No discriminatory value of interferon gamma release assay added to clinical algorithms to detect smear-negative TB in HIV-infected patients

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No discriminatory value of interferon release added to smear negative HIV-tuberculosis algorithms
Rangaka M.X, Gideon H.P, Wilkinson K.A, Pai M, Mwansa-Kambafilwe J, Maartens G, Glynn J.R, Boulle A, Fielding A, Goliath R, Titus R, Mathee S, Wilkinson RJ. ERJ 2012; 39:163-171

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Centre for Infectious Disease Epidemiology and Research

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CLINICAL INFECTIOUS DISEASES RESEARCH INITIATIVE

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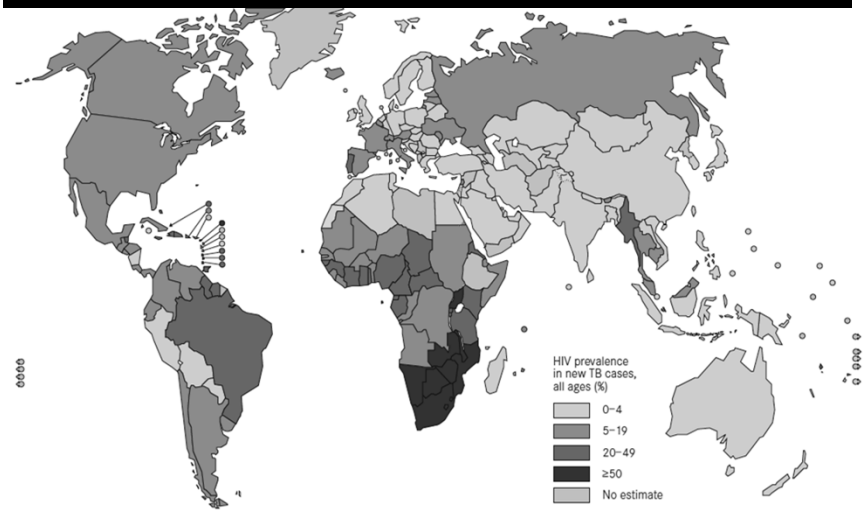
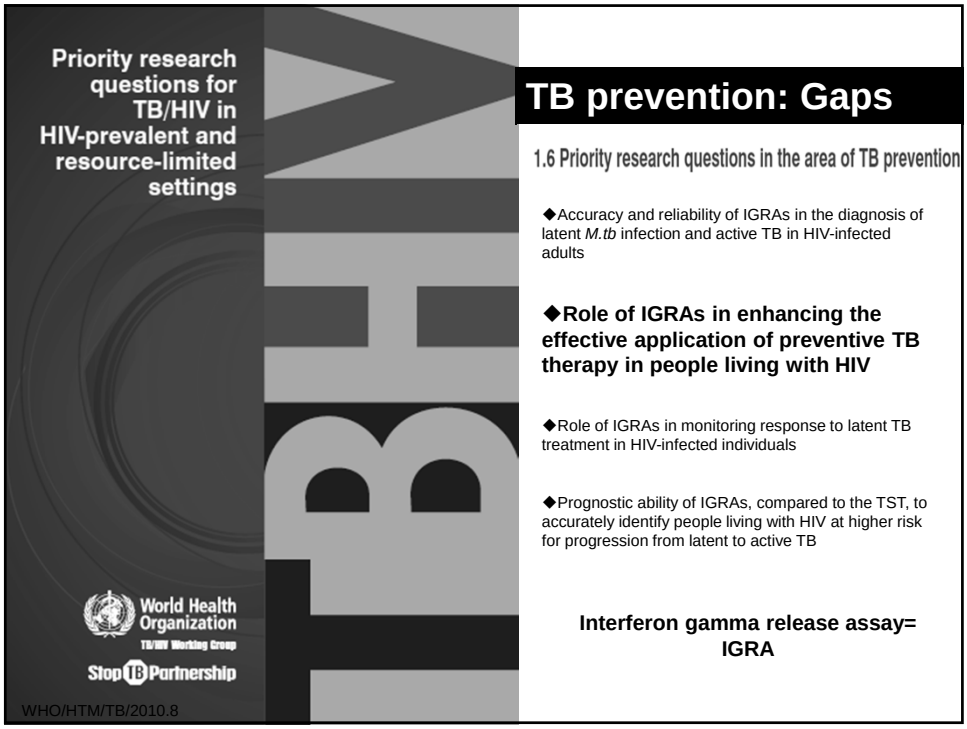
Estimated HIV prevalence in TB Cases



>50% HIV prevalence in new TB cases

WHO 2011 Global TB Report



The Big Question

Does QuantiFERON Gold In tube add to current clinical algorithms to detect smear negative TB in HIV-infected patients screened for preventive therapy?

Flow into the study (STARD-standards for reporting diagnostic accuracy studies)

Study Design: Cross-sectional evaluation of QFT-IT amongst HIV-infected
Eligibility: No exclusions except-should return to TST read

Individual Symptoms and Signs (S+S): cough, fever, N/S, LoW
1 X Culture (Spp. ID)=**reference standard**
QuantiFERON Gold-IT and TST
(Tests done regardless of TB S +S)

Baseline Screening

Eligible participants (Nov 07- Sept 09)
N=1686

Failed sputum induction=111
Sputum culture unavailable=92
Contaminated=70
Non-tuberculous mycobacteria (NTM)= 8

Reference standard available (Sputum culture)
N=1405

Missing both IGRA and TST results= 373
Missing TST alone; did not return for reading=193
Missing IGRA alone; sample not processed/not received=55

Smear positives=19

Smear negative with both TST and QFT-IT available
N=779

Assessing discriminatory value: Model Steps

Potential Predictors (pre-determined)	Clinical: Age, Gender, Weight, ART status, Prior TB, TB Symptoms and signs (any one TB symptom or sign positive), CD4+ count Simple test of TB infection: TST (5mm cutoff) More complex: QFT-IT (Standard Manufacturer's cutoffs used)	
Model Step 1 Identify best clinical model	•Multivariable logistic regression •Fit all clinical *a priori* determined predictors; sequentially in the manner collected at the first clinical visit •Stepwise selection & clinical judgement	
Model Step 2 Add simple test	Add TST (5mm cutoff)	
Model Step 3 Add complex test	Add QFT-IT (Standard Manufacturer's cutoffs used)	
Model Step 4 Both tests added	Add TST & QFT-IT	**Discriminatory Ability**

Assessing Discrimination

Discrimination: Ability of tests to classify those with active TB *and* those without- *do patients with the outcome have higher risk predictions than those without?*

Added or incremental value: Ability of new test to classify those with and without disease over and beyond existing tools

Many options, incl:

1. Area Under the Curve (AUC or **c**oncordance-statistic or ROC curve)
1. Discrimination Slope
1. Risk Reclassification: Reclassification table, Net Reclassification Index (NRI), Integrated discrimination Index
1. Decision curve analysis (to assess net clinical benefit)

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The Area Under the Curve

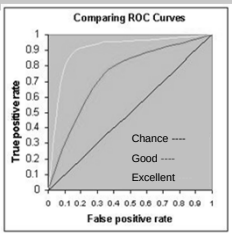
AUC (c-statistic):

-True Positive Rate (Sensitivity) vs. False Positive Rate (1-Specificity)

- For a binary prediction outcome (diseased or not diseased)

- Rank-order statistic (e.g Wilcoxon Rank Sum)

- All cutoffs for the probability of an outcome considered



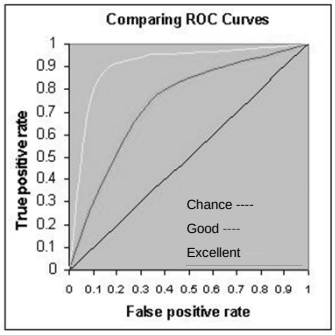
The Area Under the Curve

AUC (c-statistic):

-Interpreted for all diseased and non-diseased pairs: Overall probability that diseased individuals will score higher than non-diseased*

- AUC comparison of model with and without new test is of interest (added value)

- Main criticism: New predictor or marker has to be strongly associated with disease outcome to add value over and beyond existing tools



Reference test Test under assessment	Reference test: Culture	
	(D+)	(D-)
(T+)	True Positive	False Positive
(T-)	False Negative	True Negative

Interpretation:
Overall probability (averaged for all pairs)
AUC ~ 0.50= not better than chance

Net Reclassification Index (NRI)

NRI:

- Novel risk reclassification method; extension of risk reclassification tables

-Can examine how individual patients' risk are reclassified when a new test is added

- Requires knowledge of clinically relevant risk categories (e.g 10-year cardiovascular disease risk-Framingham risk score)

10-year cardiovascular risk
<5%
5-10%
10-20%
>20%

Net Reclassification Index (NRI)

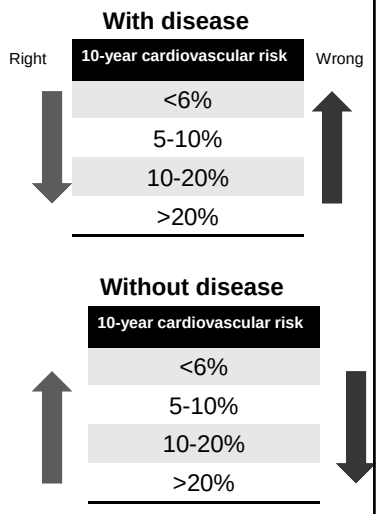
NRI

-must draw a reclassification matrix:is a cross-tabulation of risk classifications from model with new test added against one without

- cross-tabulations drawn for subset with disease and without disease (ie conditioned on outcome)

- NRI is a net calculation of changes in the right direction in the subset with disease and without disease

- Main criticism: Consensus clinically relevant risk categories are not available in ID; may tend to be arbitrary



Net Reclassification Index (NRI)

Table II. Reclassification among people who experience a CHD event and those who do not experience a CHD event on follow-up.

Model without HDL	Model with HDL			
Frequency (Row per cent)	<6 per cent	6–20 per cent	>20 per cent	Total
Participants who experience a CHD Event				
<6 per cent	39 (72.22)	15 (27.78)	0 (0.00)	54
6–20 per cent	4 (3.81)	87 (82.86)	14 (13.33)	105
>20 per cent	0 (0.00)	3 (12.50)	21 (87.50)	24
Total	43	105	35	183
Participants who do not experience a CHD Event				
<6 per cent	1959 (93.24)	142 (6.76)	0 (0.00)	2101
6–20 per cent	148 (16.78)	703 (79.71)	31 (3.51)	882
>20 per cent	1 (1.02)	25 (25.51)	72 (73.47)	98
Total	2108	870	103	3081

STATISTICS IN MEDICINE
Statist. Med. 2008; **27**:157–172
Published online 13 June 2007 in Wiley InterScience
(www.interscience.wiley.com) DOI: 10.1002/sim.2929

Evaluating the added predictive ability of a new marker: From area under the ROC curve to reclassification and beyond

Michael J. Pencina[1,*,†], Ralph B. D'Agostino Sr[1], Ralph B. D'Agostino Jr[2] and Ramachandran S. Vasan[3]

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Description of cohort by *M.tb* culture status: Clinical Observations

Total N=779
(Prevalence of smear negative TB= 6%)

Clinical and Laboratory Features	50 TB culture positive	729 TB culture negative	p-value
Clinical Observations			
Median Age (IQR)	35 (31-40)	36 (31-42)	0.71
Age ≥ 35 y.o	46%	45%	0.92
Male	68%	75%	0.25
No Prior TB	82%	62%	0.004
Median CD4+ count (IQR)	169 (98-239)	198 (136-315)	0.03
CD4 less 250	80%	66% (721)	0.05
Median Weight Kg (IQR)	60 (54-65)	66 (58-76)	<0.001
Weight less than 60kg	52%	33% (722)	0.01
Not on ART at screening	54%	34%	0.004

Description of cohort by *M.tb* culture status: TB symptoms and signs

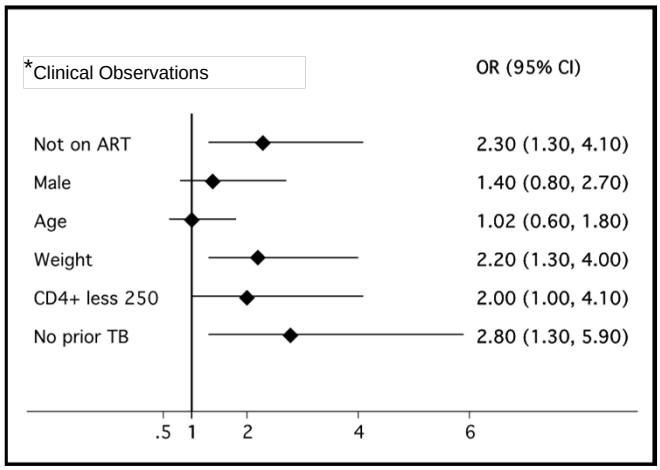
Clinical and Laboratory Features	50 TB culture positive	729 TB culture negative	p-value
Symptoms and signs of TB			
Cough ≥ two weeks	10%	4% (728)	0.05
Night sweats	10%	2% (728)	0.002
Self-reported 'Fever'	1/49	3/727	0.230 (exact)
Nodes on examination	1/49	1/728	0.122 (exact)
Loss of weight	18%	5% (728)	<0.0001
Any one TB symptom or sign positive	26%	8% (728)	<0.0001

*Anyone symptom or sign positive: Cough for >=2 weeks vs. Cough for any duration

Description of cohort by *M.tb* culture status: Tests of TB infection

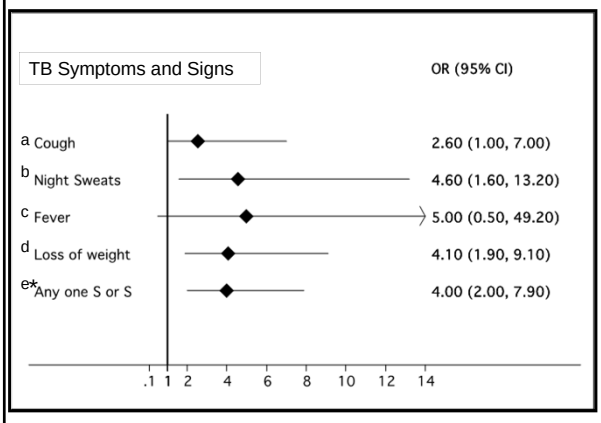
Clinical and Laboratory Features	50 TB culture positive	729 TB culture negative	p-value
Tests of TB infection			
TST positive at 5mm cut-off	68%	41%	<0.0001
TST positive at 10mm cut-off	66%	37%	<0.0001
TST positive at 15mm cut-off	54%	26%	<0.0001
Median TST mm (IQR)	15 (0-20)	0 (0-15)	<0.0001
(Manufacturer's cutoffs) QFT positive	64%	41%	0.004 (exact)
QFT negative	30%	53%	
QFT Indeterminate	6%	7%	
Median QFT quantitative (IQR)	0.5 (0.1-2.6)	0.12 (0-0.85)	0.003
Either TST 5mm/IGRA positive (Indeterminate included with negatives)	80%	56%	0.001
Either TST 5mm/IGRA positive (Indeterminate results excluded)	83% (48)	59% (692)	0.001

Univariable predictors of culture-positive TB disease



*Age>=35y.o, Weight less than 60kg

Univariate predictors of culture-positive TB disease



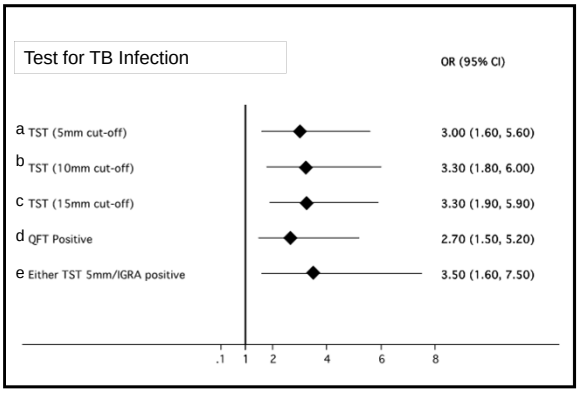
Test Accuracy

	Sensitivity	Specificity	Post-test Pr (Neg)	AUC
a	10	96	5.7	53
b	10	98	5.7	54
c	2	100	5.7	51
d	18	95	5.7	57
e	26	92	4.8	59

Pre-test probability (Prevalence): 6%

*Anyone symptom or sign positive: Includes Nodes and Cough for >=2 weeks

Univariable predictors of culture-positive TB disease

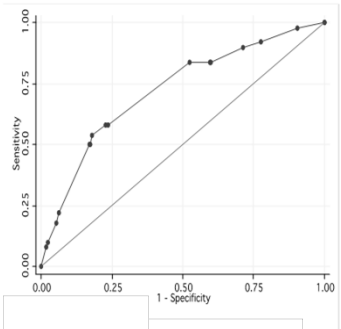


Test Accuracy

	Sensitivity	Specificity	Post-test Pr (Neg)	AUC
a	68	59	3	63
b	66	63	3	64
c	54	74	4	64
d	68	56	4	62
e	83	41	3	62

Pre-test probability (Prevalence): 6%

Discriminatory ability of TB tests (Multivariable Analyses)

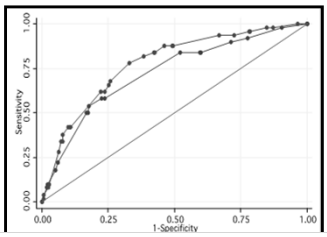


AUC=72%

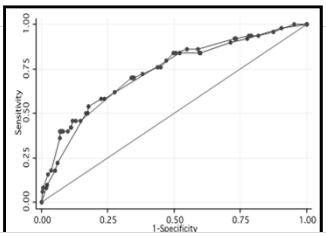
Final clinical model

1. Weight less than 60kg, OR=2
2. No prior TB, OR=3
3. Any one TB S/S positive, OR=3
4. CD4+ less than 250 cells/mm^3 OR=2
5. Not on ART at screening OR=1.2

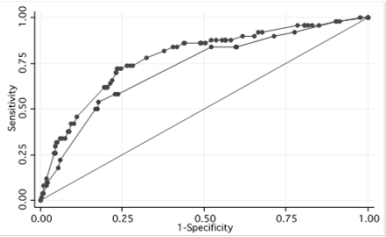
Discriminatory ability of TB tests (Multivariable Analyses)



Clinical **(blue, AUC=72%)** AND TST at 5mm **(red, AUC=77%)**
Comparison p-value=0.03



Clinical **(blue, AUC=72%)** AND QFT **(red, AUC=74%)**
Comparison p-value=0.41

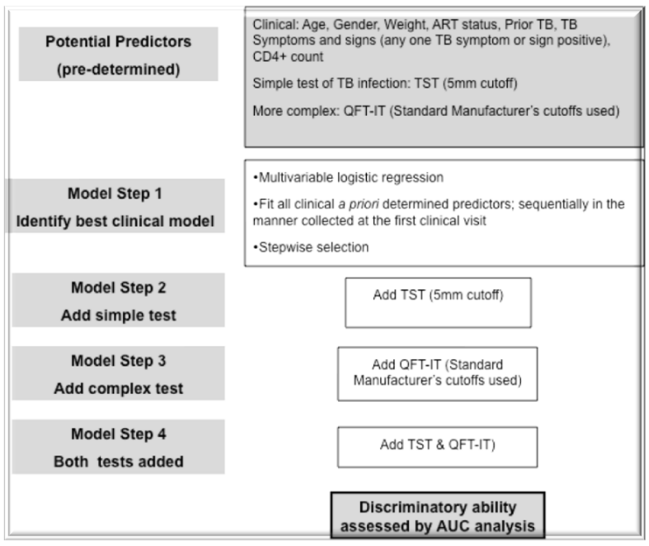


Clinical **(blue, AUC=72%)** and both TST & QFT **(red, AUC=78%)**
Comparison p-value=0.01

Summary

- High prevalence of smear negative culture-positive TB in HIV- infected patients on or starting ART screened for IPT
- Asymptomatic culture-positive TB a concern
- As stand-alone tests, current TB screening tools perform poorly against culture. Best to combine in clinical prediction rule
- QuantiFERON Gold *In Tube*, measuring interferon-gamma, adds little to TB screening tools for evaluating HIV-infected adults for IPT

Assessing discriminatory value: Lessons learnt



***A priori* selection of predictors N.B; clinical judgment**

Small number of predictors: limit over-fitting

Multivariable model set up to 'mimic' clinical set up: correct order is N.B

N.B to use an objective measure of discrimination like AUC

All probability cutoffs considered with AUC

But AUC insensitive to model changes: risk stratification may be better (?)

Risk prediction models in ID are context specific

Eur Respir J 2012; 39: 163–171
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Interferon release does not add discriminatory value to smear-negative HIV–tuberculosis algorithms

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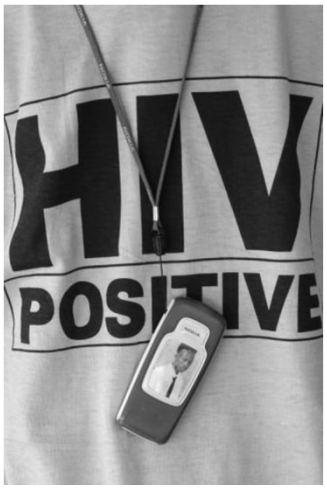

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