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

Manabe et. al. JID 2009; 199(3): 437-44.
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

Manabe et. al. JID 2009; 199(3): 437-44.
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.
Question

What is the estimated proportion of TB cases in the US and Tennessee are co-infected with HIV?

A. 2%
B. 5%
C. 10%
D. 20%
Estimated HIV Coinfection in Persons Reported with TB, United States, 1993 - 2014*

*Updated as of June 5, 2015.

Note: Minimum estimates based on reported HIV-positive status among all TB cases in the age group.
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
Exposure

Infection (LTBI) 10-30%

No Infection 70-90%

Latent Infection 70-90%

Primary Active Disease 10-30%

Reactivation

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

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

TB rate per 100,000 person-years:

<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></td>
<td>2400 (81%↓)</td>
</tr>
</tbody>
</table>

Badri et. al. Lancet 2002;359:2059-64
## 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>33,371</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>63, 132</td>
</tr>
<tr>
<td>HAART initiation-&lt;3 months</td>
<td>8</td>
<td>5,217</td>
<td>153</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>66, 302</td>
</tr>
<tr>
<td>&gt;3 months -≤6 months</td>
<td>13</td>
<td>5,112</td>
<td>254</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>135, 434</td>
</tr>
<tr>
<td>&gt;6 months</td>
<td>42</td>
<td>103,857</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>29, 55</td>
</tr>
<tr>
<td>Overall</td>
<td>94</td>
<td>147,557</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>51, 78</td>
</tr>
</tbody>
</table>

Pettit et. al. JAIDS (in press).
Hypothesis 1: Immune Reconstitution Inflammatory Syndrome (IRIS)

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>≤6 months of HAART</td>
<td>0.65 (0.28, 1.51)</td>
</tr>
<tr>
<td>&gt;6 months of HAART</td>
<td>0.29 (0.16, 0.53)</td>
</tr>
</tbody>
</table>

Pettit et al. JAIDS (in press).
## LTBI Prevalence

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Est. popln N x (1,000)</th>
<th>TST</th>
<th>QFT-GIT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>LTBI Prev (95% CI)</td>
<td>Est. popln w/ LTBI x (1,000)</td>
</tr>
<tr>
<td>All participants</td>
<td>282,460</td>
<td>4.4 (3.1-6.1)</td>
<td>12,398 (8,869-17,230)</td>
</tr>
</tbody>
</table>

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

Mancuso et. al. AJRCCM 2016 [Epub ahead of print].
## HIV and LTBI reactivation risk

<table>
<thead>
<tr>
<th></th>
<th>Est # Cases</th>
<th>Est % of US Popln w/ LTBI</th>
<th>Est US popln</th>
<th>Est p-y at risk for TB</th>
<th>Est Rate TB per 100 p-y</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV+</td>
<td>2,198</td>
<td>4.2</td>
<td>961,000</td>
<td>121,100</td>
<td>1.82 (1.74-1.89)</td>
</tr>
<tr>
<td>HIV-</td>
<td>16,568</td>
<td>4.2</td>
<td>182,243,000</td>
<td>22,850,000</td>
<td>0.073 (0.070-0.075)</td>
</tr>
</tbody>
</table>

Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents

Recommendations from the Centers for Disease Control, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America

*Mycobacterium tuberculosis* Infection and Disease  (Last updated May 7, 2013; last reviewed May 7, 2013)
Question

CDC Guidelines for the prevention of TB disease state that testing for latent TB infection should occur for ALL HIV-infected persons:

A. At the time of HIV diagnosis AND yearly after the first test regardless of risk

B. At the time of HIV diagnosis regardless of risk AND yearly after the first test only if other risk factors are identified

C. At the time of HIV diagnosis only if other risk factors are identified AND subsequent testing is not indicated
• 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
Outline

• Epidemiology of TB/HIV co-infection
• Risk of TB disease among HIV-infected persons
• Clinical Manifestations
• Diagnosis
• Treatment
• Timing of HAART initiation
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 (0.695–0.738)</td>
</tr>
<tr>
<td>Night sweats</td>
<td>31.4 (14.8–54.6)</td>
<td>82.2 (65.9–91.7)</td>
<td>0.835 (0.780–0.893)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>49.3 (27.0–71.9)</td>
<td>71.1 (50.8–85.5)</td>
<td>0.712 (0.693–0.733)</td>
</tr>
<tr>
<td>Any</td>
<td>78.9 (58.3–90.9)</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></th>
<th>HIV+ N=72</th>
<th>HIV- N=52</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal infiltrate</td>
<td>38 (53%)</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>Cavitary Disease</td>
<td>5 (7%)</td>
<td>23 (44%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LAD</td>
<td>28 (39%)</td>
<td>6 (12%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Normal</td>
<td>8 (11%)</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 54.3%</td>
<td>32 74.5%</td>
</tr>
<tr>
<td>AFB-, Number (%)</td>
<td>29 45.7%</td>
<td>11 25.5%</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=165</th>
<th>HIV- N=124</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culture+, Number (%)</td>
<td>109 (66.1%)</td>
<td>110 (88.7%)</td>
</tr>
<tr>
<td>Culture-, Number (%)</td>
<td>56 (33.9%)</td>
<td>14 (11.3%)</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 (40-81)</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>96 (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

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

The dosing interval in the continuation phase for HIV-infected persons can be:

A. Daily
B. Once-weekly
C. Twice-weekly
D. Three times weekly
E. A or D
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

*Significant correlation between CD4 and urinary RMP.

Outline

- Epidemiology of TB/HIV co-infection
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- Timing of HAART Initiation
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)

Havlir et. al. NEJM 2011; 365 (16):1482-91
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 coinfection 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.
Questions?