Interferon-γ Release Assays for the Diagnosis of Tuberculosis and Tuberculosis Infection in HIV-Infected Adults: A Systematic Review and Meta-Analysis

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Abstract

Background: Despite the widespread use of interferon-γ release assays (IGRAs), their role in diagnosing tuberculosis and targeting preventive therapy in HIV-infected patients remains unclear. We conducted a comprehensive systematic review to contribute to the evidence-based practice in HIV-infected people.

Methodology/Principal Findings: We searched MEDLINE, Cochrane, and Biomedicine databases to identify articles published between January 2005 and July 2011 that assessed QuantiFERON®-TB Gold In-Tube (QFT-GIT) and T-SPOT®.TB (T-SPOT.TB) in HIV-infected adults. We assessed their accuracy for the diagnosis of tuberculosis and incident active tuberculosis, and the proportion of indeterminate results. The search identified 38 evaluable studies covering a total of 6514 HIV-infected participants. The pooled sensitivity and specificity for tuberculosis were 61% and 72% for QFT-GIT, and 65% and 70% for T-SPOT.TB. The cumulative incidence of subsequent active tuberculosis was 8.3% for QFT-GIT and 10% for T-SPOT.TB in patients tested positive (one study each), and 0% for QFT-GIT (two studies) and T-SPOT.TB (one study) respectively in those tested negative. Pooled indeterminate rates were 8.2% for QFT-GIT and 5.9% for T-SPOT.TB. Rates were higher in high burden settings (12.0% for QFT-GIT and 7.7% for T-SPOT.TB) than in low-intermediate burden settings (3.9% for QFT-GIT and 4.3% for T-SPOT.TB). They were also higher in patients with CD4+ T-cell count < 200 (11.6% for QFT-GIT 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).

Conclusions/Significance: 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. Identifying the factors associated with indeterminate results will help to optimize the use of IGRAs in clinical practice, particularly in resource-limited countries with a high prevalence of HIV-coinflection.

Introduction

Tuberculosis is one of the leading causes of mortality in people living with human immunodeficiency virus (HIV) worldwide, particularly in sub-Saharan Africa, where it is responsible for up to half of HIV-related deaths [1,2].

HIV co-infection increases the risk of tuberculosis either by facilitating reactivation of a remote latent infection (LTBI) or by favoring the progression of a recently acquired infection towards active disease. Therefore, rapid identification and early treatment of active tuberculosis cases in order to interrupt further transmission, as well as the detection and treatment of LTBI to prevent progression to active disease, are crucial for controlling HIV-associated tuberculosis [3]. However, the lack of accuracy of clinical and radiographic manifestations of tuberculosis in HIV-infected patients and the limitations of diagnostic tests pose great obstacles to rapid diagnosis and delay the initiation of specific treatment [4]. Furthermore, the well-known shortcomings of the tuberculin skin test (TST) for diagnosing LTBI hamper the accurate targeting of HIV-infected patients for isoniazid preventive therapy (IPT) [5].

T-cell-based interferon-gamma (IFN-γ) release assays (IGRAs) constitute a promising alternative to TST for diagnosing tuberculosis infection. IGRAs use highly M. tuberculosis-specific antigens which are not present in most non-tuberculous mycobacteria or in the bacillus Calmette-Guérin vaccine [6]. Two commercial tests are available: the QuantiFERON®-TB Gold In-Tube (QFT-GIT) test (Cellestis Ltd, Carnegie, Australia), which uses ELISA to detect IFN-γ in the culture supernatant, and the T-SPOT®.TB (Oxford Immunotec, Abington, UK), which is based on the enzyme-linked immunospot (ELISpot) assay.

In low-burden tuberculosis settings, IGRAs have shown better specificity and equal or greater sensitivity than TST for the detection of tuberculosis infection, and a better correlation with

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the intensity of exposure to a source of infection [7–9]. These advantages have raised great hopes for a better assessment of tuberculosis infection in people at risk, particularly in immunosuppressed and BCG-vaccinated individuals. Although in the absence of any supporting evidence, IGRAs have also been increasingly used as diagnostic tests for active tuberculosis. This practice has raised concern, particularly in high-burden and resource-limited countries, where the high background LTBI prevalence and the HIV-associated immunosuppression may limit their potential value as rule-in or rule-out tests. Based on recently published meta-analyses showing a suboptimal accuracy for either diagnosing or predicting subsequent active tuberculosis [10–12], the World Health Organization (WHO) issued a consensus statement in which an expert panel advised against the use of IGRAs for diagnosing active tuberculosis, irrespective of HIV status, or for identifying people at risk for active tuberculosis disease in low- and middle-income countries [13]. With regard to HIV-infected people, the WHO report stressed the very low quality of evidence for using IGRAs in these patients, and recommended that these tests should not replace TST for the assessment of LTBI [13].

Although IGRAs were not developed to replace conventional microbiological methods for the diagnosis of active tuberculosis disease, they may have an adjunctive role in symptomatic patients with suspicion of active disease by complementing clinical-radiographic and epidemiological data to guide diagnosis work-up. Therefore, knowing how HIV infection compromises the IGRAs’ ability to detect tuberculosis infection in patients with active disease is essential in order to determine their role in different clinical and epidemiological settings.

We conducted a comprehensive systematic review (SR) to assess the sensitivity and specificity of IGRAs for the diagnosis of active tuberculosis disease, their value to predict development of subsequent active tuberculosis, and the proportion of indeterminate results in HIV-infected adults. Whenever feasible, we assessed how HIV-associated CD4+ T-cell depletion affects IGRA performance, and tried to identify differences according to tuberculosis burden settings and HIV infection status.

![Figure 1. Flowchart for study selection.](doi:10.1371/journal.pone.0032482.g001)
Methods

This SR was conducted in accordance with the PRISMA statement [14]. Ethical approval was not required for this study.

Search

We systematically searched for studies published between 1 January 2005 and 31 July 2011 that evaluated the diagnostic performance of IGRAs for tuberculosis or LTBI in HIV-positive adult populations (or populations with at least five HIV-positive individuals). We searched MEDLINE, the Cochrane Central Register of Controlled Trials, and the Biomedicine Database (IME) of the Spanish National Research Council (CSIC). Searches comprised a combination of the following terms: “HIV”, “immunosuppressed patients”, “tuberculosis”, “latent tuberculosis infection”, “QuantiFERON”, “QuantiFERON-TB Gold”, “T-SPOT.TB”, “interferon-gamma release assays”, and “T-cell assays”, as listed in titles, abstracts or text words. Searches were limited to studies published in English or Spanish. We also reviewed citations of the original and review articles, and guidelines for additional references. When necessary, we contacted the authors of the studies for additional information.

Selection

For our analysis, we selected only prospective studies that used the commercial tests QuantiFERON®-TB Gold In-Tube and T-SPOT®.TB performed in blood with 16–24 h of incubation. We excluded studies of non-commercial IGRAs or studies based on the old version of the ELISA assay (QuantiFERON®-TB Gold), as well as studies presenting non-original data, conference abstracts, editorials, reviews, guidelines, and studies conducted in animals.

Quality assessment

We checked the quality of the studies used to calculate assay accuracy with the QUADAS check list [15].

In the case of indeterminate results, we appraised the quality of the studies by assessing whether or not a definition was given in the methods section (“performed and interpreted according to the manufacturer’s instructions” was acceptable), and whether or not data for the two types of indeterminate tests (low IFN-γ production in the positive control or high IFN-γ production in the negative control) were reported separately. In addition, since an insufficient number of peripheral blood mononuclear cells (PBMCs) precludes performance of the T-SPOT.TB test, we also checked whether or not these unsuccessful test attempts (failure tests) had been reported.

To evaluate the quality of the studies that assessed the risk of subsequent tuberculosis according to the result of an IGRA assay, we used the Newcastle-Ottawa Scale (NOS) for non-randomized cohort studies [16].

Data extraction

Two researchers (M.S. and L.M.) independently compiled the data using a standardized data extraction sheet. Discrepancies

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Table 1. General and outcome-related characteristics of the 38 studies.

| Variable | Studies | Overall Diagnosis of active tuberculosis | Development of tuberculosis | Indeterminate results |
|----------|---------|------------------------------------------|-----------------------------|-----------------------|
|          |         | 38                                        | 20                          | 3                     | 36                     |

Tuberculosis burden setting

|                      |         |                                           |                            |                       |
|----------------------|---------|------------------------------------------|-----------------------------|-----------------------|
| High-burden countries| 19      | 13                                        | –                           | 18                    |
| Low/intermediate-burden countries | 18      | 7                                         | 3                           | 17                    |
| Both*               | 1       | –                                         | –                           | 1                     |

Individuals enrolled

|                      |         |                                           |                            |                       |
|----------------------|---------|------------------------------------------|-----------------------------|-----------------------|
| Total                |         | 6514                                     | 3155                        | 1166                  | 6434                  |
| -HIV-infected        | 3437    | 1034                                     | 135                         | 3437                  |
| -HIV-uninfected      |         |                                           |                            |                       |
| Median (IQR)         |         | 90 (160)                                  | 98 (138)                    | 266 (362)             | 107 (166)             |
| -HIV-infected        | 90 (160)| 106 (194)*                                | 106 (180)                  | –                     | 105 (178)             |
| -HIV-uninfected      | 106 (194)*|                                             |                            |                       |
| Male : female ratio  |         | 2.8 : 1                                   | 1.5 : 1                     | 2.3 : 1               | 2.6 : 1               |

CD4+ counts, cells/μL

|                      |         |                                           |                            |                       |
|----------------------|---------|------------------------------------------|-----------------------------|-----------------------|
|                    |         | Median (16 studies), n/N (%)              |                            |                       |
|                     |         |                                          |                            |                       |
| ≤200                |         | 7/18 (39)                                | 2/3 (67)                    | 12/16 (75)            |
| >200                |         | 7/8 (88)                                 |                            |                       |
|                     |         |                                          |                            |                       |
| ≤350                |         | 12/18 (67)                               | 2/3 (67)                    | 12/16 (75)            |
| >350                |         | 7/8 (88)                                 |                            |                       |

Test evaluated

|                      |         |                                           |                            |                       |
|----------------------|---------|------------------------------------------|-----------------------------|-----------------------|
| QFT-GIT              | 17      | 10                                       | 2                           | 17                    |
| T-SPOT.TB            | 11      | 5                                        | 1                           | 17                    |
| QFT-GIT & T-SPOT.TB  | 10      | 5                                        | 0                           | 9                     |

IQR: interquartile range; n/N: number of studies with the condition/total number of studies.
*Switzerland and sub-Saharan area.
**Calculated from 17 studies enrolling HIV-uninfected individuals.
*Data available for 34 studies;
**Only HIV-infected individuals.
\*doi:10.1371/journal.pone.0032482.t001
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| Reference                  | Country       | Sensitivity (95% CI) |
|----------------------------|---------------|----------------------|
| Tsiouris et al (2006)      | South Africa | 0.61 (0.45-0.82)     |
| Dheda et al (2009)         | South Africa | 0.40 (0.01-0.71)     |
| Kabeer et al (2009)        | India         | 0.66 (0.50-0.79)     |
| Veldsman et al (2009)      | South Africa | 0.30 (0.16-0.50)     |
| Markova et al (2009)       | Bulgaria      | 0.74 (0.62-1.00)     |
| Leidl et al (2010)         | Uganda        | 0.62 (0.44-0.87)     |
| Kabeer et al (2010)        | India         | 0.67 (0.55-0.82)     |
| Legesse et al (2010)       | Ethiopia      | 0.83 (0.37-0.99)     |
| Ling et al (2011)          | South Africa | 0.67 (0.51-0.81)     |
| Rangaka et al (2012)       | South Africa | 0.64 (0.49-0.77)     |
| **Subtotal ($I^2=55.6\%$, p=0.04)** | | **0.61 (0.53-0.69)** |

**Low-burden settings**

| Reference                  | Country       | Sensitivity (95% CI) |
|----------------------------|---------------|----------------------|
| Chee et al (2008)          | Singapore     | 0.53 (0.21-0.88)     |
| Aichelburg et al (2009)    | Austria       | 0.71 (0.57-1.00)     |
| Garcia-Gasalla et al (2010)| Spain         | 0.61 (0.39-0.90)     |
| Sauzullo et al (2010)      | Italy         | 0.67 (0.47-0.82)     |
| Bua et al (2011)           | Italy         | 0.22 (0.04-0.60)     |
| **Subtotal ($I^2=52.3\%$, p=0.18)** | | **0.59 (0.46-0.71)** |

**Overall ($I^2=46.6\%$, p=0.04)**

| Reference                  | Country       | Sensitivity (95% CI) |
|----------------------------|---------------|----------------------|
| Dheda et al (2009)         | South Africa | 0.67 (0.47-0.98)     |
| Markova et al (2009)       | Bulgaria      | 0.62 (0.32-0.85)     |
| Tan et al (2010)           | China         | 0.89 (0.51-1.00)     |
| Cattamanchi et al (2010)   | Uganda        | 0.55 (0.45-0.64)     |
| Leidl et al (2010)         | Uganda        | 0.90 (0.66-0.98)     |
| Oni et al (2010)           | South Africa | 0.68 (0.57-0.78)     |
| Chen et al (2010)          | China         | 0.33 (0.15-0.59)     |
| Ling et al (2011)          | South Africa | 0.81 (0.66-0.91)     |
| **Subtotal ($I^2=71.5\%$, p=0.004)** | | **0.65 (0.54-0.74)** |

**Low-burden settings**

| Reference                  | Country       | Sensitivity (95% CI) |
|----------------------------|---------------|----------------------|
| Chee et al (2008)          | Singapore     | 0.69 (0.47-0.99)     |

**Overall ($I^2=67.5\%$, p=0.006)**

| Reference                  | Country       | Sensitivity (95% CI) |
|----------------------------|---------------|----------------------|
| Dheda et al (2009)         | South Africa | 0.67 (0.47-0.98)     |
| Markova et al (2009)       | Bulgaria      | 0.62 (0.32-0.85)     |
| Tan et al (2010)           | China         | 0.89 (0.51-1.00)     |
| Cattamanchi et al (2010)   | Uganda        | 0.55 (0.45-0.64)     |
| Leidl et al (2010)         | Uganda        | 0.90 (0.66-0.98)     |
| Oni et al (2010)           | South Africa | 0.68 (0.57-0.78)     |
| Chen et al (2010)          | China         | 0.33 (0.15-0.59)     |
| Ling et al (2011)          | South Africa | 0.81 (0.66-0.91)     |
| **Subtotal ($I^2=71.5\%$, p=0.004)** | | **0.65 (0.54-0.74)** |

**Low-burden settings**

| Reference                  | Country       | Sensitivity (95% CI) |
|----------------------------|---------------|----------------------|
| Chee et al (2008)          | Singapore     | 0.69 (0.47-0.99)     |

**Overall ($I^2=67.5\%$, p=0.006)**
were resolved by discussion and consensus. The following data were extracted: year of publication, period and country, number of participants, gender, test evaluated, CD4+ cell count, development of active tuberculosis, TST results, indeterminate test results (overall and by two CD4+ cell count thresholds) and fraction of individuals with true positive, false negative, true negative and false positive results for the calculation of the test sensitivity and specificity.

Quantitative data synthesis and analysis

We assessed the following outcomes for each study and pooled them when feasible: sensitivity and specificity for active tuberculosis, predictive value for incident active tuberculosis, and rates of indeterminate results. The following definitions were used: sensitivity refers to the proportion of culture-proven tuberculosis patients who had a positive IGRA test, and specificity refers to the proportion of symptomatic non-tuberculosis patients who had a negative IGRA test. For the sensitivity calculation, we included only patients with confirmed tuberculosis (either with a positive culture for M. tuberculosis, a positive nucleic acid amplification test, or characteristic histopathological findings and response to specific treatment) that was still untreated or had been treated for less than two weeks. Indeterminate results were included as false negatives. For the specificity calculation, we selected studies that had enrolled patients with suspected active tuberculosis (either symptoms potentially caused by tuberculosis or a clinical and radiographic picture suggestive of tuberculosis). Results due to low IFN-γ production in the phytohaemagglutinin (PHA)-stimulated well or high background IFN-γ production were defined as indeterminate.

Eight of the 20 studies (40%) used to calculate sensitivity and specificity met all the quality indicators, ten (50%) met between 75% and 100%, and two (10%) met less than 75%.

Indeterminate results due to high production of IFN-γ in the negative control were either not defined as such or excluded from the analysis in 32% of studies with QFT-GIT and in 28% with T-SPOT.TB. The results for the two types of indeterminate results were reported separately in 27% of studies with QFT-GIT and in 32% with T-SPOT.TB. Only three studies (16%) provided data on the T-SPOT.TB tests not performed because of insufficient quantities of cells.

As for the studies evaluating the ability of IGRA to predict subsequent tuberculosis, follow-up was adequate in all three (12, 19 and 20 months respectively), and the exposed sample was representative of the HIV population; however, there was no adequate outcome assessment (pre-test and during follow-up) in any of them, and the number of incident tuberculosis cases was low (zero, two and three cases respectively). More detailed information on the quality of the studies is available upon request.

**Table 2.** Head-to-head comparison of sensitivity between QFT-GIT and T-SPOT.TB in HIV-infected patients with culture-confirmed tuberculosis.

| Reference     | Country     | Sensitivity QFT-GIT n/N (%) | Sensitivity T-SPOT.TB n/N (%) | Sensitivity difference QFT-GIT (%) – T-SPOT.TB (%) |
|---------------|-------------|-----------------------------|-----------------------------|-----------------------------------------------|
| Chee et al. [20] | Singapore  | 4/7 (57)                    | 7/7 (100)                   | −43                                           |
| Markova et al. [21] | Bulgaria | 12/13 (92)                   | 8/13 (62)                   | 30                                            |
| Leidl et al. [24] | Uganda    | 13/19 (68)                   | 17/19 (89)                  | −21                                           |
| Ling et al. [31] | South Africa | 29/43 (67)                | 35/43 (81)                  | −14                                           |
| Dheda et al. [33] | South Africa | 1/5 (20)                     | 5/5 (100)                   | −80                                           |

QFT-GIT: QuantiFERON®-TB Gold In-Tube; n/N: positive cases/cases with active tuberculosis.

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Sensitivity and specificity for active tuberculosis

**Sensitivity.** The sensitivity of QFT-GIT was estimated from 15 studies with a total of 356 participants with culture-proven active tuberculosis [19–33], and the sensitivity of T-SPOT.TB was estimated from nine studies with 311 participants with culture-proven active tuberculosis [20,21,24,31,33–37]. The pooled sensitivity was 61% (95% CI 54–67; $I^2 = 46.6\%$) for QFT-GIT and 65% (95% CI 56–74; $I^2 = 67.5\%$) for T-SPOT.TB (Figure 2). Five studies compared the sensitivity of QFT-GIT and T-SPOT.TB head to head [20,21,24,31,33]. The pooled sensitivity was 69% (95% CI 57–79; $\hat{I}^2 = 35.9\%$) for QFT-GIT and 79% (95% CI 75–83; $\hat{I}^2 = 24.9\%$) for T-SPOT.TB. The results of simultaneous TST and QFT-GIT in patients with active tuberculosis were reported in five studies [19,22,23,25,32]. The pooled sensitivity was 67% (95% CI 58–74; $\hat{I}^2 = 0.0\%$) for QFT-GIT and 60% (95% CI 34–82; $\hat{I}^2 = 46.2\%$) for TST. T-SPOT.TB. The results of simultaneous TST and QFT-GIT in patients with active tuberculosis were reported in five studies [19,22,23,25,32]. The pooled sensitivity was 75% (95% CI 64–84; $\hat{I}^2 = 39.1\%$) in HIV-infected and 90% (95% CI 84–94; $\hat{I}^2 = 74\%$) in HIV-uninfected patients. Six studies, covering 634 participants with tuberculosis (113 HIV-infected and 521 HIV-uninfected) evaluated the sensitivity of QFT-GIT according to HIV status [19,20,25,29,31,33]. The pooled sensitivity was 65% (95% CI 55–74; $I^2 = 9.8\%$) and 79% (95% CI 75–83; $I^2 = 24.9\%$) in HIV-infected and HIV-uninfected patients respectively. As for T-SPOT.TB, three studies compared sensitivity between HIV-infected and uninfected patients (55 HIV-infected and 364 HIV-uninfected) [20,31,33]. The pooled sensitivity was 75% (95% CI 64–84; $I^2 = 39.1\%$) in HIV-infected and 90% (95% CI 84–94; $I^2 = 74\%$) in HIV-uninfected patients. The effect of CD4+ cell counts on sensitivity was evaluated in three studies with QFT-GIT [23,28,31] and three studies with T-SPOT.TB [31,34,37]. While one study on QFT-GIT reported a decrease in its sensitivity with fewer than 200 circulating CD4+ cells [23], another found no differences in CD4+ T-cell counts between patients with positive and negative results [28].

### Table 3. Head-to-head comparison of sensitivity between IGRAs and TST in HIV-infected patients with culture-confirmed tuberculosis.

| Reference            | Country     | IGRA          | Sensitivity IGRA | Sensitivity TST | Sensitivity difference |
|----------------------|-------------|---------------|------------------|-----------------|------------------------|
| Tsiouris et al. [19] | South Africa| QFT-GIT       | 17/26 (65)       | 22 (85)         | –20                    |
| Aichelburg et al. [22]| Austria     | QFT-GIT       | 10/11 (91)       | 8 (80)*         | 11                     |
| Kabeer et al. [23]   | India       | QFT-GIT       | 29/44 (66)       | 11 (25)         | 41                     |
| Garcia-Gasalla et al. [25]| Spain | QFT-GIT       | 9/13 (69)        | 5 (42)**        | 27                     |
| Rangaka et al. [32]  | South Africa| QFT-GIT       | 32/50 (64)       | 34 (68)         | –4                     |
| Vincenti et al. [38] | Italy       | T-SPOT.TB     | 11/13 (85)       | 6 (46)†         | 39                     |

### Table 4. Comparison of sensitivity of IGRAs between HIV-infected and HIV-uninfected patients with culture-confirmed tuberculosis.

| Reference            | Country     | Sensitivity in HIV-pos | Sensitivity in HIV-neg | Sensitivity difference |
|----------------------|-------------|------------------------|------------------------|------------------------|
| QFT-GIT              |             | n/N (%)                | n/N (%)                | HIV-pos (%) – HIV-neg (%) |
| Tsiouris et al. [19] | South Africa| 17/26 (65)             | 11/15 (73)             | –8                     |
| Chee et al. [20]     | Singapore   | 4/7 (57)               | 220/273 (81)           | –24                    |
| Garcia-Gasalla et al. [25]| Spain | 12/13 (92)             | 85/105 (81)            | 11                     |
| Legesse et al. [29]  | Ethiopia    | 13/19 (68)             | 20/31 (65)             | 3                      |
| Ling et al. [31]     | South Africa| 29/43 (67)             | 67/82 (82)             | –15                    |
| Dheda et al. [33]    | South Africa| 1/5 (20)               | 11/15 (73)             | –53                    |
| T-SPOT.TB            |             |                        |                        |                        |
| Chee et al. [20]     | Singapore   | 7/7 (100)              | 247/267 (93)           | 7                      |
| Ling et al. [31]     | South Africa| 35/43 (81)             | 70/82 (85)             | –4                     |
| Dheda et al. [33]    | South Africa| 5/5 (100)              | 14/15 (93)             | 7                      |

IGRAs: Interferon-γ release assays; QFT-GIT: QuantiFERON®-TB Gold In-Tube; TST: Tuberculin skin test; n/N: positive cases/cases with active tuberculosis.

*8 positive tests of 10 cases; **5 positive tests of 12 cases; †Indeterminate results of T-SPOT.TB excluded.

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Figure 3. Specificity of QuantiFERON-TB Gold In-Tube (A) and T.SPOT.TB (B), in HIV-infected patients with confirmed tuberculosis, stratified for tuberculosis burden setting. Pooled estimates derived from random effects (DerSimonian-Laird) modeling.
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study found higher sensitivity in patients with <200 CD4+ cells (76%; 95% CI 53–92) than in those with ≥200 CD4+ cells (61%; 95% CI 36–83) [31]. None of the three studies assessing T-SPOT.TB reported a relationship between lower sensitivity and lower CD4+ T-cell counts [31,34,37]. In fact, as in the case of QFT-GIT, the sensitivity of T-SPOT.TB in one study was higher in patients with CD4+ cells <200 (90%; 95% CI 67–99) than in those with CD4+ cells ≥200 cells (78%; 95% CI 52–94) [31].

**Specificity.** The specificity of QFT-GIT was calculated from eight studies covering a total of 1334 participants without active tuberculosis [21,23,26,27,29–32], whilst that of T-SPOT.TB was calculated from six studies with a total of 326 participants without active tuberculosis [21,31,34–36,38]. The pooled specificity was 72% (95% CI 56–84; \( I^2 = 93.2\% \)) for QFT-GIT, and 70% (95% CI 55–83; \( I^2 = 87.8\% \)) for T-SPOT.TB (Figure 3).

**Predictive value of IGRA for incident active tuberculosis**

Three longitudinal studies assessed incident active tuberculosis [22,43,52]; all of them were conducted in low-burden countries. In a prospective cohort study, 830 HIV-infected patients who underwent QFT-GIT testing were left untreated and were followed periodically [22]. Of 822 individuals without active tuberculosis at baseline, 36 were positive. After a median follow-up of 19 months, three (3.8%) patients with positive QFT-GIT developed tuberculosis, but none of the 705 patients with a negative QFT-GIT developed active disease. In another study with 201 HIV-seropositive individuals, two out of 20 infected patients with positive T-SPOT.TB who did not receive preventive treatment developed active tuberculosis during the first year [52]. In a third study assessing 135 HIV-infected patients, none of the 103 patients who had a negative or indeterminate QFT-GIT result and negative TST at baseline developed tuberculosis after a median follow-up of 20 months [43] (Table 5).

**Indeterminate IGRA results**

Twenty-six studies reported data on indeterminate results in patients tested with QFT-GIT, with a total of 5209 participants [19–33,39–49]. The pooled indeterminate rate was 8.2% (95% CI 6.0–11.2; \( I^2 = 46.8\% \)) (Figure 4A). When the analysis was restricted to the seven studies that differentiated the two types of indeterminate results, 11 out of 120 (9.2%) indeterminate results were due to high background IFN-\( \gamma \) production (negative control), and the other 109 (90.8%) were due to low IFN-\( \gamma \) production in the positive control.

Eighteen studies including a total of 2236 participants reported data on indeterminate results with T-SPOT.TB [20,21,24,31–34,36,37,41,46,47,50–56]. The pooled indeterminate rate was 5.9% (95% CI 3.5–9.8; \( F = 47.0\% \)) (Figure 4B). When the analysis was restricted to the three studies that provided data on failure results (not performed due to an insufficient number of PBMCs), the pooled indeterminate rate was 20.6% (95% CI 11.1–34.9; \( F = 48.3\% \)). Of the 135 indeterminate results derived from these three studies, 51 (33.3%) were due to failure to perform the test, 50 (32.7%) were due to low IFN-\( \gamma \) production in the PHA-stimulated well, and 52 (34%) to high background IFN-\( \gamma \) production.

In eight studies that compared QFT-GIT and T-SPOT.TB head to head [20,21,24,31,33,41,46,47]. Pooled proportion was 5.7% (95% CI 2.1–14.7; \( F = 46.9\% \)) for QFT-GIT and 6.1% (95% CI 3.2–11.2; \( F = 40.5\% \)) for T-SPOT.TB (Table 6).

The pooled indeterminate rates for high-burden countries were 12.0% (95% CI 8.6–16.4; \( F = 44.5\% \)) for QFT-GIT and 7.7% (95% CI 3.6–15.5; \( F = 47.6\% \)) for T-SPOT.TB. Pooled indeterminate rates in low/intermediate-burden countries were 6.4% (95% CI 1.1–12.9; \( F = 47.6\% \)) for QFT-GIT and 3.5% (95% CI 1.4–8.4; \( F = 44.8\% \)) for T-SPOT.TB. When stratified for type of patients (patients evaluated because of suspicion of tuberculosis, patients with culture-confirmed tuberculosis and patients screened for LTBI), pooled indeterminate rates for QFT-GIT were higher for patients with active tuberculosis (15.3%; 95% CI 10.8–21.2; \( F = 17.1\% \)) and for symptomatic patients (12.3%; 95% CI 6.9–39.4; \( F = 48.4\% \)) than for those screened for LTBI (3.9%; 95% CI 2.4–6.4; \( F = 45.3\% \)). Pooled indeterminate rates for T-SPOT.TB were higher for symptomatic patients (9.1%; 95% CI 4.0–19.3; \( F = 48.2\% \)) than for those screened for LTBI (4.3%; 95% CI 2.2–8.1; \( F = 42.9\% \)).

Eleven studies allowed a comparison of rates of indeterminate results between HIV-infected and HIV-uninfected individuals [19,20,24,29,31,33,42,43,50,53]. Indeterminate rates were higher in HIV-infected than in HIV-uninfected individuals for the QFT-GIT test, but the difference did not reach statistical significance (difference 4.6%; 95% CI -1 to 10; \( F = 58.8\% \)), as was the case of T-SPOT.TB (difference 0.7%; 95% CI -2 to 3; \( F = 0.0\% \)) (Figure 5).

**Effect of CD4+ cell counts on indeterminate results.** Indeterminate result rates according to 200 CD4+ T-cell count threshold could be pooled from seven studies with QFT-GIT [21,22,39,41–44] and six with T-SPOT.TB [21,34,36,41,50,51]. The pooled indeterminate rates were 11.6% (95% CI 7.0–18.6; \( F = 34.7\% \)) for CD4+<200, and 3.1% (95% CI 1.1–8.5;
### A

**Reference**

| High-burden settings | Country          | Proportion (95%CI) |
|-----------------------|------------------|--------------------|
| Tsiouris et al (2006) | South Africa     | 0.19 (0.08-0.39)  |
| Raby et al (2008)     | Zambia/S. Africa | 0.17 (0.09-0.29)  |
| Markova et al (2009)  | Bulgaria         | 0.06 (0.02-0.13)  |
| Veldsman et al (2009) | South Africa     | 0.15 (0.08-0.26)  |
| Dheda et al (2009)    | South Africa     | 0.20 (0.10-0.35)  |
| Kabeer et al (2009)   | India            | 0.17 (0.11-0.26)  |
| Kabeer et al (2010)   | India            | 0.20 (0.11-0.33)  |
| Legesse et al (2010)  | Ethiopia         | 0.04 (0.01-0.22)  |
| Ish et al (2010)      | Ethiopia         | 0.03 (0.00-0.17)  |
| Leidl et al (2010)    | Uganda           | 0.03 (0.01-0.08)  |
| Shanaboa et al (2011) | Zambia           | 0.11 (0.09-0.13)  |
| Ling et al (2011)     | South Africa     | 0.25 (0.18-0.34)  |
| Rangaka et al (2012)  | South Africa     | 0.07 (0.05-0.09)  |

Subtotal ($\chi^2=44.6\%$, $p=0.000$) 0.12 (0.09-0.17)

**Low-burden settings**

| Reference                          | Country   | Proportion (95%CI) |
|------------------------------------|-----------|--------------------|
| Brock et al (2006)                 | Denmark   | 0.03 (0.02-0.05)   |
| Luetkemeyer et al (2007)           | USA       | 0.05 (0.03-0.08)   |
| Jones et al (2007)                 | USA       | 0.05 (0.03-0.09)   |
| Domínguez et al (2008)             | Spain     | 0.00 (0.00-0.030)  |
| Chee et al (2008)                  | Singapore | 0.00 (0.00-0.067)  |
| Richelhi et al (2009)              | Italy     | 0.06 (0.03-0.12)   |
| Aichelburg et al (2009)            | Austria   | 0.06 (0.04-0.08)   |
| Talati et al (2009)                | USA       | 0.02 (0.01-0.04)   |
| Latorre et al (2010)               | Spain     | 0.01 (0.00-0.09)   |
| Garcia-Gasilla et al (2010)        | Spain     | 0.00 (0.00-0.040)  |
| Sauzullo et al (2010)              | Italy     | 0.24 (0.19-0.31)   |
| Bua et al (2011)                   | Italy     | 0.16 (0.10-0.27)   |
| Santin et al (2011)                | Spain     | 0.02 (0.00-0.06)   |

Subtotal ($\chi^2=47.5\%$, $p=0.000$) 0.05 (0.03-0.09)

Overall ($\chi^2=46.7\%$, $p=0.000$) 0.08 (0.06-0.11)

### B

**Reference**

| High-burden settings | Country          | Proportion (95%CI) |
|----------------------|------------------|--------------------|
| Dheda et al (2005)   | South Africa     | 0.03 (0.01-0.21)  |
| Hoffmann et al (2007)| Sud-S. Africa    | 0.05 (0.01-0.18)  |
| Rangaka et al (2007) | South Africa     | 0.01 (0.00-0.09)  |
| Mandalakas et al (2008) | South Africa | 0.10 (0.03-0.32)  |
| Markova et al (2009) | Bulgaria         | 0.12 (0.07-0.21)  |
| Dheda et al (2009)   | South Africa     | 0.05 (0.01-0.28)  |
| Leidl et al (2010)   | Uganda           | 0.05 (0.02-0.10)  |
| Ori et al (2010)     | South Africa     | 0.00 (0.00-0.05)  |
| Cattamanchi et al (2010) | Uganda | 0.33 (0.27-0.39)  |
| Chen et al (2010)    | China            | 0.18 (0.12-0.24)  |
| Ling et al (2011)    | South Africa     | 0.02 (0.01-0.07)  |

Subtotal ($\chi^2=46.9\%$, $p=0.000$) 0.07 (0.03-0.13)

**Low-burden settings**

| Reference                          | Country   | Proportion (95%CI) |
|------------------------------------|-----------|--------------------|
| Clark et al (2007)                 | U. Kingdom | 0.05 (0.02-0.08)  |
| Hoffmann et al (2007)              | Switzerland | 0.13 (0.06-0.26)  |
| Chee et al (2008)                  | Singapore | 0.00 (0.00-0.05)  |
| Domínguez et al (2008)             | Spain     | 0.00 (0.00-0.030) |
| Stephan et al (2008)               | Germany   | 0.03 (0.02-0.06)  |
| Talati et al (2009)                | USA       | 0.14 (0.11-0.18)  |
| Rivas et al (2009)                 | Spain     | 0.00 (0.00-0.16)  |
| Latorre et al (2010)               | Spain     | 0.01 (0.00-0.09)  |

Subtotal ($\chi^2=44.1\%$, $p=0.000$) 0.05 (0.03-0.11)

Overall ($\chi^2=46.8\%$, $p=0.000$) 0.06 (0.04-0.10)
Discussion

This SR provides a comprehensive summary of the current evidence on the performance of the two commercial IFN-γ-based assays for the immunodiagnosis of tuberculosis and tuberculosis infection in HIV-infected adults. The main results can be summarized as follows. First, the sensitivity and specificity of either IGRA in HIV-infected people is suboptimal for being used alone to rule in or rule out active tuberculosis disease. Second, the risk of tuberculosis in the short- to medium-term in HIV-infected adults with a negative QFT-GIT seems to be low. Third, indeterminate results of IGRA were more frequent in HIV-infected patients with active tuberculosis from high-burden tuberculosis countries. Fourth, HIV-associated immunosuppression, measured by circulating CD4+ T-lymphocytes, negatively affects the performance of QFT-GIT, and to a lesser extent, T-SPOT.TB.

The sensitivity of IGRA for culture-confirmed tuberculosis in the current SR was lower than that reported in three meta-analyses including predominantly immunocompetent people [0,9,11], and similar to that reported for HIV-infected patients in the three previous SRs [10,11,12]. Taken together, the results of the previous SRs and our own show that the sensitivity of QFT-GIT is roughly 65%, ranging between 61% reported by Cattamanchi et al. [10] in low-income countries and 68% reported by Chen et al. [12] in both high and low-income countries. For T-SPOT.TB, the sensitivity was close to 70%, ranging between 65% obtained in the current SR and 72% reported by Cattamanchi et al. [10] in low-income countries. These figures mean that, at best, IGRA will miss one in three cases of active tuberculosis (Table 7).

HIV-associated immunosuppression, measured by circulating CD4+ T-cells, weakens the ability of IGRA to detect tuberculosis infection. A previous SR [10] explored the impact of immunosuppression on the proportion of positive results according to a 200 CD4+ T-cell threshold, regardless of whether they had active tuberculosis or not. However, the value of the information provided by this approach is limited because the analysis included healthy people with unknown LTBI status. In the current SR, we tried to determine the impact of CD4+ T-cell counts on the sensitivity of IGRA in HIV-infected patients with active tuberculosis disease, but the results were inconclusive. While one of the three studies with QFT-GIT [23,26,31] observed lower sensitivity with CD4+ below 200 cells/mm3 [23], one another found higher sensitivity with CD4+ below 200 cells/mm3 [31], and a third one did not find significant differences in CD4+ T-cell counts between patients with either positive or negative QFT-GIT [28]. As for T-SPOT.TB, while two of the three studies [31,34,37] found no change in sensitivity with CD4+ T-cell counts [34,37], the other one found higher sensitivity in patients with CD4+ below 200 cells/mm3 [31]. Since the decrease in sensitivity of IGRA in HIV-infected patients is largely due to high rates of indeterminate results, the correct reporting of these results is essential for an accurate assessment of the sensitivity of the IGRA tests. Unfortunately, indeterminate results due either to a high-background production of interferon-γ (negative control) or to a failure test due to an insufficient number of PBMCs are often explicitly excluded or not reported. In fact, in the three studies that provided these data, a third of all invalid T-SPOT.TB results were due to failed T-SPOT.TB tests because of a lack of cells [36,37,47]. This may lead to an overestimation of the sensitivity of T-SPOT.TB assay in HIV-infected patients, and challenges the commonly held assumption that the performance of T-SPOT.TB is less affected if at all by CD4+ T-cell depletion than QFT-GIT.

It has been suggested that IGRA are less affected than TST by HIV-associated immunosuppression. However, there is no consistent evidence that the IGRA are more sensitive for detecting tuberculosis infection in patients with active disease. Data from the five studies reporting comparisons between QFT-GIT and TST yielded a pooled sensitivity of 67% and 60% respectively. Actually,

### Table 6. Head-to-head comparison of the proportion of indeterminate results between QFT-GIT and T-SPOT.TB in HIV-infected patients.

| Reference          | Country   | Population tested                  | Indeterminate results QFT-GIT n/N (%) | Indeterminate results T-SPOT.TB n/N (%) | Difference indeterminate results QFT-GIT (%) - T-SPOT.TB (%) |
|--------------------|-----------|------------------------------------|--------------------------------------|----------------------------------------|------------------------------------------------------------|
| Chee et al. [20]   | Singapore | Active TB                           | 0/7                                  | 0/7                                    | -                                                          |
| Markova et al. [21]| Bulgaria  | Symptomatic ptes                    | 5/90 (5.6)                           | 11/90 (12.2)                           | -6.6                                                       |
| Leidl et al. [24]  | Uganda    | Screened for LTBI                   | 4/128 (3.1)                          | 6/128 (4.7)                            | -1.6                                                       |
| Ling et al. [31]   | South Africa | Symptomatic ptes           | 27/108 (25.0)                         | 2/108 (2.0)                            | 23.0                                                       |
| Dheda et al. [33]  | South Africa | Symptomatic ptes           | 8/20 (40.0)                           | 1/20 (5.0)                             | 35.0                                                       |
| Latorre et al. [41]| Spain     | Screened for LTBI                  | 1/75 (1.3)                           | 1/75 (1.3)                             | 0                                                          |
| Dominguez et al. [46]| Spain       | Screened for LTBI                  | 0/19                                 | 0/19                                   | -                                                          |
| Talati et al. [47] | USA       | Screened for LTBI                  | 6/336 (1.8)                          | 47/336 (13.9)                         | -12.1                                                      |

IGRAs: Interferon-γ release assays; QFT-GIT: QuantiFERON®-TB Gold In-Tube; n/N: indeterminate results/individuals tested; TB: tuberculosis; LTBI: latent tuberculosis infection; ptes: patients.

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in the largest study, which included more than 800 patients, TST was at least as sensitive as QFT-GIT [32].

As might be expected, the specificity of either IGRA for active tuberculosis disease was suboptimal for use as a rule-in test [9]. Although IGRA use highly \textit{M. tuberculosis}-specific antigens, since they do not distinguish between latent and active infection they cannot provide optimal specificity. Besides, they reflect the high prevalence of LTBI in the countries in which most of the studies were conducted [57]. Whether the specificity of IGRA in low-burden tuberculosis settings is better is currently unclear. The present SR identified only three studies in low-burden settings, all from Italy: two with QFT-GIT [26,27] and one with T-SPOT.TB [38]. Specificity was 89% for QFT-GIT in both studies, and 64% for T-SPOT.TB (Table 7).

Although culture-confirmed tuberculosis has been commonly used as a surrogate for tuberculosis infection, tuberculosis-associated immunodeficiency may impair the ability of IGRA to detect the infection, particularly in HIV-infected patients. Therefore, their actual sensitivity for LTBI may be underestimated by extrapolating from patients with active disease [58]. Determining the capability of IGRA to predict the risk of subsequent active tuberculosis is another way of evaluating the IGRA suitability for detecting LTBI. A comprehensive SR, including mainly studies with non-HIV-infected individuals, showed a marginal advantage of IGRA over the TST for predicting incident active tuberculosis [59]. Two studies identified in the current SR, both conducted in low-burden tuberculosis countries, showed modest associations between positive IGRA result and incident active tuberculosis in the short-to-medium term [22,52]. Conversely, a negative result of QFT-GIT had a high negative predictive value (100%) in two studies [22,43]. These data, if further confirmed in large, longitudinal and properly designed studies, would help to improve the targeting of at-risk patients by reducing the number of people considered for preventive treatment.

Indeterminate results, due either to low IFN-\(\gamma\) production in the positive control or to high IFN-\(\gamma\) production in the negative control, may negatively affect the overall utility of IGRA. The proportion of indeterminate results in the current SR showed huge differences across studies, ranging from no indeterminate results at all to rates as high as 25% and 33% for QFT-GIT and T-SPOT.TB respectively [31,36]. These differences are related to host characteristics (CD4\(^+\) cell counts), type of evaluated people (patients with active tuberculosis vs. people evaluated for LTBI), and setting (high-burden and resource-limited vs. low-burden and high-income settings), but are also due to differences in the criteria

| Reference | Country | Difference (95%CI) |
|-----------|---------|--------------------|
| **QFT-GIT** | | |
| Tsiouris et al (2006)\(^{39}\) | South Africa | 0.19 (0.02-0.36) |
| Chee et al (2008)\(^{30}\) | Singapore | -0.01 (-0.18-0.16) |
| Raby et al (2008)\(^{45}\) | Zambia/S. Africa | 0.03 (-0.11-0.18) |
| Dheda et al (2009)\(^{33}\) | South Africa | 0.13 (-0.12-0.37) |
| Leidl et al (2010)\(^{24}\) | Uganda | 0.01 (-0.16-0.18) |
| Legesse et al (2010)\(^{29}\) | Ethiopia | -0.02 (-0.10-0.06) |
| Idh et al (2010)\(^{42}\) | Ethiopia | 0.00 (-0.07-0.06) |
| Ling et al (2011)\(^{31}\) | South Africa | 0.18 (0.10-0.27) |
| Santin et al (2011)\(^{43}\) | Spain | 0.02 (-0.01-0.04) |
| **Subtotal (\(I^2=59.0\%, p=0.013\))** | | 0.05 (-0.01-0.10) |
| **T-SPOT.TB** | | |
| Dheda et al (2005)\(^{30}\) | South Africa | 0.03 (-0.06-0.13) |
| Rangaka et al (2007)\(^{33}\) | South Africa | 0.01 (-0.02-0.05) |
| Chee et al (2008)\(^{30}\) | Singapore | -0.02 (-0.18-0.15) |
| Dheda et al (2009)\(^{33}\) | South Africa | 0.01 (-0.10-0.12) |
| Leidl et al (2010)\(^{24}\) | Uganda | 0.05 (-0.13-0.22) |
| Ling et al (2011)\(^{31}\) | South Africa | -0.01 (-0.03-0.03) |
| **Subtotal (\(I^2=0.0\%, p=0.96\))** | 0.01 (-0.02-0.03) | 0.01 (-0.02-0.03) |
| **Overall (\(I^2=35.6\%, p=0.08\))** | 0.02 (-0.01-0.05) | 0.02 (-0.01-0.05) |

Figure 5. Comparison of the proportion of indeterminate results between HIV-infected and HIV-uninfected individuals. Pooled estimates derived from random effects (DerSimonian-Laird) modeling. doi:10.1371/journal.pone.0032482.g005
used for reporting data. Indeterminate results due to high-background IFN-γ production, as well as failure T-SPOT.TB tests due to an insufficient number of PBMCs, are often not counted as such and are excluded from the analyses. Therefore, the calculation of indeterminate result rates and their association with potentially influencing factors will inevitably be compromised by these limitations. Interestingly, the types of indeterminate results were not equally distributed for the two assays. While low IFN-γ production upon stimulation with PHA (positive control) accounted for more than 90% of the indeterminate results with the QFT-GIT assay, half of the indeterminate T-SPOT.TB assays were due to high-background IFN-γ production (negative control).

The pooled indeterminate rates for the two assays were higher in high-burden settings than in low-burden settings. They were also higher in patients with symptoms suggestive of tuberculosis or culture-confirmed tuberculosis than in those screened for LTBI. Because studies that enrolled patients with active tuberculosis were mainly carried out in high-burden countries, whilst those that enrolled patients screened for LTBI were from low-burden countries, further analyses to determine which of the two factors has a greater influence on the occurrence of indeterminate results cannot be performed. On the one hand, HIV-infected patients usually have profound CD4+ T-lymphocyte depletion either as a cause or as a consequence of the disease, which may cause anergy and indeterminate IGRA results [58]. On the other hand, indeterminate results have been related to operational factors mainly linked to resource-limited settings, such as delayed incubation [60–62], and the location of the laboratory at which the samples are processed (according to data from Zambia; K. Shanaube, personal communication) (Table 8).

Our SR has limitations. First, the validity of the results is limited by the inconsistency across the studies. This heterogeneity persisted after performing subgroup analyses. Second, the main body of literature on active tuberculosis comes from high-burden tuberculosis and resource-limited settings, which limits the generalization of our estimates. Conversely, studies for the prediction of subsequent development of active disease in HIV-infected patients were exclusively from low-burden countries. Therefore, the low risk of subsequent active tuberculosis for patients testing negative on QFT-GIT obtained in two low-burden countries in Europe cannot be extrapolated to countries with high burdens of tuberculosis such as Sub-Saharan African countries. Finally, the lack of an adequate standard for latent tuberculosis infection is a inherent limitation to every SR to draw confident

**Figure 6. Differences in the proportion of indeterminate results of IGRA by 200 CD4+ cell count threshold.** Pooled estimates derived from random effects (DerSimonian-Laird) modeling. doi:10.1371/journal.pone.0032482.g006
estimates on the capacity of IGRA tests to detect tuberculosis infection in people without evidence of active disease. Nonetheless, some relevant conclusions may be drawn from this SR. First, the current evidence indicates that neither IGRA is able to replace conventional microbiological diagnosis of tuberculosis in HIV-infected patients. Second, QFT-GIT, if the low risk of subsequent active tuberculosis in HIV-infected patients testing negative is confirmed, could replace TST for targeting at-risk patients for chemoprophylaxis in low-burden tuberculosis countries. Third, potential causes of invalid tests, such as delayed incubation and other operational factors, should be addressed in order to improve the performance of IGRA, particularly in resource-limited high-burden tuberculosis countries with high HIV-coinfection prevalence.

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Author Contributions

Conceived and designed the experiments: MS. Analyzed the data: MS LM DR. Wrote the paper: MS.

Table 7. Sensitivity and specificity of the IGRA in HIV-infected patients in four systematic reviews.

|                | Cattamanchi (Ref. [10]) | Metcalfe (Ref. [11]) | Chen (Ref. [12]) | Current SR          |
|----------------|--------------------------|----------------------|------------------|---------------------|
| **Sensitivity**|                          |                      |                  |                     |
| High-burden TB settings |                          |                      |                  |                     |
| -QFT-GIT       | 61% (47–75)              | 65% (52–77)          | N.D.             | 61% (53–69)         |
| -T-SPOT.TB     | 72% (62–81)              | 68% (56–80)          | N.D.             | 65% (54–74)         |
| Low-burden TB settings |                          |                      |                  |                     |
| -QFT-GIT       | 67% (47–83)†             | N.D.                 | N.D.             | 59% (46–71)         |
| -T-SPOT.TB     | 94% (73–100)†            | N.D.                 | N.D.             | 69% (47–99)†        |
| **Specificity**|                          |                      |                  |                     |
| High-burden TB settings |                          |                      |                  |                     |
| -QFT-GIT       | N.D.                     | 50% (35–65)          | 57% (54–60)      | 62% (49–74)         |
| -T-SPOT.TB     | N.D.                     | 52% (40–63)          | 63% (58–68)      | 73% (54–85)         |
| Low-burden TB settings |                          |                      |                  |                     |
| -QFT-GIT       | N.D.                     | N.D.                 | 94% (93–96)      | 89%‡                |
| -T-SPOT.TB     | N.D.                     | N.D.                 | 64% (44–81)†     | 64% (44–81)†        |
| **Overall**    |                          |                      |                  |                     |
| -QFT-GIT       | N.D.                     | N.D.                 | 63% (58–68)      | 70% (55–83)         |

NOTE: Stratification for high-burden and low-burden TB settings is roughly equivalent to low-income and high-income settings used by Cattamanchi [10]. Metcalfe [11] and Chen [12] in their systematic reviews; TB = tuberculosis; QFT-GIT = QuantiFERON Gold In-Tube; N.D. = Not done.

*Only one study; †Two studies: 89% each respectively.
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Table 8. Proportion of indeterminate results of IGRA in HIV-infected patients in four systematic reviews.

|                | Cattamanchi (Ref. [10]) | Metcalfe (Ref. [11]) | Chen (Ref. [12]) | Current SR          |
|----------------|--------------------------|----------------------|------------------|---------------------|
| **Setting**    |                          |                      |                  |                     |
| High-burden TB |                          |                      |                  |                     |
| -QFT-GIT       | 4% (1–9)*                | 15% (9–21)†          | 11.4% (9.7–13.2) | 12.0% (8.6–16.4)   |
| -T-SPOT.TB     | 2% (0–3)*                | 9% (0–17)†           | 14% (11.4–17.1)† | 7.7% (3.6–15.5)    |
| Low-burden TB  |                          |                      |                  |                     |
| -QFT-GIT       | 4% (3–6)*                | N.D.                 | 8.4% (6.8–10.2)† | 6.4% (1.1–12.9)    |
| -T-SPOT.TB     | 5% (1–9)*                | N.D.                 | 0% (0–0.9)†      | 3.5% (1.4–8.4)     |
| **Population evaluated** |                          |                      |                  |                     |
| Active TB      |                          |                      |                  |                     |
| -QFT-GIT       | N.D.                     | N.D.                 | N.D.             | 15.3% (10.8–21.2)  |
| -T-SPOT.TB     | N.D.                     | N.D.                 | N.D.             | 9.1% (4.0–19.3)    |
| Screened for LTBI |                          |                      |                  |                     |
| -QFT-GIT       | N.D.                     | N.D.                 | N.D.             | 3.9% (2.4–6.4)     |
| -T-SPOT.TB     | N.D.                     | N.D.                 | N.D.             | 4.3% (2.2–8.1)     |
| **Difference by 200 CD4+ count threshold** |                          |                      |                  |                     |
| -QFT-GIT       | N.D.                     | N.D.                 | N.D.             | 8.1% (2.6–13.7)    |
| -T-SPOT.TB     | N.D.                     | N.D.                 | N.D.             | 4.0% (–0.5 to 8.5) |
| **Overall**    |                          |                      |                  |                     |
| -QFT-GIT       | N.D.                     | N.D.                 | N.D.             | 10.0% (8.8–11.3)   |
| -T-SPOT.TB     | N.D.                     | N.D.                 | N.D.             | 8.2% (6.0–11.2)    |

NOTE: Stratification for high-burden and low-burden TB settings is roughly equivalent to low-income and high-income settings used by Cattamanchi [10], Metcalfe [11] and Chen [12] in their systematic reviews; LTBI = latent tuberculosis infection; QFT-GIT = QuantiFERON Gold In-Tube; N.D. = Not done.

Only patients screened for LTBI included; *Symptomatic patients, with and without active TB. doi:10.1371/journal.pone.0032482.t008
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