Research gaps for eliminating TB deaths among people living with HIV

GJ Churchyard
25th July 2017
Overview

• Research gaps for preventing TB deaths among PLWHIV
  • Programmatic management of LTBI
    • Tests of infection
    • Short / ultra-short course regimens & durability
    • Treating MDR TB infection
    • Barriers to scaling up programmatic management of LTBI
  • HIV and TB co-treatment
• Conclusion

NO more people living with HIV dying of TB
Programmatic management of LTBI
Tests of LTBI: research gaps

- Current tests of infection are poorly predictive for developing active TB
- Diagnostic tests that are highly predictive of development of TB disease in the near future are urgently needed
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.,
Short & ultra short course regimens & durability
Research gaps

• To develop treatment regimens that are shorter and better tolerated than current short course regimens

• To evaluate strategies to improve durability of LTBI treatment in high transmission settings
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.
Ultra-short-course TB preventive therapy in HIV-infected persons with LTBI (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)
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
Treating MDR TB infection
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.
- ~10% of household contacts are HIV-infected.
WHO 2014 Guidelines for Preventive Therapy for MDR TB Contacts

Research Gaps

- Randomized controlled trials in adult and paediatric populations are required
- The potential role of new drugs with good sterilization properties should be investigated
<table>
<thead>
<tr>
<th>Trials of treatment for MDR TB infection</th>
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<tbody>
<tr>
<td><strong>Intervention</strong></td>
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<tr>
<td>TB-CHAMP</td>
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<tr>
<td>LVF (paediatric dispersible tablet formulation) vs. placebo daily for 6 months</td>
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<tr>
<td>V-QUIN</td>
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<tr>
<td>LVF vs placebo daily for 6 months</td>
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<tr>
<td>PHOENIX</td>
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<tr>
<td>DLM vs INH daily for 26 weeks</td>
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<tr>
<td><strong>Design</strong></td>
</tr>
<tr>
<td>TB-CHAMP</td>
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<tr>
<td>Cluster randomized; superiority</td>
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<tr>
<td>Community-based</td>
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<td>PHOENIX</td>
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<tr>
<td>Cluster randomized; superiority</td>
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<tr>
<td><strong>Target Population</strong></td>
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<tr>
<td>0-5 years of age regardless of TST or HIV status</td>
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<tr>
<td>V-QUIN</td>
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<tr>
<td>All ages (including infants &lt; 6 mo), TST +</td>
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<tr>
<td>PHOENIX</td>
</tr>
<tr>
<td>1. Children 0-5 yrs, HIV +, TST/IGRA + over 5 year olds</td>
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<tr>
<td><strong>Assumptions</strong></td>
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<tr>
<td>TB-CHAMP</td>
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<tr>
<td>LVF decreases incidence from 7 to 3.5%; 80% power</td>
</tr>
<tr>
<td>V-QUIN</td>
</tr>
<tr>
<td>LVF decreases incidence by 70% from 3% untreated; 80% power</td>
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<tr>
<td>PHOENIX</td>
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<tr>
<td>DLM decreases incidence by 50% from 5% to 2.5%; 90% power</td>
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<tr>
<td><strong>Sample size</strong></td>
</tr>
<tr>
<td>788 HH</td>
</tr>
<tr>
<td>1565 contacts</td>
</tr>
<tr>
<td>1326 HH</td>
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<tr>
<td>2785 contacts</td>
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<tr>
<td>1726 HH</td>
</tr>
<tr>
<td>3452 contacts</td>
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<tr>
<td><strong>Sites</strong></td>
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<tr>
<td>South Africa</td>
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<tr>
<td>Viet Nam</td>
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<tr>
<td>ACTG &amp; IMPAACT sites</td>
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</tbody>
</table>
Barriers to programmatic management of LTBI
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.
Universal vs. Symptom-based TB Screening of HIV+ Pregnant Women
A Cluster-randomized Trial

Baseline Characteristics by Arm

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

Yield of TB diagnoses by Arm

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

P = 0.01

Martinson, et al. IAS 2017  TUPDB0204LB
**IMPAACT4TB**: Comparing health system models of 3HP delivery to increase % of eligible PLWHIV starting 3HP

- **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.
Co treatment of HIV and TB disease & infection
Modern ART, Rx of TB disease & infection & DDIs

- Rifamycins likely to remain part of first line TB treatment for some time to come
- Rifamycins are all potent inducers of hepatic drug metabolizing enzymes and drug transport proteins
- Magnitude of induction depends on dose and frequency of dosing
Modern ART, Rx of TB disease & infection & DDIs

- High dose rifamycins may be more effective in
  - PTB, TBM, PLWHIV with low CD4 counts
- Higher-dose Rifampin and Rifapentine are promising candidates for shortened treatment regimens for DS-TB
- Rifamycin based regimens recommended for treatment of LTBI
  - 3HP (high dose isoniazid and rifapentine weekly for 3 months)

Pharmacology of TAF

- **P-glycoprotein (P-gp)** is a transporter found on intestinal enterocytes (and blood-brain-barrier).
- Its job is to keep foreign substances out of the body.
  - Inducing intestinal P-gp reduces bioavailability.
  - Tenofovir is a P-gp substrate; Rifamycins Induce (>inhibit) P-gp.

**Definitions:**
- TDF = tenofovir disoproxil fumarate
- TAF = tenofovir alafenamide
- TFV-DP = tenofovir diphosphate


n.b. This is what you care about

How much do you need?

What is the target exposure?
Rifamycins induce both UGT1A1 and CYP3A4.

How much DTG do we need? What is the ‘target’ exposure?

DTG with RIF - healthy volunteers

DTG with RBT - healthy volunteers

The INSPIRING trial: DTG- vs. EFV-based ART for TB/HIV patients taking HRZE

**Design:** Phase IIIb, randomized, open label trial of DTG and EFV-containing ART regimens in HIV/TB co-infected patients receiving HRZE

- **Arm 1:** DTG (50 mg BID), plus 2NRTI
- **Arm 2:** EFV plus 2NRTI

**Duration:** 48 weeks, plus open-label extension

**Sample size:** 125 adult patients with HIV/TB, ART-naïve; randomized 3:2

**Endpoint:** Proportion with HIV VL < 50 c/mL at Week 48 (snapshot)

**Status:** Fully enrolled, top-line results expected Q3 2017
The effect of Rif on plasma PK of FTC & TAF & intracellular TFV-DP & FTC-TP (RIFT) Trial

Screening of HIV negative healthy volunteers (N = 20 completing all PK phases)

PHASE 1
TAF/FTC 25/200
28 days

PHASE 2
TAF/FTC 25/200 + RIF 600 mg
28 days

PHASE 3
TDF 300 mg
28 days

Study days:
1-28
29-56
57-84

24 h PK
3HP a potential game changer

- WHO prioritized scaling up TB preventive therapy as part of the End TB Strategy
- 3HP a potential “game changer” for TB prevention in HBCs
  - Shorter
  - Less toxic
  - Better adherence
  - Higher barrier to resistance
  - At least similar efficacy
  - Less burden to health programmes to implement
  - Safe with EFV-based regimens
DTG with once-weekly HP: healthy volunteers (n=4)

Total number of HP doses: 3
DTG with once-weekly HP: *healthy volunteers* (n=4)

<table>
<thead>
<tr>
<th>Participant</th>
<th>Tolerability</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Nausea, vomiting, headache, fever with Dose #3 of HP&lt;br&gt; Symptom resolution by 72 hours post-dose&lt;br&gt; Transaminase elevations 72 hours post-dose</td>
</tr>
<tr>
<td>2</td>
<td>Tolerated regimen</td>
</tr>
<tr>
<td>3</td>
<td>Withdrew prior to 3rd dose (family/work obligations)</td>
</tr>
<tr>
<td>4</td>
<td>Nausea, vomiting, fever, orthostatic hypotension with Dose #3 of HP&lt;br&gt; Transaminase elevations 24 hours post-dose&lt;br&gt; Symptom resolution by 72 hours post-dose</td>
</tr>
</tbody>
</table>

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

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

HP dosing: Days 5, 12, 19

Brooks et al  CROI 2017 Poster 409A
**IMPAACT4TB: DTG and 3HP in PLWHIV**

**Objectives**

**Primary Objectives:**
- To evaluate effect of RPT & INH on DTG PK
- To assess the safety of 3HP given with DTG

**Secondary Objectives**
- To determine optimal DTG dose with 3HP
- To estimate % maintaining virologic suppression
- To describe the PK of INH & RPT with DTG
Implications for 3HP implementation

- If safe and no or minimal PK interaction 3HP can continue to be scaled up for PLWHIV
- If PK issue, DTG dose can be adjusted
- 3HP remains an option for household contacts
- Could INH/CTX FDC be an alternative to 3HP for PLWHIV if there is a serious safety concern?
## Use of RIFAMYCINS with DTG or TAF

<table>
<thead>
<tr>
<th>Indication</th>
<th>Rifamycin, Dose</th>
<th>‘DDI’ Trials, ART, TB drugs Study population</th>
<th>Results expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latent TB Infection</td>
<td>Once-weekly Rifapentine (900 mg, as 3HP)</td>
<td>NIH Clinical Centers (NCT02771249) DTG 50 mg QD, DRV/Co 800/150 mg QD Healthy volunteers</td>
<td>CROI 2017, poster 409A Study of DTG with RPT/INH in PLWHIV planned No studies of TAF with 3HP</td>
</tr>
<tr>
<td>TB Disease</td>
<td>Daily standard-dose rifampin (10 mg/kg daily)</td>
<td>INSPIRING EFV, DTG 50 mg BID + HRZE HIV/TB co-infection RADIO DTG 50 or 100 mg QD + RIF Healthy volunteers</td>
<td>Q3 2017 (24-week results) Q4 2017 (HV, PLWHIV to follow)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RIFT TAF/FTC + RIF only Healthy volunteers</td>
<td>Q4 2017 (HV, PLWHIV to follow)</td>
</tr>
<tr>
<td>High-dose rifampin (20-35 mg/kg daily)</td>
<td>Rifavirenz EFV 600 or 800 + HRZE HIV/TB co-infection</td>
<td>No studies of DTG or TAF with high dose RIF</td>
<td></td>
</tr>
<tr>
<td>High-dose Rifapentine (1200 mg daily)</td>
<td>TBTC 31/ACTG 5349 EFV + HPZE or HPZM HIV/TB co-infection</td>
<td>Study of DTG or TAF with high dose RPT proposed</td>
<td></td>
</tr>
</tbody>
</table>
Conclusion

• PLHIV are at high risk of developing TB
• HIV associated TB is associated with worse outcomes
• Research is required to address knowledge gaps to Step up the TB/HIV response
  • Research to optimize HIV/TB co-treatment of TB disease and infection is a high priority
Acknowledgements

- Kelly Dolley
- Richard Chaisson
- Mark Hatherill
- PHOENIx team
**IMPACT4TB: DTG and 3HP in PLWHIV Proposed Study design**

**Design:** Single-arm Phase I/II PK and safety study

**Regimens:** Group 1A: DTG 50mg daily + TDF/FTC +3HP (900/900) → interim analysis

Group 1B and 2: DTG, dose TBD, + TDF/FTC + 3HP

**Duration:** 8 weeks DTG+TDF/FTC (EFV washout)

12 weeks DTG+TDF/FTC+HP

post-treatment DTG access 12 months

**Sample size:** 60 (30 in Group 1 (12 in 1A, 18 in 1B), 30 in Group 2)
Bedaquiline

Overview

- Is an oral diarylquinoline
- MOA: inhibits ATP synthase
- Active against replicating & non-replicating MTB
- Resistance
  - Spontaneous mutations: $1 \times 10^7$ to $10^8$
  - Up regulation of efflux pumps
  - Cross resistance with clofazamine
  - High barrier to resistance
- 99.9% protein bound
- Terminal half life of ~6 months
**Bedaquiline Practice**

- WHO recommends BDQ for 6 months for treatment of:
  - Pre-XDR TB
  - XDR TB
  - MDR TB with intolerance to other drugs
- BDQ may be used to substitute for SLID
- BDQ may be used with caution with renal dysfunction/failure
Bedaquiline

*Use with ARTs*

- Metabolized by CYP3A to M2 metabolite
- BDQ levels reduced by ~50% with efavirenz
- BDQ levels increased by 28% with LPV/r
- BDQ can be combined with 2 NRTIs & NVP or LPV/r, integrase inhibitors
Delamanid

Overview

- Is an oral nitroimidazole
- Inhibits mycolic acid synthesis & releases NO within *MTB*
- Active against replicating & non-replicating bacilli
- Resistance
  - May be due to mutations in nitroreductase gene or genes involved in F420 synthesis or activation
  - Spontaneous mutations occur in $1 \times 10^5$ to $10^6$
  - Low barrier to developing resistance
- Highly protein bound (>99.5%)
- Metabolised by albumin
- Half-life: DLM-34 hrs, DM-6705>150 hours
Delamanid

**Practice**

- DLM has low bioavailability and should be given with food
- DLM must be taken separately from other treatment
- Requires twice daily dosing (100mg BD)
  - Once daily dosing during maintenance phase being studied
- DLM recommended for 24 weeks
- Recommended novel drug for
  - Children (Otsuka 233 PK study in children 0-6+ yrs nearing completion)
  - Efavirenz based ART regimen
  - Patients with prior clofazamine exposure
Delamanid

*Use with ARTs*

- DLM levels not affected by co-administration with Effavirenz
- LPV/r may increase DLM concentration