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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University of Cape Town
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No discriminatory value of interferon release added to smear negative HIV-tuberculosis algorithms
Rangaka M.X, et al.
ERJ 2011 (published head of print on 30 June 2011)
Estimated HIV prevalence in TB Cases

>50% HIV prevalence in new TB cases

WHO 2009 Global TB Report
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?
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
South Africa.net

southafrica.net
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

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**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

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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

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Smear negative with both TST and QFT-IT available

N = 779

Smear positives = 19
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)

- Multivariable logistic regression
- Fit all clinical *a priori* determined predictors; sequentially in the manner collected at the first clinical visit
- Stepwise selection & clinical judgement

**Potential Predictors**
(pre-determined)

**Assessing discriminatory value: Model Steps**

**Model Step 1**
Identify best clinical model

**Model Step 2**
Add simple test

**Model Step 3**
Add complex test

**Model Step 4**
Both tests added

- Add TST (5mm cutoff)
- Add QFT-IT (Standard Manufacturer’s cutoffs used)
- Add TST & QFT-IT

Discriminatory ability assessed by AUC analysis
**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

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

### Reference test

<table>
<thead>
<tr>
<th>Test under assessment</th>
<th>Reference test: Culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>(D+)</td>
<td>(D-)</td>
</tr>
<tr>
<td>(T+)</td>
<td>True Positive</td>
</tr>
<tr>
<td>(T-)</td>
<td>False Negative</td>
</tr>
</tbody>
</table>
Description of cohort by *M. tb* culture status: Clinical Observations

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

<table>
<thead>
<tr>
<th>Clinical and Laboratory Features</th>
<th>50 TB culture positive</th>
<th>729 TB culture negative</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Observations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median Age (IQR)</td>
<td>35 (31-40)</td>
<td>36 (31-42)</td>
<td>0.71</td>
</tr>
<tr>
<td>Age ≥ 35 y.o</td>
<td>46%</td>
<td>45%</td>
<td>0.92</td>
</tr>
<tr>
<td>Male</td>
<td>68%</td>
<td>75%</td>
<td>0.25</td>
</tr>
<tr>
<td>No Prior TB</td>
<td>82%</td>
<td>62%</td>
<td>0.004</td>
</tr>
<tr>
<td>Median CD4+ count (IQR)</td>
<td>169 (98-239)</td>
<td>198 (136-315)</td>
<td>0.03</td>
</tr>
<tr>
<td>CD4 less 250</td>
<td>80%</td>
<td>66% (721)</td>
<td>0.05</td>
</tr>
<tr>
<td>Median Weight Kg (IQR)</td>
<td>60 (54-65)</td>
<td>66 (58-76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight less than 60kg</td>
<td>52%</td>
<td>33% (722)</td>
<td>0.01</td>
</tr>
<tr>
<td>Not on ART at screening</td>
<td>54%</td>
<td>34%</td>
<td>0.004</td>
</tr>
<tr>
<td>Clinical and Laboratory Features</td>
<td>50 TB culture positive</td>
<td>729 TB culture negative</td>
<td>p-value</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>------------------------</td>
<td>-------------------------</td>
<td>---------</td>
</tr>
<tr>
<td><strong>Symptoms and signs of TB</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough ≥ two weeks</td>
<td>10%</td>
<td>4% (728)</td>
<td>0.05</td>
</tr>
<tr>
<td>Night sweats</td>
<td>10%</td>
<td>2% (728)</td>
<td>0.002</td>
</tr>
<tr>
<td>Self-reported ‘Fever’</td>
<td>1/49</td>
<td>3/727</td>
<td>0.230 (exact)</td>
</tr>
<tr>
<td>Nodes on examination</td>
<td>1/49</td>
<td>1/728</td>
<td>0.122 (exact)</td>
</tr>
<tr>
<td>Loss of weight</td>
<td>18%</td>
<td>5% (728)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Any one TB symptom or sign positive</strong></td>
<td>26%</td>
<td>8% (728)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Anyone symptom or sign positive: Cough for >=2 weeks vs. Cough for any duration*
<table>
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<tr>
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<th>50 TB culture positive</th>
<th>729 TB culture negative</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Tests of TB infection</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TST positive at 5mm cut-off</td>
<td>68%</td>
<td>41%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TST positive at 10mm cut-off</td>
<td>66%</td>
<td>37%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TST positive at 15mm cut-off</td>
<td>54%</td>
<td>26%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Median TST mm (IQR)</td>
<td>15 (0-20)</td>
<td>0 (0-15)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>(Manufacturer’s cutoffs)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QFT positive</td>
<td>64%</td>
<td>41%</td>
<td>0.004 (exact)</td>
</tr>
<tr>
<td>QFT negative</td>
<td>30%</td>
<td>53%</td>
<td></td>
</tr>
<tr>
<td>QFT Indeterminate</td>
<td>6%</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>Median QFT quantitative (IQR)</td>
<td>0.5 (0.1-2.6)</td>
<td>0.12 (0-0.85)</td>
<td>0.003</td>
</tr>
<tr>
<td>Either TST 5mm/IGRA positive (Indeterminate included with negatives)</td>
<td>80%</td>
<td>56%</td>
<td>0.001</td>
</tr>
<tr>
<td>Either TST 5mm/IGRA positive (Indeterminate results excluded)</td>
<td>83% (48)</td>
<td>59% (692)</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Univariable predictors of culture-positive TB disease

*Clinical Observations  OR (95% CI)

Not on ART  2.30 (1.30, 4.10)
Male  1.40 (0.80, 2.70)
Age  1.02 (0.60, 1.80)
Weight  2.20 (1.30, 4.00)
CD4+ less 250  2.00 (1.00, 4.10)
No prior TB  2.80 (1.30, 5.90)

*Age>=35y.o, Weight less than 60kg
Univariate predictors of culture-positive TB disease

TB Symptoms and Signs

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Cough</td>
</tr>
<tr>
<td>b</td>
<td>Night Sweats</td>
</tr>
<tr>
<td>c</td>
<td>Fever</td>
</tr>
<tr>
<td>d</td>
<td>Loss of weight</td>
</tr>
<tr>
<td>e</td>
<td>Any one S or S</td>
</tr>
</tbody>
</table>

Test Accuracy

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Post-test Pr (Neg)</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>10</td>
<td>96</td>
<td>5.7</td>
<td>53</td>
</tr>
<tr>
<td>b</td>
<td>10</td>
<td>98</td>
<td>5.7</td>
<td>54</td>
</tr>
<tr>
<td>c</td>
<td>2</td>
<td>100</td>
<td>5.7</td>
<td>51</td>
</tr>
<tr>
<td>d</td>
<td>18</td>
<td>95</td>
<td>5.7</td>
<td>57</td>
</tr>
<tr>
<td>e</td>
<td>26</td>
<td>92</td>
<td>4.8</td>
<td>59</td>
</tr>
</tbody>
</table>

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 for TB Infection

<table>
<thead>
<tr>
<th>Test</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a TST (5mm cut-off)</td>
<td>3.00 (1.60, 5.60)</td>
</tr>
<tr>
<td>b TST (10mm cut-off)</td>
<td>3.30 (1.80, 6.00)</td>
</tr>
<tr>
<td>c TST (15mm cut-off)</td>
<td>3.30 (1.90, 5.90)</td>
</tr>
<tr>
<td>d QFT Positive</td>
<td>2.70 (1.50, 5.20)</td>
</tr>
<tr>
<td>e Either TST 5mm/IGRA positive</td>
<td>3.50 (1.60, 7.50)</td>
</tr>
</tbody>
</table>

Pre-test probability (Prevalence): 6%

Test Accuracy

<table>
<thead>
<tr>
<th></th>
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<th>Specificity</th>
<th>Post-test Pr (Neg)</th>
<th>AUC</th>
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</thead>
<tbody>
<tr>
<td>a</td>
<td>68</td>
<td>59</td>
<td>3</td>
<td>63</td>
</tr>
<tr>
<td>b</td>
<td>66</td>
<td>63</td>
<td>3</td>
<td>64</td>
</tr>
<tr>
<td>c</td>
<td>54</td>
<td>74</td>
<td>4</td>
<td>64</td>
</tr>
<tr>
<td>d</td>
<td>68</td>
<td>56</td>
<td>4</td>
<td>62</td>
</tr>
<tr>
<td>e</td>
<td>83</td>
<td>41</td>
<td>3</td>
<td>62</td>
</tr>
</tbody>
</table>
Discriminatory ability of TB tests (Multivariable Analyses)

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/mm³ OR=2
5. Not on ART at screening OR=1.2

AUC=72%
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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Shaheed Mathee

Department of Health

Wellcome Trust

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

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