Comparison of Interferon-γ Release Assays and the Tuberculin Skin Test for Diagnosis of Tuberculosis in Human Immunodeficiency Virus: A Systematic Review

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Background: It remains uncertain if interferon-γ release assays (IGRAs) are superior to the tuberculin skin test (TST) for the diagnosis of active tuberculosis (TB) or latent tuberculosis infection (LTBI) in immunosuppressed populations including people with human immunodeficiency virus (HIV) infection. The purpose of this study was to systematically review the performance of IGRAs and the TST in people with HIV with active TB or LTBI in low and high prevalence TB countries.

Methods: We searched the MEDLINE database from 1966 through to January 2017 for studies that compared results of the TST with either the commercial QuantiFERON-TB Gold in Tube (QFTGT) assay or previous assay versions, the T-SPOT.TB assay or in-house IGRAs. Data were summarized by TB prevalence. Tests for concordance and differences in proportions were undertaken as appropriate. The variation in study methodology was appraised.

Results: Thirty-two studies including 4,856 HIV subjects met the search criteria. Fourteen studies compared the tests in subjects with LTBI in low TB prevalence settings. The QFTGT had a similar rate of reactivity to the TST, although the first-generation version of that assay was reactive more commonly. IGRAs were more frequently positive than the TST in HIV infected subjects with active TB. There was considerable study methodology and population heterogeneity, and generally low concordance between tests. Both the TST and IGRAs were affected by CD4 T-cell immunodeficiency.

Conclusion: Our review of comparative data does not provide robust evidence to support the assertion that the IGRAs are superior to the TST when used in HIV infected subjects to diagnose either active TB or LTBI.

Keywords: Interferon-Gamma Release Assays; Tuberculin Test; HIV Infection; Latent Tuberculosis; Review, Systematic

Introduction

Infection with *Mycobacterium tuberculosis* (MTb) continues to be a major cause of morbidity and mortality throughout the world, with a disproportionate burden occurring in individuals infected with the human immunodeficiency virus (HIV). In 2015, the World Health Organization (WHO) estimated there were 10.4 million new cases of tuberculosis (TB) worldwide with 1.2 million of these in people co-infected with HIV resulting in 400,000 deaths¹. HIV infected patients with latent MTb infection (LTBI) have a 5%–10% annual risk of developing active disease². Unlike active TB, LTBI does not produce clinical symptoms and, although the host is infected, it does
not result in cultivable organisms. There is no gold standard for the diagnosis of LTBI. Until recently, the diagnosis of LTBI has relied on the tuberculin skin test (TST), which is based on a delayed hypersensitivity response to MTb within the host. It has a number of limitations including cross reaction against the bacille Calmette-Guerin (BCG) vaccine strain and environmental mycobacteria, reported low sensitivity and anergy in HIV infected patients (resulting in false-negative results), operator variability and the requirement of two consultations. Interferon-γ release assays (IGRAs) are an attractive alternative to the TST. There are a number of commercial IGRAs that have been studied: the QuantiFERON-TB Gold in Tube (QFTGT) (Cellestis, Carnegie, Australia) and earlier versions including QuantiFERON-TB (QFT) and QuantiFERON-Gold (QFTG) assays, as well as the T-SPOT.TB (TS.TB) (Oxford Immunotec, Abingdon, UK) assay. The QFTGT measures the release of interferon (IFN)-γ by T cells, through an enzyme linked immunosorbent assay (ELISA), from a stimulated whole blood sample, in response to antigens including the region of difference 1 antigen, culture filtrate protein 10 (CFP-10), early secreted antigen target 6 (ESAT-6), and TB antigen 7.7 peptides. This assay has more antigens than the previous versions. More recently a fourth generation QuantiFERON TB Gold Plus has been released and is currently being evaluated. In contrast to the QuantiFERON assays, the TSTB utilizes an enzyme linked immunosorbent (ELISPOT) method, on a sample of peripheral blood mononuclear cells. In contrast to the TST, indeterminate results may be generated with IGRAs usually due to failure of production of IFN-γ after stimulation with a potent mitogen used as a positive control. Indeterminate results imply abnormal T-cell function or technical error. The frequency of indeterminate IGRA results in HIV infected individuals may increase with increasing levels of immunodeficiency.

As there is no gold standard for the diagnosis of LTBI, the evaluation of IGRAs has been undertaken in subjects with active TB as a marker of true MTb infection. A number of studies and systematic reviews have assessed the performance of these assays in HIV negative subjects, which identified some of the advantages of the IGRA compared to the TST. In contrast, IGRA do not appear to react with exposure to certain non-tuberculous mycobacteria or BCG and test reactivity has been shown to correlate with either risk factors associated with acquisition of TB, or exposure to cases of active TB. However, as these assays depend on intact T-cell function it is plausible that such assays may perform differently in the immunocompromised host.

Our aim was to systematically review the performance of IGRAs and the TST in HIV infected subjects with active TB or LTBI in different TB prevalence settings.

Materials and Methods

This study was conducted and reported in concordance with PRISMA guidelines for systematic reviews. Ethics approval was not required for completion of this systematic review.

1. Search strategy

A MEDLINE search for English language articles published between 1966 and January 2017 was undertaken. The search strategy used search terms including (TB infection OR TB disease) AND [(QuantiFERON OR ELISPOT) OR (interferon gamma release assays) OR (tuberculin skin test) OR (t-cell assay)] AND (HIV OR AIDS). Manufacturers of the commercial assays were contacted for any additional material of relevance.

2. Study selection

Three independent reviewers assessed article titles and abstracts for selection for full text review. Articles excluded were commentary, guidelines, policy, review, case studies, those with HIV negative or unknown status patients, immune reconstitution studies, in vitro studies, non-diagnostic, behavioural or modelling studies, serological, therapeutic and vaccine studies. After full text review only studies that presented data in a format allowing comparison between TST and the IGRAs were included. The population included HIV-1 or HIV-2 infected adults or children. Data from studies that recruited subjects of mixed HIV seropositivity were included only if the data pertaining to the HIV infected group could be extracted. TB referred to pulmonary or extra pulmonary disease due to MTb infection. The IGRAs included the commercial assays QFT, QFTG, QFTGT, and TS.TB. In-house ELISPOT (IHE) assays were included if they used antigens against ESAT-6 and CFP-10. Studies were included if the IGRAs were performed on samples from peripheral blood.

3. Data extraction

Once identified studies were separated into studies of active TB disease or LTBI, based on the case definitions employed by the authors, which included variable assessments of clinical, radiological (including computed tomography scan or plain X-ray), microbiological (including detection of acid fast bacilli on light microscopic examination and/or growth in culture media and/or polymerase chain reaction) and/or histological parameters as listed in the study methodology. Countries were determined to be a low incidence TB country if they reported less than 20 cases of TB per 100,000 people and/or were not one of the 63 high TB/HIV burden countries as per WHO definitions. Study methodology and review of potential bias was extracted in a standardized format and in-
cluded: recruitment method and exclusion criteria, inclusion of patients with a past history of active TB or LTBI, inpatient or outpatient setting of the study, age (classified into adult or child) and ethnicity of the study population. We assessed the laboratory methods detailed by the authors, including definitions of test positivity (for both TST and IGRA), indeterminate (IGRA only) and whether technicians were blinded to the TST result. HIV specific data including mean or median CD4 T-cell count and proportion of patients taking antiretroviral therapy were also extracted.

4. Statistical analyses

We calculated the proportion of reactive assays and 95% confidence intervals using paired data. To test the measurement of agreement between IGRA and TST Cohen’s kappa statistic (k) and p-values reported in studies was used. Statistical calculators were sourced from VasserStats: Website for Statistical Computation (http://vassarstats.net/). Meta-analysis was not undertaken due to heterogeneity of study methodology (population, setting, type of IGRA, type of TST, and non-consecutive recruitment).

Results

Our search identified a total of 1024 articles (Figure 1) of which 32 studies with a total of 4,856 HIV infected subjects were selected for final review.

1. Active TB disease

We identified nine studies in which IGRA and TST were performed in 431 patients with active TB (Table 1)\(^{14-22}\). Only two studies\(^{16,21}\) reported a greater proportion of positive results in IGRA than the TST. There was inter- and intra-test variability in test positivity and proportion of indeterminate results. Concordance between the TST and QFTGT was reported in only one Indian study and was found to be low (k=0.27)\(^{16}\). There was considerable heterogeneity in the study design including the case definition of active TB disease and exclusion criteria including varying durations of anti-tuberculous therapy (ATT) at the time of testing (Table 2)\(^{14-22}\).

2. LTBI

Fourteen studies from low TB prevalence countries were
Table 1. Performance of TST and various IGRAs in HIV infected individuals with evidence of active TB

| Country          | Subject            | Assay   | No. | TST +/Total tested | TST not read (%) | IGRA +/Total tested | Indeterminate IGRA (%) |
|------------------|--------------------|---------|-----|--------------------|------------------|----------------------|------------------------|
|                  |                    |         |     | No. (%)            | 95% CI           | No. (%)              | 95% CI                 |
| Romania          | Children           | QFTG    | 36  | 14/36 (39)         | 25–55            | 0 (0)                | 17/36 (47)            |
|                  | Adults             | IHE     | 45  | 14/39 (36)         | 23–52            | 6 (13)               | 24/45 (53)            |
| Italy            | Children           | IHE     | 40  | 26/47 (55)         | 55–74            | 0 (0)                | 26/47 (55)            |
|                  | Adults             | IHE     | 36  | 21/32 (66)         | 56–85            | 1 (3)                | 21/32 (66)            |
| South Africa     | Adults             | QFTG    | 45  | 13/38 (35)         | 27–41            | 0 (0)                | 13/38 (35)            |
|                  | Adults             | TSTB    | 30  | 17/26 (65)         | 17–26            | 0 (0)                | 17/26 (65)            |
|                  | Adults             | IHE     | 32  | 9/25 (36)          | 20–55            | 5 (17)               | 9/25 (36)             |
| China            | Children           | TSTB    | 20  | 23/30 (77)         | 56–86            | 0 (0)                | 23/30 (77)            |
|                  | Adults             | IHE     | 26  | 22/25 (88)         | 66–94            | 0 (0)                | 22/25 (88)            |
| Zambia           | Adults             | QFTG    | 59  | 26/47 (44)         | 41–69            | 12 (20)              | 26/47 (44)            |
|                  | Adults             | QFTG    | 59  | 37/59 (63)         | 50–74            | 0 (0)                | 37/59 (63)            |
| Africa           | Adults             | TSTB    | 10  | 14/39 (36)         | 13–38            | 17 (28)              | 14/39 (36)            |
|                  | Children           | IHE     | 60  | 29/60 (48)         | 10–30            | 17/60 (28)           | 29/60 (48)            |

*Study population aged 15–60 years old.
TST: tuberculin skin test; IGRA: interferon-γ release assay; HIV: human immunodeficiency virus; TB: tuberculosis; CI: confidence interval; QFTG: QuantiFERON Gold; IHE: in house ELISPOT assay; QFTGT: QuantiFERON Gold in Tube; TSTB: T-SPOT.TB.

analysed comprising a total of 2,959 HIV adult subjects (Table 3)\(^15,21-45\). There was significant heterogeneity in the studies (Table 4)\(^15,21-45\). There were only three studies where significant differences between IGRA and TST were identified although the direction of difference was inconsistent. The TSTB (but not the QFTG) had greater reactivity than the TST in one study from Germany\(^25\). In contrast the TST had greater reactivity than an IHE in an Italian study\(^15\). The TST also had greater reactivity than both the QFTGT and TSTB in an anti-retroviral naïve French cohort\(^35\). The rate of positive reactions was higher in the first generation QFT compared to the TST based on two studies with a total sample size of 201 subjects, in which the study population were from the same cohort of mainly injecting drug users (IDU) in urban United States (Table 4)\(^15,35\). These findings were not replicated with the more recent versions of the QuantiFERON assay or other IGRA. Concordance between IGRA and the TST ranged from extremely poor (k=0.02) to strong (k=0.69). Some authors did not present complete data on all test outcomes in subjects who were excluded from statistical analyses due to an indeterminate IGRA or “technical failure of the sample,” potentially introducing bias (Table 4)\(^25,28,32,33\). A significant proportion of subjects in some of these studies did not return to have the TST read\(^28,32\).

Twelve studies (eight in adult subjects) comprising a total of 1,466 subjects (401 children) from high TB prevalence countries were analysed. There were generally higher rates of positive results in all assays (IGRAs and TST) when compared to studies that took place in lower TB prevalence settings. The results were variable with one study finding higher rates of positivity in the TST\(^27\) and five with the IGRA being positive more frequently than the TST\(^21,36,38,42,45\).

The rate of reactivity of both IGRA and TST was affected by the level of HIV associated CD4 T-cell deficiency (Table 5)\(^21,28,30,35,39\).

**Discussion**

The performance characteristics of the TST, including the previously discussed limitations, are well described in HIV populations and other risk groups. Direct comparative studies of new assays with the TST provide data to assist clinicians when considering which test to use in the diagnosis of LTBI in HIV positive patients. Our analysis highlighted three main issues. Subjects with active TB had higher rates of reactivity in IGRA when compared to the TST, although neither test type had sufficient sensitivity to be useful diagnostically. Secondly, the TST had similar rates of reactivity as the IGRA when used in subjects without evidence of active TB. There was variability in rates of test reactivity and concordance between the TST and the different generations of the ELISA and ELISPOT based assays when all three tests were used in the same studies. Lastly, the heterogeneity of study methodology and population precluded a definitive conclusion on test superiority.

In the absence of a gold standard test for LTBI, active TB is commonly used as a surrogate when assessing the per-
Table 2. Methodological differences between studies comparing TST and various IGRA s in subjects with evidence of active TB disease

| Country       | Setting and Subject | CR | TB site | CD4 (mean cells/mm³) | % on cART | BCG vaccinated (%) | TST type; induration positive | Patients with prior TB | ATT duration (wk) | IGRA blinded to TST | Comment                                      |
|---------------|---------------------|----|---------|----------------------|-----------|-------------------|------------------------------|------------------------|-------------------|------------------|---------------------------------------------|
| Countries with low TB prevalence                                               |
| Romania¹⁴     | H, Ch               | NS | P, EP   | NS                   | NS        | 100               | 2TU IC65; 5 mm               | NS                     | Any or complete | NS               | Children aged 12–18 years exclusions NS     |
| Italy¹⁵       | H, Ad               | NS | P, EP   | 179                  | 48        | 51                | 5TU PPD; 5 mm                | NS                     | N                 | Y                | Exclusions NS                                      |
| Countries with high TB prevalence                                              |
| India¹⁶       | H, Ad               | NS | P, EP   | 116                  | 0         | NS                | 2TU RT23; 5 mm               | N                      | <2                | NS               | Included non-microbiologically confirmed TB in case definition. Ten percent dual HIV 1+2 infection; excluded ESF; IMM, prior TST, cART, silicosis. |
| Ethiopia¹⁷    | OP, Ad, Ch          | Y  | P       | 219                  | 0         | 24                | 2TU RT23; 10 mm              | N                      | 0                 | NS               | Included non-microbiologically confirmed TB in case definition. Excluded subjects <15 years or >60 years old; hospitalized patients, pregnancy, concurrent other disease. |
| South Africa¹⁸| OP, Ad              | NS | P, EP   | NS                   | NS        | NS                | 2TU RT23; 10 mm              | Y                      | <1                | NS               | Self-reported HIV status                      |
| Zambia¹⁹      | OP, Ad              | Y  | P       | 212                  | 13        | NS                | 2TU RT23; 5 mm               | Y                      | <4                | NS               | TST reading between 48–164 hr; excluded ATT >4 wk |
| South Africa²⁰| H, OP, Ch           | Y  | P, EP   | NS                   | 0         | NS                | 2TU RT23; any induration     | N                      | <4                | Y                | Included non-microbiologically confirmed TB in case definition. Children aged up to 14 yr. Ten percent ELISPOT assays not analyzed (bacterial contamination). |
| China²¹       | NS, Ad              | NS | P       | 62                   | 100       | 5TU PPD; 5 mm     | NS                           | Any                    | Y                 | Data in text and flow chart not consistent; text data analyzed; exclusions NS. |
| South Africa²²| H, OP, Ch           | NS | P, EP   | NS                   | 25        | 39                | 2TU RT23; 5 mm               | NS                     | <1                | Y                | Included non-microbiologically confirmed TB in case definition. Exclusions NS. |

TST: tuberculin skin test; IGRA: interferon-γ release assay; TB: tuberculosis; CR: consecutive recruitment; cART: combination antiretroviral therapy; BCG: bacille Calmette-Guerin; ATT: anti-tuberculous therapy; H: hospital; Ch: children; NS: not stated in text; P: pulmonary TB; EP: extra pulmonary TB; TU IC65: Romanian purified protein derivative; Ad: adults; N: no; Y: yes; PPD: purified protein derivative; TU RT23: international tuberculin units of purified protein derivative; Staten Serum Institute, Copenhagen, Denmark; HIV: human immunodeficiency virus; ESF: end stage renal failure; IMM: immunosuppressant including steroids; OP: outpatient.
Table 3. Performance of TST and various IGRAs in HIV infected individuals without evidence of active TB infection

| Country               | Subject | Assay | No. | TST +/Total tested | TST not read | IGRA +/Total tested | Indeterminate IGRA (%) | Kappa | p-value* |
|-----------------------|---------|-------|-----|--------------------|--------------|----------------------|------------------------|-------|----------|
|                       |         |       |     | No. (%) 95% CI     | (%)          | No. (%) 95% CI       |                        |       |          |
| **Countries with low TB prevalence** |         |       |     |                    |              |                      |                        |       |          |
| France²³ | Adults | QFTGT | 415 | 66/415 (16) 13–20 | 0 (0)       | 43/415 (10) 8–14    | 23 (6) 0.27 NA         |       |          |
| USA²⁴ | Adults | QFTGT | 294 | 19/205 (9) 6–14  | 89 (30)     | 25/294 (8) 6–12     | 15 (5) 0.37 1.00       |       |          |
| USA²⁵ | Adults | QFTGT | 207 | 13/201 (6) 4–11  | 3 (1)       | 11/201 (5) 3–9      | 10 (5) 0.38 0.79       |       |          |
| USA²⁶ | Adults | QFTGT | 578 | 18/533 (3) 2–5  | NA          | 26/553 (5) 3–7       | NA 0.15 0.18           |       |          |
| USA²⁷ | Adults | QFTGT | 336 | 7/278 (2) 1–5   | 58 (17)     | 9/336 (3) 1–5       | 6 (2) 0.23 0.77        |       |          |
| Italy²⁸ | Adults | QFTGT | 133 | 6/116 (5) 2–11  | 17 (13)     | 5/116 (4) 2–10       | 7 (6) 0.52 NA          |       |          |
| Spain²⁹ | Adults | QFTGT | 75  | 9/75 (12) 6–21  | 0 (0)       | 5/75 (7) 3–15        | 1 (1) 0.37 NA          |       |          |
| Spain³⁰ | Adults | QFTGT | 167 | 9/135 (7) 4–12  | NA          | 13/135 (10) 6–16     | 2 (1) 0.60 0.28        |       |          |
| Chile³¹ | Adults | QFTGT | 116 | 12/110 (11) 6–18 | 5 (4)       | 17/115 (15) 9–22     | 0 (0) 0.59 0.05        |       |          |
| Germany³² | Adults | QFTGT | 286 | 33/275 (12) 9–16 | 11 (4)     | 52/275 (19) 15–24    | 1 (0.4) 0.33 NA        |       |          |
| Switzerland³³ | Adults | TSTB  | 85  | 5/85 (6) 2–13   | 0 (0)       | 9/85 (10) 6–19       | 8 (9) 0.69 NA          |       |          |
| USA³⁴ | Adults | QFT   | 167 | 16/167 (10) 6–15 | 0 (0)       | 32/167 (19) 14–26    | 0 (0) 0.28 <0.01†       |       |          |
| USA³⁵ | Adults | QFT   | 34  | 9/34 (26) 15–43 | 0 (0)       | 17/34 (50) 34–66     | 0 (0) 0.41 0.02†        |       |          |
| Italy³⁶ | Adults | IHE   | 66  | 16/66 (24) 16–36 | 0 (0)       | 3/66 (4) 2–12        | 12 (18) 0.11 NA        |       |          |
| **Countries with high TB prevalence** |         |       |     |                    |              |                      |                        |       |          |
| India³⁷ | Adults | QFTGT | 252 | 27/252 (11) 7–15  | 12 (5)      | 71/252 (28) 23–34    | 8 (3) 0.25 <0.005       |       |          |
| South Africa³⁸ | Children | QFTGT | 93/299 (31) 26–37 | 4 (1) 0.50 | 59/299 (20) 16–25    | 28 (9) NA              |       |          |
| South Africa³⁹ | Adults | TSTB  | 39/297 (13) 10–17 | 34 (11) 0.45 | 59/297 (13) 10–17    | 34 (11) 0.45 NA        |       |          |
| South Africa³⁹ | Adults | QFTGT | 109 | 42/89 (47) 37–57 | 20 (18)     | 74/109 (68) 59–76    | 4 (4) 0.34 NA          |       |          |
| South Africa³⁹ | Adults | TSTB  | 59/109 (54) 45–63 | 4 (4) 0.37 | 59/109 (54) 45–63    | 4 (4) 0.37 NA          |       |          |
| South Africa³⁹ | Adults | QFTGT | 74  | 35/67 (52) 40–64 | 7 (9)       | 32/74 (43) 32–54     | 5 (7) 0.58 NA          |       |          |
| South Africa³⁹ | Adults | TSTB  | 38/74 (51) 40–62 | 1 (1) 0.60 | 38/74 (51) 40–62     | 1 (1) 0.60 NA          |       |          |
| South Africa³⁹ | Adults | TSTB  | 38/74 (51) 40–62 | 1 (1) 0.60 | 38/74 (51) 40–62     | 1 (1) 0.60 NA          |       |          |
Table 3. Continued

| Country          | Subjects | Assay  | No. | TST +/Total tested | TST not read (%) | IGRA +/Total tested | Indeterminate IGRA (%) | Kappa | p-value* |
|------------------|----------|--------|-----|-------------------|------------------|----------------------|------------------------|-------|----------|
|                  |          |        |     |                   |                  |                      |                        |       |          |
| South Africa‡‡  | Children | QFTG   | 23  | 6/23 (26)         | 12–46            | 0 (0)                | 2/12 (17)              | 5–45  | 0 (0)    | 0.44     | NA       |
|                  |          | TS. TB |     |                   |                  |                      |                        |       |          |
| Trinidad and     | Adults   | QFTG   | 70  | 12/64 (19)        | 11–30            | 0 (0)                | 26/70 (37)             | 27–49 | 6 (8)    | NA       | NA       |
| Tobago*          |          |        |     |                   |                  |                      |                        |       |          |
| China‡‡‡         | Adults   | TS. TB | 68  | 28/68 (41)        | 30–53            | 0 (0)                | 46/68 (68)             | 59–78 | 0 (0)    | NA       | NA       |
| China‡‡         | Adults   | TS. TB | 93  | 3/93 (3)          | 1–9              | 0 (0)                | 16/93 (17)             | 11–26 | 0 (0)    | NA       | NA       |
| Zimbabwe*        | Adults   | IHE    | 73  | 33/73 (45)        | 34–56            | 0 (0)                | 22/73 (30)             | 21–41 | 0 (0)    | 0.40     | 0.03‡ |
| Zambia‡‡        | Adults   | IHE    | 21  | 5/14 (36)         | 16–61            | 7 (33)               | 9/21 (43)              | 24–63 | 0 (0)    | 0.25     | 1.00     |
| South Africa‡‡  | Children | IHE    | 79  | 7/48 (14)         | 7–27             | 31 (39)              | 20/79 (25)             | 17–36 | 5 (6)    | 0.12     | 0.06     |
| Senegal‡‡       | Adults   | IHE    | 285 | 61/285 (21)       | 17–26            | 0 (0)                | 125/285 (44)           | 38–50 | 38 (13)  | 0.23     | NA       |

*McNemars test. †Statistically significant. ‡Pregnant women.

TST: tuberculin skin test; IGRA: interferon-γ release assay; HIV: human immunodeficiency virus; TB: tuberculosis; QFTGT: QuantiFERON Gold in Tube; TS. TB: T-SPOT. TB; NA: not available; QFTG: Quantiferon Gold; QFT: Quantiferon; IHE: in house ELISPOT assay.

The spectrum of the kinetics of the IGRA response to TB infection has not been established. Studies in mainly HIV infected patients have analysed the IGRA during ART, with/without antiretroviral therapy prior to the IGRA being undertaken. The population groups studied were diverse. Some of the subjects in studies from low prevalence countries included individuals born in high TB incidence countries. A number of the studies included subjects with HIV-2 seropositivity. Additionally, there was substantial study heterogeneity, with different immunological and clinical phenotypes and are not equivalent immunological and clinical phenotypes and are not equivalent conditions.

Studies used different criteria to include and exclude cases of active TB infection. The clinical evaluation of HIV-TB co-infected patients is challenging, particularly with more advanced states of immunodeficiency. The clinical presentation of active TB infection can be varied with higher rates of disseminated disease, lower rates of sputum smear positivity and atypical radiological appearances. The spectrum of the kinetics of the IGRA response to TB infection has not been established. Studies in mainly HIV infected patients have analysed the IGRA during ART, with/without antiretroviral therapy prior to the IGRA being undertaken. The population groups studied were diverse. Some of the subjects in studies from low prevalence countries included individuals born in high TB incidence countries. A number of the studies included subjects with HIV-2 seropositivity. Additionally, there was substantial study heterogeneity, with different immunological and clinical phenotypes and are not equivalent conditions.
| Country | Setting and Subject | Ethnicity | CR | Active TB excluded | CD4 (mean cells/mm$^3$) | % on cART | BCG vaccinated (%) | TST type; define positive | Patients with prior TB infected | Patients previous Rx for LTBI included | IGRA blinded to TST | Comment and exclusion |
|---------|---------------------|-----------|----|-------------------|-------------------------|-----------|------------------|------------------------|----------------------------|--------------------------------|----------------|------------------|
| France  | OP, Ad              | 60% European | Y  | 483               | 0                       | 61                    | 5TU PPD; 5 mm     | Y                      | NS                        | NS                            | 57 % Born/stay high prevalence country; excluded allergy TST, active TB, immunosuppressive medication |
| USA     | OP, Ad              | 47% Black   | NS | 364               | 69                      | 6                     | 5TU Tube; 5 mm    | Y                      | Y                         | Y                             | 37% History IDU; excluded current TB suspect, current IPT, prior reaction to TST |
| USA     | OP, Ad              | 47% AA      | Y  | 452               | 75                      | NS                    | 5TU PPD; 5 mm     | Y                      | Y                         | NS                            | Excluded: prior reaction to TST, IMM <3/12, chemotherapy <1 yr; six subjects (three TST not read and three discordant QFT results on repeat testing), excluded from statistical analysis |
| USA     | OP, Ad              | 80% Black   | NS | NA                | NA                      | 7                     | 5TU PPD; 5 mm     | N                      | Y                         | NS                            | 25/578 Subjects excluded due to TST not read or indeterminate IGRA or insufficient venipuncture; data not presented |
| USA     | OP, Ad              | 85% AA      | N  | NA                | 70                      | 7                     | 5TU Tube; 4 mm    | Y                      | Y                         | Y                             | High numbers mitogen failure; exclusions NS |
| Italy   | OP, Ad              | 90% White   | Y  | 120               | 60                      | 6                     | 5TU PPD; 5 mm     | NS                     | NS                        | Y                             | Excluded subjects post-enrollment with high negative control values in IGRA; data did not specify if excluded patients were HIV positive group; IGRA data on 17 subjects excluded from analyses due to NR for TST |
| Spain   | OP, Ad              | NS         | Y  | A, B              | 461                     | NS                    | 2TU RT23; 5 mm    | NS                     | N                         | NS                            | 8% Immigrants from high TB prevalence countries |
| Country     | Setting and Subject | Ethnicity | CR | Active TB excluded | CD4 (mean cells/mm³) | % on cART | BCG vaccinated (%) | TST type; define positive | Patients with prior TB included | Patients previous Rx for LTBI included | IGRA blinded to TST | Comment and exclusion |
|-------------|---------------------|-----------|----|--------------------|----------------------|----------|-------------------|--------------------------|-------------------------------|-----------------------------|----------------|----------------------|
| Spain       | OP, Ad              | 60% Spanish | NS | A                  | 300*                 | 11       | 34                | 2TU RT23; 5mm             | NS                           | NS                         | NS                  | 38% Subjects born in a high TB prevalence country; 20% IDU; excluded subjects with current AIDS illness, current TB or therapy for LTBI; 32/167 (19%); subjects were excluded from analysis on basis of not returning for collection of blood samples for IGRA and or reading of TST; data not presented |
| Chile       | OP, Ad              | NS        | Y  | A, B               | 393                  | NS       | 88                | 2TU RT23; 5mm             | Y                           | NS                         | Y                    | Seven patients excluded from paired analysis: insufficient blood volume for IGRA test, five NR for TST reading, one patient had TST performed prior to IGRA; excluded CD4 <100, TST in past 2 yr, current use IMM |
| Germany     | OP, Ad              | 85% White | NS | A                  | 408*                 | 17       | 7                 | 2TU RT23; 5mm             | Y                           | NS                         | Y                    | Subjects excluded from analyses due to technical reasons (seven QFT, seven TST; TB) and four patients where samples for both IGRA were missing; k-value based on 256/286 patients with valid results; excluded current TB suspect, prior reaction to TST, current AIDS or illness |
| Switzerland | OP, Ad              | 46% High TB prevalence origin | NS | NS                 | NS                   | NS       | NS                | 2TU RT23; 5mm             | NS                           | NS                         | NS                  | Comparison of low risk TB HIV subjects with those from high TB prevalent origin; subjects with IND results excluded from statistical analyses |
| USA         | OP, Ad              | NS        | NS | NS                 | 318                  | NS       | NS                | 5TU Tube; 5mm              | Y                           | NS                         | NS                  | IDU cohort of mixed HIV sero-positivity n=1,008 all given TST; data presented on subjects who returned for reading of TST; n=167; exclusions NS |
| USA         | OP, Ad              | 97% AA    | N  | NS                 | NS                   | NS       | NS                | 5TU; 5mm                  | NS                           | Y                          | NS                  | Study population recruited from the same cohort as Kimura et al; exclusions NS |
| Country     | Setting and subjects | Ethnicity | CR | Active TB excluded | CD4 (mean cells/mm$^3$) | % on cART | BCG vaccinated (%) | TST type; define positive | Patients with prior TB included | Patients previous Rx for LTBI included | IGRA blinded to TST | Comment and exclusion |
|-------------|----------------------|-----------|----|--------------------|-------------------------|-----------|-------------------|--------------------------|---------------------------------|-------------------------------|-----------------|---------------------|
| Italy$^{52}$ | H, Ad                | 20% African | Y  | A, B, C, D         | NS                      | NS        | 30                | 5TU PPD; 5 mm             | NS                              | NS                            | Y               | Symptomatic patients, analyses based on patients in whom TB excluded |
| India$^{56}$ | OP, Ad               | NS        | NS | Y                  | 400$^*$                 | 46        | NS                | 5TU PPD; 5 mm             | Y                               | N                            | NS              | Excluded allergy TST, active TB, immunosuppressive condition |
| South Africa$^{57}$ | OP, Ch             | 74% Black | NS | Y                  | 1317$^*$                | 88        | 87                | 2TU RT23; 5 mm             | Y                               | NS                            | NS              | Children 3 mo to 15 yr included; excluded weight <5 kg, Hb <9 g/dL and current TB treatment |
| Uganda$^{58}$  | OP, Ad               | NS        | NS | A+B, C             | 283$^*$                 | 0         | NS                | 2TU RT23; 5 mm             | N                               | N                            | Y               | Excluded: patients with a Karnofsky score less than 60, current OI, prior steroids; discrepancy between TST positive results in figure and tables; data from tables used in analyses |
| South Africa$^{59}$ | OP, Ad              | 100% Black | Y  | A                  | 392                    | 0         | 51                | 2TU RT23; 5 mm             | N                               | N                            | Y               | Excluded subjects with current OI, Karnofsky score less than 60, IMM |
| South Africa$^{60}$ | OP, Ad, Ch       | NS        | Y  | A                  | 334 (Ad) 1,162 (Ch)    | 0         | 70                | 2TU RT23; 5 mm             | NS                              | NS                            | NS              | TSTB preferentially completed when inadequate phlebotomy; excluded acutely unwell and current IPT |
| Trinidad and Tobago$^{51}$ | OP, Ad         | NS        | NS | NS                 | NS                     | 100       | NS                | 5TU Tube; 5 mm             | NS                              | NS                            | Y               | Protocol defined TST positivity=10 mm; redefined post-analyses as 5 mm; no HIV patients had TST >10 mm |
| China$^{21}$   | OP, Ad               | NS        | NS | A, B, C, D         | NS                      | NS        | 100               | 5TU PPD; 5 mm              | NS                              | NS                            | Y               | Excluded patients with a positive prior IGRA |
| China$^{62}$   | OP, Ad               | NS        | NS | A+B                | 151$^*$                 | 0         | 100               | 5TU PPD; 5 mm              | N                               | N                            | NS              | Subjects recruited from a cART hospital clinic; exclusion criteria limited to presence of active TB only; venipuncture performed post-TST |
| Zimbabwe$^{43}$ | OP, Ad               | NS        | N  | NS                 | NS                      | NS        | 2TU RT23; 10 mm   | NS                       | NS                              | NS                            | NS              | Two-step TST protocol; population studied were contacts of TB cases; exclusions NS |
TBI was lower than that observed in the studies in patients with active TB. This may reflect the impact of severe immuno-suppression and malnutrition occurring within this patient group.

Previous studies have assessed IGRAs within HIV subjects and have reported increased "sensitivity" in diagnosing L TBI in a high and low TB prevalence settings in comparison to the TST. This increased "sensitivity" usually represents increased rates of assay reactivity rather than true sensitivity as there is no gold standard. However, studies were included that did not perform direct comparisons with the TST and studies using other generation commercial IGRA as well as TTE and TST, were excluded. There are limitations of this review. We have presented data on the first generation commercial QFT test that is no longer commonly available. Most studies had small sample sizes and the interim clinicians should be cognizant of the limitations of the data and variable test reactivity when considering which test to use to diagnose LTBI in this population.

Table 4. Continued

| Country     | Setting and subjects | Ethnicity | CR | Active TB excluded | CD4 (mean cells/mm$^3$) | % on cART | BCG vaccinated (%) | TST type; define positive | Patients with prior TB included | Patients previous Rx for LTBI included | IGRA blinded to TST | Comment and exclusion |
|-------------|----------------------|-----------|----|-------------------|------------------------|-----------|-------------------|--------------------------|---------------------------------|--------------------------------|-----------------|----------------------|
| Zambia$^{21}$ | OP, Ad               | NS        | NS | A, B              | NS                     | NS        | NS                | 5TU RT23; 10 mm          | N                               | NS                             | N               | Exclusions NS        |
| South Africa$^{22}$ | OP, Ch              | NS        | NS | Y                 | NS                     | 51        | 81                | 2TU RT23; 5 mm           | NS                             | NS                             | Y               | Excluded current IPT |
| Senegal$^{25}$ | OP, Ad               | NS        | NS | A, B              | 179*                   | 0         | 73                | 2TU RT23; 5 mm           | NS                             | NS                             | NS               | 216/247 dual HIV 1+2 infected; excluded: patients diagnosed with HIV more than 3 months ago; patients with a Karnofsky score <80 |

*Median.

TST: tuberculin skin test; Rx: radiotherapy; IGRA: interferon-γ release assay; TB: tuberculosis; CR: consecutive recruitment; cART: combination antiretroviral therapy; BCG: bacille Calmette-Guerin; LTBI: latent tuberculosis infection; OP: outpatient; Ad: adults; NS: not stated in text; Y: yes; N: no; TU: international tuberculin units; PPD: purified protein derivative; Tub.: tubersol purified protein derivative; IDU: injecting drug use; IPT: isoniazid preventative therapy; AA: African American; IMM: immunosuppressant including steroids; QFT: QuantiFERON-TB: A clinical evidence of TB; B: radiological features consistent with TB; TU RT23: international tuberculin units of purified protein derivative Staat Serum Institute, Copenhagen, Denmark; AIDS: acquired immune deficiency syndrome; TS.TB: T-SPOT.TB; HIV: human immunodeficiency virus; H: hospital; C: acid fast bacilli-positive smear; D: TB Culture positive; OE: opportunistic infection; Ch: children; Hb: hemoglobin.
### Table 5. Performance of TST and IGRAstratified by CD4 T-cell count in patients without active TB infection

| Country (assay) | No. | CD4 (mean cells/mm³) | TST +/total tested (%) | TST not read (%) | ELISA based IGRA +/total tested (%) | Indeterminate ELISA IGRA (%) | TS.TB +/total tested | Indeterminate TS.TB IGRA (%) |
|-----------------|-----|----------------------|------------------------|-----------------|--------------------------------------|-------------------------------|----------------------|---------------------------|
| USA²⁴ (QFTGT)   | 294 | 364                  | 12/205 (9)             | 0/30 (0)        | 25/99 (8)                            | 15 (5)                       | NA                   | -                         |
|                 |     | <100                 | 0/21 (0)               |                 | 0/31 (0)                             | 5 (16)                       |                      |                           |
|                 |     | 100–350              | 7/83 (8)               |                 | 6/111 (5)                            | 4 (4)                        |                      |                           |
|                 |     | >350                 | 12/101 (12)            |                 | 19/152 (12)                          | 6 (4)                        |                      |                           |
| Spain²⁵ (QFTGT)| 75  | 461                  | 9/75 (12)              | 0 (0)           | 5/75 (7)                             | 1/75 (1)                     | 7/75 (9)             | 1/75 (1)                 |
|                 |     | <200                 | 0/20 (0)               |                 | 0/20 (0)                             | NS                           | 1/20 (5)             | NS                       |
|                 |     | >200                 | 9/55 (16)              |                 | 5/55 (9)                             | NS                           | 6/55 (11)            | NS                       |
| Spain³⁰ (QFTGT)| 135 | 300                  | 9/135 (7)              | NA              | 13/135 (10)                          | 2 (1)                        |                      |                           |
|                 |     | <100                 | 0/21 (0)               |                 | 0/21 (0)                             | NS                           |                      |                           |
|                 |     | 101–300              | 0/47 (0)               |                 | 3/47 (6)                             | NS                           |                      |                           |
|                 |     | 301–500              | 9/29 (10)              |                 | 4/29 (14)                            | NS                           |                      |                           |
|                 |     | >500                 | 6/38 (16)              |                 | 6/38 (16)                            | NS                           |                      |                           |
| South Africa³⁰ (QFTG)* | 74 | 392                  | 35/67 (52)             | 7 (9)           | 32/74 (43)                           | 5 (7)                        | 38/73 (52)           | 9 (44)                   |
|                 |     | <200                 | NS                    |                 | NS (26)                             | NS                           | 13 (54)              | NS                       |
|                 |     | >250                 | 12 (33)                |                 | NS                                  | NS                           | 25 (48)              | NS                       |
|                 |     | >350                 | NS                    |                 | NS                                  | NS                           | NS                   | NS                       |
| Uganda³⁸ (QFTGT)| 109 | 283                  | 42/89 (47)             | 20 (18)         | 74/109 (68)                          | 4 (4)                        | 59/109 (54)          | 4 (4)                    |
|                 |     | <100                 | 1/8 (12)               | 1/10 (10)       | 1 (10)                              | 7/10 (70)                    | 0 (0)                |                           |
|                 |     | 100–250              | 9/27 (33)              |                 | 0 (0)                                | 19/33 (58)                   | 2 (6)                |                           |
|                 |     | >250                 | 32/54 (59)             |                 | 51/66 (77)                           | 3 (5)                        | 33/66 (50)           | 2 (3)                    |

*Proportion (%) of positive IGRA individuals within CD4 count stratification, denominator not available.
TST: tuberculin skin test; IGRA: interferon-γ release assay; TB: tuberculosis; ELISA: enzyme linked immunosorbent assay; TS.TB: T-SPOT.TB; QFTGT: QuantiFERON Gold in Tube; NA: not available; NS: not stated in text; QFTG: QuantiFERON Gold.

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