Short-course rifamycin-based regimens for TB infection (LTBI):
Why countries should scale up this silver bullet for TB prevention among PLHIV

TB/HIV Research Meeting organized by WHO
In conjunction with CROI, Boston, MA, USA
March 4, 2018

Presented by: Kelly Dooley MD, PhD
Johns Hopkins University School of Medicine
Latent TB infection (LTBI)


http://www.who.int/tb/challenges/ltbi_factsheet_25nov15.pdf?ua=1;
Treatment of LTBI reduces risk of TB disease & death in patients with HIV infection, independent of ART

IPT for 6 months
HIV+, TST+, Rio de Janeiro

Temprano ANRS Study
IPT for 6 months
HIV+, TST not done, Côte d’Ivoire

Golub et al CID 2015
Badje et al., Lancet Global Health, 2017
Not prescribed, not taken

Completion rates varied from 6% to 94%

“... and were inversely proportional to the duration of treatment”

WHO 2018 Guidelines on the management of latent tuberculosis infection

Fox et al 2017 IJID
Whither *shorter*-course rifamycin-based treatments?
3HP- Once-weekly rifapentine + INH (900/900mg) x 12 doses

See also:
Schechter et al Am J Respir Crit Care Med 2006
Martinson et al NEJM 2011

Sterling et al AIDS 2016

<table>
<thead>
<tr>
<th></th>
<th>3HP</th>
<th>9H</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td>0.39/p-y</td>
<td>1.25/p-y</td>
</tr>
<tr>
<td><strong>Treatment completion</strong></td>
<td>89%</td>
<td>64%</td>
</tr>
<tr>
<td><strong>Drug d/c from hepatotoxicity</strong></td>
<td>1%</td>
<td>4%</td>
</tr>
</tbody>
</table>

3HP is more likely to be completed, more efficacious, less likely to cause liver toxicity than 9H in PLWH...
**1HP-** Daily rifapentine + INH for 4 weeks:
ACTG A5279, the BRIEF TB trial

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

**Drugs:** Rifapentine 600 mg + Isoniazid 300 mg DAILY x 28 days (vs. 9H)

**Sample size:** 3000 participants

**Population:** HIV-infected individuals ≥13 years old and no evidence of active TB

**Stratification:**
1) CD4+ cell count at entry (<100, 100-250, and >250 cells/mm³)
2) ART use at entry (Yes/No – 50% on ART at entry)

**ART:** Efavirenz or nevirapine based ART permitted while on RPT/INH

**Duration:** 3 years (156 weeks) after the last participant is enrolled
New ART agents, new LTBI options—are they compatible?

**CURRENT ROLE OF NEW ARV OPTIONS IN 2016 WHO GUIDELINES**

<table>
<thead>
<tr>
<th>ARV</th>
<th>Population</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; line</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt; line</th>
<th>3&lt;sup&gt;rd&lt;/sup&gt; line</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFV&lt;sub&gt;400&lt;/sub&gt;</td>
<td>Adult/Adol</td>
<td>✓</td>
<td></td>
<td></td>
<td>• dose reduction in children is not needed (already pK adjusted).</td>
</tr>
<tr>
<td>DTG</td>
<td>Adult/Adol</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>• Twice daily dose probably needed in patients using rifamycins</td>
</tr>
</tbody>
</table>

**MAJOR CLINICAL AND PROGRAMMATIC CHALLENGES WITH NEW ARVS**

**Drug**

- **New**: WHO-recommended treatment option for LTBI
- Filings for registration in multiple countries underway
- Manufacturing scale-up in progress

**DTG**

- 2017/2018
- • Clinical & pK studies (PW, TB, children)
- • Pharmacoeconomic studies

**TAF**

- 2019
- • Clinical & pK studies PW, TB, children, PreP

... and 3HP for treatment of LTBI

Adapted from Meg Doherty, WHO
# Safety, drug interactions of 3HP and 1HP with ART

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>3HP</th>
<th>1HP</th>
<th>Relevance for companion ART</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosing schedule</strong></td>
<td>Once-weekly</td>
<td>Daily</td>
<td>Magnitude of enzyme induction-&gt; QD vs. BID dosing Risk of hypersensitivity?</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>3 months</td>
<td>1 month</td>
<td>Duration of co-treatment Considerations for ART initiation</td>
</tr>
<tr>
<td><strong>H, P doses</strong></td>
<td>900/900</td>
<td>300/600</td>
<td>Toxicity risk</td>
</tr>
</tbody>
</table>

**Questions:**
- Can DTG (and TAF) be given with Rifamycin-based LTBI-Rx without dose adjustment?
- Is the combination safe?
- Are considerations different for patients who are ART-naïve versus on stable ART regimen?
## Use of RIFAMYCINS with DTG or TAF- relevant scenarios

<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><strong>Latent TB Infection</strong></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 DOLPHIN Trial, IMPAACT4TB (NCT03435146), UNITAID TDF/FTC/DTG HIV/LTBI</td>
<td>CROI 2017; Brooks et al CID 2018 No studies of TAF with 3HP Enrolling</td>
</tr>
<tr>
<td></td>
<td>Daily Rifapentine (600 mg, as 1HP)</td>
<td></td>
<td>CROI 2018 Main Study Results No studies of TAF or DTG with 1HP</td>
</tr>
<tr>
<td><strong>TB Disease</strong></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 RIFT TAF/FTC + RIF only, Healthy volunteers</td>
<td>CROI 2018 Wk-24 Results Summer 2018, Wk-48 results Q4 2017 (HV, PLWHIV to follow) CROI 2018 (HV, PLWHIV to follow)</td>
</tr>
<tr>
<td></td>
<td>High-dose Rifapentine (1200 mg daily)</td>
<td>TBTC 31/ACTG 5349 EFV + HPZE or HPZM HIV/TB co-infection</td>
<td>CROI 2018 EFV with high-dose P No studies of TAF or DTG with high-dose RPT</td>
</tr>
</tbody>
</table>
### Use of Rifamycins with DTG or TAF - data gaps

<table>
<thead>
<tr>
<th>Dx</th>
<th>TB Rx</th>
<th>&quot;DDI&quot; Trials</th>
<th>Results expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>LTBI</td>
<td>3HP</td>
<td>NIH Clinical Centers <em>(NCT02771249)</em> DTG 50 mg QD, Healthy volunteers DOLPHIN Trial, IMPAACT4TB <em>(NCT03435146)</em>, UNITAID TDF/FTC/DTG, HIV/LTBI</td>
<td>CROI 2017; Brooks CID 2018 No studies of TAF with 3HP Enrolling</td>
</tr>
<tr>
<td></td>
<td>1HP</td>
<td>CROI 2018 Main Study Results No studies of TAF or DTG with 1HP</td>
<td></td>
</tr>
<tr>
<td>DS-TB</td>
<td>Standard TB Rx</td>
<td>INSPIRING EFV, DTG 50 mg BID + HRZE HIV/TB co-infection RADIO DTG 50 or 100 mg QD + RIF, HV RIFT TAF/FTC + RIF only, HV</td>
<td>CROI 2018 Wk-24 Results Summer 2018, Wk-48 results Q4 2017 (HV, PLWHIV to follow) CROI 2018 (HV, PLWHIV to follow)</td>
</tr>
<tr>
<td></td>
<td>HR₁₀ZE</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>High-dose RPT</td>
<td>TBTC 31/ACTG 5349 EFV + HPZE or HPZM HIV/TB co-infection</td>
<td>No studies of TAF or DTG with high-dose RPT</td>
</tr>
</tbody>
</table>

**KNOWLEDGE GAPS**

- **Is 3HP safe with DTG in patients with HIV/LTBI?**
  - If so, what dose of DTG should be given?
- **Can 3HP and TAF be given together without dose adjustment?**

- **Is 1HP safe with DTG in patients with HIV/LTBI?**
  - If so, what dose of DTG should be given?
- **Can 1HP and TAF be used without dose adjustment?**

- Is DTG 50mg BID (with 2 NRTI) effective for HIV treatment with HRZE?
- Is IRIS more or less common with INSTI compared with other ARVs?
- Would DTG 100 mg once a day work?
- Can TAF be given together with standard dose RIF (plus HZE)? Dose?

- **Can DTG and/or TAF be used with high-dose daily RPT? If so, at what doses?**
What do we know so far?
**Pharmacology of DTG**

- **How much DTG do we need? What is the target?**
  - Target exposure should be greater than the trough concentration ($C_T$) observed at 10 mg once daily (0.30 mcg/mL)
  - Equivalent to the $EC_{90}$ based on $E_{max}$ model from PK/PD analysis of monotherapy study
  - With 50 mg daily, $C_T$ is 1.20 mcg/mL; 0.30 mcg/mL is 25% of that value
  - Requirement that boundaries of the 90% GMR (comparing DTG alone vs. DTG with companion drug) does not fall below 0.25 for the drug interaction

Rifamycins induce both UGT1A1 and CYP3A4

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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
  - Inhibiting intestinal P-gp enhances bioavailability
  - Inducing intestinal P-gp reduces bioavailability (absorption)
- Tenofovir is a P-gp substrate; Rifamycins Induce (>inhibit) P-gp

TDF=tenofovir disoproxil fumarate  TAF=tenofovir alafenamide  TFV-DP=tenofovir diphosphate

Adapted from http://blogs.nature.com/spoonful/files/2013/07/Res2.gif

n.b. This is what you care about
Quick side note apropos TAF+RIF

Study Design & Methods: The RIFT Trial

- **Day 1**: TAF/FTC 25/200 mg once daily for 28 days
- **Day 28**: TAF/FTC 25/200 mg once daily plus rifampicin 600 mg once for 28 days
- **Day 56**: TDF 300 mg once daily for 28 days (DAYS 56-84)
- **Day 84**: TDF 300 mg once daily for 28 days (DAYS 56-84)

- 21 Healthy participants
- Plasma PK sampling: pre-dose, 1, 2, 4, 6, 8, 12, 24h post-dose
- PBMC PK sampling: pre-dose, 2, 8, and 24h post dose
- Measuring Plasma TFV, FTC, and TAF concentrations
- Measuring intracellular (PBMC) tenofovir diphosphate (TFV-DP)

Please visit CROI presentation by Maddalena Cerrone on Monday at 11:30
Thanks to Omamah Alfirisi for sharing this design slide
The **INSPIRING** trial - **DTG** - vs. EFV-based ART for patients with TB/HIV co-infection 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:** Complete, 24-wk results to be presented Monday at CROI

What did we learn from this trial that is relevant for the question at hand?

DTG 50 mg twice daily was well-tolerated with daily rifampicin-based full TB treatment
DTG with once-weekly HP: *healthy volunteers* (n=4)

Total number of HP doses: 3

Brooks et al. CID 2018 PMID 29415190
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 Symptom resolution by 72 hours post-dose 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 3(^{rd}) dose (family/work obligations)</td>
</tr>
<tr>
<td>4</td>
<td>Nausea, vomiting, fever, orthostatic hypotension with Dose #3 of HP Transaminase elevations 24 hours post-dose Symptom resolution by 72 hours post-dose</td>
</tr>
</tbody>
</table>

*Study terminated early because of AE in two healthy volunteers*
Cytokine elevations, RPT and INH PK

Note: RPT, desRPT, and DTG levels were not elevated; INH levels very high
Impact of HP on DTG concentrations

**Figure 6. Steady-state DTG Cₜ Levels**

- **HP dosing:** Days 5, 12, 19
- **5.3x protein-adjusted IC₉₀ for DTG (0.064 ug/mL)**
  - **(range 0.9 – 11.0)**

<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>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 4 (n=4)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Day 5 (n=4)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Day 14 (n=4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Day 15 (n=4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Day 18 (n=4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Day 19 (n=3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 20 (n=3)</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

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

Fig 6. Cₜ = 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 Cₜ value. *p<0.05
But what do we know about 3HP in PLHIV (vs. HIV-)?

From TBTC 26/ACTG 5259

<table>
<thead>
<tr>
<th></th>
<th>HIV-uninfected</th>
<th>HIV-infected</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy 3HP- TB rate</strong></td>
<td>0.83%</td>
<td>0.83%</td>
<td>0.018</td>
</tr>
<tr>
<td>(Efficacy 9H) – TB rate</td>
<td>0.53%</td>
<td>3.50%</td>
<td></td>
</tr>
<tr>
<td><strong>Flu-like symptoms/systemic drug reactions</strong></td>
<td>4.6%</td>
<td>1.0%</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Treatment completion</strong></td>
<td>80%</td>
<td>89%</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Discontinuation due to ADR</strong></td>
<td>5.3%</td>
<td>3.4%</td>
<td>0.32</td>
</tr>
<tr>
<td><strong>Discontinuation due to liver toxicity</strong></td>
<td>0.5%</td>
<td>1.0%</td>
<td>0.30</td>
</tr>
<tr>
<td><strong>SAE</strong></td>
<td>2.2%</td>
<td>3.9%</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td>0.9%</td>
<td>2.9%</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Completion rate higher, efficacy is similar (unlike 9H), flu-like symptoms less common

Sterling et al AIDS 2016 (dig deep to find supplemental materials)
Findings, rationale to test 3HP+DTG in patients with LTBI/HIV

• Both DTG and 3HP are being rolled out globally, both now recommended by WHO

• 3HP is likely better than 9H in PLHIV-- more effective, better-tolerated, higher completion, less hepatotoxic

• In healthy volunteers, reductions in DTG exposures did not seem to surpass a 75% reduction in exposures for significant time over a week of treatment (DTG dose adjustment may not be needed; must check to be certain)

• In healthy volunteers, two had adverse reactions; need to characterize/understand safety in patients with HIV/LTBI
  • Healthy volunteer effect? Isoniazid hypersensitivity? DTG+RPT?
  • RPT and DTG levels were not elevated
  • DTG well-tolerated with daily rifampicin (in INSPIRING trial)
  • Once-weekly HP well-tolerated in PLHIV, including patients taking EFV or RAL
  • INH levels very high in pts with reaction
  • Acute elevations in cytokines
DOLutegravir-P(rifapentine)-H(isoniazid) INvestigation (DOLPHIN trial) in IMPAACT4TB DTG and 3HP in patients with LTBI & HIV

Study design

Design: Single-arm Phase I/II PK and safety study of DTG-based ART and once-weekly rifapentine plus isoniazid (3HP) in adults with HIV infection (on ART with suppressed viral load) who have indication for treatment of LTBI

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)
But will it be available? Affordable?
Activism, pressure from civil society, demonstration projects, drug company commitment, generics?, public funding...

Application to add rifapentine to the Essential List of Medicines
Will be in GDF catalogue imminently

as a medicine for the treatment of latent tuberculosis infection
IMPAACT4TB
Scaling up 3HP for TB Prevention

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

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

High Middle Income Countries
South Africa, Brazil

Funded by UNITAID
Summary

• TB killed 400,000 persons with HIV infection last year, it’s the #1 cause of death in PLWHIV in many settings.

• Current prevention strategies are insufficient.

• 3HP may be better than 9H for PLHIV- easier to complete, more effective, better tolerated

• Dolutegravir and TAF for HIV, and 3HP for treatment of latent TB are being scaled up globally; 1HP, if promising, may follow

• Data gaps for use of new HIV drugs (e.g. DTG, TAF) with what might be the best treatments for LTBI are being filled– important, to ensure these treatments are available for all
  • Specifically we need to characterize and understand the safety and PK of dolutegravir when it’s given with 3HP, in the target population
  • Healthy volunteers ≠ patients

• Complacency can take many forms
Thank you.
Extra slides