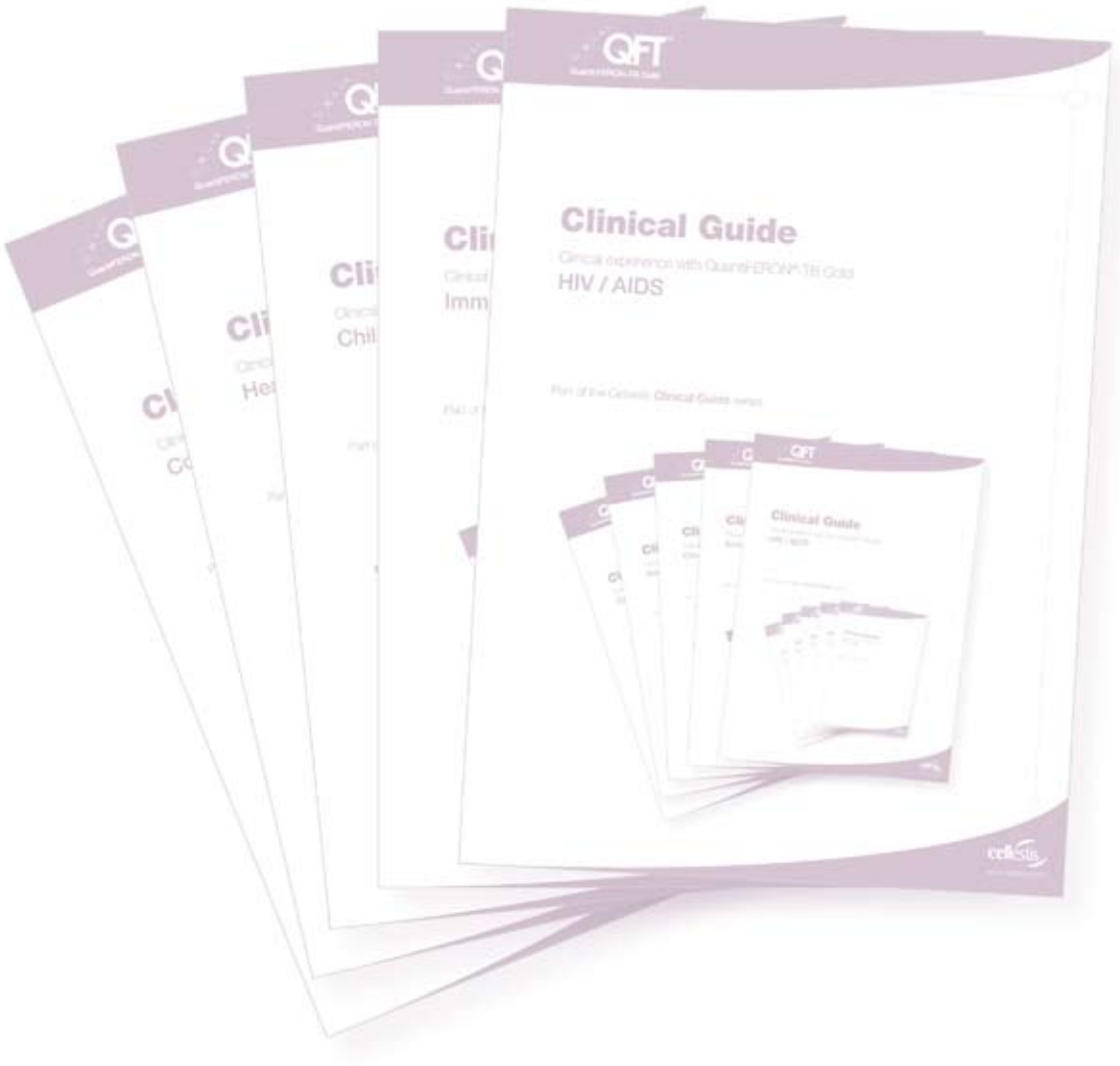
QFT™
QuantiFERON-TB Gold

Clinical Guide

Clinical experience with QuantiFERON®-TB Gold

HIV / AIDS



Cellestis Clinical Guide series 2008

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This clinical guide is intended to provide healthcare professionals with an overview of current clinical information on the use of QuantiFERON®-TB Gold (QFT™)—in patients whose immune system has been compromised by **Human Immunodeficiency Virus (HIV)** or **Acquired Immune Deficiency Syndrome (AIDS).**

Common Questions

Why does one need to screen for latent TB in HIV positive individuals?

Conversion of latent to active TB usually occurs as a result of the immune system being severely compromised. Human immunodeficiency virus (HIV) infection is the biggest known risk factor for reactivation of latent TB infection. Individuals co-infected with HIV and *M. tuberculosis* have a 50–200 fold increased risk of reactivation of latent tuberculosis to active TB.[1] The risk of active TB is also increased among HIV-infected individuals receiving anti-retroviral therapy (HAART).[2] TB is the main cause of death in persons with HIV/AIDS. Furthermore the incidence of TB is increasing in regions where HIV is prevalent.[3]

What are the limitations of the Tuberculin Skin Test (TST) in individuals with HIV infection?

The TST is widely used in the assessment of individuals with suspected TB—despite its well known limitations. A variety of factors, other than infection with *M. tuberculosis*, are known to induce a positive TST. These include Bacille Calmette-Guérin (BCG) vaccination, exposure to non-tuberculous mycobacteria, the inherent inability of the test to distinguish a current infection from past resolved infection and subjectivity when reading the test results. These false positive results often lead to unnecessary treatment for TB infection with possible detrimental side effects.

The TST has poor sensitivity for detecting active TB in HIV positive individuals. Is QFT any better?

In HIV infected individuals QFT has been shown to be more sensitive than the TST. Studies have shown that the sensitivity of QFT (in HIV positive patients with active TB) is 77–85% compared to 15–46% for the TST.[4,5] Unlike the TST, QFT is not subject to boosting, as it is not affected by prior BCG vaccination, and most non-tuberculous mycobacteria (except *M. marinum*, *M. szulgai* and *M. kansasii*).

The TST has limited reproducibility in HIV infected individuals. Is QFT any better?

Unlike the TST, QFT results are highly reproducible. In a US study, only 3 of 206 specimens run in duplicate yielded discordant results.[6]

False negative TST results can occur in severely immunosuppressed HIV infected individuals. How about QFT?

Among individuals with HIV infection the likelihood of false negative TST results increases with decreasing CD4 counts.[7] Indeterminate QFT results are more prevalent in those with a CD4 count $< 100/\mu L$.[6,8,9] In indeterminate QFT subjects, the TST is generally negative, highlighting the need for care in interpreting a negative TST in those with potential immunosuppression.[8] An indeterminate QFT result is meaningful—suggesting possible anergy—and does not indicate a failed test. By including an internal positive control (phytohemaglutinin tube), the QFT test enables the distinction between indeterminate tests and those that are truly QFT negative. The phytohemaglutinin positive control can be affected by blood mishandling, and should not be used as the sole assessment of immune status. In contrast, a negative TST does not differentiate between those individuals who are anergic and those who have a truly negative TST.

Due to the nature of the test, obtaining a TST result can take up to 72 hours. Is QFT any better?

QFT is a blood test, and results are generally available within 24 hours.

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

Unlike the TST, a positive QFT result has statistically significant association to a number of risk factors for LTBI in HIV positive individuals (O.R. 1.6). These risk factors include a history of TB exposure, homelessness and drug use.[6] **The authors concluded "QFT-G testing may be more useful than TST in individuals with HIV infection".**[6]

Summary of Published Studies

Publication	Main Finding
Vincenti D, Carrara S, Butera O, Bizzoni F, Casetti R, Girardi E, Goletti D. Response to region of difference 1 (RD1) epitopes in human immunodeficiency virus (HIV)-infected individuals enrolled with suspected active tuberculosis: a pilot study. *Clin Exp Immunol 2007; 150:91–8.*	A prospective study that evaluated RD1 selected peptides (not commercially available) to the TST, QFT and Elispot in 111 HIV-infected individuals with signs and symptoms of active TB. QFT and Elispot were shown to be more sensitive (85%) than either the RD1 selected peptides (67%) or the TST (46%) in HIV patients with active TB.
Nagai H, Kawabe Y, Ariga H, Shigiyama F, Shimada M, Kunogi M, Matsui Y, Kawashima M, Suzuki J, Ooshima N, Masuda K, Matsui H, Tamura A, Nagayama N, Akagawa S, Machida K, Kurashima A, Yotsumoto H. Usefulness of a whole blood interferon gamma assay (QuantiFERON-TB-2G) for detecting tuberculosis infection in HIV-infected persons. *Kekkaku 2007; 82:635–40 (Article in Japanese).*	Investigators compared TST to QFT, for detecting TB in 13 patients infected with both HIV and TB. It was found that the QFT had a greater sensitivity compared to the TST (77% vs. 15.4%).
Jones S, de Gijsel D, Wallach FR, Gurtman AC, Shi Q, Sacks H. Utility of QuantiFERON-TB Gold in-tube testing for latent TB infection in HIV-infected individuals. *Int J Tuberc Lung Dis 2007; 11:1190–5.*	A cross-sectional study evaluating QFT and TST in 207 HIV infected subjects relative to the presence of risk factors for latent tuberculosis infection (LTBI). It was found that positive QFT results were more likely than the TST to be associated with risk factors for LTBI (O.R. 1.6). In this study the QFT indeterminate rate was 4.9%, with the majority of indeterminate results obtained from individuals with CD4 counts < 100 cells/mm^3.
Luetkemeyer AF, Charlebois ED, Flores LL, Bangsberg DR, Deeks SG, Martin JN, Havlir DV. Comparison of an interferon-gamma release assay with tuberculin skin testing in HIV-Infected individuals. *Am J Respir Crit Care Med 2007; 175:737–42.*	A cross-sectional study comparing QFT to the TST for detecting LTBI in 294 HIV infected patients. It was found that 8.5% of the patients were QFT positive while 9.3% were TST positive. In this study the QFT indeterminate rate was 5.1% and QFT indeterminate results were more common in individuals with CD4 counts < 100 cells/mm^3.
Brock I, Ruhwald M, Lundgren B, Westh H, Mathiesen LR, Ravn P. Latent tuberculosis in HIV positive, diagnosed by the M. tuberculosis specific interferon-gamma test. *Respir Res 2006; 7:56.*	Investigators screened 590 HIV-positive individuals with QFT (TST was not performed) and found that the prevalence of LTBI was 4.6% (27 of 590). Among QFT positive patients, 78% had risk factors such as long-term residency in TB endemic area or TB exposure. QFT predicted progression as 2 of the 27 QFT positive developed active TB. Overall QFT indeterminate rate was 3.4%, with indeterminate results more common in individuals with CD4 counts < 100 cells/mm^3.
Rangaka MX, Wilkinson KA, Seldon R, Van Cutsem G, Meintjes GA, Morroni C, Mouton P, Diwakar L, Connell TG, Maartens G, Wilkinson RJ. Effect of HIV-1 infection on T-cell based and skin test detection of tuberculosis infection. *Am J Respir Crit Care Med. 2007; 175:514–20.*	Investigators used QFT, Elispot and the TST to detect LTBI in 74 HIV infected and 86 uninfected subjects. It was found that both tests had similar performance in both populations: QFT (43% and 46%) versus Elispot (52% and 59%).

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References

1. Nunn P, Williams B, Floyd K, Dye C, Elzinga G, Raviglione M. Tuberculosis control in the era of HIV. *Nat Rev Immunol 2005; 5:819-26.*
2. Girardi E, Sabin CA, d'Arminio Monforte A, Hogg B, Phillips AN, Gill MJ, Dabis F, Reiss P, Kirk O, Bernasconi E, Grabar S, Justice A, Staszewski S, Fätkenheuer G, Sterne JA. Incidence of tuberculosis among HIV-infected patients receiving highly active antiretroviral therapy in Europe and North America. *Clin Infect Dis 2005; 41:1772-82.*
3. WHO: Global tuberculosis control - surveillance, planning, financing. *WHO report 2005. WHO/HTM/TB/2005 2005 http://www.who.int/tb/publications/global_report/2005/en/.*
4. Vincenti D, Carrara S, Butera O, Bizzoni F, Casetti R, Girardi E, Goletti D. Response to region of difference 1 (RD1) epitopes in human immunodeficiency virus (HIV)-infected individuals enrolled with suspected active tuberculosis: a pilot study. *Clin Exp Immunol 2007; 150:91-8.*
5. Nagai H, Kawabe Y, Ariga H, Shigiyama F, Shimada M, Kunogi M, Matsui Y, Kawashima M, Suzuki J, Ooshima N, Masuda K, Matsui H, Tamura A, Nagayama N, Akagawa S, Machida K, Kurashima A, Yotsumoto H. Usefulness of a whole blood interferon gamma assay (QuantiFERON-TB-2G) for detecting tuberculosis infection in HIV-infected persons. *Kekkaku 2007; 82:635-40 (Article in Japanese).*
6. Jones S, de Gijsel D, Wallach FR, Gurtman AC, Shi Q, Sacks H. Utility of QuantiFERON-TB Gold in-tube testing for latent TB infection in HIV-infected individuals. *Int J Tuberc Lung Dis 2007; 11:1190-5.*
7. Converse PJ, Jones SL, Astemborski J, Vlahov D, Graham NM. Comparison of a tuberculin interferon-gamma assay with the tuberculin skin test in high-risk adults: effect of human immunodeficiency virus infection. *J Infect Dis 1997; 176:144-50.*
8. Luetkemeyer AF, Charlebois ED, Flores LL, Bangsberg DR, Deeks SG, Martin JN, Havlir DV. Comparison of an interferon-gamma release assay with tuberculin skin testing in HIV-Infected individuals. *Am J Respir Crit Care Med 2007; 175:737-42.*
9. Brock I, Ruhwald M, Lundgren B, Westh H, Mathiesen LR, Ravn P. Latent tuberculosis in HIV positive, diagnosed by the *M. tuberculosis* specific interferon-gamma test. *Respir Res 2006; 7:56.*

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