New data in HIV/TB and role of the Working Group

Beijing, November 11, 2011
What is new in ...

- Timing of ART start in TB patients
- Use of new ART drugs in TB patients
- Use of ART to prevent TB
Reluctance to start ART in TB patients

1. CD4 high and ART not needed
2. ART needed but not urgent because co-treatment

- Increases risk for TB immune reconstitution disease
- Increases drug toxicity from ART and TB
- Could adversely affect adherence for either TB or HIV
- Could reduce ART efficacy because of drug interactions
SAPIT Study

- 642 HIV+ adults in Durban, South Africa
- AFB smear + pulmonary TB
- CD4 <500
- Randomized to
  - ART during TB therapy at 2 weeks
  - ART during TB therapy after induction
  - ART after TB therapy completion

Mortality reduced when ART started during vs. after TB treatment: SAPIT

When should ART be started during TB treatment? 3 RCTs-- CAMELIA, STRIDE, and integrated arms of SAPIT

Immediate ART” (within 2 weeks)  
TB treatment
ART

“Early ART” (2-3 months)
TB treatment
ART

### 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)

Greater reduction in mortality at lower CD4

All studies showed significant reduction in death/AIDS among those with CD4 < 50

Timing is everything – why does a 6 week delay in ART matter so much?

[Graph showing the proportion of patients with AIDS/Death over weeks since randomization for different groups: Immediate (CD4 < 50), Immediate (CD4 => 50), Early (CD4 < 50), Early (CD4 => 50).]

116 Events in 806 Participants

<table>
<thead>
<tr>
<th>N at risk</th>
<th>0</th>
<th>8</th>
<th>16</th>
<th>24</th>
<th>32</th>
<th>40</th>
<th>48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immed</td>
<td>368</td>
<td>346</td>
<td>341</td>
<td>335</td>
<td>324</td>
<td>226</td>
<td></td>
</tr>
<tr>
<td>Early</td>
<td>371</td>
<td>342</td>
<td>329</td>
<td>325</td>
<td>318</td>
<td>218</td>
<td></td>
</tr>
</tbody>
</table>
Are there any trade-offs or benefits for starting ART immediately?

- Rates of Immune Reconstitution
- ART response
- Drug toxicity
- TB response
TB IRIS Greater in Immediate vs Early Arms

- Immediate: p=0.009
- Early: p=0.02
HIV RNA and CD4 Responses Similar at 48 weeks

HIV RNA suppression 74% at 48 weeks
No difference between arms

CD4 change from entry 156 cells/mm$^3$
No difference between arms
**Toxicity similar between immediate and early arms**

<table>
<thead>
<tr>
<th>Event (%)</th>
<th>Immediate</th>
<th>Early</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constitutional</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Respiratory</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Cardiac/Circulatory</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>4</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Skin</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Neurological</td>
<td>5</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>ANC &lt; 750/mm³ *</td>
<td>9</td>
<td>17</td>
<td>13</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>7</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Platelets</td>
<td>&lt;1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Liver transaminase &gt; 5x UNL</td>
<td>6</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td><strong>ANY</strong></td>
<td>44</td>
<td>47</td>
<td>46</td>
</tr>
</tbody>
</table>

*P<0.05
Does immediate ART enhance clearance of TB?

- No differences in TB Rx response by ART use
- No TB therapy failures occurred in either study arm
- TB recurrences: ART = 3, No ART = 4 (p = 0.5)

![Graphs showing time to MTB Culture Negative and Time to AFB Smear Negative with no difference between ART and No ART groups.](Chamie, CID, 2010)
What about other populations?

- High CD4 populations– PART study
- TB Meningitis– Viet Nam study
- Children– No data
PART Study– CD4>350 population

- 232 HIV+ adults in Kampala, Uganda
- Confirmed (AFB smear + or culture) TB
- CD4>350
- Randomized to ART (abacavir/3TC/zidovudine)
  - Immediately for 6 months
  - Start when CD4 reaches 250

Survival probability

0.0 0.5 0.6 0.7 0.8 0.9 1.0

Months since randomization

0 6 12 18 24 30 36

Wilcoxon P-value : 0.06

Intervention
Control

6 mo
Wilcoxon
p=0.09

12 mo
Wilcoxon
p=0.03

Time to AIDS/Death

Time to clinical event slower with immediate ART start

69% reduction in clinical outcomes
(95% CI: -51%, 93%)


TB Meningitis – Viet Nam study

**Study Design**
- 253 HIV+ adults
- TB meningitis
- Immediate or early (2 months) ART
- Adjunctive steroids
- Primary endpoint: mortality at 9 months

**Population**
- CD4 44 (16-84)
- TB cx + 60%
- TB MDR 5%

Torok, CID, 2011
TB meningitis: No benefit to immediate vs. early ART

58% mortality at 9 months

Torok, CID, 2011
Summary– Timing of ART

- HIV and TB co-treatment reduces AIDS/mortality at all CD4
- It is safe to start ART at onset of TB
- There is mortality benefit to start ART at 2 (vs 8) weeks in 1 study when CD4 at start of TB < 200
- AIDS/Mortality benefit to start ART at 2 (vs 8 to 12) weeks only when CD4 at start of TB < 50 in 2 other studies
- Immune reconstitution higher when CD4 lower and when ART is started earlier
- 1 study showed no benefit of starting ART at 2 vs 8 weeks in HIV infected patients with TB meningitis
ART and TB Drug Interactions– General Principles

- Rifampin potent inducer of CYP3A4 and interacts with a number of ART drugs
- Rifabutin is a less potent inducer of CYP3A4 than rifampin and preferred TB rifamycin agent when rifampin cannot be used
- Using rifabutin complicates TB management because not co-formulated
- ART+ TB treatment regimens may call for adjustment of ART dose, rifabutin dose or both
- Data covering all possible drug interactions are incomplete
# Dose Adjustments with ART and TB Medications

<table>
<thead>
<tr>
<th></th>
<th>Rifampin</th>
<th>Rifabutin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz</td>
<td></td>
<td>Increase rifabutin</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>No NVP lead in</td>
<td></td>
</tr>
<tr>
<td>Etravirine</td>
<td></td>
<td>Increase RPV</td>
</tr>
<tr>
<td>Rilpivirine</td>
<td></td>
<td>Decrease rifabutin</td>
</tr>
<tr>
<td>DRV/r or ATZ/r</td>
<td></td>
<td>Decrease rifabutin</td>
</tr>
<tr>
<td>Lopinavir/r</td>
<td>Increase LPV/r</td>
<td>Decrease rifabuin</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>Increase RTG</td>
<td></td>
</tr>
<tr>
<td>Maraviroc</td>
<td>Increase MVC</td>
<td></td>
</tr>
<tr>
<td>Enfurvitide</td>
<td></td>
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</tr>
</tbody>
</table>
Efficacy and Safety of ART in HIV+: HPTN 052

HIV-infected subjects with CD4 350 to 550 cells/mm$^3$
Serodiscordant couples

Immediate ART
CD4 350-550

Delayed ART
CD4 <250

Primary Clinical Endpoint
WHO stage 4 clinical events, pulmonary tuberculosis, severe bacterial infection and/or death

Cohen, NEJM, 2011
HIV-1 RNA and CD4 Over Time in HPTN 052 study

Cohen, NEJM, 2011
HR: 0.6 [0.4, 0.9], P=0.01

Probability of Death, AIDS or TB

Delayed Immediate

Failure Probability

Years since randomization

Cohen, NEJM, 2011
### Clinical Events and Median CD4 Levels

What were clinical events and at what CD4 did they occur?

<table>
<thead>
<tr>
<th>Event</th>
<th>Immediate N=53</th>
<th>Median CD4</th>
<th>Delayed N=76</th>
<th>Median CD4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (N=129)</td>
<td>53</td>
<td>506</td>
<td>76</td>
<td>340</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>17</td>
<td>518</td>
<td>33</td>
<td>316</td>
</tr>
<tr>
<td>Severe bacterial infection</td>
<td>16</td>
<td>551</td>
<td>11</td>
<td>337</td>
</tr>
<tr>
<td>Death</td>
<td>10</td>
<td>476</td>
<td>13</td>
<td>372</td>
</tr>
<tr>
<td>Chronic herpes simplex</td>
<td>3</td>
<td>753</td>
<td>7</td>
<td>413</td>
</tr>
<tr>
<td>Bacterial pneumonia (recurrent)</td>
<td>2</td>
<td>445</td>
<td>2</td>
<td>220</td>
</tr>
<tr>
<td>Esophageal candidiasis</td>
<td>2</td>
<td>301</td>
<td>2</td>
<td>256</td>
</tr>
<tr>
<td>Cervical carcinoma</td>
<td>0</td>
<td>--</td>
<td>2</td>
<td>445</td>
</tr>
<tr>
<td>Kaposi’s sarcoma</td>
<td>1</td>
<td>459</td>
<td>1</td>
<td>364</td>
</tr>
<tr>
<td>Wasting syndrome</td>
<td>0</td>
<td>--</td>
<td>2</td>
<td>366</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>488</td>
<td>3</td>
<td>217</td>
</tr>
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</table>
## Tuberculosis

<table>
<thead>
<tr>
<th></th>
<th>Immediate</th>
<th></th>
<th>Delayed</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Median CD4</td>
<td>N</td>
<td>Median CD4</td>
</tr>
<tr>
<td></td>
<td>[ incidence ]</td>
<td></td>
<td>[ incidence ]</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>17</td>
<td>518</td>
<td>33</td>
<td>316</td>
</tr>
<tr>
<td><strong>Pulmonary TB</strong></td>
<td>14</td>
<td>521</td>
<td>16</td>
<td>295</td>
</tr>
<tr>
<td></td>
<td>[ 0.8 /100PY ]</td>
<td></td>
<td>[ 0.9 /100PY ]</td>
<td></td>
</tr>
<tr>
<td><strong>Extrapulmonary TB</strong></td>
<td>3</td>
<td>443</td>
<td>17</td>
<td>342</td>
</tr>
<tr>
<td><strong>Peripheral Lymph Nodes</strong></td>
<td>2</td>
<td>432</td>
<td>4</td>
<td>492</td>
</tr>
<tr>
<td><strong>Abdominal</strong></td>
<td>0</td>
<td>--</td>
<td>8</td>
<td>324</td>
</tr>
<tr>
<td><strong>Pleural</strong></td>
<td>1</td>
<td>443</td>
<td>3</td>
<td>316</td>
</tr>
<tr>
<td><strong>Skeletal</strong></td>
<td>0</td>
<td>--</td>
<td>1</td>
<td>417</td>
</tr>
<tr>
<td><strong>Meningeal</strong></td>
<td>0</td>
<td>--</td>
<td>1</td>
<td>302</td>
</tr>
</tbody>
</table>
Many other cohort studies correlate ART with reduced TB rates

Lawn, 2011
Conclusions

- New studies shed light into the optimal timing of ART
- Optimal timing of ART is a key approach to reducing TB mortality in HIV patients
- Implementation of these findings must be a major focus and will require country policy change and programmatic adaptations with attention to HIV-TB drug interactions and management of TB IRIS
- ART is the most powerful tool for TB prevention and early ART should be supported as part of HIV-TB policy