

**Southeastern National
Tuberculosis Center**
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HIV & TB Co-Infection

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The Foundation for The Gator Nation

Faculty Disclosure Information

In the past 12 months, I have no relevant financial relationships with the manufacturers of any commercial products and/or providers of commercial services discussed in this educational activity.

I do NOT intend to discuss an unapproved/investigative use of a commercial product in my presentation.

Objectives

At the end of this session, participants will be able to:

- Describe the epidemiology of HIV and tuberculosis (TB) and their close relationship
- Recognize the clinical manifestations of TB in HIV infected children and adolescents
- Discuss the diagnostic work-up when suspecting TB in this group of patients
- Briefly discuss the management of TB in HIV infected children and adolescents

Case

DL is 4 year old male who is a recent adoptee from an orphanage in Africa. Very little is known about his birth history. He did receive the BCG vaccine in Africa. He has an HIV test done on arrival which is positive. His viral load is 154,000 and CD4 count is 199.

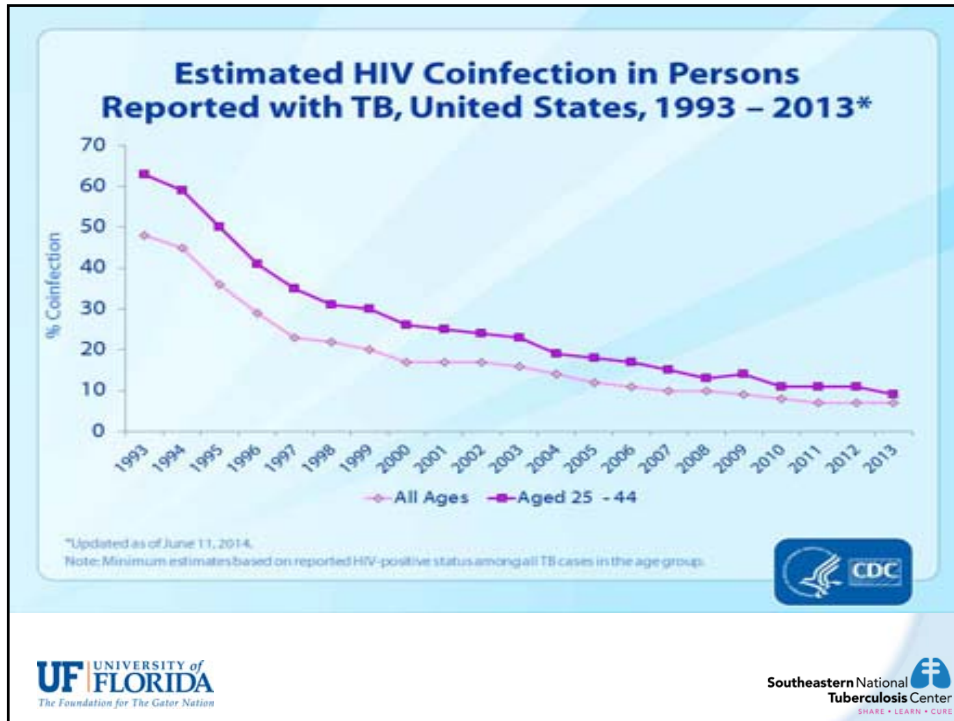
He also has a PPD placed which is 19 mm and a CXR with prominent hilar and mediastinal lymphadenopathy.

Case continued

1. What would be the next steps in his management?
2. What would you start first? HAART? Anti-tubercular treatment?
3. Given his age, what would be the considerations for starting HAART therapy?
4. How would you monitor his treatment?
5. What complications would be anticipated during his treatment?
6. Any thoughts about the history of BCG vaccination?

Epidemiology- United States

- 9,582 cases of TB were reported to the CDC in 2013- an incidence of 3.0/100,000 cases
- Lowest number reported since 1953
- HIV status was known for 88% of the 2013 reported cases
- Among those with a known result, 9% were reported HIV positive (ages 25-44 yrs)



Pediatric TB Cases by HIV Status, 1993–2011* N=19,354

Information on HIV results are not available for the majority of pediatric TB cases (75.9%)

Pediatric TB cases with HIV-positive test results, minimum estimate**	0.9%
Pediatric cases with HIV-positive test results of those patients with known results	3.7%

Epidemiology- United States

- The major risk factor for Mycobacterium tuberculosis (MTB) in all children including those that are HIV infected is *exposure to an adult with TB*
- Individuals with HIV infection and latent TB infection (LTBI) are **30** times more likely to progress to TB disease
- Unlike other opportunistic infections decreased CD4⁺ cell count is not necessary for increased risk of TB
- TB disease in an HIV infected individual constitutes an AIDS defining condition

Global TB & HIV

- Globally TB is the leading cause for death among people living with HIV/AIDS
- 2 billion people infected with TB (LTBI)
- 34 million are infected with HIV and at least 1/3rd of this number also have TB
- In sub-Saharan Africa 80% of people with active TB disease also have HIV
- WHO estimates that HIV prevalence among children with TB is 10-60% (moderate to high prevalence countries)

PATHOGENESIS

Pathogenesis- HIV & TB Co-Infection

- *MTB* and HIV infection potentiate one another, accelerating the deterioration of immunological functions and resulting in premature death if untreated
- Both infections up-regulate the function of macrophages which produce various cytokines in response to infection

Pathogenesis- HIV & TB Co-Infection

- It has also been suggested that TB patients have a microenvironment that facilitates HIV infection by:
 - i) increasing the expression of co-receptors CXCR4 and CCR5 regulated by *MTB* products
 - ii) increasing pro-inflammatory cytokines, especially tumor necrosis factor (TNF)
 - iii) down-regulation of other cytokines

Pathogenesis- HIV & TB Co-Infection

- While TNF production in response to *MTB* infection is required for control of bacterial growth, TNF is known to activate HIV replication in macrophages
- This indicates that the host immune response initiated against one pathogen may promote the replication of another

Pathogenesis- HIV & TB Co-Infection

- Decreased apoptosis of alveolar macrophages may also facilitate the development of TB in HIV infected individuals
- Further, the depletion of CD4⁺ cells by HIV facilitates the reactivation of TB
- Depletion of CD4 cells in advanced HIV disease also facilitates the development of extra-pulmonary disease

CLINICAL MANIFESTATIONS

Clinical Manifestations

- Generally clinical signs and symptoms of TB in HIV infected vs non-infected children are similar with intermittent fever, failure to thrive and cough
- HIV infected children are more prone to rapid progression and disease dissemination
- All forms of extra-pulmonary TB have been described in HIV infected patients

Clinical Manifestations

- Atypical features such as diffuse interstitial disease and multi-lobar infiltrates maybe seen in HIV infected children
- High index of suspicion is required to diagnose TB in HIV infected children

DIAGNOSIS

Diagnosis

- Thorough medical history and physical examination
- Tuberculin Skin Test (TST)
- Interferon gamma release assays (IGRA)
- Chest radiograph
- Bacteriologic or histologic evaluation
- Nucleic Acid Amplification tests

Diagnosis

- A reaction ≥ 5 mm is considered positive in an HIV infected individual
- TST has poor sensitivity to detect *MTB* infection in HIV infected children- 50% or less of these children with bacteriologically confirmed TB are TST positive
- Effective contact investigation of adults with pulmonary TB particularly those with HIV co-infection is the most efficient way to identify at-risk children both HIV infected and not infected

Diagnosis

- IGRAs require T-cell activity therefore HIV infection as well as the degree of immune function may diminish the utility of these tests
- Younger age, HIV infection, and reduced numbers of CD4⁺ cells also increase the rate of indeterminate IGRA results
- The T SPOT[®]-TB assay has been shown to perform better than both the TST and QFT in HIV infected children and adults independent of CD4⁺ counts

Recommendations for Testing

- All children diagnosed with TB should be tested for HIV infection
- Annual TB testing is recommended for HIV infected children beginning at 3-12 months of age and annually thereafter for those who previously tested negative

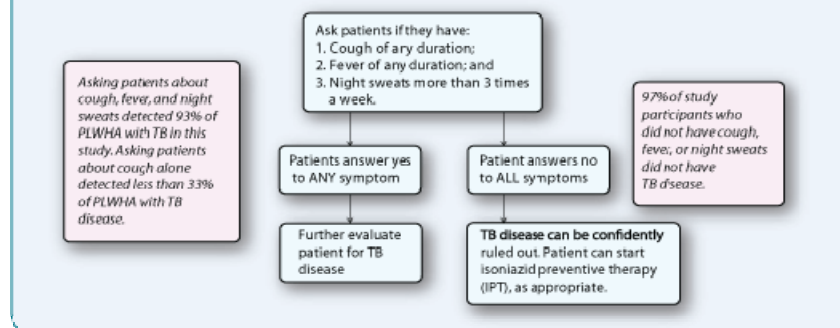
Recommendations for HIV Screening in TB Clinics

- CDC recommends HIV screening for all TB patients using the 'opt-out' approach
- Routine HIV testing should also be recommended for patients suspected of having TB disease, persons with LTBI and contacts to TB patients
- Rapid HIV tests can be used in these settings

Diagnosis in Resource Poor Settings

- A new evidence based screening and diagnostic approach tested in Thailand, Cambodia and Vietnam identified 93% of patients with TB in this particular study
- This screening approach detected 93% of patients with TB in this study, performing much better than earlier approaches which detected fewer than 33% of cases

Figure 1: The Best Evidence-Based Approach to Screening for TB Disease Among PLHWA



This figure represents the steps taken to screen for TB among people living with HIV/AIDS (PLHWA) and identify those individuals who need further evaluation. The health care provider first asks the patient if they have experienced any of these symptoms: cough of any duration; fever of any duration, or night sweats more than three times a week. If the patient answers NO to ALL of these symptoms they are considered not to be a suspect for TB disease and should be considered for isoniazid preventive therapy (IPT) to prevent TB. In this study, 97% of patients with none of these symptoms were free of TB. If the patient answers YES to ANY symptom, they should be further evaluated for TB disease, usually including smear microscopy, culture, and chest x-ray.

MANAGEMENT: DRUG TREATMENT & INTERACTIONS

Treatment for LTBI

- After the exclusion of TB disease, all HIV positive individuals with a positive TST or IGRA should be treated for LTBI*
- Preferred treatment regimen is INH (10-15 mg/kg/day) for 9 months
- Liver functions tests should be performed for HIV infected children before starting INH
- If compliance with daily treatment cannot be ensured, twice weekly therapy (INH 20-30 mg/kg/day) given by directly observed therapy should be considered

*If CD4 counts <200 cells/mm³ at the time of entry into care, screen for TB and repeat screen once counts >200 cells/mm³ if initial screen negative

Treatment for LTBI

- The alternate regimen of 12 dose once weekly INH plus Rifapentine by DOT has been successful in adults however it is NOT RECOMMENDED for
 - children aged < 2years
 - for HIV infected children and adults receiving combination antiretroviral therapy (cART)

Treatment of TB Disease

- Empiric treatment for TB disease using DOT should be started in all HIV infected infants and children in whom the diagnosis is strongly suspected and continued until the diagnosis has been confirmed or ruled out
- **The total recommended treatment duration in uncomplicated pulmonary TB disease is 9 months**
- For extrapulmonary disease involving bones or joints, CNS or disseminated disease, the minimum treatment duration is 12 months

Treatment of TB Disease

- For HIV infected children treatment of drug susceptible TB should consist of the four drugs: INH, RIF, Pyrazinamide (PZA) and Ethambutol (ETH)
- After the initial 2 month period, continuation phase treatment using only INH & RIF may be continued with thrice weekly therapy via DOT provided there has been good treatment response and adherence
- Once or twice weekly treatment is not recommended due to high risk of treatment failure or relapse

Treatment of TB Disease

- HIV infected children with minimal disease, without significant immune compromise and fully drug susceptible TB, a 3 drug regimen with INH, RIF and PZA may be considered (x 2 months) followed by INH and RIF (x 7 months)
- Injectable aminoglycosides or ethionamide may be considered as the fourth drug in place of ETH in cases of TB meningitis due to superior CSF penetration

Concurrent Use of ART & TB Medications

- Treatment is complicated by multiple drug interactions and toxicities
- No dosage adjustment is necessary when INH alone is used for LTBI treatment
- Drug levels should be obtained whenever possible
- Liver function tests should be monitored before starting therapy, then at 2, 4, and 8 weeks of TB treatment.

Concurrent Use of ART & TB Medications

- Beyond 2 months, liver function tests should be done every 2-3 months until the end of therapy
- When treatment failure is suspected change the entire drug regimen rather than a single drug alone

Concurrent Use of cART & TB Medications: Role of Rifampin

- Choice of cART regimens must consider:
- The critical role of RIF because of its bactericidal and sterilizing properties
- Potent induction of the CYP3A enzyme system and p-glycoprotein-mediated efflux that lowers cART drug levels, especially protease inhibitors (PIs) except Ritonavir which partially reduces this effect
- Moderate reduction in NVP levels
- NRTIs and Efavirenz levels are least affected

Concurrent Use of cART & TB Medications

- Rifabutin, a rifamycin-class semi-synthetic antibiotic related to rifampin, exhibits minimal CYP3A induction and has been used in place of Rifampin, data in children are limited
- Rifabutin has fewer drug interactions than RIF but requires dosage adjustments for cART drugs
- Combined use of integrase inhibitors and other cART drug classes with RIF have not been evaluated in children
- Ongoing studies in adults suggest that dosage adjustment may be necessary with these medications as well

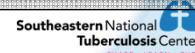
Concurrent Use of cART & TB Medications

- CCR5 inhibitors- since these drugs are also metabolized by the cytochrome P-450 isoenzyme 3A4 would need dosage adjustments when co-administered with rifampin
- Once again obtaining drug levels where available and close monitoring for toxicities is essential when administering concomitant cART and TB medications

Concurrent Use of cART & TB Medications

Age/Weight	Choice of HAART
<3 years or < 10 kg	<p><u>Retain or Start</u> NRTI backbone (use 2)</p> <p><u>Third Drug</u> <i>Already on NVP consider:</i> Switch to lopinavir/ritonavir OR Continue NVP high dose</p> <p><i>If Already on Lopinavir/Ritonavir</i> Adjust dose of Ritonavir Switch to NVP</p> <p><u>HAART Initiation</u> Triple NRTI therapy if VL <100,000 copies/ml</p>

Concurrent Use of cART & TB Medications	
Age/Weight	Choice of HAART
<p>≥3 years or ≥10 kg</p>	<p>Retain or Start NRTI backbone (use 2)</p> <p>Third Drug A. <i>If on Efavirenz continue on same dose</i></p> <p>B. <i>Receiving NVP consider: Switch to Efavirenz OR Continue NVP high dose</i></p> <p>C. <i>If Already on Lopinavir/Ritonavir Consider change to Efavirenz if VL undetectable & no prior NNRTI exposure Continue Lopinavir/Ritonavir and Adjust dose of Ritonavir Switch to NVP if above 2 options not possible provided VL undetectable and no prior NNRTI exposure</i></p> <p>HAART Initiation Triple NRTI therapy if VL <100,000 copies/ml</p>



Multi-Drug Resistant TB Treatment

- A minimum of 4 drugs to which the organism is susceptible should be administered
- If the strain is resistant to INH then a RIF containing regimen should be administered for 9-12 months
- RIF resistance is rare, when detected by a rapid test should be considered a marker of MDR-TB until susceptibilities to both INH and RIF are available
- Those with extensive or disseminated disease should be treated with a minimum of 5 drugs with daily DOT



Special Considerations for HIV Infected Patients

Immune Reconstitution Inflammatory Syndrome (IRIS)

- TB associated IRIS may occur after initiation of anti-tubercular therapy
- It may present with new onset symptoms such as high fever, worsening adenopathy, pulmonary infiltrates, pleural effusions, expanding CNS lesions
- It is more likely to occur in those with advanced immune-suppression
- Should be suspected when exacerbation of symptoms develop within 3-6 months (or sooner) of initiating cART

IRIS Management

- IRIS may occur in the setting of a) presence of TB in the host prior to the initiation of cART or b) paradoxical worsening of TB in HIV-TB co-infected patients
- Mild-to-moderate symptoms of IRIS can be treated symptomatically with non-steroidal anti-inflammatory agents
- Short-term use of systemic corticosteroids can be considered in more severe cases
- Treatment for TB and cART should not be discontinued

When to Start Treatment?

- For children not yet receiving HAART early treatment preferably within 2-8 weeks of starting anti-tubercular treatment (ATT) should be planned
- Results from studies in both adults and children suggest that early initiation of cART (within 2-8 weeks) of starting ATT are associated with a significant reduction in mortality
- Children with advanced disease may need to start cART treatment earlier as well

Management of HIV Infected Persons who are Contacts to Active Cases

- Evaluation
 - TST/IGRA
 - CXR
 - Symptom review and physical exam
- If all of the above are negative
 - Treat as LTBI with INH for 9 months

Risk of Recurrent Disease

- Re-infection disease should be managed the same as first-time TB
- Secondary (post-treatment) prophylaxis is not recommended
- However, regular TB exposure screening should continue after completion of treatment, and preventive therapy should be considered whenever repeat exposure occurs

Risk of Relapse & Recurrent Disease

- TB recurrence can represent relapse or re-infection
- The relapse rate is low in children with drug susceptible TB who receive DOT and cART
- Recurrence within 6 to 12 months of treatment completion should be regarded as relapse & managed the same as treatment failure
- Recurrence > 6 to 12 months post treatment completion is probably re-infection disease, especially after new TB exposure or a visit to a TB endemic setting

BACK TO THE CASE DISCUSSION

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Selected References

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THANK YOU!