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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Clinical Infectious Diseases


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Treatment of Drug-Susceptible Tuberculosis
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Treatment of Drug-Susceptible Tuberculosis
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- 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.

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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

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## Treatment of Drug-Susceptible Tuberculosis Guideline Contents

### 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
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 Dose</th>
<th>Continuation Phase</th>
<th>Range of Total Doses</th>
<th>Comments</th>
<th>Regimen Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>INH</td>
<td>7 days for 56 doses (8 wk), or 6 days for 40 doses (8 wk)</td>
<td>INH RIF</td>
<td>182-380</td>
<td>This is the preferred regimen for patients with newly diagnosed pulmonary tuberculosis.</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 (8 wk)</td>
<td>INH RIF</td>
<td>110-380</td>
<td>Preferred alternative regimen in situations in which more frequent (DOT) during continuation phase is difficult to achieve.</td>
<td>Greater</td>
</tr>
<tr>
<td>3</td>
<td>INH</td>
<td>3 times weekly for 24 doses (8 wk)</td>
<td>INH RIF</td>
<td>78</td>
<td>Use regimen with caution in patients with HIV and/or other carbohydrate disease. Missed doses can lead to treatment failure, relapse, and acquired drug resistance.</td>
<td>Greater</td>
</tr>
<tr>
<td>4</td>
<td>INH</td>
<td>7 days for 14 doses, then twice weekly for 12 doses</td>
<td>INH RIF</td>
<td>63</td>
<td>Do not use twice-weekly regimens in INH-infections patients with other symptoms of and/or other disease. If doses are missed, then therapy is equivalent to once weekly, which is inferior.</td>
<td>Greater</td>
</tr>
</tbody>
</table>
Nine PICOs 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/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)

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

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2016 ATS/CDC/IDSA TB Treatment Guidelines
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)
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/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*

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)