Treatment of Latent Tuberculosis Infection: Research Landscape and Gaps

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TB Preventive Therapy

- Whom to treat?
  - Highest risk to ensure personal benefit
- What to treat with?
  - Safer, shorter, more patient-friendly regimens
- How long and how often to treat?
  - Duration of IPT or rifamycin-based regimens
  - HIV+ in high-burden area
- What about MDR?
- Making it happen – implementation science
## What to Treat With
Approved Treatments for Latent TB

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Adult Dosage</th>
<th>Duration</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid daily</td>
<td>300 mg/day</td>
<td>9 months</td>
<td>A II</td>
</tr>
<tr>
<td>Isoniazid daily</td>
<td>300 mg/day</td>
<td>6 months</td>
<td>B I</td>
</tr>
<tr>
<td>Rifampin daily</td>
<td>600 mg/day</td>
<td>3-4 months</td>
<td>B II</td>
</tr>
<tr>
<td>Rifapentine and isoniazid weekly</td>
<td>900 mg/900 mg once weekly (supervised)</td>
<td>3 months</td>
<td>A I</td>
</tr>
<tr>
<td>Isoniazid daily</td>
<td>300 mg</td>
<td>36 months – life</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Pioneers of TB Preventive Therapy

Edith Lincoln, MD

George Comstock, MD, DrPH

Jacques Grosset, MD
Conclusions of 3HP trials:

- Non-inferior to INH in adults, adolescents and children >2 years
- Safer than INH
- Better adherence and treatment completion
Expanded use of isoniazid/rifapentine (HP) to prevent TB

• Use in special populations
  • Pregnant and post-partum women
  • Children and infants
  • HIV+ on ART
• Self-administered 3HP
• Daily HP
• Cyclical HP
Tolerability and Effectiveness in Children
TBTC S26 + IMPAACT

• Study 26 amended to enroll 352 additional children; 1,058 total
  There were 908 for efficacy evaluation
• Follow-up complete September 30, 2013
• No hepatotoxicity, grade 4 events, or deaths

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>3HP N=472</th>
<th>9H N=436</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment completion</td>
<td>88%</td>
<td>81%</td>
<td>0.003</td>
</tr>
<tr>
<td>D/C—adverse drug reaction</td>
<td>2%</td>
<td>0.5%</td>
<td>0.11</td>
</tr>
<tr>
<td>Grade 3 toxicity</td>
<td>0.6%</td>
<td>0.2%</td>
<td>0.49</td>
</tr>
<tr>
<td>TB</td>
<td>0 (0%)</td>
<td>3 (0.78%)</td>
<td>Upper bound of difference: 0.44%</td>
</tr>
</tbody>
</table>

Rifaximic INH (HP) for treating latent tuberculosis in pregnant women and young children

- IMPAACT 2001 - A Phase I/II Trial of 3HP in HIV-infected and uninfected Pregnant and Postpartum Women With Latent Tuberculosis Infection
- PK, safety and tolerability study

- TBTC Study 35 – PK study of HP in children 0-12 y.o.
I-Adhere: TBTC Study 33

• Phase IV open label, randomized trial of 3HP
• Target Population: adults with LTBI
• All patients received 3HP, randomized to:
  1. DOT (control)
  2. Standard SAT
  3. SAT with weekly SMS reminders
• Sample size to detect a difference in study arms of 15% or greater based on cost modelling
• Enrollment targeted > 75% from U.S.
I-Adhere: TBTC Study 33

Differences in Completion Rates for DOT minus SAT and DOT minus eSAT: Total and U.S. only

Belknap, et al., 2015
Self-administered 3HP with or without SMS reminders is NOT non-inferior to supervised 3HP in this population with latent TB.

Self-administered 3HP without SMS reminders is non-inferior to supervised 3HP in a US population, but not an international population.

Self-administered 3HP with SMS reminders is NOT non-inferior to supervised 3HP in a US population.

Adherence to self-administered 3HP is poorer than to supervised treatment, but the impact on efficacy is not known.

Belknap, et al., 2015
1HP daily vs 9H daily
ACTG A5279 Study

• Design: Multicenter, randomized, open-label, phase III clinical trial

• Population: 3000 participants
  HIV-infected individuals ≥13 years old and no evidence of active TB who:
  • Have tuberculin skin test (TST) reactivity ≥ 5 mm or a positive Interferon
    Gamma Release Assay (IGRA), OR
  • Live in high burden areas, defined as TB prevalence
    ≥ 60/100,000 population/year

• Stratification
  • 1) CD4+ cell count at entry (<100, 100-250, and >250 cells/mm$^3$)
  • 2) ART use at entry (Yes/No)

• Only NRTI/NNRTI-based ART permitted while on RPT

• Duration: 3 years (156 weeks) after the last participant is enrolled
## A5279 Study Regimens

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Arm A (Experimental)</th>
<th>Arm B (Standard)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 – 4</td>
<td>RPT/INH daily (450 or 600 mg/300 mg)*</td>
<td>INH daily (300 mg)</td>
</tr>
<tr>
<td>5 – 36</td>
<td>No treatment</td>
<td>INH daily (300 mg)</td>
</tr>
<tr>
<td>37-close to follow-up</td>
<td>No treatment</td>
<td>No treatment</td>
</tr>
</tbody>
</table>

*450 mg RPT for participants weighing < 45 kg and 600 mg for participants weighing > 45 kg for an average dose of ~10 mg/kg/administration

• Participants also received Vitamin B6 (25 mg) with each dose of INH
ACTG A5279 cumulative enrollment – all sites
Effect of daily HP on Efavirenz concentrations in HIV+ patients

Podany et al., CID, 2015:61:1322-7
TBTC/TBESC/MRC Trial of Daily HP for 4-6 Weeks

- Pragmatic randomized trial of daily HP for 4-6 weeks for high risk individuals with latent TB
  - Household contacts
  - Recent converters
  - HIV+
- Test regimen: daily INH 600 mg and Rifapentine 600 mg
- Control arm: 3-4 months of RIF-based regimen per local standard
- Stage 1: Safety and tolerability of HP for 6 weeks
- Stage 2: Efficacy of HP for 4 weeks (if A5279 successful) or 6 weeks (if A5279 unsuccessful)
Shorter course RIF trials

- Randomized Clinical Trial Comparing 4RIF vs. 9INH for LTBI Treatment-effectiveness (Menzies)
- A Randomized Trial to Compare Effectiveness of 4 RIF vs. 9 INH in the Prevention of Active TB in Children: The P4v9 Trial (Menzies)
TB Preventive Therapy

- Whom to treat?
- What to treat with?
- **How long and how often to treat?**
- **What about MDR?**
- Making it happen – implementation science
Duration of IPT and Rates of Tuberculosis

Comstock GW, Woolpert SF, Baum C. ARRD 1974,110:195-7
6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo-controlled trial

Taroz Samandari, Tefora B Agizew, Samba Nyirenda, Zegabriel Tedla, Thabiso Sibanda, Nong Shang, Barudi Mosimaneotsile, Oaitso I Motsumai, Lorna Bozeman, Margaret K Davis, Elizabeth A Talbot,Themba L Moeti, Howard J Moffat, Peter H Kilmanx, Kenneth G Castro, Charles D Wells

Days after enrollment

TST negative (control group)  
TST positive (control group)  
TST negative (continued isoniazid group)  
TST positive (continued isoniazid group)

TST-positive, 6 months IPT
TST-negative, 6 months IPT
TST-negative, 36 months IPT
TST-positive, 36 months IPT

Lancet. 2011;377:1588-1598.
Long term (7 years) efficacy of 6 months of INH preventive therapy in TST+, HIV+ adults in a medium TB burden setting: Rio de Janeiro

Golub, et al. CID, 2015
Effectiveness of 3HP, 3HR, 6H or lifelong H in HIV+ Adults in South Africa

Kaplan-Meier Curves of TB or Mortality by Study Arm

Martinson et al., NEJM 2011;365:11-20
A trial of 3HP as a single round or given annually in HIV-infected individuals – Periodic 3HP
The WHIPP TB Study

6H

3HP

p3HP

G. Churchyard et al.
Randomized Trials of Treatment of MDR TB Infection

PHOENIx MDR TB
TB CHAMP
V-QUIN
<table>
<thead>
<tr>
<th></th>
<th>TB-CHAMP</th>
<th>V-QUIN</th>
<th>PHOENIx</th>
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<tbody>
<tr>
<td><strong>Intervention</strong></td>
<td>Levofloxacin vs. placebo daily for 6 months</td>
<td>Levofloxacin vs placebo daily for 6 months</td>
<td>Delamanid vs INH daily for 26 weeks</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>Cluster randomized; superiority</td>
<td>Cluster randomized; superiority</td>
<td>Cluster randomized; superiority</td>
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<tr>
<td></td>
<td>Community-based</td>
<td>Community-based</td>
<td></td>
</tr>
<tr>
<td><strong>Target Population</strong></td>
<td>• 0-5 y regardless of TST or HIV status</td>
<td>• All ages (including infants &lt; 6 mo)</td>
<td>• HIV + any age</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• &lt;15y currently on hold</td>
<td>• Children 0-5 yrs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• TST +</td>
<td>• TST/IGRA + &gt; 5 y</td>
</tr>
<tr>
<td><strong>Assumptions</strong></td>
<td>LVF will decrease TB incidence from 7% to 3.5%</td>
<td>LVF will decrease TB incidence from 3% to 0.9%</td>
<td>DLM will decrease TB incidence from 5% to 2.5%</td>
</tr>
<tr>
<td></td>
<td>80% power</td>
<td>80% power</td>
<td>90% power</td>
</tr>
<tr>
<td><strong>Sample size</strong></td>
<td>778 Households 1556 contacts</td>
<td>1326 Households 2785 contacts</td>
<td>1726 Households 3452 contacts</td>
</tr>
<tr>
<td><strong>Sites</strong></td>
<td>South Africa</td>
<td>Viet Nam</td>
<td>ACTG &amp; IMPAACT sites</td>
</tr>
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Improving Uptake, Completion and Safety
Selected Examples

• IMPAACT 1078 – Randomized trial of INH during pregnancy or following delivery in HIV-infected pregnant women (NIAID/NICHD - Mathad)

• TEKO Study – Cluster-randomized trial comparing QGIT vs TST screening of newly diagnosed HIV patients to initiate IPT (NIAID – Golub/Martinson)

• Project SOAR TB Kids Study – Cluster-randomized trial comparing nurse-initiated IPT for children <5 who are household contacts of adult TB cases vs standard of care (USAID – Salazar-Austin/Chaisson)
Effect of improved tuberculosis screening and isoniazid preventive therapy on incidence of tuberculosis and death in patients with HIV in clinics in Rio de Janeiro, Brazil: a stepped wedge, cluster-randomised trial

Betina Duronvi, Valeria Saraceni, Lawrence H Moulton, Antonio G Pacheco, Solange C Cavalcante, Bonnie S King, Silvio Cohn, Anne Efron, Richard E Chaisson, Jonathan E Golub

## Barriers and challenges to treating latent TB

<table>
<thead>
<tr>
<th>Challenges</th>
<th>Research Needs</th>
</tr>
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<tbody>
<tr>
<td>Excluding active TB</td>
<td>Use of clinical algorithms (symptom screening), x-rays, Xpert Ultra et al.</td>
</tr>
<tr>
<td>Need for TST or IGRA</td>
<td>POC test, symptom screening, epidemiologic risk stratification</td>
</tr>
<tr>
<td>Poor adherence</td>
<td>Short course regimens, mHealth, education/empowerment, incentives</td>
</tr>
<tr>
<td>Clinician resistance</td>
<td>Education, benchmarks, incentives, patient advocacy</td>
</tr>
<tr>
<td>Inadequate supply of providers</td>
<td>Task shifting</td>
</tr>
<tr>
<td>Weak program performance</td>
<td>Improved monitoring, incentives (or sanctions)</td>
</tr>
</tbody>
</table>
Tuberculosis among the Homeless — Preventing Another Outbreak through Community Action

Vin Gupta, M.D., Nancy Sugg, M.D., M.P.H., Marite Butners, J.D., LL.M., Gillian Allen-White, B.A., and Alexandra Molnar, M.D.

• Community partnership for treating LTBI in homeless
  • Businesses, public health, advocacy groups, NGOs
• DOPT with 3HP
• Voucher for free meal at neighborhood bakery when getting DOPT
  • Vouchers designed to mimic gift cards to avoid stigma
Thank you