American Thoracic Society / Centers for Disease Control / Infectious Diseases Society of America Clinical Practice Guidelines:

Treatment of Drug-Susceptible Tuberculosis

On behalf of the writing committee
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Professor of Medicine
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Presentation 1: Payam Nahid
Treatment of Drug-Susceptible Tuberculosis
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Treatment of Drug-Susceptible Tuberculosis
Writing Committee Leadership and GRADE Methodology Group

- **Chairs:** Susan Dorman (IDSA), GB Migliori (ERS), Andrew Vernon (CDC), Payam Nahid (ATS)

- **GRADE Methodology Group:** Narges Alipanah, Jan Brozek, Adithya Cattamanchi, Lelia Chaisson, Richard Menzies, Payam Nahid, Giovanni Sotgiu
Disclosures

• P. Barry relative previously owned stocks or options of Merck.
• R. Chaisson consultant and ownership of stocks or options for Merck.
• C. Daley received research support from Insmed and served on data and safety monitoring boards of Otsuka America Pharmaceutical and Sanofi Pasteur.
• C. Peloquin received research support from Jacobus Pharmaceuticals.
• J. Starke reported service on a data safety and monitoring board of Otsuka Pharmaceuticals.
• A. Vernon reported serving as the chief of a US Centers for Disease Control and Prevention clinical research branch doing clinical trials in tuberculosis collaborates with pharmaceutical companies, that may provide support such as drug supplies or laboratory funding for pharmacokinetic studies.

American Thoracic Society / Centers for Disease Control / Infectious Diseases Society of America Clinical Practice Guidelines:

Treatment of Drug-Susceptible Tuberculosis

Applies to settings in which mycobacterial cultures, molecular and phenotypic drug susceptibility tests, and radiographic studies, among other diagnostic tools, are available on a routine basis.
Treatment of Drug-Susceptible Tuberculosis Guideline Contents

1. ORGANIZATION AND SUPERVISION OF TREATMENT
   - PATIENT-CENTERED CARE AND CASE MANAGEMENT
   - ENSURING ADHERENCE AND TREATMENT SUCCESS

2. RECOMMENDED TREATMENT REGIMENS
   - DECIDING TO INITIATE TREATMENT
   - PREFERRED REGIMENS
   - ALTERNATIVE REGIMENS
   - PATIENTS AT INCREASED RISK OF RELAPSE
   - INTERRUPTIONS IN THERAPY

3. TREATMENT IN SPECIAL SITUATIONS
   - HIV INFECTION
   - CHILDREN
   - PREGNANCY AND BREASTFEEDING
   - RENAL DISEASE
   - HEPATIC DISEASE
   - ANTI-TNF DRUGS
   - DIABETES
   - ADVANCED AGE
   - LYMPH NODE TUBERCULOSIS
   - BONE, JOINT AND SPINAL TUBERCULOSIS
   - PERICARDIAL TUBERCULOSIS
   - PLEURAL TUBERCULOSIS
   - TUBERCULOUS MENINGITIS
   - DISSEMINATED TUBERCULOSIS
   - GENITOURINARY TUBERCULOSIS
   - ABDOMINAL TUBERCULOSIS
   - CULTURE-NEGATIVE PULMONARY TUBERCULOSIS
Treatment of Drug-Susceptible Tuberculosis Guideline Contents

4. PRACTICAL ASPECTS OF TREATMENT
   — MANAGEMENT OF COMMON ADVERSE EFFECTS
   — DRUG-DRUG INTERACTIONS
   — THERAPEUTIC DRUG MONITORING

4. RECURRENT TUBERCULOSIS, TREATMENT FAILURE, AND DRUG RESISTANCE
   — RECURRENT TUBERCULOSIS
   — POOR TREATMENT RESPONSE AND TREATMENT FAILURE, INCLUDING BRIEF OVERVIEW OF DRUG RESISTANCE.

6. RESEARCH AGENDA FOR TUBERCULOSIS TREATMENT
   — NEW ANTITUBERCULOSIS DRUGS AND REGIMENS
   — BIOMARKERS OF TREATMENT EFFECT AND INDIVIDUALIZATION OF THERAPY
   — TREATMENT OF TUBERCULOSIS IN SPECIAL SITUATIONS
   — IMPLEMENTATION RESEARCH
GRADE METHODOLOGY (Grading of Recommendations Assessment, Development, and Evaluation)

Recommendations based on the certainty in the evidence assessed according to the GRADE methodology to address PICO questions, incorporating patient values and costs as well as judgments about tradeoffs between benefits and harms.

PICO = Population, Intervention, Comparison, Outcome

Table 1. Interpretation of “Strong” and “Conditional” Grading of Recommendations Assessment, Development, and Evaluation-Based Recommendations

<table>
<thead>
<tr>
<th>Implications for:</th>
<th>Strong Recommendation</th>
<th>Conditional Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>Most individuals in this situation would want the recommended course of action, and only a small proportion would not.</td>
<td>The majority of individuals in this situation would want the suggested course of action, but many would not.</td>
</tr>
<tr>
<td>Clinicians</td>
<td>Most individuals should receive the intervention. Adherence to this recommendation according to the guidelines could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.</td>
<td>Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their values and preferences.</td>
</tr>
<tr>
<td>Policy</td>
<td>The recommendation can be adopted as policy in most situations.</td>
<td>Policymaking will require substantial debate and involvement of various stakeholders.</td>
</tr>
</tbody>
</table>

Source: Grading of Recommendations Assessment, Development and Evaluation Working Group (1, 3).

Drug Regimens for Microbiologically Confirmed Pulmonary Tuberculosis Caused by Drug-Susceptible Organisms

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Drug*</th>
<th>Interval and Doseb (Minimum Duration)</th>
<th>Continuation Phase</th>
<th>Interval and Doseb (Minimum Duration)</th>
<th>Range of Total Doses</th>
<th>Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>INH</td>
<td>7 days for 56 doses (8 wk), or 6 days for 40 doses (6 wk)</td>
<td>INH/RIF</td>
<td>7 days for 126 doses (18 wk), or 6 days for 90 doses (13 wk)</td>
<td>182-130</td>
<td>Greater</td>
</tr>
<tr>
<td>2</td>
<td>INH</td>
<td>7 days for 56 doses (8 wk), or 6 days for 40 doses (6 wk)</td>
<td>INH/RIF</td>
<td>3 times weekly for 54 doses (18 wk)</td>
<td>110-94</td>
<td>Lesser</td>
</tr>
<tr>
<td>3</td>
<td>INH</td>
<td>3 times weekly for 24 doses (8 wk)</td>
<td>INH/RIF</td>
<td>3 times weekly for 54 doses (18 wk)</td>
<td>78</td>
<td>Lesser</td>
</tr>
<tr>
<td>4</td>
<td>INH</td>
<td>7 days for 14 doses then twice weekly for 12 doses (6 wk)</td>
<td>INH/RIF</td>
<td>Twice weekly for 36 doses (18 wk)</td>
<td>63</td>
<td>Lesser</td>
</tr>
</tbody>
</table>

*Do not use twice-weekly regimens in INH-infected patients or patients with smear-negative and/or culture-negative disease. If doses are missed, then therapy is equivalent to once weekly, which is inferior.
Nine PICO(s) addressed:

1. Should case management be provided to patients receiving curative tuberculosis therapy to improve outcomes?
   
   *Case management: patient education/counseling, field/home visits, integration/cooperation of care with specialists and medical home, patient reminders, incentives/enablers.

   Recommendation 1: We suggest using case management interventions during treatment of patients with tuberculosis. (Conditional recommendation/low certainty in the evidence)

2. Does self administration (SAT) of medications have similar outcomes compared to directly observed therapy (DOT) in patients tuberculosis?
2. Does self administration (SAT) of medications have similar outcomes compared to directly observed therapy (DOT) in patients tuberculosis?

**Recommendation 2:** We suggest using DOT rather than SAT for routine treatment of patients with all forms of tuberculosis. (Conditional recommendation/low certainty in the evidence)
3. Should tuberculosis medications be dosed daily or intermittently in the intensive phase of treatment?

**Recommendation 3a:** We recommend the use of daily rather than intermittent dosing in the intensive phase of therapy for drug-susceptible pulmonary tuberculosis (Strong recommendation / Moderate certainty in the evidence).

4. Should tuberculosis medications be dosed daily or intermittently in the continuation phase of treatment?

**Recommendation 4a:** We recommend the use of daily or three times weekly dosing in the continuation phase of therapy for drug-susceptible pulmonary tuberculosis (Strong recommendation / Moderate certainty in the evidence).
5. Does initiation of anti-retroviral therapy during tuberculosis treatment compared to at the end of tuberculosis treatment improve outcomes among tuberculosis patients co-infected with HIV?
5. Does initiation of anti-retroviral therapy during tuberculosis treatment compared to at the end of tuberculosis treatment improve outcomes among tuberculosis patients co-infected with HIV?

Recommendation 6: We recommend initiating antiretroviral therapy during tuberculosis treatment.

By 8-12 weeks of tuberculosis treatment initiation for patients with CD4 cell counts ≥50/mm³
Within the first 2 weeks of tuberculosis treatment for patients with CD4 cell counts <50/mm³*
(Strong recommendation / High certainty in the evidence).
*Note: an exception is patients with HIV infection and tuberculous meningitis

6. Does extending treatment beyond 6 months improve outcomes compared to the standard 6-month regimen among tuberculosis patients co-infected with HIV?

Recommendation 5a: For HIV-infected patients receiving antiretroviral therapy, we suggest using the standard 6-month daily regimen

Recommendation 5b: In uncommon situations in which HIV-infected patients do NOT receive antiretroviral therapy during tuberculosis treatment, we suggest extending the continuation phase to 7 months in duration, corresponding to a total of 9 months of therapy (Conditional recommendation / Very low certainty in the evidence).
7. Does the use of adjuvant corticosteroids in tuberculous *pericarditis* provide mortality and morbidity benefits?

**Recommendation 7:** We suggest initial adjunctive corticosteroid therapy not be routinely used in patients with tuberculous pericarditis (Conditional recommendation / Very low certainty in the evidence).
8. Does the use of adjuvant corticosteroids in tuberculous meningitis provide mortality and morbidity benefits?

**Recommendation 8:** We recommend initial adjunctive corticosteroid therapy with dexamethasone or prednisolone given for six weeks for patients with tuberculous meningitis (Strong recommendation / Moderate certainty in the evidence).

9. Among HIV-negative patients (adults and children) with paucibacillary TB (i.e., confirmed to be smear negative, culture negative), does a shorter duration of treatment have similar outcomes compared to the standard 6-month treatment duration?

**Recommendation 9:** We suggest that a 4-month treatment regimen is adequate for treatment of HIV-negative adult patients with AFB smear- and culture-negative pulmonary tuberculosis (Conditional recommendation / Very low certainty in the evidence).
2016 ATS/CDC/IDSA TB Guidelines

Key Changes/Updates from 2003 edition

- Early initiation of ART in HIV/TB patients
- Duration of TB treatment in HIV w/o ART extended
- Evidence base for intermittent therapy reviewed
  - Once weekly regimen NOT recommended
- Evidence base for case management (patient education, incentives, enablers, DOT) reviewed
- TB treatment in pregnancy, language updated for PZA
- Steroids not routinely recommended for TB pericarditis

Thank you

- Strong commitment and leadership from ATS/CDC/ERS/IDSA
- ATS Documents Editor Kevin Wilson and GRADE Methodologist Jan Brozek
- Reviewers: ATS, IDSA, CDC, NTCA, ERS, ACET (>350 reviewer comments)
- Community Research Advisors Group of the CDC-TBTC and Treatment Action Group
- Susan Dorman (IDSA), GB Migliori (ERS), Andrew Vernon (CDC)
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>Failure</th>
<th>Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily</td>
<td>0/200 (0%)</td>
<td>1/200 (0.5%)</td>
</tr>
<tr>
<td>3X weekly</td>
<td>1/199 (0.5%)</td>
<td>5/198 (2.5%)</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 ≥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
78 abstracts excluded after review
9 Reviews
25 Not RCT/Cohort (case control, prevalence, cross sectional design, program report)
1 Regimen not reported
8 Outcomes not by Regimen
17 No outcomes
4 Individualized treatment
4 Latent TB/Non M.TB Non pulmonary TB
3 MDR TB
2 Not drug therapy

135 additional full texts identified from references and reviews

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

2\textsuperscript{nd} Review (2008 to 2012)
2293 Titles identified
   2233 Excluded based on title & abstract
60 Retrieved for full text review
   \textbf{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 \textsuperscript{a}
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>Daily</td>
<td>2.7% (1.6, 3.7)</td>
<td>6.3% (1.2, 11.4)</td>
<td>11.8% (8.5, 15.0)</td>
<td>4.2% (0, 12.9)</td>
</tr>
<tr>
<td></td>
<td>99/2813</td>
<td>142/1267</td>
<td>480/3293</td>
<td>2/60</td>
</tr>
<tr>
<td>Thrice weekly</td>
<td><strong>5.2% (1.5, 8.8)</strong></td>
<td><strong>18.2% (0, 39)</strong></td>
<td>10.1% (4.3, 16)</td>
<td><strong>11.4% (0, 66)</strong></td>
</tr>
<tr>
<td></td>
<td>32/464</td>
<td>44/210</td>
<td>52/516</td>
<td>18/188</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>Daily (reference)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Thrice weekly</td>
<td><strong>2.0 (0.8, 5.0)</strong></td>
<td><strong>2.2 (0.7, 7.3)</strong></td>
<td><strong>0.7 (0.3, 1.4)</strong></td>
<td><strong>3.7 (0.7, 18.9)</strong></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)⁴</th>
<th>Relapse: aOR (95% CI)⁴</th>
<th>Death: aOR (95% CI)⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ART: None / NRb</td>
<td>ART: All / Somec</td>
<td>ART: None / NRb</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>
<tr>
<td></td>
<td>2.2 (0.2, 27.9)</td>
<td>0.7 (0.4, 1.2)</td>
<td>2.0 (0.4, 11.5)</td>
</tr>
</tbody>
</table>

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

Dr. James Johnston  
University of British Columbia  
BC Centre for Disease Control  
Vancouver, British Columbia

Dr. Dick Menzies  
McGill University  
Respiratory Epidemiology and Clinical Research Unit  
Montreal, Quebec

Jonathon Campbell, BSc Phd (cand)  
Faculty of Pharmaceutical Sciences  
University of British Columbia  
Vancouver, British Columbia

Presentation 2: Richard Menzies
Evidence review for Intermittent therapy

**Search Strategy - update**

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

**Evidence review for Intermittent therapy (from Johnston 2016, do not cite, show or copy)**

**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”)

<table>
<thead>
<tr>
<th>Initial Phase Schedule</th>
<th>Arms (N)</th>
<th>Events/Participants</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>
</tr>
<tr>
<td>3x per week</td>
<td>19</td>
<td>28/2310</td>
<td>0.6% (0 - 1.4)</td>
</tr>
<tr>
<td>Relapse</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily</td>
<td>59</td>
<td>254/7475</td>
<td>2.5% (1.8 - 3.2)</td>
</tr>
<tr>
<td>3x per week</td>
<td>19</td>
<td>128/2130</td>
<td>6.8% (3.8 - 9.9)</td>
</tr>
<tr>
<td>Acquired Drug Resistance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily</td>
<td>43</td>
<td>11/4700</td>
<td>0.1% (0 - 0.2)</td>
</tr>
<tr>
<td>3x per week</td>
<td>15</td>
<td>16/1778</td>
<td>0.3% (0 - 0.8)</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>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>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>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>

Evidence review for Intermittent therapy *(from Johnston 2016, do not cite, show or copy)*

### 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

**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:**
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- And Information from authors: Dr. Judith Glynn and the Karonga Prevention Study, Dr. Paul Kelly, Dr. Gisele Klautau, Dr. Jürgen Noeske, Dr. Andrew Nunn, Dr. Estève 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><strong>14.3 (2.1, 98)</strong></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</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>
</tr>
</thead>
<tbody>
<tr>
<td>ART / ART / ART</td>
<td>None / NR(^b)</td>
<td>All / Some(^c)</td>
<td>None / NR(^b) All / Some(^c)</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>
</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>
</tr>
<tr>
<td>≥ 8 Months (ref)</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>
</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