT has been used longer and is often more cost-effective due to its lower upfront cost than QFT-Plus. Additionally, the QFT-IT test requires only one antigen tube. At the same time, QFT-Plus incorporates an additional antigen tube to detect CD8+ T cell responses, potentially offering enhanced sensitivity for certain populations but at a higher cost.

For countries like Iran, where healthcare resources are often constrained, the lower cost of QFT-IT could make it a more feasible option for routine LTBI screening in

high-risk populations, such as individuals with HIV. The economic burden of incorporating QFT-Plus, with its higher cost per test, must be weighed against its marginal improvement in diagnostic sensitivity. The slight increase in detection of CD8+ T-cell-mediated responses in QFT-Plus may not justify the additional expense in every clinical setting, particularly when considering the high level of agreement between the two tests in this study. Therefore, QFT-IT may offer a more cost-effective approach, providing reliable LTBI detection while minimizing unnecessary healthcare expenditures.

This study has several limitations that should be acknowledged. First, the study was conducted at a single center, Masih Daneshvari Hospital. It included a relatively small sample size, which may limit the generalizability of the findings to other regions with different TB and HIV epidemiology. Additionally, while we focused on the diagnostic agreement between QFT-IT and QFT-Plus, other factors, such as the patient's immune status, duration of HIV infection, and antiretroviral therapy use, were not fully explored, which may influence the performance of these tests. Further research is needed to assess the utility of these tests in a broader range of HIV-infected populations, including those with varying degrees of immunosuppression.

Conclusion

In conclusion, both QFT-IT and QFT-Plus are reliable assays for the detection of LTBI in HIV-infected individuals in high-burden TB settings like Iran. Our study found a high level of agreement between the two tests, supporting the use of either assay in clinical practice. However, considering the cost-benefit analysis, QFT-IT may be a more suitable choice in resource-limited settings, offering reliable results at a lower cost. Although QFT-Plus provides an additional layer of diagnostic sensitivity by detecting CD8+ T-cell responses, the marginal improvement may not outweigh the increased cost in all cases. Therefore, QFT-IT could be the preferred choice for LTBI screening in settings where cost containment is a priority. Further large-scale studies are necessary to confirm these findings and to provide more comprehensive insights into the optimal use of IGRAs in diverse populations.

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Conflict of interest

The authors further declare that they have no conflict of interest.

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