TB Prevention for HIV Patients: Priorities and Ongoing Research Efforts

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What is Known – 1

- INH preventive therapy (IPT) reduces risk of TB in HIV+ people
  - by 62% in PPD+
  - By 36% overall
- Evidence of survival benefit in children and in adults in cohort studies
- Benefit of IPT *may* wane after 1-2 years in high prevalence settings
What is Known – 2

• HAART reduces TB risk, but not enough
• Risk of selecting for resistance with IPT appears very low
• Active TB can be ruled out by clinical or laboratory screening in most patients
• No evidence of increased toxicity with IPT and HAART
Efficacy of IPT in HIV+ Adults: Risk of TB

- 11 randomised trials with 8,130 HIV+ participants → overall reduction in TB = 36%, reduction PPD+ = 62%

Woldehanna and Volmink, Cochrane Review 2006
Efficacy of Secondary INH PT in HIV+ Patients

- Three studies show benefit of INH PT following treatment of active TB in HIV+ patients

### Incidence Rate Ratios & 95% CI

<table>
<thead>
<tr>
<th>Reference</th>
<th>Incidence Rate Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference</td>
<td>1.0</td>
<td>0.3</td>
</tr>
<tr>
<td>Haller (1999)</td>
<td>0.18</td>
<td>0.3</td>
</tr>
<tr>
<td>Fitzgerald (2000)</td>
<td>0.45</td>
<td></td>
</tr>
<tr>
<td>Churchyard (2002)</td>
<td>0.45</td>
<td></td>
</tr>
</tbody>
</table>

Woldehanna and Volmink, Cochrane Review 2006
Durability of TB Preventive Therapy Following Randomization

Mwinga et al., AIDS 1998;12:2447
Treatment of Latent TB in HIV+ Patients and Survival in Brazil

Fig. 1. Kaplan–Meier curves comparing survival according to the use of anti-tuberculosis chemoprophylaxis. The dashed vertical line indicates the median interval to the start of chemoprophylaxis.
Time to TB Diagnosis in the Khayelitsha Cohort

**Survival free of subsequent TB diagnosis**

<table>
<thead>
<tr>
<th></th>
<th>Pre-ART</th>
<th>Failed</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>1333</td>
<td>433</td>
<td>162</td>
</tr>
<tr>
<td>Failed</td>
<td>301</td>
<td>84</td>
<td>39</td>
</tr>
<tr>
<td>Survival</td>
<td>72 (69-74)</td>
<td>53 (49-57)</td>
<td>39 (34-44)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>ART</th>
<th>Failed</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>1243</td>
<td>493</td>
<td>187</td>
</tr>
<tr>
<td>Failed</td>
<td>165</td>
<td>32</td>
<td>11</td>
</tr>
<tr>
<td>Survival</td>
<td>85 (82-87)</td>
<td>76 (72-79)</td>
<td>68 (61-73)</td>
</tr>
</tbody>
</table>

**Cox HR for ART vs pre-ART**

\[ \text{Cox HR for ART vs pre-ART} = 0.41 (0.38 – 0.51) \]

Logrank \( p < 0.0001 \)

Boulle et al., 9th International workshop in HIV Observational Databases – Budapest, April 2005
TB Rates in HIV+ Patients With Access to ART and IPT in Rio de Janeiro

<table>
<thead>
<tr>
<th>Exposure category</th>
<th>Person-Years</th>
<th>TB cases</th>
<th>IR (per 100 PYs)</th>
<th>IRR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naïve</td>
<td>3,865</td>
<td>155</td>
<td>3.98 (3.38-4.67)</td>
<td>1.0</td>
</tr>
<tr>
<td>HAART only</td>
<td>11,627</td>
<td>221</td>
<td>1.91 (1.67-2.18)</td>
<td>0.48 (0.39-0.59)</td>
</tr>
<tr>
<td>IPT only</td>
<td>395</td>
<td>5</td>
<td>1.27 (0.41-2.95)</td>
<td>0.32 (0.10-0.76)</td>
</tr>
<tr>
<td>Both</td>
<td>1,253</td>
<td>10</td>
<td>0.80 (0.38-1.47)</td>
<td>0.20 (0.09-0.91)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>17,142</td>
<td>391</td>
<td>2.28 (2.06-2.52)</td>
<td></td>
</tr>
</tbody>
</table>

Golub et al., IAC Toronto, 2006
Ruling Out Active TB

• Symptom screening (cough, fever, chest pain)
  – Symptom screening of HIV+ pregnant women, followed by culture, detected active TB in 2.2%

• Chest X-ray
  – CXR screening of 563 asymptomatic HIV+ patients beginning IPT in Botswana yielded only 1 case
  – CXR of HIV+ gold miners increased sensitivity

• Sputum smear vs. culture
  – Smear has low sensitivity in screening setting, culture is superior

TB Preventive Therapy and Drug Resistance

- Review of 13 IPT trials with ~35,000 participants shows low risk of selecting resistance (RR 1.45, 95% CI 0.85-2.47)
- For INH-resistant LTBI, rifampin effective
- For MDR or XDR exposure, no regimen has been shown to be effective
- Future options for MDR and XDR
  - New agents: TMC 207, PA 824, FQs, others

Balcells et al. EID 2006;12:744; Nuermberger et al. AJRCCM 2005;172:1452
TB Prevention for HIV+ People: Priorities

- Alternatives to INH x 6-9 months
- IPT plus ART
- Screening algorithm to rule out active TB
- Diagnostic tests for latent TB
  - IGRA (Quantiferon, T-Spot TB)
- Assessment of risk of resistance
- Secondary preventive therapy
- Preventive therapy for MDR and XDR TB
Ongoing Studies

- Randomized, controlled clinical trials
- Cluster randomized trials
PHRU/JHU Trial of Novel TB Preventive Regimens for HIV+/PPD+ Adults in Soweto

• Patients: HIV+, PPD >5 mm, >18 y.o., CD4 >200

• Regimens
  – Rifapentine/INH weekly x 12 weeks
  – Rifampin/INH twice weekly x 12 weeks
  – INH daily indefinitely (lifelong)
  – INH daily x 6 months (control)

• Assumptions – superiority trial, INH-6 will be inferior to alternative regimens

• Sample size = 1148, randomized 2:2:1:2
• Fully enrolled in 2005
• Median follow up ~ 3 years
Botswana IPT Trial Study Design

Randomized Double-Blind Placebo Controlled Trial

2,000 participants - 1,000 per study arm

Healthy HIV+ adult

6 mo INH qd → 30 mo placebo

36 mo INH qd

CDC – BOTUSA Project
TBTC Study 26: RPT/INH vs INH for Contacts and HIV+/PPD+ Persons

- Phase III RCT
  - INH/Rifapentine weekly x 3 months
  - INH daily x 9 months
- Primary endpoint: TB incidence
- Design: equivalence trial
- Sample size = 4000 per arm
- Current enrollment ~6900
  - 184 HIV+
Thibela TB: Mass Preventive Therapy with INH in South African Gold Miners

- **Design:** Cluster randomized trial
- **Setting:** 16 mine shafts with 2-3000 workers each
  - Mines randomized to intervention or control
- **Intervention:** INH for all
  - Control = standard of care (VCT, IPT for HIV+)
- **Endpoint:** TB incidence and prevalence after 5 years
The THRiO Study: A Clinic - Randomized Trial of INH Preventive Therapy in HIV+ Patients

- 29 clinics randomized to time IPT policy initiated
- TB rates will be compared in clinics that have not yet phased-in IPT vs. those that have

### Intervention vs. Control

<table>
<thead>
<tr>
<th>Clinic</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>30</th>
<th>36</th>
<th>42</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td>29</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Follow-up

Month
TB Prevention for HIV+ People: Priorities

- Alternatives to INH x 6-9 months
- IPT plus ART
- Screening algorithm to rule out active TB
- Diagnostic tests for latent TB
  - IGRA (Quantiferon Gold IT, T-Spot TB)
- Assessment of risk of resistance
- Secondary preventive therapy
- Preventive therapy for MDR and XDR TB
- Operational research – why isn’t IPT given?
Need for Secondary Preventive Therapy in HIV+ Patients

- Golub et al., Rio
  Risk of TB for patients with prior TB
  $RR = 1.37 \ (1.04-1.80)$

- Churchyard et al., S Africa
  Miners with prior TB
  2º IPT – 5.7 cases/100 PY
  No IPT – 29.3 cases/100 PY
  $RR = 0.19 \ (0.04-0.42)$
Risk of TB Drug Resistance After IPT

Balcells et al., EID 2006
TB Rates in HIV+ Patients With Access to ART and IPT in Rio de Janeiro: Multivariate model

<table>
<thead>
<tr>
<th>Category</th>
<th>Adjusted RH (95%CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naïve</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>HAART only</td>
<td>0.45 (0.34-0.58)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>IPT only</td>
<td>0.70 (0.29-1.73)</td>
<td>0.44</td>
</tr>
<tr>
<td>HAART and IPT</td>
<td>0.25 (0.13-0.48)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Previous TB</td>
<td>1.37 (1.04-1.80)</td>
<td>0.02</td>
</tr>
<tr>
<td>CD4 &lt; 200</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>200 – 349</td>
<td>0.40 (0.30-0.53)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>350 – 499</td>
<td>0.28 (0.20-0.40)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>≥ 500</td>
<td>0.16 (0.11-0.24)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Viral Load &lt; 10K</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>10-100K</td>
<td>1.28 (0.96-1.69)</td>
<td>0.09</td>
</tr>
<tr>
<td>≥ 100K</td>
<td>2.57 (1.96-3.36)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Age &lt; 30</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>30-39</td>
<td>0.93 (0.70-1.22)</td>
<td>0.58</td>
</tr>
<tr>
<td>40-49</td>
<td>0.70 (0.51-0.96)</td>
<td>0.03</td>
</tr>
<tr>
<td>≥ 50</td>
<td>0.51 (0.33-0.78)</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Golub et al., IAC Toronto, 2006