TB diagnosis and ART/ HIV management

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SAHCS Continuing Medical Education : TB Course
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Outline

• Epidemiology
• Natural history
• Clinical presentation and investigation of TB/HIV
• ART and TB
• Adherence

PREVALENCE
(rate per 100 000 population)

ININCIDENCE (HIV+TB red), notifications (black)
(rates per 100 000 population)

715 /100 000

All:860/100 000
HIV:520/100 000
HIV & TB epidemics in South Africa


Note: The lines are based on fitted mathematical models developed by E Gouws (HIV) and A Grobler (TB)
Risk of Developing Active TB in individuals with latent TB infection (LTBI)

Patients at risk of progression to TB disease compared to general population

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Relative Risk of TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS</td>
<td>170</td>
</tr>
<tr>
<td>HIV infection</td>
<td>40-50</td>
</tr>
<tr>
<td>Silicosis</td>
<td>30</td>
</tr>
<tr>
<td>Fibrotic lesions on chest x-ray</td>
<td>4-26</td>
</tr>
<tr>
<td>Cancer (head or neck)</td>
<td>16</td>
</tr>
<tr>
<td>Immunosuppressive treatment</td>
<td>12</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>10-15</td>
</tr>
<tr>
<td>PPD conversion &lt;1 yr</td>
<td>10</td>
</tr>
</tbody>
</table>
Impact of HIV on TB

• HIV accelerates TB progression following exposure
• Increase risk of TB outbreaks: including MDR-TB
• Increase in smear negative TB
  – lower risk of TB transmission from HIV-infected
• TB associated with decreased HIV survival
• Acceleration to AIDS or death following TB treatment
• Increased risk of recurrent TB: usually exogenous re-infection
Natural history: TB and CD4 count

• Relationship between CD4 and TB incidence per 100 person years: natural history pre-ART cohort
• CD4 count determines incidence and clinical and radiographic presentation of TB
• Risk of TB increases after HIV seroconversion and progressive increase with decreasing immunity
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 or sub-acute TB infection
  ▪ Autopsy studies: show unsuspected TB(sub-acute infection) 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
• Extra pulmonary forms TB are more common
• Rapid clinical deterioration in untreated
Diagnosis of TB (in HIV)

- **One** sputa: Spot :GeneXpert® (sensitivity 67-98%)
  - Smear negative TB : higher yield from GeneXpert® and sputum culture (85-100%)
  - Sputum induction: ultra-sonic nebulization
    - Improves sputum yield by 25%
  - Bronchoscopy and lavage (BAL) with or without biopsy
## TB Diagnostic Tests

<table>
<thead>
<tr>
<th>Investigation</th>
<th>TB</th>
<th>Rif/INH</th>
<th>TAT</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>GXP</td>
<td>MTB</td>
<td>Rif S/R</td>
<td>2/7</td>
<td>95.9%</td>
<td>98%</td>
</tr>
<tr>
<td>GXP Ultra</td>
<td>MTB</td>
<td>Rif S/R</td>
<td>1/7</td>
<td>100%</td>
<td>96%</td>
</tr>
<tr>
<td>LPA</td>
<td>MTB, MOTT</td>
<td>Rif and INH S/R</td>
<td>7/7</td>
<td>88%</td>
<td>94.6%</td>
</tr>
<tr>
<td>Culture</td>
<td>MTB, MOTT</td>
<td>Rif and INH S/R</td>
<td>6-10/52</td>
<td>82%</td>
<td>100</td>
</tr>
<tr>
<td>Sputum Smear Microscopy (AFB)</td>
<td>TB</td>
<td>No resistance detection</td>
<td>2/7</td>
<td>50-60%</td>
<td>99-100%</td>
</tr>
<tr>
<td>LF-LAM</td>
<td>TB in HIV+ with CD4 &lt;200</td>
<td></td>
<td></td>
<td>13-93%</td>
<td>87-99%</td>
</tr>
</tbody>
</table>
Diagnosis of TB (in HIV)

• Atypical radiographic findings: adjunctive: not diagnostic
  • Non-cavitatory pulmonary infiltrates
  • Often lower lobes

• Abdominal imaging: supplementary
  – Intra-abdominal lymphadenopathy: central hypo-density of lymph nodes
  – Ascites, peritoneal thickening, small bowel thickening, splenic hypo-densities
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%
  – Urine mycobacterial lipoarabinomannan (LAM): hospitalised patient with CD4 < 100 cells/ul : disseminated TB with renal involvement

• **Pleura**
  – Pleural fluid : lymphocytes, exudate, ADA, culture :15-60%
  – pleural biopsy : AFB :69%, granuloma :88%
Effect of ART on incidence of TB

Data from AIDS clinic in Cape Town, South Africa

Highly active anti-retroviral treatment (HAART): reduced the incidence of HIV-1-associated-tuberculosis by more than 80% in some studies

Source: Badri, Lancet 2006
**TB incidence and serial CD4 counts**

<table>
<thead>
<tr>
<th>CD4 count stratum</th>
<th>No. of incident TB cases</th>
<th>Person-years of observation (PYO)</th>
<th>Rate per 100 PYO (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100</td>
<td>59</td>
<td>352.0</td>
<td>16.70 (12.76-21.02)</td>
</tr>
<tr>
<td>101-200</td>
<td>65</td>
<td>701.2</td>
<td>9.27 (7.15-11.82)</td>
</tr>
<tr>
<td>201-300</td>
<td>38</td>
<td>693.7</td>
<td>5.48 (3.88-7.52)</td>
</tr>
<tr>
<td>301-400</td>
<td>23</td>
<td>499.1</td>
<td>4.61 (2.02-6.91)</td>
</tr>
<tr>
<td>401-500</td>
<td>13</td>
<td>307.1</td>
<td>4.23 (2.25-7.24)</td>
</tr>
<tr>
<td>&gt;500</td>
<td>5</td>
<td>334.2</td>
<td>1.50 (0.49-3.49)</td>
</tr>
</tbody>
</table>
Early vs. Standard ART : Haiti

- Randomized study : 816 HIV infected
  - Baseline CD4 : 200-350 cells/ul
- Early ART (within 2 weeks after enrollment) vs. standard (start ART when CD4 < 200 cells/ul or AIDS event)
  - INH and co-trimoxazole prophylaxis to all participants
- 2 fold (36 vs 18 cases) decline in TB in early arm (median follow-up : 21 months)

Source: Severe P et al NEJM 2010
# When to Start ART in TB – Building on previous studies

<table>
<thead>
<tr>
<th></th>
<th>A5221/ STRIDE&lt;sup&gt;1&lt;/sup&gt;</th>
<th>CAMELIA&lt;sup&gt;2&lt;/sup&gt;</th>
<th>SAPIT&lt;sup&gt;3&lt;/sup&gt;</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>

Source: <sup>1</sup>Havlir, <sup>2</sup>Blanc, IAC, 2010 <sup>3</sup>Abdool Karim, NEJM, 2010
Kaplan-Meier estimates of cumulative probability of IRIS

- HIV suppression rates did not differ in the ART strategies
- More ART drug changes in early arm and risk of IRIS higher
- IRS 16% in 4 week group vs 7% in 8-12 week group
<table>
<thead>
<tr>
<th></th>
<th>Early Integrated Therapy</th>
<th>Late Integrated Therapy</th>
<th>IRR (95% CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 &lt;50 cells/mm³</td>
<td>n=37</td>
<td>n=35</td>
<td></td>
<td></td>
</tr>
<tr>
<td># drug switches</td>
<td>3</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CD4 &lt;50 cells/mm³</td>
<td>n=177</td>
<td>n=180</td>
<td>6.8 (0.8-55)</td>
<td>0.04</td>
</tr>
<tr>
<td># drug switches</td>
<td>7</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Rates calculated as events per 100 person-years
Timing of ART and TB Meningitis

- Different to pulmonary TB
- “immediate” ART vs. 2 months later: did not reduce mortality
- “immediate” ART: increased risk of severe adverse events
**CAPRISA 005: TRuTH Study**

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

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**Incidence rate**

3.6 (95% CI: 2.8 – 4.7) per 100PY

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<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>3.5</td>
<td>3.5</td>
<td>3.5</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>
TB and ART

- 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 (2 NRTIs + NNRTI):
  - Tenofovir (TDF), lamivudine (3TC), efavirenz (EFV)
  - Tenofovir (TDF), lamivudine (3TC), dolutegravir (DTG)
  - renal failure: ZDV/3TC/EFZ
  - renal failure + anemia: ABC/T3TC/EFZ
- 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
Clinical Management

- CD4 ≥ 50 cells/ul
- Severe HIV disease: low Karnofsky score
  - Low BMI, low Hb, low Albumin, organ dysfunction
  - Start ART: 2-4 weeks
- Absence of severe disease: start after 8-12 weeks
- Other correlates: tolerance of TB medication
- Initiating ART and TB therapy simultaneously: not recommended
TB treatment, ART and co-trimoxazole

- Co-trimoxazole (CTM) therapy: deferred until ART is tolerated due to the risks of additive side-effects and drug toxicity.
- CTM: associated with decreased AIDS related mortality and opportunistic infections
- Also reduced incidence of: malaria, bacterial pneumonia and enteritis
Other benefits of ART

- Improved general health: weight gain
  - Opportunistic infections reduced (malaria, Cryptococcus, septicemia, bacterial enetritis)
- Reduced HIV transmission: sexual, mother to child
Co-administration of ART/TB treatment

- Drug interactions
- Shared or cumulative toxicity
- High pill burden
- IRS: worsen TB symptoms
MDR-TB and HIV

- Substantial increase in MDR/XDR-TB in SA
- Treatment success of MDR-TB and XDR-TB low
- Challenge to diagnose and manage
- ART potential to improve outcomes in HIV/MDR-TB co-infected
# Overlap of Adverse Drug Reactions

<table>
<thead>
<tr>
<th>ADR</th>
<th>TB Drugs</th>
<th>HIV Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>Most, esp. Z, R, H, FQ</td>
<td>EFV, NVP, D4T, CTM</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>H, R, E, Z, Eto, FQ</td>
<td>EFV, NVP, all PI, all NRTI</td>
</tr>
<tr>
<td>Nausea</td>
<td>Z, H, E, Eto, FQ</td>
<td>Most, esp. RTV, D4T, NVP</td>
</tr>
<tr>
<td>Cytopenias</td>
<td>RBT, R</td>
<td>AZT, CTM</td>
</tr>
<tr>
<td>CNS</td>
<td>H, Cs/Trd, Eto, FQ</td>
<td>EFV</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>H, Cs/Trd, Eto, Km/Am, E</td>
<td>D4T (also HIV disease)</td>
</tr>
<tr>
<td>Renal Toxicity</td>
<td>Km/Am, Cm</td>
<td>TDF</td>
</tr>
</tbody>
</table>
Adherence
Example Pill Burden for MDR-TB/HIV Patient

- Ethionamide
- Moxifloxacin
- Terizidone
- Pyridoxine
- Kanamycin
- Ethambutol

Flow Chart for ART in Adult Patients with MDR-TB
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 ‘challenge’ in the presence of HIV

• TB-HIV coinfection: commence ART at any CD4 count

• Beware IRS and drug related effects especially if CD4 count is low, monitor for overlapping toxicity and drug interactions

• Additional counseling because of pill burden and side effects
Acknowledgements

- Dr Nesri Padayatchi
- Dr Kogie Naidoo
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 as efavirenz metabolism clower in S.Africans

- 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 BUT risk of hepatotoxicity: especially first 2 months
Other NNRTIs

- Rilpivirine and etravirine: should not be used with rifampicin
- Rifampicin: decreases rilpivirine and etravirine
TB and Protease Inhibitors

- Most protease inhibitor levels are significantly reduced when co-administered with rifampicin and should not be used alone, except with 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 (enzyme induction).
TB and Protease Inhibitors

• Atazanavir: rifampicin is contraindicated
  – Instead use rifabutin, oral, 150 mg 3 times weekly

• Darunavir: no data available, expect drug-drug interactions
Rifabutin

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

• Rifabutin 300mg daily: equivalent to rifampicin
  – Far weaker enzyme inducer than rifampicin
  – Expensive
  – Dose adjustment with efavirenz (600mg rifabutin daily)
  – ritonavir (150mg rifabutin daily)
  – atazanavir (3 times rifabutin weekly)
  – raltegravir (300mg rifabutin daily)

• Side effects: blurred vision, floaters, reduced visual acuity—differentiate from CMV retinitis
Integrase Inhibitors and Rifampicin

- Integrase inhibitors: raltegravir and rifampicin: caution
  - Raltegravir levels: reduced by 40-61%
  - Recommend double dose: 800mg bd (healthy volunteers)
  - Recent study: 400mg bd sufficient with small decrease in raltegravir levels: need to monitor viral loads
  - Dolutegravir: bd dosing-did not effect rifampicin-need more data
  - No data on integrase inhibitors and rifabutin