Treating HIV and TB: New evidence, Challenges & Prospects
Pre-IAS International consultative meeting
on Transforming the HIV/TB response: defining the next 10 years
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Outline

• Review the recent data on when to start ART in TB/HIV co-infected patients
• Obstacles to implementation
• PEPFAR Program (MJAP) experience
• Opportunities for scale up of rapid ART start in TB/HIV in Africa.
Mortality reduced when ART started during vs. after TB treatment: SAPIT

Trial Design for CAMELIA, STRIDE, and integrated arms of SAPIT

"Early ART (within 2 weeks)

TB treatment

ART

Primary endpoint

HIV+ TB

Later ART (2-3 months)

TB treatment

ART

Study week

0 8 24 48

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)

All studies showed significant reduction in death/AIDS among those with \textbf{CD4 < 50}.

Are there any risks for starting ART at 2 weeks?

- Immune Reconstitution
- ART response (no difference)
- Drug toxicity (no difference)
- TB response (no difference)
TB IRIS Greater in Early vs Later Arms

Blanc, NEJM, 2011; Havlir, NEJM, 2011,
Summary points

• Delaying ART until end of TB treatment increases mortality.

• Critical that ART is started within 2 weeks among TB/HIV with advanced immune suppression (CD4 <50) and by 8 weeks in others

• WHO recommendation:
  – All TB patients co-infected with HIV should be offered ART irrespective of CD4 cell count no later than 8 weeks and by 2 weeks for CD4 <50
This is going to be challenging
Obstacles- Provider factors

- In HIV clinics, patients are not routinely screened for TB symptoms. Reasons include:
  - work overload
  - inadequate provider knowledge about assessing smear-negative and extra-pulmonary TB
- Lack of knowledge about results of clinical trials
- HIV and TB providers lack knowledge in TB-HIV treatment and how to co-manage patients on ART who later develop TB.
- Tendency to stop ART in co-infected patients until after 2 months of TB treatment.
- Management of side effects of HAART and anti TB drugs particularly hepato-toxicity
Diagnostic Barriers

- High proportion of negative sputum smears in HIV
- Revisiting facilities for the two requisite sputum smear checks.
- High costs for chest X-rays and
- Inaccessibility of more accurate diagnostic tests; Mycobacterial cultures, GeneXpert
Clinical and Radiographic Factors Do Not Accurately Diagnose Smear-Negative Tuberculosis in HIV-infected Inpatients in Uganda: A Cross-Sectional Study

J. Lucian Davis¹,³,⁴,⁵,William Worodria⁵,⁶, Harriet Kismombo⁷, John Z. Metcalfe¹,³,⁴, Adithya Cattamanchi¹,³,⁴,⁵, Michael Kawooya⁷, Rachel Kyeyune⁵, Saskia den Boon⁵, Krista Powell³, Richard Okello⁷, Samuel Yoo⁵,⁶, Laurence Huang¹,²,³,⁵

- 216 adult HIV patients who were sputum AFB negative
- No clinical and radiographic criteria were predictive of culture proven TB
Obstacles- Structural/System factors

- Guidelines take long to be adapted and implemented
- Inadequate dissemination of TB-HIV policy guidelines
- ARV shortages particularly EFV
- TB and ART failure…. Lack rifabutin
- Separate clinic days or locations for TB and HIV services
- Work-up of patient and preparation for HAART takes longer than it should
Obstacles: Patient factors

- Psychological impact of multiplicity of drugs with inadequate nutrition
- Presence of serious co-morbidities other than TB.
- Some patients are too ill to swallow many pills
PEPFAR Program (MJAP) experience
Progress in TB-HIV in Uganda

- Improving indicators
  - Proportion TB patients tested
  - Proportion receiving cotrimoxazole
  - Proportion receiving HAART biggest gaps
  - Differential level of decentralisation of TB and ART services
Figure 2: Kaplan-Meier estimates of time from TB diagnosis to ART initiation in a MJAP clinic in southwestern Uganda. Estimates are stratified by CD4 level at the time of TB diagnosis.
Prospects
Scale up of early ART start in TB

- Supply of both HAART and Anti-TB drugs in one stop centre increases uptake
- ‘one-stop service’, which entails provision of TB and HIV diagnosis and treatment services in the same setting by the same clinicians (the Khayelitsha model and KwaZulu-Natal) OR improving proximity and interclinic referrals
Scale up of early ART start in TB

• Training
• Policy/guideline dissemination
• Clear messages such as Test and Treat all TB/HIV co-infected patients
• Must incorporate routine screening for cryptococcal antigenemia in TB/HIV patients, treatment for those identified to be positive
• Implementation science studies to better understand overcoming the obstacles
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Univariate HR, (95% CI)</th>
<th>P</th>
<th>Adjusted HR, (95% CI)</th>
<th>P</th>
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<tbody>
<tr>
<td>Age</td>
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<tr>
<td>≥40 versus, yrs 1.24 (0.72 to 2.14)</td>
<td>0.438</td>
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<tr>
<td>&lt;40 years</td>
<td>1</td>
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<tr>
<td>Sex</td>
<td></td>
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<tr>
<td>Males</td>
<td>1.84 (1.02 to 3.31)</td>
<td>0.043</td>
<td>2.19 (1.19 to 4.03)</td>
<td>0.011</td>
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<tr>
<td>Females</td>
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<tr>
<td>BMI (kg/m²)*</td>
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<tr>
<td>&lt;18.5</td>
<td>1.12 (0.65 to 1.93)</td>
<td>0.685</td>
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<tr>
<td>≥18.5</td>
<td>1</td>
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<td>Recruitment site</td>
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<tr>
<td>In-patient</td>
<td>2.10 (1.19 to 3.70)</td>
<td>0.010</td>
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<tr>
<td>Outpatient</td>
<td>1</td>
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<tr>
<td>Hemoglobin (g/L)</td>
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<tr>
<td>&lt;100</td>
<td>1.52 (0.83 to 2.77)</td>
<td>0.173</td>
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<tr>
<td>≥100</td>
<td>1</td>
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<td>CD4 counts (cells/µL)</td>
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<tr>
<td>&lt;50</td>
<td>1.70 (0.97 to 2.95)</td>
<td>0.062</td>
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<tr>
<td>≥50</td>
<td>1</td>
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<td>TB category</td>
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<tr>
<td>EPTB</td>
<td>0.92 (0.48 to 1.75)</td>
<td>0.792</td>
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<tr>
<td>PTB</td>
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<tr>
<td>Tuberculin skin test</td>
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<tr>
<td>Negative</td>
<td>2.84 (1.21 to 6.67)</td>
<td>0.016</td>
<td>2.59 (1.10 to 6.12)</td>
<td>0.030</td>
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<tr>
<td>Positive</td>
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<tr>
<td>ART†</td>
<td></td>
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<tr>
<td>No ART use</td>
<td>5.39 (2.80 to 10.38)</td>
<td>&lt;0.001</td>
<td>4.63 (2.37 to 9.03)</td>
<td>&lt;0.001</td>
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<tr>
<td>ART use</td>
<td>1</td>
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<tr>
<td>TB-IRIS†</td>
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<tr>
<td>Developed TB-IRIS</td>
<td>0.61 (0.26 to 1.44)</td>
<td>0.257</td>
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<tr>
<td>No TB-IRIS</td>
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<tr>
<td>Serum CrAG*</td>
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<tr>
<td>Positive</td>
<td>4.40 (1.58 to 12.22)</td>
<td>0.005</td>
<td>4.27 (1.50 to 12.13)</td>
<td>0.006</td>
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<tr>
<td>Negative</td>
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MJAP HIV clinic March 1\textsuperscript{st} to May 31\textsuperscript{st} 2012

• 18 (5.7\%) of 316 TB suspects were sputum positive
• 6 out of 18 were already on ART
• Median CD4=260 (only 2 below CD4 50 cells)
• Average ART start was 20 days (range 11-35 days)
Thank you

Acknowledge: Drs. Havlir, Geng, Semitala, Kirenga, Worodria and Okwera