HIV Tuberculosis co-infection problems and challenges

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• Introduction
• Magnitude of problem
• Immunology of TB
• Effect of co-infection
• Clinical manifestations
• Role of molecular diagnostics
• Treatment guidelines

Introduction

• HIV pandemic has caused a resurgence of tuberculosis cases world wide after 1980s
• The occurrence of co infection is major problem in developing countries
• Risk factors for both infections are similar: poor socioeconomic class, homeless and IVDU

Resurgence of TB
**Distribution of TB 1990-99**

**Magnitude : HIV burden**

<table>
<thead>
<tr>
<th>WHO region</th>
<th>HIV inf</th>
<th>Prevalence of TB</th>
<th>Coinfection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>18.7M</td>
<td>48%</td>
<td>9M</td>
</tr>
<tr>
<td>SEA/W pacific</td>
<td>6.0M</td>
<td>40%</td>
<td>2.4M</td>
</tr>
<tr>
<td>Americas</td>
<td>1.3M</td>
<td>30%</td>
<td>0.4M</td>
</tr>
<tr>
<td>East Mediteran</td>
<td>0.18M</td>
<td>23%</td>
<td>0.04M</td>
</tr>
<tr>
<td>Europe/USA</td>
<td>1.35M</td>
<td>11%</td>
<td>0.15M</td>
</tr>
</tbody>
</table>

**Tuberculosis burden**

- 1.9 billion people infected each year
- 8 million new cases each year
- 2 million deaths each year (75% 15-50 yrs)
- 95% cases and 98% deaths occur in developing nations
- South east Asian region : India, Indonesia, Thailand and Myanmar account for majority of cases of TB
- Prevalence of drug resistance higher in this region

**Indian scenario**

- 40% of the Indian population has TB infection.
- Every year, nearly 5 lakh die of TB – 1,000 deaths per day, one death every minute.
- Each infectious patient can infect 10-15 individuals in a year unless effectively treated.
- In India, TB kills 14 times more people than all tropical diseases combined, 21 times more than malaria,
Indian scenario

- After the first HIV positive case was detected in a commercial sex worker in Tamil Nadu in the year 1986
- Highest number of AIDS cases have been reported from Tamil Nadu, Maharashtra, Karnataka, Andhra Pradesh, Manipur and Nagaland.
- Total no of HIV infection ~3.97 million
- AIDS cases - 60% had Tuberculosis

HIV TB pandemic

- TB is the leading opportunistic infection in HIV infected patients
- Often the first indicator of immune deficiency (AIDS defining illness)
- World wide 40 million HIV infected of whom 15 million are co infected with TB
- Tuberculosis accelerates the progression of HIV infection and HIV increases the likelihood of active TB disease.

Immune response to Tuberculosis

- Two classes of CD4 T helper cells
  - T helper 1- produce IL2 and IFN gamma
  - T helper 2- produce IL 4,5,10
- Th 1 cells are major effector cell in the CMI (granulomatous response) and enhance clearing of infection by Tubercle bacilli
- Th 2 cells impairs the granulomatous response to Tubercle bacilli and immunity

Immune response to TB

- Mycobacteria → alv macrophages → phagocytosis
- Primary infection
  - 5% progressive primary
  - 5% reactivation TB
- CD4 Th1 response
  - IL 12 → IFN gamma → IL 2 → bacteria killed within activated macrophages (granuloma)
### Immune response - HIV TB

- HIV infection impairs the immune response
- Progressive depletion & dysfunction of CD4 lymphocytes
- Impaired macrophage function
  - impaired phagocytosis
  - Intracellular killing (ROI)
  - Altered cytokine production
  - Defective antigen presentation

### Immune response - HIV TB

- Advanced HIV infection reduced number & dysfunction of alveolar macrophages hence high proportion of those infected develop active disease
- Mycobacteria could invade even the bronchial tree as inflamed airways have increased number macrophages which serve as breeding sites

### Endogenous reactivation

- HIV is the most potent risk factor for reactivation of latent tuberculosis
  - HIV negative rate ≤1% per year
    - (10% lifetime)
  - HIV positive rate ~ 7-10% per year
    - (approx 100% lifetime)
- Incidence of TB is 100 times in HIV than in general population

### Exogenous infection

- Patient with HIV infection develops infection with Myco Tuberculosis ~ 40% develop active disease within weeks and progresses rapidly.
- Associated with increased morbidity and mortality despite optimal treatment
- Spread the disease rapidly among contacts and health care workers leading to nosocomial outbreaks
Evidence: exogenous infection

- HIV patients with low CD4 counts are likely to visit hospitals where TB transmission is likely
- Usually have pattern of L Zone infiltrates, adenopathy, pleural effusion suggestive of recent infection
- RFLP analysis has confirmed 40% of such patients have identical strain of MTB suggesting clustering of contacts

**POTENTIATION OF HIV REPLICATION**

- Tubercle bacilli
- Induces n FKB which binds promoter region of HIV
- CD4 T cell
- IFN Gamma
- Activated macrophages
- Increased viral replication in monocytes T cells
- IL1/ TNF a

Effects of TB on HIV

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

Effects of HIV on TB

- One year mortality 20-35 % (four times than TB in HIV negative with TB)
- Cause of death is complication other than TB due to accelerated progression of HIV
- Increased incidence of ADR to ATT
- Increased emergence of drug resistance
**Clinical features**

- Manifestations depend on the state of immunesuppression
- Early stage CD4 > 200 /mm³
  - Typical reactivation TB involving upper lobes with focal infiltrates and cavitations
- Advance stage CD4 < 200/mm³
  - Atypical disease with varied manifestations including extrapulmonary /disseminated TB

**Atypical manifestations**

- Diffuse pulmonary involvement, often LL
- Absence of cavity formation
- Prominent hilar /mediastinal LNE
- Pleural effusions more common
- Serositis- pericardial /peritoneal
- Miliary tuberculosis
- CNS tuberculosis- tuberculoma ,meningitis
- Lymph node,BM,liver&spleen, testes
- Cutaneous /chest wall abscess

**Atypical manifestations**

- Sputum smears negative despite extensive involvement
- Normal chest x rays & sputum positive for AFB – endobronchial TB or mycobacteremia
- Mycobacteria may be isolated from blood, marrow, urine & fluids
- Lymph node aspirate/Bx- poorly formed granulomas , focal areas of necrosis teeming with AFB

**Extrapulmonary tuberculosis**

- EPTB with HIV negative 15%
- Found in 20-50% with HIV infection
- Gen lymphadenopathy, hepatosplenomegaly,anemia, leucopenia, elevated liver enzymes, miliary infiltrates
- Kidney and genitourinary involvement common
- More likely to have disseminated disease concurrent pulmonary, abdominal and Lymph nodal disease
### EPTB
- Mycobacteremia - positive blood cultures in 56%
- Cultures of urine, stool positive in 40-70%
- Sputum culture yield diagnosis in 90% though smear shows AFB in 40%
- Tuberculin anergy ~75%
- EPTB has inverse relation with CD4 counts

### Unusual manifestations
- Massive abdominal lymphadenopathy
- Hemophagocytosis syndrome
- Broncho-esophageal fistulae
- Multiple visceral / brain abscesses
- Cutaneous, soft tissue abscess
- Osteomyelitis
- Sepsis with septic shock

### Mortality
- EPTB associated with shorter survival
- Pulmonary - 30.4 months
- Extrapulmonary - 15.6 months
- Disseminated TB - 8.4 months
- Factors associated with mortality were lymphopenia, mycobacteremia, peripheral lymphadenopathy, anemia, tuberculin anergy
  - Richter C et al, Tuberc lung dis 1995

### Differential diagnosis of PTB
- Pneumococcal pneumonia
- Typhoid septicemia
- Fungal pneumonia
- Pneumocystis carinii pneumonia
- Lymphocytic interstitial pneumonia
- Kaposi’s sarcoma
- Lymphoma
### Clinical features: TB with HIV

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>HIV negative</th>
<th>Early HIV</th>
<th>Advanced HIV/AIDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculin reactivity &gt;10mm</td>
<td>75-85%</td>
<td>40-70%</td>
<td>50-30%</td>
</tr>
<tr>
<td>Chest X Ray</td>
<td>50-70% typical (UL fibronodular lesions) 50% cavities</td>
<td>Mixed typical and atypical</td>
<td>Increased adenopathy effusions, L. Zone inv miliary infiltrates Reduced Cavitation</td>
</tr>
<tr>
<td>Sites Involved</td>
<td>Pulmonary 80% Extra pulmonary 16% Both 4%</td>
<td>Intermediate</td>
<td>Pulmonary 20-30% Extrapulmonary 20-50% Both 30-70%</td>
</tr>
<tr>
<td>Sputum smear positivity</td>
<td>70-80%</td>
<td>~50%</td>
<td>30-40%</td>
</tr>
</tbody>
</table>

### Radiologic features in HIV-TB

<table>
<thead>
<tr>
<th>Series</th>
<th>HIV negative</th>
<th>Early HIV CD 4&gt;200</th>
<th>Advanced HIV/AIDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abouya et al</td>
<td>Cavitary   56%  Noncavitary 42%</td>
<td>53%</td>
<td>28%</td>
</tr>
<tr>
<td>Ivory Coast 1990-92</td>
<td>Hilal LNE  2%  Miliary 2%  Effusions 4%</td>
<td>8%</td>
<td>11%</td>
</tr>
<tr>
<td>Batungwanyo et al</td>
<td>Cavitary   91%  Upper lobe 55%</td>
<td>69%</td>
<td>28%</td>
</tr>
<tr>
<td>Rwanda 1988-89</td>
<td>Hilal LNE  0%  Miliary 9%  Effusions 9%</td>
<td>7%</td>
<td>16%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Advanced HIV/AIDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abouya et al</td>
<td>14%</td>
</tr>
<tr>
<td>Ivory Coast 1990-92</td>
<td>14%</td>
</tr>
<tr>
<td>Batungwanyo et al</td>
<td>14%</td>
</tr>
</tbody>
</table>
Tuberculin skin testing

- Tuberculin reactivity fourfold less in HIV infection
- Reactivity declines with increasing immune suppression
- Early HIV 40-70%
- Advanced HIV 10-30%
- Annual tuberculin testing for HIV infection to detect latent infection
- Tuberculin anergy assoc. with risk of active TB is controversial
**Tuberculin skin testing**

- Since the reaction decline with immunesuppression, 5mm induration is considered significant in HIV infection (CDC/ATS)
- Some have advocated reducing to 2mm
- Recommended to give prophylactic therapy in such cases to prevent disease
- Close contacts of infectious cases and populations with high prior probability of TB are also recommended to be given prophylactic therapy

**Role of FOB**

- Valuable in early diagnosis
- Diagnosis of endobronchial TB
- TBLB yield is greater (82%) than BAL (26%)
  
  *Miro et al Chest, 1992*

- TBNA has a role in mediastinal lymph nodal tuberculosis with negative sputum smears
  
  *Harkin et al Am J Resp Crit Care Med, 1998*
Molecular diagnosis—RFLP

1. Chromosomal DNA
   - restriction site
   - missing restriction site in isolate #2
   - IS6110 site

2. DNA digested using PvuII

3. Fragments separated by gel electrophoresis

4. Agarose blotted onto nitrocellulose and hybridization performed with labelled IS6110

Bacteriophage Assay

- Utilizes specific mycobacteriophage to identify presence of viable tubercle bacilli in sputum
- Virucidal solution added to media to kill free phages
- Bacilli infected with phage amplified by adding nonpathogenic mycobacteria
- Colony of phages visualized as plaques on lawn of mycobacteria
- Drug susceptibility results can be obtained in 48 hours

RFLP

- Identify the specific strains of Myco TB by pattern of gene fragments
- Has shown that recent infection is responsible for upto 50% TB cases in both HIV negative and HIV infected
- Used to confirm that cluster of TB cases are linked by recent transmission especially during nosocomial outbreaks
  Halvir DV, Barnes PF N Engl J Med 1999
Fast plaque rapid TB assay

**Impact**

- Increased in morbidity and mortality due to active tuberculosis and HIV infection
- Increases spread to contacts – horizontal transmission in community
- Increased incidence of drug resistant organism
- Nosocomial outbreaks of MDR tuberculosis

**Drug resistance and HIV**

**HIV – MDR TB**

- Poor immune response leads to increased rapidly dividing bacilli and spontaneous mutations
- Noncompliance due to frequent ADR
- Large pill burden
- Malabsorption of ATT
- Use of Rifabutin prophylaxis for MAC

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**Figure 2. Diagrammatic representation of the FASTPlaque TB MDR assay**

**Table 2. Percentage of tuberculosis (TB) patients with drug-resistant isolates by drug and human immunodeficiency virus (HIV) serostatus — United States, 1995-1996**

<table>
<thead>
<tr>
<th>Drug</th>
<th>HIV positive (no.%)</th>
<th>HIV negative (no.%)</th>
<th>HIV status unknown (no.%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>11.8 (125)</td>
<td>0.6 (756)</td>
<td>6.9 (7,000)</td>
</tr>
<tr>
<td>Rifampin</td>
<td>0.9 (10)</td>
<td>0.1 (756)</td>
<td>2.5 (7,000)</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>5.1 (51)</td>
<td>1.8 (756)</td>
<td>2.1 (7,000)</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>6.7 (77)</td>
<td>4.1 (756)</td>
<td>6.6 (7,000)</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>3.6 (36)</td>
<td>1.5 (756)</td>
<td>2.6 (7,000)</td>
</tr>
<tr>
<td>Isoniazid and rifampin</td>
<td>6.2 (62)</td>
<td>1.3 (756)</td>
<td>1.5 (7,000)</td>
</tr>
<tr>
<td>Rifabutin only</td>
<td>2.4 (24)</td>
<td>0.2 (756)</td>
<td>0.8 (7,000)</td>
</tr>
</tbody>
</table>

CDC guidelines, MMWR, Oct 1998
Strategies to prevent MDR

- Early diagnosis: previous therapy for TB
- Isolation of MDR cases
- Active treatment with second line drugs under direct supervision
- Culture and drug susceptibility testing
- Proper reporting of MDR cases
- Chemoprophylaxis for contacts

Adverse drug reactions

- Occur more frequently with HIV infected 20-25%
- Related to level of immune activation and immune suppression
- Thiacetazone induced exfoliative dermatitis, TEN, Steven Johnson syndrome can be fatal (contraindicated with HIV)
- ATT induced hepatitis four fold higher than seronegative patient
- Risk factors: anergy, lymphopenia, Elevated Neopterin levels

Therapy outcomes

- Early clinical and microbiological response similar to HIV negative patients with TB
- Relapse rates higher in developing world compared to the developed nations
- Data conflicting about higher rate of relapse in HIV infected than HIV negative

CDC guidelines, MMWR, Oct 1998

Post treatment relapse rates

- Data not available

CDC guidelines, MMWR, Oct 1998
**Post treatment relapse rates**

<table>
<thead>
<tr>
<th>Location</th>
<th>HIV status</th>
<th>Posttreatment relapses (%)</th>
<th>CD4+ T-cell counts (median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>HIV positive</td>
<td>10</td>
<td>197 cells/µL²</td>
</tr>
<tr>
<td>CDC/ATS Group</td>
<td>HIV positive</td>
<td>29</td>
<td>70 cells/µL²</td>
</tr>
</tbody>
</table>

CDC guidelines, MMWR, Oct 1998

**Recommendations**

- CDC/ATS recommendation: 6 months ATT with drug sensitive TB & prolongation to 9 months if slow clinical/micro response
- Factors assoc with poor outcome –advanced immune suppression, noncompliance, delayed clinical/microbiological response
- Physician should prolong duration of ATT

**Paradoxical reaction**

- Defined as temporary worsening of clinical condition, appearance of new radiologic manifestations after initiation of Tt and are not due to Tt failure or a second process
- Due to recovery of immunological Th 1 response to mycobacterial antigen
- Heightened granulomatous response may clear the organism but itself may cause tissue damage

**Mimickers**

- Treatment failure
- Drug resistance
- Non compliance
- Drug fever
- Development of another OI
- Condition not related to TB or HIV
“HAART attacks”

- Incidence with ATT alone ~7%
  with ART+ATT ~36%
- Substantial reduction in viral load and increase in CD4 counts found (immune reconstitution)
- Increased tuberculin reactivity noted
- Stronger immune response to Mycobact TB results in PR

Kunimoto et al Int J Tuberc Lung Dis 1999

Clinical findings

- Hectic fever, peripheral/mediastinal lymphadenopathy, miliary infiltrates, pleural effusion
- Worsening of original lesions: pulmonary infiltrates, tuberculomas may be life threatening
- Self limited, usually lasts 10-40 days

Treatment

- Rarely requires stopping ATT / HAART
- Requires NSAID for symptomatic relief
- For life threatening states: short course steroids may be give to suppress inflammation while ATT and ART are continued

Initiating ART in HIV infection

<table>
<thead>
<tr>
<th>Clinical Category</th>
<th>CDC* Cell Count</th>
<th>Plasma HIV-RNA</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic, AIDS</td>
<td>Any value</td>
<td>Any value</td>
<td>Treat</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>CD4+ T cells &gt;500/mm³</td>
<td>Any value</td>
<td>Treatment should be offered, although controversial</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>CD4+ T cells &gt;500/mm³</td>
<td>&lt;50,000 HIV RNA copies/mL</td>
<td>Most asymptomatic patients demonstrated virological and immunological benefit with ART. When enrolling a patient, consider CD4 count and Vl. Recommend ART in 3-6 months after initiating therapy.</td>
</tr>
</tbody>
</table>

*CDC: Centers for Disease Control and Prevention
ART drug Classes

- Nucleoside reverse transcriptase inhibitors (NRTI)
- Non nucleoside reverse transcriptase inhibitors (NNRTI)
- Protease inhibitors (PI)
- Fusion inhibitors

Life cycle of HIV

NRTIs

- Zidovudine
- Lamivudine
- Stavudine
- Zalcitabine
- Didanosine
- Abacavir
- Tenofovir
- Emtricitabine

Protease Inhibitors

- Indinavir
- Ritonavir
- Nelfinavir
- Saquinavir
- Amprenavir
- Lopinavir
- Atazanavir
NNRTIs

- Nevirapine
- Delavirdine
- Efavirenz

FUSION INHIBITORS

- Enfuviritide

Combinations never used

- AZT+ Stavudine - antagonistic
- Ddi+ Stavudine
- Stavudine+Zalcitabine
- Zalcitabine+ Ddi
- Atazanavir+Indinavir
- Etravirine +lamivudine ~ resistance profile
- Efavirenz based regime in pregnancy

ART regimen

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Possible Advantages</th>
<th>Possible Disadvantages</th>
<th>Drug Interaction Complications</th>
<th>Impact of Failure Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI-based NNRTI combinations</td>
<td>• Cytotoxic and immunologic efficacy well documented</td>
<td>• Resistance occurs early</td>
<td>• AZT + DDI antagonistic</td>
<td>• Must be complete, if resistance to PI develops.</td>
</tr>
<tr>
<td></td>
<td>• Majority of resistance occurs early</td>
<td>• Azidothymidine-measured</td>
<td>• Enfuviritide at time of virologic failure (II) and DDI</td>
<td>• Must be complete, if resistance to PI develops.</td>
</tr>
<tr>
<td>NNRTI-based PI combinations</td>
<td>• Yields, and immunologic efficacy well documented</td>
<td>• Nucleotide related side effects</td>
<td>• Efavirenz combined in a nucleotide failure</td>
<td>• Must be complete, if resistance to PI develops.</td>
</tr>
<tr>
<td></td>
<td>• Easier to use and adhere to, compared with PI</td>
<td></td>
<td></td>
<td>• Must be complete, if resistance to PI develops.</td>
</tr>
</tbody>
</table>

Drug interactions

<table>
<thead>
<tr>
<th>Cytchrome P450 inducer</th>
<th>Cytochrome P450 inhibitor</th>
<th>Mixed inducer/inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampicin(++)</td>
<td>Ritonavir</td>
<td>Delavirdine(-)</td>
</tr>
<tr>
<td>Rifapentine(+)</td>
<td>Indinavir</td>
<td>Nevirapine(+)</td>
</tr>
<tr>
<td>Rifabutin(+)</td>
<td>Nelfinavir</td>
<td>Efavirenz(both)</td>
</tr>
<tr>
<td>Amprenavir</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Drug interactions

- Use of Rifampicin with PI/NNRTI based ART is contraindicated.
- NRTI are not metabolized by hepatic cytochrome P 450 enzyme system hence they can safely be used with Rifampicin based ATT
- Other first line ATT (SHEZ) no interactions with ART and can be used safely: SHEZ x 2 months followed by SHZx7months

Drug interactions

- Rifabutin: less potent inducer and can be used in place of Rifampicin in ATT with PI NNTRI based ART (equivalent bactericidal action, clinical cure rates)
- Ritonavir retards Rifabutin metabolism (levels 35 fold) toxic reactions -uveitis, neutropenia, arthralgia occur. combination is contraindicated

Management strategies

- CDC guidelines, MMWR, Oct 1998

WHO Recommendations 2002

- Start TB therapy: Start one of these regimens as soon as TB therapy is tolerated:
  - ZOVA/T/ABC
  - ZOVA/T/C/FZ
  - ZOVA/T/C/S/CVR
  - ZOVA/T/C/NVP

- Start TB therapy: Start one of these regimens after 2 months of TB therapy:
  - ZOVA/T/CA ABC
  - ZOVA/T/C/EFZ
  - ZOVA/T/C/S/CVR
  - ZOVA/T/C/NVP

- Treat TB. Monitor CD4 counts if available. Start ART
Chemoprophylaxis

- Latent infection in HIV patients detected by TST >5mm must be treated to prevent disease and spread in community.
- INH daily x 9 months
- Rifabutin+ PZI daily x 2 months (On ART)
- Rifampicin + PZI daily x 2 months (No ART)
- Rifampicin daily x 9 months

Chemoprophylaxis

- Rifampicin regime- INH resistant strain, intolerance, poor compliance
- In India ,INH resistance is significant the use of combination drugs is advised
- For HIV positive contacts of MDR TB
  - PZI + Fluoroquinolone daily x 12 months
  - PZI + Ethambutol daily x months
- WHO does not recommend CP in region where prevalence is high

Chemoprophylaxis

- Tuberculin anergic patients use of chemoprophylaxis is not proven to be effective
- Not recommended except when working in areas of high transmission of TB ie hospital, jails
- Use if tuberculin negative person becomes reactive after antiretroviral drug therapy

Role of BCG

- Contraindicated with persons with advanced HIV disease/AIDS because of risk of “disseminated BCGiosis”
- But in countries where risk of TB is high, WHO recommends BCG should be given as soon after birth.
- Disseminated BCGiosis treated with INH+Rifampicin
Conclusions

• Screen all cases of TB for HIV infection
• Initiate ATT preferably with DOT
• Consider optimal antiretroviral therapy
• Understand drug interactions of Rifamycins with PI/NNRTI based ART
• Observe for paradoxical reactions
• Identify drug resistant tuberculosis