

# Comparison of an Interferon Gamma Release Assay to Conventional Tuberculin Skin Testing for Latent TB Diagnosis in HIV-Infected Individuals

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## Background

- Latent tuberculosis infection (LTBI) detection and treatment are crucial in HIV-infected individuals as they have a higher rate of progression to active TB than HIV-uninfected infected persons, even with the effective use of antiretroviral therapy (ART).
- Recently developed interferon- $\gamma$  release assays (IGRAs) utilizing TB specific antigens, ESAT-6 and CFP-10, have shown promise as alternatives to tuberculin skin testing (TST) for LTBI diagnosis.
- Although the QuantiFERON® IGRA is currently FDA approved for the diagnosis of LTBI, limited data exist regarding its performance in HIV infection.

## Study Objective

To compare of the performance of the QuantiFERON® TB-Gold In-Tube Test (QFT) with conventional tuberculin skin testing for the diagnosis of LTBI in an HIV-infected population

## Methods

### Study Participants

- Adults  $\geq 18$  years old recruited from two established San Francisco cohorts of chronically HIV-infected adults, SCOPE and REACH.
- Excluded if ongoing treatment for TB or LTBI, status as a current TB suspect, prior severe reaction to TST, and current pregnancy

### Study Measurements

#### One Step Tuberculin Skin Testing:

- 5 TU of PPD solution
- Skin tests interpreted between 48-72 hours after placement,
- Blinded calipers used,  $\geq 5$  mm = Positive TST

#### QFT Assay:

- Whole blood collected in 3 QFT tubes:
  - TB antigens (ESAT-6, CFP-10, TB7.7)
  - Negative Control (phytohemagglutinin)
  - Negative Control

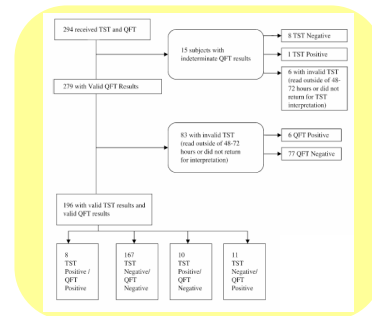
#### ELISA for IFN- $\gamma$ performed:

- Positive Result:** TB Ag- negative control  $\geq 0.35$  IU/ml and  $\geq 25\%$  of negative control
- Negative Result:** TB Ag - negative control  $< 0.35$  IU/ml or  $\geq 0.35$  and  $\geq 25\%$  of negative control
- Indeterminate Result:** Either a) negative control  $\geq 8.0$  IU/mL or b) positive control  $< 0.5$  IU/ml with TB Ag-negative control either  $< 0.35$  IU or  $\geq 0.35$  and  $< 25\%$  of negative control value

- Positive QFT results were repeated in duplicate, using the original sample, in accordance with manufacturer's recommendation.
  - Performed to evaluate how this recommendation would impact QFT results
  - QFT results not reclassified on the basis of duplicate testing, as reclassification only recommended if TB infection not suspected. All subjects were felt to be at risk for LTBI

Demographics	All Subjects n= 294	TST Positive <sup>2</sup> n=19	QFT positive <sup>3</sup> n=25
Age, median (years)	46 (42-51)	47 (42-51)	47.5(44- 50)
Male	229 (78%)	13 (68%)	18 (72%)
Ethnicity			
White	86 (29%)	4 (21%)	4 (16%)
Black	139 (47%)	11 (58%)	11(44%)
Latino	26 (9%)	2 (10.5%)	6 (24%)
Asian/Pacific Islander	12 (4%)	2 (10.5%)	1(4%)
Other	31 (11%)	0	3 (12%)
Homeless in past year	52 (18%)	4 (21%)	4 (16%)
History of IDU (lifetime)	108 (37%)	6 (32%)	8 (32%)
<b>HIV related factors</b>			
Median CD4 <sup>+</sup> cell count (IQR)	363 (214-581)	551(296 - 768)*	438 (351 - 596)
CD4 <sup>+</sup> cell count by strata			
$< 100$ cells/mm <sup>3</sup>	31 (10.5%)	0	0
100- 350 cells/mm <sup>3</sup>	111 (37.8%)	7 (37%)	6 (24%)
$> 350$ cells/mm <sup>3</sup>	152 (51.7%)	12 (63%)	19 (76%)
Median CD4 <sup>+</sup> nadir (IQR)	132 (60-273)	209(156 - 428)**	186(92-273)
Median log <sub>10</sub> HIV RNA	2.42 (2.03- 4.37)	2.47 (2.03-3.76)	2.2 (2.03-3.56)
HIV RNA $< 75$ copies/ml	131(45%)	7 (58%)	12 (48%)
On ART, at enrollment	202 (69%)	9 (75%)	15 (60%)
<b>Tuberculosis history</b>			
Previous TST performed	273 (93%)	18 (95%)	23(92%)
Previous positive TST	44 (15%)	12 (63%)**	11 (44%)*
Prior LTBI treatment	36 (12%)	12 (63%)**	9 (36%)*
Prior active tuberculosis	4 (1%)	1 (5%)	3 (12%)*
Self-reported BCG vaccination	18 (6%)	1 (5%)	0
<b>Risk factors for TB Infection</b>			
Lived or worked in homeless shelter, prison, hospital, or drug rehabilitation unit	142 (48%)	14 (74%)*	11 (44%)
Born in high TB incidence country <sup>1</sup>	13 (4%)	1 (5%)	3 (12%)
Self-reported contact with active TB case	37 (13%)	1 (5%)	2 (8%)
Any of the above risk factors for TB Infection	162 (55%)	14 (74%)	14 (56%)

## Results



### QFT Results by CD4+ Cell Count Strata (n=294)

QFT Positive	CD4 <sup>+</sup> cells/mm <sup>3</sup>			Total
	$< 100$	100-350	$> 350$	
QFT Positive	0	6 (5.4%)	19 (12.5%)	25 (8.5%)
QFT Negative	26 (83.9%)	101 (91%)	127 (83.6%)	254 (86.4%)
Indeterminate	5 (16.1%)	4 (3.6%)	6 (3.9%)	15 (5.1%)
	31	111	152	294

$p=0.007$ , Fisher's Exact test

### TST Results by CD4+ Cell Count Strata (n=205)

TST Positive	CD4 <sup>+</sup> cells/mm <sup>3</sup>			Total
	$< 100$	100-350	$> 350$	
TST Positive	0	7 (8.4%)	12 (11.9%)	19 (9.3%)
TST Negative	21	76 (91.6%)	89 (88.1%)	186 (90.7%)
	21	83	101	205

$p=0.098$ , test for trend

- Overall agreement of TST and QFT: 89.3% (kappa 0.37,  $p=0.001$ )
  - 85.2% concordant in negative results (TST-/QFT-)
  - 4.1% concordant in positive results (TST+/QFT+)
  - 8/29 (28%) with a positive result on either QFT or TST had a positive result on both tests
- 5.6% with TST-/QFT+
  - More likely to have been born in a country with high TB prevalence, compared with TST-/QFT- OR 5.1 (95% CI 1.2- 21.7,  $p=0.3$ )
- 5.1% with TST+/QFT-
  - Only 1 out of 10 TST+/QFT- with history of BCG vaccination
  - 6/10 with prior reactive TSTs, all with subsequent INH therapy
- Indeterminate QFT results in 5.1% of subjects
  - All indeterminate results due to a failure to respond to the positive control, rather than elevated negative control IFN- $\gamma$  levels.
  - 16.1% of subjects with CD4<sup>+</sup> cell counts  $< 100$  cells/mm<sup>3</sup> had indeterminate results
  - RR of indeterminate result 4.24 (95%CI, 1.55-11.61,  $p=0.0003$ ) for CD4<sup>+</sup>  $< 100$  cells/mm<sup>3</sup>
- Repeat duplicate testing of positive QFT results:
  - 5/25 (20%): both repeat tests negative
  - 3/25 (12%): one repeat test negative
  - 17/25 (68%): both repeat test positive

## Conclusions

- Overall agreement between TST and QFT was high and similar to that reported in immunocompetent populations
- Low concordance in subjects with positive test results on either assay raises question of whether QFT should be used in conjunction with TST, rather than instead of TST, for LTBI diagnosis in HIV infection
- Elevated rate of indeterminate QFT results in subjects with low CD4<sup>+</sup> cell counts may limit utility of QFT testing in advanced HIV disease
- Intra-assay variability should be explored further