Tuberculosis and Co-Morbidities
Lisa Y. Armitige, MD, PhD
March 13, 2015

TB for Pulmonologist
Phoenix, AZ
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Lisa Y. Armitige, MD, PhD has the following disclosures to make:

- No conflict of interests
- No relevant financial relationships with any commercial companies pertaining to this educational activity
Diabetes

Type 2 Diabetes

- Increased risk has been noted in many racial and ethnic populations
  - African Americans
  - Hispanic/Latino Americans
  - Native Americans
  - Asian Americans

- Globally urbanization has fueled an increasing incidence in Africa, India, Asia
  - Areas of world with high rates of tuberculosis
US cases of diabetes

US cases of DM, 2011
Age/Race
Age-adjusted Prevalence of Obesity and Diagnosed Diabetes Among US Adults


Does Diabetes Predispose to TB?
Diabetes: a Moderate to Strong Risk Factor for TB

- 2008 Meta analysis
  - 13 studies many areas of world showed increased risk of TB in persons with diabetes
    - 3 prospective cohort studies showed RR 3.1
    - 8 case-control studies and 2 other types- OR 1.2-7.8
  - Association of Diabetes and TB stronger
    - With higher background TB incidence
    - In younger age groups
    - In Central America, Asia, Europe
    - Among North Americans the RR for Hispanics 2.69

Jeon, PLoS Medicine, 2008

Diabetes Predisposes to TB

- Hong Kong prospective study of 4661 close contacts of active TB cases
  - RR 3.4 in diabetics for both
    - early – primary progressive disease (3 month)
    - and late- reactivation disease (within 5 years)

Lee MS, Int J Tuberc Lung 2008
Global Prevalence of Tuberculosis and Diabetes, 2008

Tuberculosis
- 12.7 million people (9.4 WHO 2010)
- 95% in developing countries

Diabetes Mellitus
- 171 million people (285 WHO 2010)
- 70% in developing countries

(Source: World Health Organization, 2008)

Linkage Between Tuberculosis and Diabetes

- Patient diagnosed with Diabetes
- Immune Response is weakened
- Exposure to M. Tuberculosis
- Increased susceptibility for LBTI or TB Disease
Latent TB Infection (LTBI) in Diabetic Patients

• Persons with high incidence areas with diabetes should be screened for TB with an IGRA or TST
  – Communicate risk of progression to disease to community physicians caring for diabetics
  – If LTBI is found, treat for latent infection
  – INH for 9 months is the best known approach but there are other shorter options. Rifamycins are safe but may have medication interactions
  – Be sure to include Vitamin B6 if you treat with INH
    • Neuropathy is complication of diabetes and a side effect of INH

Presentation of TB in Diabetics

• Various reports of more severe disease

• Varying findings as to the radiographic presentation
  – ? More cavities
  – ? Isolated lower lung involvement
Classic Article Prior to Availability of TB Medications
Howard Root MD, Deaconess Hospital, Boston
NEJM, 1934

- Autopsy series of 126 patients: no pathological findings unique to “the tubercular diabetic”
- 245 TB cases in diabetic patients, “no special insidiousness” of signs or symptoms and similar CXR findings to non-diabetics
- Did note that TB developed most frequently in patients with poor diabetic control

TB and Diabetes, CXR Findings

Table 2: Studies assessing chest radiographic findings in patients with tuberculosis, comparing diabetic to non-diabetic patients

Dooley, & Chaisson, Lancet ID, Dec, 2009
Does Diabetes Impact TB Treatment and Cure?

- Previously thought not to affect treatment

- Four new studies from Baltimore, Texas, Taiwan and Indonesia reveal:
  - Delayed culture conversion
  - Higher mortality

Dooly, 2009; Restrepo 2008; Wang 2008; Alisahlanda, 2007
Response to Treatment

• Relapse may be more frequent
  – Recent Shanghai study 203 diabetics with TB followed for 2 years after standard treatment

  • 20% relapse rate in patients with DM (most Type 2)
  • 5% relapse rate in patients without DM

  Zhang et al. Jpn J Infect Dis, 2009

Hyperglycemia in Patients with TB

• Blood glucose control may worsen while patients are taking Rifampin
  – Rifampin augments intestinal absorption of glucose
  – Does so in both diabetics and non-diabetics

• Infections impair glucose tolerance early in disease in both diabetics and non-diabetics
  – Independent of rifampin, infection can lead to poor glucose control
Low Blood Levels of Rifampin in Diabetics: Indonesia

- 17 Patients with Diabetes and Tuberculosis
- Rifampin levels decreased 50%
  - Perhaps related to higher BMI in diabetics
- Is a different dose of rifampin needed?
  - Mg/kg?

Hanneke M. J. Nijland Clinical Infectious Diseases, 43 2006

Treatment Issues – Rifampin

- Rifampin induces CYP450 enzyme system increasing production of enzymes that metabolize many drugs
  - Increased metabolism results in lower blood levels of drug (20 – 40+%)
  - Affects many classes of diabetic medications
TB and Diabetes - Treatment Issues

• **Diabetic neuropathy** at baseline complicates therapy due to INH-related neuropathy
  – Baseline assessment of neuropathy
  – Vitamin B6 (pyridoxine) to all diabetics on INH or ethionamide

• **Renal insufficiency** is associated with diabetes, especially long standing or poorly controlled diabetes
  – Adjust dose and dosing interval of EMB & PZA in those with Creatinine Cl < 30

TB and Diabetes - Treatment Issues

• Diabetics have an increased risk of hepatotoxicity
  – Multiple medications
  – Fatty liver

• Monitoring and education are very important
  – Baseline and monthly liver enzymes

  – Educate regarding risk of liver toxicity, symptoms to watch for, and what to do should these occur
    • Contact provider
    • Hold TB medications until liver injury excluded
HIV

Estimated Incidence of TB per 100,000 Population in African Countries in 1990 and 2005

Estimated HIV Coinfection in Persons Reported with TB, United States, 1993 – 2013*

*Updated as of June 11, 2014.

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

Outcomes of Exposure to M. tuberculosis

Inhalation of Droplet Nuclei

Regional replication in lungs, dissemination

~90% ~5% ~5%

Killing, clearance of organisms  Latent disease  Active disease
Outcomes of Exposure to *M. tuberculosis* in HIV-negative and HIV-positive patients

Inhalation of Droplet Nuclei

↓

Regional replication in lungs, dissemination

~90%

10% reactivation per year

~5% reactivation lifetime

Killing, clearance of organisms

Latent disease

Active disease

~5% lifetime

Up to 36% active disease

Clinical Presentation

HIV-positive vs. HIV-negative patients

• Driven mostly by degree of immunity

• HIV-positive patients are more likely to have:
  
  – Isolated extrapulmonary localization (53-63% in some studies)
  – Primary infection
  – Pulmonary basilar involvement
  – Tuberculous pneumonia
  – Hilar or mediastinal lymphadenopathies
  – Miliary or disseminated TB
  – Normal CXR (8-20% in some studies)
Classifying the Tuberculin Reaction

5 mm is classified as positive in

- HIV-positive persons
- Recent contacts of TB case
- Persons with fibrotic changes on chest radiograph consistent with old healed TB
- Patients with organ transplants and other immunosuppressed patients

Diagnosis

Table 1. Bacteriological and histological results observed during HIV-associated TB as a function of immune status

<table>
<thead>
<tr>
<th></th>
<th>CD4 &lt; 200/mm³</th>
<th>CD4 &gt; 200/mm³</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive tuberculin skin test reaction (&gt; 5 mm without BCG)</td>
<td>30%*</td>
<td>50%*</td>
<td>[23]</td>
</tr>
<tr>
<td>Acid-fast bacilli on smear</td>
<td>56–60%</td>
<td>50–58%</td>
<td>[22,23,25]</td>
</tr>
<tr>
<td>Acid-fast bacilli on biopsy</td>
<td>60–65%</td>
<td>50–56%</td>
<td>[22]</td>
</tr>
<tr>
<td>Granuloma in biopsy</td>
<td>60–75%</td>
<td>67–100%</td>
<td>[23,31,32]</td>
</tr>
<tr>
<td>Mycobacteraemia</td>
<td>20–49%</td>
<td>0–7%</td>
<td>[22,30]</td>
</tr>
</tbody>
</table>
Role of interferon-gamma release assays in the diagnosis of pulmonary tuberculosis in patients with advanced HIV infection

Cattamanchi et al. BMC Infectious Diseases 2010, 10:75

- 372 HIV+ patients received all 3 tests
- Demographics:
  - 50% IVDU,
  - 74.5% on ART,
  - 16.6% with CD4 count < 200,
  - some with history of TB or LTBI

Figure 1 Venn diagram illustrating how often the tuberculin skin test (TST), Quantiferon-TB Gold (QFG), and T-SpotTB tests coincide in terms of positives as defined by the manufacturers in 372 HIV-infected patients (A) and in 302 HIV-infected patients with no past or current TB nor treated for latent tuberculosis infection (B).
All patients who could produce a sputum screened
- 881 patients enrolled, 70.9% HIV positive
- Culture confirmed TB in 201
- HIV patients:
  - 88.2% sensitivity overall
  - 74.7% sensitive in culture +, smear negative specimens

CXR – HIV infected persons

- May cause infiltrates without cavities in any lung zone
- May cause mediastinal or hilar lymphadenopathy with or without infiltrates or cavities

In HIV-infected persons, almost any abnormality on CXR may indicate TB
Clinical Presentation
HIV-positive vs. HIV-negative patients

• Driven mostly by degree of immunity

• HIV-positive patients are more likely to have:
  – Isolated extrapulmonary localization (53-63% in some studies)
  – Primary infection
  – Pulmonary basilar involvement
  – Tuberculous pneumonia
  – Hilar or mediastinal lymphadenopathies
  – Miliary or disseminated TB
  – Normal CXR (8-20% in some studies)

Primary Tuberculosis
### Tuberculosis and HIV

An Algorithm for Tuberculosis Screening and Diagnosis in People with HIV


**Appendix Table 1.** Smear and culture results of patients with TB (N=267), stratified by symptoms and chest radiograph result.

<table>
<thead>
<tr>
<th>Symptoms*</th>
<th>Chest radiograph</th>
<th>Enrolled patients, n</th>
<th>TB diagnosed, n</th>
<th>Positive acid-fast smear, n</th>
<th>Number of positive cultures, n (% of TB diagnosed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>Normal</td>
<td>493</td>
<td>7 (1)</td>
<td>0</td>
<td>5 (71) 2 (29)</td>
</tr>
<tr>
<td>Present</td>
<td>Normal</td>
<td>865</td>
<td>87 (10)</td>
<td>26 (30)</td>
<td>40 (46) 47 (54)</td>
</tr>
<tr>
<td>Absent</td>
<td>Abnormal</td>
<td>56</td>
<td>11 (20)</td>
<td>3 (27)</td>
<td>2 (18) 9 (82)</td>
</tr>
<tr>
<td>Present</td>
<td>Abnormal</td>
<td>334</td>
<td>162 (49)</td>
<td>92 (57)</td>
<td>21 (13) 140 (87)</td>
</tr>
</tbody>
</table>

*Any one of: any cough in the past 4 weeks, any fever in the past 4 weeks, or night sweats for ≥3 weeks.
Bacteriologic or histologic exam

- **Sputum**
  - Three (8-24 hours apart, at least one first thing in the morning)

- **Tissue**
  - Lymph node biopsy
  - Bone marrow biopsy

- **Other specimens**
  - Urine
  - CSF
  - Peritoneal fluid
  - Pleural fluid (pleural biopsy)

Testing for TB Infection - Some Principles to Consider

- **Individuals who have a**
  - + TST result,
  - a + IGRA result or
  - symptoms suggestive of TB (regardless of TST/IGRA results)
  - should be evaluated with an chest x-ray

- **Patients with HIV who may not react to testing by TST or IGRA should have a chest x-ray if TB is suspected or if exposed to an active TB case**

- **If abnormalities are noted, or the client has symptoms suggestive of extrapulmonary TB, additional diagnostic tests should be conducted**
Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents

HIV-infected persons, regardless of age, should be treated for LTBI if they have no evidence of active TB and exhibit the following characteristics:

- 1) a positive diagnostic test for LTBI and no prior history of treatment for active or latent TB (AI);
- 2) a negative diagnostic test for LTBI but are close contacts of persons with infectious pulmonary TB (AII); and
- 3) a history of untreated or inadequately treated healed TB (i.e., old fibrotic lesions on chest radiography) regardless of diagnostic tests for LTBI (AII)

Risk reduction by treatment of Latent TB Infection (LTBI) in HIV-infected patients
Initiating Treatment for LTBI

Before initiating treatment for LTBI

- Rule out TB disease
  - i.e. wait for culture results if specimen obtained
- Determine prior history of treatment for LTBI or TB disease
- Assess risks and benefits of treatment
- Determine current and previous drug therapy

LTBI treatment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interval and duration</th>
<th>Comments</th>
<th>Rating (Evidence)</th>
<th>HIV-negative</th>
<th>HIV-infected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>Daily for 9 months**</td>
<td>In HIV-infected persons, isoniazid may be administered concurrently with nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors, or non-nucleoside reverse transcriptase inhibitors (NNRTIs).</td>
<td>A (B)</td>
<td>A (B)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Twice weekly for 9 months*</td>
<td>Directly observed therapy (DOT) must be used with twice-weekly dosing.</td>
<td>B (B)</td>
<td>B (B)</td>
<td></td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Daily for 6 months*</td>
<td>Not indicated for HIV-infected persons, those with fibrotic lesions on chest radiographs, or children.</td>
<td>B (B)</td>
<td>C (B)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Twice weekly for 6 months*</td>
<td>DOT must be used with twice-weekly dosing.</td>
<td>B (B)</td>
<td>C (B)</td>
<td></td>
</tr>
<tr>
<td>Rifaximin**</td>
<td>Daily for 4 months</td>
<td>Used for persons who are contacts of patients with isoniazid-resistant, rifampin-susceptible TB.</td>
<td>B (B)</td>
<td>B (B)</td>
<td></td>
</tr>
<tr>
<td>Rifaximin plus</td>
<td>Daily for 2 months</td>
<td>In HIV-infected persons, most protease inhibitors or deoxyxymethamphetamine should not be administered concurrently with rifampin. Rifabutin with appropriate dose adjustments can be used with protease inhibitors (saquinavir should be augmented with ritonavir) and NNRTIs (except delavirdine). Clinicians should consult web-based updates for the latest specific recommendations.</td>
<td>D (B)</td>
<td>D (B)</td>
<td></td>
</tr>
<tr>
<td>Pyrazinamide (RZ)</td>
<td>Twice weekly for 2-3 months</td>
<td>RZ generally should not be offered for treatment of LTBI for HIV-infected or HIV-negative persons.</td>
<td>D (B)</td>
<td>D (B)</td>
<td></td>
</tr>
</tbody>
</table>

MMWR August 8, 2003 / Vol. 52 / No. 31
ATS recommendations for treatment of tuberculosis

### Table 2: Drug regimens for culture-positive pulmonary tuberculosis caused by drug-susceptible organisms

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Drugs</th>
<th>Initial phase</th>
<th>Continuous phase</th>
<th>Range of total doses (median duration)</th>
<th>Rating/level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ISH</td>
<td>7 days per week for 4 months (5 x/week) for 40 doses (20 x/week)</td>
<td>1a</td>
<td>20 days</td>
<td>A (0)</td>
</tr>
<tr>
<td></td>
<td>ISA</td>
<td>7 days per week for 4 months (5 x/week) for 40 doses (20 x/week)</td>
<td>2a</td>
<td>20 days</td>
<td>A (0)</td>
</tr>
<tr>
<td></td>
<td>EMB</td>
<td>7 days per week for 4 months (5 x/week) for 40 doses (20 x/week)</td>
<td>3a</td>
<td>20 days</td>
<td>A (0)</td>
</tr>
<tr>
<td>2</td>
<td>ISH</td>
<td>7 days per week for 4 months (5 x/week) for 40 doses (20 x/week)</td>
<td>1b</td>
<td>20 days</td>
<td>A (0)</td>
</tr>
<tr>
<td></td>
<td>ISA</td>
<td>7 days per week for 4 months (5 x/week) for 40 doses (20 x/week)</td>
<td>2b</td>
<td>20 days</td>
<td>A (0)</td>
</tr>
<tr>
<td></td>
<td>EMB</td>
<td>7 days per week for 4 months (5 x/week) for 40 doses (20 x/week)</td>
<td>3b</td>
<td>20 days</td>
<td>A (0)</td>
</tr>
</tbody>
</table>

**Treatment of MTB in HIV (+) Pts**

- Vitamin B6 should be added for all HIV (+) pts
- Daily (or 5x/week) for first 2 months
- For patients with CD4 <100, the continuation phase (4-7 months) should be given either daily or 3x/week
  - Not twice weekly
- 6 months vs 9 months
  - New data suggest longer courses should be considered

Khan et al CID August 2012
ART reduces the risk of TB relapse.
Use of rifamycins for ≥8 months improves TB treatment outcomes.
Daily dosing in the intensive phase improves TB treatment outcomes.
Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

Developed by the HHS Panel on Antiretroviral Guidelines for Adults and Adolescents – A Working Group of the Office of AIDS Research Advisory Council (OARAC)

http://aidsinfo.nih.gov/guidelines

Rifamycins

- Have significant interaction with all ARVs except nucleoside analogues (other than AZT) and enfuvirtide

- Once or twice weekly regimens show high rate of rifampin resistance in HIV patients with CD4 cell count <100

- Most common locus of interaction is the cytochrome P450 system
  - As inducers, rifampin > rifapentine > rifabutin
Rifampin and PIs

Table 3. Pharmacokinetic interactions between rifampicin or rifabutin

<table>
<thead>
<tr>
<th>Rifampicin</th>
<th>PI</th>
<th>PI's effect on PI</th>
<th>Rifabutin</th>
<th>PIs' effect on RFB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Saquinavir</td>
<td>80% decrease saquinavir level</td>
<td></td>
<td>Data not reported</td>
</tr>
<tr>
<td></td>
<td>Ritonavir</td>
<td>35% decrease ritonavir level</td>
<td></td>
<td>Unchanged R level</td>
</tr>
<tr>
<td></td>
<td>Indinavir</td>
<td>92% decrease indinavir level</td>
<td></td>
<td>Data not reported</td>
</tr>
<tr>
<td></td>
<td>Nelfinavir</td>
<td>81% decrease nelfinavir level</td>
<td></td>
<td>Data not reported</td>
</tr>
<tr>
<td></td>
<td>Lopinavir + ritonavir</td>
<td>75% decrease lopinavir level</td>
<td></td>
<td>Data not reported</td>
</tr>
<tr>
<td></td>
<td>Amprenavir</td>
<td>81% decrease ampranavir level</td>
<td></td>
<td>Unchanged R level</td>
</tr>
</tbody>
</table>

R, rifampicin; RFB, rifabutin; PI, protease inhibitor.

Note: Decrease in serum protease inhibitor level is NOT overcome by low dose ritonavir

Rifabutin

- Has much less effect than rifampin on drugs metabolized by CYP3A
- Requires dosage adjustment due to effects by many other drugs (such as ritonavir).
- PIs (especially if boosted with ritonavir) cause a marked increase in serum rifabutin serum concentrations and toxicity
- Rifabutin dose should be decreased when using PI-based regimens. Concerns regarding adequate dosing if patient is not compliant with PI medication
Antiretrovirals and Rifamycins

- Contraindicated combinations
  - Rifapentine and any ARV
  - Rifampin and
    - Protease inhibitors
    - Etravirine, nevirapine, rilpivirine
    - Maraviroc
    - EVG/cobi/TDF/FTC
  - Rifabutin and
    - Etravirine with a protease inhibitor
    - Rilpivirine
    - EVG/cobi/TDF/FTC

HIV medication and rifamycin combinations that do not require dose adjustment

- Efavirenz (Sustiva/Atripla) and rifampin
- Etravirine and rifabutin
- Dolutegravir and rifabutin
- Raltegravir and rifabutin

Antiretrovirals and Rifamycins

• Combinations requiring dosing adjustments
  – Rifampin and raltegravir
    • ↑ raltegravir to 800 mg BID
  – Rifampin and Dolutegravir
    • ↑ dolutegravir to 50 mg BID
  – Rifabutin and protease inhibitors (boosted and not)
    • ↓ rifabutin to 150 mg daily or 300 mg TIW
  – Rifabutin and efavirenz
    • ↑ rifabutin to 450-600 mg daily or 600 mg TIW
  – Rifabutin and maraviroc with a strong CYP3A inhibitor
    • ↓ maraviroc to 150 mg BID (300 mg without a strong inhibitor)

**IRIS**
*(Immune Reconstitution Inflammatory Syndrome)*

- Initial response to therapy then worsening of symptoms, radiographic findings or physical exam findings

- Rule out other causes
  - Drug resistance (do you have susceptibilities?)
  - Other opportunistic infections

- Management
  - Mild cases use NSAIDS
  - More severe cases use steroids

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**THEY ALWAYS COME BACK**

*Do It Right The First Time!*

Barbara Seaworth, MD

**Resident Heartland Guru**
and contributor of many of the DM slides
Questions?