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AETC AIDS Education & Training Center Program Southeast

HIV and Tuberculosis

***also includes discussion of Mycobacterium avium** complex*

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Slide Credit

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Learning Objectives

- Describe the epidemiology of HIV and TB globally and in the U.S.
- Distinguish latent TB Infection (LTBI) from active TB disease.
- Identify screening methods for LTBI in HIV+ individuals.
- Discuss HIV and TB treatment recommendations in co-infected individuals.

Epidemiology of HIV and TB

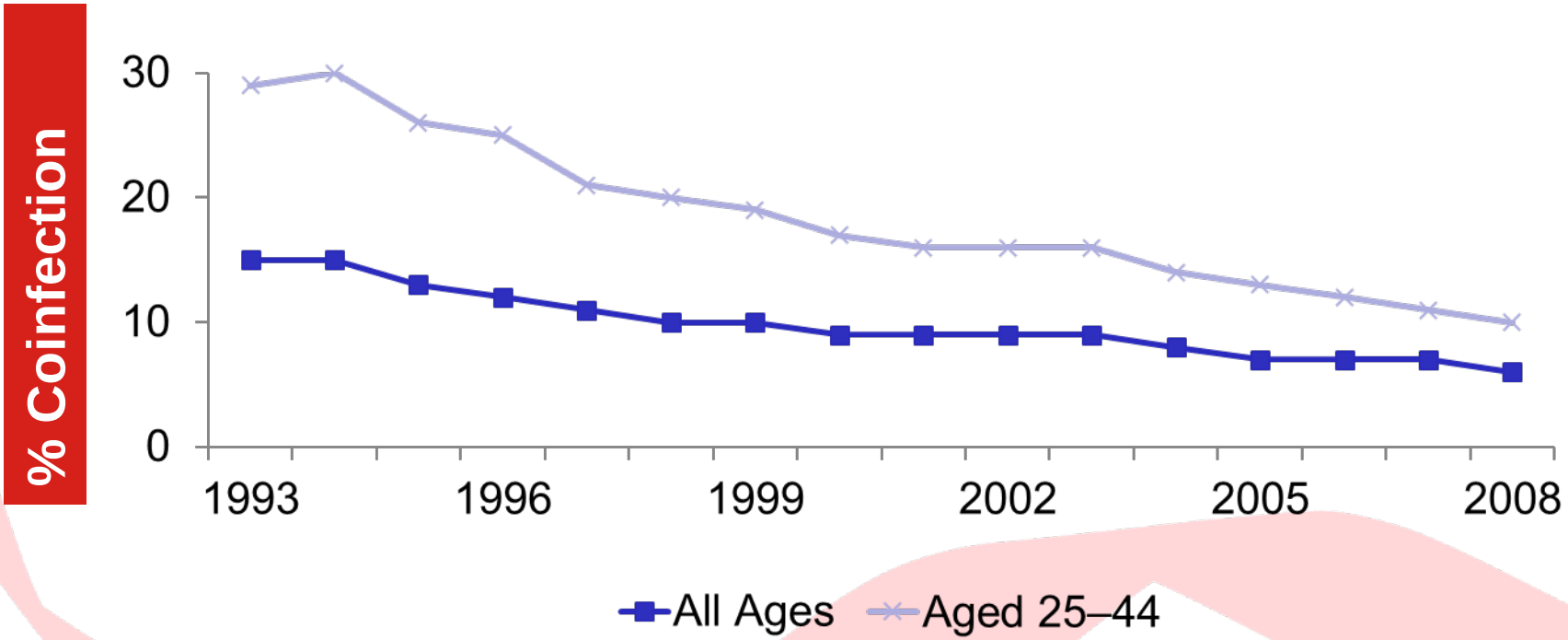
- Globally
  - TB is a leading cause of death in HIV+
  - 1.4 million co-infected in 2008; 500,000 died
  - One-third of HIV+ are infected with TB
    - 20-30 times more likely to develop TB than HIV-
    - One in four with HIV die due to TB
  - In last 20 years, new TB cases have tripled in high prevalence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

World Health Organization TB/HIV Fact Sheet 2009

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.

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.

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

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

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

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

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.

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

Screening Tests for LTBI

- http://www.bcgatlas.org/
- 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

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 active TB while awaiting further diagnostic test results
- Concordance between tests is not complete
- IGRA can be used in place of TST and preferred in:
  - prior BCG history
  - Groups that have low rates of return for TST read

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

* Akolo C, Adetifa I, Shepperd S, and Volmink J, Cochrane Database Syst Rev 2010 Jan 20

Treatment of LTBI in HIV: Indications

- Positive screening test for LTBI, with no evidence of active TB, and no prior treatment for active TB or LTBI, or
- Close contact with a person with infectious TB, with no evidence of active TB, regardless of screening test results.

http://aidsinfo.nih.org, accessed 5/17/16

Treatment of LTBI in HIV: Regimens

- Preferred Regimen (include pyridoxine if on INH)
  - INH 300 mg daily x 9 mos
  - INH 900 mg twice weekly as directly observed therapy (DOT) X 9 mos
- Alternative Regimen
  - Rifampin 600 mg daily for 4 months
    - Must take into account drug interactions
  - Rifabutin
    - (Dose-adjusted based on concomitant ART) x 4 months

For persons exposed to drug-resistant TB, select anti-TB drugs after consultation with experts or public health authorities

http://aidsinfo.nih.org, accessed 5/17/16

Case #2

- A 33 year old man from Honduras is hospitalized with cough and pneumonia. He was just tested for HIV and is positive. CD4 is 180. He is empirically treated for both *Pneumocystis jiroveci* pneumonia (PJP) and community acquired pneumonia (CAP) 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.

Case #2
What is the best course of action?

A. Continue treatment for both PJP and CAP 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 pulmonology consultation for bronchoscopy

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

Diagnosis of Active TB Disease

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

Treatment of Active TB in HIV

- If TB suspected, empirically treat until diagnostic workup completed
- DOT strongly recommended
- Must remember that ART may complicate TB treatment as a result of drug toxicities and drug interactions and worsen (or unmask) active TB as part of the immune reconstitution inflammatory syndrome (IRIS)

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 – consult an expert

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 disoproxil fumarate (TDF) / emtricitabine / darunavir (cobicistat-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.

Case #3
Which is NOT an option for therapy here?

A. Starting INH/RIF/PZA/EMB and maintaining current ART
B. Starting INH/RIF/PZA/EMB and changing ART to tenofovir disoproxil fumarate (TDF) / emtricitabine / raltegravir (at dose of 800 mg twice daily)
C. Starting INH/RFB (150 mg daily or 300 mg 3x per week) /PZA/EMB and maintaining current ART
D. Starting INH/RIF/PZA/EMB and changing ART to TDF / emtricitabine / efavirenz (at dose of 800 mg nightly)

HIV ART and TB Treatment

Drug interactions with Rifampin (RIF) & Rifabutin (RBT)*

Nucleoside/tide reverse transcriptase inhibitors (NRTIs) & Fusion inhibitor (Enfuvirtide, T20):

- No interactions with NRTIs or fusion inhibitor

*http://aidsinfo.nih.gov, accessed 5/17/16

HIV ART and TB Treatment (2)

Drug interactions with Rifampin (RIF) & Rifabutin (RBT) (cont'd)

Protease inhibitors (PIs):

- RIF should be avoided with PIs (whether ritonavir-boosted PIs or cobicistat-boosted PIs)
- RBT can be used at ½ dose (150 mg/day or 300 mg 3x per week)
- Some suggest that "… rifabutin 150 mg daily may be preferred when co-administered with lopinavir/ritonavir in patients with HIV-associated [TB]"*

**Lan NT *et al*, PLoS One, 2014 Jan 22

HIV ART and TB Treatment (3)

Drug interactions with Rifampin (RIF) & Rifabutin (RBT) (cont'd)

Integrase strand transfer inhibitors (INSTIs), a.k.a. Integrase inhibitors (InIs)

- INSTIs that can be co-administered with RIF or RFB:
  - Raltegravir (RAL) (increase dose to 800 mg twice daily when given with RIF) (no dose adjustment with RFB)
  - Dolutegravir (DTG) (when given with RIF, increase dose to 50 mg twice daily – instead of administering 50 mg once daily – for patients without suspected or documented INSTI mutation). Alternative to RIF should be used in patients with certain suspected or documented INSTI-associated resistance substitutions. Consider using RFB, with which there is no DTG dose adjustment.

HIV ART and TB Treatment (4)

Drug interactions with Rifampin (RIF) & Rifabutin (RFB) (cont'd)

Integrase strand transfer inhibitors (INSTIs), a.k.a. Integrase inhibitors (InIs) (cont'd)

- INSTIs that cannot be co-administered with RIF or RFB:
  - Elvitegravir (EVG) / cobicistat / emtricitabine / tenofovir disoproxil fumarate (TDF)
  - EVG / cobicistat / emtricitabine / tenofovir alafenamide (TAF)

HIV ART and TB Treatment (5)

Drug interactions with Rifampin (RIF) & Rifabutin (RBT) (cont'd)

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

- Efavirenz (EFV):
  - With RIF: If >60kg, increase EFV to 800 mg/day
  - With RFB: Administer RBT at a dose of 450-600 mg/day or, if EFV is not co-administered with a protease inhibitor (PI), 600 mg 3 times/week
- Rilpivirine (RPV):
  - With RIF: Do not co-administer
  - With RFB: Increase RPV to 50 mg/day

HIV ART and TB Treatment (6)

Drug interactions with Rifampin (RIF) & Rifabutin (RBT) (cont'd)

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) (cont'd)

- Nevirapine (NVP):
  - With RIF: Do not co-administer
  - With RFB: No dosage adjustment necessary. Use with caution.
- Etravirine (ETR):
  - With RIF: Do not co-administer
  - With RFB: If ETR is used with a ritonavir- (RTV-) (or cobicistat-) boosted protease inhibitor (PI), rifabutin should not be coadministered. If ETR is not coadministered with an RTV- or cobicistat-boosted PI, administer RFB at a dose of 300 mg/day.

Optimal Timing of HIV ART in Active 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 < 50, start ART within 2 weeks of TB Rx start*
  - If CD4 < 200, start ART within 2-4 wks of starting TB Rx
  - If CD4 200-500, start ART within 2-4 wks or at least within 8 weeks of TB Rx start
  - If CD4 > 500, start ART within 8 wks of TB Rx start

*IAS-USA: JAMA 2012; 308(4):387-402

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.

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 inflammatory syndrome (IRIS)

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

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

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

MAC – Clinical Manifestations

- Uncommonly a localized or focal infection
  - Seen in those on (or who have just begun) 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

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 2200 and Hb is 8.1. He has a mildly swollen left cervical lymph node and abdominal tenderness on exam. You suspect disseminated MAC, but need a diagnosis due to the presence of other diagnostic possibilities.

Case #5

Possible methods to get a definitive diagnosis of disseminated MAC include all of the following except:

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

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

MAC – Primary Prevention

- Prophylaxis with those CD4 < 50 and no dz
  - Azithromycin 1200 mg weekly OR
  - Azithromycin 600 mg 2x weekly OR
  - Clarithromycin 500 mg twice daily OR
  - Alternative
    - Rifabutin 300 mg daily (adjust dosage based on drug interactions with ARV; first must rule out active TB)
- Can stop prophylaxis once on ART and CD4 > 100 for more than 3 months

MAC - Treatment

- Minimum duration of therapy is 12 months and depends on immune reconstitution (CD4 > 100 for at least 6 months)
- 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 (esp among patients with prior macrolide exposure)
- NSAIDs and/or steroids can be used in patients who develop MAC disease as part of IRIS

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, 20-40 mg daily prednisone for 4-8 weeks

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

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 disseminated MAC
- Treatment involves multiple medications for lengthy durations
- IRIS can be seen in both diseases

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