The role of ART and IPT in TB prevention: Latest updates

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Johns Hopkins University

Consortium to Respond Effectively To the AIDS-TB Epidemic (CREATE)
Effect of 6-12 months of IPT on TB: meta-analysis of clinical HIV trials

Relative risk, 95% CI

- Placebo: 0.36
- Overall: 0.67
- TST+: 1.0
- TST-: 0.86

Akolo 2010, Cochrane review
2010 WHO Guidelines for TB Preventive Therapy in HIV

• INH preventive therapy (IPT) should be given to all HIV+ patients in high burden areas once active TB is excluded
  – Includes pregnant women, children and those on ART

• TST (PPD) can be used to identify those most likely to benefit from IPT

• Duration of therapy – at least 6 months, 36 months may be more effective (US – 9 months)
Options for Improving Uptake of TB Preventive Therapy

• Strengthen national guidelines and promotion of INH preventive therapy
• New drugs and/or drug regimens
  – Shorter duration of treatment
  – Reduced risk of toxicity
  – Prevention of emergence of resistance
  – Treatment of latent MDR/XDR infections
• Novel treatment delivery strategies
New Regimens to Prevent Tuberculosis in Adults with HIV Infection

Neil A. Martinson, M.B., B.Ch., M.P.H., Grace L. Barnes, B.S.N., M.P.H., Lawrence H. Moulton, Ph.D., Reginah Msandiwa, R.N., Harry Hausler, M.D., Ph.D., Malathi Ram, Ph.D., James A. McIntyre, M.B., B.Ch., Glenda E. Gray, M.B., B.Ch., and Richard E. Chaisson, M.D.
Project Site – Perinatal HIV Research Unit, Chris Hani Baragwanath Hospital, Soweto, South Africa
Novel Regimens for TB Preventive Therapy for HIV+ Adults with a Positive TST

Short (12 weeks)
- Rifapentine 900mg +INH 900mg  weekly – 12 doses
  - Directly observed in clinic
- Rifampin 600 mg+INH 600mg twice weekly – 24 doses
  - directly observed, in clinic

Long (throughout duration of trial, up to 6 years)
- INH 300mg daily continuously – may be effective to prevent re-infection

Comparator
- INH 300mg daily for 6 months – standard of care
## Primary Outcomes: Event Rates by Study Arm

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RPT/INH-3 (N=329)</th>
<th>RIF/INH-3 (N=329)</th>
<th>INH-cont (N=164)</th>
<th>INH-6 (N=328)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median F/U (yrs)</td>
<td>3.98</td>
<td>3.99</td>
<td>3.81</td>
<td>3.78</td>
</tr>
<tr>
<td><strong>TB or death</strong></td>
<td><strong>3.03</strong></td>
<td><strong>2.87</strong></td>
<td><strong>2.67</strong></td>
<td><strong>3.53</strong></td>
</tr>
<tr>
<td>Rate ratio 95% CI</td>
<td>0.86, 0.53-1.4</td>
<td>0.81, 0.50-1.3</td>
<td>0.76, 0.39-1.4</td>
<td>1 (ref)</td>
</tr>
</tbody>
</table>
“As treated” analysis – risk of TB or death

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH-6</td>
<td>1(ref)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RPT/INH</td>
<td>0.85</td>
<td>0.54, 1.3</td>
<td>0.48</td>
</tr>
<tr>
<td>RIF/INH</td>
<td>0.81</td>
<td>0.52, 1.3</td>
<td>0.37</td>
</tr>
<tr>
<td>INH-Cont</td>
<td>0.32</td>
<td>0.12, 0.80</td>
<td>0.015</td>
</tr>
</tbody>
</table>
# Resistance Testing of Isolates

<table>
<thead>
<tr>
<th>Arm</th>
<th>Resistance Testing (N)</th>
<th>MDR (N)</th>
<th>Resistant to</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>INH (N)</td>
<td>R (N)</td>
<td>Strept. (N)</td>
<td>E (N)</td>
<td></td>
</tr>
<tr>
<td>RPT/INH-3</td>
<td>20/23</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>RIF/INH-3</td>
<td>16/24</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>INH-6</td>
<td>14/19</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>INH/Cont</td>
<td>7/7</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>57/73 (78%)</strong></td>
<td><strong>2</strong></td>
<td><strong>3</strong></td>
<td><strong>3</strong></td>
<td><strong>2</strong></td>
<td><strong>1</strong></td>
<td></td>
</tr>
</tbody>
</table>

- No evidence for selection of resistant strains
Conclusions

- Short courses of RPT/INH or RIF/INH are not superior but appear to be as effective as INH for 6 months.
- Lifelong INH is more effective when taken, but non-adherence limits benefit.
- All regimens were well tolerated.
- There was no evidence of selection for resistance.
The Prevent TB Study
TB Trials Consortium Study 26

3 months of once-weekly rifapentine plus INH vs. 9 months of daily INH for treatment of latent TB infection: Results of a multi-center, randomized clinical trial


Funded by the Centers for Disease Control and Prevention
## Clinical and Demographic Characteristics
### MITT Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>9H</th>
<th>3HP</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=3,745</td>
<td>N=3,986</td>
<td></td>
</tr>
<tr>
<td><strong>Indication for TLI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Close contact</td>
<td>2,609 (70)</td>
<td>2,857 (72)</td>
</tr>
<tr>
<td>Recent TST converter</td>
<td>972 (26)</td>
<td>953 (24)</td>
</tr>
<tr>
<td>HIV-infected</td>
<td>74 (2)</td>
<td>87 (2)</td>
</tr>
<tr>
<td>Fibrosis on CXR</td>
<td>90 (2)</td>
<td>89 (2)</td>
</tr>
<tr>
<td><strong>Co-morbid liver disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV</td>
<td>97 (3)</td>
<td>99 (3)</td>
</tr>
<tr>
<td>HBV</td>
<td>60 (2)</td>
<td>42 (1)</td>
</tr>
</tbody>
</table>

Sterling et al., ATS 2011
Conclusions

• The effectiveness of 3RPT/INH is non-inferior to 9INH
  – 97.5% CI of difference = 0.01%; margin = 0.75%
  – There is a suggestion that the 3RPT/INH TB rate (0.19%) is lower than 9INH (0.43%)

• The completion rate of 3RPT/INH (81.9%) is significantly higher than 9INH (69.5%)
Botswana IPT Trial 2004–2009

- Randomized, double-blind, placebo-controlled trial
- Approximately 2,000 patients enrolled
- TST+ and TST- patients included
- ART provided as needed through national program
  - When CD4 <200 cells/μL

Healthy PLHIV

<table>
<thead>
<tr>
<th>Isoniazid</th>
<th>Placebo</th>
<th>6 IPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months</td>
<td>± 30 months</td>
<td>36 IPT</td>
</tr>
</tbody>
</table>
## Efficacy of 36 Months IPT vs 6 Months IPT for reducing TB incidence

<table>
<thead>
<tr>
<th>Sub-group</th>
<th>TB rate 36 IPT</th>
<th>TB rate 6 IPT</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MITT (N=1,995)</td>
<td>All</td>
<td>0.72</td>
<td>1.26</td>
</tr>
<tr>
<td></td>
<td>TST+</td>
<td>0.57</td>
<td>2.22</td>
</tr>
<tr>
<td></td>
<td>TST-</td>
<td>0.76</td>
<td>1.01</td>
</tr>
</tbody>
</table>

TB incidence rate per 100 person-years; * \( P<0.05 \)

ART reduced the risk of TB additively by 50% in both arms and was independent of IPT’s protective effect

Samandari et al., Lancet, April 11, 2011
Continuous IPT for 36 Months Prevents TB Better than IPT for 6 Months in TST-positive PLHIV

Samandari et al., Lancet, April 11, 2011
Primary Isoniazid Prophylaxis against Tuberculosis in HIV-Exposed Children

Shabir A. Madhi, M.D., Ph.D., Sharon Nachman, M.D., Avy Violari, M.D., Soyeon Kim, Sc.D., Mark F. Cotton, M.D., Ph.D., Raziya Bobat, M.D., Patrick Jean-Philippe, M.D., George McSherry, M.D, and Charles Mitchell, M.D., for the P1041 Study Team
Pediatric INH Primary Preventive Therapy Study

- HIV+ and HIV- South African children – 91-120 days old
- Vaccinated with BCG at birth
- Access to HAART for HIV+
- INH 10-20 mg/kg or placebo
- Open-label INH if household TB exposure
- Followed for 96-108 weeks
TB or death during follow up

- **HIV+**
  - INH group – 19.0%
  - Placebo group – 19.3%
  - Overall TB incidence = 12.1 per 100 PY

- **HIV-**
  - INH group – 10%
  - Placebo group – 11%
  - Overall TB incidence = 4.1 per 100 PY

The TB/HIV in Rio Study: A Clinic-Randomized Trial of INH Preventive Therapy in HIV+ Patients

Betina Durovni, Jonathan Golub, Lawrence Moulton, Valeria Saraceni, Richard Chaisson
Intervention

• Training for 2 clinics every other month
• Implementation of TB screening and TST policy for all HIV-infected patients
• TST to be done for all eligible clinic patients
  – No prior TB history
  – No prior IPT
  – No prior +TST

• IPT x 6 months for all TST+ without active TB and all contacts of active TB cases
THRio Study Timeline
Stepped-Wedge Design

Control period

Intervention period

Intervention and Follow-up Period (for all clinics)

Sep 05
Jan 08
Dec 09
Time to TST and Time to IPT Before and After THRio Intervention

- Time to TST and time to IPT are both markedly improved post-intervention

Durovni et al., AIDS 2010, 24 (suppl 5):S49–S56
### THRio Results: Unadjusted Cox Models

<table>
<thead>
<tr>
<th></th>
<th>Outcome</th>
<th>Cases</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intent To Treat</strong></td>
<td>TB</td>
<td>475</td>
<td>0.87 (0.68-1.10)</td>
<td>0.233</td>
</tr>
<tr>
<td></td>
<td>TB or Death</td>
<td>1313</td>
<td>0.72 (0.62-0.82)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Modified Intent To Treat (Stayers)</strong></td>
<td>TB</td>
<td>403</td>
<td>0.57 (0.44-0.76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>TB or Death</td>
<td>1073</td>
<td>0.56 (0.47-0.66)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

- Intent-to-treat – Among all eligibles
- Stayers – mITT - Among those remaining in clinic contact
  (Patients censored at the moment they go one year without a clinic contact)
Impact of ART on Risk of TB in Patients with HIV

Lawn et al., Int J Tbc Lung Dis 2011

Adjusted hazards of tuberculosis

Jones et al. 2000, USA
Girardi et al. 2000, Italy
Santoro-Lopes et al. 2002, Brazil
Badri et al. 2002, South Africa
Golub et al. 2007, Brazil
Miranda et al. 2007, Spain
Muga et al. 2007, Spain
Moreno et al. 2008, Spain
Golub et al. 2009, South Africa

Summary Hazard Estimate (n=37,879)
## Impact of early ART on rates of TB in HIV+ adults with initial CD4 counts between 350 and 550

**HPTN 052 Trial**

<table>
<thead>
<tr>
<th>Study Arm</th>
<th>TB Events</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early ART</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Extrapulmonary</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>All TB</td>
<td>17/886</td>
<td>(1.9%)</td>
</tr>
<tr>
<td><strong>Delayed ART</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Extrapulmonary</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>All TB</td>
<td>33/877</td>
<td>(3.7%)*</td>
</tr>
</tbody>
</table>

*P= 0.03

*Cohen et al., N Engl J Med 2011; on line supplement*
General Observations and Conclusions

- TB preventive therapy in high risk adults works and is necessary for TB control
- Short-course, rifapentine-based regimens are effective and well-tolerated
- Long-term INH is more efficacious but may be no more effective than short-course therapy in HIV-infected adults in Africa
- Population-based approaches are promising but challenging
- ART and IPT have additive effects in reducing the risk of TB
Thank you