Simplifying TB Treatment

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**Disclaimer**

Opinions herein are those of the author, and do not reflect an official position of the Centers for Disease Control and Prevention
Prof Mitchison and team at Hammersmith Hospital, London ~1975
Profs Jindani and Mitchison during visit to CDC Atlanta, 2012
What is “simplified TB treatment”? 
to make less complicated, clearer, or easier; to reduce (an equation, fraction, etc) to a simpler form by cancellation of common factors, regrouping of terms in the same variable, etc.

to make something less complicated and therefore easier to understand:

to make simple or simpler: such as
a : to reduce to basic essentials
b : to diminish in scope or complexity : streamline
c : to make more intelligible : clarify
Components of TB treatment:

- Selection of drugs
- Number of drugs
- Dosing of drugs
- Sequence of drugs
- Rhythm of administration
- Ensuring/monitoring efficacy:
  - Bacteriologic
  - Pharmacokinetic
- Monitoring/managing toxicity
- Monitoring/managing acquired resistance
- Monitoring/assuring adherence
- Duration of treatment
What might be Simplified TB Treatment?

• Specific (?)simpler) drugs
• Fewer drugs
• Uniform doses
• No sequencing (IP→CP)
• Less frequent administration
• More effective therapies
• Less toxicity
• Less risk of acquired resistance
• Easier ways to assure adherence
• Shorter treatments
Selection of Drugs

• Recommendations have followed the availability and investigation of new drugs

• Initially, streptomycin, PAS, INH became the 18-month standard (mid 1950’s)

• Rifamycins reduced duration by 50% (1970’s)

• PZA allowed shortening from 9 to 6 months (1990)

• Need for MDR therapy drives choices of new drugs
Selection of Drugs

MDR Trials recently/currently underway:

• STREAM st 1-2  - 9MC+Inj→6-9LxCB+-Inj
• Otsuka 213        - Delamanid + OBR
• NeXT            - BLzLx+(Eth/PZA/hdINH)
• NIX and ZeNiX    - BPaLz
• MDR-END         - DLzLxZ
• end TB          - 9BLzMZ/BLzCLxZ/BLzDLxZ/
                          DLzCLxZ/DCMZ
• TB PRACTECAL    - 6BPaMLz/6BPaLzC/6BPaLz
• SIMPLICITB      - BPaMZ
• BEAT TB         - 6BD+Lx/Lz
Number of drugs

• Early trials 1948-52 established need for >1 drug; by mid-1950s the standard had become 3 drugs
• Since MRC trials, SCC has included 4 drugs: SHRZ
• BTA and CDC trials led to EHRZ, and confirmed treatment shortening effect of PZA
• MDR therapy has favored 5 active drugs, in part due to relative weak efficacy of available agents
Dosing of Drugs

• Weight based vs standardized

• Establishment of dosing represented compromises on diverse features (e.g., efficacy, toxicity, cost); not optimized

• Varied by frequency of administration

• Adjustment for renal/hepatic function

• Adjustment for toxicity
Sequence of Drugs

• May be responsive to phasing of TB therapy
  • Early phase arrests replication with rapid killing action
  • Latter phase sterilizes by eliminating persisting bacilli
**Sequence of Drugs**

- May be responsive to phasing of TB therapy
  - Early phase arrests replication with rapid killing action; may be a maximum
  - Latter phase sterilizes by eliminating persisting bacilli; unclear if can be accelerated

- Special position of PZA, now influenced by synergy with bedaquiline

- Would rapid drug sequencing allow bacilli less time to adapt to each agent’s challenge?
Rhythm of administration

- Intermittent regimens thought to be of great programmatic advantage:
  - MRC’s thrice weekly;
  - Denver regimen twice weekly;
  - RPT trials seeking once-weekly;
  - Long-acting injectable goal of $\geq 30$ days
Rifapentine and isoniazid once a week versus rifampicin and isoniazid twice a week for treatment of drug-susceptible pulmonary tuberculosis in HIV-negative patients: a randomised clinical trial

The Tuberculosis Trials Consortium*

Methods We did a randomised, multicentre, open-label trial in the USA and Canada of HIV-negative people with drug-susceptible pulmonary tuberculosis who had completed 2 months of a 6-month treatment regimen. We randomly allocated patients directly observed treatment with either 600 mg rifapentine plus 900 mg isoniazid once a week or 600 mg rifampicin plus 900 mg isoniazid twice a week. Primary outcome was failure/relapse. Analysis was by intention to treat.
USPHS Study 22 found 5 factors independently associated with risk of failure/relapse:

- 2-month culture result,
- cavitation on CXR,
- being underweight,
- bilateral disease on CXR, and
- non-Hispanic white race.

Other studies also identified: increased age, alcohol abuse, irregular compliance, male gender, shorter therapy, more intermittent therapy, weaker regimens (e.g., thiacetazone) [in Poland, East Africa, Hong Kong]
Identification of patients at high risk for treatment failure or relapse with directly observed short-course therapy for pulmonary tuberculosis

A Report from the Tuberculosis Trials Consortium (TBTC)

[A listing of contributors appears at the end of this report]

Running head: Risk factors for relapse after TB treatment

Word count: 2071

Requests for reprints:
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This study was funded by the Centers for Disease Control and Prevention, U.S. Public Health Service. Rifapentine was provided by Hoechst Marion Roussel Inc., Kansas City MO

This study was presented in part at the 38th Annual Conference of the Infectious Diseases Society of America, September 8, 2000, New Orleans, LA

Date of revision: July 31 2001

Key words: tuberculosis, rifampin, rifapentine, isoniazid, multicenter clinical trial, relapse, treatment failure, risk factor analysis, directly observed therapy
The rate of failure/relapse was 3.5% for patients with 0-2 risk factors, but 21% among patients with 3-5 risk factors.
<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Pos Pred Value</th>
<th>Neg Pred Value</th>
<th>Nr needed to treat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cavity</td>
<td>84%</td>
<td>48%</td>
<td>12%</td>
<td>97%</td>
<td>8.6</td>
</tr>
<tr>
<td>2m smear +</td>
<td>27%</td>
<td>88%</td>
<td>16%</td>
<td>94%</td>
<td>6.3</td>
</tr>
<tr>
<td>2m cult +</td>
<td>53%</td>
<td>83%</td>
<td>21%</td>
<td>95%</td>
<td>4.9</td>
</tr>
<tr>
<td>2m sm+cav</td>
<td>25%</td>
<td>91%</td>
<td>19%</td>
<td>94%</td>
<td>5.2</td>
</tr>
<tr>
<td>2m cul+cav</td>
<td>46%</td>
<td>87%</td>
<td>25%</td>
<td>95%</td>
<td>4.0</td>
</tr>
</tbody>
</table>
Event rates were especially high in patients with multiple risk factors (for example, for patients with both cavitation and positive sputum culture at 2 months, 26.8% in the rifapentine group and 21.8% in the rifampicin group).

**TABLE 11. Percentage of culture-positive relapse**\(^4\) **by continuation phase regimen, radiographic status, and 2-month sputum culture: USPHS Study 22**

<table>
<thead>
<tr>
<th>Cavity</th>
<th>Culture-positive at 2 months</th>
<th></th>
<th>Culture-positive at 2 months</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
<td>20.8 (48)(^4)</td>
<td>4.7 (150)</td>
<td>22.2 (72)</td>
<td>9.1 (154)</td>
</tr>
<tr>
<td>No</td>
<td>5.9 (17)</td>
<td>1.7 (181)</td>
<td>11.8 (17)</td>
<td>1.9 (162)</td>
</tr>
</tbody>
</table>
• Assuring/Monitoring efficacy:
  • Bacteriologic
  • Pharmacokinetic

• Most available bacteriologic measures not adequate

• PK monitoring remains poorly accessible
Monitoring for toxicity

- Hepatotoxicity persists as a problem with INH; most trials using INH in low resource settings include liver deaths.
- Hepatotoxicity challenges some novel agents (e.g., pretomanid) and increases need for monitoring.
- QT effect of multiple agents poorly understood; simple means to monitor are not validated; cause of sudden death is difficult to assess in most trials.
Monitoring for Acquired Drug Resistance

- Uncertain contributions of multiple quantitative processes (bacillary load, rate of replication, relative types of drug exposures, degree of immunologic impairment)
- Ability to assess RR with Xpert, soon to be supplemented with IR
- Very limited ability to monitor novel agents, with consequent risk of loss of utility
Monitoring for/assuring adherence

• Non-completion of therapy is perhaps the most severe problem confronting TB control
• It is NOT a new problem
• Our sophistication in addressing this is poor, despite better understanding of its importance
<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of unfavorable outcomes/ number of study participants (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total doses</td>
<td></td>
<td>Reference</td>
</tr>
<tr>
<td>144 (6 doses per week)</td>
<td>50/533 (9)</td>
<td>2.4 (1.2–4.8)</td>
</tr>
<tr>
<td>112–143 (on average 5 doses per week)</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>

A patient-level pooled analysis of treatment-shortening regimens for drug-susceptible pulmonary tuberculosis

**Duration of treatment**

- Developments have paralleled selection of drugs:
  - 18 mo H+PAS+Strep
  - 9 mo HR(E)
  - 6 mo HRS or HRSZ/HR
  - 6 mo HREZ/HR

- Driven by roles of key drug(s)
A Nested Case-Control Study on Treatment-related Risk Factors for Early Relapse of Tuberculosis

Kwok C. Chang, Chi C. Leung, Wing W. Yew, Suzanne C. Ho, and Cheuk M. Tam

In the Treatment of Tuberculosis, You Get What You Pay for...
Effect of Duration and Intermittency of Rifampin on Tuberculosis Treatment Outcomes: A Systematic Review and Meta-Analysis

Dick Menzies¹*, Andrea Benedetti¹, Anita Paydar¹, Ian Martin¹, Sarah Royce², Madhukar Pai¹, Andrew Vernon³, Christian Lienhardt⁴, William Burman⁵

Table 7. Stratified estimates of relapse in RCT in new cases.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Studies (N)</th>
<th>Events/Participants (N)</th>
<th>Pooled Event Rate (Across All Trials)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of rifampin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampin 1–2 mo</td>
<td>70</td>
<td>367/3,349</td>
<td>16.0</td>
</tr>
<tr>
<td>Rifampin 3–5 mo</td>
<td>42</td>
<td>185/2,389</td>
<td>7.1</td>
</tr>
<tr>
<td>Rifampin 6–7 mo</td>
<td>171</td>
<td>364/8,639</td>
<td>3.8</td>
</tr>
<tr>
<td>Rifampin 8+ mo</td>
<td>18</td>
<td>14/1,181</td>
<td>1.0</td>
</tr>
</tbody>
</table>
**Table 9.** Adjusted incidence rate ratios of failure, relapse, and acquired drug resistance (from negative binomial regression).

<table>
<thead>
<tr>
<th>Factor</th>
<th>Failure IRR (95% CI)</th>
<th>Relapse IRR (95% CI)</th>
<th>Acquired Drug Resistance(^a) IRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duration of rifampin(^b)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–2 mo</td>
<td>5.8 (2.9 to 11.0)</td>
<td>3.6 (2.5 to 5.3)</td>
<td>4.6 (2.0 to 0.4)</td>
</tr>
<tr>
<td>3–4 mo</td>
<td>1.3 (0.6 to 3.0)</td>
<td>2.6 (1.6 to 4.0)</td>
<td>1.2 (0.4 to 3.1)</td>
</tr>
<tr>
<td>5–7 mo</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>8+ mo</td>
<td>2.0 (0.8 to 4.9)</td>
<td>0.4 (0.2 to 0.7)</td>
<td>2.1 (0.8 to 5.3)</td>
</tr>
<tr>
<td>Overall significance (p value)(^c)</td>
<td>(&lt;0.0001)</td>
<td>(&lt;0.0001)</td>
<td>(&lt;0.002)</td>
</tr>
<tr>
<td>Isoniazid resistant</td>
<td>10.9 (5.9 to 20)</td>
<td>1.8 (1.2 to 2.6)</td>
<td>5.1 (2.3 to 11.0)</td>
</tr>
<tr>
<td><strong>Schedule of drug administration(^b)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily throughout</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>Daily then thrice weekly</td>
<td>0.7 (0.2 to 2.1)</td>
<td>1.0 (0.6 to 1.5)</td>
<td>0.7 (0.2 to 2.6)</td>
</tr>
<tr>
<td>Daily then twice weekly</td>
<td>0.9 (0.5 to 1.6)</td>
<td>0.8 (0.5 to 1.2)</td>
<td>0.5 (0.3 to 1.2)</td>
</tr>
<tr>
<td>Thrice weekly throughout</td>
<td>0.7 (0.3 to 1.4)</td>
<td>1.2 (0.8 to 1.6)</td>
<td><strong>2.4 (1.05 to 5.5)</strong></td>
</tr>
</tbody>
</table>
Conclusion
This review provides evidence against continued use of regimens that utilize rifampin for the first 2 mo only, as they are significantly and substantially inferior to regimens that use rifampin for at least 6 mo. This review also has identified an important need for adequately powered clinical trials that address dosing schedules, management of isoniazid mono-resistance, and the optimal duration of treatment to prevent relapse.
Duration of treatment-2

- May be limited by issues related to tissue architecture, lesion repair, and drug penetration
HYPOTHESIS

If TB drugs reach all bacterial populations at sufficient concentration in lesions, cure rates will increase and treatment duration will decrease.

Two populations:
1. Intracellular in macrophages
2. Mostly extracellular in caseum
<table>
<thead>
<tr>
<th>Year</th>
<th>Regimen (14 wk)</th>
<th>CFU at EOT</th>
<th>CF dep at EOT</th>
<th>Relapse after 2 mo of HC (lung or spleen)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2018</td>
<td>R10HZ</td>
<td>Negative</td>
<td>Positive</td>
<td>86%</td>
</tr>
<tr>
<td>2018</td>
<td>R30HZ R40HZ</td>
<td>Negative</td>
<td>Negative</td>
<td>0%</td>
</tr>
<tr>
<td>2019</td>
<td>R10HZE</td>
<td>Negative</td>
<td>Positive</td>
<td>90%</td>
</tr>
<tr>
<td>2019</td>
<td>R10HZB</td>
<td>Negative</td>
<td>Negative</td>
<td>0%</td>
</tr>
</tbody>
</table>

Liu et al, JAC 2018 and Hu et al, JAC 2019
...to get to
Smarter
Simplified TB Treatment

• Increase engagement with laboratory scientists
• Increase use of animal models
• Increase emphasis on phase 2
• Increase use of quantitative data
• Increase collaboration among trial groups
• Develop more accessible program platforms for trials
The End

Thank You
for
your Attention