TB and HIV

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Objectives

• Describe the global and local epidemiology of TB/HIV coinfection
• Utilize TSTs and IGRAs appropriately in the diagnosis of LTBI in HIV-positive individuals
• Identify the signs and symptoms of active TB in an HIV-positive individual
• Develop a treatment plan for an TB/HIV coinfected individual
TB and HIV

• In 2014, 1.2 million (12%) of the 9.6 million people who developed TB worldwide were HIV positive

• 74% of these HIV-positive TB cases were in the African Region

• TB is the most common presenting illness among people living with HIV, including among those taking antiretroviral treatment

• TB deaths among HIV-positive people accounted for 25% of all TB deaths and 1/3 of the estimated 1.2 million deaths from HIV/AIDS

WHO Global Tuberculosis Report, 2015
Reported TB Cases
United States, 1982–2014*

No. of Cases

Year

*Updated as of June 5, 2015.
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.
• As of 12/2014, 28,526 people were living with HIV in NC
• New diagnoses of HIV infection: 1,351
• Highest rates of newly diagnosed HIV: 20-24 and 25-29 age groups (40%), African-American men (60%), MSM
HIV and Tuberculosis

• HIV increases the risk of TB reactivation enormously.
• TST+, HIV- ⇒ lifetime risk ≈ 10%
• TST+, HIV+ ⇒ YEARLY risk ≈ 10%
• A deadly duo
Effect of HIV on TB

- Risk of TB increases after HIV seroconversion due to depletion of TB-specific T helper cells
- Risk of TB progressively increases with declining immunity
- HIV is a risk factor for accelerated progression following TB exposure
Effect of TB on HIV

• TB increases the risk of progression to AIDS or death
• Multiple theories as to why this may happen: increased HIV viremia in those with TB disease, increased CD4 activation
WHEN A VIRUS (HIV) AND A BACTERIA (TB) CAN WORK SO WELL TOGETHER – WHY CANT WE?

MICHEL SIDIBE
Impact of Antiretroviral Therapy (ART)

- ART reduces the risk of developing TB
- Rates of TB among patients receiving ART remain persistently higher than among HIV-negative individual
Double Trouble

People with HIV Infection face a greater risk of also developing TB. Don’t take chances. Get tested.

Call your physician or county health department for a tuberculosis test today.


**CD4 Cells (or “T-cells”)** are a type of white blood cells that play a major role in protecting your body from infection.

![Graph showing the relationship between CD4 count and viral load over time.](image)

- **High** CD4 count indicates a very infectious period.
- **Low** CD4 count helps show how well your immune system is working.

- **The higher your CD4 count, the better able you are to fight HIV and other infections.**

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*Image credit: [Source URL]*
Opportunistic Infections

Brain
- Cryptococcal Meningitis
- Toxo (toxoplasmosis)

Eyes
- CMV (cytomegalovirus)

Mouth and Throat
- Cold sores and ulcers
- Thrush (candidiasis)

Lungs
- Histoplasmosis
- PCP (pneumocystis carinii pneumonia)
- TB (tuberculosis)

Stomach
- CMV (cytomegalovirus)
- Crypto (cryptosporidiosis)
- MAC (mycobacterium avium complex)

Liver
- HCV (hepatitis C virus)

Reproductive system
- Genital Ulcers
- HPV (human papillomavirus) and cervical cancer
- Menstrual Problems
- PID (pelvic inflammatory disease)
- UTI (urinary tract infections)
- Vaginal Yeast Infections (candidiasis)
When to Test for LTBI

- Test for LTBI at initiation of HIV care
- Repeat LTBI testing:  
  - If initial test negative and subsequent CD4 cell count rises to $>200$ cells/mm$^3$ after the initiation of antiretroviral therapy

CDC. MMWR 2009; 58:1-198
Repeat LTBI testing (if baseline test negative) **annually** if there is ongoing high risk for TB exposure:

- Current or history of incarceration
- Live in congregate settings
- Active drug abuse
- Marginal housing or homelessness
- Travel to TB-endemic locations

CDC. MMWR 2009; 58:1-198
Classification of the Tuberculin Skin Test Reaction

<table>
<thead>
<tr>
<th>Classification</th>
<th>An induration of 5 or more millimeters is considered positive in</th>
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<tbody>
<tr>
<td>HIV-infected persons</td>
<td>• A recent contact of a person with TB disease</td>
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<td>• Persons with fibrotic changes on chest radiograph consistent with prior TB</td>
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<td>• Patients with organ transplants</td>
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<td>• Persons who are immunosuppressed for other reasons (e.g., taking the equivalent of ( \geq 15 ) mg/day of prednisone for 1 month or longer, taking TNF-alpha antagonists)</td>
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<td>An induration of 10 or more millimeters is considered positive in</td>
<td>• Recent immigrants (( \leq 5 ) years) from high-prevalence countries</td>
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<td></td>
<td>• Injection drug users</td>
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<tr>
<td></td>
<td>• Residents and employees of high-risk congregate settings</td>
</tr>
<tr>
<td></td>
<td>• Mycobacteriology laboratory personnel</td>
</tr>
<tr>
<td></td>
<td>• Persons with clinical conditions that place them at high risk</td>
</tr>
<tr>
<td></td>
<td>• Children ( \leq 4 ) years of age</td>
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<tr>
<td></td>
<td>• Infants, children, and adolescents exposed to adults in high-risk categories</td>
</tr>
<tr>
<td>An induration of 15 or more millimeters is considered positive in</td>
<td>• Any person, including persons with no known risk factors for TB. However, targeted skin testing programs should only be conducted among high-risk groups.</td>
</tr>
</tbody>
</table>
IGRA Performance in Diagnosing LTBI in HIV+ Patients

- HIV+ individuals with a negative IGRA may have a low progression to active TB

- IGRAs (particularly TSPOT) may be more sensitive than TST in HIV-affected individuals and less affected by advanced immunosuppression

- IGRAs perform similarly to the TST in identifying HIV+ individuals who could benefit from LTBI therapy

Cattamanchi et al. J Acquir Immune Defic Syndr 2011;56:230-238
LTBI testing of ANY kind is preferable to NO TESTING.
Evaluation of LTBI in HIV

- Assess for symptoms: fever, night sweats, weight loss, cough
- CXR
- Assess for extrapulmonary TB:
  - more common in HIV
  - more common when CD4<200
Treatment options for LTBI

• INH/B6 x 9 months

• Rifampin x 4 months
  • Rifamycins may be considered in HIV-positive patients who develop INH hepatotoxicity
  • Rifampin contraindicated with protease inhibitors
  • Dose adjustments of integrase inhibitors necessary if used with rifampin

• INH/Rifapentine: once weekly via DOT x 3 months
  • Only used in HIV patients not on antiretroviral therapy

*Treatment of LTBI decreases the risk of TB disease in HIV-positive individuals by 62%
Dr. K presents to the ER with weakness, fever and productive cough that has been worsening over the past two weeks

- Originally from Zimbabwe
- Pmhx: Malaria, Tx for LTBI with INH x 6 months in 1995
- Living in US but has travelled back and forth to Africa over the past few years
- As a physician, she has cared for many TB patients
ER Course

- Temp to 101
- Tachycardic
Hospital Course

- ER decides to admit for “Community-acquired pneumonia in immunocompetent patient.”
- Hospitalist notices “thrush” on exam → HIV test ordered
- Concern for possible lymphoma due to extensive lymphadenopathy seen on CT of chest/abdomen/pelvis
- Due to prior history of TB exposure, plans made to evaluate for TB with sputum smears
Hospital Course

• Remains quite ill with no improvement on antibiotics
• Unable to produce sputum $\rightarrow$ bronchoscopy performed with bacterial/fungal/AFB cultures sent
• AFB sputum smear negative $\rightarrow$ released from airborne isolation
• Widespread lymphoma felt to be cause of illness $\rightarrow$ plans for LN biopsy
Hospital Course

• Around this time CD4 count returns: 178 (prior to HIV test results which eventually came back positive; Viral Load > 2000000)
• Axillary lymph node biopsy → pathology showed “extensive necrotizing granulomas”
• AFB sputum smear → AFB culture positive
• AFB blood culture → eventually became positive (approximately 4 weeks later)
• Diagnosis: Disseminated Tuberculosis
Diagnosis of Active TB in HIV

- Presentation of disease influenced by degree of immunodeficiency
- In HIV+ without pronounced immunodeficiency (CD4>350), TB clinically resembles disease seen in HIV-negative → pulmonary disease with typical x-ray
- Lower CD4 counts → atypical presentation of disease
- Extrapulmonary TB is also more common in HIV regardless of CD4 count:
  - lymphadenitis
  - meningitis
- High level of suspicion necessary
Diagnosis of Pulmonary TB in HIV

- CXR atypical or even normal with CD4 <200
- “Atypical” CXR findings include: lower lobe, middle lobe, interstitial or miliary infiltrates
- Cavitation also less common
- Lymphadenopathy (mediastinal >hilar) common

http://www.searo.who.int/EN/Section10/Section18/Section356/Section421_1626.htm
Diagnosis of Pulmonary TB in HIV

- Most HIV-infected patients with pulmonary TB have symptoms:
  - fever, cough, weight loss, night sweats

- The absence of these 4 symptoms have a 97% negative predictive value for culture-positive pulmonary TB

- More likely to have AFB smear negative pulmonary disease than HIV-negative counterparts

- 25% of HIV+ individuals with pulmonary TB will have negative TST or IGRA
TB Treatment

• After collecting specimens for culture/molecular testing, empiric treatment should be initiated in HIV+ persons with clinical and radiographic presentation suggestive of HIV-related TB

• Start 4-drug therapy:
  - Isoniazid
  - Rifampin/Rifabutin
  - Ethambutol
  - Pyrazinamide

• Vitamin B6 given to prevent neuropathy

• Always give medications via directly-observed therapy (DOT)
Treating Active TB Disease

• After collecting specimen for culture and molecular diagnostic tests, empiric treatment should be initiated in HIV-infected persons with clinical and radiographic presentation suggestive of HIV-related TB (AIII).
• DOT is recommended for all patients requiring treatment for HIV-related TB (AII).
• Please refer to the table below for TB drug dosing recommendations and to Table 5 for dosing recommendations of ARV drugs when used with RIF or RFB.

For Drug-Sensitive TB

Intensive Phase (2 Months)

• Daily therapy (5–7 days per week) given as DOT is recommended for all patients during the intensive phase (AII).
• INH + (RIF or RFB) + PZA + EMB (AI); if drug susceptibility report shows sensitivity to INH & RIF, then EMB may be discontinued.

Continuation Phase (For Drug Susceptible TB)

• INH + (RIF or RFB) daily (5–7 days per week) or TIW (AII)

Total Duration of Therapy:

• Pulmonary, drug-susceptible TB—6 months (BII)
• Pulmonary TB & positive culture at 2 months of TB treatment—9 months (BII)
• Extrapulmonary TB w/CNS—9 to 12 months (BII)
• Extrapulmonary TB w/bone or joint involvement—6 to 9 months (BII)
• Extrapulmonary TB in other sites—6 months (BII)
• The total duration of therapy should be based on number of doses received, not on calendar time (BIII).
Mrs. S is a 42 yo Indian woman who presents with a recurrent breast abscess:

- She has lived in the US for 5 years and has not travelled back to India
- She is married and has a 17 yo son
- The abscess is surgically drained 3 times
- Finally sample sent for AFB and culture is positive for TB
Mrs. S

- Symptom screen, chest x-ray are normal
- No evidence of cervical or axillary lymphadenopathy on exam
- HIV test: positive
- CD4: 300
- Husband also tests positive
- Started on 4-drug TB therapy
- HIV treatment: Atripla
Mr. R is a 46 yo African-American gentleman started to feel poorly last July:

- Caretaker for best friend with cancer; thought he was "just worn out."
- In August, he finally presented to local ER with weight loss, malaise, fever
Mr. R

• Biopsy of pretracheal lymph node performed and showed:
  “poorly formed granulomatous inflammation with acute lymphadenitis and numerous acid fast organisms.”
• Started on 4-drug TB therapy
• HIV test ordered
Timing of ART in TB/HIV Disease

• Concurrent therapy is challenging due to:
  - High pill burden
  - Increased potential drug toxicity
  - Increased risk of drug interactions
  - Risk of TB-associated IRIS

• Delaying HAART until after completion of TB therapy increases AIDS-associated morbidity and mortality
Timing of HAART in TB/HIV Disease

• CD4<50: start ART within two weeks of TB therapy

• CD4 50-200 or > 200 with severe TB disease: start ART within 2-4 weeks of starting TB therapy

• CD4 50-500 or >500 without severe clinical disease: ART can be deferred >2-4 weeks but should be started within 8-12 weeks

• When TB occurs in patients already on ART, start TB medications immediately and choose rifamycin that does not lead to drug interactions with ART
### Table 1a. Recommendations for regimens for the concomitant treatment of tuberculosis and HIV infection in adults

<table>
<thead>
<tr>
<th>Combined regimen for treatment of HIV and tuberculosis</th>
<th>PK effect of the rifamycin on ART</th>
<th>Tolerability / toxicity</th>
<th>Antiviral activity when used with rifamycin</th>
<th>Recommendation (comments)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz-based antiretroviral therapy (ART)* with rifampin-containing tuberculosis treatment</td>
<td>Well-characterized, modest decrease in concentrations in some patients</td>
<td>Low rates of discontinuation</td>
<td>Excellent</td>
<td>Preferred (efavirenz should not be used during the first trimester of pregnancy)</td>
</tr>
<tr>
<td>PI-based ART* with rifabutin-containing tuberculosis treatment</td>
<td>Little effect of rifabutin on PI concentrations, but marked increases in rifabutin concentrations</td>
<td>Low rates of discontinuation (if rifabutin is appropriately dose-reduced)</td>
<td>Favorable, though published clinical experience is not extensive</td>
<td>Preferred for patients unable to take efavirenz? (caution to ensure patients who discontinue PIs do not continue to receive reduced rifabutin dose)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Rifampin</th>
<th>Rifabutin</th>
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<tbody>
<tr>
<td>Raltegravir</td>
<td>↑ RAL to 800 bid</td>
<td>No change in dose of either</td>
</tr>
<tr>
<td>Dolutegravir</td>
<td>↑ DTG to 50 bid</td>
<td>No change in dose of either</td>
</tr>
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Daily DOT

• HIV/AIDS patients whose CD4 count is <100 at the initiation of therapy should receive a daily DOT regimen for the entire course of TB therapy

• Intermittent regimens were associated with increased risk of treatment failure or relapse with acquired rifampin resistance
TB-IRIS

- Relatively common in patients starting ART while on TB treatment (8%-43%)
- Risk factors: CD4<100, extrapulmonary or disseminated TB, short interval between starting TB meds and ART
- Symptoms typically occur 1-4 weeks after ART initiated
TB-IRIS

- Patients usually improve on TB therapy, then develop new or recurrent symptoms within the first few weeks of ART
- Common manifestations:
  - hectic fevers
  - new or worsening lymphadenopathy
  - new or worsening pulmonary infiltrates
- Diagnosis based on: clinical presentation with typical timeline, demonstration of response to ART (↑CD4, ↓VL), r/o alternative causes for deterioration
TB-IRIS

• Treatment:
  - most cases self-limiting
  - most cases require antipyretics
  - steroids used in cases with significant symptoms (tapered over 4 weeks)
Resources

• Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents

• Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis