HIV Tuberculosis co-infection problems and challenges

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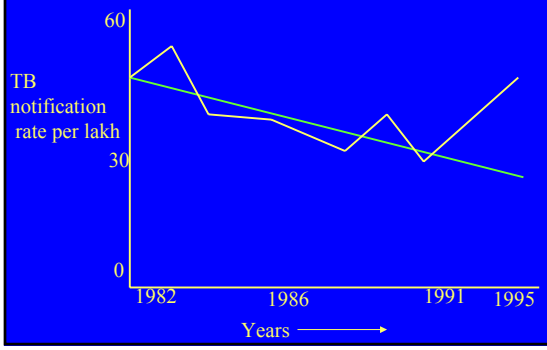
- Introduction
- Magnitude of problem
- Immunology of TB
- Effect of co-infection
- Clinical manifestations
- Role of molecular diagnostics
- Treatment guidelines

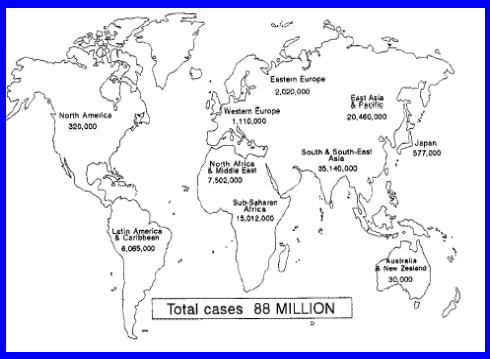
Introduction

- 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

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

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

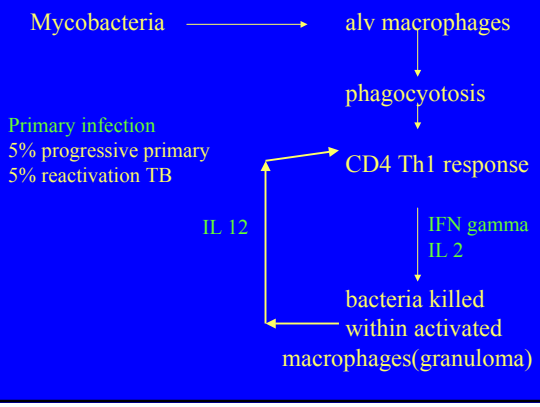
HIV TB pandemic

- 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



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
  (apprx 100% lifetime)
- Incidence of TB is 100 times in HIV than in general population

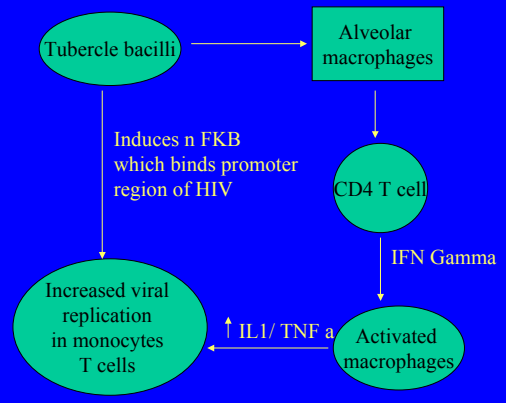
Exogenous infection

- 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



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 – Oppurtunistic 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 /mm^3

  Typical reactivation TB involving upper lobes with focal infiltrates and cavitations
- Advance stage CD4 < 200/mm^3

  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
- extrapulm - 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

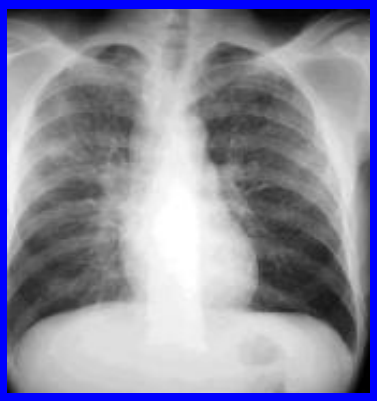
- Pneumococcal pneumonia
- Typhoid septicemia
- Fungal pneumonia
- Pneumocystis carinii pneumonia
- lymphocytic interstitial pneumonia
- Kaposi's sarcoma
- Lymphoma

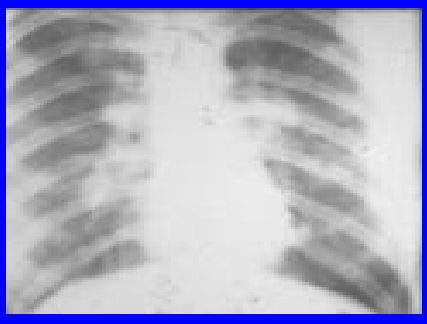
Clinical features: TB with HIV

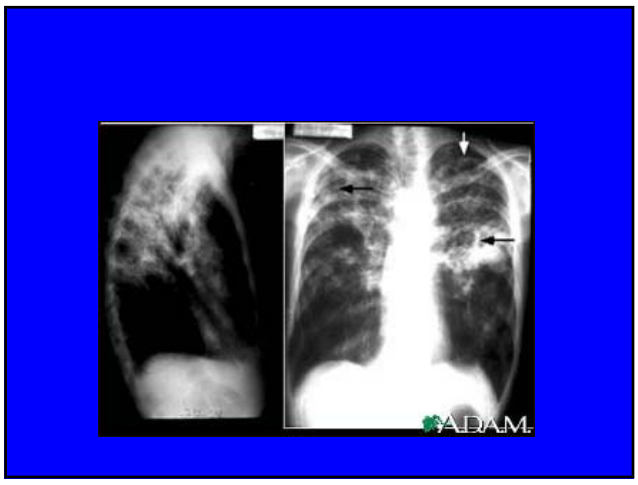
Clinical feature	HIV negative	Early HIV	Advanced HIV/AIDS
Tuberculin reactivity >10mm	75-85%	40-70%	10-30%
Chest X Ray	50-70% typical(UL fibronodular lesions) 50% cavities	Mixed typical and atypical	Increased adenopathy effusions,L Zone inv miliary infiltrates Reduced Cavitation
Sites Involved	Pulmonary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

Radiologic features in HIV-TB

Series	HIV negative	Early HIV CD 4>200	Advanced HIVAIDS
Abouya et al Ivory Coast 1990-92	Cavitary 56% Noncavitary 42% Hilar LNE 2% Miliary 2% Effusions 4%	53% 39% 8% 3% 8%	29% 58% 20% 9% 11%
Batungwanyo et al Rwanda 1988-89	Cavitary 91% Upper lobe 55% Hilar LNE 0% Miliary 9% Effusions 9%	69% 30% 7% 23% 46%	28% 16% 40% 26% 42%



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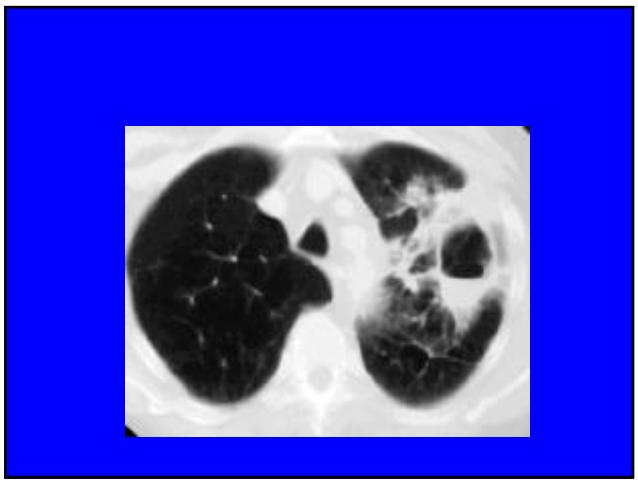

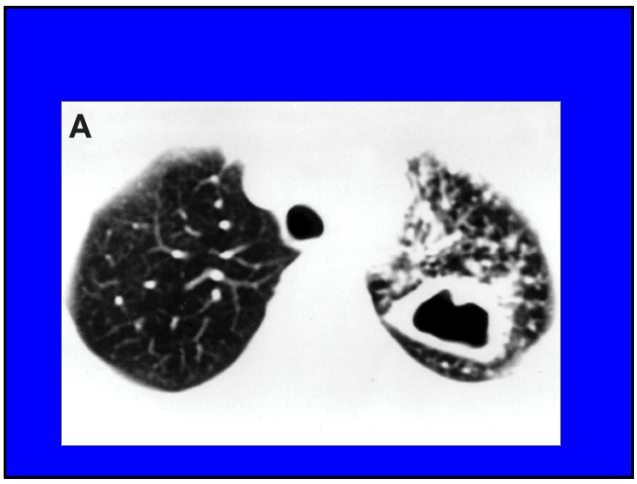
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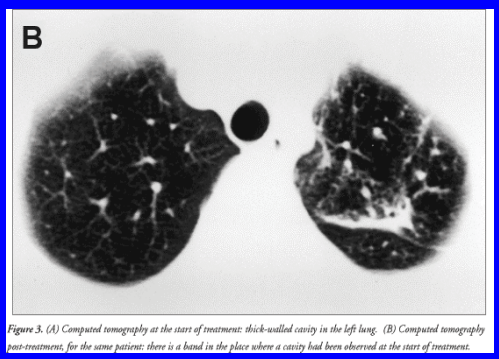
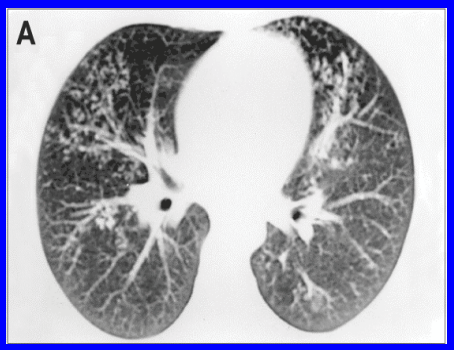


Figure 3. (A) Computed tomography at the start of treatment: thick-walled cavity in the left lung. (B) Computed tomography post-treatment, for the same patient: there is a band in the place where a cavity had been observed at the start of treatment.



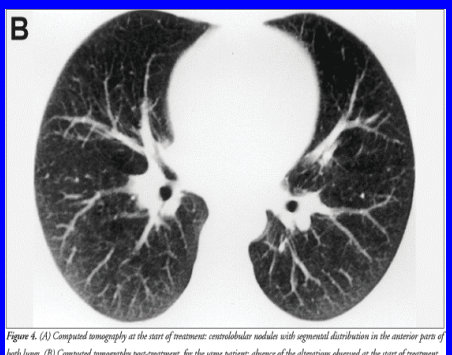


Figure 4. (A) Computed tomography at the start of treatment: centrolobular nodules with segmental distribution in the anterior parts of both lungs. (B) Computed tomography post-treatment, for the same patient: absence of the alterations observed at the start of treatment.

Tuberculin skin testing

- Tuberculin reactivity four fold 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

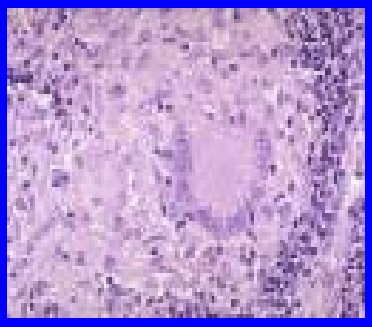
- Since the reaction decline with immunesuppression, 5mm induration is considered significant in HIV infection (CDC/ATS)
- some have advocated reducing to 2mm
- Recommended to give prophylactic therapy in such cases to prevent disease
- Close contacts of infectious cases and populations with high prior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

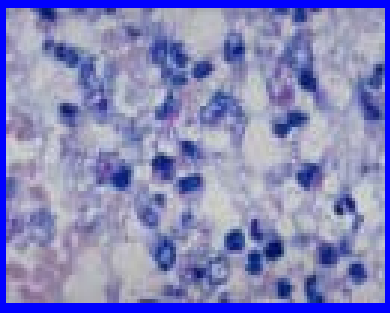
Role of FOB

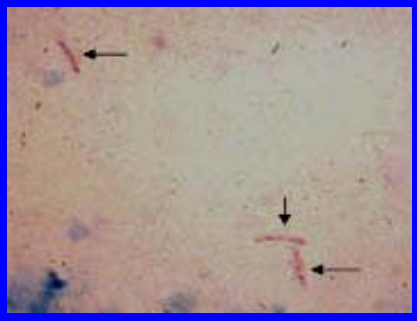
- Valuable in early diagnosis
- Diagnosis of endobronchial TB
- TBLB yield is greater (82%) than BAL (26%)

  Miro et al Chest, 1992
- TBNA has a role in mediastinal lymph nodal tuberculosis with negative sputum smears

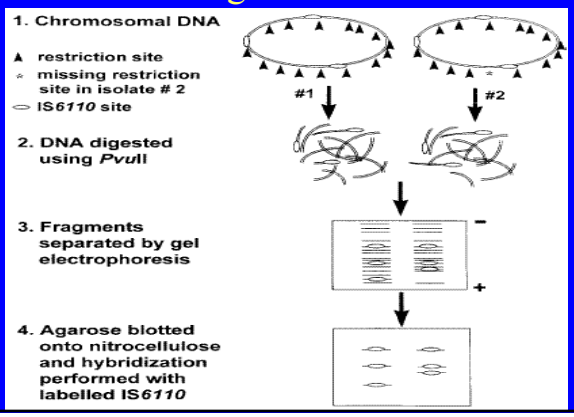
  Harkin et al AmJ Resp Crit Care Med ,1998







Molecular diagnosis-RFLP



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

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

Fast plaque rapid TB assay

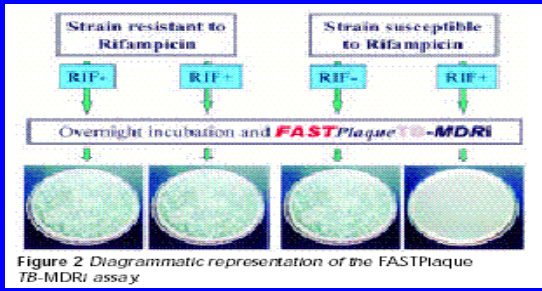


Figure 2 *Diagrammatic representation of the* FASTPlaque *TB-MDRi assay*

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

TABLE 2. Percentage of tuberculosis (TB) patients* with drug-resistant isolates,† by drug and human immunodeficiency virus (HIV) serostatus — United States, 1993–1996

	HIV serostatus (%)		
Drug§	HIV positive (n=5,112)	HIV negative (n=3,754)	HIV status unknown (n=7,186)
Isoniazid	11.3	5.5	6.8
Rifampin	8.9	1.6	2.5
Pyrazinamide	5.1	1.8	2.2
Streptomycin	6.7	4.1	5.0
Ethambutol	3.9	1.5	2.0
Isoniazid and rifampin	6.2	1.3	1.5
Rifampin only¶	2.4	0.2	0.8

CDC guidelines, MMWR, Oct 1998

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

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 susceptibilty 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

Location and source	HIV status	Posttreatment relapses (%)	CD4+ T-cell counts (median)
Zaire Perriens et al., 1995 (*66*)	HIV positive (n=124)	9.0	*338* cells/μL[3]
	HIV negative (n=183)	5.3	
Côte d'Ivoire Kassim et al., 1995 (*49*)	HIV-1 positive (n=106)	3.0	Data not available
	HIV negative (n=194)	3.0	
Haiti Chaisson et al., 1996 (*67*)	HIV positive (n=177)	5.4	475 cells/μL[3]
	HIV negative (n=250)	2.7	

CDC guidelines, MMWR, Oct 1998

Post treatment relapse rates

Location and source	HIV status	Posttreatment relapses (%)	CD4+ T-cell counts (median)
United States U.S. Public Health Service Rifapentine Trial Group et al., 1998 (29)	HIV positive (n=30)	10	137 cells/μL[4]
United States[1] El-Sadr et al., 1998 (30)	HIV positive (n=50)	3.9	70 cells/μL[3]

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

Treatment

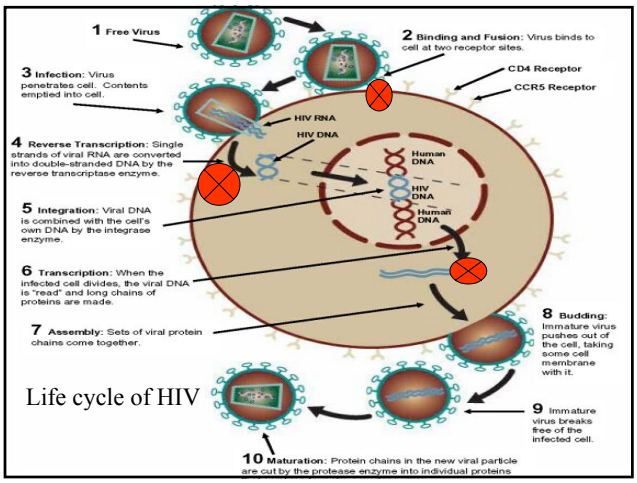
- Rarely requires stopping ATT / HAART
- Requires NSAID for symptomatic relief
- For life threatening states : short course steroids may be give to suppress inflammation while ATT and ART are continued

Initiating ART in HIV infection

Clinical Category	$CD4^+$ Cell Count	Plasma HIV RNA	Recommendation
Symptomatic (AIDS or severe symptoms)	Any value	Any value	Treat
Asymptomatic, AIDS	$CD4^+$ T cells $<200/mm^3$	Any value	Treat
Asymptomatic	$CD4^+$ T cells $>200/mm^3$ but $\leq 350/mm^3$	Any value	Treatment should be offered, although controversial.[a]
Asymptomatic	$CD4^+$ T cells $>350/mm^3$	>55,000 (by RT-PCR or bDNA)[g]	Some experienced clinicians recommend initiating therapy, recognizing that the 3-year risk for untreated patients to develop AIDS is >30%; in the absence of increased levels of plasma HIV RNA, other clinicians recommend deferring therapy and monitoring the $CD4^+$ T cell count and level of plasma HIV RNA more frequently; clinical outcome data after initiating therapy are lacking.
Asymptomatic	$CD4^+$ T cells $>350/mm^3$	<55,000 (by RT–PCR or bDNA)[g]	Most experienced clinicians recommend deferring therapy and monitoring the $CD4^+$ T cell count, recognizing that the 3-year risk for untreated patients to experience AIDS is <15%.

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

ART regimen

Regimen	Possible Advantages	Possible Disadvantages	Drug-Interaction Complications	Impact on Future Options
PI-based HAART regimen (NNRTI-sparing)	• Clinical, virologic, and immunologic efficacy well-documented • Resistance requires multiple mutations • Avoid NNRTI-associated side effects • Targets HIV at two steps of viral replication (RT and PI)	• Some regimens are difficult to use and adhere to • Long-term side effects often include lipodystrophy*, hyperlipidemia, and insulin resistance	• Mild to severe inhibition of cytochrome P450 pathway; ritonavir is most potent inhibitor, (but this effect can be exploited to boost levels of other PIs)	• Preserves NNRTIs for use in treatment failure • Resistance primes for cross-resistance with other PIs
NNRTI-based HAART regimen (PI-sparing)	• Virologic, and immunologic efficacy well-documented • Spares PI-related side effects • Easier to use and adhere to, compared with PIs	• Resistance conferred by a single or limited number of mutations	• Fewer drug interactions compared with PIs	• Preserves PIs for use in treatment failure • Resistance usually leads to cross-resistance across entire NNRTI class
Triple NRTI regimen (NNRTI- and PI-sparing)	• Generally easier to use and adhere to compared with PIs • Sparing PI and NNRTI side effects • Cross-resistance to all drugs in the NRTI class is unlikely with initial regimen failure	• Virological efficacy inferior to EFV-based regimen	• No cytochrome P450 interaction	• Preserves both PI and NNRTI classes for use in treatment failure

Combinations never used

- AZT+ Stavudine - antagonistic
- Ddi+ Stavudine
- Stavudine+Zalcitabine
- Zalcitabine+ Ddi
- Atazanavit+Indinavir

} additive toxicity

- Emtricitabine +lamivudine ~ resistance profile
- Efavirenz based regime in pregnancy

Drug interactions

Cytochrome P450 inducer	Cytochrome P450 inhibitor	Mixed inducer/inhibit
Rifampicin(+++)	Ritonavir	Delavirdine(-)
Rifapentine(++)	Indinavir	Nevirapine(+)
Rifabutin(+)	Nelfinavir	Efavirenz(both)
	Amprenavir	

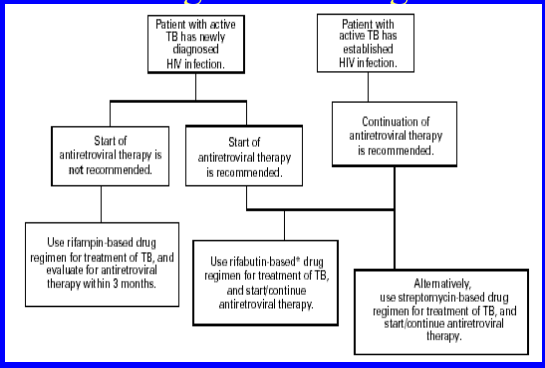
Drug interactions

- 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

Situation	Recommendations
Pulmonary TB and CD4 count <50/mm^3 or Extra-pulmonary TB	Start TB therapy. Start one of these regimens as soon as TB therapy is tolerated: · ZDV/3TC/ABC · ZDV/3TC/EFZ · ZDV/3TC/SQV/r · ZDV/3TC/NVP
Pulmonary TB and CD4 50-200/mm^3 or total lymphocyte count <1000-1200/mm^3	Start TB therapy. Start one of these regimens after 2 months of TB therapy: · ZDV/3TC/ABC · ZDV/3TC/EFZ · ZDV/3TC/SQVr · ZDV/3TC/NVP
Pulmonary TB and CD4 >200/mm^3 or total lymphocyte count >1000-1200/mm^3	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 2months(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 + Flouroquinolone 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