Tuberculosis in the Setting of HIV Infection

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Tuberculosis Clinical Intensive
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Disclosure

• Gilead
• Janessen
• Viiv
• Pfizer
• Merck
Objectives

• Describe the epidemiology of TB/HIV co-infection

• Describe clinical presentation of TB disease in populations with HIV

• Explain treatment and management strategies for TB patients with HIV.
TB/HIV Coinfection

• Epidemiology
• Natural History
• Diagnosis
• Treatment
Epidemiology
Tuberculosis: 2011 Global Burden of Disease

- 12 million prevalent cases (10-13 million)
- 8.7 million incident cases (8.3-9 million)
  - 125 cases per 100,000 population
  - Asia (59%)
  - Africa (26%)
  - Eastern Mediterranean Region (7.7%)
  - Europe (4.3%)
  - Americas (3%)
- 1.4 million people died from TB in 2011
  - 1 million deaths among HIV-negative individuals
  - 430,000 among people who were HIV-positive.
Estimated tuberculosis (TB) incidence rates, 2011

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. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Tuberculosis: High-Burden Countries

- Afghanistan
- Bangladesh
- Brazil
- Cambodia
- China
- DR Congo
- Ethiopia
- India
- Indonesia
- Kenya
- Mozambique
- Myanmar
- Nigeria
- Pakistan
- Philippines
- Russian Federation
- South Africa
- Thailand
- Uganda
- UR Tanzania
- Viet Nam
- Zimbabwe
United States: Reported TB Cases
United States, 1982–2012

2012 Data
9,951 Cases
Rate
3.2/100,000

Data are updated as of 2/22/13 and are provisional.
Reported new tuberculosis cases, by county — United States, 2010–2012

Data are updated as of 3/6/13 and are provisional.
Rate* of TB Cases by Race/Ethnicity — United States, 2012

<table>
<thead>
<tr>
<th>Race</th>
<th>Rate</th>
<th>Rate</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hispanic</td>
<td>5.2</td>
<td>5.2</td>
<td>5.2</td>
</tr>
<tr>
<td>Asian</td>
<td>19.8</td>
<td>19.8</td>
<td>19.8</td>
</tr>
<tr>
<td>Black</td>
<td>5.7</td>
<td>5.7</td>
<td>5.7</td>
</tr>
<tr>
<td>White</td>
<td>0.8</td>
<td>0.8</td>
<td>0.8</td>
</tr>
</tbody>
</table>

* Per 100,000 population

Data are updated as of 2/22/13 and are provisional.

7.3x

6.6x

25.0x
Adults and children estimated to be living with HIV | 2011

Total: 34.0 million [31.4 million – 35.9 million]
TB and HIV Coinfection

• Of the 8.7 million incident cases in 2011, 1.1 million (13%) were among people living with HIV

• In Africa, 39% of TB cases were estimated to be coinfected

• Africa accounted for 79% of TB cases among people living with HIV worldwide
Estimated HIV prevalence in new tuberculosis cases, 2011

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Estimated HIV Coinfection\(^1\) in Persons with HIV Test Results, United States, 1993–2012

\(^1\)Includes persons with positive, negative, or indeterminate HIV test results.

Data are updated as of 2/22/13 and are provisional.
Natural History
Impact of Tuberculosis on the Natural History of HIV Infection

- TB coinfection increases the risk of HIV progression and death
  - Increases replication of HIV in vitro
  - Increased immune activation
  - Increased expression of the CCR5 and CXCR4 coreceptors on CD4 cells
  - Activation of latent HIV in macrophages
  - Dysregulated cytokines
  - 2.6 greater risk of mortality (meta-analysis of cohort studies)

Natural History of TB Infection

Exposure to TB

No infection (70-90%)

Infection (10-30%)

Latent TB (90%)

Never develop Active disease

Active TB (10%)

Untreated

Die within 2 years

Survive

Treated

Die

Cured

Never develop Active disease
Natural History of Tuberculosis

Transmission

Primary Tuberculosis

Skin-test conversion in 6 to 8 weeks

Spontaneous healing in 6 months

Latent Tuberculosis

Progression after 2 years, 5%

“Reactivation” Tuberculosis

Progression within 2 years, 5%

Progression with concurrent HIV infection, 10% each year
Pathogenesis of TB

- Droplet nuclei containing tubercle bacilli are inhaled, enter the lungs, and travel to the alveoli.

- Tubercle bacilli multiply in the alveoli.

- A small number of tubercle bacilli enter the bloodstream and spread throughout the body.
Pathogenesis of TB

• Within 2 to 10 weeks, the body's immune system intervenes, halting multiplication and further spread.

• Macrophages directly phagocytize TB, processing and presenting antigens to lymphocyte

• T lymphocytes (CD4+): induce protection through the production of lymphokines
Tuberculosis: Primary Disease

• Immediate onset of active disease
• Noted in approx. 5% of individuals infected with tuberculosis
• HIV increases the risk of rapid progression to active (primary) disease
• In one study, 30-40% HIV-infected patients progressed to active TB disease within 3-6 months following infection
Natural History of Tuberculosis

Transmission

Primary Tuberculosis

Skin-test conversion in 6 to 8 weeks

Spontaneous healing in 6 months

Latent Tuberculosis

Progression after 2 years, 5%

"Reactivation" Tuberculosis

Progression within 2 years, 5%

Progression with concurrent HIV infection, 10% each year
Latent Tuberculous Infection: LTBI

- When the immune system manages to stop the multiplication of TB bacilli and contain the infection, the patient is said to have latent tuberculous infection (LTBI).

- Persons with LTBI are not infectious and do not spread organisms to others.

- Over time, in some, reactivation of LTBI occurs - the granulomas break down, bacilli escape and multiply, resulting in TB disease.
Latent Tuberculous Infection: LTBI

- In individuals with normal immunity, the life-time risk of reactivating LTBI is 10%
  - 5% in first 1–2 years post infection
  - Another 5% later in life
- In HIV-infected individuals, the risk of reactivating TB is about 10% each year
- HIV-infected patients with LTBI are 30 to 100 times more likely to reactivate with TB disease
- HIV represents the greatest risk for reactivation of tuberculosis
## Risk Factors for Reactivation of TB

### Table 3. Relative Risk of Reactivation Tuberculosis among Persons with Medical Conditions That Impair Immune Control of *M. tuberculosis.*

<table>
<thead>
<tr>
<th>Condition</th>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced HIV infection</td>
<td>Pablos-Mendez et al.(^{27})</td>
<td>9.9 (8.7–11.3) †</td>
</tr>
<tr>
<td></td>
<td>Moss et al.(^{26})</td>
<td>9.4 (3.5–25.1) †</td>
</tr>
<tr>
<td>Old, healed tuberculosis</td>
<td>Ferebee,(^{13}) Ferebee et al.(^{20})</td>
<td>5.2 (3.4–8.0)</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>Pablos-Mendez et al.(^{27})</td>
<td>2.4 (2.1–2.8) †</td>
</tr>
<tr>
<td>Infliximab therapy</td>
<td>Keane et al.(^{28})</td>
<td>2.0 (0.7–5.5) †</td>
</tr>
<tr>
<td>Poorly controlled diabetes</td>
<td>Pablos-Mendez et al.(^{27})</td>
<td>1.7 (1.5–2.2) †</td>
</tr>
<tr>
<td>Silicosis</td>
<td>Cowie(^{29})</td>
<td>1.7 (1.3–2.1) †</td>
</tr>
<tr>
<td></td>
<td>Corbett et al.(^{30})</td>
<td>1.3 (1.1–1.7) †</td>
</tr>
<tr>
<td></td>
<td>Kleinschmidt and Churchyard(^{31})</td>
<td>1.2 (1.0–1.5) †</td>
</tr>
<tr>
<td>Underweight (≤10 percent below normal)</td>
<td>Palmer et al.(^{22}) Edwards et al.(^{23})</td>
<td>1.6 (1.1–2.2)</td>
</tr>
<tr>
<td>Gastrectomy</td>
<td>Thorn et al.(^{32})</td>
<td>1.4 (1.1–1.9) †</td>
</tr>
<tr>
<td></td>
<td>Steiger et al.(^{33})</td>
<td>1.3 (1.2–1.4) †</td>
</tr>
</tbody>
</table>

Proposed mechanism of HIV-induced reactivation of latent TB. (Stage 1) Necrotic granuloma functioning “normally” in an individual with latent TB. (Stage 2) HIV enters the granuloma and induces functional changes within T cells and macrophages.

Recurrence of TB

- HIV-negative patients with 4-drug therapy and DOT
  - 2-3% recurrence
- HIV-positive patients
  - 14+ % recurrence rate
    - Some relapse with original strain
    - Most re-infect with new strain
    - Recurrence may herald drug resistance
Diagnosis of Tuberculosis
Diagnosing TB Infection

• Tuberculin skin test (TST)
  • Among HIV-infected patients, a TST with ≥5 mm of induration is considered reactive
  • False negative results may occur in advanced HIV

• Interferon Gamma Release Assays
  • QuantiFERON-TB Gold In-Tube (QFT-GIT)®
  • T-Spot.TB®

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST</td>
<td>90-100%</td>
<td>29-39%</td>
<td>2.7-3.1%</td>
<td>99-100%</td>
</tr>
<tr>
<td>IGRA</td>
<td>80-90%</td>
<td>56-83%</td>
<td>4-8%</td>
<td>99-100%</td>
</tr>
</tbody>
</table>
Diagnosing Active Tuberculosis

• Sputum smear
  • HIV-infected patients are more likely to have smear-negative pulmonary TB
  • Range 31 – 81%

• CXR
  • Individuals with advanced HIV are likely to have atypical presentations
    • Lower lobe locations
    • Less cavities

• More extrapulmonary TB
Treatment of Tuberculosis
## Treatment of LTBI

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Duration</th>
<th>Interval</th>
<th>Minimum doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>9 months</td>
<td>Daily</td>
<td>270</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Twice weekly*</td>
<td>76</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>6 months</td>
<td>Daily</td>
<td>180</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Twice weekly</td>
<td>52</td>
</tr>
<tr>
<td>Isoniazid and Rifapentine</td>
<td>3 months</td>
<td>Once weekly</td>
<td>12</td>
</tr>
<tr>
<td>Rifampin</td>
<td>4 months</td>
<td>Daily</td>
<td>120</td>
</tr>
</tbody>
</table>
Treatment of Active TB Disease

- TB treatment regimens and principles are the same in HIV-positive as in HIV-negative patients
- Initial phase: 2 months INH, RIF, PZA, EMB
- Continuation phase: 4 months INH and RIF
TB and HIV coinfection: Treatment Issues

• Drug-drug interactions
• Overlapping drug toxicities
• Pill Burden
• Immune-reconstitution inflammatory syndrome (IRIS)
• Sequencing with antiretroviral therapy
• Highly intermittent Dosing
• TB treatment outcome in HIV
• ART treatment effect on TB incidence
TB/HIV Treatment Issues: Drug Interactions

• Rifamycins induce hepatic cytochrome P450 (CYP3A4) enzymes, accelerating metabolism of:
  • Protease inhibitors (PIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), etc.
  • Rifampicin >> Rifabutin
• For patients receiving PIs or NNRTIs, substitute rifabutin for rifampin, if available
• Alternative non-rifamycin regimens less optimal, longer duration of therapy
Rifampicin decreases blood levels of NVP and EFV

<table>
<thead>
<tr>
<th>NNRTI</th>
<th>Effect of Rifampicin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nevirapine</td>
<td>↓ 37–58%</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>↓ 22%</td>
</tr>
</tbody>
</table>
### PIs and Rifamycins

Rifampicin decreases blood levels of all PIs

<table>
<thead>
<tr>
<th>Protease Inhibitor</th>
<th>Effect of Rifampicin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saquinavir</td>
<td>↓ by 84%</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>↓ by 35%</td>
</tr>
<tr>
<td>Indinavir</td>
<td>↓ by 89%</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>↓ by 82%</td>
</tr>
<tr>
<td>Amprenavir</td>
<td>↓ by 81%</td>
</tr>
<tr>
<td>Lopinavir/ritonavir</td>
<td>↓ by 75%</td>
</tr>
</tbody>
</table>
Rifamycins and Intermittent Therapy

• Evidence for development of acquired rifamycin resistance with intermittent therapy
  • Intermittent therapy not recommended during initial phase of TB treatment in patients with HIV infection
  • No twice-weekly continuation phase with advanced immune suppression
# Overlapping Side Effects

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>TB Drug</th>
<th>ARV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin rash*</td>
<td>PZA, RIF, INH</td>
<td>▪ Nevirapine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▪ Efavirenz</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▪ Abacavir</td>
</tr>
<tr>
<td>Nausea, vomiting</td>
<td>PZA, RIF, INH</td>
<td>▪ Zidovudine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▪ Ritonavir</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▪ Amprenavir</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▪ Indinavir</td>
</tr>
</tbody>
</table>

* May also see rash with cotrimoxazole

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## Overlapping Side Effects

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>TB Drug</th>
<th>ARV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis</td>
<td>PZA, RIF, INH</td>
<td><em>Nevirapine</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Protease inhibitors</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>IRIS (with chronic hepatitis)</em></td>
</tr>
<tr>
<td>Leukopenia, anemia</td>
<td>RIF</td>
<td><em>Zidovudine</em></td>
</tr>
</tbody>
</table>

TB/HIV: Barriers to Adherence

- Higher pill burden
- Greater number of potential drug side effects
- Dual social stigma
- Additional illness (opportunistic infections)
- Difficult medical access, drug-supply interruptions
IRIS

Immune Reconstitution Inflammatory Syndrome (IRIS)

- Clinical worsening in the setting of an adequate response to ART
  - “Paradoxical” worsening of previously known treated (completed or ongoing) opportunistic pathogen
  - “Unmasking” of subclinical opportunistic pathogen
IRIS

• Risk factors
  • Disseminated TB
  • Shorter delay between onset of TB and ART drugs
  • Low baseline CD4, higher baseline viral load
  • Greater CD4 or viral load response to ART

• Timing of onset
  • Usually within first 6 weeks of ART (often 2–3 weeks, but can be months after ART started)
IRIS

Clinical presentation:

• Fever
• Nodal enlargement
• Worsening pulmonary infiltrates (with or without respiratory symptoms)
• Local worsening in extrapulmonary sites
IRIS Differential Diagnosis

- TB treatment failure
- Drug-resistant TB
- ART failure
- Other opportunistic (or non-opportunistic) infections
  - Lymphoma, Kaposi’s sarcoma
  - Hypersensitivity drug reactions
IRIS Management

- Continue TB treatment
- Continue ART
- Exclude TB treatment failure
  - Adherence
  - Drug resistance
- Exclude additional/new diagnosis
- Consider NSAIDS, steroids
- Drainage of lesions
When to Start Antiretrovirals

HIV-infected TB patients not yet on ART

<table>
<thead>
<tr>
<th>CD4</th>
<th>Start ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\leq 50)</td>
<td>Within 2 weeks of TB Rx</td>
</tr>
<tr>
<td>(\geq 50) and TB severe</td>
<td>Within 2 - 4 weeks of TB Rx</td>
</tr>
<tr>
<td>(\geq 50) but TB not severe</td>
<td>Can defer ART beyond 2 - 4 weeks but should start within 8-12 weeks</td>
</tr>
</tbody>
</table>
FIGURE 1.26
Treatment outcomes for HIV-positive and HIV-negative TB patients, 2006 cohort. The numbers under the bars are the numbers of patients included in the cohort.

- HIV+ (12,931)
  - New smear-positive (data from 55 countries)
  - Cured: [Cured percentage]
  - Completed: [Completed percentage]
  - Died: [Died percentage]
  - Failed: [Failed percentage]
  - Defaulted: [Defaulted percentage]
  - Transferred: [Transferred percentage]
  - Not evaluated: [Not evaluated percentage]

- HIV- (722,667)
  - New smear-negative and extrapulmonary (data from 48 countries)
  - Cured: [Cured percentage]
  - Completed: [Completed percentage]
  - Died: [Died percentage]
  - Failed: [Failed percentage]
  - Defaulted: [Defaulted percentage]
  - Transferred: [Transferred percentage]
  - Not evaluated: [Not evaluated percentage]

- HIV+ (18,298)
  - New smear-negative and extrapulmonary (data from 48 countries)
  - Cured: [Cured percentage]
  - Completed: [Completed percentage]
  - Died: [Died percentage]
  - Failed: [Failed percentage]
  - Defaulted: [Defaulted percentage]
  - Transferred: [Transferred percentage]
  - Not evaluated: [Not evaluated percentage]

- HIV- (601,518)
  - New smear-negative and extrapulmonary (data from 48 countries)
  - Cured: [Cured percentage]
  - Completed: [Completed percentage]
  - Died: [Died percentage]
  - Failed: [Failed percentage]
  - Defaulted: [Defaulted percentage]
  - Transferred: [Transferred percentage]
  - Not evaluated: [Not evaluated percentage]

- HIV+ (4,765)
  - Retreatment (data from 31 countries)
  - Cured: [Cured percentage]
  - Completed: [Completed percentage]
  - Died: [Died percentage]
  - Failed: [Failed percentage]
  - Defaulted: [Defaulted percentage]
  - Transferred: [Transferred percentage]
  - Not evaluated: [Not evaluated percentage]

- HIV- (80,293)
  - Retreatment (data from 31 countries)
  - Cured: [Cured percentage]
  - Completed: [Completed percentage]
  - Died: [Died percentage]
  - Failed: [Failed percentage]
  - Defaulted: [Defaulted percentage]
  - Transferred: [Transferred percentage]
  - Not evaluated: [Not evaluated percentage]
Antiretroviral Therapy (ART) Significantly Reduces TB Incidence

Decrease in TB incidence after starting ART in resource-limited, high-burden area

Impact of ART on TB Incidence

TB among AIDS patients in Brazil

Annual incidence in AIDS cases


www.aids.gov.br/boletim/bol_htm/boletim.htm

Pulmonary TB

Disseminated TB

Mono        Dual               Triple   therapy
Tuberculosis/HIV Coinfection: Summary

- Substantial global disease burden, individually and as coinfection
- Bidirectional impact on natural history
- Difficulties in diagnosis and treatment
- TB, even in the setting of HIV, is curable
- ART has tremendous impact on TB incidence in the population