Comparison of QuantiFERON-TB In Tube test and T-SPOT.TB with tuberculin skin test in HIV- infected individuals from an intermediate tuberculosis burden country

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Comparison of QuantiFERON-TB In Tube test and T-SPOT.TB with tuberculin skin test in HIV- infected individuals from an intermediate tuberculosis burden country

Directed by Professor June Myung Kim

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This certifies that the Master's Thesis (Doctoral Dissertation) of Suk Hoon Choi is approved.

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ABSTRACT

Comparison of QuantiFERON-TB In Tube test and T-SPOT.TB with tuberculin skin test in HIV- infected individuals from an intermediate tuberculosis burden country

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Objective: The objective of this study was to evaluate the performance of T-SPOT.TB and QuantiFERON-TB In Tube test(QFT-IT) assays and tuberculin skin test(TST) for the diagnosis of latent tuberculosis infection in HIV infected individuals in South Korea.

Design: A cross-sectional study was carried out at a tertiary hospital in South Korea to compare two forms of the interferon-γ release assays to TST.

Results: We enrolled 95 patients with a median CD 4 cell count 429 cells/μl (range 18-1134) for the study. More positive assay results were obtained with T-SPOT.TB than for both TST and QFT-IT: 27.4 %

compared to 11.6% and 15.8% (P = 0.002 and P = 0.003) respectively. Positive results for TST were similar to those obtained with QFT-IT (P = 0.727). Agreement between the 3 tests was fair to good (QFT-IT vs TST, κ = 0.665 : T-SPOT.TB vs TST , κ = 0.456 : QFT-IT vs T-SPOT.TB, κ = 0.593) in all cases. Patients with positive results of QFT-IT, TST and T-SPOT.TB did not have statistically significant higher mean CD4 cell counts than those with negative results.

Conclusion: When tested on HIV infected patients from South Korea, T-SPOT.TB, QFT-IT and TST showed fair to good agreement. T-SPOT.TB is more sensitive than both TST and QFT-IT. The result of all 3 tests was not affected by CD4 cell counts

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Key words : tuberculosis, latent tuberculosis, HIV, interferon-gamma

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I. INTRODUCTION

HIV infected patients with latent tuberculosis infection(LTBI) have an greater risk of progression to the active tuberculosis. [1]Given the high progression rate, exact diagnosis and treatment of latent tuberculosis infection(LTBI) among HIV infected individuals is important. The tuberculin skin test (TST) has been the only diagnostic tool for LTBI since the early 1930s but has a number of limitations including false positive results due to prior Bacille Calmette-Guerin (BCG) vaccination and infection with nontuberculous mycobacteria (NTM) infection (with the exception of *Mycobacterium kansasii, Mycobacterium szulgai,* and *Mycobacterium marinum*),[2] false negative results due to anergy in immunocompromised patients, especially HIV co- infected patients,[3] and lastly reader variability and the requirement of a return visit to evaluate results.

In order to ensure an effective tuberculosis control, a new LTBI diagnostic test is needed.

Recently, *in vitro* blood tests measuring production of interferon (IFN)-γ by T-cells exposed to the highly specific *Mycobacterium tuberculosis* antigens were introduced to detect LTBI. These included QuantiFERON Gold In Tube test (QFT-IT) and T-SPOT.TB (TSPOT) collectively referred to as IFN-γ release assays (IGRAs). IGRAs are based on the specific IFN-γ release from activated T-cells after exposure to *Mycobacterium tuberculosis* antigens. These include early secreted antigenic target 6 (ESAT-6) and culture filtrate protein 10 (CFP-10).[4] An additional antigen TB 7.7 is included in QFT-IT. QFT-IT measures the level of IFN-γ produced in whole blood by enzyme-linked immunosorbent assay (ELISA) while the TSPOT assay detects the number of IFN-γ producing cells. Promising results in the diagnosis of tuberculosis in HIV negative individuals by both tests have been reported. [5-11]

Recently, three studies carried out on HIV infected patients to evaluate the comparative performance of two IGRAs and TST were published. One study from Germany, compared two IGRAs and TST in 286 HIV infected individuals, 22% of which were from high TB countries outside Germany. Agreement between all three tests was poor [TSPOT vs TST(κ=0.201), QFT-IT vs TST(κ=0.335), and TSPOT vs QFT-IT(κ=0.146)].[12] Another study done in Atlanta, USA (8.6%, born outside USA) compared two IGRAs and TST in 336 HIV infected individuals. Concordance between all 3 tests (TST, TSPOT, and

QFT-IT) was also poor [TSPOT vs TST(κ=0.16), QFT-IT vs TST(κ=0.23), and TSPOT vs QFT-IT(κ=0.06)].[13] The third study, in this case from South Africa, a high TB county, compared two IGRAs and TST in 74 HIV infected individuals. Agreement between TSPOT and TST (κ=0.60) respectively, QuantiFERON-TB Gold and TST(κ=0.58) was fair, but poor between the two IGRAs(κ=0.34).[14] These three studies were undertaken in low and high- prevalence tuberculosis countries. To date, however, no similar study but carried out in intermediate TB countries has been published. The incidence of active TB in South Korea is intermediate (96/100,000 cases per year), and BCG vaccination at birth has been mandatory.[15] The purpose of this study was to compare the prevalence of positive results for the 3 tests and to assess concordance between these tests in HIV infected individuals not suffering from active tuberculosis in South Korea.

II. MATERIALS AND METHODS

1. Study Design, Setting and Population

A cross-sectional study was carried out between July 2007, and August 2008 at Severance hospital, at the Yonsei University College of Medicine (a 2000-bed tertiary care teaching hospital). The study was approved by the local research ethics committee. Patients enrolled were all above 18 and tested positive for HIV but did not have active TB. All participants provided their written informed consent and demographic data, medical history, history of BCG vaccination, laboratory and radiologic results were collected through medical records and interviews.

2. Interferon- γ Release Assay and Tuberculin Skin Testing

After obtaining blood samples for the two IFN-γ assays, TST was performed according to the Mantoux method with two tuberculin units of tuberculin RT-23(PPD RT 23 SSI; State Serum Institutes, Denmark). The reactions were read after 48-72 hours and a positive TST was defined as an induration of ≥ 5 mm for HIV individuals.[16]

The blood samples obtained before performing the TST were processed within 4 hours and QFT-IT(Cellesis, Carnegie, Australia) and T-SPOT.TB(Oxford Immunotec, Abingdon, UK) tests were done following the instructions of the

manufacturer.

A positive QFT-IT result was defined as TB antigen minus negative control IFN-γ of 0.35 IU/ml or more and 25% or more of negative control IFN-γ value. Indeterminate results were defined as either (1) a negative control IFN-γ level of more than 8.0 IU/ml or (2) a positive control IFN-γ response of 0.5 IU/ml or less with a TB antigen minus a negative IFN-γ response of either less than 0.35 IU/ml or less than 25% of the negative control value. Because the IFN-γ ELISA cannot accurately quantify levels above 10 IU/ml, such levels in QFT-IT were treated as 10 IU/ml during analysis

A positive TSPOT was considered if the response to either the ESAT 6 or CFP 10 minus the negative control was ≥ 6 spot forming cells(SFC), or 2 x the negative control. The result was considered indeterminate if the negative control was > 10 SFC or if the positive control was < 20 SFC.

3. Statistical analysis

Student´s t-test was used to compare continuous variables between groups. Categorical variables were compared applying Pearson's χ^2-test or Fisher's exact test as appropriate. McNemar paired analysis was used to compare proportions between the three tests. Values of $P < 0.05$ were considered significant. The agreement between 3 tests was determined using kappa(κ) coefficients(κ 0.21– 0.40, poor agreement; κ 0.4-0.75, fair to good agreement, κ

> 0.75, excellent agreement).[13] Logistic regression analysis was applied to identify factors associated with positive results for TST, QFT-IT, and TSPOT.TB and with indeterminate results for TSPOT.TB or QFT-IT. Correlation was also assessed between CD4 counts and IFN-γ levels using QFT-IT, and CD4 counts and spot forming cells (SFC) using TSPOT.TB with Spearman's rank correlation coefficient(ρ). All analyses were performed using SPSS for Windows (Version 11.5).

III. RESULTS

1. Characteristics of Participants.

A total of 103 HIV-infected persons were enrolled. Among the 103 patients, 8 participants were excluded due to invalid TST results. Table 1 shows the baseline characteristics of the patients which were included. The median age was 39 years (range 17-69), and 90 participants were males (94.7%). All participants were born in South Korea. A total of 17(17.9%) participants had a history of active TB disease and 61(64.2%) had BCG scars. The median CD4 count was 429 (range 18-1134 cells/μl) and 9 (9.5%) patients had a CD4 count ≤ 200 CD4 cells/μl. Median HIV viral load was < 40 (range < 40 – 453,000 copies/ml), and 66 (69.5%) were under antiretroviral therapy at the time of enrollment.

2. Diagnostic Tests for Latent Tuberculosis Infection (LTBI)

A total of 29 (30.5%) patients underwent more than one diagnostic test for LTBI, and 10(10.5%) patients had all 3 diagnostic tests (TST, QFT-IT, and TSPOT). Among the 95 patients who had valid TST results, thirteen (13.7%) were positive, 15(15.8%) tested positive with QFT-IT; and 26(27.4%) with TSPOT(Table 2).

Table 1. Baseline characteristics for all the HIV-positive individuals included in the study(N=95)

Patient Characteristics	Numbers and Percentages
Age, median years(range)	39(17 – 69)
Male, n(%)	90(94.7%)
BCG scar, n(%)	61(64.2%)
History of TB prophylaxis, n(%)	1(1.1%)
Past medical History	
Diabetes mellitus	5(5.26%)
Chronic renal insufficiency	0(0%)
History of malignancy	1(1.1%)
History of active TB	17(17.9%)
Risk factors for LTBI, n(%)	
Chest X-ray signs of past TB	6(6.3%)
Known household contact to a TB patient	4(4.2%)
Long term residence in a high TB prevalence country[a]	0(0%)
Residence in prison, healthcare worker,	0(0%)
History of drug use	0(0%)
HIV status	
Currently on HAART, n(%)	66(69.5%)
CD4 cell count, median(range)	429(18-1134 cells/μl)
HIV RNA viral load, median(range)	< 40 (<40 – 453,000 copies/ml)
CD4 cell count at enrollment, n(%)	
≤100 CD4 cells/μl	2(2.1%)
100-199 CD4 cells/μl	7(7.4%)
200-349 CD4 cells/μl	23(24.2%)
350-499 CD4 cells/μl	31(32.6%)
≥500 CD4 cells/μl	32(33.7%)
HIV RNA viral load at enrollment, n(%)	
<40 copies/ml	60(63.2%)
40-1000 copies/ml	7(7.4%)
1000-50,000 copies/ml	23(24.2%)
50,000-100,000 copies/ml	2(2.1%)
>100,000 copies/ml	3(3.2%)

TB, tuberculosis; BCG, bacilli Calmette-Guerin; HAART, highly active antiretroviral therapy; LTBI, latent tuberculosis infection, [a]Incidence of TB > 100/100,000 cases per year.

Table 2. Prevalence of a positive results TST, QFT-IT, and TSPOT

Test	Positive result(Percentage Positive)
TST	13(13.7%)
QFT-IT	15(15.8%)
TSPOT	26(27.4%)
More than 1 positive result	29(30.5%)
All 3 tests positive result	10(10.5%)

TST, Tuberculin Skin test; QFT-IT, QuantiFERON-TB Gold In Tube; TSPOT, T-SPOT.TB.

3. Tuberculin Skin Test (TST)

A positive TST result with a mean induration of 13 mm (range 5 – 22 mm) was obtained in 13 cases (13.7%), all of which had a CD4 count ≥ 200 cells/μl. A stastically significant association was found between a positive TST and a history of prior active TB. The logistic regression analysis showed that patients with a history of prior active TB had an approximately seven-fold increased probability of having a positive TST result [odds ratio(OR) 6.9, 95% confidence interval(CI): 1.3 – 37.1, $p = 0.024$] while BCG vaccination was not significantly statistically associated with a positive TST result [OR 5.3, 95% CI: 0.8 – 36.3, $p = 0.09$] . No difference in the mean CD4 count of patients with positive or negative results was detected.(510 versus 421 cells/μl, p=0.103).

4. QuantiFERON-TB Gold In Tube (QFT-IT)

A positive QFT-IT result was obtained for 15 patients (15.8%) while 79 (83.2%) tested negative, and one patient (1.1%) had an indeterminate result. In

this case all patients with a positive QFT-IT had a CD4 count ≥ 200 cells/μl. The median value of IFN-γ using QFT-IT was 0.02 IU/ml (range -0.25 ~ 10 IU/ml). Among patients with a positive QFT-IT result, the median value of IFN-γ was 1.65 IU/ml (range 0.36 ~ 10 IU/ml). The logistic regression analysis showed that patients with a history of prior active TB had about nine times more chances of a positive QFT-IT result [OR 9.3, 95% CI: 2.1 – 41.9, p = 0.04] whereas no statistically significant correlation was observed with BCG vaccination [OR 2.3, 95% CI: 0.5 – 11.0, p = 0.288]. There was no difference in the mean CD4 count of patients with positive or negative results (509 versus 420 cells/μl, p=0.88) and neither was any significant correlation observed between CD4 count and IFN-γ produced by TB specific antigens (ρ = 0.144, p = 0.167).

5. T-SPOT.TB(TSPOT)

Among patients tested with TSPOT, 26 (27.4%) had positive results, 61 patients (64.2%) were negative and 8 patients (8.5%) had an indeterminate result. The mean number of spots for ESAT-6 was 5.3 SFC (range -7 ~ 71) and 7.1 SFC (range -5 ~ 111) for CFP 10. Logistic regression analysis revealed that there was no statistically associated factor for a positive TSPOT result and neither was any difference of the mean CD4 count of patients on positive or negative results (443 versus 441 cells/μl, p=0.953) detected .There was no

significant correlation between CD4 count and IFN-γ response to ESAT-6 or CFP-10(ρ = -0.014, p = 0.895 and ρ = 0.015, p = 0.890 respectively).

6. Risk factors for an indeterminate TSPOT or QFT-IT result

Indeterminate TSPOT results were obtained for 8 patients (8.5%) , and 1(1.1%) had an indeterminate QFT-IT result. Because of the low number of indeterminate QFT-IT results, the risk factors responsible for this were not analyzed. Multivariate analysis revealed that there was statistically significant protective association between antiretroviral therapy at the time of enrollment and indeterminate TSPOT results [OR 0.057, 95% CI: 0.006 – 0.505, p=0.01].

Pooling data for the indeterminate QFT-IT and TSPOT results showed that antiretroviral therapy on enrollment had a statistically significant inverse association with indeterminate TSPOT or QFT-IT results [OR 0.098, 95% CI: 0.019 – 0.509, p=0.006].

7. Concordance between three diagnostic tests

More statistically significant positive results were observed for TSPOT than for both TST (P = 0.002) and QFT-IT(P = 0.003). There was no statistically significant difference between TST and QFT-IT (P = 0.727). Agreement between all 3 diagnostic tests for LTBI was fair to good [QFT-IT vs TST,(κ =

0.665, $p < 0.001$),T-SPOT.TB vs TST ,($\kappa = 0.456$, $p < 0.001$), QFT-IT vs T-SPOT.TB($\kappa = 0.593$, $p < 0.001$)](Table 3).

In univariate analysis, no factors associated with all discordant groups were detected(TST-positive/QFT-IT-negative,TST-positive/TSPOT-negative,TSPOT-positive/QFT-IT-negative,TSPOT-positive/TST-negative,QFT-IT-positive/TSPOT-negative, and QFT-IT-positive / TSPOT-negative).

Table 3. Agreement between three diagnostic tests in study patients

	QFT-IT -	QFT-IT +	QFT-IT indeterminate
TSPOT -	59	1	1
TSPOT +	12	14	0
TSPOT indeterminate	8	0	0

QFT-IT vs TSPOT; Agreement(%): 84.9, κ: 0.593, $p < 0.001$.

	QFT-IT -	QFT-IT +	QFT-IT indeterminate
TST -	76	5	1
TST +	3	10	0

QFT-IT vs TST; Agreement(%): 91.5, κ: 0.665, $p < 0.001$.

	TSPOT -	TSPOT +	TSPOT indeterminate
TST -	59	15	8
TST +	2	11	0

TST vs TSPOT; Agreement(%): 80.5, κ: 0.456, $p < 0.001$.

TST, Tuberculin Skin test; QFT-IT, QuantiFERON-TB Gold In Tube; TSPOT, T-SPOT.TB.

IV. DISCUSSION

This cross-sectional study was designed to compare the usefulness of TST, QFT-IT and TSPOT for the diagnosis of LTBI in HIV- positive individuals in South Korea, an intermediate TB-burden county. Among the 95 patients with valid results, the number of TSPOT positive participants was higher than both TST and QFT-IT (TST 13.7%, QFT-IT 15.8%, TSPOT 27.4%). These results are consistent with those of other studies.[13] and may be attributed to either a higher sensitivity of the TSPOT assay or to false positives. In order to investigate TSPOT assay sensitivity, risk factors associated with discordant groups (TST+/TSPOT-,TSPOT+/QFT-IT-, TSPOT+/TST-, QFT-IT+/ TSPOT-, and QFT-IT+/TSPOT-) were analyzed, finding none which could be related to the discordance. Several studies have reported a higher sensitivity of TSPOT as compared to both QFT-IT or TST[6,14,17-19] and the expected prevalence of LTBI (33%) in all Koreans [11], therefore suggesting that TSPOT may be a more sensitive test. However the interpretation of these results is limited because of the absence of a diagnostic gold standard for LTBI. However they reflect the need for a prospective study to determine which test can best predict the progression to active TB. In our patients, a history of active TB was the only risk factor associated to positive TST and QFT-IT assays but not for positive TSPOT results. The significance of this finding is unclear.

An Atlanta study, the largest study carried out to date to compare all 3 tests (TST, TSPOT, and QFT-IT), revealed that concordance between them was poor [TSPOT vs TST(κ=0.16), QFT-IT vs TST(κ=0.23), and TSPOT vs QFT-IT(κ=0.06)].[13] This finding is inconsistent with our results [TSPOT vs TST(κ=0.456), QFT-IT vs TST(κ=0.665), and TSPOT vs QFT-IT(κ=0.593)]. Considering a study carried out in South Africa, a high TB country [TSPOT vs TST(κ=0.60), QFT-IT vs TST(κ=0.58), and TSPOT vs QFT-IT(κ=0.34)][14] and one from Italy, a low TB country [TSPOT vs TST(κ=0.16), QFT-IT vs TST(κ=0.52), and TSPOT vs QFT-IT(κ=0.19)],[20] it may be concluded that the TB incidence in a country is probably an important explanation for the variability of agreement between studies designed to compare these 3 tests.

Our results revealed even more indeterminate TSPOT results than indeterminate QFT-IT results (eight vs one patient, or 8.5% vs 1.1%). This coincided with the Atlanta study(TSPOT: 14%, QFT-IT: 1.8%)(13). In this study, a CD4 count ≤ 200 cells/μl was shown to be associated with an indeterminate TSPOT result and Ferrara *et al.* reported that indeterminate results for TSPOT were associated with immunosuppressive treatments (only a minority of participants were HIV-infected).[14] Although we expected a similar result to the previous study, we were not able to prove that low CD4 count was associated with an indeterminate IGRAS result due to the fact that we enrolled a low number of cases of immunosuppressed patients (cancer: 1%, other immunosuppressive disease: 0%) and the proportion of CD4 cell counts below

200 cells/μl did not exceed a 10% of the enrolled patients. All these factors may explain the difference in risk factors for indeterminate IGRAs. In the present study, being under antiretroviral therapy at the time of enrollment constituted a a protective factor associated with an indeterminate IGRAs result, but both HIV RNA loads and CD4 counts were not associated with an indeterminate IGRAs result. It was unclear why just the fact of having antiretroviral therapy could constitute a protective factor for an indeterminate result while neither HIV RNA loads or CD4 counts were found to be risk factors for this IGRAs result.

In our study, BCG vaccination had no association with the positive results of any diagnostic test for LTBI. Kang et al.[11] compared TST and QuantiFERON-TB Gold(QFT) in the diagnosis of LTBI according to the intensity of exposure. They explained that a higher positive rate of TST as compared to that of QFT might be the effect of BCG vaccination. False negative results due to anergy in HIV co- infected patients may be an explanation for this discrepancy between our study and Kang et al.'s study

Although other studies reported that in low CD4 counts, there may be more cases of anergic TST responses and indeterminate IGRAs [12,14,21] we did not detect any effect of a low CD4 count on the positivity of all 3 diagnostic tests. The low number of cases with CD4 cell counts below 200 cells/μl(9.5%) present in this study may contribute to the difference in our results.

To our knowledge, the present study is the first to compare TST, QFT-IT and TST in the diagnosis of LTBI in HIV-infected individuals from an intermediate

TB prevalence country. One limitation of this study was an insufficient amount of HIV patients with low CD4 counts (below 100 cells/μl). Our study, therefore, does not allow a good assessment of the contribution of low CD4 counts to positivity of all 3 diagnostic tests for LTBI. A second limitation of our study is that we did not include long-term follow-up data of the progression to active TB. In addition, there is no gold standard for a diagnosis of LTBI. Therefore, it is impossible to make a valid conclusion on the accuracy of the TST, QFT-IT, and TSPOT for the diagnosis of LTBI in HIV infected individuals and the superiority of one test over the other.

In summary, all 3 diagnostic tests for LTBI (TST, QFT-IT, and TSPOT) showed fair to good agreement. TSPOT showed more positive results than both TST and QFT-IT, suggesting that TSPOT may be more sensitive than other tests. TSPOT had even more indeterminate results than QFT-IT. (8.5% vs 1.1%). The result of all 3 tests was not affected by CD4 cell counts. A history of active TB was statistically associated with positive results of TST and QFT-IT but not with positive TSPOT results.

V. CONCLUSION

All 3 diagnostic tests for LTBI (TST, QFT-IT, and TSPOT) showed fair to good agreement. TSPOT showed more positive results than both TST and QFT-IT, suggesting that TSPOT may be more sensitive than other tests. TSPOT had even more indeterminate results than QFT-IT. (8.5% vs 1.1%). The result of all 3 tests was not affected by CD4 cell counts. A history of active TB was statistically associated with positive results of TST and QFT-IT but not with positive TSPOT results.

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ABSTRACT(IN KOREAN)

중등도의 결핵 발생 지역에서 사람면역결핍바이러스 감염증 환자의 잠복결핵 진단을 위한 QuantiFERON-TB In Tube test, T-SPOT.TB, 및 투베르쿨린 피부 반응 검사의 비교

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연구 목적: 본 연구의 목적은 사람면역결핍바이러스에 감염된 한국인의 잠복결핵 진단을 위한 QuantiFERON-TB In Tube test, T-SPOT.TB, 및 투베르쿨린 피부 반응 검사의 결과를 비교하는 것이다.

연구 설계: 본 연구는 두 종류의 인터페론 감마 어세이와 투베르쿨린 피부 반응 검사에 대한 한국인의 결과를 비교하기 위하여 연세대학교 의과대학 세브란스 병원에서 시행했다.

결과: 총 95명의 환자가 등록되었고 환자의 중앙값 CD 4 세포 수는 429 cells/μl(range18-1134)였다. T-SPOT.TB(27.4 %) 검사의 양성률은 TST(11.6%)와 QFT-IT(15.8%)보다 높았다.

(각각의 *P*값은 0.002 및 0.003이었다) TST의 양성률은 QFT-IT와 비슷했다(P = 0.727). 세 검사의 일치율은 fair to good이었다(QFT-IT vs TST, κ = 0.665 : T-SPOT.TB vs TST , κ = 0.456 : QFT-IT vs T-SPOT.TB, κ = 0.593). QFT-IT, TST 및 T-SPOT.TB 양성 환자의 평균 CD4 세포수는 음성 환자의 그것보다 통계적으로 유의하게 높지 않았다.

결론: 사람면역결핍바이러스에 감염된 한국인을 대상으로 T-SPOT.TB, QFT-IT 와 TST를 검사했을 때, 일치율은 fair to good이었고, T-SPOT.TB는 다른 두 검사에 비하여 더 예민했으며 세 검사법의 결과는 CD4 세포 수에 영향을 받지 않았다.

핵심되는 말 : 결핵, 잠복결핵, 사람결핍바이러스, 인터페론감마