Clinical Review

Clinical experience with QuantiFERON®-TB Gold

HIV/AIDS

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Overview of key information about TB testing

This literature is intended to provide information on using QuantiFERON-TB Gold (QFT®) for tuberculosis (TB) testing in individuals living with human immunodeficiency virus (HIV). The global TB burden in HIV positive patients and related TB mortality rates varies by region.

QFT – an interferon-gamma release assay

Interferon-gamma release assays (IGRAs) are immunological assays used to assess latent TB infection (LTBI) status. QFT and its latest generation, QuantiFERON-TB Gold Plus (QFT-Plus), are innovative whole-blood tests that measure the cell-mediated immune response of TB-infected individuals, by measuring the release of a biomarker called interferon-gamma (IFN-γ). The tests use unique blood collection tubes, coated on the inner surface with highly specific *Mycobacterium tuberculosis* antigens, along with negative and positive control tubes (Figures 1 and 2). This allows immediate exposure to blood lymphocytes. These TB-specific antigens are encoded within two regions of the *M. tuberculosis* genome that are not present in all Bacille Calmette-Guérin (BCG) vaccine strains and most non-tuberculosis mycobacterial (NTM) species (except *M. marinum*, *M. szulgai* and *M. kansasii*) (1).

As a result, QFT and QFT-Plus are not affected by BCG vaccination or reactivity to NTM (except *M. marinum*, *M. szulgai* and *M. kansasii*) (2). QFT and QFT-Plus are based on a robust enzyme-linked immunosorbent assay (ELISA) technology which produces a numerical result and is therefore not subject to reader variability or errors (1). In addition, the tests include a positive control (mitogen) that allows distinction between valid results and anergic reactions.

Figure 1. QFT Tubes.

Figure 2. QFT-Plus Tubes.

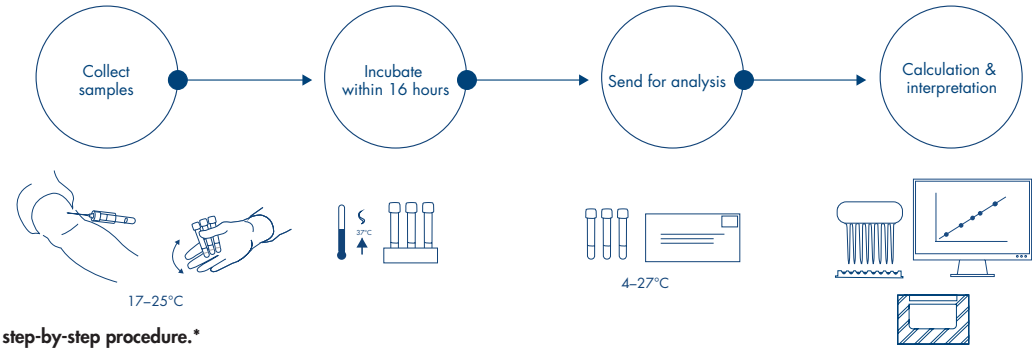

Figure 3. QFT step-by-step procedure.*

*QFT-Plus includes 4 tubes.

Common Questions

Why should I screen for latent TB in HIV positive individuals?

One in 3 people in the world are infected with LTBI, with a 10% average lifetime risk of developing active TB (3). The conversion from LTBI to active TB disease can occur as a result of the immune system being significantly compromised. HIV infection is the biggest known risk factor for reactivation of LTBI (Figure 4).

- Individuals co-infected with HIV and *M. tuberculosis* have a 26 to 31 times increased risk of reactivation of LTBI to active TB (4).
- Although antiretroviral therapy (ART) reduces the incidence of tuberculosis, tuberculosis rates remains unacceptably high after ART is initiated, and many individuals develop tuberculosis before being eligible to receive ART (5-9).
- The incidence of TB is increasing in regions where HIV is prevalent (4).
- Tuberculosis is a leading cause of death in persons with HIV/AIDS (3).

Therefore, early identification and early treatment of LTBI can have a significant impact on the health outcomes of individuals infected with HIV.

What are the diagnostic options available for latent TB infection?

Previously, the only tool available for identifying LTBI was the tuberculin skin test (TST), or Mantoux test. The TST is an in vivo test that measures immune responses to tuberculin purified protein derivative (PPD), which is made up of a multitude of bacterial proteins. Most of these proteins are present in the BCG vaccine, and shared with many environmental mycobacteria. As such, immunological reactions to the PPD reagent used in the TST may be nonspecific and may contribute to increased rates of false-positive results (2). IGRAs offer a new paradigm in diagnosing TB infection. QFT is the most clinically tested and proven IGRA, with over 1000 peer-reviewed, published clinical papers.

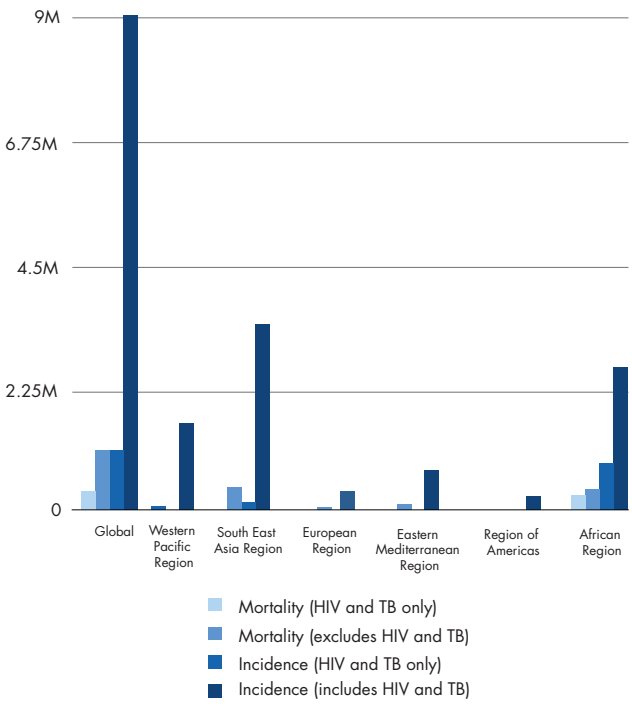

Figure 4. Global estimated epidemiological burden of TB (4).

What are the limitations of the TST in individuals with HIV?

A variety of factors, other than TB infection, are known to induce a false-positive TST result. These include BCG vaccination, exposure to NTM, the inherent boosting effects of prior TST testing, and subjectivity and variability (intra-observer and inter-observer) when reading test results (1, 2). Decreased specificity has been shown to occur in those who have been BCG vaccinated. False-positive results often lead to unnecessary treatment for TB infection with possible detrimental side effects (10). False-negative results are also a common limitation of the TST (11). The TST is unable to distinguish between anergic reactions and negative results. Following the initial intradermal injection of PPD, recipients are required to return within 72 hours to permit reading of the result. Failure to return for TST reading, often in the range of 30-50% of those tested, is common in HIV-infected populations, thereby undermining the sensitivity of TST and increasing the costs of screening (12–14).

What is the correlation between QFT and *M. tuberculosis* exposure in HIV-positive individuals?

HIV-positive individuals are at risk of progressing to active TB disease and outbreaks, due to the combination of immune suppression from HIV and population risks such as homelessness, incarceration and drug use (15).

What are the negative predictive value (NPV) and positive predictive value (PPV) of QFT in the HIV population?

Both NPV and PPV are heavily dependent on the prevalence of infection in the population being tested. In most developed countries, the prevalence of *M. tuberculosis* infection is relatively low. The largest study in a low-endemic region is by Aichelburg et al., who studied the PPV of QFT longitudinally in 830 HIV-positive individuals. Of the 37 who were QFT-positive/HIV positive, 3 (8.1%) developed active TB during the follow-up period of 19 months. None of the 793 QFT-negative individuals progressed to active TB, indicating an excellent NPV, in this case, an NPV of 100%. One important limitation of the Aichelburg et al. data is the relative scarcity of study individuals with very low (<200) $CD4^+$ cell counts. There is a high likelihood that individuals with such low $CD4^+$ cell counts, and infected with MTB, would have already progressed to active disease and these individuals would be excluded from this study and therefore the results (10).

In a similar study, Soborg et al. conducted a 6 year follow-up study on HIV-positive patients in Denmark. QFT accurately identified all those tested who would progress to active TB, and no one who was QFT-negative developed TB (16) (Figure 5).

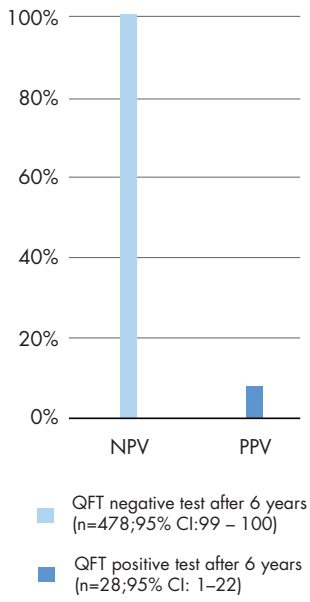

Figure 5. QFT Negative/Positive Predictive Value in HIV cohort (16)

What is the impact of QFT test performance on the $CD4^+$ T-cell count?

A large number of studies have analyzed QFT performance in individuals living with HIV. Some studies have shown that the sensitivity of QFT in HIV co-infected individuals is impaired compared with HIV-negative patients with TB disease, although to a lesser degree than the TST (5).

A significant benefit of QFT over the TST is that it incorporates a positive control (15). However, like the TST, QFT relies on functional $CD4^+$ cells, and its performance can be negatively influenced by low and impaired $CD4^+$ cell counts in HIV-infected individuals (16). Unlike the TST, the positive control of QFT provides an indicator of the overall immune function. An indeterminate QFT result in an HIV-infected person with a low $CD4^+$ cell count can provide valuable information. It suggests possible anergy and does not necessarily indicate a failed test (17, 18) (Table 1).

Do I need to investigate active TB based upon a positive QFT test?

A positive QFT result indicates the person tested is likely infected with *M. tuberculosis*. The individual with a positive QFT result should have a medical evaluation that includes a symptom review, risk factor assessment, chest x-ray and physical examination to determine the diagnosis of active TB or LTBI.

What does the literature say about QFT use in the HIV population?

Numerous studies have investigated the use of QFT in HIV-positive populations. The characteristics of these studies are outlined in the Summary of Published Studies (Table 2) below. Of note is that QFT has been shown to have equal or higher sensitivity when compared with the TST. Perhaps the biggest disadvantage of the TST is that it lacks an internal control to distinguish false negative results due to anergy from true negative results.

Table 1. Indeterminate results by CD4 count (18)

CD4 count	Indeterminate QFT result*
CD4<100	16.1%
CD4 100-350	3.6%
CD4>350	3.9%

* All indeterminate results were due to a failure to respond adequately to the positive control.

"Interestingly, one study found that indeterminate QFT-GIT results in HIV-infected patients independently predict progression to AIDS or death. This may be because an indeterminate IGRA provides indirect evidence of poor global T-Cell function." (19)

Table 2. Summary of clinical studies

Ref. no.	Publication	Main Findings
20	**First Author:** Bourgarit **Year (ref):** 2015 **Country:** France **Patient population:** LTBI, active TB **n:** 415, 8 **CD4⁺ count, Median (QR):** 466 (337–615)	In 415 individuals, 43 (10.4%) were QFT positive, 34 (8.2%) were T-SPOT.*TB* positive, and 66 (15.6%) were TST positive (≥ 5mm). Multivariate analysis showed positive IGRA being correlated with birth in a high prevalence country (8.4% for French birth against 17.9% for immigrants from high prevalence countries, p=0.004). 8 (14.5%) of 55 patients with at least 1 IGRA positive result developed active TB during follow-up. Systemic screenings for latent TB infection with IGRA can identify individuals at increased risk of developing active TB.
21	**First Author:** Andrews **Year (ref):** 2013 **Country:** Global	Evaluation of cost-effectiveness of diagnostic techniques in HIV-associated TB infection. Diagnostic tests for tuberculosis have great potential to reduce the burden of morbidity and mortality from HIV-associated tuberculosis. Tuberculosis diagnostics in HIV-endemic settings face unique challenges in the estimation of incremental effectiveness, incremental costs (which are largely driven by HIV care), and cost-effectiveness thresholds.
22	**First Author:** Aung **Year (ref):** 2013 **Country:** Global **Patient population:** Potential LTBI	Review aimed to facilitate the development of preventive strategies for HIV/TB co-morbidity in the Southeast Asia region. Prevalence of HIV among TB infected individuals was estimated as 5.7% by WHO. Advantages of IGRAs over TST include objective test results, without a booster effect for multiple testing, avoidance of a second clinical visit and higher specificity. However, IGRAs do have some limitations. They are unable to distinguish between recent and remote infection, or active TB and LTBI. Additionally, sensitivity of IGRAs has been shown to be affected by CD4⁺ T-cell counts. It has been reported that IGRAs generally perform better than TST in HIV-infected populations.
23	**First Author:** García-Elorriaga **Year (ref):** 2013 **Country:** Mexico **Patient population:** LTBI **n:** 25 **CD4⁺ count, Median (QR):** 364 (7-842)	Of 25 HIV-positive individuals tested with QFT and TST, 19 (76%) patients were positive with QFT and 4 (16%) patients were positive with TST for LTBI. No agreement between TST and QFT was found in the study population, κ=-0.004 (95% CI: -0.2219, 0.2210).
24	**First Author:** Sultan **Year (ref):** 2013 **Country:** United Kingdom **Patient population:** Potential LTBI **n:** 117 **CD4⁺ count, Median (QR):** 530 (140 – 1250)	Comparison of results from the 2 IGRAs showed a moderate concordance (κ=0.56, 95% confidence interval = 0.27–0.85). A total of 12 (10.3%) tested patients had positive IGRA results; 11 (9.4%) patients were QFT positive, 6 (5.1%) patients were T-SPOT.*TB* positive, and 5 (4.3%) patients were positive in both IGRA tests. 7 (6%) patients had discordant IGRA results (one positive for T-SPOT.*TB* result, six positive for QFT results). 1 patient was shown to have indeterminate QFT results and one patient was shown to have borderline T-SPOT.*TB* results. Indeterminate results in study population was uncommon.
11	**First Author:** Ramos **Year (ref):** 2012 **Country:** Spain **Patient population:** Potential LTBI **n:** 373 **CD4+ count, Median (QR):** 470 (10 – 1760)	IGRAs were more sensitive than TST in the diagnosis of latent *M. tuberculosis* infection in HIV positive individuals. TST, QFT and T-SPOT.*TB* were positive in 13.3%, 7.5% and 18.5% cases respectively of 373 HIV positive individuals tested. 277 patients with no past history of TB were tested. 20 (7.2%) of patients showed a positive TST result. QFT and/or TST concurrent testing produced 26 (8.6%) LTBI positive patients. Testing with QFT and/or T-SPOT.*TB* showed 54 (17.9%) LTBI positive patients. Concurrent testing with TST, QFT and/or T-SPOT.*TB* showed 56 (18.5%) LTBI positive individuals.

Ref no.	Publication	Main Findings
25	**First Author:** Santin **Year (ref):** 2012 **Country:** Global **Patient population:** Potential LTBI, Active TB **n:** 6514 HIV-infected patients, 1166.	The pooled sensitivity and specificity reported for tuberculosis were 61% and 72% for QFT, and 65% and 70% for T-SPOT.*TB*. For patients tested positive (one study each), the cumulative incidence of subsequent active tuberculosis was 8.3% for QFT and 10% for TSPOT.*TB* and for patients tested negative the cumulative incidence of subsequent active tuberculosis was 0% for QFT (two studies) and T-SPOT.*TB* (one study). Pooled indeterminate rates were 8.2% for QFT and 5.9% for T-SPOT.*TB*. Rates were higher in high burden settings (12.0% for QFT and 7.7% for T-SPOT.*TB*) than in low-intermediate burden settings (3.9% for QFT and 4.3% for T-SPOT.*TB*). They were also higher in patients with CD4⁺ T-cell count ≤200 (11.6% for QFT and 11.4% for T-SPOT.*TB*) than in those with CD4⁺ T-cell count ≥200 (3.1% for QFT-GIT and 7.9% for T-SPOT.*TB*) IGRAs have suboptimal accuracy for confirming or ruling out active tuberculosis disease in HIV-infected adults. While their predictive value for incident active tuberculosis is modest, a negative QFT-GIT implies a very low short- to medium-term risk.
26	**First Author:** Cattamanchi **Year (ref):** 2011 **Country:** Global **Patient population:** LTBI/HIV	To determine whether interferon-gamma release assays (IGRAs) improve the identification of HIV-infected individuals who could benefit from latent tuberculosis infection therapy. Current evidence suggests that IGRAs perform similarly to the tuberculin skin test at identifying HIV-infected individuals with latent tuberculosis infection. Given that both tests have modest predictive value and suboptimal sensitivity, the decision to use either test should be based on country guidelines and resource and logistic considerations.
27	**First Author:** Santin **Year (ref):** 2011 **Country:** Spain **Patient population:** Potential LTBI **n:** 135 **CD4⁺ count, Median (QR):** 300 (156–522)	The prevalence of latent TB was 6.7% by the TST and 9.6% by QFT (p=0.3) in HIV-seropositive subjects, and 34.8% by the TST and 21.5% by QFT (p=0.02) among controls. TST reactivity declined sharply as CD4⁺ cells fell. A less pronounced fall occurred with QFT. No cases of tuberculosis occurred during follow-up (0.26 per 100 person-years). Simultaneous testing with the TST and QFT early in the course of HIV infection might minimize the risk of tuberculosis in these patients.
28	**First Author:** Sauzullo **Year (ref):** 2010 **Country:** Italy **Patient population:** Potential LTBI, Active TB **n:** 197, 44 **CD4⁺ count, Median (QR):** 219(4–995)	In HIV-infected patients, the level of agreement between the TST and QFT tests was 68%, and QFT sensitivity was 66%. The proportion of indeterminate QFT results was 33.4%, which correlated with CD4⁺ count <200 cells/µl (p<0.0001). When excluding the indeterminate results, the QFT sensitivity increased to 86.6%.
29	**First Author:** Aabye **Year (ref):** 2009 **Country:** Tanzania **Patient population:** Active TB **n:** 68 **CD4⁺ count, Median (QR):** 272 (172–478)	Sensitivity of the QFT test was higher in HIV-negative (75/93) than in HIV-positive (44/68) patients (81% vs. 65%, p=0.02) and increased with CD4⁺ cell count in HIV-positive patients (test for trend p=0.03). Twenty-three patients (14%) had an indeterminate result and this proportion decreased with increasing CD4⁺ cell count in HIV-positive patients (test for trend p=0.03). Sensitivity when excluding indeterminate results was 86% (95% CI: 81–92%) and did not differ between HIV-negative and HIV-positive patients (88 vs. 83%, p=0.39).

Ref no.	Publication	Main Findings
10	**First Author:** Aichelburg **Year (ref):** 2009 **Country:** Austria **Patient population:** Potential LTBI, Active TB **n:** 822, 8 **CD4⁺ count, Median (QR):** 393 (264–566)	The QFT assay yielded positive or indeterminate results in 44 (5.3%) and 47 (5.7%) of the 830 patients, respectively. A positive QFT result occurred at significantly higher frequencies among patients from high-prevalence countries than among patients from low-prevalence countries ($p<0.001$). In patients with indeterminate QFT results, both median actual and nadir CD4⁺ counts were significantly lower than in patients with interpretable QFT results ($p<0.001$). During the follow-up period, progression to active tuberculosis occurred exclusively in patients with a positive QFT result, at a rate of 8.1% (3 of 37 patients; $p<0.001$). Collectively, the sensitivity of the QFT assay for active tuberculosis was 90.9%.
30	**First Author:** Raby **Year (ref):** 2008 **Country:** Zambia **Patient population:** Active TB **n:** 59 **CD4⁺ count, Median (QR):** 212 (109-332)	Marked decrease in sensitivity was observed in HIV-positive patients with 37/59 (63%) being QFT-positive compared to 31/37 (84%) HIV-negative patients [chi^2, $p=0.033$]. Low CD4⁺ count was associated with increases in both indeterminate and false-negative results. The TST test was impaired in HIV-positive subjects with only 26/47 (55%) having a positive TST compared to 25/31 (81%) in the HIV-negative group (chi^2, $p=0.021$). A CD4⁺ count of <200 cells/µl was clearly associated with negative TST ($p<0.001$). Although there was little difference in the overall sensitivities, agreement between TST and QFT was poor.
18	**First Author:** Luetkemeyer **Year (ref):** 2007 **Country:** USA **Patient population:** Potential LTBI **n:** 294 **CD4⁺ count, Median (QR):** 363 (214–581)	Of 294 participants, 70% returned for an evaluable TST. Concordance between QFT and TST was 89.3% (kappa=0.37, $p=0.007$). However, in subjects with positive test results by either TST or QFT, only 28% (8/29) had positive test results by both modalities. TST-positive/QFT-negative discordant results were found in 5.1% of subjects and TST-negative/QFT-positive discordance in 5.6%. Indeterminate QFT results occurred in 5.1%, all due to a failure to respond to the phytohemagglutinin-positive control. Subjects with a CD4⁺ count of less than 100 cells/mm3 had a relative risk of an indeterminate result of 4.24 (95% confidence interval, 1.55–11.61; $p=0.003$) compared with those with a CD4⁺ count of 100 or more.
31	**First Author:** Brock **Year (ref):** 2006 **Country:** Denmark **Patient population:** Potential LTBI **n:** 590 **CD4⁺ count, Median (QR):** 523	In 590 individuals, 27 (4.6%) of the individuals were QFT positive, indicating the presence of latent TB infection. Among QFT-positive patients, 78% had risk factors such as long-term residency in a TB high endemic area, known TB exposure or previous TB disease. The prevalence of latent TB infection in these groups was 13%, 16% and 19% respectively. There was a strong correlation between low CD4⁺ cell count and a low mitogen response ($p<0.001$) and more patients with low CD4⁺ cell count had indeterminate results.

Ordering Information

Product	Contents	Cat. no.
QFT-Plus 2 Plate Kit ELISA	2-plate kit, includes: Microplate strips; IFN-γ Standard, lyophilized; Green Diluent; Conjugate 100X Concentrate, lyophyilized; Wash Buffer 20X Concentrate; Enzyme Substrate Solution, Enzyme Stopping Solution	622120
QFT-Plus Blood Collection Tubes Single Patient Pack (10 tests)	10 QFT-Plus Blood Collection Tubes packs, each including: Nil, TB1, TB2 and Mitogen Tubes	622222
QFT-Plus Blood Collection Tubes (200)	QFT-Plus Blood Collection Tubes: Nil, TB1, TB2 and Mitogen tubes (50 each)	622526
QFT 2 Plate Kit ELISA	2-plate kit, includes: Microplate strips; Human IFN-γ Standard, lyophilized; Green Diluent; Conjugate 100X Concentrate, lyophyilized; Wash Buffer 20X Concentrate; Enzyme Substrate Solution, Enzyme Stopping Solution	0594-0201
QFT Blood Collection Tubes*	300 tubes for 100 preps, including: 100 QuantiFERON Nil Tubes,100 QuantiFERON TB Antigen Tubes, 100 QuantiFERON Mitogen Tubes*	0590-0301
QFT Dispenser Pack*	25 sets of tubes: Nil tube, TB Antigen tube, Mitogen tube	0597-0403

*Not all product configurations are available in every region. Please contact QIAGEN Customer Care (details at www.qiagen.com) for more information on which configurations are available. QFT High Altitude (HA) Tubes are for use above 1020 meters (3350 feet) and below 1875 meters (6150 feet).

Visit **www.QuantiFERON.com** for more information.

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QFT and QFT-Plus have been CE marked.

QFT and QFT-Plus are in vitro diagnostic aids for the detection of *Mycobacterium tuberculosis* infection (including disease) and are intended for use in conjunction with risk assessment, radiography, and other medical and diagnostic evaluations. QFT or QFT-Plus results cannot distinguish active TB disease from latent infection. QFT and QFT-Plus Package Inserts, available in multiple languages, as well as up-to-date licensing information and product specific disclaimers can be found at **www.QuantiFERON.com**.