Evidence review for Intermittent therapy for drug-susceptible TB:

Dr. Dick Menzies
Montreal Chest Institute,
McGill University
Montreal, Canada

Questions addressed: intermittent therapy

1: Does intermittent dosing in the intensive phase have similar outcomes compared to daily dosing in the intensive phase for treatment of drug-susceptible pulmonary tuberculosis?

2: Does intermittent dosing in the continuation phase have similar outcomes compared to daily dosing in the continuation phase in patients with drug susceptible pulmonary tuberculosis?
Evidence review for Intermittent therapy

Summary of evidence available

- Review of ‘Head-to-Head’ RCTs 1970-2009; Mwandumba, Cochrane 2001
- Review of RCTs and Cohorts: Chang AJRCCM 2006
- Review of 4 pediatric studies: Menon Ind J Ped 2009
- HIV-TB review: Khan CID 2010 & 2012
- Updated review of RCTs: Johnston, Campbell & Menzies: 1970 – 2016 (not yet published)

Head-to-Head RCTs of Intermittent vs daily therapy for TB in adults – meta-analysis.
(Mwandumba & Squires. Cochrane; 2001)

Systematic review and meta-analysis – adults older than 16. Only one trial with 299 pulmonary TB. Daily vs 3X weekly. INH/RIF/PZA/EMB for 6 months

<table>
<thead>
<tr>
<th></th>
<th>Daily</th>
<th>3X weekly</th>
<th>3X weekly</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure</td>
<td>0/200 (0%)</td>
<td>1/199 (0.5%)</td>
<td>5/198 (2.5%)</td>
<td></td>
</tr>
<tr>
<td>Relapse</td>
<td>1/200 (0.5%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In Total: Intermittent had fail/relapse more than 4 times higher, but very low power as few events.
Dosing schedules of 6-month regimens and relapse.

Systematic review of 17 studies with 5,208 patients, and 200 relapse events.

Daily through-out – Lowest: RR= 1.0
Daily then 3X weekly: RR = 1.6
Daily then 2X weekly: RR = 2.8
3x weekly through-out: RR = 5.0
- greatest risk if cavitation or 2 month culture positive
- Also greater if followed by 1X weekly Rifapentine

Evidence review for Intermittent therapy
Menzies PLOS Med review - Search Strategy

- First review: Jan 1 1970 to June 30 2008
- English, French, Spanish
- Embase, Medline, Cochrane databases
- Searched references, prior reviews, guidelines
Evidence review for Intermittent therapy - Menzies PLOS Med review - Study inclusion criteria:

- RCTs that reported treatment outcomes of new bacteriologically-confirmed pulm. TB
- Reported microbiologically confirmed outcomes of failure, or relapse.
- Acquired drug resistance – if DST done initially plus DST with fail/relapse
- Arms using $\geq 6$ months INH & Rifampin (if rifapentine, or rifabutin, or monotherapy at any point – excluded)
- Drug sensitive patients only (or New cases but no DST done)

Evidence review for Intermittent therapy
Menzies PLOS Med review: Summary of study selection

Identified from PubMed, EMBASE, Cochrane Database literature search: (after eliminating duplicates)
2215 titles

1978 titles excluded

135 additional full texts identified from references and reviews

Titles retained for review of abstracts: 237

Full text reviewed: 301

75 Reports included (57 Trials)
Menzies PLOS Med review - Intermittent therapy and outcomes – from Meta-regression (RCT in New cases and no HIV)

<table>
<thead>
<tr>
<th>Intermittent schedule</th>
<th>Failure IRR (95% CI)</th>
<th>Relapse IRR (95% CI)</th>
<th>ADR IRR (95% CI)</th>
</tr>
</thead>
<tbody>
<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>0.8 (0.5, 1.3)</td>
<td>1.0 (0.7, 1.3)</td>
<td>0.9 (0.4, 1.8)</td>
</tr>
<tr>
<td>Daily then twice weekly</td>
<td>1.3 (0.9, 1.8)</td>
<td>0.8 (0.7, 1.1)</td>
<td>0.7 (0.4, 1.1)</td>
</tr>
<tr>
<td>Thrice weekly throughout</td>
<td>1.3 (1.0, 1.7)</td>
<td>1.1 (0.9, 1.3)</td>
<td>4.9 (3.3, 7.4)</td>
</tr>
</tbody>
</table>

Intermittent or daily therapy for TB in children – meta-analysis. (Ramesh Menon et al, Indian Pediatrics. 2009; May 20)

Systematic review and meta-analysis – children less than 16. Four trials with 466 children

Odds of cure: Daily: 1.0 (reference)
Twice weekly: Per protocol: 0.27 (0.15, 0.51)
Intention to treat: 0.66 (0.23, 1.84)

Daily therapy had significantly higher cure rates - in children who were adherent
Treatment of active tuberculosis in HIV co-infected patients:

Faiz A. Khan MD, Dick Menzies MD MSc.

Methods- Inclusion criteria

- Randomized controlled trials or cohort studies
- Standardized regimens that contained rifampin or rifabutin
- Serologically confirmed HIV status
- Microbiologically confirmed active TB
- Failure or relapse microbiologically confirmed
- Patients with pre-treatment MDR-TB were excluded from all analyses (if separable)
First review: 1970 to 2008
5158 Titles identified

4913 Excluded based on title & abstract

245 Retrieved for full text review

30 articles (27 studies) included

2nd Review (2008 to 2012)
2293 Titles identified

2233 Excluded based on title & abstract

60 Retrieved for full text review

53 Excluded:
- 30: Individualized/modifiable treatment regimens
- 11: Outcomes of interest not reported
- 3: Outcomes not stratified by TB treatment regimen
- 2: Atypical definitions of TB treatment outcomes (2 journal articles from the same study)
- 2: Insufficient number of patients with confirmed diagnosis of TB
- 5: other

7 articles added from the update (1 RCT and 6 cohorts)
### Intermittency and Pooled treatment outcomes – all studies

<table>
<thead>
<tr>
<th></th>
<th>Risk of Failure (95%CI) events/subjects</th>
<th>Risk of Relapse (95%CI) events/subjects</th>
<th>Risk of Death (95%CI) events/subjects</th>
<th>Risk of ADR (95%CI) events/subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Daily</strong></td>
<td>2.7% (1.6, 3.7) 99/2813</td>
<td>6.3% (1.2, 11.4) 142/1267</td>
<td>11.8% (8.5, 15.0) 480/3293</td>
<td>4.2% (0, 12.9) 2/60</td>
</tr>
<tr>
<td><strong>Thrice weekly</strong></td>
<td><strong>5.2% (1.5, 8.8) 32/464</strong></td>
<td><strong>18.2% (0, 39) 44/210</strong></td>
<td><strong>10.1% (4.3, 16) 52/516</strong></td>
<td><strong>11.4% (0, 66) 18/188</strong></td>
</tr>
</tbody>
</table>

### Intermittency and Adjusted odds of treatment outcomes – all studies

<table>
<thead>
<tr>
<th></th>
<th>Failure: aOR (95% CI)a</th>
<th>Relapse: aOR (95% CI)a</th>
<th>Death: aOR (95% CI)a</th>
<th>ADR: aOR (95% CI)b</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Daily</strong> (reference)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Thrice weekly</strong></td>
<td>2.0 (0.8, 5.0)</td>
<td>2.2 (0.7, 7.3)</td>
<td>0.7 (0.3, 1.4)</td>
<td>3.7 (0.7, 18.9)</td>
</tr>
<tr>
<td>p value for difference</td>
<td>0.13</td>
<td>0.18</td>
<td>0.33</td>
<td>0.11</td>
</tr>
</tbody>
</table>
### Intermittency and Adjusted odds of outcomes –stratified by ART use

<table>
<thead>
<tr>
<th>Dosing Schedule</th>
<th>Failure: aOR (95% CI)a</th>
<th>Relapse: aOR (95% CI)a</th>
<th>Death: aOR (95% CI)b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ART</td>
<td>ART</td>
<td>ART</td>
</tr>
<tr>
<td>Daily (reference)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Thrice weekly</td>
<td>4.1 (1.9, 9.1)</td>
<td>0.4 (0.1, 2.7)</td>
<td>2.1 (0.6, 6.9)</td>
</tr>
</tbody>
</table>

### Intermittent therapy for drug-susceptible TB: Update review

Dr. James Johnston  
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Vancouver, British Columbia

Dr. Dick Menzies  
McGill University  
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Montreal, Quebec

Jonathon Campbell, BSc PhD (cand)  
Faculty of Pharmaceutical Sciences  
University of British Columbia  
Vancouver, British Columbia
Evidence review for Intermittent therapy

**Search Strategy - update**

- First review: Jan 1 1970 to June 30 2008
- 2nd review: June 1, 2008 – March 15, 2016

**Studies included in updated analysis**

- First search
  - Jan 1965-June 2008
  - (n = 57 trials; 312 arms)
- Second search
  - June 2008 – March 2016
  - (n = 7 trials; 10 arms)

- All treatment durations
  - Failure: 320 arms
  - Relapse: 311 arms
  - ADR: 258 arms
- <6 months Rif: 104 arms
- Drug resistant TB: 98 arms

- DS-TB (or no DST)
  - And, >6 months of rifampin
  - Failure: 108 arms with 13,401 patients
  - Relapse: 105 arms with 12,184 patients
  - ADR: 72 arms with 7,443 patients

Presentation 2: Richard Menzies
Evidence review for Intermittent therapy

**Primary analysis**

- Population with DS-TB or no DST
- Patients at least 6 months Rifampin
- Proportion treatment failure, relapse, ADR with the following treatment schedules:
  1. Daily (≥5 days per week) throughout
  2. Daily intensive phase then twice weekly
  3. Daily intensive phase then thrice weekly
  4. Thrice weekly throughout

*Note: No trials found with Twice weekly through-out (Initial & Continuation phase – the “Denver regimen”)*

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**Initial Phase: Daily vs Intermittent**

<table>
<thead>
<tr>
<th>Initial Phase Schedule</th>
<th>Arms (N)</th>
<th>Events/Participants (N)</th>
<th>Failure Events/Participants (N)</th>
<th>Point Estimate 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily</td>
<td>62</td>
<td>112/8223</td>
<td>0.2% (0 - 0.4)</td>
<td></td>
</tr>
<tr>
<td>3x per week</td>
<td>19</td>
<td>28/2310</td>
<td>0.6% (0 - 1.4)</td>
<td></td>
</tr>
</tbody>
</table>

**Relapse**

<table>
<thead>
<tr>
<th>Initial Phase Schedule</th>
<th>Arms (N)</th>
<th>Events/Participants (N)</th>
<th>Failure Events/Participants (N)</th>
<th>Point Estimate 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily</td>
<td>59</td>
<td>254/7475</td>
<td>2.5% (1.8 - 3.2)</td>
<td></td>
</tr>
<tr>
<td>3x per week</td>
<td>19</td>
<td>128/2130</td>
<td>6.8% (3.8 - 9.9)</td>
<td></td>
</tr>
</tbody>
</table>

**Acquired Drug Resistance**

<table>
<thead>
<tr>
<th>Initial Phase Schedule</th>
<th>Arms (N)</th>
<th>Events/Participants (N)</th>
<th>Failure Events/Participants (N)</th>
<th>Point Estimate 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily</td>
<td>43</td>
<td>11/4700</td>
<td>0.1% (0 - 0.2)</td>
<td></td>
</tr>
<tr>
<td>3x per week</td>
<td>15</td>
<td>16/1778</td>
<td>0.3% (0 - 0.8)</td>
<td></td>
</tr>
</tbody>
</table>

*Note: No trials found with Twice weekly through-out (Initial & Continuation phase – the “Denver regimen”)*
### Evidence review for Intermittent therapy (from Johnston 2016, do not cite, show or copy)

#### Continuation Phase

<table>
<thead>
<tr>
<th>Factor</th>
<th>Arms (N)</th>
<th>Failure Events/Participants (N)</th>
<th>Point Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily throughout</td>
<td>62</td>
<td>112/8223</td>
<td>0.2% (0.1 - 0.4)</td>
</tr>
<tr>
<td>Daily then 3x per week</td>
<td>18</td>
<td>19/2075</td>
<td>0.4% (0 - 1.1)</td>
</tr>
<tr>
<td>Daily then 2x per week</td>
<td>9</td>
<td>21/793</td>
<td>1.3% (0 - 2.9)</td>
</tr>
</tbody>
</table>

#### Relapse

<table>
<thead>
<tr>
<th>Factor</th>
<th>Arms (N)</th>
<th>Failure Events/Participants (N)</th>
<th>Point Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily throughout</td>
<td>59</td>
<td>254/7475</td>
<td>2.5% (1.8 - 3.2)</td>
</tr>
<tr>
<td>Daily then 3x per week</td>
<td>18</td>
<td>72/2007</td>
<td>3.0% (1.0 - 5.1)</td>
</tr>
<tr>
<td>Daily then 2x per week</td>
<td>9</td>
<td>49/572</td>
<td>7.3% (3.5 - 11.1)</td>
</tr>
</tbody>
</table>

#### Acquired Drug Resistance

<table>
<thead>
<tr>
<th>Factor</th>
<th>Arms (N)</th>
<th>Failure Events/Participants (N)</th>
<th>Point Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily throughout</td>
<td>43</td>
<td>11/4700</td>
<td>0.1% (0 - 0.2)</td>
</tr>
<tr>
<td>Daily then 3x per week</td>
<td>9</td>
<td>1/588</td>
<td>0.1%(0 - 0.3)</td>
</tr>
<tr>
<td>Daily then 2x per week</td>
<td>5</td>
<td>2/377</td>
<td>0.2% (0 - 0.6)</td>
</tr>
</tbody>
</table>

### Adjusted analyses (meta-regression)

#### DS-TB, or no DST, Rif duration ≥6 months

<table>
<thead>
<tr>
<th>Factor</th>
<th>Failure IRR</th>
<th>Relapse IRR</th>
<th>ADR IRR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily throughout</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Daily then 3x per week</td>
<td>1.5 (0.4-5.4)</td>
<td>1.2 (0.6-2.3)</td>
<td>0.6 (0.1-5.7)</td>
</tr>
<tr>
<td>Daily then 2x per week</td>
<td>3.0 (1.0-8.8)</td>
<td>1.8 (0.98-3.3)</td>
<td>0.96 (0.2-5.0)</td>
</tr>
<tr>
<td>3x per week throughout</td>
<td>3.7 (1.1-12.6)</td>
<td>2.2 (1.2-3.9)</td>
<td>10.0 (2.1-47)</td>
</tr>
</tbody>
</table>

Negative binomial regression performed in Stata, Variables in model: Rifampin duration, Use of pyrazinamide, Use of streptomycin, Administration schedule, Number of drugs in initial and continuation phases, Use of DOT
Evidence review for Intermittent therapy

Sensitivity Analysis

- We examined the following:
  1. Drug sensitive TB only (No DST dropped)
  2. All studies (i.e. like Menzies *PLOS Med.* 2009)
  3. Streptomycin-based regimens removed
  4. Streptomycin resistant strains included
  5. Drug resistant strains only
  6. Regimen of 2HRZ(E), 4HR(E) only
  7. Removed arms with only HIV infected patients

Findings essentially **unchanged** with all these

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Evidence review for Intermittent therapy

FAQS (Frequently asked questions)

- How many studies used DOT
  - Used DOT throughout therapy: 57% (most of intermittent)
  - Used DOT in part of therapy: 14%
  - Did not use DOT: 29% (mostly daily)

- How many studies had <10% total of loss to follow-up & default & transfer & unknown?
  - <10% loss: 66% of studies
  - >10% loss: 33% of studies
Evidence review for Intermittent therapy

**FAQS (Frequently asked questions)**

- How many HIV infected patients were included in these studies?
  - 1509 Patients were HIV positive (11% of all patients)
  - In 67% of the studies 0 (zero) patients had HIV
- How many studies were published since 1990 and how many since 2000?
  - Prior to 1990: 69%,
  - 1990 – 2000: 19%
  - Post 2000: 12%

Evidence review for Intermittent therapy

**Conclusions**

- **Intermittent treatment Three times/week - from beginning** (or after 2 weeks) has higher rates of failure and relapse, and ADR in multiple reviews:
  - In a 2001 Cochrane review of Direct head-to-head studies
  - In a 2006 review of RCTs and Cohorts – (Relapse)
  - In a 2009 review children (Failure)
  - In a 2009 review of adults (Failure and ADR)
  - In 2012 review of treatment of HIV-TB (Failure & Relapse - but significant only if ARV NOT given)
  - In a 2016 updated review (Failure, Relapse and ADR)
- Note: there is VERY little published evidence for twice weekly from beginning (“Denver regimen”). No RCTs
Evidence review for Intermittent therapy

**Conclusions**

- **Daily initially then Twice weekly intermittent in continuation phase** (after first 2 months) has higher rates of relapse:
  - In a 2016 updated review
- **Daily initially, followed by Thrice weekly therapy** has very good results:
  - In a 2009 review of adults
  - In 2012 review in HIV-infected
  - In a 2016 updated review

**Discussion - Limitations**

- Very few large scale randomized trials with direct comparison of Intermittent vs Daily. Could not pool data from Head-to-Head comparisons
- Most studies conducted in Low and Middle income countries. But drop-out rates and non-adherence low in most studies. Quality of care could be considered similar to US programme standards
- Some studies/regimens did not use PZA
  - But sensitivity analyses – Arms with PZA only = same findings
- Even though differences are significant, and odds ratios are high, the **absolute effect size is small** – difference in relapse rates of 4%, and of acquired drug resistance of 1%
Evidence review for Intermittent therapy

Discussion - Strengths

- Large number of trials identified. Only studies with bacteriologically confirmed diagnoses & outcomes (fail and relapse were confirmed) were included.
- Consistent results from multiple reviews in different populations (adults, children, HIV infected). Even if not always significant, consistent trends seen.
- In 3 reviews multivariate analysis used – to adjust for confounding factors (eg use of PZA). Findings stronger
- Studies from many countries, including resource-poor, “real-life” settings - more applicable/generalizable

Acknowledgements – Intermittent review

- Update: Jay Johnston
- Jonathon Campbell
- Victoria Cook

- 2008 Review
  - Andrea Benedetti
  - Anita Paydar
  - Sarah Royce
  - Andrew Vernon
  - Madhukar Pai
  - Christian Lienhardt
  - William Burman
Acknowledgements: HIV-TB review

- **Update:**
- Faiz Khan

And Information from authors: Dr. Judith Glynn and the Karonga Prevention Study, Dr. Paul Kelly, Dr. Gisele Klautau, Dr. Juergen Noeske, Dr. Andrew Nunn, Dr. Esteve Ribera, Dr. Soumya Swaminathan, Dr. Joep van Oosterhout, Dr. Jay Varma, Ms. Erin Bliven, Dr. Wafaa El-Sadr, Dr. Atul Patel, Dr. Nahid Payam, Dr. David Moore, Dr. Weerawat Manosuthi, Dr. Wanitchaya Kittikraisak, & Dr. Alison Rodger & Angella Lambrou

- **2008 Review**
- Dr. Jessica Minion
- Dr. Madhukar Pai
- Dr. Bill Burman
- Dr. Sara Royce
- Dr. Anthony Harries
- Malgorzata Grzemska

HIV-TB: Other questions
Use of ART, and Duration of therapy:
Questions addressed: HIV-TB

In patients with HIV-TB:
1: Is it necessary to prolong therapy – past usual 6 months?
2. Does ART modify these two answers?

Use of ART and Pooled treatment outcomes – all studies

<table>
<thead>
<tr>
<th></th>
<th>Failure Rate (95%CI) events/subjects</th>
<th>Relapse Rate (95%CI) events/subjects</th>
<th>Death Rate (95%CI) events/subjects</th>
<th>ADR Rate (95%CI) events/subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ART // NR</td>
<td>3.2% (1.8, 4.6) 98/2481</td>
<td>14.4% (4.9, 23.9) 178/1194</td>
<td>12.4% (8.7, 16.1) 407/2888</td>
<td>16.6% (10.7, 22.4) 19/157</td>
</tr>
<tr>
<td>Some or All on ART</td>
<td>2.0% (0.5, 3.5) 33/796</td>
<td>1.1% (0, 2.8) 8/283</td>
<td>9.8% (5.2, 14.3) 125/921</td>
<td>3.3% (0, 7.0) 1/91</td>
</tr>
</tbody>
</table>
### Use of ART and Adjusted odds of treatment outcomes – all studies

<table>
<thead>
<tr>
<th></th>
<th>Failure: aOR (95% CI)</th>
<th>Relapse aOR (95% CI)</th>
<th>Death: aOR (95% CI)</th>
<th>ADR aOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None // NR</td>
<td>1.7 (0.7, 4.0)</td>
<td>14.3 (2.1, 98)</td>
<td>1.4 (0.7, 2.8)</td>
<td>2.0 (0.5, 7.9)</td>
</tr>
<tr>
<td>Some or All</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>p value for differences</td>
<td>0.22</td>
<td>&lt;0.01</td>
<td>0.33</td>
<td>0.33</td>
</tr>
</tbody>
</table>

### Duration of Rifampin and Pooled treatment outcomes – all studies

<table>
<thead>
<tr>
<th></th>
<th>Risk of Failure (95% CI) events/subjects</th>
<th>Risk of Relapse (95% CI) events/subjects</th>
<th>Risk of Death (95% CI) events/subjects</th>
<th>Risk of ADR (95% CI) events/subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2 Months</strong></td>
<td>3.5% (1.3, 5.8) 47/999</td>
<td>10.8% (0, 28) 38/222</td>
<td>13.4% (7.9, 20) 216/1215</td>
<td>No studies.</td>
</tr>
<tr>
<td><strong>6 Months</strong></td>
<td>2.6% (1.2, 4.0) 55/1620</td>
<td>9.1% (0.4, 18) 119/830</td>
<td>9.2% (5.9, 12.5) 209/1829</td>
<td>10.4% (0, 21) 209/1829</td>
</tr>
<tr>
<td><strong>8+ Months</strong></td>
<td>2.7% (0.5, 5.0) 29/658</td>
<td>4.7% (0, 11.2) 29/425</td>
<td>13.9% (7.3, 20) 107/765</td>
<td>9.7% (1.6, 18) 13/146</td>
</tr>
</tbody>
</table>
### Duration of Rifampin and Adjusted odds of treatment outcomes – all studies

<table>
<thead>
<tr>
<th>Duration of Rifampin</th>
<th>Failure: aOR (95% CI)a</th>
<th>Relapse: aOR (95% CI)a</th>
<th>Death: aOR (95% CI)a</th>
<th>ADR: aOR (95% CI)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 Months</td>
<td>1.4 (0.6, 3.2)</td>
<td>5.0 (1.9, 13)</td>
<td>0.9 (0.5, 1.6)</td>
<td>No studies</td>
</tr>
<tr>
<td>6 Months</td>
<td>0.8 (0.4, 1.5)</td>
<td>2.4 (1.2, 5.0)</td>
<td>0.7 (0.5, 1.1)</td>
<td>0.8 (0.3, 1.9)</td>
</tr>
<tr>
<td>≥ 8 Months (ref)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Overall p value</td>
<td>0.34</td>
<td>&lt;0.01</td>
<td>0.24</td>
<td>0.55</td>
</tr>
</tbody>
</table>

### Duration of Rifampin and Adjusted odds of outcomes – stratified by ART use

<table>
<thead>
<tr>
<th>Duration of Rifampin</th>
<th>Failure: aOR (95% CI)a</th>
<th>Relapse: aOR (95% CI)a</th>
<th>Death: aOR (95% CI)a</th>
<th>ADR: aOR (95% CI)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>ART</td>
<td>ART</td>
<td>ART</td>
<td>ART</td>
<td></td>
</tr>
<tr>
<td>None / NRb</td>
<td>All / Somec</td>
<td>None / NRb</td>
<td>All / Somec</td>
<td></td>
</tr>
<tr>
<td>2 Months</td>
<td>0.9 (0.4, 2.0)</td>
<td>3.8 (0.7, 21.2)</td>
<td>6.7 (2.4, 19)</td>
<td>.01 (0, 0.2)</td>
</tr>
<tr>
<td>6 Months</td>
<td>0.7 (0.4, 1.4)</td>
<td>1.8 (0.3, 12.2)</td>
<td>3.1 (1.4, 6.7)</td>
<td>0.2 (0.01, 2.2)</td>
</tr>
<tr>
<td>≥ 8 Months (ref)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>p value</td>
<td>0.63</td>
<td>0.30</td>
<td>0.001</td>
<td>0.005</td>
</tr>
</tbody>
</table>
Adjusted incidence rate ratios (aIRR) of failure and relapse in HIVTB cases by dosing schedule (Source – 2010 review)

<table>
<thead>
<tr>
<th>Dosing schedule</th>
<th>Failure: aIRR* (95% CI)</th>
<th>Relapse: aIRR* (95% CI)</th>
<th>Death during Treatment: aIRR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial phase daily</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>Initial phase thrice weekly</td>
<td>4.0 (1.5, 10.4)</td>
<td>4.8 (1.8, 12.8)</td>
<td>1.3 (0.7, 2.3)</td>
</tr>
<tr>
<td>Overall p value</td>
<td>(.02)</td>
<td>(.002)</td>
<td>(0.42)</td>
</tr>
</tbody>
</table>

Conclusions

- In this review outcomes of treatment of HIV-TB better if:
  - At least 8months duration of rifampin therapy - IF NO ARV GIVEN
  - daily dosing (but significant only if ARV NOT given)
  - ARV given – most important effect detected