Issues in HIV-TB co-infection

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Case 1

27 y/o man from Ethiopia, admitted with cough, fevers, and 20 lb. weight loss over one month

Sputum - rare AFB
HIV-positive, CD4 - 18, viral load > 1,000,000

Dramatic initial improvement with IRZE
TB case mortality rates, by HIV status (HIV+, green), HIV- (orange)

1. Should antiretroviral therapy be started during TB treatment?
2. When during TB therapy should antiretroviral therapy be started?
3. What regimens can be used for co-treatment of HIV and TB therapy?
Complicating factors: antiretroviral therapy during TB therapy

- Need for coordination between TB and HIV treatment programs
- Challenge of adherence to multidrug therapy for both diseases
- Overlapping drug toxicity profiles
- Drug interactions
- Immune reconstitution (paradoxical) reactions
SAPiT: Starting Antiretroviral therapy (ART) in three Points in TB

Primary Objective:
- To determine the optimal time to initiate ARVs in TB patients

Inclusion Criteria:
- Smear pulmonary TB
- HIV positive with CD4 count < 500 cells/mm³
- Women must agree to use contraception (efavirenz)

Endpoint
- \(1^0\) – all-cause mortality

Initiation of ART during vs. after TB treatment: SAPIT

Effects of timing of ART on mortality, by baseline CD4 cell count: SAPIT

Effects of timing of ART on mortality, by baseline CD4 cell count: SAPIT

All patients with HIV-TB should receive ART during TB treatment

Competing risks in the timing of ART during TB treatment

Immediate (< 2 wks)

Benefits:
• ↓ risk of other OIs

Risks:
• ↑ adverse effects
• ↑ incidence of IRD

Early (2 months)

Benefits:
• ↓ risk of IRD

Risks:
• ↑ incidence of OIs
• feasibility

Mortality
General schema for CAMELIA, STRIDE, and integrated arms of SAPIT

- **“Immediate ART”** (within 2 weeks)
- **“Early ART”** (2-3 months)

- **HIV+ TB**
- **ART**
- **TB treatment**

Study week

Primary endpoint
# Key characteristics of trials of timing of ART during TB treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>Key enrollment criteria</th>
<th>Median CD4 (IQR)</th>
<th>Primary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAMELIA</td>
<td>Cambodia</td>
<td>Smear +, CD4 &lt; 200</td>
<td>25 (10 - 56)</td>
<td>Death</td>
</tr>
<tr>
<td>STRIDE</td>
<td>Multi-national</td>
<td>Clinical TB, CD4 &lt; 250</td>
<td>77 (36 – 145)</td>
<td>AIDS or death</td>
</tr>
<tr>
<td>SAPIT</td>
<td>South Africa</td>
<td>Smear +, CD4 &lt; 500</td>
<td>150 (77 – 254)</td>
<td>AIDS or death</td>
</tr>
</tbody>
</table>

*N Engl J Med* 365; 2011; 1471-501
Effect of ART timing on death (CAMELIA) or death/AIDS (STRIDE, SAPIT)

N Engl J Med 2011; 1471-501
Relationship between median baseline CD4 count and the effect of immediate ART on death (CAMELIA) or death/AIDS (STRIDE, SAPIT)

N Engl J Med 2011; 1471-501
Effects of ART timing on outcomes in CAMELIA and patients with CD4 < 50 in STRIDE and SAPIT

- **CAMELIA**
  - Immediate: 34% (p=0.004)
  - Early: Not provided

- **STRI DE**
  - Immediate: Not provided
  - Early: 42% (p=0.02)

- **SAPI T**
  - Immediate: Not provided
  - Early: 68% (p=0.06)

*N Engl J Med 2011; 1471-501*
Effects of ART timing on death/AIDS among patients with **CD4 > 50** in STRIDE and SAPI T

```
0 2 4 6 8 10 12 14

STRIDE

p=0.67

SAPI T

p=0.34

N Engl J Med 2011; 1471-501

Immediate  Early
```
Effects of ART timing on Immune Reconstitution Disease among patients with \textbf{CD4 > 50} in STRIDE and SAPIT

\[ \begin{array}{c|c|c}
\text{IRD} & \text{STRIDE} & \text{SAPIT} \\
\hline
\text{Immediate} & 10 & \text{p}=0.009 \\
\text{Early} & 4 & \text{p}=0.02 \\
\end{array} \]

\textit{N Engl J Med} 2011; 1471-501
Timing of ART in patients with TB

- Advanced AIDS (CD4 < 50): **immediate ART** (within 2 weeks) improves survival
  - Markedly increased risk of IRD, including fatal IRD events
  - Overall survival benefit despite IRIS
- CD4 > 50: **early ART** (~ 2 months) provides good balance of competing risks of death/AIDS vs. IRIS

**Caveats**

- CNS involvement – no benefit to immediate therapy, and there may be increased risk (Clin Infect Dis. 2011;52:1374-83)
- Programmatic complexities of early ART
Programmatic challenges of immediate ART during TB treatment

- Rapid HIV diagnosis
- Rapid provisional diagnosis of TB
- Rapid way to identify those in need of immediate ART: CD4 cell count, BMI, clinical status
- ART available in settings where TB is diagnosed (hospital or clinic)
- Training in diagnosis and management of IRD events
Effect of rifampin on exposure (AUC) of NNRTIs

% of normal AUC

- Efavirenz
- Nevirapine
Effect of EFV dose (600 vs. 800 mg) on mid-dose levels, patients on RIF

Outcomes at 48 wks

On EFV
- 600 mg – 81%
- 800 mg – 74%

VL < 50
- 600 mg – 91%
- 800 mg – 87%

Virological failure of efavirenz-based ART, among patients with and without rifampin for TB

Months of co-treatment

% with viral load > 400

TB
No TB

JAMA 2008; 300: 530-9
Patients who cannot be treated with EFV-based ART

- Efavirenz intolerance
- Resistance to efavirenz (other 1st-generation NNRTIs)
- Pregnancy (at least for the first 1-2 trimesters)
- Very young children (< 3 years)
Comparison of the effects of RIF vs. RBT on trough concentrations of boosted PIs

- LPV/r: 1% normal trough concentration
- ATZ/r: 2.5% normal trough concentration
- DRV/r: ND
- FPV/r: ND

AAC 2204;48:1553-60, AAC 2006; 50:3336-42, AAC 2010;54:4440-5, AAC 2008;52:534-8,
## Effect of protease inhibitors on serum concentrations (AUC) of rifamycins

<table>
<thead>
<tr>
<th>PI</th>
<th>Rifabutin</th>
<th>Rifampin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritonavir</td>
<td>↑ 400%</td>
<td>unchanged</td>
</tr>
<tr>
<td>Indinavir</td>
<td>↑ 270%</td>
<td>unchanged</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>↑ 200%</td>
<td>NR</td>
</tr>
<tr>
<td>Amprenavir</td>
<td>↑ 400%</td>
<td>NR</td>
</tr>
<tr>
<td>Lopinavir/ritonavir</td>
<td>↑ 300%</td>
<td>NR</td>
</tr>
<tr>
<td>Atazanavir</td>
<td>↑ 250%</td>
<td>NR</td>
</tr>
</tbody>
</table>

Clin Infect Dis 1999; 28: 419-30
Clinical relevance of increased rifabutin concentrations due to ritonavir

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>% of patients on ritonavir + rifabutin</th>
<th>% of patients on ritonavir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthralgia</td>
<td>9.2</td>
<td>0.6</td>
</tr>
<tr>
<td>Joint stiffness</td>
<td>4.1</td>
<td>0</td>
</tr>
<tr>
<td>Uveitis</td>
<td>4.7</td>
<td>0.6</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>38</td>
<td>19</td>
</tr>
</tbody>
</table>
Rifabutin PK with lopinavir/R in TB patients (n = 16)

<table>
<thead>
<tr>
<th>PK parameter</th>
<th>RBT 300 mg/day</th>
<th>RBT 150 mg QOD + LPV/r</th>
<th>RBT 150 mg/day + LPV/r</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median AUC (exposure)</td>
<td>3026</td>
<td>2307</td>
<td>5010</td>
</tr>
<tr>
<td>Median Cmax (peak)</td>
<td>297</td>
<td>168</td>
<td>311</td>
</tr>
</tbody>
</table>

Naiker S, et al. 2011 CROI, abstract 650
Rifabutin and TB therapy

- Rifabutin is as active as rifampin
- No dose adjustments of ART needed for commonly-used drugs (ATZ, lopinavir/R)
- Decrease RBT from 300 mg daily to 150 mg daily when given with boosted PIs
- Give remainder of TB drugs daily

Caution – RBT dose would be inadequate if patient stopped PI
Drug interactions in HIV-TB are regrettably complex, but should not prevent HIV-TB co-treatment.

Co-treatment regimen of choice: rifampin-based TB treatment + efavirenz-based ART.

Drug interactions should be managed, not avoided – use a rifamycin-based regimen.

New drug interaction guidelines at http://www.cdc.gov/tb/TB_HIV_Drugs
Case 1 – Chest x-ray response to therapy
Case 3 – Chest x-ray response to therapy - II

3 months

Started antiretroviral therapy at 8 weeks of TB therapy

Developed fever, cough, left pleuritic chest pain 10 days after starting HAART
Types of immune reconstitution inflammatory syndrome (IRIS) events in HIV-TB

- Hectic fever
- New or worsening adenitis - peripheral or central nodes
- New or worsening pulmonary infiltrates, including respiratory failure
- New or worsening pleuritis, pericarditis, or ascites
- Intracranial tuberculomas, worsening meningitis
- Disseminated skin lesions
- Epididymitis, hepatosplenomegaly, soft tissue abscesses
### Severity of immune reconstitution events in TBTC Study 23

<table>
<thead>
<tr>
<th>NCI toxicity scale</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 or 2</td>
<td>7 (28%)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>9 (36%)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>8 (32%)</td>
</tr>
<tr>
<td>Grade 5 (death)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>12 (48%)</td>
</tr>
<tr>
<td>Median duration, days (IQR)</td>
<td>7 (3-12)</td>
</tr>
<tr>
<td>Severe (grade 4 / 5 or hosp.)</td>
<td>14 (56%)</td>
</tr>
<tr>
<td>Median duration of event (IQR)</td>
<td>64 (44 – 99)</td>
</tr>
</tbody>
</table>

Int J Tuberc Lung Dis, 2007; 11: 1282-8
IRIS events - implications for use of antiretroviral therapy (ART)

- Those who need ART the most (patients with low CD4 cell counts) have the highest risk for an IRIS event.
- Delaying ART decreases risk of severe paradoxical reactions, but increases risk of another OI or death.
- Anticipate IRIS events – discuss beforehand with patient and other care providers.
- Schedule early follow-up after starting ARV - detect and manage IRIS events.
Management of IRIS

- Anticipate IRIS events – warn patients and other care providers
- Rule out other possible causes – bacterial infections, a 2nd OI, inadequate Rx for OI, drug-resistant pathogen
- For relatively severe manifestations, prednisone is reasonable
  - 1 mg/kg (1.5 mg/kg with rifampin), tapering over 4-6 weeks
Summary – treatment of HIV-related TB: issues with antiretroviral therapy

- Should antiretroviral therapy be used during TB treatment?
  - Yes, for all patients

- What regimens can be used for co-treatment of HIV and TB?
  - Preferred: efavirenz-based HAART + rifampin-based TB treatment
  - Alternative: PI-based HAART + rifabutin-based TB treatment

- When should HAART be started?
  - 2 weeks to 2 months after starting TB treatment