

# Poor Concordance between Interferon- $\gamma$ Release Assays (IGRAs) and Tuberculin Skin Test (TST) in the Diagnosis of Latent Tuberculosis Infection (LTBI) among HIV-Infected Individuals

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# Diagnosis of Latent Tuberculosis Infection in HIV+ individuals

- HIV+ patients with LTBI have ~10% per year risk of progressing to active TB
- TST has a number of limitations including **false positive tests** (cross reactions with BCG, NTM), **false negative tests** (due to anergy), and **2 visits to complete the test**
- **IGRA:** New generation of diagnostic tests for LTBI that measure interferon- $\gamma$  release from activated T-cells in response to TB specific antigens (ESAT6, CFP10)
  - **QuantiFERON-TB Gold in Tube (QFT-3G)**
  - **T-SPOT.TB (TSPOT)**

# Performance of IGRAs in Persons with Impaired Immune Systems, Including HIV/AIDS

- There is inadequate data on the utility of IGRAs in HIV+ and other immunocompromised patient populations **(MMWR 2005; 54[RR15]:49-55)**
- Limitations of published studies include:
  - Small sample size
  - CD4 counts not performed in all studies
  - Few published studies comparing TST, QFT-3G and TSPOT

# Specific Aims

- Describe the prevalence of LTBI in HIV + individuals using three different tests TST, QFT-3G, and TSPOT
- Describe the agreement between the 3 diagnostic tests for LTBI
- Describe the risk factors associated with an indeterminate test result
- Assess the utility of IGRA tests in HIV+ patients

# Methods

## Study Population

- HIV+ individuals enrolled, 2 urban HIV Clinics in Atlanta
- June 2004 - June 2006

## LTBI Diagnostic Tests

- TST placed using Mantoux method; read at 48 -72 hours
- Blood drawn for QFT-3G in all patients (n=692) and TSPOT in patients enrolled after Sept 2005 (n=338)
- Tests performed per manufacturer's instructions
- Criteria for **positive test** result
  - QFT-3G  $\geq 0.35$  IU/ml (IFN- $\gamma$ )
  - TSPOT  $\geq 6$  spot forming cells or  $> 2 \times$  neg control
  - TST  $\geq 5$ mm of induration

# Methods

## Medical Records

- Reviewed and data abstracted

## Data analysis:

- SAS 9.1 (SAS Inc., Cary, N.C.)
  - Univariate and multivariate analysis
- $\kappa$ -statistic used to assess concordance
  - $\kappa > 0.75$  excellent agreement
  - $\kappa 0.4 - 0.75$  fair to good agreement
  - $\kappa < 0.4$  poor agreement

# RESULTS: Demographic Characteristics (n=692)

<b>Patient characteristic</b>	<b>Number (%)</b>
Mean Age	42 ( <b>22-79 years</b> )
Male	477 ( <b>69%</b> )
African American	549 ( <b>79%</b> )
History of BCG	50 ( <b>7%</b> )
Foreign born	61 ( <b>9%</b> )
On antiretroviral therapy	477 ( <b>69%</b> )
Median HIV viral load	400 ( <b>&lt;50 - &gt;750,000 copies/ml</b> )
Mean CD4 count	351 ( <b>0-1380/<math>\mu</math>l</b> )

# Prevalence of a Positive Diagnostic Test for LTBI: TST and QFT-3G (n=692)

<u>Test for LTBI</u>	<u>+ Test</u>	<u>Prevalence</u>
TST	19/692	2.8%
QFT-3G	32/692	4.6%
At least one + test	47/692	6.8%

- Only 4 patients had both tests positive.

# Prevalence of a Positive Diagnostic Test for LTBI (n= 338)

<u>Test for LTBI</u>	<u>+ Test</u>	<u>Prevalence</u>
TST	7/338	2.1%
QFT-3G	10/338	3%
TSPOT	14/338	4.2%
At least one + test	27/338	8%

- Only 1 patient was positive for all 3 tests
- Only 3 patients had >1 test positive

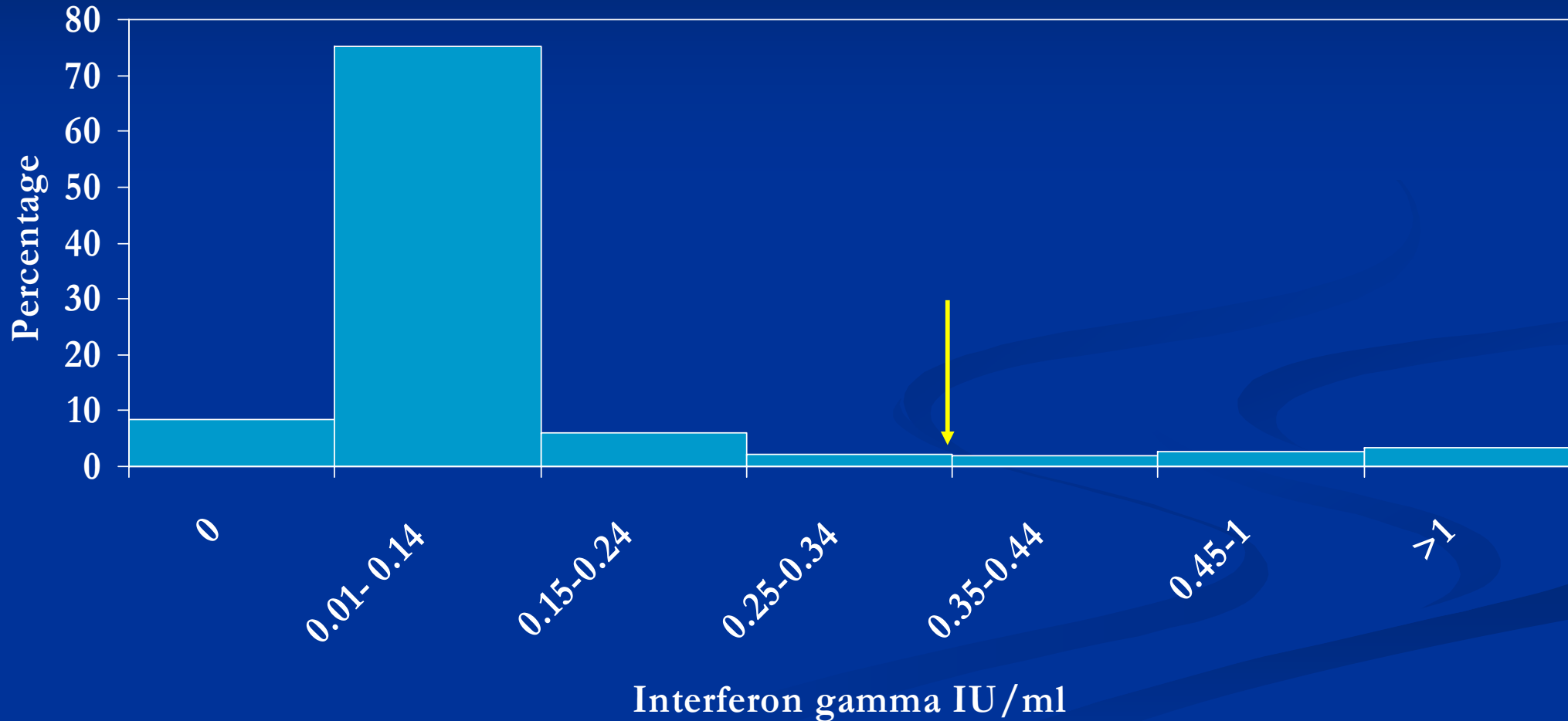
# Concordance between TST and QFT-3G

	QFT + n = 26	QFT -	QFT indeterminate
TST + n = 19	4	13	2
TST -	22	504	24

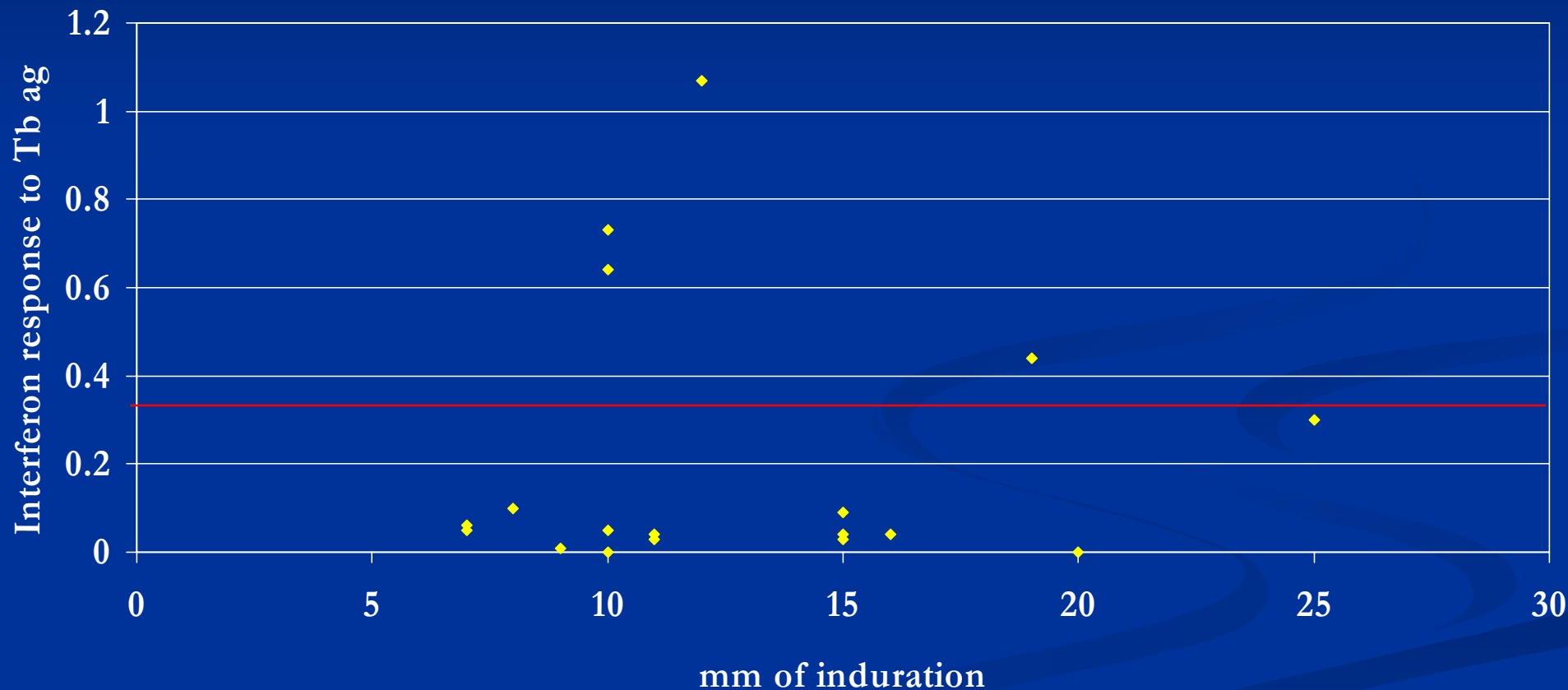
$\kappa = 0.12$ , 95% CI -0.01 - 0.26 [poor concordance]

\* 122 patients did not return to have the TST read

# Interferon- $\gamma$ response: QFT-3G (n=692)



# Comparison of amount of interferon released with QFT to mm of induration with TST in patients with a positive TST n=19



# Concordance between TST and TSPOT (n=338)

	TSPOT + n = 12	TSPOT -	TSPOT indeterminate
TST + n = 7	2	4	1
TST -	10	219	42

$\kappa = 0.2$ , 95% CI -0.06-0.46 [poor concordance]

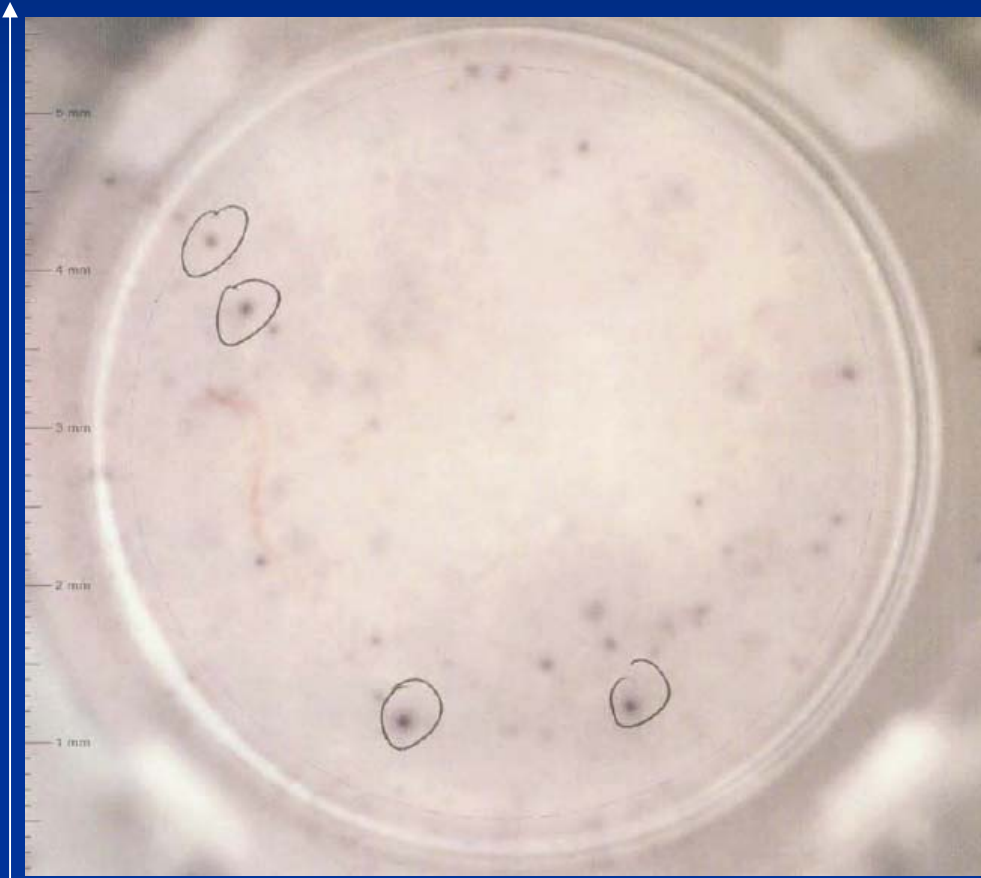
\* 58 patients did not return to have their TST read

# Concordance between TSPOT and QFT-3G (n=338)

	TSPOT + n=14	TSPOT -	TSPOT indeterminate
QFT + n=10	1	7	2
QFT -	13	264	44
QFT indeterminate	0	4	1

$\kappa = 0.05$ , 95% CI -0.10-0.20 [poor concordance]

# Comparison of TSPOT results with ELISPOT reader vs Visual exam



- 31 patients tested + by visual exam
- 14 patients tested + using Elispot reader
- $\kappa = 0.57$ , 95% CI 0.47-0.68
- moderate concordance

# Indeterminate Result with QFT-3G and TSPOT

- **“Indeterminate” test result**
  - Inadequate interferon- $\gamma$  response to positive control (PHA/mitogen) due to anergy
  - Excessive interferon- $\gamma$  in the negative control
  - Insufficient cells 250,000 cells/100  $\mu$ l (Only for TSPOT)
- **32 (4.6%) patients had an indeterminate QFT-3G**
  - All had an inadequate interferon- $\gamma$  response to + control
- **47 (14%) patients had an indeterminate TSPOT**
  - 28 inadequate response to positive control
  - 14 had insufficient cells
  - 5 had excess interferon- $\gamma$  in the negative control

# Multivariate analysis: Indeterminate result

Test	Variable	Odds Ratio	95% CI	P value
<b>QFT-3G</b>	CD4 $\leq$ 200	3.4	1.5 - 7.7	0.004
<b>TSPOT</b>	CD4 $\leq$ 200	3.9	1.8 - 8.1	0.0004

The model included: age, sex, race, HIV viral load, and CD4 count

# Summary

- The prevalence of a positive test for LTBI was low as measured by each of the tests
  - TST 2.8%, QFT-3G 4.6% (n=692)
  - TST 2.1%, QFT-3G 3%, TSPOT 4.2% (n=338)
- There was poor concordance, between the 3 tests
  - TST vs QFT-3G  $\kappa=0.12$ , TST vs TSPOT  $\kappa=0.2$ , QFT-3G vs TSPOT  $\kappa=0.05$
- In multivariate analysis, patients with a CD4 count  $\leq 200$  were more likely to have an indeterminate test result
  - QFT-3G OR=3.4, TSPOT OR=3.9

# Conclusions

- **Poor concordance between diagnostic tests for LTBI among HIV+ persons** raises concerns about the utility of IGRAs among HIV+ individuals
- **Indeterminate results** were more likely to occur at  $CD4 \leq 200$
- **Further studies needed to assess the utility of IGRAs in immunosuppressed persons (especially HIV+ individuals)** particularly in high TB prevalence areas

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**Questions?**