American Thoracic Society / Centers for Disease Control / Infectious Diseases Society of America
Clinical Practice Guidelines:
Treatment of Drug-Susceptible Tuberculosis

Susan Dorman, MD
On behalf of the writing committee
WHERE THE RUBBER MEETS THE ROAD:

Key changes in the ATS/CDC/IDSA TB treatment guidelines and some thoughts on their implementation


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The American Thoracic Society, Centers for Disease Control and Prevention, and Infectious Diseases Society of America jointly sponsored the development of this guideline for the treatment of drug-susceptible tuberculosis, which is also endorsed by the European Respiratory Society and the US National Tuberculosis Controllers Association. Representatives from the American Academy of Pediatrics, the Canadian Thoracic Society, the International Union Against Tuberculosis and Lung Disease, and the World Health Organization also participated in the development of the guideline. This guideline provides recommendations on the clinical and public health management of tuberculosis in children and adults in settings in which mycobacterial cultures, molecular and phenotypic drug susceptibility tests, and radiographic studies, among other diagnostic tools, are available on a routine basis. For all recommendations, literature reviews were performed, followed by discussion by an expert committee according to the Grading of Recommendations, Assessment, Development and Evaluation methodology. Given the public health implications of prompt diagnosis and effective management of tuberculosis, empiric multidrug treatment is initiated in almost all situations in which active tuberculosis is suspected. Additional characteristics such as presence of comorbidities, severity of disease, and response to treatment influence management decisions. Specific recommendations on the use of case management strategies (including directly observed therapy), regimen and dosing selection in adults and children (daily vs intermittent), treatment of tuberculosis in the presence of HIV infection (duration of tuberculosis treatment and timing of initiation of antiretroviral therapy), as well as treatment of extrapulmonary disease (central nervous system, pericardial among other sites) are provided. The development of more potent and better-tolerated drug regimens, optimization of drug exposure for the component drugs, optimal management of tuberculosis in special populations, identification of accurate biomarkers of treatment effect, and the assessment of new strategies for implementing regimens in the field remain key priority areas for research. See the full-text online version of the document for detailed discussion of the management of tuberculosis and recommendations for practice.

Keywords. Mycobacterium tuberculosis; HIV infections; antitubercular agents; case management; public health.
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Treatment of Drug-Susceptible Tuberculosis
Writing Committee Leadership
and GRADE Methodology Group

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

• **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.
Approach

1. Panel composed
2. Prioritized topics for PICO questions
3. Formulated PICO questions
4. Methodologists prepared evidence profiles for each question using the GRADE approach and the GRADEpro GDT web-based tool to summarize and present information
5. Assessed risk of bias at the outcome level using Cochrane Collaboration’s tool
6. Assessed certainty of the evidence (i.e. confidence that the estimated effects are true) using GRADE based on
   - Risk of bias, precision, consistency and magnitude of estimates of effects, directness of evidence, risk of publications bias, presence of dose-effect relationship, effect of residual opposing confounding
   - Categorized into 4 levels (very low, low, medium, high)
7. Prepared evidence profiles that described summary of findings and quality of evidence
8. Prepared evidence-to-decision tables that described the estimates of health effects, values and preferences, and resource use.
9. Guideline panel used 7 and 8 to formulate recommendations
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 guideline 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, 2].
### PICO: Does initiation of ART during TB tx compared to at the end of tx improve outcomes among TB pts with HIV?

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Events / # of patients</th>
<th>Effect</th>
<th>Certainty in the Evidence</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early</td>
<td>Late ART</td>
<td>Relative (95% CI)</td>
<td>Absolute (95% CI)</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>randomized trials</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td></td>
<td>175/2349 (7.4%)</td>
<td>207/2041 (10.1%)</td>
<td>RR 0.76 (0.57 to 1.01)</td>
<td>24 fewer per 1000 (from 1 more to 44 fewer)</td>
</tr>
<tr>
<td><strong>AIDS-defining illness or death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>randomized trials</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td></td>
<td>126/1168 (10.8%)</td>
<td>151/900 (16.7%)</td>
<td>RR 0.77 (0.58 to 1.03)</td>
<td>22 fewer per 1000 (from 18 fewer to 46 fewer)</td>
</tr>
<tr>
<td><strong>Treatment success</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>randomized trials</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td></td>
<td>907/1057 (85.9%)</td>
<td>692/816 (84.9%)</td>
<td>RR 1.02 (0.98 to 1.07)</td>
<td>16 more per 1000 (from 16 fewer to 56 more)</td>
</tr>
<tr>
<td><strong>Grade 3-4 adverse event</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>randomized trials</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td></td>
<td>617/1998 (31.1%)</td>
<td>578/1807 (32.1%)</td>
<td>RR 0.95 (0.87 to 1.04)</td>
<td>16 fewer per 1000 (from 13 more to 42 fewer)</td>
</tr>
<tr>
<td><strong>Relapse</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>randomized trials</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>very serious</td>
</tr>
<tr>
<td></td>
<td>33/1272 (2.6%)</td>
<td>30/1247 (2.4%)</td>
<td>RR 0.97 (0.52 to 1.83)</td>
<td>1 fewer per 1000 (from 12 fewer to 20 more)</td>
</tr>
</tbody>
</table>

1. Serious 2. Very serious
The end result

- Executive summary (13 pages)
- Complete text (27 pages)
- Appendix A: Methods
- Appendix B: GRADE Evidence Profiles
- Appendix C: Drugs in Current Use

Strived to incorporate the required methodologic rigor (centered around circumscribed PICO questions) in a document that included foundational principles of TB treatment as well as important practical clinical information, and was approachable/easy to read.
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
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PICO 6. Does initiation of anti-retroviral therapy during TB treatment compared to at the end of TB treatment improve outcomes among TB patients co-infected with HIV?

Recommendation:
We recommend initiating antiretroviral therapy during tuberculosis treatment. By 8–12 weeks of tuberculosis treatment initiation for patients with CD4 cell counts ≥50/mm$^3$. Within the first 2 weeks of tuberculosis treatment for patients with CD4 cell counts <50/mm$^3$.* (Strong recommendation / High certainty in the evidence).

*Note: an exception is patients with HIV infection and tuberculous meningitis.
PICO 6. Does initiation of anti-retroviral therapy during TB treatment compared to at the end of TB treatment improve outcomes among TB patients co-infected with HIV?

Recommendation: 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*

2016 ATS/CDC/IDSA TB Treatment Guidelines
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2016 ATS/CDC/IDSA TB Treatment Guidelines
PICO 5. Does extending treatment beyond 6 months improve outcomes compared to the standard 6-month regimen among tuberculosis patients co-infected with HIV?
PICO 5. Does extending treatment beyond 6 months improve outcomes compared to the standard 6-month regimen among tuberculosis patients co-infected with HIV?

Recommendation (a): For HIV-infected patients receiving antiretroviral therapy, we suggest using the standard 6-month daily regimen (*Conditional recommendation / Very low certainty in the evidence*).

Recommendation (b): 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*).
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2016 ATS/CDC/IDSA TB Treatment Guidelines
Systematic review of published trials of adults with PTB treated with 6-month rifamycin-containing regimens of varying dosing schedule: odds of relapse relative to daily regimens:

<table>
<thead>
<tr>
<th>INTENSIVE PHASE</th>
<th>CONTINUATION PHASE</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily</td>
<td>3 times per week</td>
<td>1.6</td>
<td>0.6-4.1</td>
</tr>
<tr>
<td>Daily</td>
<td>2 times per week</td>
<td>2.8</td>
<td>1.3-6.1</td>
</tr>
<tr>
<td>3 times per week</td>
<td>3 times per week</td>
<td>2.8</td>
<td>1.4-5.7</td>
</tr>
<tr>
<td>Daily</td>
<td>Once weekly RPT</td>
<td>5.0</td>
<td>2.5-10.5</td>
</tr>
<tr>
<td>3 times per week</td>
<td>Once weekly RPT</td>
<td>7.1</td>
<td>3.3-15.3</td>
</tr>
</tbody>
</table>

Overall dose-response relationship

In the presence of cavitation, only the following attained best-estimate relapse risk <5%:
  - Daily x 6 months
  - Daily intensive phase plus 3 times per week continuation phase
PICO 3: Does intermittent dosing in the *intensive* phase have similar outcomes compared to daily dosing in the *intensive* phase? 
(in other words...) 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)

Recommendation 3b: Use of thrice-weekly therapy in the intensive phase may be considered in patients who are not HIV infected and are also at low risk of relapse (noncavitary and/or smear-negative at start of treatment) (Conditional recommendation / Low certainty in the evidence)

Recommendation 3c: In situations where daily or thrice-weekly DOT therapy is difficult to achieve, use of twice-weekly therapy after an initial 2 weeks of daily therapy may be considered for patients who are not HIV infected and are also at low risk of relapse (Conditional recommendation / Very low certainty in the evidence)
PICO 3: Does intermittent dosing in the intensive phase have similar outcomes compared to daily dosing in the intensive phase? (in other words...) 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)

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PICO 4. Does intermittent dosing in *continuation* phase have similar outcomes compared to daily dosing in *continuation* phase?

(In other words...) Should tuberculosis medications be dosed daily or intermittently in the continuation phase of treatment?
PICO 4. Does intermittent dosing in continuation phase have similar outcomes compared to daily dosing in continuation phase?
(In other words...) 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).

Recommendation 4c: We recommend against the use of once-weekly INH900/RPT600 mg in continuation phase (Strong recommendation / High certainty in the evidence).
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• Steroids not routinely recommended for TB pericarditis

2016 ATS/CDC/IDSA TB Treatment Guidelines
PICO 1. Does adding case management interventions to curative therapy improve outcomes compared to curative therapy alone?

In other words, should case management be provided to patients receiving curative tuberculosis therapy to improve outcomes?

*Case management: patient education/counseling, field/home visits, integration/coordination 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)

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2016 ATS/CDC/IDSA TB Treatment Guidelines
• H, R, E, Z previously all classified as ‘C’
  – C: “animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks”
  – 2003 US TB guidelines: “PZA can probably be used safely during pregnancy”
    • But most programs did not use PZA during pregnancy
  – WHO recommends use of PZA (standard tx) during pregnancy
  – 2016 TB guidelines:
    “We suggest that clinicians evaluate the risks and benefits on a case-by-case basis...” [discuss with patient]
    “Potential benefits warrant use of the drug in pregnant women despite potential risks.”
    “Expert opinion is that in pregnant women with TB/HIV, extrapulm TB, or severe TB, it is more beneficial to include PZA in the regimen than to not include PZA”
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• **Steroids not routinely recommended for TB pericarditis**
PICO 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*). “However, selective use of corticosteroids in patients who are at highest risk for inflammatory conditions might be appropriate. Such patients might include those with large pericardial effusions, those with high levels of inflammatory cells or markers in pericardial fluid, or those with early signs of constriction.”
What do the guidelines have to say about fluoroquinolones for DS-TB?

• “In scenarios in which EMB or INH cannot be used, the role of moxifloxacin or levofloxacin has not been established through clinical trials. Experts on occasion use moxifloxacin or levofloxacin in place of EMB during IP in adults in whom EMB cannot be used, or in place of INH throughout treatment in adults in whom INH cannot be used.”

• “There is no evidence that moxifloxacin or levofloxacin can be used in place of a rifamycin or PZA while maintaining a 6-month treatment duration.”

• “There is definitive trial evidence that 4-month daily regimens that substitute moxifloxacin or gatifloxacin for EMB, or moxifloxacin for INH, are significantly less effective [than the standard daily 6-month regimen].”
What do the guidelines have to say about fluoroquinolones for DS-TB?

- A single randomized trial showed that daily MRZE for 2 months then weekly P(1200mg)M had relapse rates similar to standard regimen given daily for 6 months. Use of this regimen (including daily moxifloxacin-containing intensive phase) may be considered. It is important to note that each dose of RPT was preceded by a meal of 2 boiled eggs and bread to increase absorption of RPT. If this regimen used, it is ideally implemented within the context of program-based operational research with suitable monitoring. Of note, there is no evidence that a once-weekly P(1200mg)M regimen after 2 months of HRZE intensive phase would achieve similar outcomes.
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
- Pahim Nahid (ATS), Susan Dorman (IDSA), GB Migliori (ERS), Andrew Vernon (CDC)
Extra Slides
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

2016 ATS/CDC/IDSA TB Treatment Guidelines
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

2016 ATS/CDC/IDSA TB Treatment Guidelines
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
2. Does self administration (SAT) of medications have similar outcomes compared to directly observed therapy (DOT) in patients with tuberculosis?
<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Events / No of patients</th>
<th>Effect</th>
<th>Certainty in the Evidence</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SAT</td>
<td>DOT</td>
<td>Relative (95% CI)</td>
<td>Absolute (95% CI)</td>
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<tr>
<td>Mortality (follow up: range 6-9 months)</td>
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<tr>
<td>randomized trials</td>
<td>25/689</td>
<td>42/914</td>
<td>RR 0.73 (0.45 to 1.19)</td>
<td>12 fewer per 1000 (from 9 more to 25 fewer)</td>
</tr>
<tr>
<td>serious ¹</td>
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</tr>
<tr>
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<td>other considerations</td>
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<td>Treatment success (follow up: range 6-9 months)</td>
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<tr>
<td>randomized trials</td>
<td>568/775</td>
<td>747/1001</td>
<td>RR 0.94 (0.85 to 1.00)</td>
<td>45 fewer per 1000 (from 15 fewer to 82 fewer)</td>
</tr>
<tr>
<td>serious ¹</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>not serious</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>indirectness</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>imprecision</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment completion (follow up: range 6-9 months)</td>
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<tr>
<td>randomized trials</td>
<td>56/889</td>
<td>76/914</td>
<td>RR 0.97 (0.88 to 1.14)</td>
<td>2 fewer per 1000 (from 26 fewer to 30 more)</td>
</tr>
<tr>
<td>serious ¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>not serious</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>indirectness</td>
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<tr>
<td>imprecision</td>
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<tr>
<td>Relapse (follow up: 24 months; assessed with: two or &gt; cultures + in a 2-month period)</td>
<td></td>
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<tr>
<td>randomized trials</td>
<td>15/280</td>
<td>23/259</td>
<td>RR 0.58 (0.31 to 0.99)</td>
<td>37 fewer per 1000 (from 8 more to 61 fewer)</td>
</tr>
<tr>
<td>serious ¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>not serious</td>
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<td></td>
</tr>
<tr>
<td>indirectness</td>
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</tr>
<tr>
<td>imprecision</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Adherence (follow up: range 6 or more months)</td>
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</tr>
<tr>
<td>randomized trials</td>
<td>78/866</td>
<td>84/87</td>
<td>RR 0.94 (0.87 to 1.19)</td>
<td>58 fewer per 1000 (from 19 more to 126 fewer)</td>
</tr>
<tr>
<td>serious ¹</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>not serious</td>
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</tr>
<tr>
<td>indirectness</td>
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<tr>
<td>imprecision</td>
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<tr>
<td>Time to smear conversion (follow up: mean 6 months)</td>
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</tr>
<tr>
<td>randomized trials</td>
<td></td>
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</table>
2. Does self administration (SAT) of medications have similar outcomes compared to directly observed therapy (DOT) in patients with 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)
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?
<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Summary of Findings</th>
<th>Certainty in the evidence</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of Treatment arms</td>
<td>Design</td>
<td>Limitations</td>
<td>Inconsistency</td>
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<tr>
<td>Failure</td>
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<tr>
<td>47</td>
<td>randomized trials &amp; observational</td>
<td>serious</td>
<td>serious</td>
</tr>
<tr>
<td>Relapse</td>
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<tr>
<td>27</td>
<td>randomized trials &amp; observational</td>
<td>serious</td>
<td>serious</td>
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<tr>
<td>Relapse – in patients NOT taking ART (anti-retroviral therapy)</td>
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</tr>
<tr>
<td>8</td>
<td>randomized trials &amp; observational</td>
<td>serious</td>
<td>serious</td>
</tr>
<tr>
<td>Death</td>
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<tr>
<td>47</td>
<td>randomized trials &amp; observational</td>
<td>serious</td>
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</tr>
</tbody>
</table>
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).
Drug Regimens for Microbiologically Confirmed Pulmonary Tuberculosis Caused by Drug-Susceptible Organisms

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Intensive Phase</th>
<th>Continuation Phase</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Drug(^a)</td>
<td>Drug(^b)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>INH RIF PZA EMB</td>
<td>INH RIF</td>
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</tr>
<tr>
<td></td>
<td>7 d/wk for 56 doses (8 wk), or 5 d/wk for 40 doses (8 wk)</td>
<td>7 d/wk for 126 doses (18 wk), or 5 d/wk for 90 doses (18 wk)</td>
<td>182–130</td>
</tr>
<tr>
<td>2</td>
<td>INH RIF PZA EMB</td>
<td>INH RIF</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7 d/wk for 56 doses (8 wk), or 5 d/wk for 40 doses (8 wk)</td>
<td>3 times weekly for 54 doses (18 wk)</td>
<td>110–94</td>
</tr>
<tr>
<td>3</td>
<td>INH RIF PZA EMB</td>
<td>INH RIF</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 times weekly for 24 doses (8 wk)</td>
<td>3 times weekly for 54 doses (18 wk)</td>
<td>78</td>
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<tr>
<td>4</td>
<td>INH RIF PZA EMB</td>
<td>INH RIF</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7 d/wk for 14 doses then twice weekly for 12 doses (^g)</td>
<td>Twice weekly for 36 doses (18 wk)</td>
<td>62</td>
</tr>
</tbody>
</table>