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

Treatment of Drug-Susceptible Tuberculosis

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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.
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
Nine PICO(s) addressed:

• The **PICO process** is a technique used in evidence based practice to frame and answer a clinical or health care related question; Also used to develop literature search strategies.

• Guidelines include 9 PICO questions and associated recommendations
  
  P – population  
  I – intervention  
  C – comparator  
  O – outcomes  

http://guides.mclibrary.duke.edu/ebm/pico  
https://sph.uth.edu/charting/handouts/ebph_handouts/pico.pdf
GRADE METHODOLOGY (Grading of Recommendations, Assessment, Development, and Evaluation)

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

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].
Objectives of Tuberculosis Treatment

The objectives of TB therapy are:

1. To reduce the bacillary population rapidly thereby decreasing severity of the disease, preventing death and halting transmission of *M. tuberculosis*;

2. To eradicate persisting bacilli in order to achieve durable cure (prevent relapse) after completion of therapy; and

3. To prevent acquisition of drug resistance during therapy.
9 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 quality of evidence
## Patient-Centered Treatment Strategy

<table>
<thead>
<tr>
<th>Enablers</th>
<th>Incentives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interventions to assist the patient in completing therapy [130]</td>
<td>Interventions to motivate the patient, tailored to individual patient wishes and needs and, thus, meaningful to the patient [130]</td>
</tr>
<tr>
<td>Transportation vouchers [30]</td>
<td>Food stamps or snacks and meals [30]</td>
</tr>
<tr>
<td>Clinic personnel who speak the languages of the populations served [428]</td>
<td>Assistance in finding or provision of housing [429]</td>
</tr>
<tr>
<td>Reminder systems and follow-up of missed appointments [28]</td>
<td>Clothing or other personal products [30]</td>
</tr>
<tr>
<td>Social service assistance (referrals for substance abuse treatment and counseling, housing, and other services) [429]</td>
<td>Books [428]</td>
</tr>
<tr>
<td>Outreach workers (bilingual/bicultural as needed; can provide many services related to maintaining patient adherence, including provision of directly observed therapy, follow-up on missed appointments, monthly monitoring, transportation, sputum collection, social service assistance, and educational reinforcement) [429]</td>
<td>Stipends [30]</td>
</tr>
<tr>
<td>Integration of care for tuberculosis with care for other conditions [428]</td>
<td>Patient contract [30]</td>
</tr>
</tbody>
</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 quality of evidence*
Table 5. Examples of Priority Situations for the Use of Directly Observed Therapy

Patients With the Following Conditions/Circumstances [17, 130, 137, 139, 430, 431]:

- Positive sputum smears
- Delayed culture conversion (sputum obtained at/after completion of intensive-phase therapy is culture-positive)
- Treatment failure
- Relapse
- Drug resistance
- Homelessness
- Current or prior substance abuse
- Use of intermittent dosing
- HIV infection
- Previous nonadherence to therapy
- Children and adolescents
- Mental, emotional or physical disability (i.e., cognitive deficits such as dementia; neurological deficits; medically fragile patients; or patients with blindness or severe loss of vision)
- Resident at correctional or long-term care facility
- Previous treatment for active or latent tuberculosis

Abbreviation: HIV, human immunodeficiency virus.
Deciding to Initiate TB Treatment

**Figure 1.** Factors to be considered in deciding to initiate treatment empirically for active tuberculosis (TB) (prior to microbiologic confirmation). Abbreviations: AFB, acid-fast bacillus; TB, tuberculosis; IGRA, interferon-gamma release assay; TST, tuberculin skin test.
Deciding to Initiate Treatment

- Decision to start TB therapy based on clinical, radiographic, laboratory, patient and public health factors
  - Clinical judgement and index of suspicion play a critical role
- Empiric therapy with a 4-drug regimen is initiated:
  - In patients with high likelihood of having TB
  - In seriously ill patients with a disorder suspicious for TB

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**Figure 1.** Factors to be considered in deciding to initiate treatment empirically for active tuberculosis (TB) (prior to microbiologic confirmation). Abbreviations: AFB, acid-fast bacilli; HIV, human immunodeficiency virus; IGRA, interferon-γ release assay; Mtb, *Mycobacterium tuberculosis*; TNF, tumor necrosis factor; TST, tuberculin skin test.
Drug Regimens for Microbiologically Confirmed Pulmonary Tuberculosis Caused by Drug-Susceptible Organisms

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Drug</th>
<th>Intensive Phase</th>
<th>Continuation Phase</th>
<th>Range of Total Doses</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>INH</td>
<td>7 d/wk for 56 doses (8 wk)</td>
<td>INH RIF</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</td>
<td>7 d/wk for 56 doses (8 wk)</td>
<td>INH RIF</td>
<td>3 times weekly for 54 doses (18 wk)</td>
<td>110–94</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>
</tr>
<tr>
<td>4</td>
<td>INH</td>
<td>7 d/wk for 14 doses then twice weekly for 12 doses</td>
<td>INH RIF</td>
<td>Twice weekly for 36 doses (18 wk)</td>
<td>62</td>
</tr>
</tbody>
</table>

Regimen Effectiveness: Greater or Lesser
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 quality 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 quality evidence
Tables Providing Practical Support for TB Treatment

• **Table 3.** Doses of Antituberculosis Drugs for Adults and Children

• **Table 7.** Other causes of abnormal liver function tests that should be excluded

• **Table 8.** Clinically significant drug-drug interactions involving the rifamycins

• **Table 9.** Conditions or situations in which therapeutic drug monitoring may be helpful
Figure 2. Monitoring

<table>
<thead>
<tr>
<th>Activity</th>
<th>Baseline</th>
<th>Month of Treatment Completed</th>
<th>End of Treatment Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td><strong>MICROBIOLOGY</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sputum smears and culture</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug susceptibility testing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>IMAGING</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest radiograph or other imaging</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CLINICAL ASSESSMENT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptom and adherence review</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vision assessment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LABORATORY TESTING</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST, ALT, bilirubin, alkaline phosphate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet count</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis B and C screen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes Screen</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 2. Baseline and follow-up evaluations for patients treated with first-line tuberculosis medications (1)

- **Sputum C&S**: Obtain sputa for smear and culture at baseline, then monthly until 2 consecutive spec are (-).
  - Collecting sputa more often early in treatment for assessment of response and at end of treatment is optional.
  - At least 1 baseline spec should be tested using rapid molecular test

- **Drug susceptibility testing**: Obtain DST for INH, RIF, EMB, PZA.
  - Repeat DST if patient remains culture (+) after completing 3 mos of tx.
  - Molecular resistance testing for patients with risk for drug resistance.

- **CXR/Imaging**: Obtain CXR at baseline for all patients, also at mo. 2 if baseline cultures (-).
  - End-of-treatment CXR optional.
  - Other imaging for monitoring of extrapulmonary disease
Figure 2. Baseline and follow-up evaluations for patients treated with first-line tuberculosis medications (2)

- **Weight**: Monitor monthly to assess response to treatment; adjust medication dose if needed.

- **Symptom and adherence review**: Assess adherence and monitor improvement in TB symptoms (eg, cough, fever, fatigue, night sweats) as well as development of medication adverse effects (eg, jaundice, dark urine, nausea, vomiting, abdominal pain, fever, rash, anorexia, malaise, neuropathy, arthralgias).

- **Vision assessment (Patients on EMB)**: baseline visual acuity (Snellen test) and color discrimination tests, followed by monthly inquiry about visual disturbance and monthly color discrimination tests.
Figure 2. Baseline and follow-up evaluations for patients treated with first-line tuberculosis medications (3)

- **Laboratory testing:**
  - **AST, ALT, bili, alk phos:** only at baseline unless abnl at bl, symptoms c/w hepatotoxicity develop, or for patients who chronically consume alcohol, take other potentially hepatotoxic meds, have viral hepatitis or history of liver disease, HIV, or prior drug-induced liver injury.
  - **Platelets:** Baseline for all patients. Further monitoring if baseline abnormalities or as clinically indicated.
  - **HIV:** test all patients. CD4 lymph count and HIV RNA load if positive.
  - **HBV, HCV:** Screen patients with hepatitis B or C risk factor (eg, injection drug use, birth in Asia or Africa, or HIV)
  - **Diabetes screen:** Fasting glucose or HgbA1c for patients with risk factors for DM (ADA: age >45 years, BMI>25 kg/m2, first-degree relative with diabetes, and race/ethnicity of AA, Asian, Hispanic, American Indian/Alaska Native, or Hawaiian Native/Pacific Islander).

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.
## Dosing Recommendations (1)

### Table 10. Suggested Pyrazinamide Doses, Using Whole Tablets, for Adults Weighing 40–90 kg

<table>
<thead>
<tr>
<th>Regimen</th>
<th>40–55</th>
<th>56–75</th>
<th>76–90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily (mg/kg)</td>
<td>1000 mg (18.2–25.0)</td>
<td>1500 mg (20.0–26.8)</td>
<td>2000 mg (22.2–26.3)</td>
</tr>
<tr>
<td>Thrice weekly (mg/kg)</td>
<td>1500 mg (27.3–37.5)</td>
<td>2500 mg (33.3–44.6)</td>
<td>3000 mg (33.3–39.5)</td>
</tr>
<tr>
<td>Twice weekly (mg/kg)</td>
<td>2000 mg (36.4–50.0)</td>
<td>3000 mg (40.0–53.6)</td>
<td>4000 mg (44.4–52.6)</td>
</tr>
</tbody>
</table>

*a* With normal renal function.

*b* Based on estimated lean body weight. Optimal doses for obese patients are not established.

*c* Numbers in parentheses are the calculated mg/kg doses for patients at the highest and lowest body weights in the weight band.

### Table 11. Suggested Ethambutol Dosages, Using Whole Tablets, for Adults Weighing 40–90 kg

<table>
<thead>
<tr>
<th>Regimen</th>
<th>40–55</th>
<th>56–75</th>
<th>76–90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily (mg/kg)</td>
<td>800 mg (14.5–20.0)</td>
<td>1200 mg (16.0–21.4)</td>
<td>1600 mg (17.8–21.1)</td>
</tr>
<tr>
<td>Thrice weekly (mg/kg)</td>
<td>1200 mg (21.8–30.0)</td>
<td>2000 mg (26.7–35.7)</td>
<td>2400 mg (26.7–31.6)</td>
</tr>
<tr>
<td>Twice weekly (mg/kg)</td>
<td>2000 mg (36.4–50.0)</td>
<td>2800 mg (37.3–50.0)</td>
<td>4000 mg (44.4–52.6)</td>
</tr>
</tbody>
</table>

*a* With normal renal function.

*b* Based on estimated lean body weight. Optimal doses for obese patients are not established.

*c* Numbers in parentheses are the calculated mg/kg doses for patients at the highest and lowest body weights in the weight band.
### Table 12. Dosing Recommendations for Adult Patients With Reduced Renal Function

<table>
<thead>
<tr>
<th>Drug</th>
<th>Change in Frequency?</th>
<th>Recommended Dose and Frequency for Patients With Creatinine Clearance &lt;30 mL/min, or Patients Receiving Hemodialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>No</td>
<td>300 mg once daily, or 900 mg 3 times/wk</td>
</tr>
<tr>
<td>Rifampin</td>
<td>No</td>
<td>600 mg once daily, or 600 mg 3 times/wk</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Yes</td>
<td>25–35 mg/kg/dose 3 times/wk (not daily)</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Yes</td>
<td>20–25 mg/kg/dose 3 times/wk (not daily)</td>
</tr>
<tr>
<td>Levofoxacin</td>
<td>Yes</td>
<td>750–1000 mg/dose 3 times/wk (not daily)</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>No</td>
<td>400 mg once daily</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>Yes</td>
<td>250 mg once daily, or 500 mg/dose 3 times/wk</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>No</td>
<td>250–500 mg/dose daily</td>
</tr>
<tr>
<td>Para-aminosalicylic acid</td>
<td>No</td>
<td>4 g/dose twice daily</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>Yes</td>
<td>15 mg/kg/dose 2-3 times/wk (not daily)</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>Yes</td>
<td>15 mg/kg/dose 2-3 times/wk (not daily)</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>Yes</td>
<td>15 mg/kg/dose 2-3 times/wk (not daily)</td>
</tr>
<tr>
<td>Amikacin</td>
<td>Yes</td>
<td>15 mg/kg/dose 2-3 times/wk (not daily)</td>
</tr>
</tbody>
</table>

- Standard doses are given unless there is intolerance.
- The medications should be given after hemodialysis on the day of hemodialysis.
- Monitoring of serum drug concentrations should be considered to ensure adequate drug absorption, without excessive accumulation, and to assist in avoiding toxicity.
- Data currently are not available for patients receiving peritoneal dialysis. Until data become available, begin with doses recommended for patients receiving hemodialysis and verify adequacy of dosing using serum concentration monitoring.
- In patients with 30–50 mL/min creatinine clearance, standard doses are used by experts, but measurement of serum concentrations 2 and 6 hours after timed administration can be used to assist with optimizing drug dosages.

*a* Including adult patients receiving hemodialysis.

*b* The appropriateness of 250 mg daily doses has not been established. There should be careful monitoring for evidence of neurotoxicity.
## Treatment Interruptions

### Table 6. Management of Treatment Interruptions

<table>
<thead>
<tr>
<th>Time Point of Interruption</th>
<th>Details of Interruption</th>
<th>Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>During intensive phase</td>
<td>Lapse is &lt;14 d in duration</td>
<td>Continue treatment to complete planned total number of doses (as long as all doses are completed within 3 mo)</td>
</tr>
<tr>
<td></td>
<td>Lapse is ≥14 d in duration</td>
<td>Restart treatment from the beginning</td>
</tr>
<tr>
<td>During continuation phase</td>
<td>Received ≥80% of doses and sputum was AFB smear negative on initial testing</td>
<td>Further therapy may not be necessary</td>
</tr>
<tr>
<td></td>
<td>Received ≥80% of doses and sputum was AFB smear positive on initial testing</td>
<td>Continue therapy until all doses are completed</td>
</tr>
<tr>
<td></td>
<td>Received &lt;80% of doses and accumulative lapse is &lt;3 mo in duration</td>
<td>Continue therapy until all doses are completed (full course), unless consecutive lapse is &gt;2 mo If treatment cannot be completed within recommended time frame for regimen, restart therapy from the beginning (i.e., restart intensive phase, to be followed by continuation phase)</td>
</tr>
<tr>
<td></td>
<td>Received &lt;80% of doses and lapse is ≥3 mo in duration</td>
<td>Restart therapy from the beginning, new intensive and continuation phases (i.e., restart intensive phase, to be followed by continuation phase)</td>
</tr>
</tbody>
</table>

Abbreviation: AFB, acid-fast bacilli.

* According to expert opinion, patients who are lost to follow-up (on treatment) and brought back to therapy, with interim treatment interruption, should have sputum resent for AFB smear, culture, and drug susceptibility testing.

* The recommended time frame for regimen in tuberculosis control programs in the United States and in several European countries, is to administer all of the specified number of doses for the intensive phase within 3 months and those for the 4-month continuation phase within 6 months, so that the 6-month regimen is completed within 9 months.
5. Does initiation of ART *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 ART *during* tuberculosis treatment.

- **Within the first 2 weeks** of TB treatment for patients with CD4 cell counts <50/mm³ *
- **By 8-12 weeks** of TB treatment initiation for patients with CD4 cell counts ≥50/mm³

• *Strong recommendation / High quality of 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 TB 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 ART during TB 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 quality 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 quality of 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 quality of evidence*
9. Among HIV-negative patients (adults and children) with paucibacillary TB (i.e., 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 quality of evidence*
2016 ATS/CDC/IDSA TB Guidelines
Select 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
Twice Weekly Therapy for TB:
Are we throwing the baby out with the bathwater or buying a new pair of shoes?

A commentary on the new TB Treatment Recommendations

David Ashkin, M.D., F.C.C.P.
Medical Director, Southeastern National Tuberculosis Center
Medical Director, Florida Bureau of TB and Refugee Health
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2016 Treatment Guidelines for Pansusceptible Disease in Low Incidence/High Resource Countries

• Strong Document- Endorsed by Influential Multi-National TB Societies
  - American Thoracic Society (ATS)
  - Centers for Disease Control and Prevention (CDC)
  - Infectious Diseases Society of America (IDSA)
  - European Respiratory Society (ERS)
  - US National Tuberculosis Controllers Association (NTCA).
• We should be extremely grateful to the organizers/contributors of the document
• Well referenced (503!)
• Utilized GRADE/PICOS criteria
2016 ATS/CDC/IDSA TB Guidelines
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

2016 ATS/CDC/IDSA TB Treatment Guidelines
Nahid et al, CID 2016
“The Denver Regimen”

• Cohn et. al\(^1\) published in Annals of Internal Medicine their experience with RIPE for 2 weeks daily then BIW for the remaining 6 months
  - “program conditions” (large urban HD)
  - 71 (57%) patients had current/recent alcoholism
  - Very successful, only 2 relapses (1.6% ±2.2%) (6 and 56 months after completion of therapy)
  - No reported rifampin resistance

• Became one of the more popular regimens in U.S. TB programs

Reported TB Cases
United States, 1982–2015*

*Updated as of June 5, 2015.
Primary Anti-TB Drug Resistance, United States, 1993 – 2014*

*Updated as of June 5, 2015.

Note: Based on initial isolates from persons with no prior history of TB. Multidrug resistant TB (MDR TB) is defined as resistance to at least isoniazid and rifampin.
Historic Perspective of the Success of TB Therapy

- TB Therapy with standard regimens:
  - RIF and PZA containing regimens used for ≥6 months very successful; cure rates >95% and failure/relapse rates ≤5%
  - El Sadr\(^1\): U.S. based study of HIV (+)
    - DOT daily for 2 weeks then **TIW for 6 weeks then BIW for 4 months**
    - **3.9% relapses** (2 patients, both with RMR organisms; 1 was “reinfection” with new strain and other strain couldn’t be evaluated)
  - Sterling\(^2\): Baltimore-HIV (+) and HIV (-) treated with 6 mos RIF containing regimen given **BIW by DOT after 2 wks daily**
    - Overall **3.5% relapse**; HIV (+) relapse rate 6.4% vs HIV (-) 5.5%
    - Relapse rates did not differ comparing HIV (+) to HIV (-) pr unknown HIV status (6.4% versus 3.0%; P = 0.38).

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The Tuberculosis Trials Consortium (TBTC) Study 22

- RCT in U.S. and Canada; HIV (-) drug-susceptible TB
  - **RPT(600mg)/INH(900mg) 1xW** vs **RIF(600mg)/INH(900mg) BIW**
  - Crude rates of failure/relapse:
    - 9.2% for RPT once a week vs 5.6% RIF BIW (RR 1.64, p=0.04).
  - 5 characteristics independently associated failure/relapse:
    - sputum culture positive at 2 months (hazard ratio 2.8, 95% CI 1.7–4.6)
    - cavitation on chest radiography (3.0, 1.6–5.9);
    - being underweight (3.0, 1.8–4.9);
    - bilateral pulmonary involvement (1.8, 1.0–3.1); and
    - being a non-Hispanic white person (1.8, 1.1–3.0).

- “Rifapentine once a week is safe and effective for treatment of pulmonary TB in HIV-negative people without cavitation on CXR.”

The Tuberculosis Trials Consortium (TBTC) Study 23

• Prospective study, U.S. and Canada of HIV-related TB
  - 169 HIV+ patients, 45% with extrapulmonary disease and low CD4 counts; 81% on ARV
  - Rifabutin, INH, PZA, and EMB given daily for 2 weeks
  - Then either daily (5 d/wk), thrice-weekly, or twice-weekly
  - After 2 mo, all given RFB 300mg/INH 15mg/kg, max 900mg BIW
  - 5% relapse
  - 8 of 9 relapsed with same strain and rifampin monoresistance
  - Treatment failure/relapse associated with lower baseline CD4 count
    • 12.3% among patients with CD4 <100 cells/mm³ vs 0% among those with higher CD4 lymphocyte counts (p 0.01)

• Recommend at least TIW in HIV (+) individuals though no direct comparison between TIW and daily vs BIW

Twice-Weekly Dosing Throughout or Twice-Weekly Dosing After 2–3 Weeks of Daily Dosing

Twice-weekly dosing (ie, 2 times per week) either throughout treatment or after an initial period of 2–3 weeks of daily therapy is not generally recommended because of a lack of high-quality evidence to support its use, and because in twice-weekly therapy, if doses are missed then therapy is equivalent to once weekly, which is inferior (see “Once-Weekly Continuation Phase,” below). However, some tuberculosis programs have reported longstanding programmatic treatment success with an initial daily regimen followed by twice-weekly therapy [161], and this regimen remains in use by some public health programs in the United States. 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 (pulmonary tuberculosis caused by drug-susceptible organisms, that at the start of treatment is noncavitary and/or smear negative) (Recommendation 3c: conditional recommendation; very low certainty in the evidence) (see Supplementary Appendix B, Evidence Profile 7).
**Evidence profile 7**

**Date:** 2014.05.16

**PICO Question 3:** Does intermittent dosing in the intensive phase have similar outcomes compared to daily dosing in the intensive phase of treatment for drug-susceptible pulmonary tuberculosis?

**PICO Question 4:** 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 patients?

**Comparison:** Daily throughout versus 2-times weekly throughout.

*From a systematic review of 57 randomized trials published between 1965 and 2009; the systematic review performed across trial comparisons (i.e., not limited to direct head-to-head comparisons).*

<table>
<thead>
<tr>
<th>No of treatment arms</th>
<th>Study Design</th>
<th>Risk of Bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Event/No. of patients</th>
<th>Pooled estimate (95% CI)</th>
<th>Effect</th>
<th>Certainty in the Evidence</th>
<th>Importance</th>
</tr>
</thead>
</table>

**Failure**

- 279* randomized trials
- Risk of Bias: not serious
- Inconsistency: serious
- Indirectness: not serious
- Imprecision: serious
- Other considerations: none
- Event/No. of patients: 179 / 11,510
- Pooled estimate: 0.4% (0.2 to 0.7)
- Effect: Relative (95% CI): 0.8 (0.2 to 4.0)
- Absolute (95% CI): 1 fewer per 1000 (from 5 fewer to 4 more)
- Certainty in the Evidence: LOW
- Importance: CRITICAL

**Relapse**

- 268* randomized trials
- Risk of Bias: not serious
- Inconsistency: serious
- Indirectness: not serious
- Imprecision: serious
- Other considerations: none
- Event/No. of patients: 588 / 9,620
- Pooled estimate: 4.8% (3.6 to 6.0)
- Effect: Relative (95% CI): 0.7 (0.4 to 3.5)
- Absolute (95% CI): 31 fewer per 1000 (from 11 fewer to 56 more)
- Certainty in the Evidence: LOW
- Importance: CRITICAL

**Acquired Drug Resistance among patients who failed or relapsed**

- 224* randomized trials
- Risk of Bias: not serious
- Inconsistency: serious
- Indirectness: not serious
- Imprecision: serious
- Other considerations: none
- Event/No. of patients: 87 / 8,541
- Pooled estimate: 0.3% (0.1 to 0.6)
- Effect: Relative (95% CI): 0.9 (0.2 to 5.5)
- Absolute (95% CI): 1 more per 1000 (from 10 fewer to 22 more)
- Certainty in the Evidence: LOW
- Importance: CRITICAL

**Notes:**

1. The comparisons were done across trials (treating different arms as independent cohorts) rather than within trials; however, the panel decided that this was not serious enough to warrant downgrading the certainty in the evidence.
2. There was considerable heterogeneity of results between studies.
3. The effects at the ends of the confidence intervals would lead to different clinical decisions; in addition, the sample sizes in the twice-weekly arms are smaller than the optimal information size.

**Evidence Profile References:**

Study: Looked at 57 different studies between 1965 and 2008 (most <1990)
- Few head to head trials
- Data pooled to get results, which increased risk of bias/heterogeneity
- 52% trials had therapy without DOT
- Trials from many countries
- Rif dose low (450mg/d) in 2 trials
• “There was little evidence of difference in failure or relapse with daily or intermittent schedules of treatment administration, although there was insufficient published evidence of the efficacy of twice-weekly rifampin administration throughout therapy.”

• Increased risk of acquired resistance associated with thrice-weekly therapy throughout.
Limitations in the Evidence Used for Recommendations

• Systematic reviews / meta-analysis: heterogeneity limits interpretation and generalizability of results
  - Menzies 2009: “inter-study differences in providers and populations could have very important influences on these outcomes, even greater than any biologic differences in disease response”
  - Pooling results increases potential confounding from differences in treatment, patients’ disease severity, or other differences in study populations, since studies were conducted in many different countries.
  - Many trials were conducted overseas: geographic differences affect treatment response (TBTC 28 and other studies)
  - Few trials comparing intermittent regimens head to head

• Very low certainty of the evidence ....likelihood that the effect will be substantially different is very high

(www.getitglossary.org)
An updated systematic review and meta-analysis on the treatment of active TB in patients with HIV infn

- Evaluated 3 new studies reporting relapse - only 1 (El Sadr) from US
- Risk of ADR at failure or relapse significantly lower in arms using ART
- Arms receiving intermittent tx had lower mean CD4 vs. daily dosing
- Significant heterogeneity

GRADE/PICOS

- Lack of high quality studies to support the use of intermittent therapy
- BUT, there is also no high quality evidence not to support it’s use!!
Evidence Profiles 5–8). As noted above for twice-weekly regimens, an advantage of a thrice-weekly regimen is that it allows for the possibility of some doses being missed; with twice-weekly therapy, if doses are missed then therapy is equivalent to once weekly, which is inferior (see “Once-Weekly Continuation Phase,” below).
• We need to better appreciate the difference between effectiveness of the regimen versus programmatic performance

• Many programs have relapse rates well below 5%, and very little acquired rifampin resistance

• We must evaluate U.S. programmatic data in order to make appropriate decisions for US TB programs!!!
“A Solution In Search of A Problem?”

-M. Lauzardo MD, MSci
Summary (1)

- Some evidence to support daily throughout over intermittent therapy.
- Decision to switch to intermittent therapy should be made on a case by case basis taking into account extent of disease, sputum smear results, concomitant diseases.
- No strong evidence to support only using biweekly in “smear negative cases without cavitation” - programmatic evidence supports majority of patients still cured by biweekly therapy.
Summary (2)

• Programs should assess if there are adequate resources to use daily/TIW regimens exclusively without diverting resources from other important TB Control activities (Contact investigation, case finding, or DOT for 3HP for high risk LTBI patients)
• Programs should continue to monitor effectiveness of their activities
• More studies are needed, utilizing US TB control activities, to assess effectiveness of currently utilized interventions including studies of cost analysis.
Don't throw the baby out with the bathwater!
Resources

• Treatment of Drug-Susceptible Tuberculosis, CID 2016 [http://cid.oxfordjournals.org/content/63/7/e147](http://cid.oxfordjournals.org/content/63/7/e147)


• CDC Treatment for TB Disease [http://www.cdc.gov/tb/topic/treatment/tbdisease.htm](http://www.cdc.gov/tb/topic/treatment/tbdisease.htm)


1 800-4TB-INFO!!
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


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*GRADE (Grading of Recommendations Assessment, Development and Evaluation)
The following views that will be expressed are entirely my perspective and not necessarily endorsed/supported by anyone!!!!