Tuberculosis in the HIV Patient
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April 7, 2016

Tuberculosis Intensive
April 5-8, 2016
San Antonio, TX

Lisa 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
Epidemiology

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

Estimated TB incidence rates, 2013

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Detailed and shaded lines on maps represent approximate border lines for which there may not be full agreement.

Source: Global Tuberculosis Report 2014, WHO, 2014. ©WHO 2014. All rights reserved.

Global Epidemiology of TB/HIV

Estimated HIV prevalence in new and relapse TB cases, 2013

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Source: Global Tuberculosis Report 2013, WHO, 2013. ©WHO 2013. All rights reserved.
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.

Outcomes of Exposure to *M. tuberculosis*

Inhalation of Droplet Nuclei

Regional replication in lungs, dissemination

\[ \sim90\% \rightarrow \sim5\% \rightarrow \sim5\% \]

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% Killing, clearance of organisms
- ~5% Latent disease

Active disease

- Up to 36% active disease
- ~5% reactivation lifetime
- 10% reactivation per year

Signs & Symptoms - Pulmonary TB

**Pulmonary Symptoms:**
- Productive, prolonged cough of over 3 weeks duration
- Chest pain
- Hemoptysis

**Systemic Symptoms:**
- Fever
- Chills
- Night sweats
- Appetite loss
- Weight loss
- Easy fatigability
Testing for TB Infection
- TST

- The *tuberculin skin test (TST)* may help differentiate infected from uninfected people with signs and symptoms

- A negative TST does not exclude the diagnosis of TB (especially for patient’s with severe TB illness or *infection with HIV*)

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>Test</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>

Clinical Microbiology and Infection, Volume 10 Number 5, May 2004

**IFN-γ (gamma) release assays (IGRAs)**

www.cellestis.com
Antigens for Gamma-Release Assays

<table>
<thead>
<tr>
<th>Tuberculosis complex</th>
<th>Antigens</th>
<th>Environmental strains</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ESAT</td>
<td>CFP</td>
</tr>
<tr>
<td>M tuberculosis</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>M africanum</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>M bovis</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>BCG substrain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>gothenburg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>moreau</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>tice</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>tokyo</td>
<td>-</td>
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<tr>
<td>danish</td>
<td>-</td>
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<tr>
<td>glaxo</td>
<td>-</td>
<td>-</td>
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<tr>
<td>montreal</td>
<td>-</td>
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<td>pasteur</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M abscessus</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>M avium</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>M branderi</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>M colatum</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>M chelonae</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>M fortuitum</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>M gordonii</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>M intracellulare</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>M kansasii</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>M malmoense</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>M marinum</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>M oenavense</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>M scrotulaceum</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>M smegmatis</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>M szulga</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>M terreae</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>M xenopi</td>
<td></td>
<td>-</td>
</tr>
</tbody>
</table>

FDA-approved IGRAs

- Quantiferon-Gold In-Tube (IT)
- T-SPOT.TB
Quantiferon Gold In-Tube

Table 2. Distribution of Quantiferon-TB Gold In-Tube results by HIV status, CD4+ lymphocyte count, treatment period and TST result.

<table>
<thead>
<tr>
<th>QFT result</th>
<th>n (N=200)</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>200</td>
<td></td>
</tr>
<tr>
<td>HIV Status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>51 (26)</td>
<td>31.5</td>
</tr>
<tr>
<td>Positive</td>
<td>2 (10)</td>
<td>1.0</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>125 (62)</td>
<td>62.5</td>
</tr>
<tr>
<td>Unknown</td>
<td>12 (6)</td>
<td>6.0</td>
</tr>
<tr>
<td>CD4+ count, cells/μl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 100</td>
<td>13 (6)</td>
<td>6.5</td>
</tr>
<tr>
<td>100 to 199</td>
<td>14 (7)</td>
<td>7.0</td>
</tr>
<tr>
<td>200 to 349</td>
<td>2 (1)</td>
<td>0.5</td>
</tr>
<tr>
<td>350 or more</td>
<td>10 (5)</td>
<td>5.0</td>
</tr>
<tr>
<td>Treatment period</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 days</td>
<td>3 (1.5)</td>
<td>1.5</td>
</tr>
<tr>
<td>1 to 14 days</td>
<td>49 (24)</td>
<td>24.5</td>
</tr>
<tr>
<td>15 to 21 days</td>
<td>14 (7)</td>
<td>7.0</td>
</tr>
<tr>
<td>ELISPOT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 40 mm</td>
<td>5 (2.5)</td>
<td>2.5</td>
</tr>
<tr>
<td>n = 6 mm</td>
<td>4 (2.0)</td>
<td>2.0</td>
</tr>
<tr>
<td>&lt; 3 mm</td>
<td>2 (1.0)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Table 2. Performance of tuberculosis (TB) ELISPOT assay for diagnosis of active tuberculosis in HIV-1 infected patients stratified by CD4 T cell count.

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All HIV patients with active/probable TB</td>
<td>30</td>
<td>90.3</td>
</tr>
<tr>
<td>CD4 T cell count &lt; 300 cells/μl</td>
<td>22</td>
<td>95.4</td>
</tr>
<tr>
<td>CD4 T cell count &lt; 200 cells/μl</td>
<td>14</td>
<td>92.9</td>
</tr>
<tr>
<td>CD4 T cell count &lt; 100 cells/μl</td>
<td>8</td>
<td>87.5</td>
</tr>
</tbody>
</table>

S. A. Clark et al. 2007. Clinical and Experimental Immunology
Poor concordance between interferon-γ release assays and tuberculin skin tests in diagnosis of latent tuberculosis infection among HIV-infected individuals

*BMC Infectious Diseases* 2009, 9:15

- Cross-sectional study in 2 HIV clinics in Atlanta, Georgia (n=336), 85% black, 65% male, 91% US-born, 69% on HAART, 60% with a history of an OI.

- Median CD4 = 334, median viral load 400 copies/ml

- Conclusion:
  - We found a low prevalence of LTBI and poor concordance between all 3 diagnostic tests (TST, QF-IT, T-SPOT.TB).

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**RESEARCH ARTICLE**

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


- 373 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-SPOT.TB 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 of latent tuberculosis infection (B).
Role of Interferon Gamma Release Assay in **Active TB Diagnosis** among HIV Infected Individuals


- 105 HIV/TB patients in India
- 50% were culture positive
- 31% were TST positive
  - Sensitivity decreased with declining CD4 count
- 65% were positive by Quantiferon-IT
  - More indeterminate results with CD4 <200

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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

**Figure 1** Study population of 244 patients eligible for the study, 226 (92%) were included. Pulmonary tuberculosis, defined as a 1 positive culture result, was diagnosed in 126 (56%) patients.
• 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

**Table 1: Positive results utilizing light-emitting diode fluorescent microscopy and Xpert MTB/RIF assay.**

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Smear positive</th>
<th>Xpert positive</th>
<th>Absolute difference</th>
<th>Ratio Xpert/LED</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>N (%) (95% CI)</td>
<td>N (%) (95% CI)</td>
<td>(%) (95% CI)</td>
<td>(%) (95% CI)</td>
</tr>
<tr>
<td>Sputum</td>
<td>166</td>
<td>106 (63.9 to 70.8)</td>
<td>124 (74.7 to 80.8)</td>
<td>10.8 (5.2 to 16.5)</td>
<td>1.17 (1.08 to 1.26)</td>
</tr>
<tr>
<td>Sputum x3</td>
<td>166</td>
<td>116 (69.9 to 76.4)</td>
<td>124 (74.7 to 80.8)</td>
<td>4.8 (0.6 to 9.1)</td>
<td>1.07 (1.02 to 1.13)</td>
</tr>
<tr>
<td>Extrapulmonary</td>
<td>253</td>
<td>23 (9.1 to 13.3)</td>
<td>74 (29.2 to 35.2)</td>
<td>20.2 (14.8 to 25.5)</td>
<td>3.22 (2.29 to 4.52)</td>
</tr>
<tr>
<td>CSF</td>
<td>142</td>
<td>3 (2.1 to 6.4)</td>
<td>35 (24.6 to 32.4)</td>
<td>22.5 (15 to 30.1)</td>
<td>11.47 (3.95 to 34.42)</td>
</tr>
<tr>
<td>Pleural fluid</td>
<td>75</td>
<td>10 (13.3 to 23.1)</td>
<td>24 (32.2 to 43.4)</td>
<td>18.7 (8.5 to 28.8)</td>
<td>2.4 (1.49 to 3.85)</td>
</tr>
<tr>
<td>Ascitic fluid</td>
<td>18</td>
<td>2 (11.1 to 35.4)</td>
<td>5 (27.8 to 12 to 52)</td>
<td>16.7 (~6.1 to 39.4)</td>
<td>2.5 (0.85 to 7.31)</td>
</tr>
<tr>
<td>Stool</td>
<td>10</td>
<td>7 (37.5 to 90.1)</td>
<td>8 (80 (45.8 to 95)</td>
<td>10 (~18.6 to 28.6)</td>
<td>1.14 (0.88 to 1.49)</td>
</tr>
<tr>
<td>Total</td>
<td>419</td>
<td>129 (30.8 to 35.4)</td>
<td>198 (47.3 to 52.1)</td>
<td>16.5 (12.6 to 20.3)</td>
<td>1.53 (1.38 to 1.7)</td>
</tr>
</tbody>
</table>

CI: confidence interval; LED: light-emitting diode fluorescent microscopy; CSF: cerebrospinal fluid.
Screening for pulmonary tuberculosis in HIV-infected individuals: ACTG Protocol A5253
IUTLD 17(4): 532-9

• Comparison of evaluation tools for diagnosis of TB in HIV patients
  – SOC screening algorithm: cough, fever, weight loss, night sweats in previous 30 days, sputum smear; CXR (if not pregnant)
  – Expanded assessment tool added other symptoms to screening (GI, GU, neuro, derm) and fluorescent microscopy

• 801 patients, average 33 y/o, median CD4 275

• Results:
  – 51% with TB had a normal CXR
  – SOC sensitivity 54%, specificity 76%, PPV 24%, NPV 92%
  – Cough was the most sensitive symptom (especially when combined with abnl CXR, LN, or CD4 count < 200)
  – Only 6 of 54 (11.1%) with positive TB culture had positive smear

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
Miliary 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>Category</th>
<th>Enrolled patients, n</th>
<th>TB diagnosed, n (% of enrolled patients)</th>
<th>Positive acid-fast smear, n (% of TB diagnosed)</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), 40 (46), 47 (54)</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>Abnormal</td>
<td>56</td>
<td>11 (20)</td>
<td>3 (27), 2 (18), 9 (82)</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>Abnormal</td>
<td>334</td>
<td>162 (49)</td>
<td>92 (57), 21 (13), 140 (87)</td>
<td></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)

Diagnosis – Summary

- Must have a high index of suspicion

- Must utilize many pieces of information in making the diagnosis

- TB can present very differently in HIV-infected patients when compared to HIV-negative patients
Testing for TB Infection - Some Principles to Consider

- Individuals who have a
  - 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, MMWR 2009

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 (AII);
- 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

Figure 1. Efficacy of tuberculosis (TB) (includes confirmed, probable, and possible active cases of TB) preventive therapy (with any drug), compared with placebo, in reducing the incidence of active TB. "Death" denotes death due to all causes. CI, confidence interval; PPD, purified protein derivative; PPD unknown, unknown PPD status; +, positive; −, negative. A relative risk of <1 favors treatment. Copyright Cochrane Collaborations adapted with permission from [11].

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
Isoniazid Regimens for LTBI

- 9-month regimen of isoniazid (INH) is the preferred regimen

- 6-month regimen is less effective but may be used if unable to complete 9 months

- May be given daily or intermittently (twice weekly)
  - Use directly observed therapy (DOT) for intermittent regimen

Persons with the following conditions need special precautions while on isoniazid

a. Age 35 years and over
b. Taking other medications on a long term basis
c. Alcohol abusers
d. History of previous discontinuation of isoniazid because of toxicity/adverse reactions
e. Chronic liver disease
f. Peripheral neuropathy
g. Pregnancy
Rifampin Regimens for LTBI

- Rifampin (RIF) given daily for 4 months is an acceptable alternative when treatment with INH is not feasible.
- In situations where RIF cannot be used (e.g., HIV-infected persons receiving protease inhibitors), rifabutin may be substituted.
- Rifampin and PZA for 2 months should generally not be offered due to risk of severe adverse events.\(^6\)

\(^6\)MMWR August 8, 2003; 52 (31): 735-739

LTBI treatment

**TABLE. Revised drug regimens for treatment of latent tuberculosis infection (LTBI) in adults**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interval and duration</th>
<th>Comments</th>
<th>Rating (Evidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Isoniazid</strong></td>
<td>Daily for 9 months(^{<strong>TT</strong>})</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 (I) A (II)</td>
</tr>
<tr>
<td></td>
<td>Twice weekly for 9 months(^{<strong>TT</strong>})</td>
<td>Directly observed therapy (DOT) must be used with twice-weekly dosing.</td>
<td>B (II) B (II)</td>
</tr>
<tr>
<td><strong>Isoniazid</strong></td>
<td>Daily for 6 months(^{<strong>TT</strong>})</td>
<td>Not indicated for HIV-infected persons, those with fibrocavitary lesions on chest radiographs, or children.</td>
<td>B (II) C (I)</td>
</tr>
<tr>
<td></td>
<td>Twice weekly for 6 months(^{<strong>TT</strong>})</td>
<td>DOT must be used with twice-weekly dosing.</td>
<td>B (II) C (I)</td>
</tr>
<tr>
<td><strong>Rifampin</strong></td>
<td>Daily for 4 months(^{<strong>TT</strong>})</td>
<td>Used for persons who are contacts of patients with isoniazid-resistant, rifampin-susceptible TB.</td>
<td>B (II) B (III)</td>
</tr>
<tr>
<td>Rifampin plus</td>
<td>Daily for 2 months</td>
<td>In HIV-infected persons, most protease inhibitors or darunavir 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 efavirenz. Clinicians should consult web-based updates for the latest specific recommendations.</td>
<td>D (II) D (II)</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 (III) D (III)</td>
</tr>
</tbody>
</table>

MMWR August 8, 2003 / Vol. 52 / No. 31
‘3HP Regimen’ and HIV patients

• 12 week regimen of INH and Rifapentine dosed once a week

• Contraindicated in patients on ANY antiretrovirals

• Acceptable if not on HIV medications
Updates and Changes in Therapy

- Changes in dosing schedules:
  - **HIV + individuals with low CD4 counts** should NOT be given twice weekly therapy
  - **Rifabutin (RBT):** May be used as a primary drug for patients (especially HIV+) receiving medications having unacceptable interactions with rifampin (e.g. Protease Inhibitors, methadone)

ATS recommendations for treatment of tuberculosis

**TABLE 2. Drug regimens for culture-positive pulmonary tuberculosis caused by drug-susceptible organisms**

<table>
<thead>
<tr>
<th>Initial phase</th>
<th>Combination phase</th>
<th>Regimen</th>
<th>Drugs</th>
<th>Interval and doses (regimen duration)</th>
<th>Regimen</th>
<th>Drugs</th>
<th>Interval and doses (regimen duration)</th>
<th>Range of total doses (maximal duration)</th>
<th>Rating * (evidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 PIR PBZ EDB</td>
<td>1a PIRSP</td>
<td>Seven days per week for 60 doses (8 wk)</td>
<td>1b PIRSP</td>
<td>Seven days per week for 124 doses (16 wk)</td>
<td>A (I)</td>
<td>A (I)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1c PIRSP</td>
<td>Twice weekly for 56 doses (8 wk)</td>
<td>1d PIRSP</td>
<td>Twice weekly for 100 doses (13 wk)</td>
<td>A (I)</td>
<td>A (I)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 PIR PBZ EDB</td>
<td>2a PIRSP</td>
<td>Four times weekly for 14 doses (2 wk)</td>
<td>2b PIRSP</td>
<td>Four times weekly for 56 doses (8 wk)</td>
<td>A (I)</td>
<td>A (I)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2c PIRSP</td>
<td>Three times weekly for 24 doses (6 wk)</td>
<td>2d PIRSP</td>
<td>Three times weekly for 64 doses (16 wk)</td>
<td>B (I)</td>
<td>B (I)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 PIR PBZ EDB</td>
<td>3a PIRSP</td>
<td>Three times weekly for 36 doses (10 wk)</td>
<td>3b PIRSP</td>
<td>Three times weekly for 56 doses (8 wk)</td>
<td>B (I)</td>
<td>B (I)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 PIR PBZ EDB</td>
<td>4a PIRSP</td>
<td>Seven days per week for 217 doses (31 wk)</td>
<td>4b PIRSP</td>
<td>Seven days per week for 103 doses (13 wk)</td>
<td>C (I)</td>
<td>C (I)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Definitions of evidence ratings: A = patient; B = acceptable alternative; C = other when A and B cannot be given; D = should never be given.

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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
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
ART Considerations as Initial Therapy based on Specific Clinical Scenarios

- If Rifampin is Used:
  - EFV-based regimens have the least drug-drug interactions.
  - Rifampin has a less significant effect on EFV concentration than on other NNRTIs, PIs, and INSTIs.
  - If RAL is used, increase RAL dose to 800 mg BID.
  - Use DTG at 50 mg BID dose only in patients without selected INSTI mutations (refer to product label).

- If using a PI-based regimen, rifabutin should be used in place of rifampin in the TB regimen.

- Rifampin is a strong inducer of CYP3A4 and UGT1A1 enzymes, causing significant decrease in concentrations of PI, INSTI, and RPV.
  - Rifabutin is a less potent inducer and is a good option for patients receiving non-EFV-based regimens. Refer to Tables 19a, b, d and e for dosing recommendations for rifamycins used with different ARV agents.

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
    - EVG/cobi/TDF/FTC

HIV medication and rifamycin combinations that do not require dose adjustment

- Efavirenz (Sustiva/Atripla) and rifampin
- Etravirine and rifabutin
- Nevirapine and rifabutin (use with caution)
- 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/rilpivirine
    - ↑ rifabutin to 450-600 mg daily or 600 mg TIW; ↑ rilpivirine to 50 mg daily
  - Rifabutin and maraviroc with a strong CYP3A inhibitor
    - ↓ maraviroc to 150 mg BID (300 mg without a strong inhibitor)

Antiretrovirals and Rifamycins

• Combinations requiring dosing adjustments
  – Rifampin and raltegravir
    • ↑ raltegravir to 800 mg BID
      (Lancet ID 2013; 381: 459-67)
  – 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/rilpivirine
    • ↑ rifabutin to 450-600 mg daily or 600 mg TIW; ↑ rilpivirine to 50 mg daily
  – Rifabutin and maraviroc with a strong CYP3A inhibitor
    • ↓ maraviroc to 150 mg BID (300 mg without a strong inhibitor)


Treatment - Summary

• Every effort should be made to treat within the CDC guidelines to
  – increase the chances of treatment success,
  – decrease the chances of relapse and
  – minimize the length of time with toxicities.

• Rifamycins can be safely added to almost any regimen.

• TB treatment regimens that do not contain rifampin have an unacceptably high failure rate
When should treatment be started when patient is being treated for TB?

- **Considerations**
  - Treatment of HIV improves outcomes in patients with TB
    - Decreased death or relapse
  - Multiple medications with multiple potential toxicities that are overlapping
Initiation of ART in patients with HIV/TB

- In patients with CD4 counts <50 cells/mm³, ART should be initiated within 2 weeks of starting TB treatment (AI)

- In patients with CD4 counts ≥50 cells/mm³ who present with clinical disease of major severity as indicated by clinical evaluation, ART should be initiated within 2 to 4 weeks of starting TB treatment. The strength of this recommendation varies on the basis of CD4 cell count:
  - CD4 count 50 to 200 cells/mm³ (BI)
  - CD4 count >200 cells/mm³ (BIII)

- In patients with CD4 counts ≥50 cells/mm³ who do not have severe clinical disease, ART can be delayed beyond 2 to 4 weeks of starting TB therapy but should be started within 8 to 12 weeks of TB therapy initiation. The strength of this recommendation also varies on the basis of CD4 cell count:
  - CD4 count 50 to 500 cells/mm³ (AI)
  - CD4 count >500 cells/mm³ (BIII)

Recommendations for patients with HIV/TB

- Treatment support, which can include directly observed therapy (DOT) of TB treatment, is strongly recommended for HIV-infected patients with active TB disease (AII).

- Immune reconstitution inflammatory syndrome (IRIS) may occur after initiation of ART. Both ART and TB treatment should be continued while managing IRIS (AIII).

- Despite pharmacokinetic drug interactions, a rifamycin (rifampin or rifabutin) should be included in TB regimens for patients receiving ART, with dosage adjustment if necessary (AII).

- Rifapentine (RPT) is NOT recommended in HIV-infected patients receiving ART for treatment of latent TB infection (LTBI) or active TB, unless in the context of a clinical trial (AIII).
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

THEY ALWAYS COME BACK

Do It Right The First Time!

Barbara Seaworth
Thanks!!

Questions?
Lisa.Armitige@dshs.state.tx.us
Heartland National Tuberculosis Center
1-800-TEX-LUNG