Approach to Co-infection with TB and HIV: 2010

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TB and HIV Co-infection: Some Resources

- http://www.cdc.gov/tb
- http://www.umdnj.edu/globaltb/coretbresources.htm
- AETC Natl Resource Center: http://www.aidsetc.org
- http://www.aidsinfo.nih.gov/

Goals and Objectives

- Review current epidemiology of tuberculosis and HIV co-infection in the US and worldwide
- Impact of HIV Infection on the diagnosis and clinical presentation of TB (and TB on HIV)
- Specific Management issues in TB/HIV co-infection
  - Strategies for Screening for LTBI and TB Disease
  - Drug interactions and other treatment issues specific to HIV infected patients
  - TB or MAC?
  - TB and IRIS
  - When to start HAART in Co-infected patients

CLINICAL VIGNETTE: Patient 1

- A 36 year old woman is referred for management after discharge from the hospital on RIPE with newly diagnosed smear positive pulmonary tuberculosis
- She was born in South Africa, and has been living in the United States with her husband and 11 year old child
- She denies any significant past medical history and has no immigration papers
- HIV testing was not performed during her hospital stay
CLINICAL VIGNETTES: Q1

Should this woman have HIV counseling and testing performed as part of her initial clinic evaluation?

A) HIV testing should be offered
B) HIV testing should be strongly encouraged
C) No, HIV testing is not necessary or indicated
D) It doesn’t matter, knowledge of HIV status will not affect her management

CLINICAL VIGNETTE: Q2

What is the likelihood that she will be HIV positive?

A) Less than 5%
B) Less than 20%
C) Less than 50%
D) More than 50%
Estimated Incidence of Tuberculosis per 100,000 Population in African Countries in 1990 and 2005

TB and HIV Co-Infection

- 1/3 of the 33-36 million HIV positive individuals worldwide are infected with TB
- 1.37 million HIV positive TB cases in 2007 (15% of all TB cases) and 456,000 deaths
- Up to 80% of new cases of TB in sub-Saharan Africa are HIV co-infected
- HIV positives are at 10-50 fold higher risk of progression from LTBI to TB Disease
- Mortality is higher and rates of cure of TB are lower in co-infected patients

Reported TB Cases*
United States, 1982–2008

Estimated HIV Coinfection in Persons Reported with TB, United States, 1993–2008*

*Updated as of May 20, 2009.
Some Groups at Higher Risk for both HIV Infection and TB Infection

- Injection drug users
- Homeless
- Incarcerated/other congregate settings
- Non-injection drug users
- Lower socioeconomic status

TB, HIV and Immigration

- Rates of TB disease in HIV-infected individuals in developed countries such as the U.S. with low incidence of TB have been decreasing
- BUT… immigration of HIV-infected individuals from countries with higher incidence of TB infection/disease and the spread of HIV infection within poorer immigrant communities contribute to the persistence of the HIV-TB co-epidemic

Countries of Birth of Foreign-born Persons Reported with TB
United States, 2008

- Mexico (23%)
- Philippines (11%)
- India (8%)
- Vietnam (8%)
- China (6%)
- Guatemala (3%)
- Haiti (2%)
- Other Countries (38%)

HIV Testing and Tuberculosis

- All patients diagnosed with tuberculosis (TB disease) should undergo HIV testing at least by the time of initiation of TB therapy (CDC Treatment Guidelines)
  - If HIV +, should also have a CD4 count done
- All patients with LTBI should be offered HIV testing
  - Knowledge about HIV infection impacts strongly on management of LTBI
Direct Impact of HIV and TB Co-infection

- What does HIV infection do to the natural history of TB infection?
  - Risk of progression from LTBI to disease
  - Manifestations of disease
- What does TB infection and disease do to the natural history of HIV infection?

TB and HIV Interactions: Key Points

- T cells release IFN-gamma in response to TB
- Activated macrophages release cytokines, TNF and IL-1 to enhance killing of intracellular mycobacteria
- IFN-gamma and TNF enhance HIV viral replication
- TB accelerates HIV infection in both lymphocytes and macrophages
- HIV progressively diminishes the host ability to control TB by lowering CD4+ counts, decreasing IFN-gamma and decreasing cell mediated immunity
- Histopathology of TB in advanced HIV: lots of organisms, poorly formed (or no) granulomas

Natural History of HIV Infection

TB as an Opportunistic Infection

- Risk for progression from LTBI to TB disease in HIV infected (7-10% annual risk) is much greater than for HIV-negative patients (lifetime risk 5-10%)
- Increased risk for TB at all levels of immune suppression though relative risk and disease manifestations differ in different CD4 ranges
- Increased risk for TB disease occurs early after HIV infection, before significant immune suppression occurs: 2X increased risk of TB in the 1st year of HIV infection in S. African gold miners
Increased risk of TB Disease compared to HIV Negative

2 fold risk

>10x fold risk


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>Moss et al.</td>
<td>5.5 (2.1-14.1)</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>Palacios-Mendez et al.</td>
<td>2.4 (1.3-4.1)</td>
</tr>
<tr>
<td>AIDS-defining illness</td>
<td>Leventhal et al.</td>
<td>0.9 (0.7-1.3)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Palacios-Mendez et al.</td>
<td>1.2 (1.1-2.3)</td>
</tr>
<tr>
<td>Moderate TB chemotherapy</td>
<td>Corbett et al.</td>
<td>1.2 (1.1-3.1)</td>
</tr>
<tr>
<td>Underweight (&lt;80% percentile)</td>
<td>Palacios et al.</td>
<td>1.6 (1.1-2.2)</td>
</tr>
</tbody>
</table>

TB Disease in HIV

• ~1/3 Primary infection and ~2/3 Reactivation disease

• But Clinical and radiographic presentation do not necessarily correlate with traditional concepts of primary vs. reactivation disease, particularly with lower CD4 counts

• Re-infection is more common than previously thought, especially in high TB incidence areas and in patients with more severe immunosuppression

Impact of HIV on Presentation of TB

- CD4 counts > 350:
  - Disease similar to HIV negative
  - Primarily pulmonary disease
  - Most commonly upper lobe fibro-nodular infiltrates with/without cavities
  - Extra-pulmonary disease does occur more frequently than in HIV-negative, but presentations of extra-pulmonary disease are similar to HIV-negative

TB Presentations with More Advanced HIV Infection

- As CD4 counts fall, rates of extra-pulmonary TB increase
- With severe immunodeficiency (CD4 < 50) extra pulmonary disease such as diffuse lymphadenitis, pleuritis, meningitis and pericarditis even more common
- Increase in severe systemic syndromes and sepsis-like presentations that are associated with high mortality
- Organism burdens in these patients high, with high rate of disseminated disease and + mycobacterial blood cultures
- Differences in CXR appearance of pulmonary TB in advanced HIV infection

Pulmonary TB in Advanced HIV Infection

- CXR appearance may be “Atypical” i.e., resembling that seen in primary TB infection:
  - Interstitial infiltrates
  - Lower zone involvement
  - Absence of upper lobe cavitation or fibrosis
  - Can look like bacterial pneumonia or PCP
  - CXR can be clear: 20-30% (despite + sputum culture)
  - Sputum smears often negative despite + culture
- Result: delays in diagnosis, higher mortality

Geng et al, JAMA, 2005
CLINICAL VIGNETTE: Patient 2

- A 48 year old homeless man has HIV testing performed by outreach on “the van” in Camden and is found to be positive
- He is well at this time and denies any symptoms, but has a CD4 count of 138 cells/mm³
- He refuses to come to the HIV clinic for evaluation or treatment, but does agree to come to get “a TB test”

CLINICAL VIGNETTE Q3

- How should this patient be evaluated for possible TB (latent TB infection or active TB disease)?
  A) TST using 5 mm as cut off for positive
  B) IGRA
  C) Either A or B
  D) Chest X-ray
  E) Symptom assessment
Testing for Latent TB Infection in HIV +

- Tuberculin skin test (TST)
- Criteria for a positive TST in HIV infection (at any CD4 count) is 5 mm
- Likelihood of a positive skin test in those with TB infection decreases as CD4 count falls
  - Negative predictive value low when CD4 <200
  - 50 to 90% with HIV and LTBI will have positive TST when CD4 is greater than 500, but only 0 to 20% when CD4 < 200

Testing for Latent TB Infection in HIV +

- Interferon Gamma Release Assays (IGRA’s)
  - Quanti-FERON® TB-Gold
  - Quanti-FERON® TB-Gold in-Tube
  - T-Spot.TB Assay
- A + IGRA has greater "specificity" than + TST
- Role in HIV still being evaluated - studies suggest more sensitive than TST, but as with TST rate of positives decreases with more advanced immunosuppression and test can often be negative with active TB disease
- Incomplete concordance of TST and IGRA’s in HIV
- Do either? Both? CDC HIVMA/IDSA Guidelines (June 2008) recommend either test as appropriate for screening

Practical Issues in Screening

- All newly diagnosed HIV infected patients should be screened for LTBI
  - TST (5 mm cut off) OR IGRA AND symptom assessment
  - No Sx, TST negative, CD4 > 200→No Rx
  - No Sx, TST negative, CD4 < 200→No Rx but ...
  - No Sx, TST + (any CD4)→Evaluate for TB disease and treat for LTBI if active disease excluded
  - TB Sx regardless of TST result (any CD4)→Evaluate for TB disease
- HIV+ contacts of infectious cases should be treated regardless of TST status, even if prior Rx
### Treatment of LTBI in HIV

- Essentially the same as for HIV Negative
- INH: daily for 9 months plus pyridoxine
- No major interactions with HAART though toxicities may overlap (INH is a CYP 3A inhibitor)
  - Can use twice weekly (but only if receiving DOT)
- Rifampin: daily for 4 months
  - Used when INH resistance suspected or toxicity concerns (Hepatitis/ chronic liver disease common in HIV)
  - Drug interaction issues with HAART
  - Rifabutin (dose adjusted) is an alternative if PI are used

### LTBI in HIV Disease: Unanswered Questions

- How often after baseline testing should tuberculin skin testing (or IGRA) be done in HIV + individuals?
  - Annually? (recommended in many guidelines)
    - In all?
      - In CD4 < 200?
      - In CD4 > 200?
      - In all with additional risk factors?
  - Symptom assessment should be done annually
- Should HIV + with low CD4 counts and high risk for LTBI (e.g., immigrants from TB endemic regions) be treated for LTBI regardless of TST or IGRA results?

### CLINICAL VIGNETTE : Patient 2

- Our Homeless man has a TST result of 7 mm induration at 48 hours
- On further questioning now says that he has has a non-productive cough for 2 months and night sweats for a month and has lost 5 lbs over that time
- A CXR is negative

### CLINICAL VIGNETTES Q4

- What should be done now?
  A) Start treatment for LTBI with INH
  B) Start treatment for LTBI with Rifampin
  C) Start treatment for LTBI with Rifabutin
  D) Collect sputum for AFB x 3
  E) Initiate 4 drug regimen for Active TB
Identifying TB Disease in HIV Infected

- Limitations of Current Screening Tools: CXR, smear and culture
  - Smear Negative but Culture Positive Disease
  - CXR Negative but Culture Positive Disease
  - Tools more unreliable at lower CD4 counts

- Role of symptom assessment (NEJM Feb, 2010)
  - One of three symptoms - cough, fever, or night sweats - for more than 21 days over the preceding 4 weeks had 93% sensitivity and 36% specificity for the detection of active tuberculosis infection

Comparison of Study Algorithm with Other Approaches to Tuberculosis Screening and Diagnosis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Study Algorithm</th>
<th>Other Approaches</th>
<th>CXR and/or smears or culture (70% sensitivity)</th>
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</thead>
<tbody>
<tr>
<td>False positive results in smear screening</td>
<td>149</td>
<td>133</td>
<td>N/A</td>
</tr>
<tr>
<td>True negative results in smear screening</td>
<td>135</td>
<td>129</td>
<td>N/A</td>
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<tr>
<td>Cultures needed</td>
<td>135</td>
<td>134</td>
<td>N/A</td>
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<tr>
<td>False negative results in diagnostic test</td>
<td>34</td>
<td>128</td>
<td>N/A</td>
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<tr>
<td>Positive patients with false negative results</td>
<td>91</td>
<td>129</td>
<td>N/A</td>
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<tr>
<td>False positive patients with true positive results</td>
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<td>N/A</td>
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<td>False negative patients with true negative results</td>
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<td>93</td>
<td>128</td>
<td>N/A</td>
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Drug Interaction Issues in Rx of TB and HIV Co-Infection

- Major issue: use of Rifamycins and HAART, especially PIs, NNRTI’s and integrase inhibitors
- Rifamycins increase metabolism (and thus reduce serum levels) of these classes of antiretroviral drugs thru induction of CYP 3A
  - Rifampin > rifapentine > rifabutin
- Effect on PIs (80-90% reduction) greater than NNRTI’s (25-40% reduction)
- PI’s increase concentrations of rifabutin thru inhibition of CYP 3A
### Antiretroviral Medications - 2009

<table>
<thead>
<tr>
<th>Nucleoside Rev. Transcriptase Inhibitor (NRTI)*</th>
<th>Protease Inhibitor</th>
<th>Fusion Inhibitor*</th>
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<tbody>
<tr>
<td>Abacavir</td>
<td>Atazanavir</td>
<td>Enfuvirtide</td>
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<tr>
<td>Didanosine</td>
<td>Darunavir</td>
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<tr>
<td>Emtricitabine</td>
<td>Fosamprenavir</td>
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<tr>
<td>Lamivudine</td>
<td>Indinavir</td>
<td>CCR5 Antagonist</td>
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<tr>
<td>Stavudine</td>
<td>Lopinavir</td>
<td>Maraviroc</td>
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<tr>
<td>Tenofovir</td>
<td>Nelfinavir</td>
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<tr>
<td>Zidovudine</td>
<td>Ritonavir</td>
<td>Reverse Transcriptase Inhibitor</td>
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<tr>
<td>NonNRTI (NNRTI)</td>
<td>Saquinavir</td>
<td>Raltegravir</td>
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<tr>
<td>Delavirdine</td>
<td>Tipranavir</td>
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<tr>
<td>Efavirenz</td>
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<td></td>
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<tr>
<td>Etravirine</td>
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<tr>
<td>Nevirapine</td>
<td></td>
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</tr>
<tr>
<td>* No rifampin interactions</td>
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</tbody>
</table>

### Other Issues with Concurrent Rx for TB and HIV (and other OI's): Overlapping Toxicities

- Hepatotoxicity
- Nausea and vomiting
- Diarrhea
- Peripheral neuropathy
- Rash
- Ocular

HAART related toxicity increases with lower CD4 counts

### CLINICAL VIGNETTE: Patient 1

- Our 1st patient, the woman from South Africa, is HIV positive and her CD4 count is 50 cells/cu mm
- She is improving on treatment for pulmonary TB,
- She is pan-sensitive and continues on initiation phase INH 300 mg, Rif 600 mg and PZA 1500 mg
- She is referred to the HIV Clinic across town and started on a HAART regimen of: Tenofovir 300 mg plus Emtricitabine 200 mg plus Atazanavir 300 mg plus Ritonavir 100 mg

### CLINICAL VIGNETTE Q5

- She returns to the TB Clinic 2 weeks later. What should be done with her medications?
  A) Stop Rifampin and start Rifabutin
  B) Stop Rifampin and restart Ethambutol
  C) Decrease the dose of her Atazanavir and Ritonavir
  D) Speak to the HIV Clinic and coordinate her treatment regimen for both HIV and TB
Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis

Centers for Disease Control and Prevention
Coordinating Center for Infectious Diseases
Division of Tuberculosis Elimination
December 2007
http://www.cdc.gov/tb/TB_HIV_Drugs/default.htm

Coordination of TB care and HIV is Critical!!

Recommended Regimens for Concomitant Treatment of HIV & TB CDC Guidelines, 12/07

- **NNRTI based regimen**
  - Efavirenz (600 or 800 mg/d if >60kg) + usual dose Rifampin (600 mg)
  - Nevirapine (200 mg bid) + usual dose Rifabutin (300 mg/d)
  - Efavirenz (600 mg/d) + increased dose Rifabutin (600 mg/d)

- **Protease inhibitor (PI) based regimen**
  - Usual ritonavir boosted PI + less rifabutin (150 mg/every other day)

Remember: Use of a Rifamycin is always preferred to a non-Rifamycin containing regimen for RIF-susceptible TB disease

Other Treatment Issues in Management of TB in HIV Infected Individuals

- Treatment principles are similar as those for HIV negative (with some exceptions)
- **Early** initiation of Rx in TB suspect due to higher risk of overwhelming infection and mortality and potential for infectivity without the “usual” clues
- Standard Rx: Initiation of 4 drug regimen: INH + a Rifamycin + Ethambutol + PZA (unless baseline susceptibilities are known)
- **DOT** until completion of Rx for HIV co-infection is strongly encouraged, regardless of site of infection

AFB on smear or Culture: MAC or TB (or other)?

- MAC is common in HIV infected patients, though true pulmonary disease is relatively rare
  - NAAT’s are helpful for smear + pulmonary cases (new Guidelines for use of NAAT’s from CDC, Jan, 2009)
- TB is more lethal than MAC and poses public health risk (though disseminated MAC can cause significant morbidity)
- Both MAC and TB implicated as causes of IRIS
- INH and PZA not active against MAC; Ethambutol and Rifamycins have dual activity, Macrolides active only against MAC (Aminoglycosides and FQs also have dual activity)
- If necessary, can use a combined regimen to treat both until more data is available: RIPE + Azithromycin
Rifamycin Resistance and Intermittent Treatment Regimens

- Risk of RIF mono-resistance emerging on therapy with use of Rifampin or Rifabutin regimens
- Risk increased with Rifapentine OR twice weekly Rifampin and with lower CD4 counts (<100)
- Recommendations include
  - Daily (5X week Rx for 1st 2 months)
  - Daily or 3X per week intermittent regimens of CD4 less than 100 (do not use 2X per week regimens)
  - Do not use Rifapentine regimens

Duration of Treatment in HIV+

- Pulmonary TB: Standard courses (6 mo) for susceptible disease give good cure rates though relapse rates may be higher than non-HIV infected (studies varied but relapse rates up to 10% reported)
- Those who are still sputum culture positive at 2 months even without cavitation should receive longer (9 mo) Rx
- Longer courses for disseminated disease and other complicated extrapulmonary sites
- Slower responses in HIV+ may be due to absorption issues – consider drug levels early if concerns about adequacy of clinical response

CLINICAL VIGNETTE: Patient 1

- Our patient’s medications are adjusted. She has completed her initiation phase of treatment and is now on INH 300 mg plus Rifampin 600 mg daily by DOT for her TB and has been doing well
- Her HAART Regimen is now Atripla® (Tenofovir 300 mg plus Emtricitabine 200 mg plus Efavirenz 600 mg) daily and she has been on this for 3 weeks
- She develops new fevers and large, tender cervical lymph nodes

CLINICAL VIGNETTE Q6

What should be done to her TB regimen now?
A) Restart Ethambutol and PZA
B) Add 2 new drugs for possible MDR TB
C) Check TB drug levels
D) Obtain lymph node aspirates for AFB culture
E) Stop her HAART regimen
**TB, HIV and IRIS**

**Immune Restoration Inflammatory Syndrome**
- Enhanced immune mediated inflammatory response to infection already present, correlates with increase in CD4 on HAART and improved immune function: “Macrophages gone wild…”
- Multiple infections have been implicated, most commonly TB, MAC, Cryptococcus…many other
- Occasionally seen in non-HIV TB patients, especially sicker patients as they are treated
- Can occur in patients already on TB Rx (increased symptoms) or as initial manifestation of infection (unmasked infxn)
- Does not necessarily indicate treatment failure in patients on appropriate therapy

**Manifestations of TB Related IRIS**
- Common manifestations:
  - New or worsening lymphadenopathy, including spontaneously draining lesions
  - High fevers
  - New or worsening pulmonary infiltrates
  - Serositis – pleural effusion, peritonitis
  - Cutaneous lesions
  - Central nervous system lesions (tuberculomas)
- Can be severe and prolonged (months) and even (rarely) fatal

**TB Related IRIS**
- Occurrence in 8-43% of TB and HIV co-infected
- Most patients have advanced HIV disease
  - median CD4 count of 35 cells/ mm³; median viral load > 500,000 copies/ml
  - Usually severe (disseminated) TB disease with high pathogen burden
- Median 15 days after starting HAART, usually < 30 days; Most also seen within 90 days of starting TB Rx
- Diagnosis of exclusion
  - Differential Dx: Treatment failure, adherence, drug toxicity, new infection
  - Start treatment for presumed relapse or reactivation
- Management: NSAIDS, if severe- prednisone?

**IRIS: Subcutaneous abscess in Patient with AIDS & Miliary TB on ART**
Paradoxical Responses

TB and HIV: Timing of Rx

- TB therapy should always be started as quickly as possible
- In most instances HAART also should be started, but when?

Disappearance of lymph nodes under continuous anti-TB therapy.

8/07/2003

31/JAN/2003, before treatment

Note increase in size, and equalization of lymph nodes (arrows)

8/JUL/2003
To Delay or Start HAART in Active TB?

**Reasons to Delay**
- Multiple drugs, toxicities and interactions
- Decreased adherence
- TB is the priority, HIV is a chronic disease and Rx can wait
- HAART → IRIS

**Reasons to Start**
- HIV (esp. advanced HIV) has significant morbidity and mortality
- Earlier HAART beneficial for ALL HIV+
- Early initiation of HAART improves the prognosis of patients with OI’s at 6 months

**Current Recommendations**
- Multiple studies ongoing in areas of higher TB prevalence: current US recommendations
- CD4 > 350 → Delay HAART at least 8-24 weeks or to end of Rx
- CD4 100-350 → Delay HAART at least 8 weeks
  - CD4 100-200 vs. CD4 200-350
- CD4 < 100 → Delay HAART 2 weeks

**Timing of Initiation of Antiretroviral Drugs During Antituberculosis Rx: New Data**

**Clinical Outcomes of HIV Therapy**
HIV and TB Co-Infection: Key Points

• TB is the most common manifestation of HIV infection in highly TB endemic areas

• HIV and TB each enhance the pathogenicity of the other, HIV is the strongest known risk factor for progression from LTBI to TB disease

• Presentation of TB is atypical and disease is more difficult to diagnose and more lethal in advanced HIV infection

• Medical management of TB and HIV is complicated by drug interactions, especially related to rifamycins

• HIV + should be screened for LTBI but testing is imperfect, LTBI should be treated if diagnosed in HIV+

Coordination of TB care and HIV care is Critical