Ongoing research on LTBI treatment and IMPAACT4TB

GJ Churchyard
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Overview

- Who and when?
  - PLHIV
  - Household contacts
  - High risk communities
- What treatment?
- For how long
- Conclusion

NO
more people living with HIV dying of TB
TB preventive therapy

Who and when?

PLHIV
Household contacts
High risk communities
TB preventive therapy

Who and when?

PLHIV
6-12 months of IPT (Long)

Akolo. 2010, Cochrane review
ART reduces risk of TB

TB risk reduced by 67% (61%-73%)

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 estimate (n=37,879)

IPT with ART: a randomised controlled trial

South Africa

- HR: 0.63 (95% CI 0.41-0.94)
- Deaths were similar between arms (3.0% vs. 2.1%, p=0.29)
- The risk of stopping IPT due to grade 3 or more raised ALT was 2.13 (95%CI 0.97-4.67)

Cumulative TB incidence

Duration in study-in years from randomization

(Rangaka et al, AIDS2012)
IPT with ART: a randomised controlled trial in South Africa

Effect of IPT with ART by TST or IGRA status (Rangaka. Poster 189LB)

<table>
<thead>
<tr>
<th></th>
<th>TB rates (100 person years)</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>INH</td>
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<tr>
<td>TST positive</td>
<td>2.8</td>
<td>2.6</td>
</tr>
<tr>
<td>TST negative</td>
<td>4.1</td>
<td>1.7</td>
</tr>
<tr>
<td>IGRA positive</td>
<td>3.9</td>
<td>3.0</td>
</tr>
<tr>
<td>IGRA negative</td>
<td>3.4</td>
<td>1.7</td>
</tr>
</tbody>
</table>
Temprano study
Immediate ART+ 6H reduced TB and deaths*

*Including those with a CD4 count > 500 cells/mm³

(Temprano study group. NEJM. 2015)
Enhanced prophylaxis* + ART reduces death and TB

*Included INH/CTX/B6 FDC for at least 12 weeks

(Hakim. NEJM. 2017)
Efficacy of secondary preventive therapy among HIV+ individuals

(Incidence Rate Ratios & 95% CI)

Reference

Haller (1999)
Fitzgerald (2000)
Churchyard (2002)

(Churchyard GJ. Infect Dis. 2007;196 (Suppl. 1): S52-62.)
TB preventive therapy

Who and when?

Household contacts exposed to
Drug susceptible TB
Drug resistant TB
TB preventive therapy

Who and when?

Household contacts exposed to
Drug susceptible TB
Drug resistant TB
IGRA (QFT)+ and TST+ HH Contacts Have Almost 2-Fold Greater Risk of TB

HH contacts in Zambia & South Africa.
# Randomized Trial of IPT for HHCs

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Location</th>
<th>Intervention</th>
<th>Efficacy: TB</th>
<th>Efficacy: Deaths</th>
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<tbody>
<tr>
<td>Egsmose, 1965</td>
<td>Kenya</td>
<td>INH 300-500 mg x 1-2 yrs vs. placebo</td>
<td>0.36 (0.15-0.85)</td>
<td>0.93 (0.33-2.61)</td>
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<tr>
<td>[27]</td>
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<tr>
<td>Ferebee, 1962</td>
<td>US, Puerto Rico, Mexico</td>
<td>INH 300 mg x 1 yr vs. placebo</td>
<td>0.22 (0.1-0.47)</td>
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<tr>
<td>[28]</td>
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<tr>
<td>Mount, 1962</td>
<td>US</td>
<td>INH 300 mg x 1 yr vs. placebo</td>
<td>0.46 (0.17-1.22)</td>
<td>1.10 (0.94-1.28)</td>
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<tr>
<td>[29]</td>
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</tbody>
</table>
High risk populations requiring TB preventive therapy in HBCs

- People living with HIV
  - People living with HIV are **37 times** more likely to develop active TB following infection\(^1\)
  - Active TB is the leading cause of death in people with HIV

- Children under 5yrs
  - Active TB is in the top 10 killer children under 5 years
  - One million children developed active TB and 170,000 children died as a result of TB in 2015\(^2\)

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\(^1\) Source: WHO
\(^2\) Source: WHO
TB preventive therapy

Who and when?

Household contacts exposed to
Drug susceptible TB
Drug resistant TB
### HH Contacts: 4-8% Develop Active TB

**Table 1. Yield of Secondary Cases of Active Tuberculosis in 25 Included Studies**

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<thead>
<tr>
<th>Author(s)</th>
<th>Location</th>
<th>Year(s) of Enrollment</th>
<th>Drug-Resistant Source Cases, No.</th>
<th>MDR</th>
<th>Poly, MDR</th>
<th>Poly, XDR</th>
<th>Active Secondary Cases, No.</th>
<th>Active Secondary Cases, %</th>
<th>Drug-Resistant Secondary Cases Among Active Secondary Cases With DST, No.</th>
<th>Drug-Resistant Secondary Cases, %</th>
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<tr>
<td>CDC [23]</td>
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<td>2007–2009</td>
<td>5</td>
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<td>163</td>
<td>10 (10%)</td>
<td>3/3 (100%)</td>
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<td>Agerton et al [24]</td>
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<td>1992–1997</td>
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<td>3 (14%)</td>
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<td>Becerra [26]</td>
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<td>693</td>
<td>MDR, XDR</td>
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<td>4503</td>
<td>359 (8%)</td>
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<td>2112</td>
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<td>601</td>
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</table>

Abbreviations: CDC, Centers for Disease Control and Prevention; DST, drug susceptibility testing; MDR, multidrug-resistant tuberculosis; Mono, monoresistant tuberculosis (any type); NA, not applicable; Poly, polyresistant tuberculosis; XDR, extensively drug-resistant tuberculosis.

Shah S et al. CID. 2014

**Active TB in HH Contacts**
- 38/464 (8%)
- 359/4503 (8%)
- 108/2112 (5%)
- 16/302 (5%)
- 73/1766 (4%)
Majority of secondary TB cases are MDR TB

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<th>Drug-Resistant Category</th>
<th>Source Case Drug Resistance Category</th>
<th>Household Contacts Evaluated for Active Tuberculosis, No.</th>
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TB preventive therapy

Who and when?

High risk communities
HIV clinics
Mines
General communities
Emergence of an IFN response signature during disease progression

- **CoR genes**
- **Interferon module**
- **Inflammation module**

Log2FC (progressors vs controls)

Time before diagnosis (days)
Positive predictive value (PPV) of COR for South African adult population

- **Optimum TPP** - PPV: ~16%
- **COR signature** - PPV: ~7%
- **Minimum TPP** - PPV: ~6%
- **TST / IGRA** - PPV: ~2% / ~3%

Cumulative 2 year incidence: 2%
Effectiveness of IPT: 50%
Denkinger, Goletti et al.,
A clinical trial of a correlate of risk targeted screen-and-treat strategy to impact TB control

- Test whether preventive therapy (3HP) reduces the risk of TB disease, compared to standard of care
- Estimate the effect of the COR screen & treat strategy on reducing the rate of incident TB disease, compared to standard of care
TB preventive therapy

What and for how long?

Drug susceptible TB
Drug resistant TB
TB preventive therapy

What and for how long?

Drug susceptible TB
Long & very long
Short
Ultra short
The long & the short
TB preventive therapy

What and for how long?

Drug susceptible TB

*Long & very long*
Short
Ultra short
The long & the short
6-12 months of IPT (Long)

Relative Risk (Fixed) & 95% CI

Akolo. 2010, Cochrane review
36 months of IPT

Very long

TST positive participants

Cumulative TB incidence

Days after enrolment

6H

36H
TB preventive therapy

What and for how long?

Drug susceptible TB
- Long & very long
- **Short**
- Ultra short
- The long & the short
4 months of daily rifampicin (4R)

- 2 studies
- Populations: low to medium TB incidence
- Design: 4R vs 9H
- Canadian Institute for Health Research
  - Adults 5720, Children 820
- Taiwan
  - N=300
Weekly high dose 3HP is non-inferior to 9H

Study 26: High risk persons in US, Canada, Brazil & Spain

N=7731
Short course rifamycin based regimens have similar efficacy as 6-months IPT in PWHIV

TST+ South Africans

(Martinson NEJM. 2011)
3 months of daily isoniazid & rifampicin

- HALT-LTBI
- Population: Low TB incidence in the UK
- Design: 3HR vs 3HP
- Objective: to compare treatment completion rates
TB preventive therapy

What and for how long?

Drug susceptible TB
Long & very long
Short
Ultra short
The long & the short
6 weeks of daily rifapentine

- **Population**: persons with *M. tb* infection in the United States and United Kingdom (low TB incidence) at high risk for progressing to TB
  - Primarily HIV-uninfected
- **Intervention**: 6 weeks of daily rifapentine
- **Comparator arm**: combined arm of:
  - 3 months INH + rifapentine
  - 3 months of INH + rifampin, or
  - 4 months of rifampin
- **Sponsors**: Centers for Disease Control, British Medical Research Council
- **Name**: ASTERoID
- **Comment**: protocol under development
Daily INH & rifapentine for one month (A5279)

- **Design:** Phase III, individually randomised
- **Study population:**
  - HIV-1 infected men and women ≥13 years old and ≥30 kg without evidence of active TB
  - TST/IGRA+
  - Live in high TB burden areas (TB prevalence ≥60/100,000/year)
- **Objectives:** To compare the efficacy of a 4-week daily regimen of weight-based RPT/INH to 9H
- **Sample size:** 3000 (enrolment complete)
TB preventive therapy

What and for how long?

Drug susceptible TB
Long & very long
Short
Ultra short
*The long & the short*
3HP has similar efficacy as continuous IPT in the first year in high burden settings (Per protocol analysis)
Thibela TB: modelling population level impact of 9H, continuous IPT & 3HP
A trial of 3HP as a single round or given annually in HIV-infected individuals

Number of cases/100,000/year (true incidence)

Year

A trial of 3HP as a single round or given annually in HIV-infected individuals
Part A: An observational randomised comparison of 3HP vs 6H

Primary objective

- To compare treatment completion in HIV-positive participants taking 3HP to those taking 6H
Part B: A randomised controlled trial of 3HP vs p3HP

- **Primary objective:**
  To compare the efficacy of two periodic (annual) rounds of 3HP (p3HP) to a single round of 3HP

![Diagram showing 6H for 3HP and p3HP with different patterns of green and white segments for the rounds.](image-url)
Additional innovations

- Fixed dose combination of INH and rifapentine
- Paediatric fully dispersible formulation for FDC and rifapentine
- Use of Medication Event Reminder-Monitor “MERM” device (Powered By Wisepill)
Annual cycles of daily INH & rifapentine for 1 month

- **Population**: HIV+ persons on ART or starting ART (any CD4) in high-medium TB incidence settings. TST/IGRA positive or negative.
- **Intervention**: 4 weeks of INH + rifapentine annually x 3 years
- **Comparator arm**: 4 weeks of INH + rifapentine x 1
- **Sponsor**: ACTG
- **Comment**: preliminary; under development
TB preventive therapy

What and for how long?

Drug resistant TB
Efficacy of drugs in a murine model of LTBI

- Mouse studies suggest that PA824 (nitroimidazole) and levofloxacin have similar efficacy in treating LTBI as INH
## Trials of treatment for MDR TB infection

<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>LVF (paediatric dispersible tablet formulation) vs. placebo daily for 6 months</td>
<td>LVF vs placebo daily for 6 months</td>
<td>DLM 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 years of age regardless of TST or HIV status</td>
<td>All ages (including infants &lt; 6 mo), TST +</td>
<td>1. Children 0-5 yrs, HIV +, TST/IGRA + over 5 year olds</td>
</tr>
<tr>
<td><strong>Assumptions</strong></td>
<td>LVF decreases incidence from 7 to 3.5%; 80% power</td>
<td>LVF decreases incidence by 70% from 3% untreated; 80% power</td>
<td>DLM decreases incidence by 50% from 5% to 2.5%; 90% power</td>
</tr>
<tr>
<td><strong>Sample size</strong></td>
<td>788 HH 1565 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>
Barriers to programmatic management of LTBI
Global uptake of IPT

Number of people living with HIV (thousands)

- Global
- South Africa
- Rest of Africa
- Rest of world

INH is cheap and effective, yet uptake of IPT for PLHIV remains low

SOURCE: 1. IPT uptake data is from the WHO TB Report, 2. PLHIV data is from UNAIDS aidsinfo.com for all countries.
INH is cheap and effective, yet IPT uptake in high burden settings has been low due to lack of appropriate tools.

Barriers to IPT uptake:

- Long (6-36 months) and complex treatment options
- Poor adherence
- Re-infection in high burden settings
- Challenging to scale up
- Deprioritized vs. other interventions
Cascade for LTBI treatment

Alsdurf et al., Lancet ID, 2016
Universal vs. Symptom-based TB Screening of HIV+ Pregnant Women
A Cluster-randomized Trial

<table>
<thead>
<tr>
<th>Baseline Characteristics by Arm</th>
<th>Universal Clinics (8) N=941</th>
<th>Symptom Clinics (8) N=1,100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>30.2 yrs</td>
<td>29.5 yrs</td>
</tr>
<tr>
<td>Gestational age</td>
<td>24.6 wks</td>
<td>24.4 wks</td>
</tr>
<tr>
<td>TB Symptoms</td>
<td>17.3%</td>
<td>22.1%</td>
</tr>
<tr>
<td>Prior TB</td>
<td>9.8%</td>
<td>7.8%</td>
</tr>
<tr>
<td>On ART</td>
<td>99.5%</td>
<td>98.6%</td>
</tr>
<tr>
<td>CD4 count</td>
<td>426 cells/mm³</td>
<td>451 cells/mm³</td>
</tr>
<tr>
<td>Hb</td>
<td>11.4 g/dl</td>
<td>10.8 g/dl</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Yield of TB diagnoses by Arm</th>
<th>TB Cases n/N</th>
<th>Cluster-adjusted MTb Yield (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Universal Testing</td>
<td>34/941</td>
<td>3.6% (1.2-6.0)</td>
</tr>
<tr>
<td>Symptom Testing</td>
<td>4/1100</td>
<td>0.36% (0.0-1.1)</td>
</tr>
</tbody>
</table>

P = 0.01

Martinson, et al. IAS TUPDB0204LB 2017
Studies to address programmatic challenges

- DOT vs Video DOT
- Symptom vs TST screening in children requiring treatment of LTBI
- 3HP vs 9H: tolerability, cost-benefit, satisfaction (Australia)
Increase Market and Public health outcomes through scaling up Affordable Access models of short Course preventive therapy for TB

(IMPAACT4TB)

Churchyard, Cardenas, Charalambous Chaisson, Kimerling, Osih, Waning
Goal & Outcome

• **Goal:**
  • To reduce TB incidence and deaths among PLHIV and child contacts through sustainable implementation of affordable, quality-assured 3HP

• **Outcome:**
  – to increase the number of PLHIV and child contacts <5 years starting treatment with affordable, quality-assured 3HP
  – contribute to revising WHO preventive therapy guidelines based on evidence generated
**Problem**

**Low income countries**
Zimbabwe, Tanzania, Mozambique, Ethiopia, Malawi

**Low Middle Income Countries**
Indonesia, Kenya, Ghana, India, Cambodia

**High Middle Income Countries**
South Africa, Brazil
IMPAACT4TB: Implementation research

- Conduct mathematical modelling to evaluate the population-level impact and cost-effectiveness of scaling up 3HP

![Graph showing the relationship between DALYs averted and total cost (USD, millions)]
Comparison of contact investigation models for increasing 3HP uptake among child contacts

- **Strategies to be assessed**
  - SOC: New TB cases refer paediatric household members to the clinic for screening, and eligible contacts are started on TB preventive therapy
  - Household-based paediatric contact investigation conducted by community healthcare workers with in-home initiation of TB preventive therapy
  - Incentive-based contact investigation (index patient incentivised for paediatric household contacts presenting to clinic for screening.

- **Study Design**: Cluster (24+ clinics) randomized trial.
Comparison of health system models of 3HP delivery to increase proportion of eligible participants initiating 3HP among PLHIV.

- **Strategies to be assessed**
  - SOC: Clinic staff training for appropriate prescription of 3HP
  - Opt-out prescribing; where prescription of 3HP will be automatically included with HIV medications unless clinicians write order not to prescribe
  - Clinic initiated Quality improvement process

- **Study design**: Cluster (24+ clinics) randomized trial
Safety & PK studies

3HP + DTG in PLHIV
3HP in pregnancy
3HP in children
IMPAACT4TB: RPT/DTG safety & PK study

Background

- 3HP compatible with EFV based regimen
- In health volunteers 3HP with DTG was associated with
  - Hypersensitivity reactions
  - Reduction in DTG levels

Primary Objectives

1) To evaluate the effect of 3HP on the PK of DTG
2) To assess the safety of DTG and 3HP co-administration

Secondary Objectives

1) To estimate the % of participants who maintain HIV-1 virologic suppression among patients treated with DTG-based ART plus 3HP
2) To describe the PK of isoniazid and rifapentine
3) To determine the dosing for DTG, given with 3HP
Once weekly 3HP in pregnant & post partum women: PK & safety (IMPAACT2001)

- Design: Phase I/II RCT
- Study population: HIV-infected & uninfected pregnant and post partum women
- Objectives
  - Estimate population PK of RPT in second and third trimester
  - Estimate incidence of SAEs
  - Describe infant outcomes
- Sample size: 82
PK of rifapentine in children 0-12 years

- TBTC Study 35
- HIV-uninfected children
- Single site study
  - Stellenbosh, South Africa

Predicted dose (mg/kg) of rifapentine in children required to match the AUC achieved with the 15 mg/kg dose in adults
Conclusion
Conclusion

• Ongoing trials for treating TB infection include
  • Short and ultra-short course treatment
  • Treatment of MDR TB infection
  • Strategies to maximize durability of TB preventive therapy

• Further innovation is required to improve effectiveness, shorten treatment & prolong durability

• Implementation research is required to identify affordable models for scaling up preventive therapy