Controlling Tuberculosis: The Impact of Adherence on Treatment and Drug Development

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Disclosures:

- I receive funding from BMGF, NIH, UNITAID and CDC for TB-related research
- I serve as a paid consultant for WHO on various task forces related to TB Therapeutics and treatment guidelines
- I serve as a Scientific Advisor to TB Alliance, NGO
- I serve as a Scientific Advisor to Sanofi Aventis on TB Therapeutics
- I serve on Core Science Groups for TB Therapeutics in CDC and ACTG (NIH funded) Consortia
Tuberculosis: Global Scourge

- Infectious disease that kills most people in the world
- 9.4 million cases, 1.8 million deaths/year
- Most common cause of death in HIV-infected patients
- 1/3 of the world’s population latently infected
- Resistance is substantial (DR, MDR, XDR)
Current TB treatment (50 years old)

- Drug sensitive TB is treated for at least 6 months with 50-year-old drugs
- MDR-TB requires 9-24 months of highly toxic, poorly efficacious drugs

“intensive phase”
- isoniazid
- rifampin
- pyrazinamide
- ethambutol

“continuation phase”
- isoniazid
- rifampin 10 mg/kg

Controlled Settings 90-95%

months

Standard of Care
Treatment success globally

**Africa**

**South-East Asia**

**Europe**

WHO 2018 Global Report
Priority-Setting for Novel Drug Regimens to Treat TB
An Epidemiologic Model.

<table>
<thead>
<tr>
<th>Regimen characteristic</th>
<th>Values modeled for novel RS TB regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td>• Minimal: 94%</td>
</tr>
<tr>
<td></td>
<td>• Intermediate: 97%</td>
</tr>
<tr>
<td></td>
<td>• Optimistic: 99%</td>
</tr>
<tr>
<td><strong>Barrier to resistance</strong></td>
<td>• Minimal: 5%</td>
</tr>
<tr>
<td></td>
<td>• Intermediate: 0.8%</td>
</tr>
<tr>
<td></td>
<td>• Optimistic: 0%</td>
</tr>
<tr>
<td><strong>Preexisting novel-regimen resistance</strong></td>
<td>• Minimal: 10%</td>
</tr>
<tr>
<td></td>
<td>• Intermediate: 3%</td>
</tr>
<tr>
<td></td>
<td>• Optimistic: 0%</td>
</tr>
<tr>
<td><strong>Medical contraindications</strong></td>
<td>• Minimal: 11%</td>
</tr>
<tr>
<td></td>
<td>• Intermediate: 5%</td>
</tr>
<tr>
<td></td>
<td>• Optimistic: 0%</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>• Minimal: 6 mo</td>
</tr>
<tr>
<td></td>
<td>• Intermediate: 4 mo</td>
</tr>
<tr>
<td></td>
<td>• Optimistic: 2 mo</td>
</tr>
<tr>
<td><strong>Tolerability/ease of adherence</strong></td>
<td>• Minimal: 0%</td>
</tr>
<tr>
<td></td>
<td>• Intermediate: 25%</td>
</tr>
<tr>
<td></td>
<td>• Optimistic: 50%</td>
</tr>
</tbody>
</table>

Target Regimen Profile- Drug-Sensitive TB

Priority attributes

• 2-4 month duration
• >95% cure rate
• No requirement for lab testing for safety
• No drug interactions with first-line HIV drugs
• High barrier to emergence of resistance
Treatment Shortening Trials

Phase 2A
- EBA
- 2 weeks
- DOT

Phase 2B
- Culture conversion
- 2 months
- DOT

Phase 3 randomized controlled trial
- Unfavorable outcome (not relapse)
- 18 months
- Gold standard
- Various adherence strategy

Study Design and Endpoints
TB ReFLECT
One approach to improving tuberculosis therapy is to shorten the duration from 6 months to 4 months. In this trial in over 1900 patients with smear-positive tuberculosis, two 4-month moxifloxacin-based regimens did not perform as well as the standard 6-month regimen.

Shortening treatment regimens for tuberculosis may help control the disease. In this trial, patients with tuberculosis in sub-Saharan Africa received either a 4-month gatifloxacin-based regimen or the standard 6-month regimen. The gatifloxacin regimen was less effective.

In this report from sub-Saharan Africa, a 4-month regimen of moxifloxacin and rifapentine for pulmonary tuberculosis was not as beneficial as two 6-month regimens, and the benefits of a 6-month regimen based on rifapentine were similar to those of the standard 6-month regimen.
TB-ReFLECT: TB Re-Analysis of FluoroquinoLone Clinical Trials

- Individual Level Patient Meta Analysis (n=3709)

- Aimed to:
  - Identify **patient groups eligible for 4 month treatment**
    - Profile “hard-to-treat” patient populations
    - Identify **drug-specific** factors predicted of unfavorable response
    - To provide data-driven evidence for immediate impact on TB treatment implementation

- Findings validated in an independent dataset (Johnson, et al., TBRU trial)

Trials and Adherence Designs

A: OFLOTUB
Control Arm: 2EHRZ/4HR/2HR

B: REMoxTB
Control Arm: 2EHRZ/4HR

C: RIFAQUIN
Control Arm: 2EHRZ/4HR

Experimetal Arm 1: 2EHRZ/3HR
Experimetal Arm 2: 2EHRZ/3HR
Experimetal Arm 3: 2EHRZ/2PM
Experimetal Arm 4: 2EHRZ/2PM

Time (weeks)
## Standard-of-Care, Adherence impact

### Baseline characteristics, on treatment culture status, and adherence

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. unfavorable outcomes/ No. of study participants (%)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adherence</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100%</td>
<td>70/824 (8)</td>
<td>Reference</td>
</tr>
<tr>
<td>&gt; 90 and &lt; 100%</td>
<td>23/192 (12)</td>
<td>1.8 (1.1 – 3.0)</td>
</tr>
<tr>
<td>&lt;=90%</td>
<td>9/30 (30)</td>
<td>5.4 (2.5 – 11.5)</td>
</tr>
<tr>
<td><strong>HIV status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>75/884 (8)</td>
<td>Reference</td>
</tr>
<tr>
<td>Positive</td>
<td>27/162 (17)</td>
<td>3.0 (1.8 – 5.0)</td>
</tr>
<tr>
<td><strong>Month 4 culture status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>84/951 (9)</td>
<td>Reference</td>
</tr>
<tr>
<td>Positive</td>
<td>18/95 (19)</td>
<td>2.4 (1.4 – 4.3)</td>
</tr>
<tr>
<td><strong>Month 2 culture status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>62/800 (8)</td>
<td>Reference</td>
</tr>
<tr>
<td>Positive</td>
<td>40/246 (16)</td>
<td>2.1 (1.4 – 3.3)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>21/304 (7)</td>
<td>Reference</td>
</tr>
<tr>
<td>Male</td>
<td>81/742 (11)</td>
<td>1.9 (1.1 – 3.1)</td>
</tr>
</tbody>
</table>
## 4-Month Regimens, Adherence impact

### Baseline characteristics, on treatment culture status, and adherence

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<th>No. unfavorable outcomes/No. of study participants (%)</th>
<th>Hazard Ratio (95% CI)</th>
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</thead>
<tbody>
<tr>
<td><strong>Adherence</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100%</td>
<td>238/1348 (18)</td>
<td>Reference</td>
</tr>
<tr>
<td>&gt; 90 and &lt; 100%</td>
<td>64/288 (22)</td>
<td>1.4 (1.0 – 1.9)</td>
</tr>
<tr>
<td>&lt;=90%</td>
<td>15/32 (47)</td>
<td>5.7 (3.3 – 9.9)</td>
</tr>
<tr>
<td><strong>Month 2 culture status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>212/1357 (16)</td>
<td>Reference</td>
</tr>
<tr>
<td>Positive</td>
<td>105/311 (34)</td>
<td>2.2 (1.7 – 2.9)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>64/492 (13)</td>
<td>Reference</td>
</tr>
<tr>
<td>Female</td>
<td>253/1176 (22)</td>
<td>1.6 (1.2 – 2.1)</td>
</tr>
<tr>
<td><strong>Smear grade</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smear 0+ or 1+</td>
<td>53/388 (14)</td>
<td>Reference</td>
</tr>
<tr>
<td>Smear 2+</td>
<td>72/430 (17)</td>
<td>1.2 (0.8 – 1.7)</td>
</tr>
<tr>
<td>Smear 3+</td>
<td>192/850 (23)</td>
<td>1.6 (1.2 – 2.3)</td>
</tr>
<tr>
<td><strong>HIV status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>270/1463 (18)</td>
<td>Reference</td>
</tr>
<tr>
<td>Positive</td>
<td>47/205 (23)</td>
<td>1.5 (1.1 – 2.0)</td>
</tr>
<tr>
<td>BMI (per 5 kg/m² decrease)</td>
<td>†</td>
<td>1.4 (1.1 – 1.7)</td>
</tr>
<tr>
<td>Age (per 10 years increase)</td>
<td>†</td>
<td>1.1 (1.0 – 1.2)</td>
</tr>
</tbody>
</table>
Adherence and 6/7 vs 7/7 Pill Counts

A. REMoxTB and RIFAQUIN analysis (7/7 doses per week)

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. Unfavorable Outcomes/ No. Study Participants (%)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total doses</td>
<td></td>
<td>Reference</td>
</tr>
<tr>
<td>182 (7/7 doses per week)</td>
<td>26/452 (6)</td>
<td>2.4 (1.3 – 4.3)</td>
</tr>
<tr>
<td>156–181</td>
<td>22/217 (10)</td>
<td>28.9 (10.5 – 80.0)</td>
</tr>
<tr>
<td>112–155</td>
<td>13/18 (72)</td>
<td>0.9 (0.8 – 1.1)</td>
</tr>
<tr>
<td>Treatment Duration (per week)</td>
<td>*</td>
<td></td>
</tr>
</tbody>
</table>

B. OFLOTUB analysis (6/7 doses per week)

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. Unfavorable Outcomes/ No. Study Participants (%)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total doses</td>
<td></td>
<td>Reference</td>
</tr>
<tr>
<td>144 (6/7 doses per week)</td>
<td>50/533 (9)</td>
<td>2.4 (1.2 – 4.8)</td>
</tr>
<tr>
<td>112–143</td>
<td>13/65 (20)</td>
<td>0.7 (0.5 – 0.9)</td>
</tr>
<tr>
<td>Treatment Duration (per week)</td>
<td>*</td>
<td></td>
</tr>
</tbody>
</table>

C. Kaplan Meier estimates

Probability of Favorable Outcome

- 7/7 doses per week, 26 weeks, (N = 452)
- 6/7 doses per week, 24 weeks, (N = 544)

Months since Start of Treatment

0 6 12 18 24
IN ADHERENCE, PATTERNS and TIMING MATTER
Very different health outcomes are possible, indeed likely

Each of the 4 patients took 75% of prescribed doses during a 3-month period
Adherence in Continuation Phase, SOC

REMOX (7/7)  
OFLOTUB (6/7)
Monthly Adherence, SOC

REMOX (7/7)  OFLOTUB (6/7)
Distribution of Monthly Missed Doses in Nonadherent patients: Non-random patterns drive the treatment failure

80-99% adherence
Non-random Patterns Drive the Treatment Failure

100% Adherence
80-99% Adherence and Random patterns
80-99% Adherence and Non-Random patterns
Pharmacological Rationale for Impact of Clustering of Missed Doses

- **0 missed doses**: Concentration above MIC throughout.
- **4 x 1 missed doses**: Concentration significantly below MIC for 7 hours.
- **2 x 2 missed doses**: Concentration below MIC for 15 hours.
- **1 x 4 missed doses**: Concentration below MIC for 19 hours.
Catalysis Biomarker Study

Predictors

- PET-CT scan
- Chest X-ray
- GeneXpert
- RNA-seq
- Strain
- Adherence
- Bacteria RNA
- Demographic

96 MGIT TTN results

<table>
<thead>
<tr>
<th>Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 uncertain treatment outcome (EOT)</td>
</tr>
<tr>
<td>8 failed (EOT)</td>
</tr>
<tr>
<td>84 cured (EOT)</td>
</tr>
<tr>
<td>12 recurrence (EOT + 1)</td>
</tr>
<tr>
<td>72 cured (EOT + 1)</td>
</tr>
</tbody>
</table>

20 unfavorable
Adherence one of the best “biomarkers” of treatment failure

a

b

TTN category
- <= Week 4
- Week 8
- Week 12
- Week 24
- Week 24+
Hard-to-Treat Patients Benefit Most from Adherence Interventions

Control (No intervention):
% Adherence = 77.4%*

Text & Medication Monitor Intervention:
% Adherence = 88.6%*

All patients

Hard-to-Treat patients

Easy-to-Treat patients

*Data from Lui et al, PLOS Med, 2015
Cure TB Strategy with Adherence Intervention:

Clinical Trial Simulations, Pragmatic Trial with Adherence Intervention

**Strategy 1: Stratified Duration**

“one-size-fits-all

**Strategy 2: Stratified Duration and Adherence intervention**
Adherence and Forgiveness as Determinants of Efficacy vs Effectiveness and Clinical Trial Success

Randomized Clinical Trial

Control >95% Cure

A New Regimen 90% Cure

Efficacy

Implementation, Pragmatic Clinical Trial

80% Success Rates

85% Success Rates

Effectiveness (Regimens with drugs with long half-life)
Summary

- Partial- or non-adherence is the rule, rather than the exception, in clinical trials and in the field.

- HRZE is unforgiving regimen requiring large resources for optimizing adherence, but performing excellent in the trials.

- The gap between efficacy and effectiveness is much larger than for the unforgiving drug versus a ‘forgiving” drug.

- Forgiveness of the drug should be factored in non-inferiority margin.

- We will learn great deal from dosing history data collected with new devices.
Data Contributors:
• TB Alliance
• St. George's, University of London
• WHO
• Case Western

TB ReFLECT steering committee:
• Christian LIENHARDT
• Debra HANNA
• David HERMAN
• Katherine FIELDING
• Patrick PHILLIPS
• Payam NAHID
• Carl MENDEL
• Gerry DAVIS
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• William FOX
• Rada SAVIC
• Natasha STRYDOM
• Leah Jarlsberg
• Yusi CHEN

Catalysis team
• Jill WINTER

Thank you!
Value of PK in context of missing adherence data

- Minimal if no dosing history data
- Biased interpretation of exposure/response
- Up to 10 fold variation within a patient assuming full adherence
- With correct dosing histories: no significant variation

Atazanavir PK “steady-state” troughs

- Additional trough samples at week 8, 16, 24

![Graph showing trough concentrations over weeks 4 to 24]