TB and HIV Co-infection - Research Update

Tennessee 2016 Clinical TB Symposium
April Pettit, MD, MPH
March 30, 2016

Objectives

1. Describe the epidemiology of TB-HIV co-infection nationally, statewide, and locally in order to achieve early diagnosis and timely treatment for this population.
2. Identify risk factors for poor outcomes among TB-HIV co-infected persons to prevent transmission and to improve diagnosis and treatment outcomes.
3. Discuss challenges in the diagnosis and management of TB in persons with HIV co-infection to improve completion of treatment and treatment outcomes.

Case

• 25yo African American man with diarrhea, subjective fevers/chills, and 30 pound weight loss—he denies respiratory symptoms.
• PMH: HIV (CD4+ 32, VL 298K)—ART naïve
• PE unremarkable aside from being underweight
• TST no induration
• Patient had no cough and was unable to produce an induced sputum specimen
• ART was initiated

20 days later….

• Patient presented with fever to 104 and cough
• TST was repeated-24mm induration
• Induced sputum AFB smear negative
• BAL AFB smear negative
• All cultures several weeks later subsequently grew drug-susceptible MTB

Outline

• Epidemiology of TB/HIV co-infection
• Risk of TB disease among HIV-infected persons
• Clinical Manifestations
• Diagnosis
• Treatment
• Timing of HAART initiation

TB Case Rates,* United States, 2014

*Cases per 100,000.

< 3.0 (2014 national average)

> 3.0

D.C.
Estimated HIV Coinfection in Persons Reported with TB, United States, 1993 - 2014*

HIV Coinfection in Persons Reported with TB, Tennessee, 2009- 2015

Outline

- Epidemiology of TB/HIV co-infection
- Risk of TB disease among HIV-infected persons
  - CD4, ART, LTBI
- Clinical Manifestations
- Diagnosis
- Treatment
- Timing of HAART initiation

CD4 and TB Risk

- 1130 HIV+ persons not on ART (U.S. Pulmonary Complications of HIV Study Group)
  - TB risk greater with lower CD4 count
  - CD4 < 200: 1-2 TB cases per 100 p-y
  - CD4 > 200: 0.5 TB cases per 100 p-y
  - RR: 2.4 (95% CI: 1.1, 5.2)

- 944 HIV+ persons receiving ART (South Africa)
  - TB risk associated only with current CD4 count (within 4 months)
  - 25% decrease in TB risk per 100 cell ↑ in CD4 count

ART and TB Risk

<table>
<thead>
<tr>
<th></th>
<th>No ART</th>
<th>ART</th>
<th>HAART</th>
</tr>
</thead>
<tbody>
<tr>
<td>U.S.</td>
<td>720</td>
<td>470 (40%↓)</td>
<td>190 (80%↓)</td>
</tr>
<tr>
<td>S. Africa</td>
<td>9700</td>
<td>2400 (81%↓)</td>
<td></td>
</tr>
</tbody>
</table>


Lawn et. al. AIDS 2006;20:1605-12.
ART and TB risk

<table>
<thead>
<tr>
<th>Time Interval</th>
<th>TB cases</th>
<th>Follow-up (p-y)</th>
<th>TB incidence (per 100K p-y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Off HAART</td>
<td>31</td>
<td>33,577</td>
<td>93</td>
</tr>
<tr>
<td>HAART initiation—&lt;3 months</td>
<td>8</td>
<td>5,227</td>
<td>53</td>
</tr>
<tr>
<td>&gt;3 months—&lt;6 months</td>
<td>13</td>
<td>5,112</td>
<td>254</td>
</tr>
<tr>
<td>&gt;6 months</td>
<td>42</td>
<td>103,857</td>
<td>40</td>
</tr>
<tr>
<td>Overall</td>
<td>94</td>
<td>147,557</td>
<td>64</td>
</tr>
</tbody>
</table>

Pettit et al. JAcids (in press).

Hypothesis 1: Immune Reconstitution Inflammatory Syndrome (IRIS)

Pettit et. al. JAIDS (in press).

Hypothesis 2: ART Started at low CD4

Marginal Structural Model

Adjusting for time-updated CD4 and ART exposure

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ITT Analysis (aOR, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAART status</td>
<td></td>
</tr>
<tr>
<td>Not on HAART</td>
<td>Reference</td>
</tr>
<tr>
<td>&gt;6 months of HAART</td>
<td>0.29 (0.16, 0.53)</td>
</tr>
</tbody>
</table>

Mancuso et al. AJRCCM 2016 [Epub ahead of print].

HIV and LTBI reactivation risk

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Est # of NHANES subjects</th>
<th>TST LTBI Prev (95% CI)</th>
<th>QFT-GIT LTBI Prev (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All participants</td>
<td>282,460</td>
<td>4 (3.1-6.1)</td>
<td>4.8 (4.0-5.8)</td>
</tr>
</tbody>
</table>

Mancuso et al. AJRCCM 2016 [Epub ahead of print].

LTBI Prevalence

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Est popln N x (1,000)</th>
<th>TST LTBI Prev (95% CI)</th>
<th>QFT-GIT LTBI Prev (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All participants</td>
<td>16</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

LTBI Testing Guidelines

- All persons should be tested for LTBI at the time of HIV diagnosis regardless of risk
- Persons with negative diagnostic tests for LTBI and CD4+ <200 should be retested once they start ART and CD4+ >200
- Annual testing with high risk persons: incarceration, congregate settings, active drug users, etc

Clinical Manifestations

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Sensitivity 95% CI</th>
<th>Specificity 95% CI</th>
<th>Likelihood Ratio Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>38.5 (19.2–62.2)</td>
<td>81.8 (65.3–91.5)</td>
<td>0.753 (0.724–0.783)</td>
</tr>
<tr>
<td>Fever</td>
<td>42.8 (22.2–66.3)</td>
<td>79.8 (62.4–90.4)</td>
<td>0.716 (0.665–0.738)</td>
</tr>
<tr>
<td>Night sweats</td>
<td>31.4 (14.8–54.6)</td>
<td>82.2 (65.9–91.7)</td>
<td>0.812 (0.780–0.843)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>49.3 (25.6–71.9)</td>
<td>71.1 (50.3–85.5)</td>
<td>0.712 (0.669–0.753)</td>
</tr>
<tr>
<td>Any</td>
<td>38.9 (28.3–50.5)</td>
<td>49.6 (29.2–70.1)</td>
<td>0.426 (0.349–0.520)</td>
</tr>
</tbody>
</table>


Extrapulmonary TB


Outline

- Epidemiology of TB/HIV co-infection
- Risk of TB disease among HIV-infected persons
- Clinical Manifestations
- Diagnosis
- Treatment
- Timing of HAART initiation

Diagnosis - Chest Radiography

<table>
<thead>
<tr>
<th>CXR Findings</th>
<th>HIV+ N=72</th>
<th>HIV- N=52</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal infiltrate</td>
<td>18 (55%)</td>
<td>46 (89%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Upper lobe infiltrate</td>
<td>19 (26%)</td>
<td>32 (62%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Cavitory Disease</td>
<td>5 (7%)</td>
<td>23 (44%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LAD</td>
<td>28 (55%)</td>
<td>6 (12%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Normal</td>
<td>18 (35%)</td>
<td>3 (6%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Alpert et al. CID 1997; 24: 661-8.
Diagnosis-Sputum Smear

<table>
<thead>
<tr>
<th>Smear status</th>
<th>HIV+ N=64</th>
<th>HIV- N=43</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFB+, Number (%)</td>
<td>35</td>
<td>32</td>
</tr>
<tr>
<td>54.3%</td>
<td>74.3%</td>
<td></td>
</tr>
<tr>
<td>AFB-, Number (%)</td>
<td>29</td>
<td>11</td>
</tr>
<tr>
<td>45.7%</td>
<td>25.5%</td>
<td></td>
</tr>
</tbody>
</table>

Alpert et. al. CID 1997; 24: 661-8.

Diagnosis-Sputum Culture

<table>
<thead>
<tr>
<th>Culture status</th>
<th>HIV+ N=169</th>
<th>HIV- N=124</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culture+, Number (%)</td>
<td>109</td>
<td>110</td>
</tr>
<tr>
<td>66.1%</td>
<td>88.7%</td>
<td></td>
</tr>
<tr>
<td>Culture-, Number (%)</td>
<td>56</td>
<td>14</td>
</tr>
<tr>
<td>33.9%</td>
<td>11.3%</td>
<td></td>
</tr>
</tbody>
</table>


Diagnosis-Xpert MTB/RIF

<table>
<thead>
<tr>
<th>HIV Status</th>
<th>Overall Sensitivity</th>
<th>Smear Negative Sensitivity</th>
<th>Smear Positive Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>86 (76, 92)</td>
<td>67 (60-74)</td>
<td>98 (97-99)</td>
</tr>
<tr>
<td>Positive</td>
<td>79 (70, 86)</td>
<td>61 (40-83)</td>
<td>97 (90-99)</td>
</tr>
</tbody>
</table>


Diagnosis-Xpert

<table>
<thead>
<tr>
<th>Sample</th>
<th>Pooled Sensitivity Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF</td>
<td>Cannot Calculate</td>
</tr>
<tr>
<td>Pleural Fluid</td>
<td>34 (24-44%)</td>
</tr>
<tr>
<td>Non-pleural serous Fluid</td>
<td>Cannot Calculate</td>
</tr>
<tr>
<td>All Tissue</td>
<td>88 (77-95%)</td>
</tr>
<tr>
<td>Lymph node</td>
<td>98 (72-99%)</td>
</tr>
<tr>
<td>Gastric Aspirate</td>
<td>78 (69-86%)</td>
</tr>
<tr>
<td>Smear positive</td>
<td>95 (91-100%)</td>
</tr>
<tr>
<td>Smear negative</td>
<td>69 (60-80%)</td>
</tr>
</tbody>
</table>

Maynard-Smith et. al. BMD Infec Dis 2014; (14): 709.

Outline

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- Timing of HAART Initiation

Initiation Phase=2 months HRZE

- Interval
  - Daily throughout (5-7 days per week) as DOT
  - Intermittent therapy associated with treatment failure or relapse with acquired rifamycin resistance

**Initiation Phase=2 months HRZE**

- **Regimen**
  - INH 300mg daily
  - No ART interactions
  - PZA dosed by weight
  - No ART interactions
  - EMB dosed by weight and discontinued when susceptibilities known (unless PZA not used)
  - No ART interactions


**Initiation Phase=2 months HRZE**

- **Rifampin 600mg daily**
  - If patient is on NNRTI (usually Nevirapine or Efavirenz) based regimen
  - Weight-based dosing of Efavirnez is not required

- **Rifabutin 300mg daily**
  - If patient is on PI-based regimen, decrease Rifabutin dose to 150mg daily
  - If patient is on Integrase Inhibitor based therapy (Raltegravir), no dosing changes are needed


**Continuation Phase**

- **Interval**
  - Daily throughout (5-7 days per week) as DOT
  - Once or twice weekly intermittent therapy associated with treatment failure or relapse with acquired rifamycin resistance
  - Thrice weekly intermittent therapy
  - Not studied adequately in clinical trials
  - No increased risk of adverse outcomes in observational studies and meta-analyses


**Continuation Phase**

- **Regimen**
  - INH 300mg daily or 900mg tiw
  - RIF 600mg daily /tiw OR RBT 300mg daily /tiw

- **Duration-optimum unknown**
  - 4 months is recommended
  - 4-7 months for bone/joint
  - 7 months
  - +ve cultures after intensive phase
  - 7-10 months for CNS disease


**HIV and Relapse**

Adjusted Odds of Relapse Stratified by Use of ART


**Therapeutic Drug Monitoring**

- HIV-infected persons have MANY reasons for low anti-TB drug levels
  - Drug-drug interactions due to
    - Antiretroviral medications
    - Treatment for other opportunistic infections
    - Multi-way interactions between treatment for both of the above
    - Malabsorption in the setting of malnutrition or diarrhea

Therapeutic Drug Monitoring

*Significant correlation between CD4 and urinary RMP.


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When to Start ART

- **Favors early start:**
  - Improved survival
  - Decreased risk of additional opportunistic infections
  - May improve TB outcomes

- **Favors delayed start:**
  - Large pill burden leads to decreased adherence
  - Drug-drug interactions
  - Overlapping side effects
  - Immune reconstitution inflammatory syndrome (IRIS)

ACTG 5221 STRIDE Study

- Immediate (within 2 weeks of TB tx) to early ART (within 8-12 weeks of TB tx)

Guidelines-When to Start ART

- ART is recommended in all HIV-infected persons with TB (AI)
- Sequential treatment NOT recommended
  - Within 2 weeks if CD4<50 (AI)
  - Within 8-12 weeks if CD4>50 (AI)

Conclusions

- TB/HIV co-infection remains an important public health problem in the US.
- CD4, antiretroviral therapy, and latent TB infection are all important risk factors for TB disease in HIV-infected person.
- TB disease can be difficult to diagnose in HIV-infected persons.
- If clinical improvement is slower than expected, consideration should be given to longer continuation phase duration and/or therapeutic drug monitoring.