
 **19th Annual HIV CONFERENCE**
May 14-15, 2010 • Orlando, FL

Mycobacterial Infections in HIV

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- **BMS** Grant / Research Support
- **Pfizer** Grant / Research Support

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Epidemiology of HIV and TB

- **Globally**
 - TB is a leading cause of death in HIV+
 - 1.4 million co-infected in 2008; 500,000 died
 - One-third of HIV+ are infected with TB
 - 20-30 times more likely to develop TB than HIV-
 - One in four with HIV die due to TB
 - In last 20 years, new TB cases have tripled in high prevalence HIV countries

World Health Organization TB/HIV Fact Sheet 2009



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Epidemiology of HIV and TB

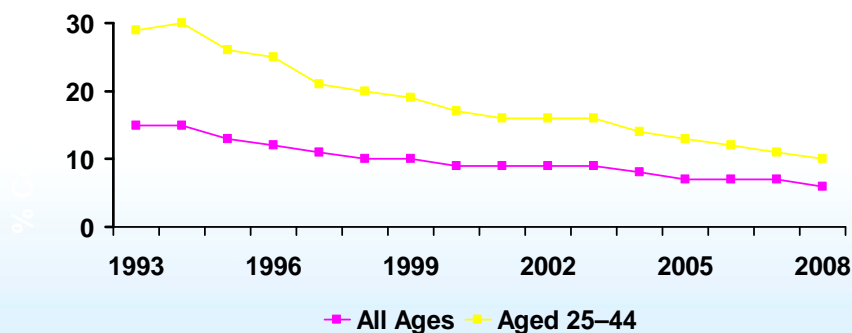
- **In the United States**
 - Overall TB rates are declining
 - Proportion of foreign-born cases now exceed those who are U.S.-born
 - The HIV epidemic plays a large role in TB cases in the U.S.



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



*Updated as of May 20, 2009.

Note: Minimum estimates based on reported HIV-positive status among all TB cases in the age group.



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Latent TB Infection versus Active TB Disease

- **Latent TB Infection (LTBI)**
 - Immune system stops replication of TB bacilli, but bacilli can remain alive and persist
- **Active TB Infection**
 - Uncontrolled and ongoing replication of TB from either primary infection or due to reactivation of LTBI
- **HIV is a major risk factor for reactivation of LTBI to active TB infection**



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Reactivation of LTBI in HIV

- **In HIV-, risk of reactivation of LTBI is ~10%**
 - 5% in first two years of TB infection
 - 5% in the remainder of lifetime
- **In HIV+, the risk of reactivation ~7-10% each year**
- **We can make a large impact in reducing active TB disease in our HIV+ patients through TB screening and treating LTBI**



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Clinical Findings in Active TB

- **May be typical in early HIV when CD4 > 350**
 - Pulmonary disease common with cavities on CXR
- **Can be atypical in advanced HIV**
 - Extrapulmonary disease more common
 - Pleuritis, lymphadenitis, meningitis, systemic dz
 - May be subclinical with few symptoms
 - May even have normal or atypical CXR



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Screening for LTBI in HIV+

- All should be screened at HIV diagnosis
- If prior (-)LTBI screen and CD4<200, those who begin ARV and attain CD4>200 should be rescreened
- Annual LTBI screening for those in “high risk” categories (prior incarcerated, congregate living settings, active drug use, other TB risk factors)
- If (+)LTBI screen, must undergo CXR and clinical evaluation to rule out active TB



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Case #1

- 27 year old Mexican-born female presents to your clinic as a new HIV+ diagnosis. Her CD4 count is 400. Her father had TB and was treated in Mexico while she was a teenager. She is currently asymptomatic with no cough or fever. Her CXR is normal. A PPD was placed and revealed an area of induration of 9mm. She is unsure if she had ever received BCG vaccine.



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Case #1

The best course of action is:

- A. Treat for active TB with 4 drugs as she was exposed to an active case in family
- B. Treat for LTBI with 1 drug
- C. Close observation but no treatment is necessary
- D. Obtain a blood test for TB (IGRA) to help guide therapy

| Option | Percentage |
|--------|------------|
| A | 25% |
| B | 25% |
| C | 25% |
| D | 25% |

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Screening Tests for LTBI

- **Tuberculin skin test (TST)**
 - HIV+ with 5mm or greater induration at 48-72 hours considered positive
- **Interferon-gamma release assay (IGRA)**
 - Blood assay that detects IFN-gamma release in response to *M. tuberculosis*-specific peptides
 - More consistent and higher specificity (92-97%) and less cross reactivity with BCG

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TST or IGRA?

- **Incidence of false neg. increases for both tests with advancing immunodeficiency**
 - If mod-high suspicion for active TB despite negative LTBI test, should treat as TB while awaiting further diagnostic test results
- **Concordance between tests is not complete**
- **Optimal use for IGRAs in HIV+ being studied**
- **TST remains useful especially for those who have not had BCG and in setting of cost constraints**



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Treatment of LTBI in HIV

- **Treating LTBI prevents active TB disease**
 - 12 randomized trials involving 8578 pts, found a reduction of active TB ~32% overall and in those +PPD of ~62%*
- **Rule out active TB: chest X ray and clinical evaluation prior to treatment**
- **Also treat those:**
 - (-)LTBI test, but close contact to active case
 - History of untreated or inadequately treated healed TB (i.e. fibrotic lung dz)

* Adetifa and Volmink, Cochrane review, 2010



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Treatment of LTBI in HIV

- **Preferred Regimen**
 - INH 300 mg daily or 900 mg twice weekly for 9 months (plus pyridoxine)
- **Alternative Regimen**
 - Rifampin: 300 mg daily for 4 months
 - Must take into account drug interactions
 - Rifabutin: dose adjusted according to concomitant ARVs for 4 months
- **DOT with intermittent dosing regimens**



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Case #2

- **A 33 year old man from Honduras is hospitalized with cough and pneumonia. He was just tested for HIV for which he is positive. His CD4 is 180. He is empirically treated for PCP and community acquired pneumonia and is somewhat improved. His CXR reveals a right upper lobe infiltrate. His 1st two sputum smears for AFB are negative, but his third sputum is “weakly positive” for AFB.**



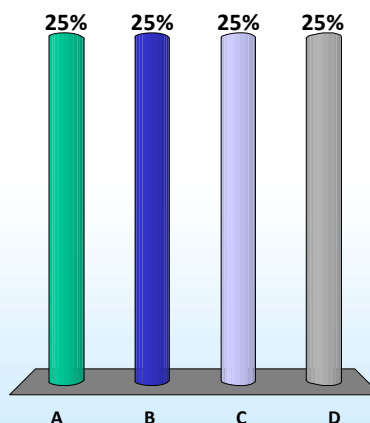
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Case #2

What is the best course of action:

- A. Continue PCP and pneumonia treatment since he appears to be better
- B. Obtain a PPD or IGRA to help guide treatment
- C. Treat empirically for TB with 4 drugs
- D. Ask for pulmonary consultation for bronchoscopy



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Diagnosis of Active TB Disease

- **CXR and sputum for AFB for active TB diagnosis**
 - Normal CXR and negative smears do not rule out TB disease
 - TST and IGRA may be falsely negative in ¼ of HIV positive who also have TB disease
- **May need to consider non-pulmonary sites**
- **Nucleic acid amplification (NAA) tests**
 - Rapidly identify M.TB in smear (+) sputum
 - Less sensitive in smear (-) or extrapulmonary



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Diagnosis of Active TB Disease

- **Not all that is AFB smear positive is TB**
 - May represent another mycobacteria
 - However, given virulence and transmissibility, patients with smear positive results should be considered to have TB until definitive identification made



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Treatment of Active TB in HIV

- In general, follow same concepts as HIV-
- If TB suspected, empirically treat until diagnostic workup completed
- DOT strongly recommended
- Must remember that ART may complicate issues due to drug toxicities, drug interactions, and immune reconstitution inflammatory reactions



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TB Therapy in HIV+

- **Initial Phase with four drugs for 2 months**
 - Isoniazid (INH)
 - Rifampin (RIF) or Rifabutin (RFB)
 - Pyrazinamide (PZA)
 - Ethambutol (EMB)
- **Continuation Phase for at least 4 months**
 - INH + RIF (or RFB) if sensitive
 - If resistance, longer duration (6-24 months) with sometimes numerous and more toxic medications



Drug Resistant TB

- **Multidrug resistant (MDR) TB**
 - Defined as resistance to INH and RIF (or RFB)
- **Extensively drug resistant (XDR) TB**
 - MDR TB + resistant to quinolones and 1 injectable agent
- **High risk for treatment failure and relapse**
- **Very complex treatment**



Case #3

- Your 34 yo homeless HIV+ man whose ART consists of tenofovir / emtricitabine / atazanavir (ritonavir-boosted) presents to your clinic with cough of 4 weeks. CXR reveals a new left upper lobe infiltrate. You order sputum AFB which is smear positive. The local health department calls you to notify you so that there can be coordination of care for HIV and TB. His CD4 = 220 and VL = 120. He weighs 65kg. He has only been on ART for 2 months.



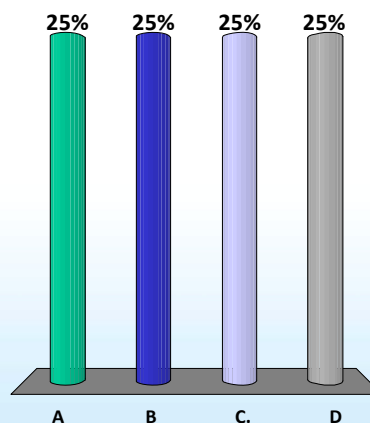
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Case #3

Which is NOT an option for therapy here:

- Starting INH/RIF/PZA/EMB and maintaining current ART
- Starting INH/RIF/PZA/EMB and changing ART to tenofovir / emtricitabine / nevirapine
- Starting INH/RFB (1/2 dose)/PZA/EMB and maintaining current ART
- Starting INH/RIF/PZA/EMB and changing ART to tenofovir / emtricitabine / efavirenz (at dose of 800mg)



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HIV ART and TB Treatment

- **Drug interactions with RIF (and RFB)**
 - No interactions with NRTIs or fusion inhibitor
 - NNRTI
 - EFV:
 - If >60kg, increase EFV to 800mg/day with RIF
 - Increase RFB dose to 450-600mg/day
 - NVP: No change in dose with RIF or RFB
 - ETV:
 - Avoid with RIF
 - No change with RFB



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HIV ART and TB Treatment

- **Drug interactions with RIF (and RFB)**
 - Protease inhibitors
 - RIF should be avoided with PIs
 - RFB can be used at ½ dose (150mg/day)
 - Some suggest drug monitoring when using RFB and lopinavir/ritonavir together*
 - CCR5 and Integrase inhibitors
 - RIF (and RFB to a lesser extent) decrease CCR5 and integrase levels
 - Increase raltegravir to 800mg twice daily when given with RIF
 - Little clinical experience so avoid if able

* Boulanger, et al. *CID*, 2009, 49, 1305-11 (summary in December 21, 2009 F/CAETC Carelink)



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Optimal Timing of HIV ART in TB

- If already on ART, assess regimen for both efficacy and reduction of drug interactions
- If not on ART, optimal timing of initiation of ART is not clear but guidelines suggest:
 - If CD4 < 100, ART after 2 weeks of TB Rx
 - If CD4 100-200, delay ART until after initial 2 month intensive phase of TB Rx
 - If CD4 > 200, start ART during continuation phase of TB Rx
 - If CD4 > 350, may delay until after TB Rx



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Case #4

- A 45 yo HIV+ man presents for his 2nd visit to you. He was diagnosed with TB by lymph node biopsy 8 weeks ago. At that time his CD4 was 100 and VL was 100,000. He was started on 4 drug TB therapy after biopsy. 4 weeks later he was started on ART (tenofovir / emtricitabine / nevirapine). Now in his 4 week follow-up after initiation of ART, he presents with worsening swelling and pain in his cervical lymph nodes, even more than when he was diagnosed with TB.



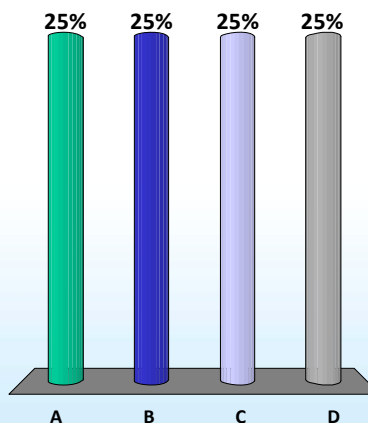
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Case #4

What is the most likely explanation for his current symptoms:

- A. Drug reaction between TB and HIV meds
- B. Multi-drug resistant TB
- C. New diagnosis of lymphoma
- D. Immune reconstitution syndrome



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Immune Reconstitution Inflammatory Syndrome (IRIS)

- IRIS and paradoxical TB reactions can occur in HIV- patients, but most common in HIV+ in 1st 1-3 months after starting ART
- Temporary worsening of symptoms, signs, or radiographic findings of TB after TB Rx
- Highest risk in those with CD4 < 100 and initiation of ART < 2 months after TB Rx
- Management includes NSAIDs for mild rxns and possibly steroids in severe rxns
 - Continue treatment for both TB and HIV



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Disseminated MAC

- **MAC (*M. avium*) is ubiquitous in nature**
- **Not associated with any specific environmental exposure or behavior**
- **If no ART or prophylaxis, found in 20-40% of patients with AIDS**
- **Disease usually seen in pts with CD4 < 50**



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MAC – Clinical Manifestation

- **Usually a disseminated infection**
 - Symptoms: fever, night sweats, weight loss, fatigue, abdominal pain, diarrhea
 - Exam: cachexia, abdominal pain, hepatosplenomegaly (HSM)
 - Labs: leukopenia, anemia, high alk phos
 - CT scan: lymphadenopathy (mesenteric, para-aortic, retroperitoneal), but less commonly peripheral adenopathy, HSM



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MAC – Clinical Manifestation

- **Uncommonly a localized or focal infection**
 - Seen in those on or just begun on ART
 - Some sites include lymphadenitis (cervical or mesenteric), pneumonitis, pericarditis...
 - Can present as manifestation of IRIS
 - Usually focal lymphadenitis and fever
 - Patients may have had subclinical MAC at initiation of ART and had rapid CD4 count rise
 - Usually self-limited but occasionally may require brief NSAIDs or prednisone therapy



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Case #5

- **44 year old man with recreational drug use who is poorly adherent to follow-up and medication presents with fever, night sweats, loose stools, and worsening abdominal pain. His CD4 is 12 and VL > 500,000 despite your attempts to get him to take ART. His WBC is 2.2 and Hb is 8.1. He has a mildly swollen left cervical lymph node and abdominal tenderness on exam. You suspect MAC, but need diagnosis due to other diagnostic possibilities.**



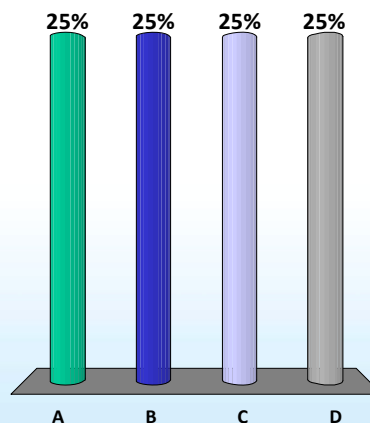
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Case #5

Possible methods to get a definitive MAC diagnosis include all, except:

- A. Lymph node biopsy with AFB smear and culture**
- B. AFB blood culture**
- C. AFB stool culture**
- A. Bone marrow biopsy with AFB culture**



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MAC - Diagnosis

- **Isolation of organism from blood, bone marrow, lymph node biopsy specimen (or any other normally sterile site)**
 - Sputum or stool sites may not necessarily indicate invasive disease
 - Usually takes several weeks for growth
 - Can have + AFB smears from specimens
- **Must send for AFB culture from these sites**
- **Need to identify to species level to distinguish TB from MAC**



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MAC – Primary Prevention

- **Prophylaxis with those CD4 < 50 and no dz**
 - Azithromycin 1200mg weekly OR
 - Clarithromycin 500mg twice daily OR
 - Alternative
 - Rifabutin 300mg daily (adjust dosage based on drug interactions with ARV)
- **Can stop prophylaxis once on ART and CD4 > 100 for more than 3 months**



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MAC - Treatment

- **Minimum duration of therapy is 12 months and depends on immune reconstitution**
- **Minimum number of effective meds are 2**
 - Preferred: clarithromycin + ethambutol
 - Alternative: azithromycin + ethambutol
 - Alternative 3rd agents when needed include rifabutin, amikacin, quinolones, streptomycin
- **Test isolates for macrolide susceptibility**
- **Consider delaying ART initiation until at least 2 weeks after MAC Rx to limit IRIS risk**



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MAC - Monitoring

- **Improvement in fever and symptoms after treatment is not immediate, but usually by 2-4 weeks (unless extensive dz or advanced immunosuppression).**
- **Repeat AFB blood culture at 4-8 weeks if no clinical response to therapy**
- **IRIS**
 - If mild, NSAIDs
 - If persistent or severe, 20-40mg daily prednisone for 4-8 weeks



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MAC – Treatment Issues

- **If failing due to macrolide resistance, use new agents including amikacin, rifabutin, streptomycin, and quinolones**
 - Limited compelling data on efficacy
- **Optimize ART as adjunct to therapy for MAC**
- **Lifelong chronic therapy unless at least 12 months Rx and 6 months of CD4 > 100**
- **Secondary prophylaxis if CD4 < 100 again**



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Summary

- **Mycobacterial infections remain common in HIV infected individuals**
- **Must maintain a level of suspicion**
 - Screening critical in TB
 - Knowledge of symptoms and prophylaxis of MAC
- **Treatment involves multiple medications for lengthy durations**
- **IRIS can be seen in both diseases**



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