Predictive Value of IGRAs during Pregnancy for Postpartum Active Tuberculosis in HIV-1 Infected Women

Jonnalagadda S¹, Brown E¹, Lohman-Payne B¹, Wamalwa D², Farquhar C¹, John-Stewart G¹

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¹ University of Washington, Seattle ² University of Nairobi, Kenya

TB and HIV – deadly combination during pregnancy and postpartum

• Postpartum TB in HIV infected women is a risk factor for maternal and infant mortality (Gupta, CID 2007)
• LTBI in pregnancy in HIV-1 infected women is a risk for (Jonnalagadda, JID 2010)
  – Maternal postpartum TB
  – Maternal and infant mortality in immunosuppressed women (CD4 <250)
• Pregnancy and postpartum an optimal time for LTBI screening and IPT
• Limited data on IGRA performance in:
  – HIV-1 infected individuals
  – Pregnancy/postpartum women

Jonnalagadda et al, JID 2010
IGRAs in HIV infected individuals

- Pooled sensitivity for LTBI in HIV infected individuals¹:
  - 72% (T-SPOT.TB)
  - 61% (QFT-GIT)
  - Gold standard: active TB, assessed concurrently with IGRA

- IGRA positivity associated with risk for future TB

<table>
<thead>
<tr>
<th>Author, Journal, Year</th>
<th>Study population</th>
<th>Measure of association (unadjusted)</th>
<th>Unadjusted Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rangaka, Lancet ID 2011</td>
<td>Meta-analysis</td>
<td>Pooled relative risk</td>
<td>2 to 3</td>
</tr>
<tr>
<td>Aichelburg, CID, 2009</td>
<td>HIV infected adults</td>
<td>Incidence in IGRA positive</td>
<td>8%</td>
</tr>
<tr>
<td>Jonnalagadda, JID 2010</td>
<td>HIV infected women</td>
<td>HR</td>
<td>2.7</td>
</tr>
</tbody>
</table>

¹ Cattamanchi, JAIDS 2010

IFN-γ response as a predictive marker for future TB

- Use of different cut-off values in IFN-γ response
  - IFN-γ response: Maximum (ESAT-6, CFP-10) minus background
  - Utilize indeterminate responses

- Sensitivity and specificity of IGRAs associated with future TB

- In HIV-1 infected individuals:
  - CD4 alone as a predictor for active TB
  - Use of IFN-γ in combination with CD4
Aim

To determine sensitivity, specificity and positive predictive value of varied cut-offs in IFN-γ response and CD4 cell count during pregnancy for (future) postpartum active TB.

- IFN-γ cut-off values (spot forming cells (SFCs)/well)
  - >0 (least conservative)
  - ≥6 (T-SPOT.TB cut-off for a positive response)
  - ≥10 (most conservative)

- CD4 cell count (cells/μL)
  - <250
  - <350

<table>
<thead>
<tr>
<th>IGRA during pregnancy</th>
<th>Postpartum active TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Above IFN-γ cut-off</td>
<td>a (true positives)</td>
</tr>
<tr>
<td>Below IFN-γ cut-off</td>
<td>c (false negatives)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pregnancy</th>
<th>Delivery</th>
<th>Postpartum</th>
<th>1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>a/a+c</td>
<td>Specificity</td>
<td>d/b+d</td>
</tr>
</tbody>
</table>

Study design

535 HIV-1 positive women enrolled at 32 weeks of pregnancy (1999 – 2005)

Pregnancy IGRA*

\[ n = 361 \]

Positive: 135 (37.4%)

Negative: 170 (47.1%)

Indeterminate: 56 (15.5%)

Eligible for current analysis \[ n = 353 \]

Women with positive control <20 \[ n = 8 \] (excluded)

Lost to follow-up \[ n = 26 \]

Women seen after delivery and included in current analysis \[ n = 327 \]

*Jonnalagadda et al, JID 2010
Analysis

- Sensitivity, Specificity
  - Estimated from a time-dependent ROC curve taking censoring into account\(^1\)

- Positive predictive value (PPV)
  - Kaplan Meier estimate of cumulative incidence rate and 95% CI

1 Heagerty, Biometrics 2000

Results
Incidence of postpartum active TB

Total number of events: 9
Incidence rate: 3.5/100 py

IFN-γ is more sensitive but less specific than CD4 for postpartum TB

<table>
<thead>
<tr>
<th>Marker</th>
<th>Cut-off value</th>
<th>Number of events</th>
<th>Person-years</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN-γ(SFCs/well)</td>
<td>&gt;0</td>
<td>7</td>
<td>164.3</td>
<td>78.9</td>
<td>35.7</td>
<td>4.3</td>
</tr>
<tr>
<td></td>
<td>&gt;=6</td>
<td>7</td>
<td>118.7</td>
<td>77.7</td>
<td>54.6</td>
<td>5.9</td>
</tr>
<tr>
<td></td>
<td>&gt;=10</td>
<td>6</td>
<td>102.1</td>
<td>65.0</td>
<td>60.5</td>
<td>5.9</td>
</tr>
<tr>
<td>CD4 cells/μL</td>
<td>&lt;250</td>
<td>4</td>
<td>44.4</td>
<td>51.5</td>
<td>82.8</td>
<td>9.0</td>
</tr>
<tr>
<td></td>
<td>&lt;350</td>
<td>5</td>
<td>84.4</td>
<td>64.6</td>
<td>64.7</td>
<td>5.9</td>
</tr>
</tbody>
</table>

1 Incidence rate per 100 person years
Sensitivity and specificity of IFN-γ in immunosuppressed women

![Graph showing sensitivity and specificity of IFN-γ in immunosuppressed women.](image_url)
IFN-γ and CD4 risk model for predicting active TB
Strengths and limitations

• Strengths
  – Two clinically and programmatically relevant markers
  – Account for time-lag between LTBI and TB diagnosis

• Limitations
  – Few events of TB
  – Absence of TST for comparison
  – Absence of culture confirmation of TB

Summary

• IFN-γ cut-off at ≥6:
  – Optimal sensitivity, specificity
  – Highest PPV

• CD4 was better predictor of active TB than IFN-γ

• IFN-γ in immunosuppressed women could identify women most at risk for active TB
Acknowledgements

• Study participants
  Kenyatta National Hospital, Pediatrics Research Lab, Nairobi, Kenya

• Funding sources
  – NIH R21 HD058477-01
  – Firland Foundation Grant

LTBI detection

• T-SPOT.TB IGRA used for LTBI detection

Positive control > 20 spots
ESAT-6
CFP-10
Positive response: ≥6 or 2x background
Negative control or background ≤ 10 spots
LTBI detection

- T-SPOT.TB IGRA used for LTBI detection

<table>
<thead>
<tr>
<th>Cut-off values</th>
<th>Positive control &lt; 20 spots</th>
<th>Indeterminate</th>
<th>Positive response: ≥6 or 2x background</th>
<th>Negative control or background &gt; 10 spots</th>
</tr>
</thead>
</table>

Cut-off values in baseline markers

- IFN-γ cut-off values (spot forming cells (SFCs)/well)
  - >0 (least conservative)
  - ≥6 (T-SPOT.TB cut-off for a positive response)
  - ≥10 (most conservative)

- CD4 cell count (cells/μL)
  - <250
  - <350
PPV of IFN-γ in immunosuppressed women

IGRA predictive value, sensitivity, specificity

- Positive predictive value
  - IGRA positivity and risk for TB
  - Association does not imply prediction

- Sensitivity, specificity
  - IGRA cut-off values are based on active TB as gold-standard
  - Concurrent measurement of outcome (TB) and marker (IGRA)

- Limited data among:
  - HIV-1 infected individuals
  - Women during pregnancy and postpartum
Cohort description

Pregnancy (~32 weeks gestation)  Delivery  Postpartum  1 year

Monthly follow-up

Study procedures
• Sociodemographics (Enrollment)
• Medical history
• Physical exam
• CD4 cell count
• HIV-1 RNA
• Peripheral blood mononuclear cells (PBMCs)