IMPACT OF HIV ON TB MANAGEMENT

Presented at the 5th International TB/HIV course for Clinicians
9 May 2013
Halima Dawood

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

When to Start ART in TB – Building on previous studies

<table>
<thead>
<tr>
<th></th>
<th>AS221/ STRIDE</th>
<th>CAMELIA(^1)</th>
<th>SAPIT(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>806</td>
<td>660</td>
<td>429</td>
</tr>
<tr>
<td>Sites</td>
<td>Africa, Asia, S Am, N Am</td>
<td>Cambodia</td>
<td>S. Africa</td>
</tr>
<tr>
<td>Arms</td>
<td>Imm vs 8-12 wk</td>
<td>Imm vs 8 wk</td>
<td>Early vs 24 wk</td>
</tr>
<tr>
<td>Endpoint</td>
<td>Death/AIDS, CD4 &lt;50 cells/ul</td>
<td>Death</td>
<td>Death</td>
</tr>
<tr>
<td>CD4 (IQR) Cells/ul</td>
<td>77 (36,145)</td>
<td>25 (11,56)</td>
<td>150 (77, 254)</td>
</tr>
</tbody>
</table>

\(^1\) Blanc, IAC, 2010 \(^2\) Abdool Karim, NEJM, 2010
CAPRISA 005: TRuTH Study

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

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

Recurrent TB: TRuTH Study
IMPRESS STUDY

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 CD₄ 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/mm³

- 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/mm³

- 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

- 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

- Nevirapine 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