Objectives

• Epidemiology of TB and HIV
• Interaction of TB and HIV
• Treatment issues associated with TB/HIV co-infection
Global TB

• 2008: 9.4 million incident TB cases
  – 139/100,000 population
  – Between 1.2 & 1.6 million TB cases are HIV+
    • 78% in Africa and Southeast Asia

• TB is the leading cause of death in HIV-infected patients globally

• Case fatality rate is about 40% or higher

• TB kills 2 million people worldwide every year
  – HIV-negative deaths: 1.3 million (28/100,000)
  – >500,000 deaths each year are associated with TB/HIV co-infection, mostly in Africa

Corbett EL et al. Arch Intern Med 2003;163:1009
Mukadi YD et al. AIDS 2000;15:143-152
WHO TB report 2009
TB Case Rates per 100,000 population, Arizona & U.S., 2000 - 2009

Leadership for a Healthy Arizona

- Other
- Mexico
- Vietnam
- Philippines
- Guatemala
- India
- China
- Honduras
- Somalia
- Bhutan
- Thailand
- Myanmar
- Nepal
## Risk Factors for TB Cases, Arizona, 2009

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>#Cases</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correctional Facility Cases</td>
<td>37</td>
<td>17</td>
</tr>
<tr>
<td>HIV Positive</td>
<td>16</td>
<td>6.9</td>
</tr>
<tr>
<td>Contact of Infectious TB Case, (&lt; 2 years)</td>
<td>10</td>
<td>4.9</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>26</td>
<td>12.6</td>
</tr>
<tr>
<td>Excess Alcohol</td>
<td>16</td>
<td>6.9</td>
</tr>
<tr>
<td>Non-injecting Drug Use</td>
<td>17</td>
<td>7.3</td>
</tr>
<tr>
<td>Injecting Drug Use</td>
<td>3</td>
<td>1.3</td>
</tr>
<tr>
<td>Homeless</td>
<td>8</td>
<td>3.4</td>
</tr>
<tr>
<td>Long-term Care Facility</td>
<td>2</td>
<td>1.0</td>
</tr>
</tbody>
</table>

*Leadership for a Healthy Arizona*
Co-pathogenicity of TB and HIV

• Immune activation from TB enhances systemic and local HIV replication
• TB treatment alone results in HIV viral load reduction
• Mortality rate of HIV-infected persons with TB is approx 4 times greater than in those with TB alone

CDC/MMWR 1998;47 (No RR-20).
Mechanisms of Enhanced Viral Replication

• Mycobacterial induction of NF-Kappa-B which binds to the promoter region of HIV
• Macrophages activated by TB release IL-1 and TNF which enhance viral replication in monocyte lines

CDC/MMWR 1998;47 (No RR-20).
Screening for TB in HIV population

- Repeated exposure history
- Screening PPD or IGRAs at presentation and every 12 months depending on exposure risk
- Consider repeat PPD after initiation of anti-retroviral therapy
- CXR
Case 1

- 21 yo F diagnosed with HIV in 2004
- Immigrated from Cameroon, West Africa in 2007
- CD4 count 166
- Had received unknown meds in Cameroon
- At first appointment, she complains of fever, cough, HA
Case 1 (cont)

- Quanteferon TB test positive
- CXR with bilateral lower lobe consolidation c/w bronchial pneumonia
- Admit for rule out meningitis (negative)
- Started on “RIPE” Rifampin, Isoniazid, Pyrazinamide, Ethambutol in March 07’
Primary Pulmonary TB
Case 1 (cont)

- TB Culture positive with pan-sensitive MTB
- HIV therapy deferred
- Completed 4 months of 4 drug therapy and then changed to INH/Rifampin
- TB meds changed to INH/Rifabutin due to interaction with HIV therapy
Case 1 (cont)

- INH/Rifabutin x 2 months
- Rifabutin changed back to Rifampin for final month of therapy
- TB meds stopped after 9 mos of therapy Dec 07’
- HAART attempted in Dec 07 but discontinued due to increasing liver enzymes
- HAART deferred until Feb 08’
- CXR infiltrates resolved
Case 1 Concerns

- IRIS avoidance
- Risk of opportunistic infections (OI) while not on HIV therapy
- Toxicity with HIV medications
- Patient education
- Co-infections
- Communications
The effect of HIV infection on symptoms and signs of TB

<table>
<thead>
<tr>
<th>Symptom/sign</th>
<th>HIV positive (%)</th>
<th>HIV negative (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>97</td>
<td>81</td>
</tr>
<tr>
<td>Fever</td>
<td>79</td>
<td>62</td>
</tr>
<tr>
<td>Sweats</td>
<td>83</td>
<td>64</td>
</tr>
<tr>
<td>Weight loss</td>
<td>89</td>
<td>83</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>23</td>
<td>4</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>41</td>
<td>21</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>40</td>
<td>15</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>35</td>
<td>13</td>
</tr>
<tr>
<td>No Symptoms</td>
<td>10-20</td>
<td></td>
</tr>
</tbody>
</table>

Chest 1994;106:1471-6
## Sites of involvement and HIV status

<table>
<thead>
<tr>
<th>Site</th>
<th>HIV positive (%)</th>
<th>HIV negative (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary</td>
<td>40</td>
<td>72</td>
</tr>
<tr>
<td>Extrapulmonary</td>
<td>34</td>
<td>16</td>
</tr>
<tr>
<td>Both</td>
<td>26</td>
<td>12</td>
</tr>
<tr>
<td>Pleural</td>
<td>31</td>
<td>19</td>
</tr>
<tr>
<td>Pericardial</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>Lymph node</td>
<td>19</td>
<td>3</td>
</tr>
</tbody>
</table>

*J Trop Med Hygiene 1993;96:1-11*
TB Presentation in HIV Infection

CD4 < 100

• More extrapulmonary
  – 70% patients with CD4 < 100
  – Miliary
  – Meningitis & tuberculomas
  – Peritoneal

• Atypical pulmonary
  – Less cavitary lung disease
  – More lower and middle lobes
TB Presentation in HIV Infection

• CD4 > 350
  – TB presentation more typical
    • Pulmonary disease
    • Apical segments
• TB often precedes other OI by few months to two years
Effect of stage of HIV disease on chest x-ray (CXR) manifestations of TB

Early HIV disease or CD4 > 300
- upper lobe predominance
- cavities
- pleural disease

Advanced HIV disease or CD4 < 200
- lack of cavitation
- intrathoracic adenopathy
- lower and middle lobe infiltrates
- nodular infiltrates
- pleural and pericardial involvement
- MAY BE NORMAL

Patients may present with positive sputum cultures for *M. tuberculosis* even if CXR is negative
Challenges to concurrent HIV and TB therapy

- Pill burden
- Overlapping drug toxicities
- Pharmacokinetic drug-drug interactions
- Increased risk of immune restoration inflammatory syndrome
Treatment of Active TB

• Rifampin is recommended as component of 4-drug regimen:
  – In patients who have not started ARV therapy due to current immune function
  – In patients that for other reasons will not be taking a PI or NNRTI-containing regimen
  – Additional agents should include INH, EMB, PZA

CDC/MMWR 2003;52 (No RR-11)
Co-administering Antiretroviral Drugs with Rifampin

- Dose adjustments of protease inhibitors may still result in liver toxicity
- Non-nucleoside reverse transcriptase inhibitors Nevaripine and Efavirens can be used without dose adjustments
- New CCR5 antagonist
- New integrase inhibitor

http://www.cdc.gov/nchstp/tb/
Monitoring Response to Treatment in HIV-Infected Patients with TB

- Monitor patients with mycobacterial cultures monthly until cultures revert to negative.

- After 2 months of therapy, if cultures are positive or symptoms do not resolve re-evaluate for:
  - Potential drug resistant disease
  - Non-adherence to drug regimen

CDC/MMWR 1998;47 (No RR-20)
When to start antiretroviral therapy in TB/HIV patients

- No data from randomized trials—yet
- Current thinking:
  - TB clearly needs to be treated; HIV treatment can follow
  - Allow patients to tolerate the 4 TB drugs before starting combination anti-retroviral therapy
  - Risk of paradoxical worsening may be increased during first 2 months of TB therapy
Factors to consider when starting antiretroviral therapy (ART) in TB/HIV patients

- High mortality rate in TB/HIV patients
  - TB accelerates HIV disease progression, death
- Beneficial impact of ART on TB/HIV
- ART increases CD4 and could ↓ relapse risk
- Large pill burden for TB and for HIV regimens
- Drug-drug interactions, toxicity
- Paradoxical worsening of TB (IRIS)
Immune Reconstitution (Paradoxical reactions)

• Occurs with restoration of immune function after initiation of ARVs
• Can present as worsening of TB disease, fevers, chills, hypotension
• Consider delay of ARVs if situation allows
• May require steroid treatment for inflammatory response

CDC/MMWR 2003;52 (No RR-11)
Types of Immune Reconstitution events among patients with HIV related TB

- Hectic fever
- New or worsening lymphadenitis - peripheral or central nodes
- New or worsening pulmonary infiltrates, including respiratory failure
- New or worsening pleuritis, pericarditis, or ascites
- Intracranial tuberculomas, worsening meningitis
- Disseminated skin lesions
- Epididymitis, hepatosplenomegaly, soft tissue abscesses
Paradoxical reactions
Management

• Diagnosis of exclusion
  – Treatment failure, drug toxicity, other infection

• Mild-to-moderate reaction
  – Re-assurance
  – NSAIDS

• Severe reactions (hypoxemia, airway obstruction, neurologic impairment, etc.)
  – Corticosteroids
Overlapping side effect profiles of first-line antituberculosis drugs and antiretroviral drugs

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Possible causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin rash</td>
<td>PZA, RIF, INH</td>
</tr>
<tr>
<td>Nausea, vomiting</td>
<td>PZA, RIF, INH</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>PZA, RIF, INH</td>
</tr>
<tr>
<td>Leukopenia, anemia</td>
<td>RIF</td>
</tr>
<tr>
<td>NVP (nevirapine), EFV (efavirenz), ABC (abacavir), ZDV (zidovudine), RIT (ritonavir), AMP (amprenavir), IND (indinavir), PI (protease inhibitors)</td>
<td>NVP, EFV, ABC, ZDV, RIT, AMP, IDV, NVP, PIs, immune reconstitution, ZDV</td>
</tr>
</tbody>
</table>
Case 2

- 23 year old HF diagnosed with HIV in 2005
- PPD + in 2005, 2006, 2007 (5mm) (no treatment for LTBI)
- History of BCG vaccine as a child
- Quanteferon positive January 2008.
- CXR negative
- On HIV therapy, CD4 400, Viral load undetectable
Case 2 Concerns

- Excluding active disease
- Interpretation of PPD in HIV-infected persons
- BCG vaccine
- Initiating treatment for LTBI
Diagnostic Points
LTBI & HIV

• False negative PPD
  – Inversely correlated with CD4 counts
  – Up to 65% in AIDS
• AFB positive sputum in AIDS
  – Suspect TB
• Brochoscopy can help when AFB negative
• Miliary disease: Blood cultures + 50%
Treatment of LTBI in HIV-infected patients

• Indications
  – PPD ≥ 5 mm
  – High-risk exposure
  – Prior + PPD
Interferon-γ testing for LTBI

• More data is needed on the use of this test for the diagnosis of LTBI in HIV patients
• Quantification of interferon-gamma released from sensitized lymphocytes in whole blood incubated overnight with purified protein derivative from MTB and control antigens
• Does not measure the same components of the immunologic response as the PPD
• Not interchangeable with PPD testing

CDC/MMWR Vol. 51 Dec 18, 2002
Summary: effects of HIV-related immunodeficiency on response to tests for latent TB

• All tests for latent TB rely on an immune response
  – Not surprising that HIV-related immunodeficiency decreases the sensitivity of all of them
  – Negative test does not rule out TB

• Response to Elispot IGRA appears to be better preserved at low CD4 counts
Treatment of LTBI Using INH

- PPD of 5mm induration or greater warrants treatment
- Rule out active disease
- 9 months of INH + pyridoxine
- Baseline hepatic studies recommended
- Follow for signs and symptoms of drug toxicity monthly with INH

Adult HIV/AIDS Treatment. 2006. 67
Sputum Testing for TB before LTBI Rx

- Unnecessary if normal chest Xray
- Need sputum if:
  - HIV with symptoms
  - Abnormal chest Xray
    - Parenchymal changes
    - Scarring
    - Upper lobe nodules
When Excluding Active Pulmonary TB with Abnormal Chest x-ray

- Get 3 sputum samples- wait for cultures
- Do **not** start single drug therapy until active disease is excluded
- Consider 4 drug TB therapy in high risk case
- May need follow up chest X-rays to decide if old scarring or active disease
HIV/TB: Profound Effect on Individuals

The annual risk of TB in HIV infected approximates the lifetime risk of HIV uninfected

Take-Home Points: HIV and TB

- Need to screen all HIV patients for TB
- Need to screen all TB patients for HIV

Thank you