Programmatic interventions to decrease the burden of TB/HIV

Report International
*Tuberculosis and Co-morbidities: Scientific Advances that will Facilitate TB Control and Elimination TB*

GJ Churchyard
MBBCh (WITS), FCP (SA), FRCP (Edin), MMED (Int Med), PhD (WITS)
12\textsuperscript{th} September 2017
Outline

• Background
• TB prevention cascade
• Addressing the gaps
  • Tests of LTBI
  • Treatment of LTBI
    • Drug susceptible
    • Drug resistant
• Scaling up programmatic management of LTBI
• Conclusion

NO more people living with HIV dying of TB
Background
Background

- In 2015 globally
  - TB is the leading cause of death from an infectious agent
  - 11% of 10.4 million new TB cases were HIV infected
  - There were 0.4 million TB deaths among PLWHIV
Burden of LTBI: Global

- 32% of 7 billion people (2.24 billion) estimated to have LTBI in 1999 based on
- Recently re-estimated to be 24%
Burden of LTBI: Global

Corbett et al, 2003 (Source: H Getahun, WHO)
Burden of LTBI: Global

Corbett et al, 2003 (Source: H Getahun, WHO)
Scaling up programmatic management of LTBI has the potential to contribute to meeting the End TB targets.

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 limited uptake of treatment 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
TB prevention cascade
Cascade for LTBI treatment

Alsdurf et al., Lancet ID, 2016
<table>
<thead>
<tr>
<th>Gap</th>
<th>Strategy</th>
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<tbody>
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<td>Treat high risk groups without testing</td>
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<td>Develop new predictive, POC tests</td>
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<tr>
<td>Treatment not started</td>
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<td>Consider periodic treatment</td>
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<td>Develop TB vaccines</td>
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</table>
### Strategies to address gaps in the prevention cascade

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</table>
The Quality Improvement cycle

Rapid Change Cycles (PDSAs)

AIM: What are we trying to accomplish?

CHANGES: What change can we make that will result in an improvement?

MEASURES: How will we know that a change is an improvement?

Run the test at full scale

Adapt the change, increase the scale, test under different conditions

Small test of change
Tests of TB infection
Persistent, incipient & clinical TB

Esmail. 2014

Persistent infection  Incipient TB / sub clinical TB
Tuberculin skin test

- Is a test of prior and current TB infection
- Remains positive for decades
- Poorly predictive of developing active TB disease
- Marked inter/intra observer variability
- Sensitivity reduced with immune suppression
- Specificity poor due to cross reactions with NTMs and BCG
- Global stock out as SSI no longer producing tuberculin
New skin tests of TB infection

- **Diaskintest (DST)**
  - >20 million tests in Russia & former Soviet Union
  - CFP10 & ESAT 6
  - Similar performance to QFT-Gold

- **CTB**
  - Uses CFP10 & ESAT 6
  - Similar performance to QFT-Gold
  - Not yet commercialised

- **DPPD**
  - Recombinant skin test antigen
  - Better performance than TST, including in HIV+s
  - Still in development
Effect of improved TB screening and IPT in HIV clinics in Rio de Janeiro

(Durovni. Lancet, 2013)
Treatment of LTBI

Whom to treat?
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)

The risk of TB on long-term ART remains
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)

(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>
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<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>INH</td>
</tr>
<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)
Reducing Early Mortality and Early Morbidity with Empiric TB Treatment

- 850 PLWHIV with advanced HIV disease (CD4 count < 50 cels/ml³) randomised to
  - 4HRZE/2HR
  - 6H

- Followed up for 48 weeks

- Comparing empirical therapy to 6H, probability of
  - Death was similar, (1.55% (95% CI: -2.11%, 5.2%))
  - TB was greater, 3.2% (95% CI: -5.9%, 0.5%)

(A5274/REMEMBER, CROI, 2016)
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

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 short & long
TB preventive therapy

What and for how long?

Drug susceptible TB

*Long & very long*

Short

Ultra short

The short & long
6-12 months of IPT (Long)

![Graph showing relative risks and 95% confidence intervals for TB and death in different groups: Reference, PPD+, PPD-, PPD-unknown, Overall. Relative risks: Reference (TB: 1.0, Death: 1.0), PPD+ (TB: 0.36, Death: 0.74), PPD- (TB: 0.86, Death: 1.02), PPD-unknown (TB: 0.86, Death: 0.81), Overall (TB: 0.67, Death: 0.95).](image)

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 short & long
4 months of daily rifampicin (4R)

- 2 studies
- Populations: low to medium TB incidence
- Design: 4R vs 9H
- Canadian Institute for Health Research
  - Mostly HIV uninfected 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

Cumulative tuberculosis rate (%) vs. Time from enrollment (days)

N=7731
Weekly high dose 3HP in HIV-infected persons

- In MITT analysis (N=399), 3HP vs. 9H
  - Had similar efficacy (cum. TB incidence: 1.01 vs. 3.5)
  - Had higher completion rates (89% vs 64%)
  - Similar treatment limiting AEs (3% vs. 4%)
  - Less hepatotoxicity (1% vs. 4%)

(Sterling et al, CROI2014, P586)
Adherence to weekly SAT & eSAT 3HP

(Belknap R et al. CROI 2015)
Short course rifamycin based regimens have similar efficacy as 6-months IPT in PWHIV

TST+ South Africans

3RPT/INH (900mg/900mg weekly x 12)

(Martinson NEJM. 2011)
Weekly RPT dosing (900 mg) with Atripla

- Repeated 900mg weekly RPT resulted in
  - No change in steady state exposure of FTC and tenofovir
  - No change in EFV $C_{\text{max}}$ and decrease by 15% in $C_{\text{min}}$ and AUC at the time-course of maximal CYP 2B6 induction

- Co-administration of 900 mg weekly RPT after 3 weeks had
  - No apparent impact on Atripla activity
  - No changes in CD4 counts and viral loads

- Co-administration Atripla / weekly 900 mg RPT well tolerated

LTBI regimen 3RPT/INH can be administered to HIV-infected patients receiving efavirenz-based ART

(TBTC Semi-annual Mtg – Decatur – March 2014, M.Maroni)
Pharmacology of DTG

- Rifamycins induce both UGT1A1 and CYP3A4.
- How much DTG do we need? What is the ‘target’ exposure?

### DTG with once-weekly HP: healthy volunteers (n=4)

<table>
<thead>
<tr>
<th>Participant</th>
<th>Tolerability</th>
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</thead>
</table>
| 1           | Nausea, vomiting, headache, fever with Dose #3 of HP  
Symptom resolution by 72 hours post-dose  
Transaminase elevations 72 hours post-dose |
| 2           | Tolerated regimen |
| 3           | Withdrew prior to 3\textsuperscript{rd} dose (family/work obligations) |
| 4           | Nausea, vomiting, fever, orthostatic hypotension with  
Dose #3 of HP  
Transaminase elevations 24 hours post-dose  
Symptom resolution by 72 hours post-dose |

**Study terminated early because of AE in two healthy volunteers**

Brooks et al  CROI 2017 Poster 409A
Impact of HP on DTG concentrations

Figure 6. Steady-state DTG $C_T$ Levels$^a$ throughout the Study

<table>
<thead>
<tr>
<th>Days after an HP dose</th>
<th>0</th>
<th>2</th>
<th>3</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 4 (n=4)</td>
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<tr>
<td>Day 5 (n=4)</td>
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<td>Day 14 (n=4)</td>
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<tr>
<td>Day 15 (n=4)</td>
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<tr>
<td>Day 18 (n=4)</td>
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<td>Day 19 (n=3)</td>
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<tr>
<td>Day 20 (n=3)</td>
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</tbody>
</table>

$^a$Protein-adjusted IC$^{90}$ for DTG (0.064 ug/mL) (range 0.9 - 11.0)

% Decrease vs. Day 4: -16.4%, -42.7%, -74.4%, -53.2%, -59.9%, -38.3%

$C_T$ = concentration at the end-of-the-dosing interval. *Reported as geometric mean of the time 0 (pre-dose) sample on the specified study day. % decrease based on the GMR of specified time point vs. Day 4 $C_T$ value. *$p<0.05$

HP dosing: Days 5, 12, 19

Brooks et al  CROI 2017 Poster 409A
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
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 short & long
6 weeks of daily rifapentine

• ASTERoID trial
• Conducted in low incidence settings
  • US & UK
• Study population mostly HIV-uninfected persons with LTBI
• Comparing 6 weeks of daily rifapentine to 3HR, 3HP, 4R
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 short & long*
3HP has similar efficacy as continuous IPT in the first year in high burden settings

(Martinson NEJM. 2011)
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

<table>
<thead>
<tr>
<th></th>
<th>6H</th>
<th>3HP</th>
<th>p3HP</th>
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</table>
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
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)
A5365: Trial of cycled ultra-short course isoniazid/rifapentine in PLWHIV

- Setting
  - ACTG sites in medium and high TB burden settings
- 1HP given annually for 3 years
- Protocol in development
TB preventive therapy

What and for how long?

Drug resistant TB
MDR TB in Household Contacts

- Contacts of MDR TB patients who become infected have a high risk of progressing to active TB and possibly death
- Approximately 10% of HHCs HIV infected
Treatment of presumptive MDR TB infection not recommended

- Quality of evidence is seriously limited

**Recommend**: strict clinical observation and close monitoring for TB disease for at least two years

**Remark**: Clinicians as part of clinical practice can consider individually tailored preventive treatment
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.
Delamanid

- Is a nitroimidazole
- Is efficacious in treating MDR TB disease
- Appears to be safe & well tolerated
- Has minimal DDIs
- Can be dosed as a single daily dose
- Being developed for infants and children
<table>
<thead>
<tr>
<th></th>
<th>TB-CHAMP</th>
<th>V-QUIN</th>
<th>PHOENIX</th>
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<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>
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<td>Cluster randomized; superiority</td>
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<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>
Scaling up programmatic management of LTBI
IPT promotion in 29 HIV clinics in Rio de Janeiro, Brazil
IPT promotion in HIV clinics in Rio de Janeiro, Brazil
Reduced TB incidence/death at a clinic-level

(Durovni, Lancet, 2013)

<table>
<thead>
<tr>
<th>Analysis</th>
<th>TB Incidence</th>
<th>% Reduction</th>
<th>HR (95% CI)</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Primary Analysis</td>
<td>TB</td>
<td>475</td>
<td>0.87 (0.69 - 1.10)</td>
<td>0.24</td>
</tr>
<tr>
<td>TB/Death</td>
<td>1313</td>
<td>0.74 (0.64 - 0.85)</td>
<td>&lt; 0.001</td>
<td></td>
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IPT durably reduced TB incidence

Golub, et al. CID, 2015
Results: 5-Year Durability

(Annual rate of IPT delivery: 20%/year to fit study data)

- IPT: 15.6% reduction
- IPT: 14.3% reduction

Population TB/HIV Incidence, per 100,000/yr
Population TB/HIV Mortality, per 100,000/yr

Year Since Initial Roll-Out

(Annual rate of IPT delivery: 20%/year to fit study data)

(David Dowdy, Union Conference 2012)
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
IMPAACT4TB countries

<table>
<thead>
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<th>Income Category</th>
<th>Countries</th>
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</thead>
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<tr>
<td>Low income countries</td>
<td>Zimbabwe, Tanzania, Mozambique, Ethiopia, Malawi</td>
</tr>
<tr>
<td>Low Middle Income Countries</td>
<td>Indonesia, Kenya, Ghana, India, Cambodia</td>
</tr>
<tr>
<td>High Middle Income Countries</td>
<td>South Africa, Brazil</td>
</tr>
</tbody>
</table>
IMPAACT4TB: Implementation research

- Conduct mathematical modelling to evaluate the population-level impact and cost-effectiveness of scaling up 3HP
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
SA NTP Strategic plan: 2017-2021

NTP Interventions
- Facility-based TB screening
- Active TB case-finding among select key populations
- Scale up short-course MDR-TB treatment
- Reduce initial loss to follow up for TB Cases
- Scale up 3HP for all household contacts & PLWHIV

Cross-cutting Interventions
- Establish TB information system to improve patient management & health service delivery
- Scale up quality improvement to support successful implementation of NTP interventions

“We can't fight AIDS unless we do much more to fight TB as well” Nelson Mandela, July 2004
# SA NTP Strategic plan: 2017-2021

**NTP Interventions**

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**Scale up 3HP for all household contacts & PLWHIV**

**Cross-cutting Interventions**

| Establish TB information system to improve patient management & health service delivery |
| Scale up quality improvement to support successful implementation of NTP interventions |

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*We can't fight AIDS unless we do much more to fight TB as well* — Nelson Mandela, July 2004
Consolidated LTBI guidelines

Consolidate LTBI guidelines expected Oct/Nov 2017
WHO LTBI app

- Free
- Adaptable
- Operates on mobile devices
- Flexible
  - Record data offline
  - Synchronize with local servers

https://www.youtube.com/watch?v=QxJknYG53jM
Conclusion
Conclusion

• HIV associated TB remains a large public health problem, particularly in sub-Saharan Africa
• The risk of HIV associated TB can be reduced by TB preventive therapy
• Scaling up programmatic management of LTBI may have a large impact on TB control
• However, gaps in the TB prevention cascade need to be addressed