Disclosures

• Relevant Financial Disclosure - none
• Off-label use - none
Objectives

• Describe the epidemiology of TB/HIV co-infection
• Describe the clinical presentation of TB disease in populations with HIV
• Explain treatment and management strategies for TB patients with HIV
• 2013 TB Incidence: 9,000,000 (126/100,000 population)
• 2013 HIV Incidence: 2,100,000
• 2013 TB prevalence: 11,000,000
• 2013 HIV prevalence: 35,000,000
- 13% of TB Globally HIV-infected
- 34% of TB cases in Africa co-infected with HIV
Estimated HIV Coinfection in Persons with HIV Test Results, United States, 1993–2012
HIV Immune Deficiency

• Diminished T cell repertoire
• Reduced lymphocyte function - decreased
• Delayed hypersensitivity response to recall antigens
• Phagocytosis
• Chemotaxis
• Intracellular killing
• Natural killer cell-mediated killing

• Loss of specific antibody responses
• Increased immune activation
• Disruption of immunoregulatory cytokine expression and production
• Decreased IL-2, γ interferon, and IL-12
• Increased IL-1, IL-6, TNFα
Proposed framework for considering tuberculosis infection as a spectrum.

Learning Objectives

At the end of this talk, participants should be able to:

• Describe the impact of HIV on the various components of the natural history of TB

• Prescribe appropriate testing for the diagnosis and treatment of LTBI in the setting of HIV infection

• Initiate antiretroviral therapy in patients newly diagnosed with TB

• Describe general principles for managing IRIS in patients coinfected with TB and HIV
Natural History
Natural History of TB Infection in Patients Without HIV

Exposure to TB

- No infection (70-90%)
- Infection (10-30%)

Infection Pathways:

- Latent TB (90%)
- Active TB (5-10%)

Latent TB:
- Never develop Active disease

Active TB:
- Treated
- Die/Relapse/Recurr
- Cured
Tuberculous infection progressed to active disease within 106 days of acquiring the infection in 37 percent (11 of 30) of HIV-infected patients.

Tuberculosis did not develop in any of 28 staff members with exposures, although there were 6 with documented tuberculin conversions and 8 others had positive tuberculin reactions of unknown duration.
7 of 18 (39%) HIV-infected inpatients developed active tuberculosis within 60 days of diagnosis of the index case
Natural History of TB Infection in Patients Without HIV

Exposure to TB

No infection (70-90%)

Infection (10-30%)

Latent TB (90%)

Never develop Active disease

Active TB (5-10%)

Treated

Die/Relapse/Recurr

Cured

Never develop Active disease
Forty-nine HIV-seropositive subjects and 62 HIV-seronegative subjects had a positive TST response.

7/8 cases of TB occurred in HIV-seropositive subjects with a prior positive PPD test (7.9 cases per 100 person-years, vs. 0.3 case per 100 person-years in those without a prior positive PPD test; rate ratio, 24.0; P<0.0001).
Natural History of TB Infection in Patients Without HIV

Exposure to TB

No infection (70-90%)

Infection (10-30%)

Latent TB (90%)

Active TB (5-10%)

Treated

Never develop Active disease

Die/Relapse/Recurr

Cured
• 23,517 culture-positive, pulmonary tuberculosis patients from the California tuberculosis case registry from 1993 to 2007 who completed anti-tuberculosis therapy.
• 148 (0.63%) had a late recurrence.
• Human immunodeficiency virus infection (adjusted hazard ratio, 1.81; p = 0.0149)
Retrospective cohort study of South African gold miners, men with known dates of seroconversion to HIV (from 1991 to 1997) and HIV-negative men were followed up to 2004.

342 HIV-positive and 321 HIV-negative men who had had 1 previous episode of tuberculosis,

Rates of tuberculosis recurrence:

- HIV-positive 19.7 cases per 100 person-years at risk (95% confidence interval [CI], 16.4–23.7)
- HIV-negative 7.7 cases per 100 PYAR (95% CI, 6.1–9.8)
Factors associated with TB treatment success among new smear-positive TB patients at Martin Preuss Centre between January 2008 and December 2010 (N=2,264).  

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total</th>
<th>Unadjusted Odds Ratio (95% CI)</th>
<th>P-value*</th>
<th>Adjusted Odds Ratio (95% CI)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HIV Status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV positive</td>
<td>1,275</td>
<td>56%</td>
<td>1.00</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>HIV negative</td>
<td>989</td>
<td>44%</td>
<td>1.34 (1.05–1.72)</td>
<td>1.49 (1.14–1.94)</td>
<td>0.019</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1,400</td>
<td>62%</td>
<td>1.00</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Female</td>
<td>864</td>
<td>38%</td>
<td>1.45 (1.12–1.87)</td>
<td>1.52 (1.17–1.99)</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>Age category</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15–24</td>
<td>460</td>
<td>20%</td>
<td>0.90 (0.65–1.25)</td>
<td>0.76 (0.54–1.06)</td>
<td>0.323</td>
</tr>
<tr>
<td>25–34</td>
<td>985</td>
<td>44%</td>
<td>1.00</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>35–44</td>
<td>505</td>
<td>22%</td>
<td>0.98 (0.71–1.36)</td>
<td>1.07 (0.77–1.48)</td>
<td>1.00</td>
</tr>
<tr>
<td>45–54</td>
<td>173</td>
<td>8%</td>
<td>0.71 (0.46–1.10)</td>
<td>0.70 (0.45–1.10)</td>
<td>0.55</td>
</tr>
<tr>
<td>≥55</td>
<td>141</td>
<td>6%</td>
<td>0.66 (0.41–1.06)</td>
<td>0.57 (0.35–0.93)</td>
<td>0.019</td>
</tr>
<tr>
<td><strong>TB Registration year</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>791</td>
<td>35%</td>
<td>1.80 (1.34–2.43)</td>
<td>1.79 (1.33–2.41)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2009</td>
<td>843</td>
<td>37%</td>
<td>1.00</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>2010</td>
<td>630</td>
<td>28%</td>
<td>1.23 (0.92–1.65)</td>
<td>1.22 (0.91–1.63)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>TB Treatment site</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPC</td>
<td>912</td>
<td>40%</td>
<td>1.20 (0.94–1.53)</td>
<td>-</td>
<td>0.147</td>
</tr>
<tr>
<td>Other</td>
<td>1,352</td>
<td>60%</td>
<td>1.00</td>
<td></td>
<td>1.00</td>
</tr>
</tbody>
</table>

http://www.plosone.org/article/info:doi/10.1371/journal.pone.0056248
FIGURE 1.26
Treatment outcomes for HIV-positive and HIV-negative TB patients, 2006 cohort. The numbers under the bars are the numbers of patients included in the cohort.

• Testing for LTBI at the time of HIV diagnosis should be routine regardless of epidemiologic risk factors
• Annual testing for LTBI only in those with ongoing exposure
• If negative screen for LTBI while CD4 count is low, repeat testing post cART once CD4 is above 200.
Diagnosis of LTBI in HIV-Infected Individuals: Which Test?
Comparison of sensitivity of IGRAs between HIV-infected and HIV-uninfected patients with culture-confirmed tuberculosis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country</th>
<th>Sensitivity in HIV-pos n/N (%)</th>
<th>Sensitivity in HIV-neg n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n/N (%)</td>
<td></td>
</tr>
<tr>
<td><strong>QFT-GIT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tsiouris et al. [19]</td>
<td>South Africa</td>
<td>17/26 (65)</td>
<td>11/15 (73)</td>
</tr>
<tr>
<td>Chee et al. [20]</td>
<td>Singapore</td>
<td>4/7 (57)</td>
<td>220/273 (81)</td>
</tr>
<tr>
<td>Garcia-Gasalla et al. [25]</td>
<td>Spain</td>
<td>12/13 (92)</td>
<td>85/105 (81)</td>
</tr>
<tr>
<td>Legesse et al. [29]</td>
<td>Ethiopia</td>
<td>13/19 (68)</td>
<td>20/31 (65)</td>
</tr>
<tr>
<td>Ling et al. [31]</td>
<td>South Africa</td>
<td>29/43 (67)</td>
<td>67/82 (82)</td>
</tr>
<tr>
<td>Dheda et al. [33]</td>
<td>South Africa</td>
<td>1/5 (20)</td>
<td>11/15 (73)</td>
</tr>
<tr>
<td><strong>T-SPOT.TB</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chee et al. [20]</td>
<td>Singapore</td>
<td>7/7 (100)</td>
<td>247/267 (93)</td>
</tr>
<tr>
<td>Ling et al. [31]</td>
<td>South Africa</td>
<td>35/43 (81)</td>
<td>70/82 (85)</td>
</tr>
<tr>
<td>Dheda et al. [33]</td>
<td>South Africa</td>
<td>5/5 (100)</td>
<td>14/15 (93)</td>
</tr>
</tbody>
</table>
Head-to-Head Comparison of Sensitivity Between IGRAs and TST in HIV-infected Patients with Culture-Confirmed Tuberculosis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country</th>
<th>IGRA</th>
<th>Sensitivity IGRA n/N (%)</th>
<th>Sensitivity TST n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tsiouris et al. [19]</td>
<td>South Africa</td>
<td>QFT-GIT</td>
<td>17/26 (65)</td>
<td>22 (85)</td>
</tr>
<tr>
<td>Aichelburg et al. [22]</td>
<td>Austria</td>
<td>QFT-GIT</td>
<td>10/11 (91)</td>
<td>8 (80)*</td>
</tr>
<tr>
<td>Kabeer et al. [23]</td>
<td>India</td>
<td>QFT-GIT</td>
<td>29/44 (66)</td>
<td>11 (25)</td>
</tr>
<tr>
<td>Garcia-Gasalla et al. [25]</td>
<td>Spain</td>
<td>QFT-GIT</td>
<td>9/13 (69)</td>
<td>5 (42)**</td>
</tr>
<tr>
<td>Rangaka et al. [32]</td>
<td>South Africa</td>
<td>QFT-GIT</td>
<td>32/50 (64)</td>
<td>34 (68)</td>
</tr>
<tr>
<td>Vincenti et al. [38]</td>
<td>Italy</td>
<td>T-SPOT.TB</td>
<td>11/13 (85)</td>
<td>6 (46)†</td>
</tr>
</tbody>
</table>
Head-to-Head Comparison of Sensitivity Between QFT-GIT and T-SPOT.TB in HIV-Infected Patients with Culture-Confirmed Tuberculosis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country</th>
<th>Sensitivity QFT-GIT</th>
<th>Sensitivity T-SPOT.TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chee et al. [20]</td>
<td>Singapore</td>
<td>4/7 (57)</td>
<td>7/7 (100)</td>
</tr>
<tr>
<td>Markova et al. [21]</td>
<td>Bulgaria</td>
<td>12/13 (92)</td>
<td>8/13 (62)</td>
</tr>
<tr>
<td>Leidl et al. [24]</td>
<td>Uganda</td>
<td>13/19 (68)</td>
<td>17/19 (89)</td>
</tr>
<tr>
<td>Ling et al. [31]</td>
<td>South Africa</td>
<td>29/43 (67)</td>
<td>35/43 (81)</td>
</tr>
<tr>
<td>Dheda et al. [33]</td>
<td>South Africa</td>
<td>1/5 (20)</td>
<td>5/5 (100)</td>
</tr>
</tbody>
</table>
Contribution of Interferon gamma release assays testing to the diagnosis of latent tuberculosis infection in HIV-infected patients: A comparison of QuantiFERON-TB Gold In Tube, T-SPOT.TB and tuberculin skin test

José M Ramos1*, Catalina Robledano3, Mar Masí3, Sofia Belda2, Sergio Padilla1, Juan C Rodríguez2 and Félix Gutierrez1,3

302 patients with HIV infection

- TST pos 20 pts (6.6%)
- TST neg 257 pts (85.1%)
- TST not read 25 pts (8.3%)

QFG pos 2 pts
- Only QFG pos 2 pts
- TST pos or QFG pos 26 pts (8.6%)

T-SPOT.TB pos 25 pts
- Only T-SPOT.TB pos 30 pts
- TST pos or T-SPOT.TB pos 54 pts (17.9%)

T-SPOT.TB pos and QFG pos 1 pts
- T-SPOT.TB pos and QFG pos 4 pts
- TST pos or T-SPOT.TB pos or QFG pos 56 pts (18.5%)

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Ramos et al. BMC Infectious Diseases 2012, 12:169
• 117 HIV-infected patients potentially nosocomially exposed to an HIV-infected patient with ‘smear positive’ pulmonary tuberculosis.
• Median CD4 count was 550 cells/mL
• QFG positive in 11 (9.4%); indeterminate in 1
• T-SPOT.TB positive in six (5.1%); borderline in 1
• both IGRAs were positive in five patients (4.3%).
• Concordance moderate (¼0.56, 95% confidence interval¼0.27–0.85).
• IGRAs positive in only 4 (29%) of 14 patients with previous culture-proven TB
• No patient developed tuberculosis during 20 months of follow-up.
Sensitivity of IGRAs in HIV-infected Patients in Four Systematic Reviews

<table>
<thead>
<tr>
<th></th>
<th>Cattamanchi (Ref. [10])</th>
<th>Metcalfe (Ref. [11])</th>
<th>Chen (Ref. [12])</th>
<th>Santin Current SR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensitivity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-burden TB settings</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- QFT-GIT</td>
<td>61% (47–75)</td>
<td>65% (52–77)</td>
<td>N.D.</td>
<td>61% (53–69)</td>
</tr>
<tr>
<td>- T-SPOT.TB</td>
<td>72% (62–81)</td>
<td>68% (56–80)</td>
<td>N.D.</td>
<td>65% (54–74)</td>
</tr>
<tr>
<td>Low-burden TB settings</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- QFT-GIT</td>
<td>67% (47–83)†</td>
<td>N.D.</td>
<td>N.D.</td>
<td>59% (46–71)</td>
</tr>
<tr>
<td>- T-SPOT.TB</td>
<td>94% (73–100)†</td>
<td>N.D.</td>
<td>N.D.</td>
<td>69% (47–99)†</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- QFT-GIT</td>
<td>N.D.</td>
<td>N.D.</td>
<td>69% (62–71)</td>
<td>61% (54–67)</td>
</tr>
<tr>
<td>- T-SPOT</td>
<td>N.D.</td>
<td>N.D.</td>
<td>66% (60–71)</td>
<td>65% (56–74)</td>
</tr>
</tbody>
</table>
Plasma..............................................
White Cells..............................................
Cell Barrier..............................................
Erythrocytes and neutrophils

1. Collect blood sample, centrifuge to separate white blood cells which are washed and counted to maximise sensitivity.

2. Add WBCs [○] & specific TB antigens [●] to wells pre-coated with antibodies to IFN-γ [●] and incubate overnight (37°C, CO₂).

3. IFN-γ [●] is released from activated T cells. Wash wells, add secondary conjugated antibody [➋]. Incubate for 1 hour.

4. Wash wells, add substrate and incubate for 7 minutes. Stop reaction with water. One spot [●] is the footprint of one activated T cell.
Which IGRA is better for CD4 < 200

- Three studies evaluated the effect of CD4 + cell counts on sensitivity of QFT-GIT
  - One study reported a decrease in its sensitivity with fewer than 200 circulating CD4 + T-cell counts
  - Another found no differences in CD4 + T-cell counts between patients with positive and negative QFT-GIT results
  - Another study found higher sensitivity in patients with <200 CD4 + cells than in those with > 200 CD4 + cells
- None of the three studies assessing TSPOT.TB reported a relationship between lower sensitivity and lower CD4 + T-cell counts
  - The sensitivity of T-SPOT.TB in one study was higher in patients with CD4 + cells < 200 than in those with CD4+ cells > 200 cells
Progressive immunodeficiency is associated with decreased sensitivity of IGRAs
  - It may have less impact on the sensitivity of IGRAs than on the sensitivity of TST
• Both TST and FDA-approved IGRAs are appropriate for TB screening in HIV-infected individuals
• No definitive comparison favoring one over the other
• Routine use of both TST and IGRAs to screen for LTBI is not recommended
Diagnosis of Active Tuberculosis in the Setting of HIV
TB in the Setting of HIV: Clinical Presentation

• In general, similar to that seen in HIV-uninfected patients

• However, differential diagnosis broader
  • HIV itself
  • Other opportunistic infections

• Extrapulmonary
  • HIV main risk factor
  • 35-80% vs. 15-50%
  • Bones and joints, lymph nodes, the pleura, peritoneum, CNS
Laboratory Diagnosis of Active TB

• Sputum smear
  • HIV-infected patients are more likely to have smear-negative pulmonary TB
  • Range 31 – 81%

• CXR
  • Individuals with advanced HIV are likely to have atypical presentations
    • Lower lobe locations
    • Less cavities
    • Consolidation
    • Intrathoracic LAD
    • May appear normal
Treatment of Tuberculosis
## Treatment of LTBI

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Duration</th>
<th>Interval</th>
<th>Minimum doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>9 months</td>
<td>Daily</td>
<td>270</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Twice weekly*</td>
<td>76</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>6 months</td>
<td>Daily</td>
<td>180</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Twice weekly</td>
<td>52</td>
</tr>
<tr>
<td>Isoniazid and Rifapentine</td>
<td>3 months</td>
<td>Once weekly</td>
<td>12</td>
</tr>
<tr>
<td>Rifampin</td>
<td>4 months</td>
<td>Daily</td>
<td>120</td>
</tr>
</tbody>
</table>
Factors associated with TB treatment success among new smear-positive TB/HIV co-infected patients at Martin Preuss Centre between January 2008 and December 2010 (N=1,275).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total</th>
<th>Unadjusted Odds Ratio (95% CI)</th>
<th>P-value*</th>
<th>Adjusted Odds Ratio (95% CI)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ART Status</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On ART</td>
<td>492</td>
<td>39%</td>
<td>1.61 (1.15–2.25)</td>
<td>0.005</td>
<td>1.83 (1.29–2.60)</td>
</tr>
<tr>
<td>Not on ART</td>
<td>783</td>
<td>61%</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>520</td>
<td>41%</td>
<td>1.43 (1.03–1.97)</td>
<td>0.031</td>
<td>1.44 (1.03–2.01)</td>
</tr>
<tr>
<td>Male</td>
<td>755</td>
<td>59%</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td><strong>Age at TB registration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15–24</td>
<td>169</td>
<td>13%</td>
<td>0.76 (0.48–1.19)</td>
<td>0.515</td>
<td>0.70 (0.44–1.12)</td>
</tr>
<tr>
<td>25–34</td>
<td>619</td>
<td>49%</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>35–44</td>
<td>350</td>
<td>27%</td>
<td>0.98 (0.67–1.43)</td>
<td>1.06</td>
<td>0.73 (0.42–1.28)</td>
</tr>
<tr>
<td>45–54</td>
<td>200</td>
<td>8%</td>
<td>0.70 (0.40–1.21)</td>
<td>0.35</td>
<td>0.47–3.90</td>
</tr>
<tr>
<td>≥55</td>
<td>37</td>
<td>3%</td>
<td>1.35</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>TB Registration year</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>421</td>
<td>33%</td>
<td>1.90 (1.30–2.79)</td>
<td>0.004</td>
<td>2.17 (1.46–3.22)</td>
</tr>
<tr>
<td>2009</td>
<td>496</td>
<td>39%</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td>358</td>
<td>28%</td>
<td>1.31 (0.91–1.90)</td>
<td>1.00</td>
<td>1.22 (0.84–1.78)</td>
</tr>
</tbody>
</table>

http://www.plosone.org/article/info:doi/10.1371/journal.pone.0056248
A comparison of TB treatment outcomes in HIV-TB co-infected patients diagnosed with TB taking and not taking ART

<table>
<thead>
<tr>
<th>Treatment outcome</th>
<th>Not on ART (n = 1024) N (%)</th>
<th>On ART (n = 4016) N (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment success</td>
<td>552 (54)</td>
<td>3191 (79.5)</td>
<td>1.47 (1.39-1.56)</td>
</tr>
<tr>
<td>Death</td>
<td>256 (25)</td>
<td>541 (13.5)</td>
<td>0.53 (0.47-0.61)</td>
</tr>
<tr>
<td>Default</td>
<td>105 (10.3)</td>
<td>118 (3)</td>
<td>0.28 (0.22-0.36)</td>
</tr>
<tr>
<td>Failure</td>
<td>10 (1)</td>
<td>13 (0.3)</td>
<td>0.33 (0.14-0.75)</td>
</tr>
</tbody>
</table>

Duration of rifamycin therapy of $\geq 6$ months and daily therapy in the initial intensive phase were associated with lower risk of failure and/or relapse in HIV-positive patients with active TB.
Acquired Rifamycin Resistance with Twice-Weekly Treatment of HIV-related Tuberculosis

William Burman, Debra Benator, Andrew Vernon, Awal Khan, Brenda Jones, Claudia Silva, Chris Lahart, Stephen Weis, Barbara King, Bonita Mangura, Marc Weiner, Wafaa El-Sadr, and the Tuberculosis Trials Consortium

Denver Public Health; University of Colorado Health Sciences Center, Denver, Colorado; Veterans Affairs Medical Center of Washington, DC; George Washington University Medical Center, Washington, DC; Centers for Disease Control and Prevention, Atlanta, Georgia; Los Angeles County–University of Southern California Medical Center, Los Angeles, California; Baylor College of Medicine, Houston; Tarrant County Public Health Department; University of North Texas Health Sciences Center, Fort Worth; University of Texas Health Science Center; South Texas Veterans Health Care System, San Antonio, Texas; University of Medicine and Dentistry of New Jersey–New Jersey Medical School National Tuberculosis Center, Newark, New Jersey; Harlem Hospital Center; and Columbia University College of Physicians and Surgeons, New York, New York

Am J Respir Crit Care. 2006;173:350–356

- 169 HIV-infected patients with culture-confirmed TB
- Median CD4 cell count 90 cells/mm³
- Median HIVRNA 5.3 log₁₀ copies/ml

Nine (5.3%) patients had culture-positive treatment failure (n=3) or relapse (n=6). Eight of these nine (89%) cases had isolates with acquired rifamycin resistance.

- DOT rifabutin, isoniazid, pyrazinamide, and ethambutol for 2 months (given daily, thrice-weekly, or twice-weekly per the local tuberculosis control program)
- Followed by rifabutin plus isoniazid for 4 months twice weekly.
Acquired rifamycin monoresistance in patients with HIV-related tuberculosis treated with once-weekly rifapentine and isoniazid


Andrew Vernon, William Burman, Debra Benator, Awal Khan, Lorna Bozeman, for the Tuberculosis Trials Consortium

- 61 adults with culture-positive, drug-susceptible pulmonary tuberculosis
- Completed 2 months of isoniazid, rifampin, pyrazinamide, ethambutol
- Median CD4 cell count 118 cells/mm$^3$ for the once weekly arm and 137 cells/mm$^3$ for the twice weekly arm

- Randomly assigned to (for an additional 16 weeks, DOT)
  - 900 mg isoniazid and 600 mg rifapentine once weekly or
  - 900 mg isoniazid and 600 mg rifampin twice weekly.

- Five of 30 patients in the once-weekly isoniazid/rifapentine group relapsed, compared with three of 31 patients in the twice weekly isoniazid/rifampin group (p=0.41).

- Four of five relapses in the once-weekly isoniazid/rifapentine group had monoresistance to rifamycin, compared with none of three in the rifampin group (p=0.05).
• Treatment of TB in HIV-infected individuals is the same as for those who are HIV uninfected
• Treatment of TB in HIV-infected individuals should include an initial 4-drug combination of isoniazid, rifampin, pyrazinamide, and ethambutol
• DOT is recommended for all patients with suspected HIV-related TB
• Daily therapy (5–7 days per week) given as DOT is recommended during the intensive phase
• Daily (5–7 days per week) or thrice-weekly dosing is recommended during the continuation phase
• Once- or twice-weekly dosing during the continuation phase assoc. with treatment failure/relapse with acquired rifamycin resistance
TB and HIV coinfection: Treatment Issues

• Drug-drug interactions
• Overlapping drug toxicities
• Pill Burden
• Immune-reconstitution inflammatory syndrome (IRIS)
• Sequencing with antiretroviral therapy
• Highly intermittent Dosing
• TB treatment outcome in HIV
• ART treatment effect on TB incidence
TB/HIV Treatment Issues: Drug Interactions

• Rifamycins induce hepatic cytochrome P450 (CYP3A4) enzymes, accelerating metabolism of:
  • Protease inhibitors (PIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), etc.
  • Rifampicin >> Rifabutin
• For patients receiving PIs or NNRTIs, substitute rifabutin for rifampin, if available
• Alternative non-rifamycin regimens less optimal, longer duration of therapy
Co-treatment of OI and ART

<table>
<thead>
<tr>
<th>Potential challenges</th>
<th>Potential benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRIS</td>
<td>Reduced HIV progression</td>
</tr>
<tr>
<td>Co-toxicities</td>
<td>Reduced mortality</td>
</tr>
<tr>
<td>Drug-drug interactions</td>
<td>Clearance of OI</td>
</tr>
<tr>
<td>Absorption</td>
<td>Prevent OI recurrence</td>
</tr>
<tr>
<td>Pill burden</td>
<td></td>
</tr>
<tr>
<td>Adherence counseling</td>
<td></td>
</tr>
</tbody>
</table>
When to start ART after recent diagnosis of OI?
# Randomized Trials of Early Versus Late ART in Patients co-infected with HIV and Tuberculosis

<table>
<thead>
<tr>
<th>Study</th>
<th>SAPIT</th>
<th>SAPIT</th>
<th>CAMELIA</th>
<th>STRIDE</th>
<th>TIME</th>
<th>TB-HAART</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>642 (429 vs 213)</td>
<td>429 (214 vs 215)</td>
<td>661 (332 vs 329)</td>
<td>806 (405 vs 401)</td>
<td>156 (79 vs 77)</td>
<td>1538 (767 vs 771)</td>
</tr>
<tr>
<td>Trial design</td>
<td>Open label</td>
<td>Open label,</td>
<td>Open label,</td>
<td>Open label,</td>
<td>Open label,</td>
<td>DB, PC</td>
</tr>
<tr>
<td>Baseline CD4 (median; cells per μL)</td>
<td>&lt;500 (150)</td>
<td>&lt;500 (150)</td>
<td>≤200 (25)</td>
<td>&lt;250 (77)</td>
<td>&lt;350 (43)</td>
<td>&gt;220 (367)</td>
</tr>
<tr>
<td>Early ART group</td>
<td>≤4 weeks</td>
<td>≤4 weeks</td>
<td>≤2 weeks</td>
<td>≤2 weeks</td>
<td>≤4 weeks</td>
<td>≤2 weeks</td>
</tr>
<tr>
<td>Late ART group</td>
<td>At 6 months</td>
<td>≤8 weeks</td>
<td>≤8 weeks</td>
<td>8-12 weeks</td>
<td>≤12 weeks</td>
<td>At 6 months</td>
</tr>
<tr>
<td>Median follow-up (months)</td>
<td>12.1</td>
<td>17.7</td>
<td>25</td>
<td>25</td>
<td>12</td>
<td>24</td>
</tr>
<tr>
<td>IRR (95% CI; p value), early vs late ART Deaths or AIDS (per 100 person years)</td>
<td>0·44 (0·25 to 0·79; p=0·003)</td>
<td>0·96 (0·44 to 2·10; p=0·91)</td>
<td>IRR 0·32, 95% CI 0·07–1·13; p=0·06 for CD4 ≤ 50</td>
<td>0·62 (0·44 to 0·86; p=0·006)</td>
<td>0·32 (–1·8 to 8·1; p=0·45) Fewer new AIDS and death For CD4 ≤ 50</td>
<td>0·84 (0·25 to 2·90; p=0·99)</td>
</tr>
</tbody>
</table>
Deferred ART 2 months post TB Rx (n = 126)

Immediate ART within 1 wk post TB Rx (n = 127)

ART-naïve, TBM suspects (N = 253)

Immediate ART associated with more grade 4 adverse events

High mortality in both groups at 9 months but no significant difference: 76 in the immediate ART vs. 70 in the deferred ART (HR 12; 95% confidence interval, .81–1.55; P 5 .50).

Median CD4+ 40
Median viral load 5.4 log10 copies
In patients with TB meningitis and low CD4 cell counts, early ART may pose a risk that calls for careful monitoring and consultation with experts.

<table>
<thead>
<tr>
<th>CD4</th>
<th>Start ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>Within 2 weeks of TB Rx</td>
</tr>
<tr>
<td>&gt;50 and TB severe</td>
<td>Within 2 - 4 weeks of TB Rx</td>
</tr>
<tr>
<td>&gt;50 but TB not severe</td>
<td>Can defer ART beyond 2 - 4 weeks but should start within 8-12 weeks</td>
</tr>
</tbody>
</table>
**IRIS**

**Immune Reconstitution Inflammatory Syndrome (IRIS)**

- Clinical worsening in the setting of an adequate response to ART
  - “Paradoxical” worsening of previously known treated (completed or ongoing) opportunistic pathogen
  - “Unmasking” of subclinical opportunistic pathogen
### Incidence of Tuberculosis Immune Reconstitution Inflammatory Syndrome (IRIS) in Human Immunodeficiency Virus (HIV)–Tuberculosis Coinfection

<table>
<thead>
<tr>
<th>Study no.</th>
<th>Study, year</th>
<th>Years studied</th>
<th>Incidence of tuberculosis IRIS among HIV-positive patients with tuberculosis, proportion (%)</th>
<th>Median baseline parameters</th>
<th>Median time, days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Age of patients, years</td>
<td>CD4 cell count, cells/μL</td>
<td>Viral load, log_{10} copies/mL</td>
</tr>
<tr>
<td>1</td>
<td>Narita et al [82], 1998</td>
<td>1996–1997</td>
<td>12/33 (36)</td>
<td>40&lt;sup&gt;a&lt;/sup&gt;</td>
<td>51&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>Breton et al [83], 2004</td>
<td>1996–2001</td>
<td>16/37 (43)</td>
<td>35</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>Breen et al [84], 2004</td>
<td>1997–2002</td>
<td>14/50 (28)</td>
<td>36</td>
<td>NA</td>
</tr>
<tr>
<td>4</td>
<td>Kumarasamy et al [85], 2004</td>
<td>2000–2003</td>
<td>11/144 (8)</td>
<td>29</td>
<td>123</td>
</tr>
<tr>
<td>5</td>
<td>Lawn et al [80], 2007</td>
<td>2002–2005</td>
<td>19/160 (12)</td>
<td>35</td>
<td>68</td>
</tr>
</tbody>
</table>

**NOTE.** ART, antiretroviral therapy; NA, not available.

<sup>a</sup> Mean.

---

IRIS

• Risk factors
  • Disseminated TB
  • Shorter delay between onset of TB and ART drugs
  • Low baseline CD4, higher baseline viral load
  • Greater CD4 or viral load response to ART

• Timing of onset
  • Usually within first 6 weeks of ART (often 2–3 weeks, but can be months after ART started)
Clinical presentation:
- Fever
- Nodal enlargement
- Worsening pulmonary infiltrates (with or without respiratory symptoms)
- Local worsening in extrapulmonary sites
IRIS Differential Diagnosis

- TB treatment failure
- Drug-resistant TB
- ART failure
- Other opportunistic (or non-opportunistic) infections
- Lymphoma, Kaposi’s sarcoma
- Hypersensitivity drug reactions
IRIS Management

- Continue TB treatment
- Continue ART
- Exclude TB treatment failure
  - Adherence
  - Drug resistance
- Exclude additional/new diagnosis
- Consider NSAIDS, steroids
- Drainage of lesions
Tuberculosis in the Setting of HIV

Summary

• Substantial global disease burden, individually and as coinfection
• HIV adversely affects the entire spectrum of the natural history of tuberculosis
• Difficulties in diagnosis and treatment
• Simultaneous ART and TB treatment is challenging
• ART is critical for a positive outcome of tuberculosis and HIV
Mrs. T.B. is a 26-year-old pregnant woman diagnosed with HIV during routine prenatal care. She has no complaints.

- Her medical history is unremarkable.
- She is not taking any medications except multivitamins.
- She was born in the US, is single, a middle school teacher, denies foreign travel, denies TB exposure.
- Complete blood count and chemistry are within normal limits.
- CD4+ count 120 mm$^3$; viral load is pending.
Which one of the statements below is correct regarding testing this patient for latent tuberculosis?

a) Defer testing for LTBI until CD4 is above 200
b) No need to test for LTBI as she has no risk factors
c) Check TST and T-SPOT
d) Prefer T-SPOT over other testing as her CD4 count is below 200
e) Use any of the 3 tests: TST, QFT, or T-SPOT
Mr. J.K., a 35yo paramedic, was referred to you for addressing a positive tuberculin skin test result. He was diagnosed with HIV a few weeks ago but had declined treatment for it because his CD4 count was high and his viral load was low. Denies TB exposure; no previous TST. Unremarkable medical history.

- He has no symptoms; feels well
- Exam unremarkable
- TST 10mm
- Chest X-ray is unremarkable
- CBC and Chemistry WNL
- CD4+ 820 mm³; viral load is 2600 copies/mL
Which one of the management options below is the most appropriate?

a) Confirm TST result with an IGRA test as it is not compatible with patient’s history

b) Offer no LTBI treatment as the CD4 count is high and the risk of reactivation is minimal

c) Offer treatment for LTBI when the CD4 count falls below 200

d) Prescribe INH 300mg daily for 6 month

e) Prescribe Isoniazid and Rifapentine once weekly for 12 weeks
You have been managing a case of smear and culture positive, pulmonary, non-cavitary TB in an HIV patient with a baseline CD4 cell count of 40 cells/mm$^3$ and HIV RNA 150,000 copies/mL. He is on INH/RIF/EMB/PZA daily in addition to EFV/TDF/FTC, all at standard doses, and has tolerated them.

- AST – 48 µ/L
- ALT – 46 µ/L
- CD4 – 210 cells/mm$^3$
- HIV RNA - undetectable
- TB DST – susceptible to all first line agents
- Sputum AFB negative at 2, 4, 8 wks.
- Cultures negative at 2 and 4 wks, 8-wk cx pending.
Based on the follow up data, which of the following would you recommend regarding your patient’s TB Rx?

a) Continue INH/RIF/PZA daily for an additional 4 months

b) Continue INH/RIF daily for an additional 7 months

c) Continue INH/RIF twice weekly for an additional 4 months

d) Continue INH/RIF three times weekly for an additional 4 months

e) Prescribe INH + Rifapentine once weekly for an additional 16 weeks
Your HIV-infected patient with drug-susceptible TB meningitis returns to you after 6 weeks on ART and anti-TB therapy with complaints of headache, vomiting and drowsiness. Positive physical examination findings include T= 38.2°C, tachycardia, drowsy but arousable, gait unsteadiness and intention tremor.

CBC, chemistry WNL
CD4 – 280 cells/mm³
HIV RNA - undetectable
Which of the following is the LEAST appropriate next step in managing this patient?

a) Evaluate patient for drug resistance
b) Evaluate patient for lymphoma
c) Evaluate patient for drug absorption issues
d) Evaluate patient for a new opportunistic condition
e) Stop antiretroviral therapy