Latest TB Science
CROI 2021

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Disclosures

Type of affiliation / financial interest

• Receipt of grants/research supports:
• Receipt of honoraria or consultation fees:
• Participation in a company sponsored speaker’s bureau:
• Stock shareholder:
• Spouse/partner:

• To my unit from Janssen, Merck, Viiv and Gilead
• To me from Janssen, Merck, Viiv and Gilead, Thera
  • None
  • None
  • None
Short Course TB therapy

High dose rifampicin in TBM

Effect of High dose rifampicin on ARVs

ARVs and Rifapentine in LTBI

Contact Tracing

Targeted TB Testing
Can TB Treatment be Made Easier?

TB treatment is Complex
– at least 6 months and multiple pills

Shorten TB treatment to 4 months
• OFLOTUB study (gatifloxacin) **FAILED**
• RIFAQUIN study (moxifloxacin/rifapentine) **FAILED**
• ReMoxTB study (moxi instead of E or H) **FAILED**

• **S31/A5349 (Hi Dose RPT/INH/PZA/MOX)** Success!

But does it work in HIV /TB?
Study 31/A5349
Shorten TB Treatment to 4 months

International, randomized, open-label, phase 3, non-inferiority trial

2HRZE / 4HR
“Control”

2HPZE / 2HP
“RPT”

2HPZM / 2HPM
“RPT-MOX”

Pettit et al CROI 2021
Study Population

214 (8%) were HIV positive
Median CD4 was 344
## Results-Baseline

<table>
<thead>
<tr>
<th>Microbiologically Eligible Population Total n=2343</th>
<th>HIV-seropositive N=194</th>
<th>HIV-negative* N=2148</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median (IQR) age, years</strong></td>
<td>36 (30 - 43)</td>
<td>30 (24 - 41)</td>
</tr>
<tr>
<td><strong>Male sex</strong></td>
<td>120 (62%)</td>
<td>1549 (72%)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>0 (0%)</td>
<td>268 (12%)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>180 (93%)</td>
<td>1495 (70%)</td>
</tr>
<tr>
<td>White</td>
<td>2 (1%)</td>
<td>34 (2%)</td>
</tr>
<tr>
<td>More than one race</td>
<td>12 (6%)</td>
<td>346 (16%)</td>
</tr>
<tr>
<td>Missing</td>
<td>0 (0%)</td>
<td>5 (0.2%)</td>
</tr>
<tr>
<td><strong>Median (IQR) baseline BMI, kg/m²</strong></td>
<td>19 (17 - 22)</td>
<td>19 (17 - 21)</td>
</tr>
<tr>
<td><strong>Cavitary Disease</strong></td>
<td>139 (72%)</td>
<td>1563 (73%)</td>
</tr>
<tr>
<td><strong>Current smoking</strong></td>
<td>41 (21%)</td>
<td>500 (23%)</td>
</tr>
<tr>
<td><strong>Diabetes Mellitus</strong></td>
<td>1 (0.5%)</td>
<td>76 (3%)</td>
</tr>
</tbody>
</table>
## Efficacy and Safety

<table>
<thead>
<tr>
<th>Efficacy outcomes (% favorable)</th>
<th>Control</th>
<th>Rifapentine Moxifloxacin</th>
<th>Rifapentine</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microbiologically eligible</td>
<td>50/64 (78%)</td>
<td>53/62 (85%)</td>
<td>48/68 (71%)</td>
<td>151/194 (78%)</td>
</tr>
<tr>
<td>Assessable</td>
<td>50/59 (85%)</td>
<td>53/58 (91%)</td>
<td>48/65 (74%)</td>
<td>151/182 (83%)</td>
</tr>
<tr>
<td>Per-Protocol 95</td>
<td>44/45 (98%)</td>
<td>43/45 (96%)</td>
<td>41/52 (79%)</td>
<td>128/142 (90%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Safety Outcomes</th>
<th>Control</th>
<th>Rifapentine Moxifloxacin</th>
<th>Rifapentine</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total safety population</td>
<td>70</td>
<td>72</td>
<td>71</td>
<td>213</td>
</tr>
<tr>
<td>Primary Safety Outcome</td>
<td>15 (21%)</td>
<td>10 (14%)</td>
<td>12 (17%)</td>
<td>37 (17%)</td>
</tr>
<tr>
<td>(Grade 3-5 AEs on treatment)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAEs during treatment</td>
<td>7 (10%)</td>
<td>2 (3%)</td>
<td>6 (8%)</td>
<td>15 (7%)</td>
</tr>
<tr>
<td>Deaths</td>
<td>2 (3%)</td>
<td>0 (0%)</td>
<td>3 (4%)</td>
<td>5 (2%)</td>
</tr>
</tbody>
</table>
Study 31- Conclusions

• 4 month Rif-Moxi combination non-inferior to standard 6 month treatment
• Combination Rif –Moxi efficacious in HIV subgroup
• Major milestone in TB Rx
Short Course
MDR/XDR Treatment

Phase 3 Trial in XDR-TB*
Followed throughout 30 months

Extensively Drug-Resistant
Treatment-Intolerant or Non-Responsive
Multidrug-Resistant
TB Participants

Pretomanid
200 mg qd
Bedaquiline
200 mg tiw after 2 week load
Linezolid
1200 mg qd*

6-9 MONTHS OF TREATMENT**
Primary endpoint
• 109 participants (65% XDR-TB, 35% MDR-TB; 51% HIV+) were enrolled and comprised the ITT population (MITT population = 107)

• All surviving participants, except 1 withdrawal, completed the full course of therapy

• At the primary endpoint six months after treatment, as previously reported, there were 98 with favorable outcomes (90% ITT, 92% mITT)

• After the primary endpoint one participant relapsed 15 months after treatment and one was lost to follow up

• Favorable outcomes 24 months post completion of treatment were sustained (88% ITT, 91% mITT) independent of sex or HIV status.
High Dose Rifampicin in TBM

• Should we use higher doses of rifampicin than we do in standard treatment?
• Rifampicin concentration may be low in the CNS.
• Data suggests link between dose and survival
• In Pulmonary TB high dose rifampicin reduces time to culture conversion in sputum
Study Design

Inclusion Criteria

HIV Pos=55/60 patients
Median CD4 50

Cresswell et al CROI 2021
Drug Exposure-Serum

Rifampicin total serum exposure - $AUC_{0-24}$

![Graph showing serum total exposure (AUC 0-24 h.mg/L) for different trial arms (IV-20, PO-35, control).]

<table>
<thead>
<tr>
<th>AUC$_{0-24}$ (h.mg/L)</th>
<th>IV-20</th>
<th>PO-35</th>
<th>control</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geometric mean (95% CI)</td>
<td>249 (202 - 306)</td>
<td>327 (248 - 430)</td>
<td>42.9 (29.2 - 63.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ratio to control</td>
<td>5.80</td>
<td>7.62</td>
<td>1 (ref)</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>
Drug Exposure-CSF

Rifampicin CSF concentration - $C_{CSF}$

<table>
<thead>
<tr>
<th>$C_{CSF}$ (mg/L)</th>
<th>IV-20</th>
<th>PO-35</th>
<th>Control</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n observations</td>
<td>15</td>
<td>19</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Geometric mean</td>
<td>1.74</td>
<td>2.17</td>
<td>0.27 $^h$</td>
<td>0.058</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(1.20 - 2.53)</td>
<td>(1.64 - 2.86)</td>
<td>(0.17 - 0.45)</td>
<td></td>
</tr>
<tr>
<td>Ratio to control</td>
<td>6.44</td>
<td>8.00</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (%) with detectable CSF level</td>
<td>15 (100%)</td>
<td>19 (100%)</td>
<td>8 (44%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>n (%) with concentration above rifampicin MIC$^1$ (1 mg/L)</td>
<td>14 (93.3%)</td>
<td>18 (94.7%)</td>
<td>2 (11.1%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Outcomes/Conclusions

K-M curve Time to death

• In PO-35 and IV-20 groups >90%
  • had CSF levels above MIC

• No Excess toxicity

• But NO difference in clinical outcome
  • but not powered to do this
What is the Effect of High dose Rifampicin on ARVs?

### Efavirenz

<table>
<thead>
<tr>
<th>EFV mid-dose concentrations</th>
<th>Arm 2A EFV + RIF 35 (n=15)</th>
<th>Arm 2B EFV + RIF 10 (n=19)</th>
<th>Fisher’s Exact P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 mg/L, n(%)</td>
<td>1 (6.7)</td>
<td>1 (5.3)</td>
<td>P&gt;0.999</td>
</tr>
<tr>
<td>≥1 mg/L, n(%)</td>
<td>14 (93.3)</td>
<td>18 (94.7)</td>
<td></td>
</tr>
</tbody>
</table>

### Dolutegravir 50mg BD

<table>
<thead>
<tr>
<th>DTG C₀</th>
<th>Arm 1A DTG+RIF 35 (n=25)</th>
<th>Arm 1B DTG+ RIF 10 (n=21)</th>
<th>Fisher’s Exact P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.064 mg/L, n(%)</td>
<td>4 (16.0)</td>
<td>1 (4.8)</td>
<td>P=0.35</td>
</tr>
<tr>
<td>≥0.064 mg/L, n(%)</td>
<td>21 (84.0)</td>
<td>20 (95.2)</td>
<td></td>
</tr>
</tbody>
</table>

Still had similar viral suppression
Short Course LTBI
Now One month of therapy is Possible

But what about drug Interactions with ARVs?
INSTIs and Rifapentine

What The Database predicts To INSTI levels with Rifapentine

Bictegravir concentrations with Rifapentine ..And 2/16 patients had viral rebound from day 15 to day 30

H-Y Sun et al  Croi 2021
What is the best way of Contact Tracing of TB?
Two different Strategies

Standard of Care
Referral Letters for all HH members
M1 telephone check-in visit

OR

Intensive Contact Tracing
Home-based Universal testing
  TB disease: sputum: Xpert and Culture
  TST
  HIV counselling and testing
Immediate referral:
  TB treatment
  ART
  Home initiation  IPT
M3 check-in visit
No Difference in Outcome

<table>
<thead>
<tr>
<th>Trial outcomes at 15 Months</th>
<th>Referral Letter</th>
<th>Int. Contact Tracing</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contacts diagnosed with TB</td>
<td>31/2551 (0.92/100py)</td>
<td>51/3188 (1.24/100py)</td>
<td>1.33 (0.83, 2.16)</td>
</tr>
<tr>
<td>Contact deaths</td>
<td>49/3961 (1.2%)</td>
<td>42/4242 (1.0%)</td>
<td>0.72 (0.47, 1.10)</td>
</tr>
<tr>
<td>TB or death</td>
<td>80/2600 (3.1%)</td>
<td>93/3230 (2.9%)</td>
<td>0.90 (0.66, 1.24)</td>
</tr>
</tbody>
</table>

Standard of Care (Letters to Contacts) saves on valuable resources used in the Intensive Strategy in a SA setting.
Targeted Universal Testing For TB in Clinics

- To ascertain if augmenting routine symptom-based sputum testing with Targeted Universal Testing for TB (TUTT) in clinics increased the number of patients diagnosed with TB per month by 25%

- Targeted clinic attendees:
  - HIV+
  - Close contact <1 year
  - Prior TB <2 year

Trial Outcome: TB patients diagnosed per month per clinic
TARGETED UNIVERSAL TESTING FOR TB IN CLINICS

Study Design

STANDARD OF CARE

30 Primary healthcare facilities

Symptom based screening for TB

Xpert Ultra MTB/RIF

STUDY INTERVENTION

30 Primary healthcare clinics

No TUTT Risk Factor or did not consent

TUTT Risk factor

Xpert Ultra MTB/RIF + Liquid culture

Symptom based screening for TB

Xpert Ultra MTB/RIF

Labinah et al CROI 2021
Results

The yield of universal risk-factor based testing for TB was high in the three targeted risk groups:

- HIV-infected: 5%
- TB contacts: 8%
- Prior TB: 12%

Clinics are diagnosing 8% fewer patients with TB year on-year under the standard of care

The TUTT intervention resulted in a 17% net increase in TB cases diagnosed per clinic per month as compared to the standard of care clinics.
Conclusions

• We now have 4 month Treatment for Drug sensitive TB and 6 months for MDR/XDR.
• High Dose Rifampicin improves CNS concentrations and trials are planned for clinical benefit.
• High dose rifampicin lowers DTG levels without effecting clinical outcomes.
• Rifapentine should not be used with Bictegravir.
• Simple Contact tracing of contacts is as efficient as intense methods and saves on resources.
• Targeted TB Testing Improves Yields.