Discriminatory value of tuberculin skin test and 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
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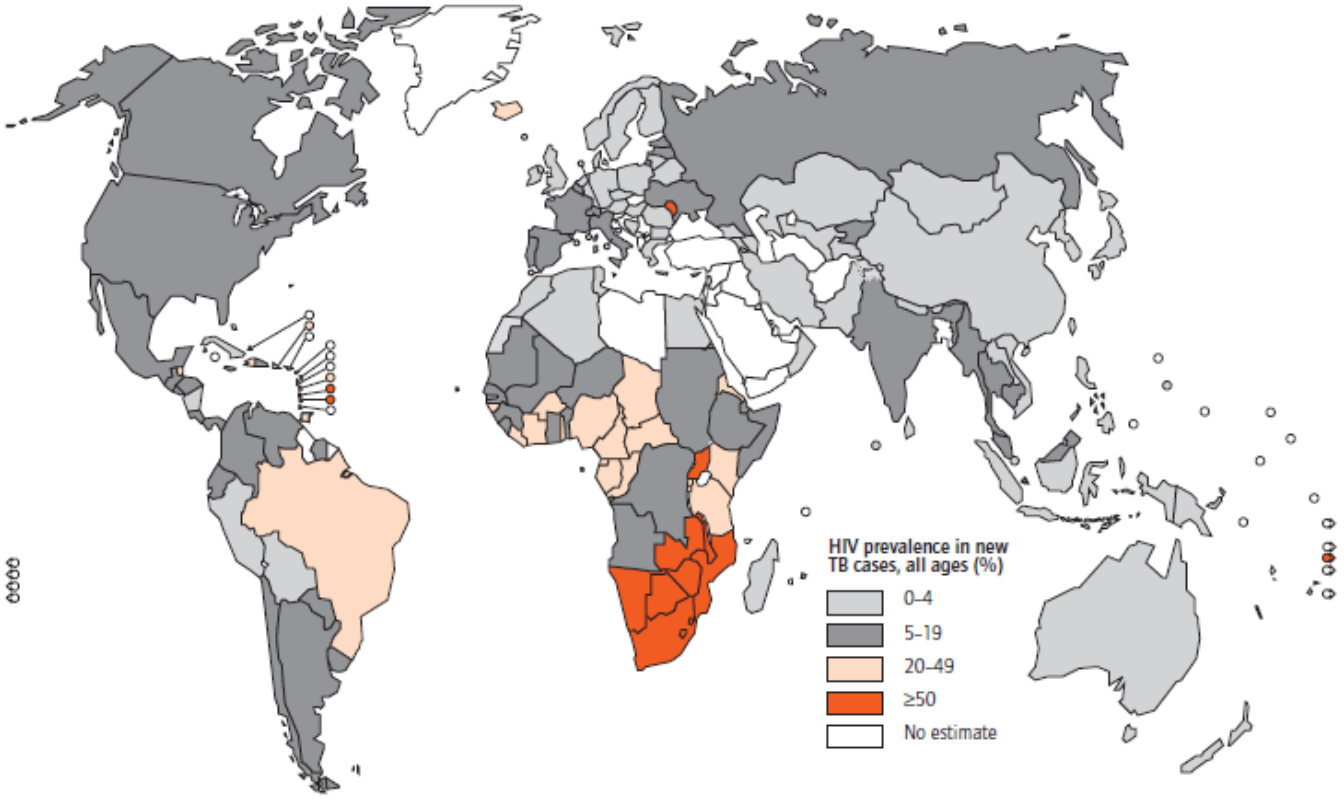
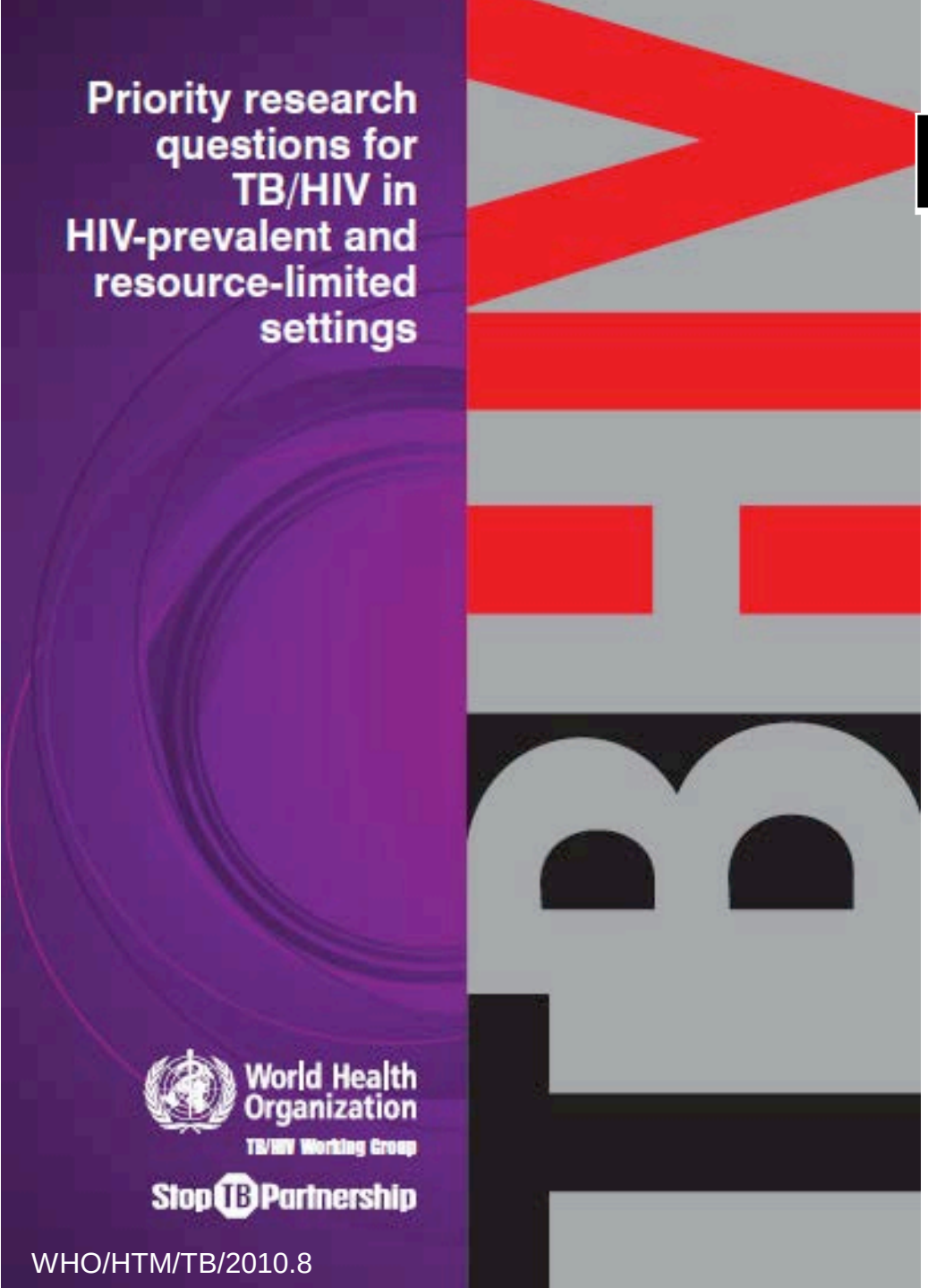
Estimated HIV prevalence in TB Cases



>50% HIV prevalence in new TB cases

WHO 2009 Global TB Report



TB prevention: Gaps

1.6 Priority research questions in the area of TB prevention

- Accuracy and reliability of IGRAs in the diagnosis of latent *M.tb* infection and active TB in HIV-infected adults

- **Role of IGRAs in enhancing the effective application of preventive TB therapy in people living with HIV**

- Role of IGRAs in monitoring response to latent TB treatment in HIV-infected individuals

- Prognostic ability of IGRAs, compared to the TST, to accurately identify people living with HIV at higher risk for progression from latent to active TB

The Big Question

Does QuantiFERON Gold In tube add to current clinical algorithms to detect smear negative tuberculosis in HIV-infected patients?


2 Nights, 5 stages, over 40 local & International artists!
12th
CAPE TOWN INTERNATIONAL
JAZZ FESTIVAL
"Africa's grandest gathering!"
Free Concert
Music Workshops
Arts Journalism
DuoTone Photo Exhibition
Masterclasses
Gigs for Kids
Golf Day
25 & 26 March 2011
Cape Town International Convention Centre
www.capetownjazzfest.com
RITEK
arts and culture
espafrika
www.southafrica.net

Courtesy, Dr E du Toit

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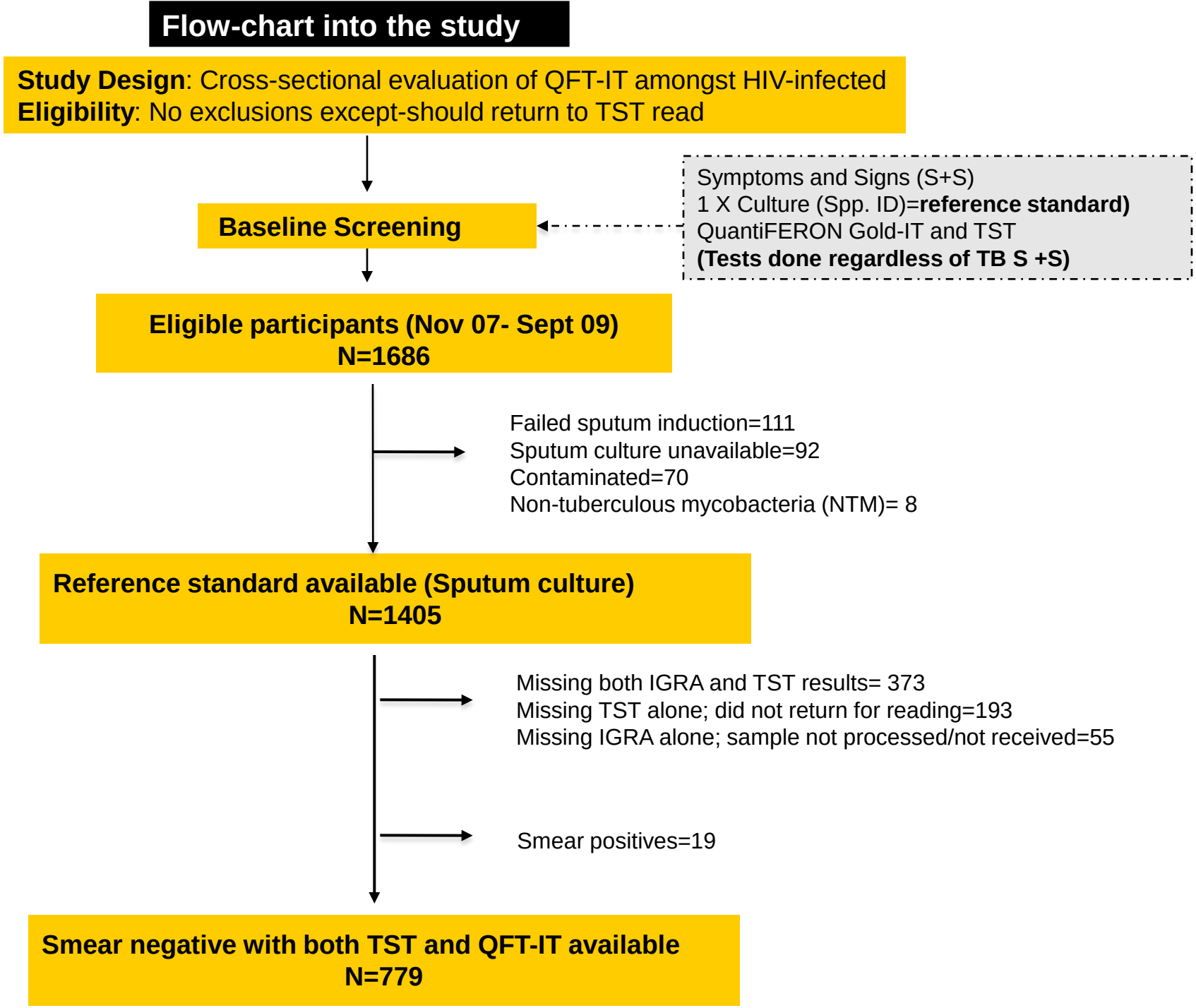

Flow-chart into the study
Study Design: Cross-sectional evaluation of QFT-IT amongst HIV-infected
Eligibility: No exclusions except-should return to TST read
Baseline Screening
Symptoms and Signs (S+S)
1 X Culture (Spp. ID)=reference standard)
QuantiFERON Gold-IT and TST
(Tests done regardless of TB S +S)
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 assessed by AUC analysis

The Area Under the Curve

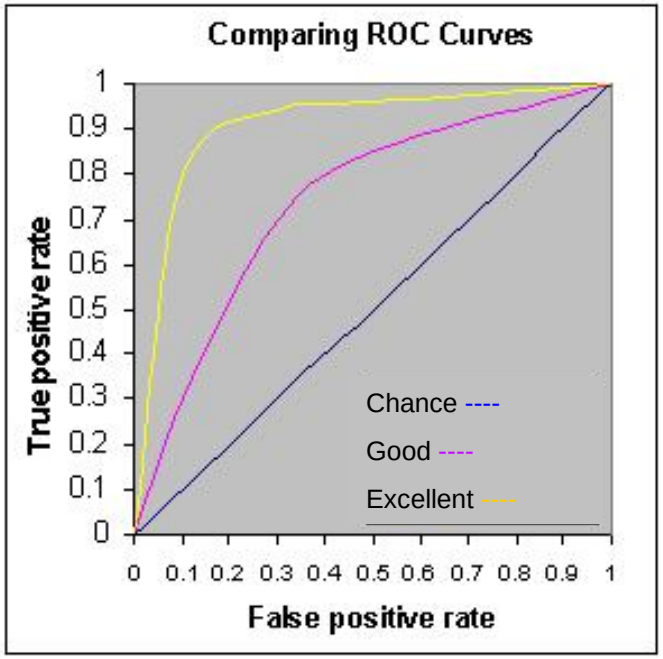
Discriminatory ability of tests to classify those with active TB *and* those without via **AUC analysis:**

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

-Overall probability that diseased individuals will score higher than non-diseased

- No arbitrary risk probability cutoffs

-AUC comparison between models



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

Interpretation:
Overall probability
AUC ~ 0.50= not better than chance

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

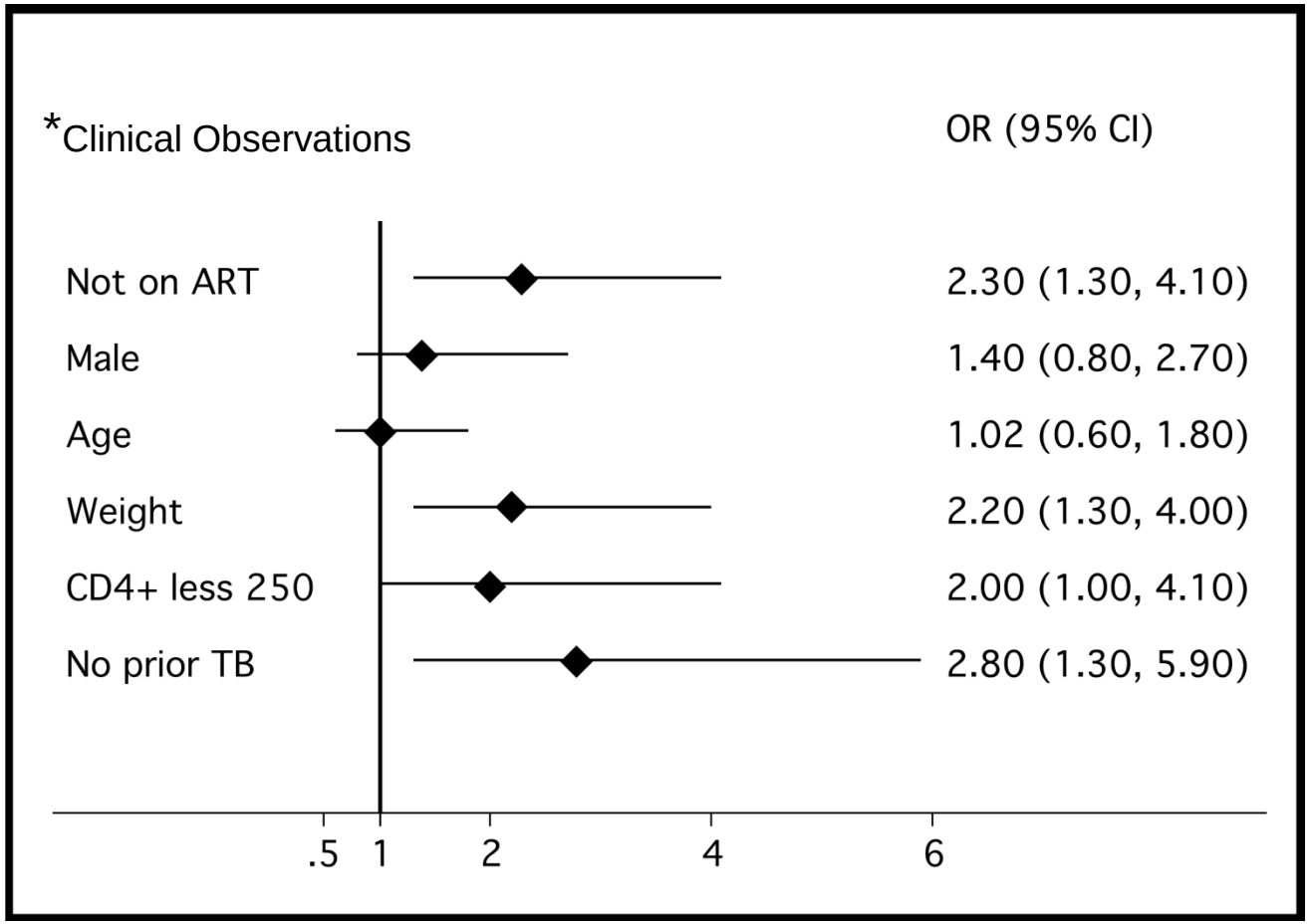
Clinical and Laboratory Features	50 TB culture positive	729 TB culture negative	p-value
Symptoms and signs of TB			
Cough ≥ two weeks	10%	4% (728)	0.05
Night sweats	10%	2% (728)	0.002
Self-reported 'Fever'	1/49	3/727	0.230 (exact)
Nodes on examination	1/49	1/728	0.122 (exact)
Loss of weight	18%	5% (728)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

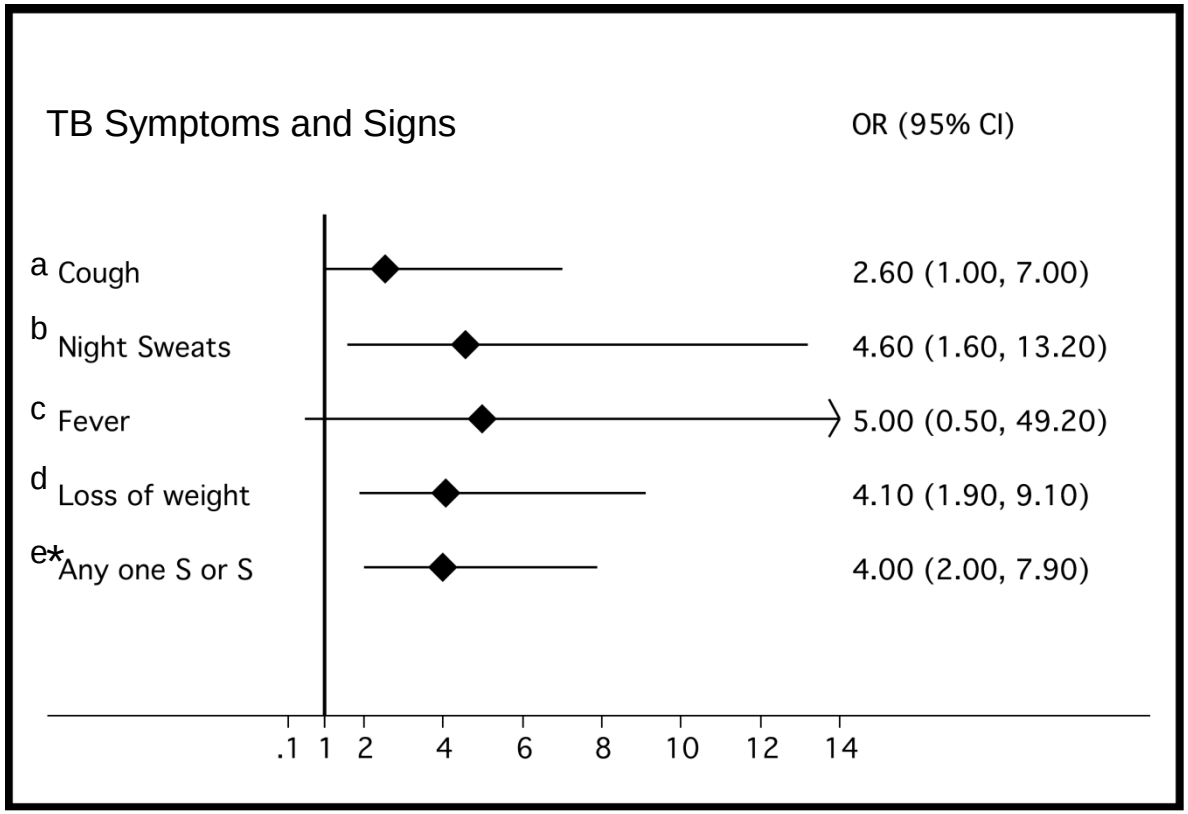
Clinical and Laboratory Features	50 TB culture positive	729 TB culture negative	p-value
Tests of TB infection			
TST positive at 5mm cut-off	68%	41%	<0.0001
TST positive at 10mm cut-off	66%	37%	<0.0001
TST positive at 15mm cut-off	54%	26%	<0.0001
Median TST mm (IQR)	15 (0-20)	0 (0-15)	<0.0001
(Manufacturer's 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



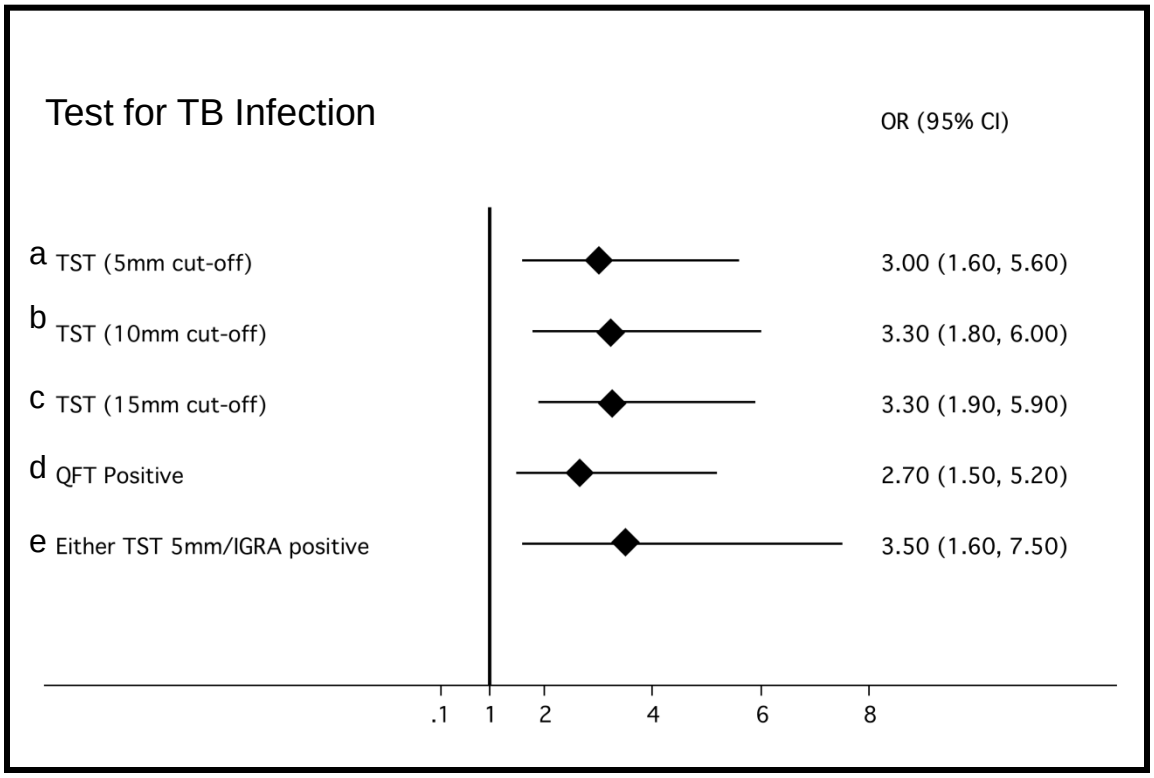
Test Accuracy

	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

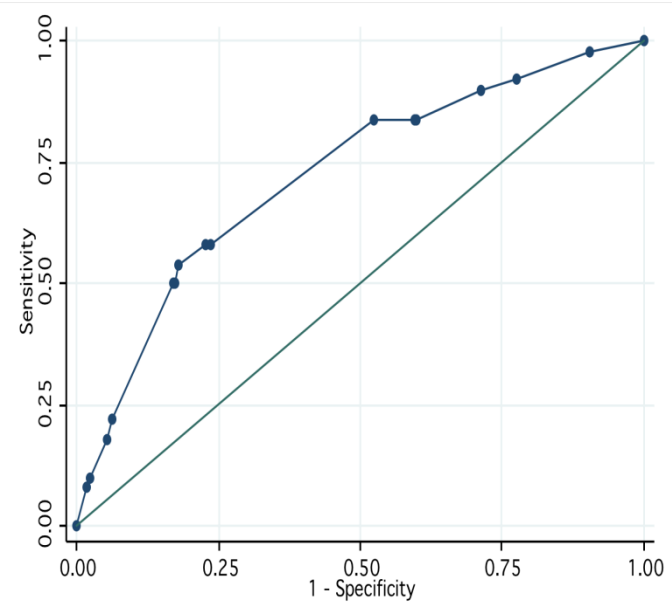


Test Accuracy

	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)

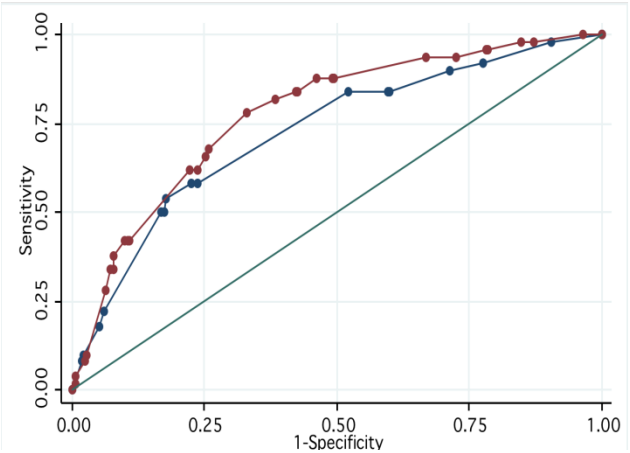


AUC=72%

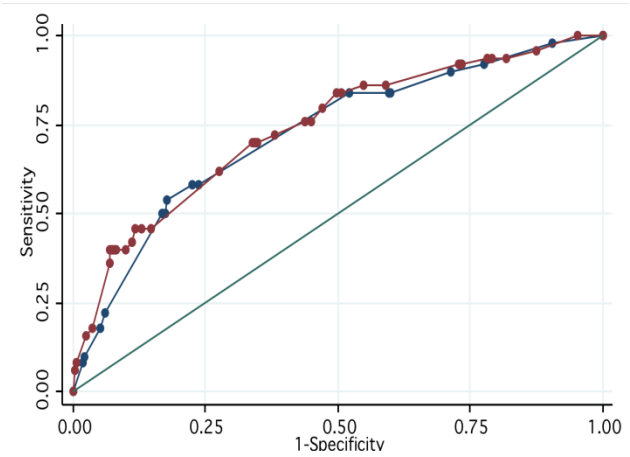
Final clinical model

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

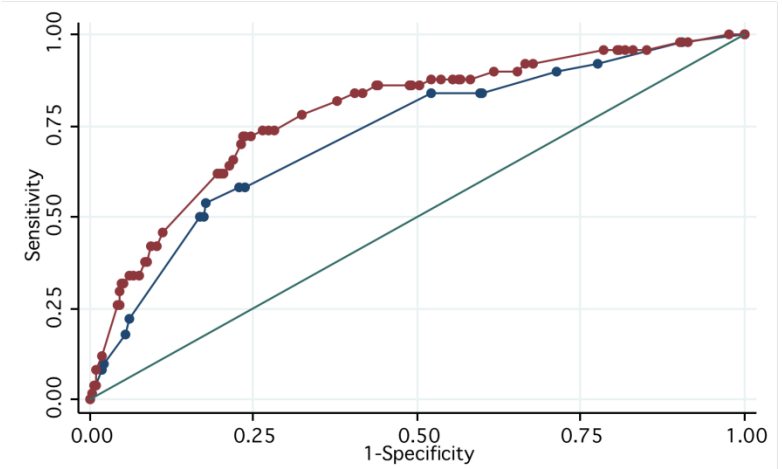
Discriminatory ability of TB tests (Multivariable Analyses)



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

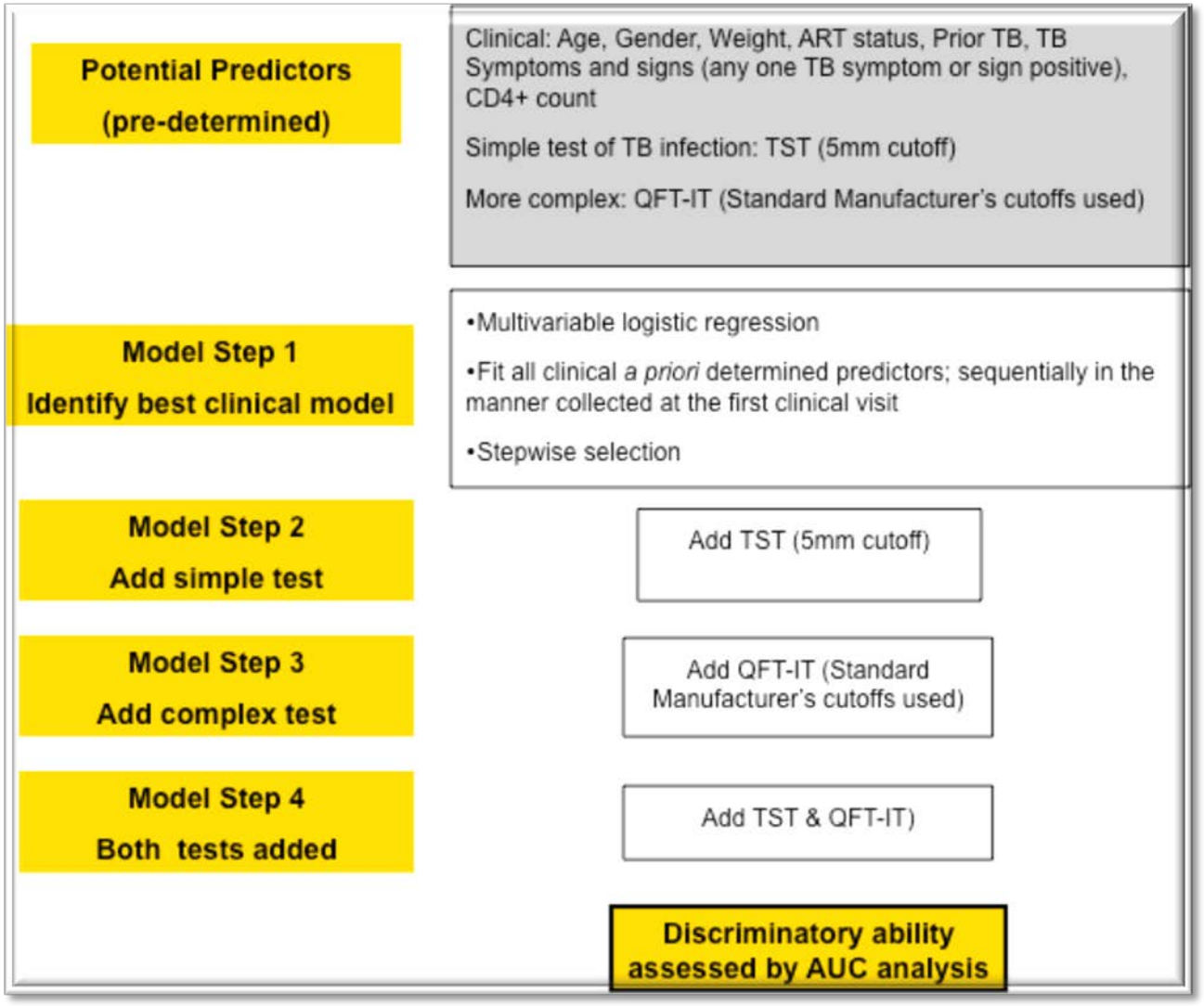


Clinical **(blue, AUC=72%)** and both TST & QFT **(red, AUC=78%)**
Comparison p-value=0.01

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

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

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No discriminatory value of interferon release added to smear negative HIV-tuberculosis algorithms

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