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)

- **CAMELIA**
  - Immediate: 34% ↓, p=0.004
  - Early: 19% ↓, p=0.45

- **STRIDE**
  - Immediate: 11% ↓, p=0.73
  - Early: 19% ↓, p=0.45

- **SAPIT**
  - Immediate: 11% ↓, p=0.73
  - Early: 19% ↓, p=0.45

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 proportion with AIDS/Death over weeks since randomization, with lines for Immediate (CD4 < 50), Immediate (CD4 => 50), Early (CD4 < 50), and Early (CD4 => 50)].

116 Events in 806 Participants

N at risk
Immediate 405
Early 401
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

<table>
<thead>
<tr>
<th></th>
<th>Immediate</th>
<th>Early</th>
</tr>
</thead>
<tbody>
<tr>
<td>STRIDE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRD</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>p=0.009</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Immediate</th>
<th>Early</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAPI T</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRD</td>
<td>18</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>p=0.02</td>
<td></td>
</tr>
</tbody>
</table>
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/mm³
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>ANY</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)

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

Time to clinical event slower with immediate ART start

Survival probability

Time to AIDS/Death

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

HIV-infected subjects with CD4 350 to 550 cells/mm³
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
Probability of Death, AIDS or TB

HR: 0.6 [0.4, 0.9], P=0.01

Cohen, NEJM, 2011
What were clinical events and at what CD4 did they occur?

<table>
<thead>
<tr>
<th>Event</th>
<th>Immediate N</th>
<th>Median CD4</th>
<th>Delayed N</th>
<th>Median CD4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (N=129)</td>
<td>53</td>
<td>506 (409 - 625)</td>
<td>76</td>
<td>340 (283 – 418)</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>
</tbody>
</table>
# Tuberculosis

<table>
<thead>
<tr>
<th></th>
<th>Immediate</th>
<th></th>
<th></th>
<th>Delayed</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>17 [ 1 /100PY ]</td>
<td>518</td>
<td>33 [ 1.9 /100PY]</td>
<td>316</td>
<td></td>
</tr>
<tr>
<td><strong>Pulmonary TB</strong></td>
<td>14 [ 0.8 /100PY ]</td>
<td>521</td>
<td>16 [ 0.9 /100PY]</td>
<td>295</td>
<td></td>
</tr>
<tr>
<td><strong>Extrapulmonary TB</strong></td>
<td>3 [ 0.2 /100PY]</td>
<td>443</td>
<td>17 [ 1 /100PY]</td>
<td>342</td>
<td></td>
</tr>
<tr>
<td>Peripheral Lymph Nodes</td>
<td>2</td>
<td>432</td>
<td>4</td>
<td>492</td>
<td></td>
</tr>
<tr>
<td>Abdominal</td>
<td>0</td>
<td>--</td>
<td>8</td>
<td>324</td>
<td></td>
</tr>
<tr>
<td>Pleural</td>
<td>1</td>
<td>443</td>
<td>3</td>
<td>316</td>
<td></td>
</tr>
<tr>
<td>Skeletal</td>
<td>0</td>
<td>--</td>
<td>1</td>
<td>417</td>
<td></td>
</tr>
<tr>
<td>Meningeal</td>
<td>0</td>
<td>--</td>
<td>1</td>
<td>302</td>
<td></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