

Treatment of TB: Management of Patients with HIV Co-Infection

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Advanced TB Training for Clinicians
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Endogenous reactivation

- HIV is the most potent risk factor for reactivation of latent tuberculosis
- HIV negative < 1% per year (10% lifetime)
- HIV positive ~ 7-10% per year (apprx 100% lifetime)
- Incidence of TB is 100 times greater in persons with HIV infection than in general population

HIV/TB co-infection

- When a patient with HIV infection develops infection with *Mycobacterium tuberculosis*, ~ 40% develop active disease within weeks and progress rapidly
- Associated with increased morbidity and mortality despite optimal treatment
- Spread the disease rapidly among contacts and health care workers leading to nosocomial outbreak

Effects of TB on HIV - 1

- Immune activation from TB enhances both systemic and local HIV replication
- Viral load increases
- CD4+T lymphocyte count falls
- Immune suppression leading to opportunistic infections
- Increased morbidity & mortality due to OI

Effects of HIV on TB - 2

- One year mortality rate 20-35 % (four times greater than TB pt. who is HIV negative)
- Cause of death is complication other than TB due to accelerated progression of HIV
- Increased emergence of drug resistance

Treatment of TB Disease in HIV-Infected Patients - 1

- Use 4-drug regimen for initial treatment: INH, RIF (or RBT), PZA, and EMB
- Initial therapy may be daily for 2-8 wks, followed by INH and a rifamycin 2-3 x/week for 4 months
- Avoid use of Rifapentine for co-infected patients
- Do not use twice-weekly therapy for patients with low CD4+ count (<100 cells/mm³)

Treatment of TB Disease in HIV-Infected Patients - 2

- For patients with delayed response (e.g., culture-positive after 2 months), treatment duration may be prolonged to 9 months
- Revise regimens, if necessary, based on results of susceptibility testing
- DOT and other adherence strategies should be used for all co-infected patients

Precautions with TB/HIV Co-infected Patients

- Potential for drug interaction (rifamycins and anti-retroviral agents)
- Paradoxical reactions that may be interpreted as clinical worsening
- Acquired drug resistance to rifamycins when treated with highly intermittent therapy
- Continuation phase extension to 7 months for slow responders

Complicated Case of TB

Patient History

- LM a 43 y/o white female has a medical history of IDU and has had a positive HIV serology since 1995
- Recently treated with Abacavir 300mg + Lamivudine 150 mg + Zidovudine 300 mg (Trizivir®)
 - Does not take it reliably
 - Trizivir was held because of renal failure
- On a methadone maintenance program (70 mg/day)
- Admitted to the hospital on 10/23/07 with c/o SOB, productive cough, generalized weakness, fever and wt. loss
- CD₄ count was low - (54)
- History of prior admissions for acute renal insufficiency that improved with IV hydration
- Serum creatinine on admission was 4.7 mg/dl

Chest X-ray and CT scan

- Revealed lingular and LLL infiltrates, right hilar mass and/or adenopathy and mediastinal lymphadenopathy

Mediastinoscopy

- Firm, enlarged, whitish lymph nodes with necrotic centers were biopsied
- AFB stains were positive

Treatment

- On 11-5-07 treatment was started with:
 - INH 300 mg/d
 - RIF 600 mg/d
 - PZA 1000 mg/d
 - EMB 800 mg/d
 - Vit B6 50 mg/d
 - Methadone 70 mg/d
 - Abacavir 300mg + Lamivudine 150 mg + Zidovudine 300 mg (Trizivir®) on hold secondary to renal failure

Questions

- When should HAART be started?
- What are the management guidelines for patients who are co-infected with HIV and TB
 - In cases of renal failure
 - In patients on methadone maintenance

Diagnosis of active TB in HIV-infected patients

Clinical and radiographic manifestations of HIV-related TB

- How does HIV change the signs, symptoms, and radiographic manifestations of TB?
- Is there an association between the stage of HIV and the clinical/radiographic manifestations of TB?
- Is it more difficult to diagnose HIV-related TB than non-HIV TB?

The effect of HIV infection on symptoms and signs of TB

Symptom/sign	HIV positive (%)	HIV negative (%)
Dyspnea	97	81
Fever	79	62
Sweats	83	64
Weight loss	89	83
Diarrhea	23	4
Hepatomegaly	41	21
Splenomegaly	40	15
Lymphadenopathy	35	13

Chest 1994;106:1471-6

Sites of involvement and HIV status

Site	HIV positive (%)	HIV negative (%)
Pulmonary	40	72
Extrapulmonary	34	16
Both	26	12
Pleural	31	19
Pericardial	15	3
Lymph node	19	3

J Trop Med Hygiene 1993;96:1-11

Effect of stage of HIV disease on chest x-ray manifestations of TB

Early HIV disease

- Upper lobe predominance
- Cavities
- Pleural disease

Advanced HIV disease

- Lack of cavitation
- Intrathoracic adenopathy
- Lower and middle lobe infiltrates
- Nodular infiltrates
- Pleural and pericardial involvement

Case LM- continued

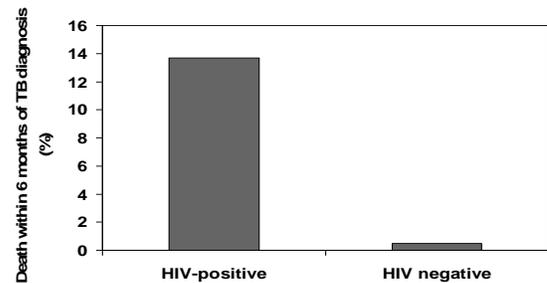
- Sputum AFB-smear positive
- Patient rapidly improved with INH, rifampin, pyrazinamide, and ethambutol
 - CD4 cell count 18 cells/mm³
 - Repeat CBC: WBC 2.1, HCT 26.2%

Questions:

- When should ARV be started?
- What are the complications of using ARV during TB treatment

Treatment of Patients with HIV-associated TB

Association between HIV serostatus and risk of death during TB treatment



Am J Respir Crit Care Med 1999;159:733-40

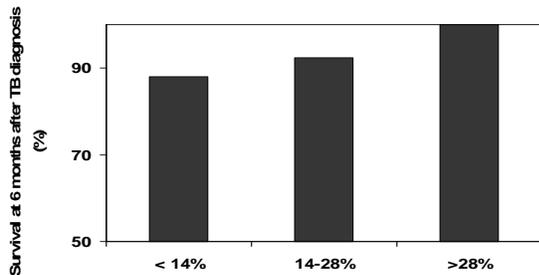
How can outcomes of HIV-related TB be improved?

- Appropriate treatment of TB
- Assure adherence with TB treatment (use of directly observed therapy, DOT)
- Use of ART to treat HIV in selected patients

Issues in using antiretroviral therapy during TB therapy

- Identification of patients who will benefit from antiretroviral therapy
- Drug-drug interactions
- Immune reconstitution events
- Overlapping ARV and TB drug side effect
- Adherence with multi-drug therapy for 2 infections
- Coordinating care between TB and HIV care providers

Association between CD4 % and survival during TB treatment



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When to Treat: Indications for Antiretroviral Therapy (ART)

- ART is recommended for all patients with a history of an AIDS-defining illness or severe symptoms of HIV infection regardless of CD4+ cell count
- ART is also recommended for asymptomatic patients with CD4+ count < 200 cells/mm³

Initiating ART in TB Patients - 1

- Optimal timing for initiation of ART during TB treatment is unknown
- Considerations:
 - TB treatment should never be delayed
 - Early initiation of ART (within 2-4 weeks of start of TB therapy) may decrease risk of HIV progression but brings higher risk of side effects and paradoxical reactions
 - Delayed initiation of ART (4-8 weeks after start of TB therapy) may make it easier to identify causes of adverse drug effects, may decrease severity of paradoxical reactions, and may improve likelihood of adherence. But, risk of HIV disease progression.

Initiating ART in TB Patients - 2

- In general, best to avoid simultaneous initiation of TB therapy and ART; wait at least 4-8 weeks to start ART
 - Individualize ART decision based on patient's clinical status, response to TB therapy, adverse effects, readiness for ART
- If patient already on ART when TB treatment is started, assess ART regimen (may require adjustment to avoid medication interactions or adverse effects)

Issues in using antiretroviral therapy during TB therapy

- Identifying patients who would benefit from antiretroviral therapy
- Drug-drug interactions
- Immune reconstitution events
- Overlapping drug side effect profiles - HIV and TB drugs
- Adherence challenge of multidrug therapy for 2 infections
- Coordinating care between TB and HIV care providers

Case presentation

- 35 year old woman with AIDS and CD4 of 45 developed active TB. Treated with 4 drug (RIPE), then 3 drugs (RIP) for 1 month by DOT
- Thoughtful HIV specialist saw pt, they agreed together to start Zidovudine 300 mg/Lamivudine 150 mg/Lopinavir 200mg/ Ritonavir 50 mg (AZT/3TC/Kaletra®)
- TB clinic changed patient from Rifampin to Rifabutin and decreased the dose by half

Case - continued

- In follow-up after 1 more month, patient decreased from 3 drugs to 2 drugs for TB
- 4 months after initial diagnosis, the TB staff noted patient coughing, losing weight and finally has a fever. Chest x-ray shows recurrent TB infection
- What is the key question in this patient's medication history?

Case - continued

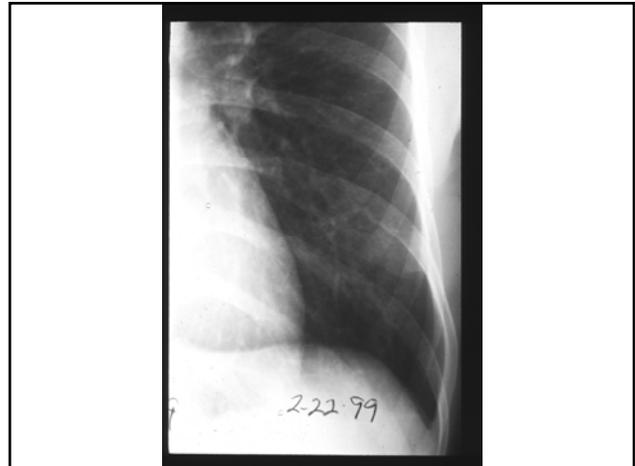
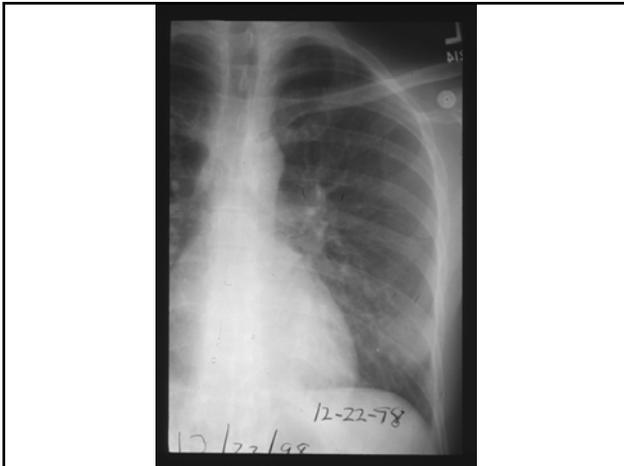
- ARE YOU STILL TAKING YOUR ARV THERAPY?
- WHY IS THIS SO IMPORTANT?

TB and HIV Drug-Drug Interactions

- If NOT TAKING Lopinavir 200 mg + Ritonavir 50 mg (Kaletra®), Rifabutin dose IS TOO LOW.
- TB resistance can develop within 30 days if on single drug therapy!!
- MUST COORDINATE HIV and TB MEDS

Case 2

- 43 yr old man from Ethiopia seen for fevers and cough
- Sputum: smear-positive for acid-fast bacilli
- Chest X-ray: Left lower lobe infiltrate
- HIV-positive, CD4 cell count = 12
- Patient started on TB treatment (INH, Rifabutin, Pyrazinamide, Ethambutol)
- Rapid clinical improvement
- Chest X-ray after 2 months of TB treatment is markedly improved



Case 2: continued

- Started on HIV treatment after 2 months of TB therapy
- 7 days later – patient developed fevers, cough and left pleuritic chest pain



- What is your diagnosis?

Issues in using antiretroviral therapy during TB therapy

- Identifying patients who would benefit from antiretroviral therapy
- Drug-drug interactions
- **Immune reconstitution events**
- Overlapping drug side effect profiles - HIV and TB drugs
- Adherence challenge of multidrug therapy for 2 infections
- Coordinating care between TB and HIV care providers

Immune reconstitution events in HIV- related TB

- Definition - increase in manifestations of TB at prior sites or new manifestations of disease
- Closely associated with starting ARV (days to weeks)
- Rarely associated with starting TB therapy
- Natural history
 - Duration - days to months
 - Waxing and waning is common

Types of immune reconstitution events among patients with HIV - related TB

- Hectic fever
- New or worsening lymphadenitis - peripheral or central nodes
- New or worsening pulmonary infiltrates, including respiratory failure
- New or worsening pleuritis, pericarditis, or ascites
- Intracranial tuberculomas, worsening meningitis
- Disseminated skin lesions
- Epididymitis, hepatosplenomegaly, soft tissue abscesses

Management of suspected immune reconstitution events

- Inform patients about the possibility of an event after starting ARV (“You may feel like the TB is coming back”)
- Evaluate for possible TB treatment failure
- Assess for other HIV-related complications, e.g. another opportunistic infection
- Management of symptoms, e.g. use non-steroidal anti-inflammatory drugs
- Steroids may be needed for severe symptoms
- (1 mg/kg)

Issues in using antiretroviral therapy during TB therapy

- Identification of patients who would benefit from antiretroviral therapy
- Drug-drug interactions
- Immune reconstitution events
- **Overlapping ARV and TB drug side effect**
- Adherence with multi-drug therapy for 2 infections
- Coordinating care between TB and HIV care providers

Managing adverse events during treatment of HIV-TB

- Do one thing at a time - make it easier to decide the cause of an event
- Stop medications for severe adverse events
- Use sequential re-challenge to decide the cause of an event
- Don't switch from the first-line TB drugs (especially INH and RIF) without evidence of an association with a significant side effect
- Remember immune reconstitution events as a possible cause of adverse events during treatment

Summary

- In patients with co-morbidities, be aware of:
 - Overlapping side effects and toxicities
 - Pill burden
 - Paradoxical reactions
 - Atypical presentations
- Case should be co-managed with additional providers
- Use of DOT can assist with adherence and monitoring of patient