TB and HIV
A Tricky Combination

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Estimated HIV Coinfection in Persons
Reported with TB, United States, 1993 – 2011*

% Coinfection

0 5 10 15 20 25 30
Aged 25-44 All Ages

*Updated as of June 25, 2012
Based: Minimum estimates based on reported HIV-positive status among all TB cases in the age group
Source: CDC, Tuberculosis in the United States, 2011

"Old TB doctors versus New HIV doctors"
**Similarities between TB & HIV**

<table>
<thead>
<tr>
<th>TB</th>
<th>HIV</th>
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<tbody>
<tr>
<td>Multiple drugs used for treatment</td>
<td>Multiple drugs used for treatment</td>
</tr>
<tr>
<td>Adherence issues</td>
<td>Adherence issues</td>
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<tr>
<td>Adverse drug effects</td>
<td>Adverse drug effects</td>
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<tr>
<td>Lifetime risk</td>
<td>Lifetime management</td>
</tr>
<tr>
<td>Drug resistance problems</td>
<td>Drug resistance problems</td>
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<tr>
<td>Multi-system disease</td>
<td>Multi-system disease</td>
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**Differences between TB & HIV**

<table>
<thead>
<tr>
<th>TB</th>
<th>HIV</th>
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<tbody>
<tr>
<td>Discovered 1890's</td>
<td>Discovered 1983</td>
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<tr>
<td>Transmitted by coughing an aerosol</td>
<td>Transmitted sexually, or blood contact</td>
</tr>
<tr>
<td>Little modern research until ~2000</td>
<td>Extensive modern research</td>
</tr>
<tr>
<td>No new 1st line drugs in &gt;40 years</td>
<td>Many medications</td>
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<tr>
<td>Imprecise and late diagnosis are frequent</td>
<td>Precise and rapid diagnosis</td>
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**Key Objectives of Today’s Presentation**

**TB Diagnosis Problems**
- Check for TB in every HIV pneumonia case
- Smear-negative pulmonary TB more common
- Extra-pulmonary TB more common
- Unusual and “normal” CXR’s

**Drug Treatment Problems**
- Drug interactions
- Drug side effects
- Proper timing of TB and HIV medications
Accurate Diagnosis

High Accuracy for Diagnosis of HIV in Contrast to TB...

Other Organisms can Interfere with TB Diagnosis
TB Testing with TST

• Mantoux skin test
• 0.1mL of PPD (5 tuberculin units) given intradermally by 0.1mL
• Read after 48-72 hours after administration
• Measure only induration
• >5 mm TST result considered positive for person with HIV infection

IGRA Tests More Specific Than TST

TST vs. IGRA in HIV-infected Persons

• No definitive comparisons have been done of TST and IGRAs for screening HIV-infected individuals in low burden settings such as the United States
• Both TST and IGRAs are appropriate for TB screening in HIV-infected individuals
• Some experts suggest using both TST and IGRA to screen for LTBI
  – Predictive value of this approach is unclear
  – More expensive and difficult to implement
• Routine use of both TST and IGRAs to screen for LTBI is not recommended in the United States
TB Granuloma

On AFB stains, organisms are found mainly in the zone of necrosis.

A granuloma represents vigorous immune reaction to a chronic infection, such as TB or fungal infection. With low CD4 counts, granuloma formation may be poor or absent.

Caseous necrosis

Acid-fast Stain of Granuloma

Changing TB Clinical Spectrum in Africa...

Before HIV epidemic
- Pulmonary 85%
- Extra Pulmonary 12%
- Pulmonary + EPTB 3%
- Smear-positive PTB 80%

After HIV epidemic
- Pulmonary 42-87%
- Extra Pulmonary 13-58%
- Pulmonary + EPTB 50-60%

References:
3/21/2014

Clinical Manifestation Pointers for TB-HIV

1. In HIV patients with CD4 >350, TB clinically resembles that among uninfected persons

2. However, extra-pulmonary TB is more common in HIV-infected persons, regardless of CD4 count

3. TB must be considered in diseases of every organ, especially with CNS disease

*Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents.* Available at: [http://aidsinfo.nih.gov/guidelines](http://aidsinfo.nih.gov/guidelines)
Clinical Manifestation Pointers for TB-HIV

4. In advanced HIV, chest X-ray findings of TB are markedly different:
   - Lower lobe, interstitial and miliary patterns seen
   - Cavitation is less common
   - Marked mediastinal adenopathy
   - Even with normal chest X-ray, HIV patients may have positive AFB smears and cultures

Clinical Manifestation Pointers for TB-HIV

5. TB may present as a systemic disease, with high fevers, rapid worsening and sepsis syndrome

6. Histology findings on biopsies are affected by the degree of immunodeficiency. Granulomas may be poorly formed, or even absent

7. In severely immunodeficient AIDS patients, TB may be subclinical

“Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents.” Available at: http://aidsinfo.nih.gov/guidelines

Weird Case in HIV Clinic

- Extra-pulmonary TB is more common in HIV-infected persons, regardless of CD4 count
- Arm swelling drained, culture grew *M. tuberculosis*
- No granulomas on histology exam

Weird Case in HIV Clinic

*Transmission of Tuberculosis and Progression from Latent Infection to Reactivated Disease*
Exposed to his aunt with pulmonary TB. 22 yr male with AIDS CD4=25, which he does not disclose. TST: 0 mm
6 weeks later, admitted with suspected *Pneumocystis pneumonia*.
Miliary TB diagnosed.

**Tricky case in your HIV clinic...**

- 40 yr female came from Sierra Leone 8 months earlier
- Dry cough x 2 months
- HIV+ new diagnosis
- Baseline CD$_4$ = 50 cells
- This is her chest Xray:

Sputum smear x2 negative
TST = 0 mm induration
Culture positive for M. tb 5 weeks later.
Improving TB Diagnosis

• Nucleic acid amplification (NAA)
  – May rapidly identify *M. tuberculosis*
  – NAA recommended on at least 1 specimen from all patients with suspected pulmonary TB
  – In AFB smear-positive specimens, highly predictive of TB
    • Can be used to direct therapy and make clinical decisions
  – More sensitive than AFB smear
    • Positive in 50%-80% of smear-negative, culture-positive specimens
  – only for sputum samples

Nobel Peace Prize Plaza
Cape Town, South Africa

Uganda Sept. 2009
Infectious Disease Institute

Source: www.jsunstrum.wordpress.com
Incidence versus Prevalence

**TB Incidence**
- Number of new cases per year/100,000 population
- Benchmark for WHO
- TB is an episodic disease

**HIV Prevalence**
- Number of all cases/100,000 population
- Benchmark for WHO
- HIV is a lifetime disease
Global TB-HIV Quiz

**QUESTION**
- What % of active TB cases in the world are confirmed by mycobacterial culture?

**ANSWER**
- A. 1%
- B. 3%
- C. 25%
- D. 80%

TB Prevalence in Uganda compared to Global Data

![Bar chart showing TB prevalence in Uganda compared to global data](chart.png)

Dr. Bbaale with new TB hut, St. Francis Hospital Nosambiya, Kampala
But note where USA was in 1940....

TB Mortality Dropped in USA Before Any Medications!

Why did TB incidence drop in USA before streptomycin?

A. Recognition of airborne transmission
B. Improved housing
C. Improved nutrition
D. TB sanatoria
E. Improved public health system
F. All of the above
What Might be the Impact of Improved TB-HIV Management?

TB Screenin...
Can there be synergy between TB and HIV care?

Is it possible for one doctor to provide modern care of both TB and HIV?

Synergy

TB Clinic
- Test all TB cases (and suspects) for HIV
- Understand how HIV changes TB presentation
- Understand drug interactions

HIV Clinic
- Screen all HIV patients for latent TB (TST or IGRA)
- Rule out TB in any pulmonary condition
- Understand how TB presentation varies with HIV
- Work with public health

TRICKY CASE IN THE TB CLINIC
Confirmed TB in 40 yr F. HIV negative, Hepatitis C +, Cocaine abuse. Treated with RIPE in hospital by Court Order

Temperature (F):  
SHE LEFT HOSPITAL AGAINST MEDICAL ADVICE IN DECEMBER....

White Blood Cells:  
TRENDLINE
Answer to Tricky Case at the TB Clinic

• HIV negative on enrollment
• Fevers, neutropenia, cervical adenopathy, shallow oral ulcers after 8 months TB therapy
• Diagnosis: acute retroviral infection: HIV antibody now positive

Discuss with an expert!

Treatment of TB-HIV Co-Infection

Question??

• Who wrote on 27 January 1989:

• “TB treatment ended”

• Answer at end of lecture
Principles of Drug Therapy

Incubating $10^{1-4}$
1 Drug

Latent $10^{4-5}$
1 Drug

TB scar $10^6$
2 Drugs

Active $10^{6-11}$
3-4 Drugs

Latent TB in HIV patient, or Window
Prophylaxis in TB – Exposed HIV

Not on ART
- Isoniazid (and B6) X 9 months, with MONTHLY follow-ups
- **NO rifampin**
- Weekly Isoniazid/rifapentine OK

On ART
- Isoniazid (and B6) X 9 months, with MONTHLY follow-ups
- Weekly Isoniazid/rifapentine in certain cases only

Treating Active TB in HIV patient...

Not on Anti-retroviral Rx (ART)
- First treat the TB with standard therapy
- Based on CD4 count, then start ART later
- Moderates risk of IRIS
- Reduces confusion when medication side effects occur

Already on Anti-retroviral Rx
- Continue ART, but if on protease inhibitor try to change to NNRTI (efavirenz, Sustiva)
- Consult an Expert
Medications

**TB**
- Isoniazid (INH)
- Rifampin
- Pyrazinamide (PZA)
- Ethambutol
- Rifabutin

**HIV**
- NRTI
- NNRTI
  - Protease Inhibitors
  - Integrase Inhibitors
- Trimethoprim/sulfa (Bactrim)

TB Disease: Starting ART

- NRTIs: no significant interactions with rifamycins
- NNRTIs:
  - **Efavirenz 600 mg QD + 2 NRTIs** is preferred ART regimen for patients taking RIF
  - Nevirapine: more significant interactions with RIF
    - Can be used for patients unable to take efavirenz
    - Monitor HIV RNA closely
    - If on RIF for ≥2 weeks, omit lead-in dose of nevirapine
  - Rifabutin: increased dosage of RBT needed if used with efavirenz

Where do I obtain information on drug interactions?

- Drug Interaction Software
- [www.hiv-druginteractions.org](http://www.hiv-druginteractions.org)
- Smartphone applications (Tarascon)
- Call ATIC for assistance with Uganda questions: Toll Free Number 0800200055
Best Time to Start ART in a TB Patient?

- Intensive (or Initial) Phase: 2 months
- Continuation Phase: 4 months

TB-HIV Treatment Regimen with IRIS

- Intensive (or Initial) Phase: 2 months
- Continuation Phase: 6 months
- AZT/3TC/EFV (Atripla)

IRIS

**Mild**
- Seen in up to 1/3 of TB-HIV cases
- Lymph node enlargement
- Fears
- Worsening infiltrates
- Treat with ibuprofen
- Usually can continue TB-HIV treatment

**Severe**
- May require steroids
- Confused with TB treatment failure (rare)
- Only rarely stop ART
- Exclude other causes of reaction
- Call for advice
- CONFUSING!
Example of Severe IRIS in my TB Clinic…

Left: Cervical lymph node TB with simultaneous TB-HIV treatment

Right: 8 wks later with massive node expansion & tracheal compression

Current Recommendations March 27, 2012 Newly Updated DHHS ART guidelines

- All with HIV and TB should be started on ART (AI)
- CD4 < 50 → Start ART within 2 weeks (AI)
- CD4 ≥ 50 →
  - With major severity* clinical disease start ART within 2 to 4 weeks (BI for CD4 50-200, BII for CD4 > 200)
  - With less severe disease can be delayed, but start ART by 8-12 weeks in all (AI for CD4 50-500, BIII for CD4 > 500)

Timing of Initiation of Antiretroviral Drugs During Antituberculosis Rx
Karim et al, NEJM 2010 (South Africa)
Who wrote on 27 January 1989: “TB treatment ended”?

- Nelson Mandela
- “Conversations with Myself” 2010

AIDS is a major problem to be tackled by the entire world. To deal with it requires resources far beyond the capacity of one continent. No single country has the capacity to deal with it.”

http://www.aidsetc.org
http://aidsinfo.nih.gov