IMPACT OF HIV ON TB MANAGEMENT

Presented at the 5h International TB/HIV course for Clinicians

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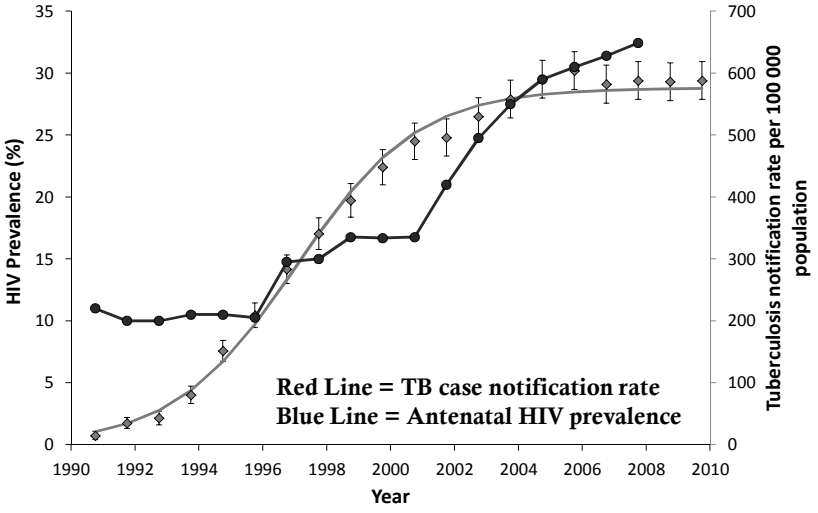
OUTLINE

- Epidemiology
- Clinical presentation and investigation
- Treatment nuances
- Adherence

HIV and tuberculosis in South Africa

- Among the greatest challenges facing post-apartheid South Africa
- South Africa 2007
  - 0·7% of the world's population
  - 17% of the global burden of HIV infection
  - amongst the world's worst TB epidemics
  - compounded by rising drug resistance and HIV
- Achievements:
  - improved access to condoms
  - expansion of TB control efforts
  - scale-up of free ART

The HIV and TB epidemics in South Africa



Source: South African Department of Health

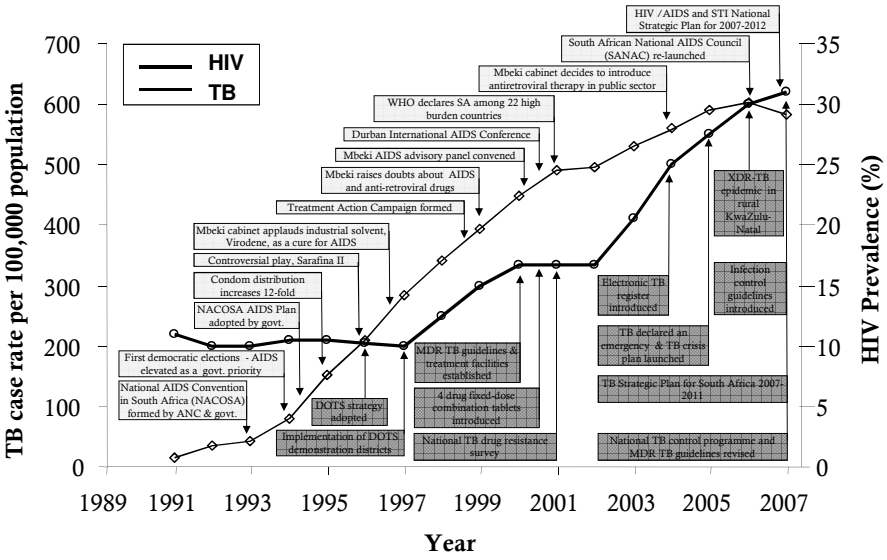


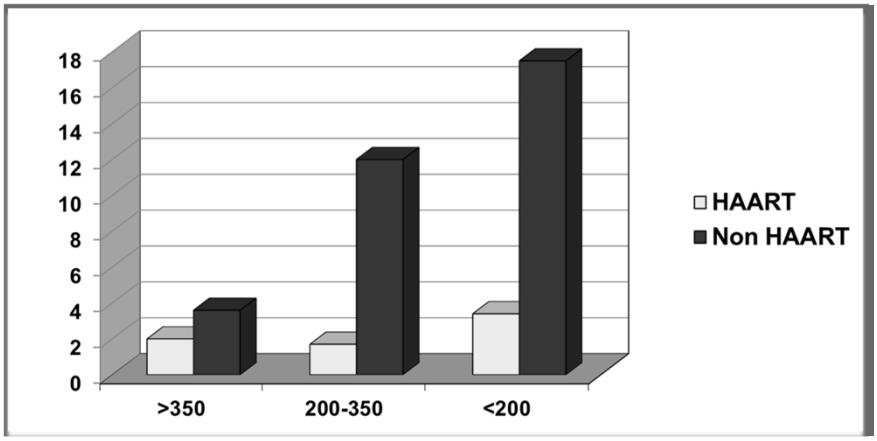
Figure 1: Historical overview of major events in the AIDS and TB epidemics in South Africa 1989 - 2007

Impact of HIV on TB

- HIV accelerates TB progression following exposure
- TB associated with decreased survival in HIV
- Acceleration to AIDS or death following TB treatment
- Increase in smear negative TB
  - lower risk of TB transmission from HIV-infected

Effect of ART on incidence of TB

Data from AIDS clinic in Cape Town, South Africa



Source: Badri, Lancet 2006

When to Start ART in TB – Building on previous studies

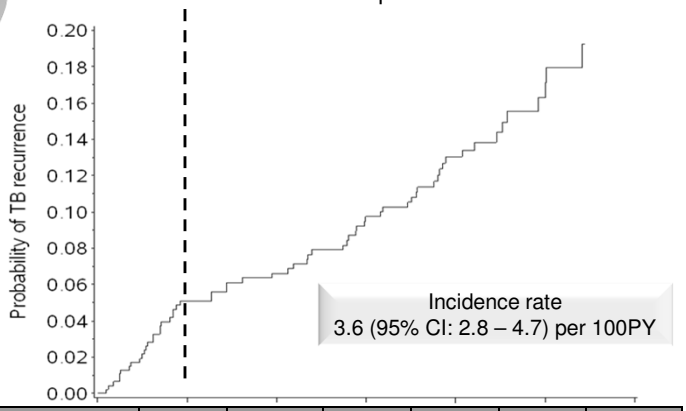
	A5221/ STRIDE	CAMELIA[1]	SAPIT[2]
N	806	660	429
Sites	Africa, Asia, S Am, N Am	Cambodia	S. Africa
Arms	Imm vs 8-12 wk	Imm vs 8 wk	Early vs 24 wk
Endpoint	Death/AIDS, CD4 <50 cells/ul	Death	Death
CD4 (IQR) Cells/ul	77 (36,145)	25 (11,56)	150 (77, 254)

[1] Blanc, IAC, 2010 [2]Abdool Karim, NEJM, 2010

Recurrent TB:
TRuTH Study
IMPRESS STUDY

CAPRISA 005: TRuTH Study

Kaplan Meier Curve: Time to TB recurrence from previous TB treatment cure/completion



Years since cure / completion	1	2	3	4	5	6
Number left at risk	409	359	343	240	100	23
Cumulative TB recurrences	23	29	41	52	59	62
Cumulative PY	443.4	817.6	1172.4	1482.4	1644.3	1700.0
Cumulative Incidence rate	**5.2**	**3.5**	**3.5**	**3.5**	**3.6**	**3.6**
95% CI	3.3 – 7.8	2.4 – 5.1	2.5 – 4.7	2.6 – 4.6	2.7 – 4.6	2.8 – 4.7

How does HIV infection affect the Clinical Presentation of TB ?

- Influenced by degree of immunosuppression
- Some presentations have remained unchanged (TBM, TB osteitis)
- Sub-clinical TB infection
  - Autopsy studies: show unsuspected TB often present amongst patients who die with AIDS *ref: Wilson et al*
- Certain peculiar TB syndromes:
  - Pulmonary Syndrome
  - Lymphadenopathy Syndrome
  - Serositis Syndrome
  - Constitutional Syndrome

Smear negative Tuberculosis

- Smear negative TB despite sputum culture positive
  - Poor immune response to TB in lung
    - less cavity formation
    - Pauci bacillary TB
- Atypical chest radiograph
- Extrapulmonary forms TB are more common
- Rapid clinical deterioration in untreated

DIAGNOSIS of TB (in HIV)

- 2 sputa: Spot and early morning
  - Smear negative TB : higher yield from sputum culture (85-100%)
  - Sputum induction: ultra-sonic nebulization
    - Improves sputum yield by 25%
  - Bronchoscopy and lavage (BAL)
- Atypical radiographic findings :
    - non-cavitatory pulmonary infiltrates
    - Often lower lobes
- Abdominal imaging
  - Intra-abdominal lymphadenopathy : central hypodensity of lymph nodes
  - Ascites, peritoneal thickening, small bowel thickening, splenic hypodensities

Other sites:

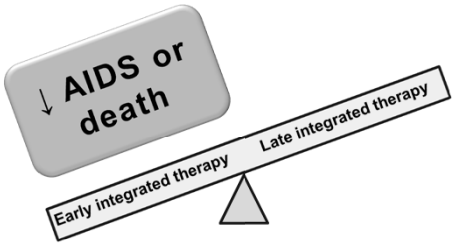
- **Lymph node (2cm):**
  - High yield (77% aspiration, biopsy + culture :96%)
  - 18 gauge needle : air dried for AFB staining
- **Genito-urinary TB** (uncommon)
  - Involved in disseminated TB even in the absence of pyuria
  - First morning urine sample : 3 consecutive days : yield 77%
- **Pleura**
  - Pleural fluid : lymphocytes, exudate, culture :15-60%; pleural biopsy : AFB :69%, granuloma :88%
  - Needle aspiration

TB and HAART

- TB-HIV: commence ART irrespective of CD_4 count
- TB treatment first, then ART.
  - May be difficult to establish patient readiness for ART within 2 weeks
- ART regimen:
  - tenofovir (TDF), lamivudine (3TC), efavirenz (EFV)
  - renal failure: ZDV/3TC/EFZ
  - renal failure + anaemia: D4/T3TC/EFZ ? (ABC)
- Nevirapine during tuberculosis should generally be avoided because of overlapping hepatotoxicity.

Balance of risks and benefits

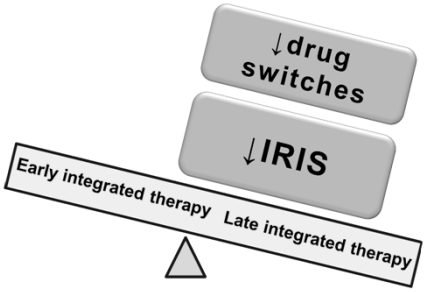
For CD4 count <50 cells/mm^3



Early integrated therapy has:
68% lower AIDS /death rate overshadows
- 5-fold higher risk of IRIS
- Increasing trend in drug switches

Recommend:
Early ART initiation as soon as possible after TB treatment initiation

For CD4 ≥50 cells/mm^3



Early integrated therapy has:
No discernable benefit in AIDS /death rate
- 2-fold higher risk of IRIS
- ↑ drug switches

Recommend:
Defer ART initiation to start of continuation phase of TB therapy

TB treatment, ART and co trimoxazole

- Co-trimoxazole therapy may be deferred until ART is tolerated due to the risks of additive side-effects and drug toxicity.

TB-HIV drug interactions

Eur J Clin Pharmacol

The influence of tuberculosis treatment on efavirenz clearance in patients co-infected with HIV and tuberculosis

Tanuja N. Gengiah · Nicholas H. G. Holford · Julia H. Botha · Andrew L. Gray · Kogieleum Naidoo · Salim S. Abdool Karim

- Previous studies: Rifampicin decreased EFV levels (RIF is a potent enzyme inducer)
- Overall 29.5% reduction in EFV clearance
- Slow EFV-metabolizer prevalence = 23.6%
- By reducing clearance, concomitant tuberculosis treatment increased EFV exposure in our patients

Interactions with Non-nucleoside reverse transcriptase inhibitors (NNRTI)

- South African guidelines do not recommend increasing efavirenz dose when co-administered with rifampicin, due to increased risk of toxicity
- Nevaripine clearance also varies between ethnic groups (Br J Clin Pharmacology 2004: 54 ; 378-385)
- However, standard doses of nevirapine are effective when co-administered with rifampicin

NNRTIs	***Dose when combined with rifampicin***	***Comments***
Efavirenz	600mg daily	CDC guidelines recommend 800mg but efavirenz metabolism is slower in S AFRICANS and increased CNS side effects may occur
Nevirapine	200mg twice daily	Possible increased risk of hepatotoxicity, particularly during the 1st two months of nevirapine-containing antiretroviral therapy

TB and Protease Inhibitors

- Most protease inhibitor levels are significantly reduced when co-administered with rifampicin and should not be used, except ritonavir
- ritonavir 400mg daily or more used to overcome the enzyme induction
- ritonavir causes gastrointestinal intolerance
  - improved by gradual dose escalation
  - after completion of TB treatment, maintain the escalated dose for 2 weeks (bec of enz ind)

RIFABUTIN

- recommend rifabutin instead of rifampicin for patients taking protease inhibitors or non-nucleoside reverse transcriptase inhibitors(NNRTI)

- rifabutin:
  - far weaker enzyme inducer than rifampicin
  - unavailable in state sector

ADHERENCE

Adherence

- Pill burden

- Overlapping toxicities
  - Side-effects that impact on adherence e.g nausea, should be actively managed
- Intensive adherence support is needed
  - If side-effects or pill burden cannot be tolerated, antiretroviral treatment interruption for the duration of tuberculosis treatment may be considered

Patient perspectives study

- Emerging themes
  - Multiple stigmas, different 'cultures' of TB vs HIV care
  - Fine balance between the conveniences of an integrated program and the social price of being identified or *owning* one's HIV status
  - Confidentiality of HIV status precludes seamless coordination between TB and HIV clinicians
- The social contexts of illness and healthcare must be considered in the design of integrated programs

SUMMARY

- HIV makes TB worse and TB accelerates the progression of HIV
- Diagnosis of TB is 'difficult' in the presence of HIV
- TB-HIV coinfection: commence ART at any CD4 count
- Beware IRIS especially if CD4 count is low
- Additional counselling because of pill burden and side effects

Acknowledgement

- Dr Nesri Padayatchi