Addressing challenges in treating TB-HIV co-infected patients

The SAPiT Trial: Starting Antiretroviral therapy at three Points in TB

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On behalf of:

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Global & South African TB and HIV epidemics in 2007

**HIV**
- **Globally:** 33 million HIV +ve
- **South Africa:** 5.4 million HIV +ve

**TB**
- **Globally:** 9.2 million cases of TB
- **South Africa:** 341,165 cases of TB

**TB - HIV co-infection**
- **Globally:** 700 000 cases & 230 000 deaths
- **South Africa:** ~250 000 cases (HIV-TB co-infection = 70%)
TB deaths per 100,000 population - 2007

<table>
<thead>
<tr>
<th>Rank</th>
<th>Country</th>
<th>Rate per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Swaziland</td>
<td>317</td>
</tr>
<tr>
<td>2</td>
<td>Zimbabwe</td>
<td>265</td>
</tr>
<tr>
<td>3</td>
<td>Lesotho</td>
<td>263</td>
</tr>
<tr>
<td>4</td>
<td>South Africa</td>
<td>230</td>
</tr>
</tbody>
</table>

Source: GLOBAL TUBERCULOSIS CONTROL WHO REPORT 2009
• TB - leading cause of morbidity and mortality in HIV/AIDS patients

• Higher TB associated CFR in HIV pos vs HIV neg despite effective chemotherapy
• Effective mechanism of identifying patients eligible for HAART

• Several solvable challenges in TB-HIV integration

- 20 TB patients started on ART
- Good adherence and clinical response
- Pilot show integration of TB and HIV treatment is feasible
TB and HIV Integration Challenges

- **Programmatic**
  - Is it feasible and practical
  - Case finding & case holding
  - Contact tracing
  - HCW & patients perspectives

- **Therapeutic**
  - When to start?
  - Which ARVs to start with?
  - Adherence
  - Drug-Drug interactions

- **Clinical**
  - Additive toxicities
  - Immune Reconstitution (IRIS)
  - Changing TB clinical features

- **TB Diagnostics**
  - Smear negative TB
  - Rapid diagnosis (resistance)
  - Extra-pulmonary TB

- **TB Prevention**
  - Better vaccines
  - Effective prophylaxis
  - Infection control

- **TB Therapy**
  - Shorter duration
  - New drugs

- **Policy and Planning**
  - Resource allocation
  - Practical implementation
Challenges in TB-HIV co-infection: When to start ART in relation to TB treatment?

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

- Why not initiate ART in TB treatment?
  - Drug interactions bet Rifampin & some ARVs
  - Pill burden / tolerability – 4 TB drugs + 3 ARVs
  - Multiple and overlapping toxicities
  - Increased risk of immune reconstitution syndrome

- Current treatment based on observational data, clinician judgement & expert opinion:
  - High variability & lack of integration of TB-HIV care
  - Country guidelines based on WHO guidance
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 +ve & on standard TB treatment regimens
- HIV positive with CD4 count < 500 cells/mm$^3$
- Women must agree to use contraception – (efavirenz)

Endpoints
- $1^0$ All-cause mortality
- $2^0$ Tolerability, Toxicity, Viral Load, TB outcomes & Immune Reconstitution Inflammatory Syndrome (IRIS)
Study design and intervention

- **Design:** Open-Label Randomized Controlled Trial
- **Randomized to one of 3 arms:**
  - Arm 1: **ART initiated during intensive phase of TB treatment**
  - Arm 2: **ART initiated after intensive phase of TB treatment**
  - Arms 1 & 2 combined: **Integrated TB-HIV treatment**
  - Arm 3: **Sequential treatment - ART initiated after TB treatment completed**
- **TB treatment:** Standard TB regimen
- **Cotrimoxazole prophylaxis:** provided to all patients
- **ART:** Didanosine (ddI) + Lamivudine (3TC) + Efavirenz
  
  *Once-a-day treatment* integrated with TB-DOT
Status of the trial at Safety Monitoring Committee review (September 2008)

- Safety Monitoring Committee review and recommended:
  - Start ART immediately in all sequential arm patients (ie. to halt the sequential treatment arm)
  - Continue the two integrated treatment arms in the trial

- Screened: N=1331
- Enrolled: N=642

Integrated Arm: N=429
- Initiated ARVs: N=358
  - Completed trial = 94 (22%)
  - Rest continuing follow up

Sequential Arm: N=213
- Initiated ARVs: N=132
  - Completed trial = 38 (18%)
  - Rest continuing follow up
## Results: Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>Integrated Arm</th>
<th>Sequential Arm</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (SD)</td>
<td>34.4 (8.38)</td>
<td>33.9 (8.18)</td>
<td>0.48</td>
</tr>
<tr>
<td>Gender - % male</td>
<td>48.7%</td>
<td>52.1%</td>
<td>0.45</td>
</tr>
<tr>
<td>CD4 count cells/mm³ (SD)</td>
<td>181 (136.2)</td>
<td>167 (124.1)</td>
<td>0.22</td>
</tr>
<tr>
<td>Log viral load (SD)</td>
<td>5.00 (0.91)</td>
<td>5.12 (0.74)</td>
<td>0.12</td>
</tr>
<tr>
<td>WHO stage 4</td>
<td>4.9% (n=21)</td>
<td>4.7% (n=10)</td>
<td>1.00</td>
</tr>
<tr>
<td>MDR-TB cases (%)</td>
<td>3.5% (n=15)</td>
<td>3.3% (n=7)</td>
<td>1.00</td>
</tr>
</tbody>
</table>
Outcome at halt of sequential arm: Mortality rates

<table>
<thead>
<tr>
<th></th>
<th>Integrated Treatment Arm n = 429</th>
<th>Sequential Treatment Arm n = 213</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of deaths</td>
<td>25</td>
<td>27</td>
</tr>
<tr>
<td>Person-years of follow-up</td>
<td>466</td>
<td>222</td>
</tr>
<tr>
<td>Mortality rate per 100 person-years</td>
<td>5.4</td>
<td>12.1</td>
</tr>
</tbody>
</table>

Hazard Ratio: 0.44 (95% CI: 0.25 to 0.79); p = 0.003

56% lower mortality with integrated TB-HIV treatment
Kaplan-Meier survival curve: SAPiT trial

- **Sequential Arm**
- **Integrated Arm**

**Months Post-Randomization**

- Intensive Phase of TB treatment
- Continuation Phase of TB treatment
- Post -TB Treatment
Mortality rates in CD4 count strata

- Reduction in mortality in the Integrated arm is present in patients with CD4 ≤ 200 and patients with CD4 > 200 cells/mm³

<table>
<thead>
<tr>
<th>CD4 count</th>
<th>≤ 200 cells/mm³</th>
<th>&gt; 200 cells/mm³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Integrated arm:</td>
<td></td>
<td></td>
</tr>
<tr>
<td># dead/ py (n)</td>
<td>23/281 (273)</td>
<td>2/186 (156)</td>
</tr>
<tr>
<td>Mortality rate (95% CI)</td>
<td>8.2 (5.2 - 12.3)</td>
<td>1.1 (0.1 - 3.9)</td>
</tr>
<tr>
<td>Rate Ratio (95% CI)</td>
<td>0.53 (0.28-1.01)</td>
<td>0.15 (0.02-0.86)</td>
</tr>
<tr>
<td>p</td>
<td>p=0.051</td>
<td>p=0.022</td>
</tr>
</tbody>
</table>

| Sequential arm: |                 |                 |
| # dead / py (n) | 21/137 (138)    | 6/86 (75)       |
| Mortality rate (95% CI) | 15.3 (9.57 - 23.5) | 7.0 (2.6 -15.3) |
| Rate Ratio (95% CI) | 0.53 (0.28-1.01) | 0.15 (0.02-0.86) |
| p               | p=0.051         | p=0.022         |
## Incidence of IRIS and ART adherence

<table>
<thead>
<tr>
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<th>Integrated arm</th>
<th>Sequential arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>% with IRIS #</td>
<td>12.1% (52/429)</td>
<td>3.8% (8/213)*</td>
</tr>
<tr>
<td>Hospitalization due to IRIS</td>
<td>10/52</td>
<td>0/8</td>
</tr>
<tr>
<td>Viral load &lt;1000 at 12 mths #</td>
<td>91.0% (201/221)</td>
<td>80.0% (72/90)</td>
</tr>
<tr>
<td>ART Adherence (pill count)</td>
<td>(n = 344)</td>
<td>(n = 132)</td>
</tr>
<tr>
<td>&lt; 90%</td>
<td>3.2% (11)</td>
<td>5.3% (7)</td>
</tr>
<tr>
<td>90-95%</td>
<td>6.4% (22)</td>
<td>7.6% (10)</td>
</tr>
<tr>
<td>&gt;95%</td>
<td>90.4% (311)</td>
<td>87.1% (115)</td>
</tr>
</tbody>
</table>

*Note: 83% Integrated arm vs 62% Sequential arm patients had initiated ART – data provisional*
# TB outcomes in SAPiT trial

<table>
<thead>
<tr>
<th>TB Outcome</th>
<th>Integrated arm n = 331 % (# cases)</th>
<th>Sequential arm n = 165 % (# cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cure</strong></td>
<td>60.7% (201)</td>
<td>59.4% (98)</td>
</tr>
<tr>
<td><strong>Successful completion</strong></td>
<td>17.5% (58)</td>
<td>13.9% (23)</td>
</tr>
<tr>
<td><strong>Successfully treated</strong></td>
<td>78.2% (259)</td>
<td>73.3% (121)</td>
</tr>
<tr>
<td><strong>Died</strong></td>
<td>5.7% (19)</td>
<td>9.7% (16)</td>
</tr>
<tr>
<td><strong>Treatment interruption</strong></td>
<td>3.9% (13)</td>
<td>7.9% (13)</td>
</tr>
<tr>
<td><strong>Treatment failure</strong></td>
<td>0.6% (2)</td>
<td>0.6% (1)</td>
</tr>
<tr>
<td><strong>Unknown</strong></td>
<td>11.5% (38)</td>
<td>8.5% (14)</td>
</tr>
</tbody>
</table>

p-value = 0.26
Conclusions

- Clinical trial evidence for combining TB & HIV treatment - reduces mortality by 56% in co-infected patients with CD4 < 500
- IRIS cases and hospitalizations increased by initiation of ART during TB treatment
- TB outcomes similar in both arms - mortality in the sequential treatment arm occurs late - mainly after TB treatment is completed, hence TB program is not aware
- Viral suppression (VL<1000) at 12 months higher in the Integrated treatment arm
- When to start ART during TB treatment?
  Awaiting completion of the SAPiT trial - the 2 integrated treatment arms are continuing…….
Limitations

- All-cause mortality: underestimates the potential impact of integrated HIV-tuberculosis treatment on deaths related only to tuberculosis and HIV.
- Ambulant adult patients enrolled.
- Focus on smear pulmonary PTB.
- Empiric confirmation of results required in patients with SNTB, EPTB, and in patients with more severe form of TB eg admitted patients, disseminated TB etc.
Implications of the findings

- **Programmatic implementation implications:**
  - All TB patients should be offered an HIV test & CD4 count
  - TB-HIV co-infected patients with CD4 <500 should be initiated on ART during TB treatment
  - Vigilance for the diagnosis and management of IRIS & toxicities
  - Monitor the proportion of TB-HIV patients on ART as an indicator of the performance of ART rollout programs

- **Implementation in South Africa:**
  - ~150,000 more TB patients initiated on ART annually
  - ~10,000 deaths averted
Acknowledgements

- 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: Wafaa El-Sadr, Gerald Friedland, Gavin Churchyard, Doug Taylor & Mark Weaver
- KwaZulu-Natal Provincial Department of Health
- University of KwaZulu-Natal & Columbia University

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