Published in final edited form as:

J Acquir Immune Defic Syndr. 2011 March ; 56(3): 230–238. doi:10.1097/QAI.0b013e31820b07ab.

Interferon-gamma release assays for the diagnosis of latent tuberculosis infection in HIV-infected individuals – A systematic review and meta-analysis

Adithya Cattamanchi, MD^{1,2}, Rachel Smith, MD¹, Karen R. Steingart, MD, MPH², John Z. Metcalfe, MD, MPH^{1,2}, Anand Date, MD, MBBS³, Courtney Coleman, MPH³, Barbara J. Marston, MD³, Laurence Huang, MD, MAS^{1,4}, Philip C. Hopewell, MD^{1,2}, and Madhukar Pai, MD, PhD⁵

¹ Division of Pulmonary and Critical Care Medicine, San Francisco General Hospital, University of California, San Francisco, USA

² Curry International Tuberculosis Center, University of California, San Francisco, San Francisco, USA

³ Division of Global HIV/AIDS, Centers for Disease Control and Prevention, Atlanta, USA

⁴ HIV/AIDS Division, San Francisco General Hospital, University of California, San Francisco, San Francisco, USA

⁵ Dept. of Epidemiology, Biostatistics & Occupational Health, McGill University, Montreal, Canada

Abstract

OBJECTIVE—To determine whether interferon-gamma release assays (IGRAs) improve the identification of HIV-infected individuals who could benefit from LTBI 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-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 pre-specified sub-groups 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 3 longitudinal studies, the risk of active TB was higher in HIV-infected individuals with positive versus negative IGRA results. However, the risk difference was not statistically significant in the 2 studies that reported IGRA results according to manufacturer-recommended criteria. In persons with active TB (a surrogate reference standard for LTBI), pooled sensitivity estimates were heterogeneous, but higher for TSPOT (72%, 95% CI 62–81%) than for QFT-GIT (61%, 95% CI

Corresponding Author: Madhukar Pai, MD, Assistant Professor & CIHR New Investigator, McGill University, Department of Epidemiology & Biostatistics, 1020 Pine Ave West, Montreal, QC H3A 1A2, Canada, Tel: 514-398-5422, Fax: 514-398-4503, madhukar.pai@mcgill.ca.

Meetings at which work was presented in part

1. World Health Organization. Guidelines Meeting on Preventive Therapy and Case Finding for TB in People Living with HIV. Geneva, Switzerland, 2010.
2. World Health Organization. Use of Interferon- γ Release Assays in Tuberculosis Control in Low-and Middle-Income Settings. Geneva, Switzerland, 2010.
3. American Thoracic Society International Conference, New Orleans, USA, 2010.

41–75%). However, neither IGRA was consistently more sensitive than the tuberculin skin test (TST) in head-to-head comparisons. While TSPOT appeared to be less affected by immunosuppression than QFT-GIT and TST, overall, differences between the three tests were small or inconclusive.

CONCLUSIONS—Current evidence suggests that IGRAs perform similarly to the TST at identifying HIV-infected individuals with LTBI. Given that both tests have modest predictive value and sub-optimal sensitivity, the decision to use either test should be based on country guidelines and resource and logistical considerations.

Keywords

latent tuberculosis infection; systematic review; interferon-gamma release assay; HIV infection; tuberculin skin test

INTRODUCTION

Tuberculosis (TB) has become the leading cause of death in persons with HIV infection and HIV is a potent risk factor for progression from latent to active TB.¹ Most of the 2 billion people estimated to have latent tuberculosis infection (LTBI) have a 10% lifetime risk of developing active TB. For the 10 million people co-infected with *Mycobacterium tuberculosis* and HIV, the risk of progression to active TB is 10% annually.¹ Administration of isoniazid preventive therapy (IPT) reduces this risk by about 36%; the risk reduction is greatest (approximately 62%) in individuals with a positive tuberculin skin test (TST).² Despite this evidence, IPT is under-used in most high TB burden countries, and TST screening prior to IPT is not considered mandatory in HIV-infected individuals.³ In this context, it is important to 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,^{4, 5} and there is strong evidence in people with and without HIV co-infection that IPT reduces this risk.^{2, 6} However, false positive TST results can occur among persons who have been given the BCG vaccine or who have been exposed to nontuberculous mycobacteria and false negative results can occur in persons with impaired cellular immunity.⁷ Additionally, completing the TST requires two health care visits and measurement of reaction size is subjective.⁸

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 BCG strains and in most nontuberculous mycobacteria.⁹ 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 cross reactivity with the BCG vaccine.^{10–12} 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.^{13, 14}

Search methods

We updated literature searches in previous systematic reviews^{10–12, 15, 16} to identify all studies evaluating IGRAs published through May 2010 (see Text, Supplemental Digital Content 1, for details). 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 non-commercial or older generation IGRAs and IGRAs performed in non-blood specimens; (2) studies focused on the effect of anti-TB treatment on IGRA response; (3) studies including <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 (see Text, Supplemental Digital Content 1, for details).

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. Since 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 (see Figure, Supplemental Digital Content 2, for overview of outcome hierarchy). Of the outcomes shown, we only evaluated the three for which there were relevant data (see Text, Supplemental Digital Content 1, for explicit definitions): 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 2 characteristics that could influence the overall utility of IGRAs in HIV-infected individuals: (1) the proportion of IGRA results that are indeterminate and (2) the impact of CD4+ T-cell 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 (NOS) for longitudinal/cohort studies.¹⁷ For the other primary outcomes, which focus on test accuracy, we used relevant criteria from QUADAS, a validated tool for diagnostic accuracy studies (see Text, Supplemental Digital Content 1, for detailed description).¹⁸

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),¹⁹ 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).²⁰ Third, we calculated pooled estimates using random effects modeling, which provides more conservative estimates than fixed effects modeling when heterogeneity is present.²¹

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 4 studies were available in any subgroup and summarized individual study results when fewer than 4 studies were available. We performed all analyses using STATA 11 (Stata Corporation, College Station, Texas, USA).

RESULTS

Search results

Our search yielded 791 citations (see Figure, Supplemental Digital Content 3, for flow chart). 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 (see Table, Supplemental Digital Content 4, for details of individual studies). 22(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 5 studies. 15(41%) studies had some industry involvement, including donation of test kits (12 studies) and a financial relationship with IGRA manufacturers (3 studies). Results presented below were similar when these studies were excluded.

Risk of progression to active TB

We identified 3 longitudinal studies that evaluated the ability of IGRAs to predict future development of active TB.^{22–24} Based on the Newcastle-Ottawa scale, all 3 studies enrolled a representative sample of patients. However, only 1 study²² had an adequate duration of follow-up (1 year) and no study performed adequate outcome assessment (did not adequately rule-out active TB at baseline or did not adequately evaluate all participants for active TB during follow-up). In addition, all studies had few (<12) incident cases of active TB.

All 3 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% vs. 0%, risk difference 8%, 95% CI –0.7% to +17%, median follow-up 19 months)²² or TSPOT results (10% vs. 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).²³ In the third study, Elliott et al adjusted QFT-GIT results for baseline CD4+ 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 ART initiation.²⁴

Sensitivity in culture-confirmed active TB

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.^{23, 25–37} 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 (see Figure, Supplemental Digital Content 5, for graph of QUADAS scoring).

Low/middle-income countries—Pooled sensitivity estimates were higher for TSPOT (72%, 95% CI 62–81%, 8 studies) than for QFT-GIT (60%, 95% CI 47–75%, 8 studies) (Figure 1A). However, there was significant heterogeneity in the pooled estimates for both IGRAs ($I^2 > 70\%$ and $p < 0.001$). Five studies compared head-to-head the sensitivity of IGRAs and TST for diagnosis of active TB. Compared to TST, TSPOT was more sensitive in 1 study (absolute difference 50%, 95% CI 29–71%),²⁹ less sensitive in 1 study (absolute difference 18%, 95% CI 2–34%),³² and as sensitive in 1 study (absolute difference –3%, 95% CI –17% to +11%).³⁵ Similarly, QFT-GIT was more sensitive than TST in 1 study (absolute difference 41%, 95% CI 22–60%)³⁰ and less sensitive than TST in 1 study (absolute difference 33%, 85% CI 16–51%).³²

High-income countries—Though data were limited, studies from high-income countries reported higher values for sensitivity when compared to the pooled estimates obtained for low/middle-income countries (Figure 1B). In the two available studies, sensitivity was 94% (95% CI 73–100%) for TSPOT²³ and 67% (47–83%) for QFT-GIT.³⁶ The sensitivity of QFT-GIT and TST were similar (–7%, 95% CI –30% to +17%) in the only head-to-head comparison.³⁶

Agreement between IGRA and TST results

Data on agreement (concordance) between TST and IGRA results in HIV-infected individuals being evaluated for LTBI were available for 15 studies.^{29, 34, 38–46} A majority of studies satisfied all QUADAS criteria assessed (see Figure, Supplemental Digital Content 5, for graph of QUADAS scoring).

Low/middle-income—2 of 3 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 4 of 5 studies. Overall, TSPOT and TST results were concordant in 77% (95% CI 67–88%) of cases but there was significant heterogeneity among individual studies ($I^2 63\%$, $p = 0.04$) (see Figure, Supplemental Digital Content 6, for forest plot). There were insufficient studies to calculate pooled estimates for QFT-GIT.

High-income countries (10 studies)—Results were similar in high-income countries, though pooled estimates of concordance were generally higher. 8 of 9 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 6 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 IGRA results

We assessed the proportion of indeterminate IGRA results among healthy HIV-infected individuals screened for LTBI. The proportion of indeterminate results was <5% in 9 of 13 studies evaluating T-SPOT (range 0–13%)^{23, 29, 31, 34, 39, 42–47} and 6 of 10 studies evaluating QFT-GIT (range 2–11%).^{22, 31, 38, 40, 41, 43, 44, 46, 48, 49}

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%, $p=0.42$) (Figure 2A). There were insufficient studies to calculate pooled estimates for QFT-GIT, but the proportion of indeterminate results was <5% in 2 of 3 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%, $p=0.03$) (Figure 2B).

Impact of immunosuppression

In 21 studies, IGRA results were available for at least 5 HIV-infected adults in the following CD4+ cell count strata: <200 and ≥200 cells/ μ l.^{22, 23, 29, 31, 34, 38–48}

Low/middle-income Countries—For TSPOT, the pooled proportion of positive test results was significantly lower when CD4+ T-cell count was <200 cells/ μ l versus ≥200 cells/ μ l (difference –18%, 95% CI –34% to –2%) (Figure 3A). However, the pooled proportion of individuals with indeterminate test results was similar among individuals in the two CD4+ T-cell count strata (4%, –3% to 10%) (Figure 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+ T-cell count was <200 cells/ μ l versus ≥200 cells/ μ l for QFT-GIT (difference –4%, 95% CI –7% to –2%), but not TSPOT (difference –3%, 95% CI –7% to 0%) (Figure 3B). Similarly, the pooled proportion of indeterminate test results was significantly higher when CD4+ T-cell count was <200 cells/ μ l versus ≥200 cells/ μ l for QFT-GIT (difference 9%, 95% CI 3–15%), but not TSPOT (difference 1%, –7% to +9%, $p=0.85$) (Figure 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 4 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+ T-cell count was <200 cells/ μ l was similar to that observed for both IGRAs.^{40, 41, 43, 45}

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 feasible³ to dual testing with TST and IGRAs.^{50, 51} Our systematic review addressed two questions relevant for determining whether IGRAs should replace TST as a screening test for LTBI in 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 co-infected with HIV, do not develop active TB.⁵² The clinical utility 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 3 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. While 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^{23, 24} and differential evaluation and/or follow-up of persons with positive and negative IGRA results.^{22–24} 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 20–60% reduction in the risk of active TB among persons with positive TST results.² 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 one year compared to persons with a negative TST result.^{1, 53} Unfortunately, similar high quality data on the clinical impact and predictive value of IGRA testing are currently lacking. Though 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 (>85%) of IGRA-positive individuals did not progress to active TB.⁵⁴

In spite of the limited data on important outcomes, it has been suggested that IGRAs may have a role for identifying MTB infection in HIV-infected individuals given the sub-optimal performance of TST in immunosuppressed individuals.⁵⁵ 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+ cell counts in whole blood.⁴⁷ 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- and middle-income countries, 2 of 5 studies of TSPOT and 1 of 2 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 vs. high-income settings are unclear but may be related to disease severity and anti-retroviral 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. Though we developed a pre-specified 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 2 strongest outcomes in the hierarchy. In addition, the majority of studies were small (<150 patients in 22 of 37 studies), only 6 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 sub-groups. Secondly, though 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, since 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 sub optimal sensitivity, it would be relevant to evaluate outcomes when both tests are used, either simultaneously or sequentially, for diagnosing LTBI in HIV-infected persons. Though we did not find any studies of a dual testing approach, the most recently updated US national guidelines endorse such an approach. While routine use of dual-testing is not recommended, the 2010 US Centers for Disease Control and Prevention (CDC) guidelines indicate that the results from both tests (IGRA and TST) may be useful in HIV-infected individuals when the initial test is negative.⁵⁰ 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.⁵¹ While 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 (i.e., 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 vs. TST vs. 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 logistical considerations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: This work was supported in part by UNICEF-UNDP-World Bank-WHO Special Programme for Research and Training in Tropical Diseases (TDR), the Stop TB Partnership's New Diagnostics Working Group, the National Institutes of Health (K23HL094141), and the Canadian Institutes for Health Research (MOP-81362 and MOP-89918).

We express our gratitude to all of the authors who responded to our requests for additional data from their studies. The authors have no conflicts of interest to declare. This work was supported in part by UNICEF-UNDP-World Bank-WHO Special Programme for Research and Training in Tropical Diseases (TDR), the Stop TB Partnership's New Diagnostics Working Group, the National Institutes of Health (K23HL094141), and the Canadian Institutes for Health Research (MOP-81362 and MOP-89918). These funding agencies had no role in the preparation or submission of this report.

References

1. Markowitz N, Hansen NI, Hopewell PC, et al. Incidence of tuberculosis in the United States among HIV-infected persons. The Pulmonary Complications of HIV Infection Study Group. *Ann Intern Med.* 1997; 126:123–132. [PubMed: 9005746]
2. Akolo C, Adetifa I, Shepperd S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. *Cochrane Database Syst Rev.* 2010:CD000171. [PubMed: 20091503]
3. World Health Organization. Geneva, Switzerland: 2010. Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. Available at http://whqlibdoc.who.int/publications/2011/9789241500708_eng.pdf
4. Comstock GW. How much isoniazid is needed for prevention of tuberculosis among immunocompetent adults? *Int J Tuberc Lung Dis.* 1999; 3:847–850. [PubMed: 10524579]
5. Golub JE, Pronyk P, Mohapi L, et al. Isoniazid preventive therapy, HAART and tuberculosis risk in HIV-infected adults in South Africa: a prospective cohort. *AIDS.* 2009; 23:631–636. [PubMed: 19525621]
6. Smieja MJ, Marchetti CA, Cook DJ, Smaill FM. Isoniazid for preventing tuberculosis in non-HIV infected persons. *Cochrane Database Syst Rev.* 2000:CD001363. [PubMed: 10796642]
7. Jasmer RM, Nahid P, Hopewell PC. Clinical practice. Latent tuberculosis infection. *N Engl J Med.* 2002; 347:1860–1866. [PubMed: 12466511]
8. Pouchot J, Grasland A, Collet C, Coste J, Esdaile JM, Vinceneux P. Reliability of tuberculin skin test measurement. *Ann Intern Med.* 1997; 126:210–214. [PubMed: 9027271]
9. Pai M, Kalantri S, Dheda K. New tools and emerging technologies for the diagnosis of tuberculosis: part I. Latent tuberculosis. *Expert Rev Mol Diagn.* 2006; 6:413–422. [PubMed: 16706743]
10. Menzies D, Pai M, Comstock G. Meta-analysis: new tests for the diagnosis of latent tuberculosis infection: areas of uncertainty and recommendations for research. *Ann Intern Med.* 2007; 146:340–354. [PubMed: 17339619]
11. Pai M, Riley LW, Colford JM Jr. Interferon-gamma assays in the immunodiagnosis of tuberculosis: a systematic review. *Lancet Infect Dis.* 2004; 4:761–776. [PubMed: 15567126]
12. Pai M, Zwerling A, Menzies D. Systematic review: T-cell-based assays for the diagnosis of latent tuberculosis infection: an update. *Ann Intern Med.* 2008; 149:177–184. [PubMed: 18593687]
13. Deville WL, Buntinx F, Bouter LM, et al. Conducting systematic reviews of diagnostic studies: didactic guidelines. *BMC Med Res Methodol.* 2002; 2:9. [PubMed: 12097142]
14. Leeflang MM, Deeks JJ, Gatsonis C, Bossuyt PM. Systematic reviews of diagnostic test accuracy. *Ann Intern Med.* 2008; 149:889–897. [PubMed: 19075208]
15. Pai M, Menzies D. Interferon-gamma release assays: what is their role in the diagnosis of active tuberculosis? *Clin Infect Dis.* 2007; 44:74–77. [PubMed: 17143819]
16. van Zyl-Smit RN, Zwerling A, Dheda K, Pai M. Within-subject variability of interferon-gamma assay results for tuberculosis and boosting effect of tuberculin skin testing: a systematic review. *PLoS One.* 2009; 4:e8517. [PubMed: 20041113]
17. Wells, GA.; Shea, B.; O'Connell, D., et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. [Accessed March 25, 2010]. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm
18. Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Med Res Methodol.* 2003; 3:25. [PubMed: 14606960]
19. World Bank. Country Classification. [Accessed March 1, 2010]. Available at: <http://www.worldbank.org/>
20. Lijmer JG, Bossuyt PM, Heisterkamp SH. Exploring sources of heterogeneity in systematic reviews of diagnostic tests. *Stat Med.* 2002; 21:1525–1537. [PubMed: 12111918]
21. Rutter CM, Gatsonis CA. A hierarchical regression approach to meta-analysis of diagnostic test accuracy evaluations. *Stat Med.* 2001; 20:2865–2884. [PubMed: 11568945]
22. Aichelburg MC, Rieger A, Breitenacker F, et al. Detection and prediction of active tuberculosis disease by a whole-blood interferon-gamma release assay in HIV-1-infected individuals. *Clin Infect Dis.* 2009; 48:954–962. [PubMed: 19245343]

23. Clark SA, Martin SL, Pozniak A, et al. Tuberculosis antigen-specific immune responses can be detected using enzyme-linked immunospot technology in human immunodeficiency virus (HIV)-1 patients with advanced disease. *Clin Exp Immunol.* 2007; 150:238–244. [PubMed: 17672869]
24. Elliott JH, Vohith K, Saramony S, et al. Immunopathogenesis and diagnosis of tuberculosis and tuberculosis-associated immune reconstitution inflammatory syndrome during early antiretroviral therapy. *J Infect Dis.* 2009; 200:1736–1745. [PubMed: 19874177]
25. Aabye MG, Ravn P, PrayGod G, et al. The impact of HIV infection and CD4 cell count on the performance of an interferon gamma release assay in patients with pulmonary tuberculosis. *PLoS One.* 2009; 4:e4220. [PubMed: 19156218]
26. Baba K, Sornes S, Hoosen AA, et al. Evaluation of immune responses in HIV infected patients with pleural tuberculosis by the QuantiFERON TB-Gold interferon-gamma assay. *BMC Infect Dis.* 2008; 8:35. [PubMed: 18366633]
27. Cattamanchi A, Ssewenyana I, Davis JL, et al. Role of interferon-gamma release assays in the diagnosis of pulmonary tuberculosis in patients with advanced HIV infection. 2010; 10:75.
28. Dheda K, van Zyl-Smit RN, Meldau R, et al. Quantitative lung T cell responses aid the rapid diagnosis of pulmonary tuberculosis. *Thorax.* 2009; 64:847–53. [PubMed: 19592392]
29. Jiang W, Shao L, Zhang Y, et al. High-sensitive and rapid detection of Mycobacterium tuberculosis infection by IFN-gamma release assay among HIV-infected individuals in BCG-vaccinated area. *BMC Immunol.* 2009; 10:31. [PubMed: 19476627]
30. Kabeer BSA, Sikhamani R, Swaminathan S, Perumal V, Paramasivam P, Raja A. Role of interferon gamma release assay in active TB diagnosis among HIV infected individuals. *PLoS One.* 2009:e5718. [PubMed: 19479058]
31. Leidl L, Mayanja-Kizza H, Sotgiu G, et al. Relationship of immunodiagnostic assays for tuberculosis and numbers of circulating CD4+ T-cells in HIV-infection. *Eur Respir J.* 2010; 35:619–626. [PubMed: 19608590]
32. Ling DI, Pai M, Davids V, et al. Incremental Value Of Interferon-Gamma Release Assays For Diagnosis Of Active Tuberculosis In Smear-Negative Patients In A High-Burden Setting: A Multivariable Analysis [Abstract]. *Am J Respir Crit Care Med.* 2010; 181:A2262. American Thoracic Society International Conference; 2010; New Orleans, USA:
33. Markova R, Todorova Y, Drenska R, Elenkov I, Yankova M, Stefanova D. Usefulness of interferon- gamma release assays in the diagnosis of tuberculosis infection in HIV-infected patients in Bulgaria. *Biotechnol & Biotechnol.* 2009; 23:1103–1108.
34. Oni T, Patel J, Gideon HP, et al. Enhanced diagnosis of HIV-1 associated tuberculosis by relating T- SPOT. TB and CD4 counts. *Eur Respir J.* 2010; 36:594–600. [PubMed: 20075047]
35. Rangaka MX, Gideon H, Wilkinson KA, et al. The incremental predictive value of IGRA for smear negative culture positive TB in HIV-infected patients in an ART program who are being screened for preventive therapy in a high-burden TB area. Unpublished.
36. Sauzullo I, Mengoni F, Scrivo R, et al. Evaluation of QuantiFERON-TB Gold In-Tube in HIV infection and in patient candidates for anti-TNF-alpha therapy. *Int J Tuberc Lung Dis.* 2010; 14:834–40. [PubMed: 20550765]
37. Veldsman C, Kock MM, Rossouw T, et al. QuantiFERON-TB GOLD ELISA assay for the detection of Mycobacterium tuberculosis-specific antigens in blood specimens of HIV-positive patients in a high-burden country. *FEMS Immunol Med Microbiol.* 2009; 57:269–73. [PubMed: 19843186]
38. Balcells ME, Perez CM, Chanqueo L, et al. A comparative study of two different methods for the detection of latent tuberculosis in HIV-positive individuals in Chile. *Int J Infect Dis.* 2008; 12:645–652. [PubMed: 18534887]
39. Hoffmann M, Reichmuth M, Fantelli K, et al. Conventional tuberculin skin testing versus T-cell-based assays in the diagnosis of latent tuberculosis infection in HIV-positive patients. *AIDS.* 2007; 21:390–392. [PubMed: 17255757]
40. Jones S, de Gijzel D, Wallach FR, Gurtman AC, Shi Q, Sacks H. Utility of QuantiFERON-TB Gold in-tube testing for latent TB infection in HIV-infected individuals. *Int J Tuberc Lung Dis.* 2007; 11:1190–1195. [PubMed: 17958980]

41. Luetkemeyer AF, Charlebois ED, Flores LL, et al. Comparison of an interferon-gamma release assay with tuberculin skin testing in HIV-infected individuals. *Am J Respir Crit Care Med*. 2007; 175:737–742. [PubMed: 17218620]
42. Mandalakas AM, Hesselning AC, Chegou NN, et al. High level of discordant IGRA results in HIV-infected adults and children. *Int J Tuberc Lung Dis*. 2008; 12:417–423. [PubMed: 18371268]
43. Richeldi L, Losi M, D'Amico R, et al. Performance of tests for latent tuberculosis in different groups of immunocompromised patients. *Chest*. 2009; 136:198–204. [PubMed: 19318676]
44. Rivas I, Latorre I, Sanvisens A, et al. Prospective evaluation of latent tuberculosis with interferon-gamma release assays in drug and alcohol abusers. *Epidemiol Infect*. 2009; 137:1342–1347. [PubMed: 19243652]
45. Stephan C, Wolf T, Goetsch U, et al. Comparing QuantiFERON-tuberculosis gold, T-SPOT tuberculosis and tuberculin skin test in HIV-infected individuals from a low prevalence tuberculosis country. *AIDS*. 2008; 22:2471–2479. [PubMed: 19005270]
46. Talati NJ, Seybold U, Humphrey B, et al. Poor concordance between interferon-gamma release assays and tuberculin skin tests in diagnosis of latent tuberculosis infection among HIV-infected individuals. *BMC Infect Dis*. 2009; 9:15. [PubMed: 19208218]
47. Dheda K, Lalvani A, Miller RF, et al. Performance of a T-cell-based diagnostic test for tuberculosis infection in HIV-infected individuals is independent of CD4 cell count. *AIDS*. 2005; 19:2038–2041. [PubMed: 16260914]
48. Brock I, Ruhwald M, Lundgren B, Westh H, Mathiesen LR, Ravn P. Latent tuberculosis in HIV positive, diagnosed by the M. tuberculosis specific interferon-gamma test. *Respir Res*. 2006; 7:56. [PubMed: 16579856]
49. Garfein RS, Lozada R, Liu L, et al. High prevalence of latent tuberculosis infection among injection drug users in Tijuana, Mexico. *Int J Tuberc Lung Dis*. 2009; 13:626–632. [PubMed: 19383197]
50. Mazurek G, Jereb J, Vernon A, et al. Updated Guidelines for Using Interferon Gamma Release Assays to Detect *Mycobacterium tuberculosis* Infection -United States, 2010. *MMWR*. 2010; 59:RR-5.
51. Canadian Tuberculosis Committee. Updated Recommendations on Interferon Gamma Release Assays for Latent Tuberculosis Infection. *CCDR*. 2010; 36:1–21.
52. Ferebee SH. Controlled chemoprophylaxis trials in tuberculosis. A general review. *Bibl Tuberc*. 1970; 26:28–106. [PubMed: 4903501]
53. Antonucci G, Girardi E, Raviglione MC, Ippolito G. Risk factors for tuberculosis in HIV-infected persons. A prospective cohort study. The Gruppo Italiano di Studio Tubercolosi e AIDS (GISTA). *JAMA*. 1995; 274:143–148. [PubMed: 7596002]
54. Diel R, Goletti D, Ferrara G, et al. Interferon-gamma release assays for the diagnosis of latent M. tuberculosis infection: A systematic review and meta-analysis. *Eur Respir J*. 2010 [Epub ahead of print].
55. Dheda K, Smit RZ, Badri M, Pai M. T-cell interferon-gamma release assays for the rapid immunodiagnosis of tuberculosis: clinical utility in high-burden vs. low-burden settings. *Curr Opin Pulm Med*. 2009; 15:188–200. [PubMed: 19387262]

Figure 1. Sensitivity of IGRAs 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 4 or more studies were available. Abbreviations: IGRAs, interferon-gamma release assay; CI, confidence interval; TSPOT, T-SPOT. *TB*, QFT-GIT, QuantiFERON-Gold In-tube.

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 sub-groups in which 4 or more studies were available.

Abbreviations: IGRA, interferon-gamma release assay; CI, confidence interval; TSPOT, T-SPOT. *TB*, QFT-GIT, QuantiFERON-Gold In-tube.

Figure 3. Impact of CD4+ 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+ cell count > 200 cells/ μ l and CD4+ cell count <100 cells/ μ l obtained from 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; CI, confidence interval; TSPOT, T-SPOT. TB, QFT-GIT, QuantiFERON-Gold In-tube.

* Difference = (% indeterminate CD4 <200 cells/μl) – (% indeterminate CD4 ≥200 cells/μl)

Figure 4. Impact of CD4+ 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+ cell count > 200 cells/μl and CD4+ cell count <100 cells/μl obtained from 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; CI, confidence interval; TSPOT, T-SPOT. TB, QFT-GIT, QuantiFERON-Gold In-tube.