Optimal timing of antiretroviral therapy during tuberculosis treatment: The SAPiT trial

17th Conference of Retroviruses and Opportunistic Infections
Boston, 28 February 2011

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The HIV and TB epidemics in South Africa

Red Line = TB case notification rate
Blue Line = Antenatal HIV prevalence

Source: South African Department of Health
Starting ART at 3 Points in TB
The SAPiT Trial: CAPRISA 003

- **Purpose of study:** To determine the optimal time to initiate ART in TB patients
- **Design:** Open-label 3-arm randomized controlled trial
- **Sample size:** 642 HIV-TB co-infected patients
- **Study site:** CAPRISA eThekwini Clinic, Durban
- **Study Population:** Ambulatory TB smear +ve, HIV +ve (CD4 count < 500 cells/mm³) and on standard TB treatment regimens. Participants attended the clinic’s TB-DOTS program.
- **Endpoints**
  - $1^0$ All-cause mortality + AIDS defining illness
  - $2^0$ Tolerability, Viral Load, TB outcomes & Immune Reconstitution Inflammatory Syndrome (IRIS)
56% lower mortality with integrated TB-HIV treatment
Continued the 2 integrated treatment arms*: When to start ART during TB treatment?

• **Why initiate ART early during TB treatment?**
  - To halt HIV progression & avert high TB-HIV mortality

• **Why initiate ART later in TB treatment?**
  - Decreased risk of immune reconstitution syndrome
  - Lower pill burden / better tolerability – 3 ARVs + (4 vs 2 TB drugs)

• **Current treatment based on observational data, clinician judgement & expert opinion:**
  - High variability
  - WHO guidelines
    - **Pre-2009:** CD4<50 initiate early & CD4=50-200 initiate later
    - **Since 2009:** Start ART in all HIV-infected individuals with active TB, irrespective of CD4 cell count and start TB treatment first, followed by ART ASAP after starting TB treatment.

*based on the trial’s Safety Monitoring Committee recommendation
Study intervention
(After Sept 2008, remaining 2 arms continued to end)

- Randomized to one of 2 arms (continued to trial end):
  - **Early integrated-therapy arm** - antiretroviral therapy to be initiated within 4 weeks of starting tuberculosis treatment,
  - **Late integrated-therapy arm** - antiretroviral therapy to be initiated within 4 weeks of completing the intensive phase of tuberculosis treatment, and

- **Cotrimoxazole prophylaxis**: provided to all patients

- **ART**: ddI + 3TC + efavirenz – once daily regimen

- **Once-a-day treatment** integrated with TB-DOT
Enrollment and Outcomes

1331 Screened

642 Enrolled

213 in Sequential Arm*

214 in Early integrated arm

198 (92.5%) started ART at median of 8 days (IQR: 7 to 22)

15 died (7%)
26 lost to follow-up (12%)
20 withdrew during follow-up (9%)
153 completed follow-up (72%)

215 in Late integrated arm

164 (76.3%) started ART at median of 95 days (IQR: 67 to 171)

15 died (7%)
34 lost to follow-up (16%)
23 withdrew during follow-up (11%)
143 completed follow-up (67%)

Retention: 76% at 18 months

*Safety Monitoring Committee review and recommended:
- Start ART immediately in all sequential arm patients but continue the two integrated treatment arms in the trial
## Results: Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline characteristic</th>
<th>Early integrated arm (N = 214)</th>
<th>Late integrated arm (N = 215)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age in years (SD)</td>
<td>34.3 ±8.0</td>
<td>34.5 ±8.7</td>
</tr>
<tr>
<td>Gender - (% male)</td>
<td>45.3</td>
<td>52.1</td>
</tr>
<tr>
<td>Median CD4+ count, cells/mm$^3$ (IQR)</td>
<td>154.5 (75 to 261)</td>
<td>149 (77 to 244)</td>
</tr>
<tr>
<td>log viral load copies/ml (IQR)</td>
<td>5.1 (4.5 to 5.6)</td>
<td>5.2 (4.5 to 5.6)</td>
</tr>
</tbody>
</table>
Overall: AIDS defining illness or death

<table>
<thead>
<tr>
<th></th>
<th>Early Integrated arm n = 214</th>
<th>Late Integrated arm n = 215</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of events</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td>Person-years</td>
<td>259.4</td>
<td>244.2</td>
</tr>
<tr>
<td>Event rate (per 100 person-years)</td>
<td><strong>6.9</strong></td>
<td><strong>7.8</strong></td>
</tr>
</tbody>
</table>

**Incidence Rate Ratio:** 0.89 (95% CI: 0.44 to 1.79); p=0.73

**Similar rates of AIDS defining illness or death**
Kaplan-Meier curve for AIDS or death in patients with CD4 <50 cells/mm$^3$

IRR: 0.32 (0.07-1.13), p=0.06

68% reduction of AIDS / death (p=0.06)
Kaplan-Meier curve for AIDS or death in patients with CD4 ≥50 cells/mm³

- Early integrated therapy
- Late integrated therapy

<table>
<thead>
<tr>
<th>Months of follow-up</th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early – Events/ # at risk</td>
<td>0/177</td>
<td>8/149</td>
<td>10/137</td>
<td>14/121</td>
</tr>
<tr>
<td>Late – Events / # at risk</td>
<td>0/180</td>
<td>4/48</td>
<td>7/129</td>
<td>9/121</td>
</tr>
</tbody>
</table>

No discernable differences in AIDS / death

IRR: 1.51 (0.61–3.95), p=0.34
HIV treatment outcomes

HIV suppression >90% after 18 months
No difference between arms irrespective of CD4 status
Successful TB treatment completion

TB treatment successfully completed in ~80% of the patients with no significant differences across groups.
### AIDS / death, IRIS rates, and drug switches stratified by CD4+ count

<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><strong>CD4 &lt;50 cells/mm³</strong></td>
<td>n=37</td>
<td>n=35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIDS / death*</td>
<td>8.5</td>
<td>26.3</td>
<td>0.32 (0.1-1.1)</td>
<td>0.06</td>
</tr>
<tr>
<td>IRIS*</td>
<td>46.8</td>
<td>9.9</td>
<td>4.7 (1.5-19.6)</td>
<td>0.01</td>
</tr>
<tr>
<td># drug switches</td>
<td>3</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>CD4 ≥50 cells/mm³</strong></td>
<td>n=177</td>
<td>n=180</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIDS / death*</td>
<td>6.6</td>
<td>4.4</td>
<td>1.51 (0.6-4.0)</td>
<td>0.34</td>
</tr>
<tr>
<td>IRIS*</td>
<td>15.8</td>
<td>7.2</td>
<td>2.2 (1.1-4.5)</td>
<td>0.02</td>
</tr>
<tr>
<td># drug switches</td>
<td>7</td>
<td>1</td>
<td>6.8 (0.8-55)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

* Rates calculated as events per 100 person-years
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

For CD4 ≥50 cells/mm³

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

• Findings support integration of TB and HIV treatment

• Recommend:
  - Patients with CD4+ counts <50 cells/mm$^3$:
    • Early ART initiation as soon as possible after TB treatment initiation
  - Patients with CD4 counts ≥ 50 cells/mm$^3$:
    • ART initiation can be deferred to start of the continuation phase of TB treatment
    • Decision on early or late initiation: use clinical judgement of capacity to manage IRIS & toxicities
Acknowledgements

- The patients in the study
- President’s Emergency Plan for AIDS Relief (PEPfAR)
- Global Fund & Enhancing Care Initiative
- eThekwini Metro & staff of Prince Cyril Zulu clinic
- CAPRISA SAPiT Team & Community Support Group
- The SAPiT Safety Monitoring Committee
- KwaZulu-Natal Provincial Department of Health
- KwaZulu-Natal, Yale & Columbia Universities
- CAPRISA was established by the Comprehensive International Program of Research on AIDS of the US National Institutes of Health (grant# AI51794)