The ART of treating TB in HIV-infected persons

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Fever and confusion in a newly-arrived visitor

- 51 year old man from Kenya
  - 2 weeks of fever, cough, weight loss
  - 1 day of confusion
- Exam: hallucinating, no focal deficits
- T – 38.4, P – 100, BP – 136/74, O2 saturation – 100%
- Mouth – dry mucous membranes, thrush
- Axillary nodes bilaterally
Follow-up

- HIV +, CD4 cell count – 18 (2%)
- Sputum smear: 4+ AFB
- Rapid assay: *M. tuberculosis* positive, no resistance to INH and RIF
- Lumbar puncture - normal
- Good initial clinical response to INH, RIF, PZA, and EMB
ART-related questions

- When should ART be started in a patient being treated for TB?
- How should drug-drug interactions between rifamycins and ART be managed?
- How should immune reconstitution disease (IRD) be diagnosed and treated?
- What are the programmatic challenges of starting ART during TB treatment?
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

ART during TB treatment: conclusions of SAPIT

- Starting ART during TB treatment decreases the high case fatality rate of HIV-TB
- Mortality benefit was present across a broad range of CD4 cell counts
- Earlier ART resulted in higher risk of IRD, but these cases were manageable
- WHO and DHHS recommendations: start ART during TB treatment for all patients
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
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General schema for CAMELIA, STRIDE, and integrated arms of SAPIT

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

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

Study week:
- 0
- 8
- 24

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>

Effect of ART timing on death (CAMELIA) or death/AIDS (STRIDE, SAPIT)

Relationship between median baseline CD4 count and the effect of immediate ART on death (CAMELIA) or death/AIDS (STRIDE, SAPIT)

Effects of ART timing on outcomes in CAMELIA and patients with CD4 < 50 in STRIDE and SAPIT

Effects of ART timing on death/AIDS among patients with CD4 > 50 in STRIDE and SAPIT

CROI 2011 abstract 38, CROI 2011 abstract 39LB
Effects of ART timing on Immune Reconstitution Disease among patients with **CD4 > 50** in STRIDE and SAPIT

CROI 2011 abstract 38, CROI 2011 abstract 39LB
Other outcomes in CAMELIA, STRIDE and SAPIT

- Immune reconstitution disease (IRD)
  - Risk factors: immediate ART, low CD4 cell count, confirmed TB (STRIDE)
  - No deaths attributed to IRD, but excess “TB deaths” (14 vs. 7) in immediate arm or STRIDE

- Viral suppression – no effect of timing of ART on suppression at the end of TB treatment

- ART switches – higher in immediate arm of SAPIT
Comments – randomized trials of when to start ART during TB treatment

- Mortality is the appropriate endpoint; it captures the competing risks of HIV disease progression and severe IRD
  - Attempts to attribute causation to events (TB, IRD, OI, toxicity) are very problematic and ultimately not helpful
- 3 trials should combine data in a meta-analysis, using death as the endpoint
  - Formal statistical test for heterogeneity by baseline CD4 count should be done
Effect of ART timing on survival of patients with TB meningitis

- Median CD4 ~ 40 (16 – 100)
- 60% + CSF culture

- KM survival estimates at 9 months
  - 35.2% in immediate arm
  - 40.3% in deferred arm

- Similar in per protocol analysis

Hazard ratio 1.1 (95% CI 0.8 – 1.6), p = 0.52

Török et al, 41st Union World Conference on Lung Health, Berlin Nov 2010
Effect of ART timing on risk of adverse events in patients with TB meningitis

Török et al, 41st Union World Conference on Lung Health, Berlin Nov 2010

Effect of ART timing on risk of adverse events in patients with TB meningitis

Grade 3 or 4

Grade 4

p = 0.04

Percentage of patients

Immediate

Early

0
10
20
30
40
50
60
70
80
90
100

Grade 3 or 4

Grade 4

Immediate

Early

p = 0.04
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 IRD
- **CD4 > 50:** early ART (~ 2 months) provides good balance of competing risks of death/AIDS vs. IRD
- **Caveats**
  - CNS involvement – no benefit to immediate therapy, and there may be increased risk
  - Programmatic complexities of early ART
Programmatic challenges of immediate ART during TB treatment

- Rapid HIV diagnosis
- Rapid provisional diagnosis of TB
- Widespread availability of a way to identify those in need of immediate ART: CD4 cell count, BMI, hemoglobin, clinical/radiographic score
- ART available in settings where TB is diagnosed (hospital or clinic)
- Training in diagnosis and management of IRD events
Starting ART among patients with HIV-TB in India

26% of those referred, started ART

Timing of ART not available


- British recommendations
  - CD4 < 100 – within 2 weeks
  - CD4 100-200 – at 2 months
  - CD4 > 200 – after completion of TB treatment

- 83 patients eligible to start ART
  - 20 patients (24%) started per the recommendations

Thorax 2008;63:935
Reasons for delayed ART among patients with \textbf{CD4 < 100}

<table>
<thead>
<tr>
<th>Reasons by the Patient</th>
<th># (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refusal to start ART</td>
<td>7 (21%)</td>
</tr>
<tr>
<td>Concern about side effects</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Poor adherence</td>
<td>3 (9%)</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Reasons by the Doctor</th>
<th># (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious side effect of TB treatment</td>
<td>8 (24%)</td>
</tr>
<tr>
<td>Concern about side effects / IRD</td>
<td>6 (18%)</td>
</tr>
<tr>
<td>Presence of another illness</td>
<td>4 (12%)</td>
</tr>
<tr>
<td>Severity of the manifestations of TB</td>
<td>5 (15%)</td>
</tr>
</tbody>
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Thorax 2008;63:935
Remaining questions: ART during TB treatment

- Optimal treatment of patients who cannot take efavirenz-based ART
  - Problems of giving boosted PIs with rifampin
  - Uncertainty about dose of rifabutin with boosted PIs
- Optimal diagnosis and management of IRD
- Prevention of IRD among subgroups with very high risk
  - 30-45% with immediate ART among patients with CD4 count < 50
Overcoming rifampin’s effect on lopinavir trough concentrations

Overcoming rifampin’s effect on lopinavir trough concentrations

Problems of trying to boost past rifampin’s effect
- Hepatotoxicity in health volunteers
- Increased variance in trough PI concentrations

Comparison of the effects of RIF vs. rifabutin on trough concentrations of boosted PIs

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
ACTG 5290: randomized trial of options for treating HIV-TB in patients who cannot use efavirenz (EFV)

Co-treatment regimens

- **LPV/r 800/200** (2 nucleosides) + RIF-based TB Rx
- **LPV/r 400/100** (2 nucleosides) + RBT-based TB Rx
- **LPV/r 400/100** (2 nucleosides + raltegravir) + RBT-based TB Rx

Outcomes

- VL at 48 weeks
- Toxicity
- ART stop
- CD4 response
- IRD
- TB outcomes
The ART of treating patients with HIV-TB

- “Co-treatment” – both infections must be treated
- Much progress on timing of ART initiation
  - CD4 < 50: immediate (2 weeks)
  - CD4 > 50: early (2-3 months)
- Research needed
  - Co-treatment when EFV/RIF can’t be used
  - Diagnosis, treatment, prevention of severe IRD
  - Programmatic issues in early co-treatment
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