

# Interferon-Gamma Release Assays for the Diagnosis of Latent Tuberculosis Infection in HIV-Infected Individuals: A Systematic Review and Meta-Analysis

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**Objective:** To determine whether interferon-gamma release assays (IGRAs) improve the identification of HIV-infected individuals who could benefit from latent tuberculosis infection therapy.

**Design:** Systematic review and meta-analysis.

**Methods:** We searched multiple databases through May 2010 for studies evaluating the performance of the newest commercial IGRAs (QuantiFERON-TB Gold In-Tube [QFT-GIT] and T-SPOT.TB [TSPOT]) in HIV-infected individuals. We assessed the quality of all studies included in the review, summarized results in prespecified subgroups using forest plots, and where appropriate, calculated pooled estimates using random effects models.

**Results:** The search identified 37 studies that included 5736 HIV-infected individuals. In three longitudinal studies, the risk of active tuberculosis was higher in HIV-infected individuals with positive

versus negative IGRA results. However, the risk difference was not statistically significant in the two studies that reported IGRA results according to manufacturer-recommended criteria. In persons with active tuberculosis (a surrogate reference standard for latent tuberculosis infection), pooled sensitivity estimates were heterogeneous but higher for TSPOT (72%; 95% confidence interval [CI], 62–81%) than for QFT-GIT (61%; 95% CI, 47–75%) in low-/middle-income countries. However, neither IGRA was consistently more sensitive than the tuberculin skin test in head-to-head comparisons. Although TSPOT appeared to be less affected by immunosuppression than QFT-GIT and the tuberculin skin test, overall, differences among the three tests were small or inconclusive.

**Conclusions:** Current evidence suggests that IGRAs perform similarly to the tuberculin skin test at identifying HIV-infected individuals with latent tuberculosis infection. Given that both tests have modest predictive value and suboptimal sensitivity, the decision to use either test should be based on country guidelines and resource and logistic considerations.

**Key Words:** latent tuberculosis infection, systematic review, interferon-gamma release assay, HIV infection, tuberculin skin test

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determine if newer tests can better identify HIV-infected individuals who could benefit from IPT.

Until recently, the TST was the only tool available for diagnosing LTBI. The risk of developing active TB in people with a positive TST is well-defined,<sup>4,5</sup> and there is strong evidence in people with and without HIV coinfection that IPT reduces this risk.<sup>2,6</sup> However, false-positive TST results can occur among persons who have been given the Bacille de Calmette et Guérin vaccine or who have been exposed to nontuberculous mycobacteria and false-negative results can occur in persons with impaired cellular immunity.<sup>7</sup> Additionally, completing the TST requires two healthcare visits and measurement of reaction size is subjective.<sup>8</sup>

Interferon-gamma release assays (IGRAs) were recently developed and address many of these limitations. IGRAs measure interferon-gamma release after exposure of whole blood (QuantiFERON-TB Gold In-Tube® [QFT-GIT]; Cellestis, Carnegie, Australia) or peripheral blood mononuclear cells (T-SPOT.TB® [TSPOT]; Oxford Immunotec, Abingdon, UK) to antigens encoded within the region of difference-1, a region of the MTB genome absent in all Bacille de Calmette et Guérin strains and in most nontuberculous mycobacteria.<sup>9</sup> Previous systematic reviews have shown that, compared with the TST, IGRAs have a higher specificity in low TB incidence settings, correlate better with surrogate measures of MTB exposure, and have no crossreactivity with the Bacille de Calmette et Guérin vaccine.<sup>10–12</sup> However, these reviews did not specifically assess the performance of IGRAs in HIV-infected individuals.

We conducted a systemic review and meta-analysis to determine if the available data support the use of IGRAs to improve the identification of HIV-infected individuals who could benefit from IPT. To address this question, we focused on the performance of IGRAs in diagnosing LTBI rather than in ruling out active TB, a distinct but important question in HIV-infected individuals initiating IPT.

## METHODS

We followed standard guidelines for systematic reviews of diagnostic tests.<sup>13,14</sup>

### Search Methods

We updated literature searches in previous systematic reviews<sup>10–12,15,16</sup> to identify all studies evaluating IGRAs published through May 2010 (for details, see **Methods, Supplemental Digital Content 1**, <http://links.lww.com/QAI/A119>). In addition to database searches, we reviewed bibliographies of reviews and guidelines, screened citations of all included studies, and contacted both experts in the field and IGRA manufacturers to identify additional unpublished or ongoing studies. We requested pertinent information not reported in the original publication from the primary authors of studies included in the review.

### Study Selection

We included studies published in all languages and in all countries that evaluated the performance of the newest commercial IGRAs (QFT-GIT and TSPOT) in HIV-infected

adults. We excluded: 1) studies that evaluated noncommercial or older generation IGRAs and IGRAs performed in nonblood specimens; 2) studies focused on the effect of anti-TB treatment on IGRA response; 3) studies including fewer than 10 HIV-infected individuals; 4) studies reporting insufficient data to determine diagnostic accuracy measures; and 5) conference abstracts, letters without original data, and reviews. At least two reviewers independently performed citation screening and data extraction (for details, see **Methods, Supplemental Digital Content 1**, <http://links.lww.com/QAI/A119>).

### Outcomes Evaluated

Studies evaluating the performance of IGRAs are hampered by the lack of an adequate gold standard to distinguish the presence or absence of LTBI. Because we could not directly assess diagnostic accuracy for LTBI, we developed a hierarchy of outcomes that could support a role for IGRAs in identifying HIV-infected individuals who could benefit from IPT (for overview of outcome hierarchy, see **Figure, Supplemental Digital Content 2**, <http://links.lww.com/QAI/A120>). Of the outcomes shown, we only evaluated the three for which there were relevant data (for explicit definitions, see **Methods, Supplemental Digital Content 1**, <http://links.lww.com/QAI/A119>): 1) the predictive value of IGRAs for development of active TB; 2) the sensitivity of IGRAs in persons with culture-confirmed active TB (as a surrogate reference standard for MTB infection); and 3) the concordance between IGRA and TST results. In addition to the primary outcomes, we evaluated two characteristics that could influence the overall use of IGRAs in HIV-infected individuals: 1) the proportion of IGRA results that are indeterminate; and 2) the impact of CD4<sup>+</sup> T-lymphocyte count on test performance.

### Assessment of Study Quality

For studies of the predictive value of IGRAs, we appraised quality with a modified version of the Newcastle-Ottawa Scale for longitudinal/cohort studies.<sup>17</sup> For the other primary outcomes, which focus on test accuracy, we used relevant criteria from QUADAS, a validated tool for diagnostic accuracy studies (for detailed description, see **Methods, Supplemental Digital Content 1**, <http://links.lww.com/QAI/A119>).<sup>18</sup>

### Data Synthesis and Meta-Analysis

We adopted the following overall approach, specified a priori, to account for the significant heterogeneity in results expected between studies of diagnostic tests. First, we separately synthesized data for each commercial IGRA and by World Bank country income classification (low-/middle-income versus high-income),<sup>19</sup> a surrogate for TB incidence. Second, we visually assessed for heterogeneity using forest plots, characterized the variation in study results attributable to heterogeneity (I-squared statistic), and statistically tested for heterogeneity (chi-squared test).<sup>20</sup> Third, we calculated pooled estimates using random effects modeling, which provides more conservative estimates than fixed effects modeling when heterogeneity is present.<sup>21</sup>

For each individual study, we assessed all outcomes for which data were available. We generated forest plots to display the individual study estimates and their 95% confidence intervals. We calculated pooled estimates when at least four

studies were available in any subgroup and summarized individual study results when fewer than four studies were available. We performed all analyses using STATA 11 (Stata Corporation, College Station, TX).

## RESULTS

### Search Results

Our search yielded 791 citations (for flow chart, see **Figure, Supplemental Digital Content 3**, <http://links.lww.com/QAI/A121>). After full-text review of 129 papers evaluating IGRAs in immunocompromised individuals, 29 were determined to meet eligibility criteria. Because some papers included more than one commercial IGRA, there were 37 unique evaluations (hereafter referred to as studies)—19 of QFT-GIT and 18 of TSPOT—that included a total of 5736 HIV-infected individuals. TST was concurrently performed in 23 (62%) studies. As expected, there was a high degree of variation in study setting, study design, and study population (for details of individual studies, see **Table, Supplemental Digital Content 4**, <http://links.lww.com/QAI/A122>). Twenty-two (59%) studies were conducted in low-/middle-income countries and 27(73%) studies included only ambulatory HIV-infected individuals. IGRAs were performed in persons with or suspected of having active TB in 13 studies, asymptomatic HIV-infected persons being evaluated for LTBI in 19 studies, and both types of individuals in five studies. Fifteen (41%) studies had some industry involvement, including donation of test kits (12 studies) and a financial relationship with IGRA manufacturers (three studies). Results presented subsequently were similar when these studies were excluded.

### Risk of Progression to Active Tuberculosis

We identified 3 longitudinal studies that evaluated the ability of IGRAs to predict future development of active TB.<sup>22–24</sup> Based on the Newcastle-Ottawa Scale, all three studies enrolled a representative sample of patients. However, only one study<sup>22</sup> had an adequate duration of follow-up (1 year or greater) and no study performed adequate outcome assessment (ie, ruled out active TB at baseline and evaluated all participants for active TB during follow-up). In addition, all studies had few (less than 12) incident cases of active TB.

All three studies reported a higher risk of active TB in HIV-infected individuals with positive versus negative IGRA results. However, there was no significant difference in the cumulative incidence of active TB in HIV-infected individuals with positive and negative QFT-GIT results (8% versus 0%; risk difference 8%; 95% confidence interval [CI], –0.7% to +17%; median follow-up 19 months)<sup>22</sup> or TSPOT results (10% versus 0%; risk difference 10%; 95% CI, –3% to +23%; median follow-up 12 months for positive TSPOT results and 3 months for negative TSPOT results).<sup>23</sup> In the third study, Elliott et al adjusted QFT-GIT results for baseline CD4<sup>+</sup> T-lymphocyte count and reported that the adjusted values could be used to stratify HIV-positive individuals into low-risk (1%) and high-risk (12%) groups for development of active TB within 6 months of antiretroviral therapy initiation.<sup>24</sup>

### Sensitivity in Culture-Confirmed Active Tuberculosis

We identified 18 studies that evaluated the sensitivity of IGRAs in HIV-infected adults with active TB, 16 of which were conducted in low-/middle-income countries.<sup>23,25–37</sup> Twelve (67%) studies did not enroll a representative spectrum of patients (consecutive, ambulatory HIV-infected patients suspected of having active TB). The majority of studies satisfied the remaining QUADAS criteria assessed (for graph of QUADAS scoring, see **Figure, Supplemental Digital Content 5**, <http://links.lww.com/QAI/A123>).

### Low-/Middle-Income Countries

Pooled sensitivity estimates were higher for TSPOT (72%; 95% CI, 62–81%; eight studies) than for QFT-GIT (61%; 95% CI, 47–75%; eight studies) (Fig 1A). However, there was significant heterogeneity in the pooled estimates for both IGRAs (I-squared >70% and  $P < 0.001$ ). Five studies compared head-to-head the sensitivity of IGRAs and TST for diagnosis of active TB. Compared with TST, TSPOT was more sensitive in one study (absolute difference 50%; 95% CI, 29–71%),<sup>29</sup> less sensitive in one study (absolute difference 18%; 95% CI, 2–34%),<sup>32</sup> and as sensitive in one study (absolute difference –3%; 95% CI, –17% to +11%) (Rangaka MX, Gideon H, Wilkinson KA, et al. The incremental value of TST and IGRA for smear-negative culture-positive TB in HIV-infected patients screened for preventive therapy in an ART program in a high-burden for TB area. The Union/CDC Late Breaker Session on Tuberculosis. 41st Union World Conference on Lung Health, Berlin, November 15, 2010). Similarly, QFT-GIT was more sensitive than TST in one study (absolute difference 41%; 95% CI, 22–60%)<sup>30</sup> and less sensitive than TST in one study (absolute difference 33%; 85% CI, 16–51%).<sup>32</sup>

### High-Income Countries

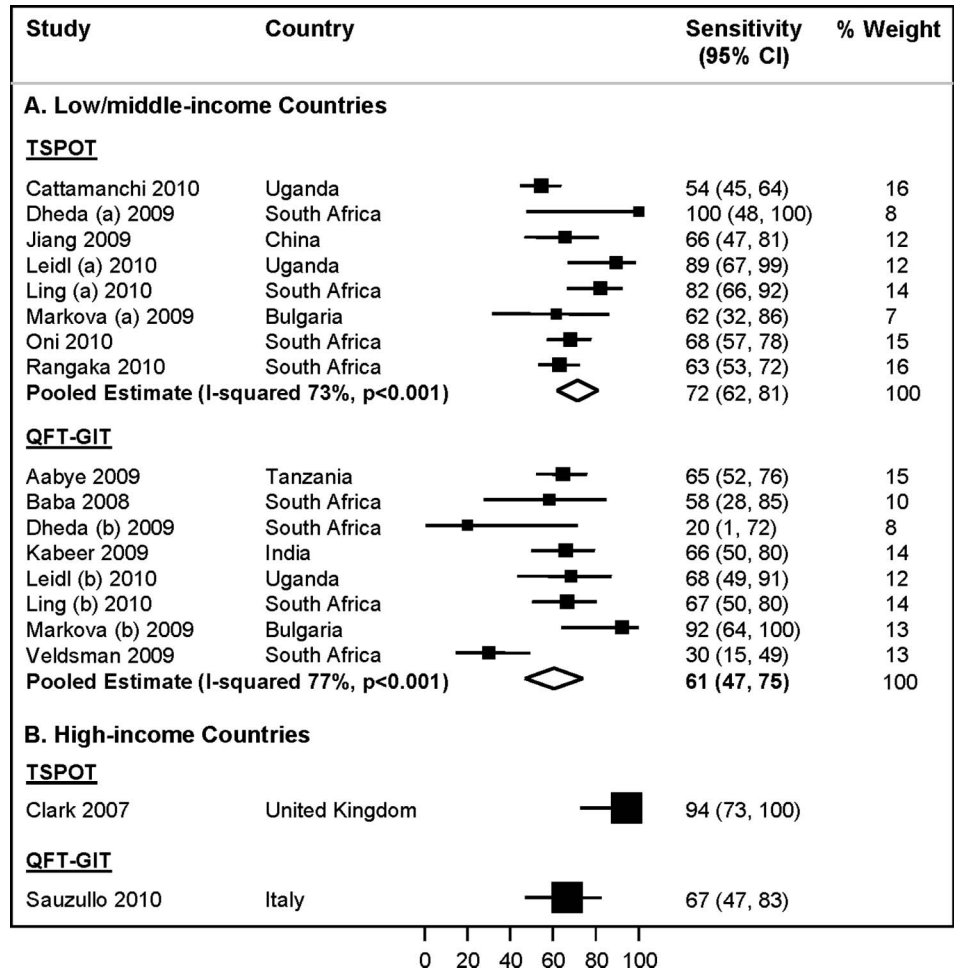
Although data were limited, studies from high-income countries reported higher values for sensitivity when compared with the pooled estimates obtained for low-/middle-income countries (Fig. 1B). In the two available studies, sensitivity was 94% (95% CI, 73–100%) for TSPOT<sup>23</sup> and 67% (47–83%) for QFT-GIT.<sup>35</sup> The sensitivity of QFT-GIT and TST were similar (–7%; 95% CI, –30% to +17%) in the only head-to-head comparison.<sup>35</sup>

### Agreement Between Interferon-Gamma Release Assays and Tuberculin Skin Test Results

Data on agreement (concordance) between TST and IGRA results in HIV-infected individuals being evaluated for LTBI were available for 15 studies.<sup>29,34,37–45</sup> A majority of studies satisfied all QUADAS criteria assessed (for graph of QUADAS scoring, see **Figure, Supplemental Digital Content 5**, <http://links.lww.com/QAI/A123>).

### Low-/Middle-Income Countries

Two of three studies that reported test agreement using kappa values reported poor or moderate agreement (kappa 0.4–0.6). IGRA-positive/TST-negative results were more common than IGRA-negative/TST-positive results in four of five



**FIGURE 1.** Sensitivity of IGRA in HIV-infected individuals with confirmed active tuberculosis. The forest plots display the sensitivity estimates obtained from individual studies and pooled estimates derived from random effects modeling. Pooled estimates are shown only for subgroups in which four or more studies were available. IGRA, interferon-gamma release assay; CI, confidence interval; TSPOT, T-SPOT.TB; QFT-GIT, QuantiFERON-TB Gold In-Tube.

studies. Overall, TSPOT and TST results were concordant in 77% (95% CI, 67–88%) of cases but there was significant heterogeneity among individual studies ( $I^2$  63%,  $P = 0.04$ ) (for forest plot, see **Figure, Supplemental Digital Content 6**, <http://links.lww.com/QAI/A124>). There were insufficient studies to calculate pooled estimates for QFT-GIT.

**High-Income Countries**

Results were similar in high-income countries, although pooled estimates of concordance were generally higher. Eight of nine studies that reported test agreement using kappa values reported poor or moderate agreement (kappa 0.4–0.6). IGRA-positive/TST-negative results were more common than IGRA-negative/TST-positive results in six of 10 studies. When results were pooled, TSPOT and TST results were concordant in 89% (95% CI, 81–98%) of cases and QFT-GIT and TST results were concordant in 94% (95% CI, 91–96%) of cases. There was significant heterogeneity in the pooled estimate for TSPOT ( $I^2$  92%,  $P < 0.001$ ) but not QFT-GIT ( $I^2$  38%,  $P = 0.17$ ).

**Indeterminate Interferon-Gamma Release Assay Results**

We assessed the proportion of indeterminate IGRA results among healthy HIV-infected individuals screened for

LTBI. The proportion of indeterminate results was less than 5% in nine of 13 studies evaluating T-SPOT (range, 0–13%)<sup>23,29,31,34,38,41–46</sup> and six of 10 studies evaluating QFT-GIT (range, 2–11%).<sup>22,31,37,39,40,42,43,45,47,48</sup>

**Low-/Middle-Income Countries**

For TSPOT, the pooled proportion of indeterminate results was 2% (95% CI, 0–3%) and results were consistent across studies ( $I^2$  0%,  $P = 0.42$ ) (Fig. 2A). There were insufficient studies to calculate pooled estimates for QFT-GIT, but the proportion of indeterminate results was less than 5% in two of three studies.

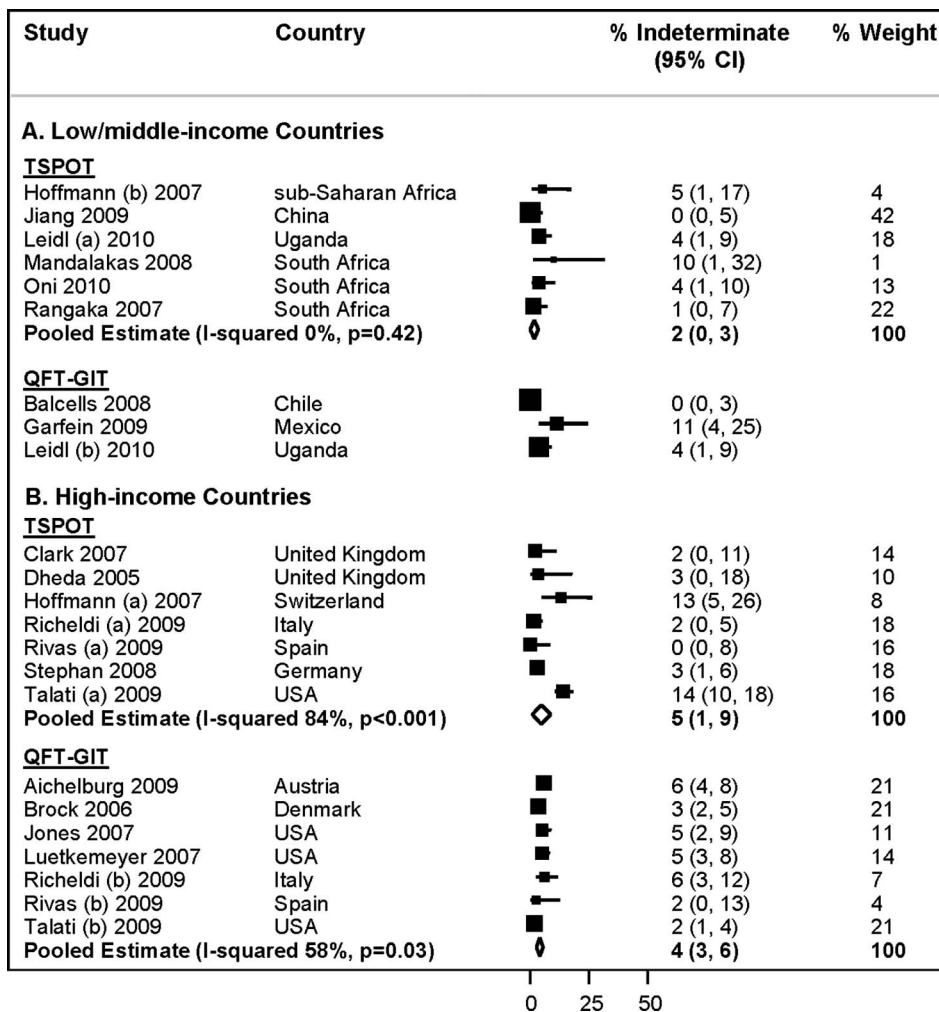
**High-Income Countries**

Indeterminate results were also infrequent in studies conducted in high-income countries. The pooled proportion of indeterminate results was 5% for TSPOT (95% CI, 1–9%;  $I^2$  84%;  $P < 0.001$ ) and 4% for QFT-GIT (95% CI, 3–6%;  $I^2$  58%;  $P = 0.03$ ) (Fig 2B).

**Impact of Immunosuppression**

In 21 studies, IGRA results were available for at least five HIV-infected adults in the following CD4<sup>+</sup> cell count strata: less than 200 and 200 cells/ $\mu$ L or greater.<sup>22,23,29,31,34,37–47</sup>

**FIGURE 2.** Proportion of indeterminate IGRA results in HIV-infected persons screened for LTBI. The forest plots display the proportion of indeterminate IGRA results obtained from individual studies and pooled estimates derived from random effects modeling. Pooled estimates are shown only for subgroups in which four or more studies were available. IGRA, interferon-gamma release assay; LTBI, latent tuberculosis infection; CI, confidence interval; TSPOT, T-SPOT.TB; QFT-GIT, QuantiFERON-TB Gold In-Tube.



### Low-/Middle-Income Countries

For TSPOT, the pooled proportion of positive test results was significantly lower when CD4<sup>+</sup> T-lymphocyte count was less than 200 cells/ $\mu$ L versus 200 cells/ $\mu$ L or greater (difference -18%; 95% CI, -34% to -2%) (Fig. 3A). However, the pooled proportion of individuals with indeterminate test results was similar among individuals in the two CD4<sup>+</sup> T-lymphocyte count strata (4%; -3% to 10%) (Fig. 4A). For QFT-GIT, there were insufficient studies to calculate pooled estimates.

### High-Income Countries

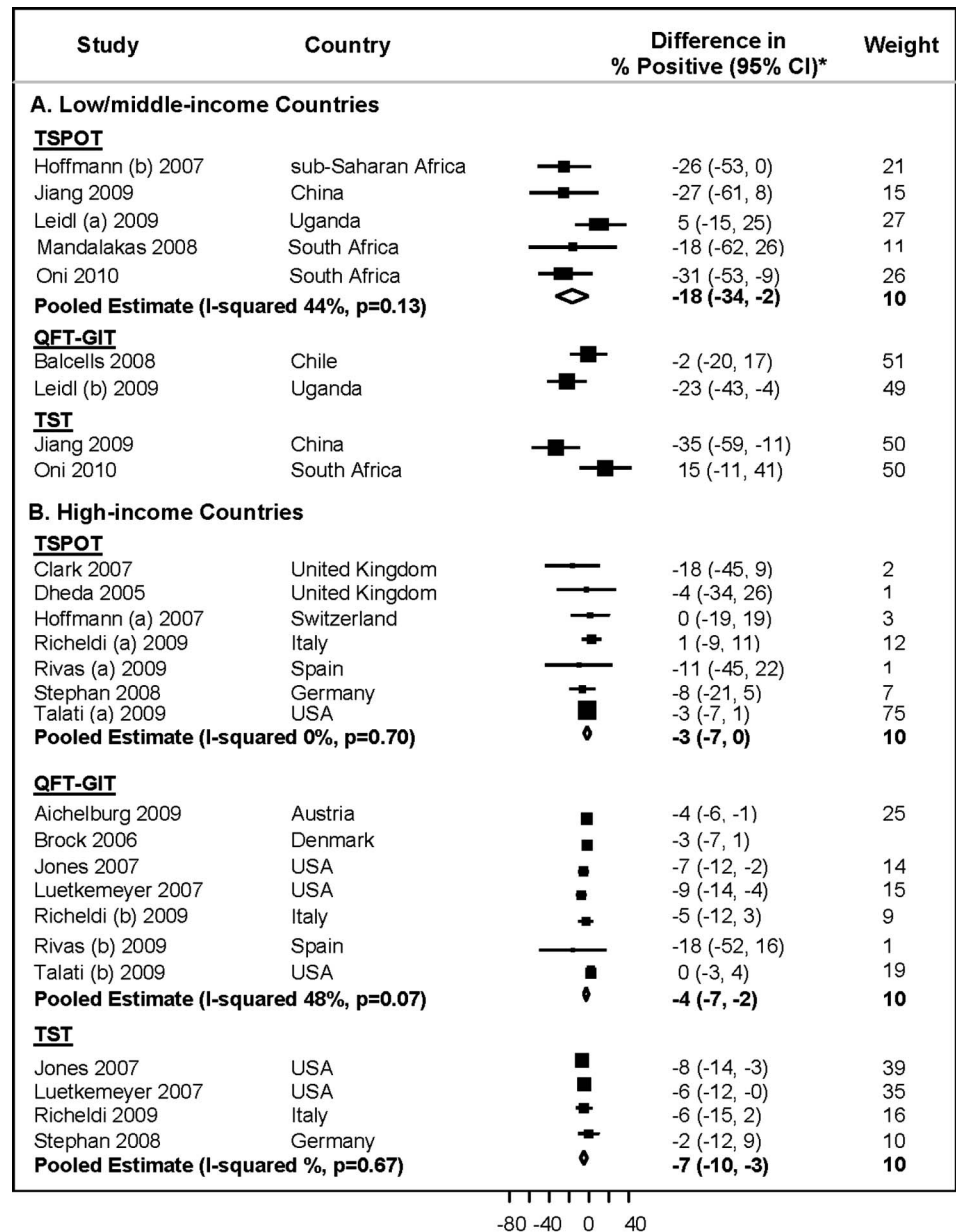
The pooled proportion of positive test results was significantly lower when CD4<sup>+</sup> T-lymphocyte count was less than 200 cells/ $\mu$ L versus greater than 200 cells/ $\mu$ L for QFT-GIT (difference -4%; 95% CI, -7% to -2%) but not TSPOT (difference -3%; 95% CI, -7% to 0%) (Fig. 3B). Similarly, the pooled proportion of indeterminate test results was significantly higher when CD4<sup>+</sup> T-lymphocyte count was less than 200 cells/ $\mu$ L versus greater than 200 cells/ $\mu$ L for QFT-GIT (difference 9%; 95% CI, 3-15%) but not TSPOT (difference 1%; -7% to +9%;  $P = 0.85$ ) (Fig. 4B). Results were inconsistent

across studies for QFT-GIT ( $I^2$  67%;  $P = 0.006$ ) but not TSPOT ( $I^2$  8%;  $P = 0.37$ ).

In four studies for which TST data were available, the decline in the proportion of positive test results (difference -7%; 95% CI, -10% to -3%) when CD4<sup>+</sup> T-lymphocyte count was less than 200 cells/ $\mu$ L was similar to that observed for both IGRAs.<sup>39,40,42,44</sup>

## DISCUSSION

TB is the most frequent opportunistic infection and a leading cause of death in people living with HIV. IPT has been shown to reduce the risk of TB and is now universally recommended in HIV-infected individuals with LTBI or at high risk of having LTBI. However, the optimal test for identifying HIV-infected individuals who would benefit most from IPT remains uncertain. Consequently, the most recent guidelines differ in their recommended LTBI screening strategies, ranging from screening with TST if feasible<sup>3</sup> to dual testing with TST and IGRAs.<sup>49,50</sup> Our systematic review addressed two questions relevant for determining whether IGRAs should replace TST as a screening test for LTBI in



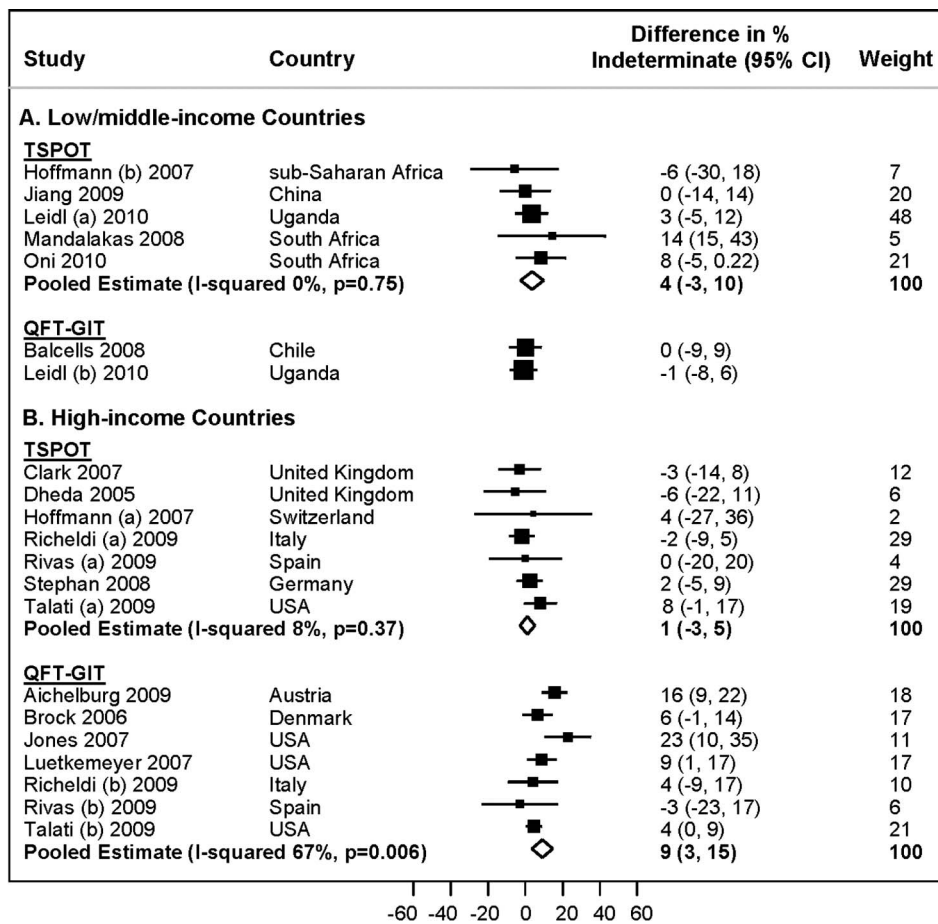
**FIGURE 3.** Impact of CD4<sup>+</sup> cell count on the proportion of positive IGRA results. The forest plots display the absolute difference in the proportion of positive IGRA results between persons with CD4<sup>+</sup> cell count greater than 200 cells/ $\mu$ L and CD4<sup>+</sup> cell count less than 100 cells/ $\mu$ L obtained from individual studies and pooled estimates derived from random effects modeling. Pooled estimates are shown only for subgroups in which four or more studies were available. IGRA, interferon-gamma release assay; CI, confidence interval; TSPOT, T-SPOT.TB; QFT-GIT, QuantiFERON-TB Gold In-Tube.

\* Difference = (% positive CD4 <200 cells/ $\mu$ L) – (% positive CD4  $\geq$ 200 cells/ $\mu$ L)

people living with HIV: 1) are IGRAs better than TST at predicting which HIV-infected individuals are at highest risk of progression to active TB; and (2) are IGRAs more sensitive than TST for diagnosis of MTB infection, particularly in HIV-infected individuals with advanced immunosuppression? For both questions, we found insufficient evidence to conclude that either test is superior to the other.

It is well established that the majority of persons latently infected with MTB, including persons coinfecting with HIV, do not develop active TB.<sup>51</sup> The clinical use of any diagnostic test for LTBI is therefore dependent on its ability to identify which persons are truly at increased risk for progression to active TB. We identified three studies of the predictive value of IGRAs in

HIV-infected individuals, each of which showed that IGRAs have poor positive predictive value but high negative predictive value for active TB. Although these results suggest that a negative IGRA result is reassuring (no person with a negative IGRA result developed culture-positive TB), the studies had serious limitations, including small sample sizes with short duration of follow-up<sup>23,24</sup> and differential evaluation and/or follow-up of persons with positive and negative IGRA results.<sup>22–24</sup> These limitations would be expected to result in an underestimation of active TB in persons with negative IGRA results. In contrast, randomized controlled trials in HIV-infected persons demonstrate that IPT confers a 20% to 60% reduction in the risk of active TB among persons with positive



**FIGURE 4.** Impact of CD4<sup>+</sup> cell count on the proportion of indeterminate IGRA results. The forest plots display the absolute difference in the proportion of indeterminate IGRA results between persons with CD4<sup>+</sup> cell count greater than 200 cells/ $\mu$ L and CD4<sup>+</sup> cell count less than 100 cells/ $\mu$ L obtained from individual studies and pooled estimates derived from random effects modeling. Pooled estimates are shown only for subgroups in which four or more studies were available. IGRA, interferon-gamma release assay; CI, confidence interval; TSPOT, T-SPOT.TB; QFT-GIT, QuantiFERON-TB Gold In-Tube.

\* Difference = (% indeterminate CD4 <200 cells/ $\mu$ L) – (% indeterminate CD4  $\geq$ 200 cells/ $\mu$ L)

TST results.<sup>2</sup> In addition, large prospective cohort studies have established that persons with a positive TST have a 1.4- to 1.7-fold higher rate of active TB within 1 year compared with persons with a negative TST result.<sup>1,52</sup> Unfortunately, similar high-quality data on the clinical impact and predictive value of IGRA testing are currently lacking. Although a recent meta-analysis that included studies of HIV-infected and -uninfected patients found that IGRA results are more strongly associated with progression to active TB than TST results, the vast majority (greater than 85%) of IGRA-positive individuals did not progress to active TB.<sup>53</sup>

Despite the limited data on patient-important outcomes, it has been suggested that IGRAs may have a role for identifying MTB infection in HIV-infected individuals given the suboptimal performance of TST in immunosuppressed individuals.<sup>54</sup> In support of this role, data from high-income countries suggest that TSPOT performance may be less affected by advanced immunosuppression, possibly because the testing platform ensures that an adequate number of peripheral blood mononuclear cells are available despite overall low CD4<sup>+</sup> cell counts in whole blood.<sup>46</sup> However, the point estimates and lower limits of the 95% CI for the difference in the proportion of positive test results in HIV-infected individuals with and without advanced

immunosuppression were similar for TSPOT, QFT-GIT, and TST. Moreover, in low-/middle-income countries, two of five studies of TSPOT and one of two studies of QFT-GIT found a large (range, 23–31%) and statistically significant absolute reduction in the proportion of positive test results in HIV-infected individuals with advanced immunosuppression. Reasons for the stronger impact of immunosuppression on IGRA performance in low-/middle-income versus high-income settings are unclear but may be related to disease severity and antiretroviral treatment status. However, overall, the available data suggest, but do not clearly confirm, that IGRAs are less affected by HIV-related immunosuppression than TST.

The major limitation of this review, and studies of IGRAs in general, is the lack of an adequate reference standard for diagnosis of LTBI. Although we developed a prespecified hierarchy that could support the use of IGRAs, there were no data on whether IGRAs identify HIV-infected individuals who would benefit from preventive therapy and minimal data on the predictive value of IGRAs for active TB, the two strongest outcomes in the hierarchy. In addition, the majority of studies were small (less than 150 patients in 22 of 37 studies), only six studies performed a head-to-head comparison of IGRA and TST results to a reference standard, and there were insufficient

studies to perform meta-analysis in many subgroups. Second, although IGRAs have potential operational advantages relative to TST, we did not find any studies that evaluated the impact of implementing IGRAs in LTBI screening programs targeting HIV-infected populations. Lastly, because we only included studies that evaluated IGRAs, we did not review historic data on the effect of HIV-related immunosuppression on TST results.

Given that both TST and IGRAs have only modest predictive value and suboptimal sensitivity, it would be relevant to evaluate outcomes when both tests are used, either simultaneously or sequentially, for diagnosing LTBI in HIV-infected persons. Although we did not find any studies of a dual testing approach, the most recently updated US national guidelines endorse such an approach. Although routine use of dual testing is not recommended, the 2010 US Centers for Disease Control and Prevention guidelines indicate that the results from both tests (IGRA and TST) may be useful in HIV-infected individuals when the initial test is negative.<sup>49</sup> Similarly, the 2010 Canadian Tuberculosis Committee guideline recommends starting with TST but performing an IGRA if the TST is negative and there is a strong clinical suspicion for LTBI in immunocompromised individuals.<sup>50</sup> Although dual testing approaches will surely increase the number of HIV-infected individuals with positive test results, clinicians should balance this potential benefit against the lack of evidence supporting the efficacy of IPT in TST-negative but IGRA-positive individuals. Other strategies should also be considered, including modifying the definition for a positive IGRA result in HIV-infected individuals, monitoring trends in IGRA results in individual patients (ie, serial testing), measuring levels of other biomarkers, and developing risk prediction models.

## CONCLUSION

Current evidence suggests that IGRAs perform similarly to the TST at identifying HIV-infected individuals who could benefit from LTBI treatment. Important questions remain unanswered despite the substantial body of literature on IGRAs. HIV-infected individuals with a negative IGRA result may have a low risk of progression to active TB, but this result should be confirmed in larger studies that simultaneously perform TST and include a longer duration of follow-up. IGRAs (particularly TSPOT) may be more sensitive than TST in HIV-infected individuals and less affected by advanced immunosuppression. However, these results have not been observed consistently in head-to-head comparisons. Clinical trials evaluating outcomes in HIV-infected individuals randomized to different LTBI screening strategies (IGRA versus TST versus dual testing) are needed to more definitively determine whether IGRAs could improve the identification of people living with HIV who could benefit from IPT. Until such data are available, the decision to use IGRA or TST (or both) will depend on national guidelines as well as resource and logistic considerations.

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## **SUPPLEMENTAL DIGITAL CONTENT 1**

### **SUPPLEMENTAL METHODS**

Two independent reviews were conducted to inform the WHO's guideline development process and were presented by their respective authors at separate WHO Expert Group Meetings in January 2010 (AD, CC, and BJM) and July 2010 (AC, JZM, KS, and MP). The results of the two reviews were very similar and the authors jointly resolved minor differences. Because the second review included additional data (studies with more recent publication dates and data obtained through contact with authors), the methods and results from the second review are presented.

**Search strategy.** We searched PubMed, Embase, Biosis and Web of Science. The search string used for PubMed was: ((interferon-gamma release assay\*) OR (T-cell-based assay\*) OR (antigen-specific T cell\*) OR (T cell response\*) OR (T-cell response\*) OR (interferon\*) OR (interferon-gamma) OR (gamma-interferon) OR (IFN) OR (elispot) OR (ESAT-6) OR (CFP-10) OR (culture filtrate protein) OR (Enzyme Linked Immunosorbent Spot) OR (Quantiferon\* OR Quantiferon-TB)) AND (tuberculosis OR mycobacterium tuberculosis). In addition to database searches, we reviewed bibliographies of reviews and guidelines, screened citations of all included studies, and contacted both experts in the field and IGRA manufacturers to identify additional published, unpublished, and ongoing studies. We requested and obtained pertinent information not reported in the original publication from the primary authors of all studies included in the review.

**Data Extraction.** At least two reviewers (AC, RS, KRS, JM) independently screened the accumulated citations for relevance, reviewed full-text articles using the pre-specified eligibility criteria, and independently extracted data using a standardized data extraction form that had initially been piloted and finalized with a subset of studies. We extracted data for the following variables: year study was published, industry sponsorship, study design, study participants (adults or children younger than 15 years old), country where study was conducted, patient population (inpatient, outpatient, or both), type of commercial IGRA, number and type of indeterminate results, timing of IGRA relative to TST, dose and formulation of PPD, TST cut-point,

median CD4+ cell count, and outcome data for positive and negative predictive values, sensitivity, and concordance.

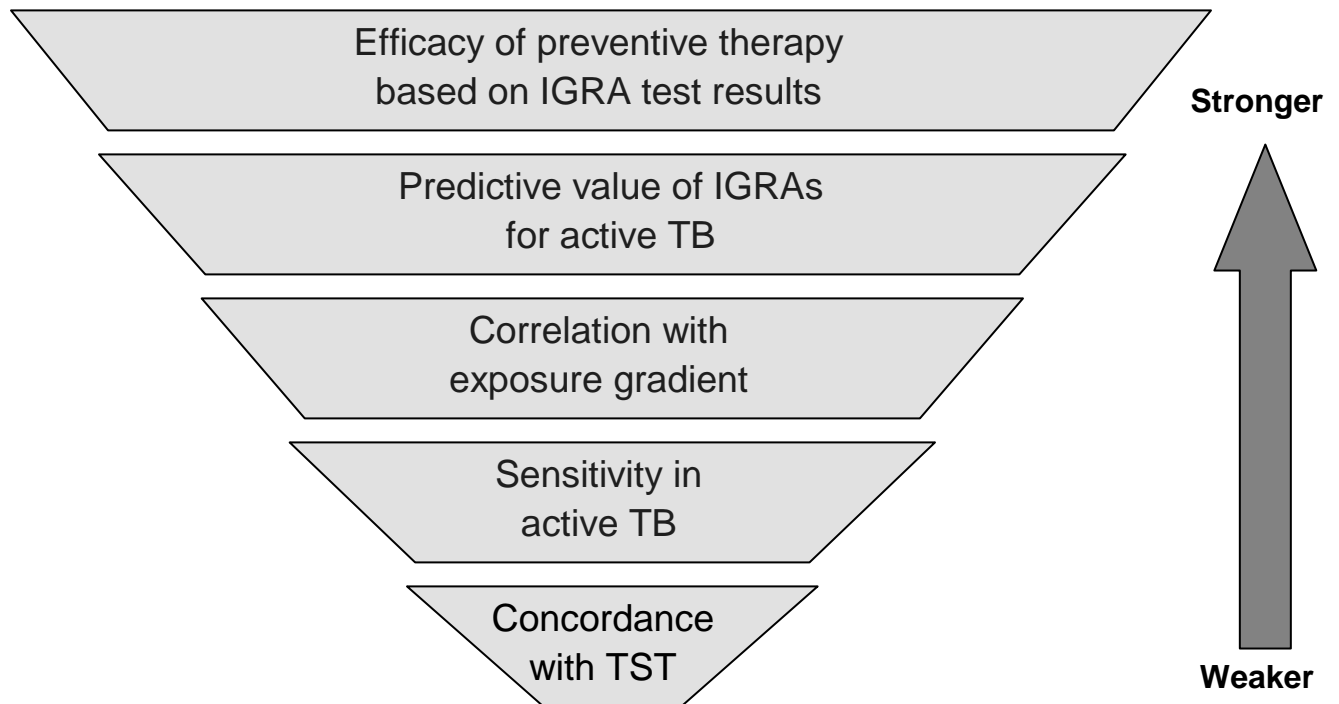
We used the following definitions for the outcomes described in Figure 1: (1) Incidence of active TB – the number of active TB cases that developed during a specified median duration of follow-up divided by the number of persons at risk (cumulative incidence) or the number of new active TB cases divided by the total person-time of follow-up (incidence rate); (2) Sensitivity – the proportion of individuals with a positive IGRA result among those with culture-positive TB (we included indeterminate IGRA results in the denominator if they occurred in individuals with culture-positive TB); and (3) Percent concordance (i.e., agreement) – the proportion of individuals for whom IGRA and TST results were both positive or both negative among all individuals tested. To assess the impact of HIV-related immunosuppression, we calculated the difference in the proportion of positive and indeterminate IGRA results, or positive TST results, between patients with a CD4+ cell count <200 cells/ $\mu$ L and  $\geq$ 200 cells/ $\mu$ L.

**Quality Assessment.** We conducted quality assessment separately for each of the three primary outcomes. For the first outcome (predictive value of IGRAs), we appraised quality with a modified version of the Newcastle-Ottawa Scale (NOS) for longitudinal/cohort studies. This tool assesses quality in three domains: selection of cohorts (representativeness of sample and absence of outcome at baseline), comparability of cohorts (adjustment for potential confounders), and assessment of outcome (blinding and complete verification). For the second (sensitivity in culture-confirmed active TB) and third (agreement between IGRA and TST results) primary outcomes, we used a subset of relevant items from QUADAS, a validated tool for diagnostic accuracy studies. We scored each of the following QUADAS items as “yes”, “no”, or “unclear”: 1) Representative spectrum – we scored as “yes” when ambulatory patients suspected of having active TB were consecutively selected; (2) Acceptable reference standard (outcome 2 only) - we scored as “yes” for all studies because we considered culture to be an acceptable reference standard; (3) Acceptable delay between index and reference tests – we scored this item as “yes” for all studies for outcome 2 and “yes” for

outcome 3 if IGRAs were performed before TST; (4) Partial verification avoided (outcome 2 only) – we scored as “yes” for all studies because all patients had culture-confirmed TB; (5) Differential verification avoided (outcome 2 only) – we scored as “yes” for all studies because all patients had culture-confirmed TB; (6) Incorporation avoided (outcome 2 only) – we scored as “yes” for all studies because IGRA results were not included in the reference standard; (7) Index test results blinded (outcome 2 only) – we scored as “yes” for all studies because IGRAs provide an automated result; (8) Reference standard blinded (outcome 2 only) – we scored this item as “yes” only if the authors stated explicitly that persons reading cultures were unaware of IGRA results; (9) Relevant clinical information available – we scored as “yes” for all studies because IGRA results are automated and unlikely to be altered by external information; (10) Uninterpretable results reported – we scored as “yes” if authors reported indeterminate results and (11) Withdrawals explained – we scored as “yes” if a flow diagram of the study population was included in the paper and/or exclusions after enrollment were explained. At least two reviewers (AC, RS, KS, JMZ) independently scored each outcome for all studies included in the review. Reviewers resolved disagreements by consensus. We requested additional information from authors when needed to adequately assess each QUADAS item.

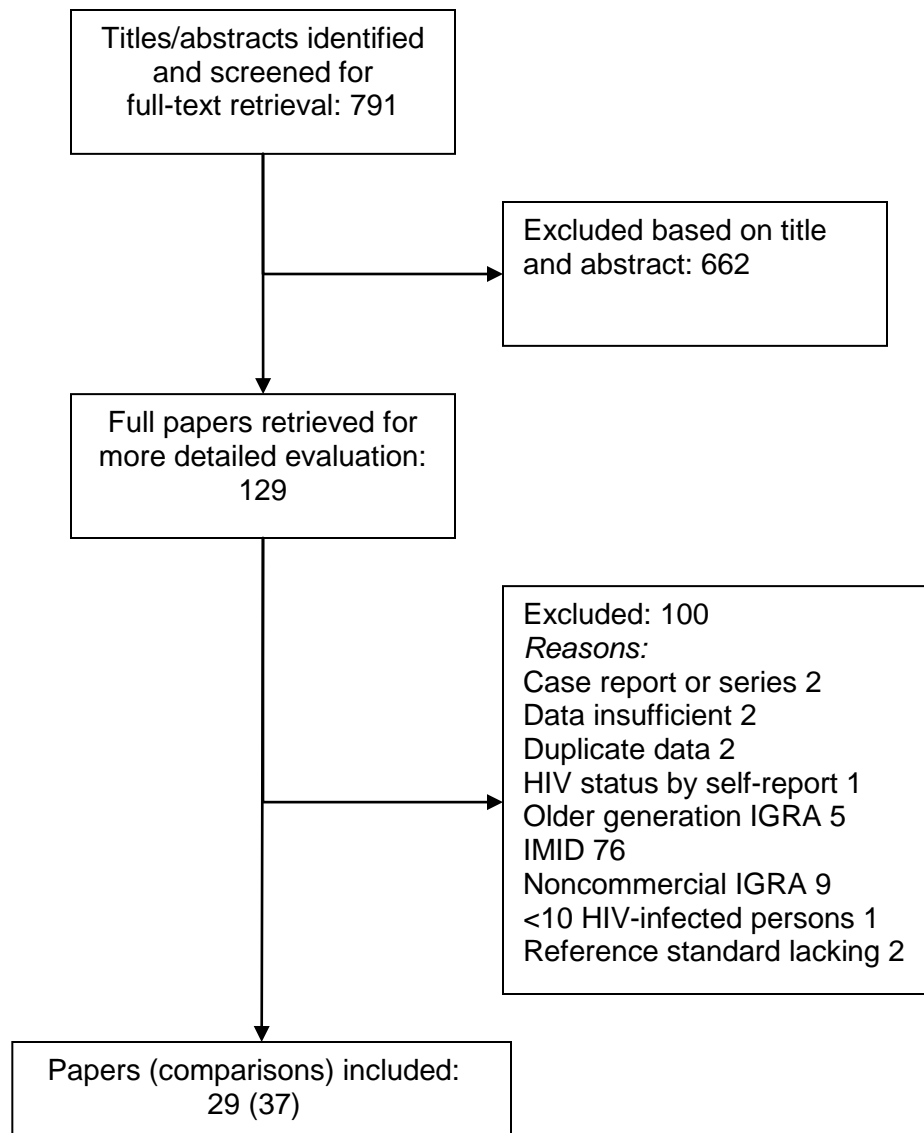
## SUPPLEMENTAL DIGITAL CONTENT 2

**Supplemental Figure 1. Hierarchy of outcomes for assessing the performance of IGRAs.** In the absence of an adequate gold standard for latent tuberculosis infection (LTBI), we developed and ranked outcomes based on their likely patient impact. Abbreviations: IGRA, Interferon-gamma Release Assay; TB, Tuberculosis; TST, Tuberculin Skin Test.



### SUPPLEMENTAL DIGITAL CONTENT 3

**Supplemental Figure 2. Flow of studies.** Of 791 citations identified, 662 were excluded after reviewing titles and abstracts. Full-text review of the remaining 129 citations yielded 29 papers meeting eligibility criteria. Because some papers evaluated more than one IGRA, there were 37 unique studies. Abbreviations: IGRA, Interferon-gamma Release Assay; PPD, Purified Protein Derivative; IMID, Immune-mediated Inflammatory Disease.



## SUPPLEMENTAL DIGITAL CONTENT 4

**Supplemental Table 1. Characteristics of Included Studies.**

Study, Year	Country	Setting	Patient Population	N	CD4 Count, Median (IQR)
<b>QFT-Gold-In Tube</b>					
<b>A. Low and Middle Income Countries</b>					
Aabye, 2009	Tanzania	Inpatient and Outpatient	Active TB	68	272 (172–478)
Baba, 2008	South Africa	Inpatient	Active TB	25	80
Balcells, 2008	Chile	Outpatient	LTBI	116	368 (264-482)
Dheda (b), 2009	South Africa	Inpatient and Outpatient	Active TB	22	NR
Elliott 2009	Cambodia	Outpatient	LTBI	231	69
Garfein, 2009	Mexico	Outpatient	LTBI	54	NR
Kabeer, 2009	India	Inpatient and Outpatient	Active TB	66	116 (48-209)
Leidl (b), 2010	Uganda	Outpatient	Active TB	19	182
			LTBI	109	283
Ling (b), 2010	South Africa	Inpatient and Outpatient	Active TB	107	177
Markova (b), 2009	Bulgaria	Outpatient	Active TB	90	NR
Veldsman, 2009	South Africa	Outpatient	Active TB	60	151
<b>B. High-income Countries</b>					
Aichelburg, 2009	Austria	Outpatient	LTBI	822	393 (264-566)
Brock, 2006	Denmark	Outpatient	LTBI	590	523
Jones, 2007	United States	Outpatient	LTBI	201	396 (224-612)
Luetkemeyer, 2007	United States	Outpatient	LTBI	294	363 (214-581)
Rivas (b), 2009	Spain	Detox Unit	LTBI	42	470 (309-662)
Richeldi (b), 2009	Italy	Outpatient	LTBI	130	439
Sauzullo, 2010	Italy	Outpatient	Active TB	207	219 (9-500)
Talati (b), 2009	United States	Outpatient	LTBI	336	335 (185-512)

**T-SPOT.TB****A. Low and Middle Income Countries**

Cattamanchi, 2010	Uganda	Inpatient	Active TB	244	49 (16-160)
Dheda (a), 2009	South Africa	Inpatient and Outpatient	Active TB	22	NR
Hoffmann (b), 2007	Sub-Saharan Africa	Outpatient	LTBI	39	366 (283-447)
Jiang, 2009	China	Inpatient and Outpatient	Active TB	32	NR
			LTBI	70	NR
Leidl (a), 2010	Uganda	Outpatient	Active TB	19	182
			LTBI	109	283
Ling (a), 2010	South Africa	Inpatient and Outpatient	Active TB	107	177
Mandalakas, 2008	South Africa	Outpatient	LTBI	20	214 (154-457)
Markova (a), 2009	Bulgaria	Outpatient	Active TB	90	NR
Oni, 2010	South Africa	Outpatient	Active TB	85	155 (73-259)
			LTBI	81	291 (189-436)
Rangaka, 2007	South Africa	Outpatient	LTBI	74	392 (263–520)
Rangaka, 2010	South Africa	Outpatient	Active TB	106	165 (101-226)

**B. High-income Countries**

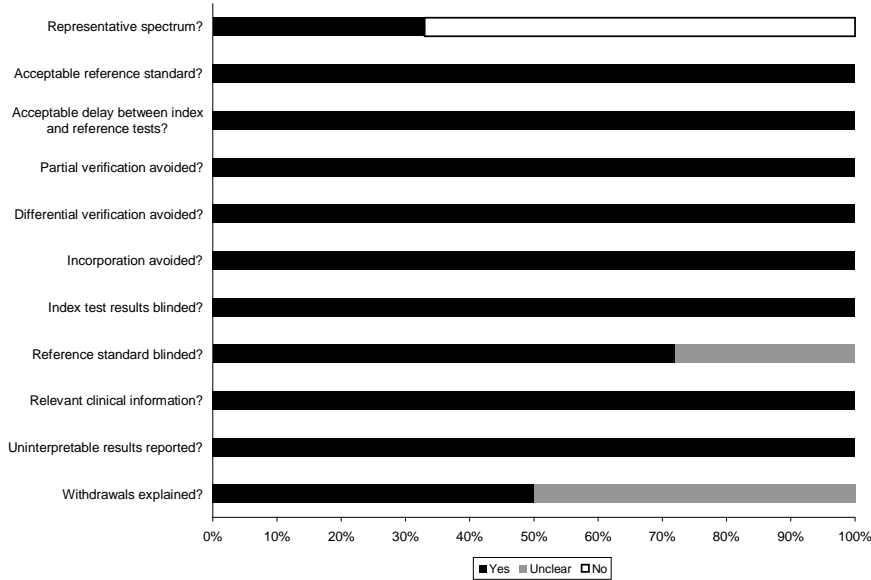
Clark, 2008	United Kingdom	Inpatient and Outpatient	Active TB	154	213 (77–367)
			LTBI	47	
Dheda, 2005	United Kingdom	Outpatient	LTBI	29	361 (159-504)
Hoffmann (a), 2007	Switzerland	Outpatient	LTBI	46	445 (300-650)
Richeldi (a), 2009	Italy	Outpatient	LTBI	130	439
Rivas (a), 2009	Spain	Detoxification Unit	LTBI	42	470 (309-662)
Stephan (a), 2008	Germany	Outpatient	LTBI	275	408 (260-554)
Talati (a), 2009	United States	Outpatient	LTBI	336	335 (185-512)

Abbreviations. IQR, interquartile range; LTBI, latent tuberculosis infection; TB, tuberculosis; NR, not reported.

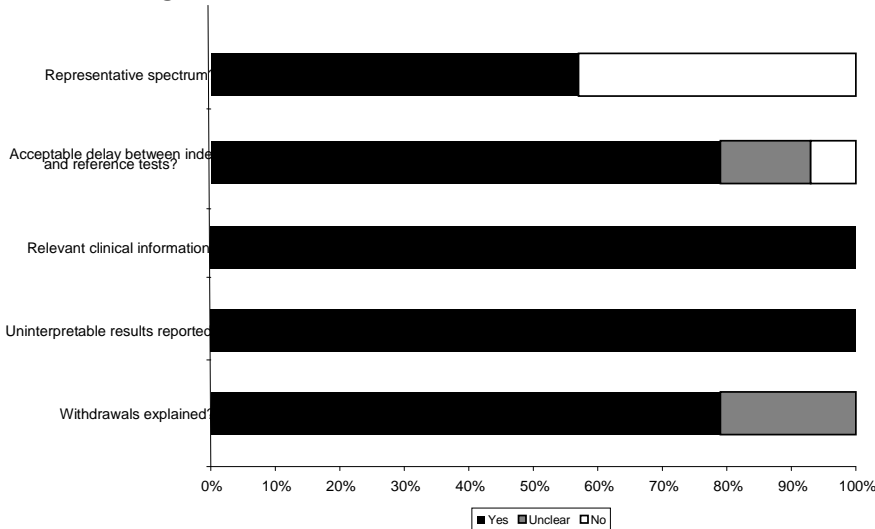
## SUPPLEMENTAL DIGITAL CONTENT 5

**Supplemental Figure 3. Assessment of study quality using the QUADAS tool.** For each QUADAS item, two reviewers independently determined whether a study did or did not meet the quality criterion, or whether it was unclear. The percentage of studies meeting each relevant QUADAS item are shown for studies evaluating sensitivity of IGRAs in HIV-infected individuals with active TB (Figure 3A) and for studies reporting agreement between IGRA and TST results in HIV-infected individuals being evaluated for latent tuberculosis infection (Figure 3B).

### A. Studies of IGRA Sensitivity in HIV-infected Individuals with Active TB



### B. Studies of agreement between IGRA and TST results



**SUPPLEMENTAL DIGITAL CONTENT 6**

**Supplemental Figure 4. Percent concordance between IGRA and TST results.** The forest plots display percent concordance between IGRA and TST results in individual studies and pooled estimates derived from random effects modeling. Pooled estimates are shown only for sub-groups in which 4 or more studies were available. Abbreviations: IGRA, interferon-gamma release assay; TST, tuberculin skin test; CI, confidence interval; TSPOT, T-SPOT.*TB*, QFT-GIT, QuantiFERON-Gold In-tube.

