New Avenues in TB Preventive Therapy:
The Long and Short of It

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Possible Effects of TB Preventive Therapy in HIV+ People

• Suppressive treatment of latent TB infection

• Sterilizing treatment of latent TB infection

• Treatment/prevention of exogenous re-infection with *M. tuberculosis*
Long or Short?
Durability of TB Preventive Therapy for HIV+ People: BOTUSA Study vs. THRIO Study

Golub, et al. CID, 2015

6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo-controlled trial


<table>
<thead>
<tr>
<th>Years since PPD+</th>
<th>No IPT</th>
<th>IPT x 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mo</td>
<td>1222 (58)</td>
<td>318 (14)</td>
</tr>
<tr>
<td>1 yr</td>
<td>400 (15)</td>
<td>241 (9)</td>
</tr>
<tr>
<td>2 yr</td>
<td>1506 (12)</td>
<td>168 (1)</td>
</tr>
<tr>
<td>3 yr</td>
<td>1470 (7)</td>
<td>123 (0)</td>
</tr>
<tr>
<td>4 yr</td>
<td>1437 (12)</td>
<td>84 (0)</td>
</tr>
<tr>
<td>5 yr</td>
<td>1149 (2)</td>
<td>189 (0)</td>
</tr>
<tr>
<td>6 yr</td>
<td>790 (5)</td>
<td>62 (0)</td>
</tr>
<tr>
<td>7 yr</td>
<td>414 (3)</td>
<td>185 (0)</td>
</tr>
</tbody>
</table>

Cumulative probability of tuberculosis

6-month IPT
36-month IPT

Life-long IPT in TST+/HIV+ Patients is No Better than 6 months IPT – or is it?

Intent-to-treat analysis

Martinson et al., NEJM 2011;365:11-20
Proportion of latent TB infections cured by 6H, 3RH and 3HP vs annual risk of infection

Houben et al., PNAS 2014; 111:5325-30
## TEMPRANO: Immediate vs Deferred ART Initiation + IPT for HIV-infected People in Cote D’Ivoire

<table>
<thead>
<tr>
<th>Primary endpoint</th>
<th>Deferred ART (N=511)</th>
<th>IPT + Deferred ART (N=512)</th>
<th>Early ART (N=515)</th>
<th>Early ART + IPT (N=518)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All events</td>
<td>75</td>
<td>60</td>
<td>41</td>
<td>28</td>
</tr>
<tr>
<td>Death</td>
<td>16</td>
<td>10</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>41</td>
<td>16</td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td>Invasive Bacterial Disease</td>
<td>14</td>
<td>28</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Cancers</td>
<td>1</td>
<td>5</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Other AIDS-related events</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

### Graph

30-Mo Probability, %
- Deferred ART: 14.1%
- Deferred ART + IPT: 8.8%
- Immediate ART: 7.4%
- Immediate ART + IPT: 5.7%

Probability of death in the Temprano Study
IPT reduces risk of death by 37% - independent of ART

Badje et al., Lancet Global Health, 2017
Enhanced prophylaxis plus ART in advanced HIV-infection
The REALITY Study

- HIV+ adults and children with CD4 <100 starting ART
- ‘Enhanced prophylaxis’ (3 mos. IPT, fluconazole, azithro, albendazole, TMP-SMZ)
- Control: ART + TMP-SMZ

Poor Global Uptake of IPT for People with HIV

Provision of TB preventive treatment to people living with HIV, 2005–2016

WHO. Global TB Report, 2017
Strategies for improving uptake of TB preventive therapy

- Make testing for infection easier and more accurate
- Make screening of potential recipients easier
- Make preventive therapy easier/safer
- Link TPT to ART – universal treatment for all
- Motivate programs, clinicians, and patients to accept preventive therapy
Conclusions of 3HP (rifapentine/isoniazid weekly x 12 weeks by DOT) trials:

- Non-inferior (or almost superior) to INH in adults, adolescents and children >2 years
- Safer than INH or RZ
- Better adherence and treatment completion
3HP vs 9H in HIV+ People in PREVENT TB Study (TBTC 26)

Sterling et al., AIDS 2016, 30:1607-15
DOT vs SAT for 3HP – The iAdhere Study

SAT is non-inferior in US (pre-specified)
SMS reminders not helpful

International sites had poorer SAT adherence

DOT = directly observed therapy; SAT = self-administered therapy.

IMPAACT4TB
Scaling up 3HP for TB Prevention

Problem

Consortium Partners

<table>
<thead>
<tr>
<th>Project countries</th>
<th>Low income countries</th>
<th>Low Middle Income Countries</th>
<th>High Middle Income Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Zimbabwe, Tanzania, Mozambique, Ethiopia, Malawi</td>
<td>Indonesia, Kenya, Ghana, India, Cambodia</td>
<td>South Africa, Brazil</td>
</tr>
</tbody>
</table>

To eliminate TB
“The 4v9 Trials – 4 months rifampin vs 9 months isoniazid for treatment of latent TB ”

Dr. Dick Menzies
Montreal Chest Institute, CORE, McGill International TB Centre
**4 months of rifampin to prevent TB in high-risk people**

**4v9 Trial – 4R vs 9H**

**Adult trial**
N=6859

Event rates, confirmed and possible TB:
- 4R 0.1/100 PY
- 9H 0.12/100 PY

Rate difference 0.01, 95% CI -0.24, 0.21

Excellent safety with both regimens

**Pediatric trial**
N=829

Events, clinical TB:
- 4R No cases → 0/100 PY
- 9H 2 cases → 0.25/100 PY

Excellent safety with both regimens

ONE MONTH OF RIFAPENTINE/ISONIAZID TO PREVENT TB IN PEOPLE WITH HIV: BRIEF-TB/A5279

Brief Rifapentine-Isoniazid Efficacy for TB Prevention
NCT01404312

Susan Swindells, MBBS, Ritesh Ramchandani, PhD, Amita Gupta, MD, Constance A. Benson, MD Jorge Leon-Cruz, MS, Noluthando Mwelase, MBCHB, Marc Antoine Jean Juste, Javier R. Lama, MD, MPH, Javier Valencia, MD, Ayotunde Omoz-Oarhe MD, Khuanchai Supparatpinyo, MD, Gaerolwe Masheto, MD, Lerato Mohapi, MD, Rodrigo Otavio da Silva Escada, MD, Sajeeda Mawlana, MBChB, Peter Banda, MBBS, Patrice Severe, MD, James Hakim, MBChB, Mmed, MMEdSc, Cecilia Kanyama, MBBS FCP, Deborah Langat, MBChB, MSc, Laura Moran, MPH, Janet Andersen, ScD, Courtney V. Fletcher, PharmD, Eric Nuermberger, MD,

and Richard E. Chaisson, MD

for the ACTG A5279/BRIEF TB Study Team
Make Preventive Therapy Even Shorter?
BRIEF TB: A5279

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

• Population: 3000 participants
  HIV-infected individuals ≥13 years old and no evidence of active TB
  97% enrolled from high-burden countries

• Treatments
  • Daily rifapentine/isoniazid for 4 weeks (1HP)
  • Daily isoniazid for 36 weeks (9H)
## BRIEF TB/A5279: 1HP vs. 9H – Primary Endpoints

<table>
<thead>
<tr>
<th>First Outcome</th>
<th>Randomized Treatment</th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>9H</td>
<td>1HP</td>
<td></td>
</tr>
<tr>
<td><strong>All Outcomes</strong></td>
<td>33</td>
<td>32</td>
<td>65</td>
</tr>
<tr>
<td>Active TB, Confirmed</td>
<td>14 (42%)</td>
<td>18 (56%)</td>
<td>32 (49%)</td>
</tr>
<tr>
<td>Active TB, Probable</td>
<td>10 (30%)</td>
<td>11 (34%)</td>
<td>21 (32%)</td>
</tr>
<tr>
<td>Death Related to TB</td>
<td>2 (6%)</td>
<td>0 (0%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Death from Unknown Cause</td>
<td>7 (21%)</td>
<td>3 (9%)</td>
<td>10 (15%)</td>
</tr>
</tbody>
</table>

### Events/PY of follow up

<table>
<thead>
<tr>
<th>Incidence per 100 PY</th>
<th>9H</th>
<th>1HP</th>
<th>IRR Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events/PY of follow up</td>
<td>33/4896</td>
<td>32/4926</td>
<td>0.023</td>
</tr>
<tr>
<td>Incidence per 100 PY</td>
<td>0.67</td>
<td>0.65</td>
<td>(95% CI -0.30-0.35)</td>
</tr>
</tbody>
</table>

**Non-Inferiority margin = 1.25 per 100 PY**
BRIEF TB – Time to endpoint

Swindells, et al., CROI 2018
Prevention of MDR-TB

• Proper treatment of initial disease to prevent selection of resistance
  – Prompt diagnosis and TB treatment
  – Rapid identification of MDR-TB and use of appropriate second line regimens
    • Avoid further evolution of resistance
  – Airborne infection control

• Most XDR and much of MDR is transmitted, not acquired

• Management of contacts of M/XDR TB cases based on expert opinion
• 232 contacts of 5 pts with 2 different MDR-TB strains
• 105 with positive TST received preventive therapy
  – MXF or LVF ± EMB or ETH x 12 months
• No cases of MDR-TB developed in those treated
  – 28 contacts not treated developed MDR-TB
<table>
<thead>
<tr>
<th></th>
<th>TB-CHAMP</th>
<th>V-QUIN</th>
<th>PHOENIx</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention</strong></td>
<td>Levofloxacin (pediatric dispersible tablet) 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 Community-based</td>
<td>Cluster randomized; superiority Community-based</td>
<td>Cluster randomized; superiority</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 +</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 decreases TB incidence from 7 to 3.5%; 80% power</td>
<td>LVF decreases TB incidence by 70% from 3% untreated; 80% power</td>
<td>DLM decreases TB incidence by 50% from 5% to 2.5%; 90% power</td>
</tr>
<tr>
<td><strong>Sample size</strong></td>
<td>778 HH 1556 contacts</td>
<td>1326 HH 2785 contacts</td>
<td>1726 HH 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>
</tbody>
</table>
Future Directions – Short or Long?

• Longer – 1.5P = 6 weeks of RPT → ASTEROID Study (TBTC, TBESC, BMRC)

• Short, but more often – Periodic 3HP or 1HP → WHIP$_3$ TB (Aurum, LSHTM, KNCV) and ERASE TB (ACTG A5365)

• Shorter and better – ??
Periodic 3HP: A single round of 3HP vs annual 3HP in HIV-infected individuals – The WHIP$_3$TB Study

G. Churchyard et al.
How low can you go? Potentially shorter LTBI regimens in the mouse model
Lung CFUs after 4 weeks of treatment

Zhang, Nuernberger et al., Am J Respir Crit Care Med, 184:732–737, 2011
Summary of Recent Advances

• TB preventive therapy SAVES LIVES for people with HIV (TEMPRANO and REALITY)

• 6 months of IPT has durable benefit, even in African settings
  • ART is essential and has additional benefit

• 3HP is a promising option for HIV+ people

• 1HP could be transformational for global TB control

• We can probably do even better
  • Bedaquiline alone or in combination with rifapentine
  • Injectable bedaquiline?
Preventing tuberculosis in people with HIV—no more excuses

In 2014, tuberculosis eclipsed HIV as the leading infectious killer on earth and it remains the foremost cause of death for people with HIV infection. The risk of tuberculosis doubles after HIV is acquired, skyrockets with falling CD4 counts, and remains substantially elevated even after immune reconstitution with antiretroviral therapy (ART). From the earliest days of the HIV epidemic, it was evident that preventive therapy with isoniazid—a cheap, widely available, well-tolerated drug that has been around for more than 60 years—was protective against tuberculosis in people with HIV infection, and WHO recommended its use as a personal health measure (ie, not as a programmatic imperative) in 1993. Over the past 20 years, numerous clinical trials and observational cohort studies have demonstrated the effectiveness of isoniazid preventive therapy (IPT) in preventing tuberculosis in people with HIV infection in the absence of ART in settings

In this issue of The Lancet Global Health, Anani Badje and colleagues’ publish the long-term follow-up data from the TEMPRANO study—a randomised, factorial design trial testing the impact of IPT and/or early ART for individuals with HIV infection and CD4 counts of less than 800 cells per μl but above the threshold for initiating treatment during the trial, prior to universal ART being endorsed. The initial results of TEMPRANO found that IPT and early ART each reduced the risk of developing serious HIV events, a large proportion of which were tuberculosis, and that receiving both IPT and early ART provided the best protection from disease. The post-trial phase doubles the duration of observation and shows that 6 months of IPT given early in the course of HIV infection provides a durable survival benefit, with a 37% reduction in the risk of death that was independent of ART over an average of 4.9 years of follow-up.
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