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2017

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TB INFOLINE: 1-800-4TB-DOCS

Treatment of Drug-Susceptible Tuberculosis (TB) in Adults

Based on the 2016 Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America *Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis*.

This card provides an overview of the treatment of drug-susceptible TB. Consult guidelines for complete information.

This material was supported by the grant U52PS004090 funded by the Centers for Disease Control and Prevention. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the Centers for Disease Control and Prevention or the Department of Health and Human Services.

INTRODUCTION TO TB TREATMENT

- TB treatment requires a combined public health and clinical approach.
- The goals of TB treatment are to:
  - Minimize risk of disability and death in individual patients and prevent transmission of *M. tuberculosis*.
  - Achieve durable cure and prevent relapse.
  - Prevent acquisition of drug resistance during therapy.
- Standard TB therapy is comprised of four drugs provided in two phases (see Drug Regimens panel):
  - Intensive phase: 2 months of Isoniazid (INH), Rifampin (RIF), Pyrazinamide (PZA), and Ethambutol (EMB).
  - Continuation phase: 4 months of INH and RIF.
- Some situations may require extension or modification of therapy (see Special Situations panel).
- Empiric TB treatment with 4 drugs should be initiated prior to laboratory confirmation in patients for whom there is a high index of suspicion for TB, especially seriously ill patients.
- Persons with confirmed or suspected TB disease must be promptly reported to state and/or local health departments as per public health regulations.
- Health departments have a responsibility to provide and support case management and directly observed therapy (DOT).
- An individualized patient-centered case management approach is recommended (e.g., patient education, coordinated care, and incentives); patients should be involved in decisions concerning care.
- DOT is recommended for all patients with TB disease; a plan for DOT should be made collaboratively with the patient.
- In conjunction with the health department, providers are responsible for prescribing an appropriate regimen and ensuring patient safety, adherence, and completion of therapy using DOT.
- Treatment should be undertaken in consultation with a physician experienced in TB management.
- For access to expert TB clinicians or additional sources of guidance, consult your TB program (cdc.gov/tb/links/tboffices.htm).

FIRST-LINE MEDICATIONS FOR TREATMENT OF DRUG-SUSCEPTIBLE TB[1]

Educate patients about possible adverse effects of medications at treatment initiation and throughout the course of therapy.

DRUG	DOSAGE MG/KG[2] [TYPICAL DOSE]		ADVERSE REACTIONS	COMMENTS
	Daily	3x/wk[3]		
Isoniazid INH	5 mg/kg [typically 300 mg]	15 mg/kg [typically 900 mg]	Hepatitis, rash/ allergy, peripheral neuropathy, mild CNS effects, drug interactions, optic neuritis	Add 25-50 mg/day pyridoxine (vitamin B6) in pregnant women, patients with malnutrition, alcoholism, diabetes, and other conditions associated with neuropathy; patients with peripheral neuropathy should receive 100 mg/day.
Rifampin RIF	10 mg/kg [typically 600 mg]	10 mg/kg [typically 600 mg]	GI intolerance, hepatitis, drug interactions, rash, thrombocytopenia, flu-like symptoms	Educate patients about expected orange discoloration of bodily fluids. Drug-drug interactions may require monitoring and dose adjustments (e.g., methadone). Women on hormonal contraceptives should use barrier methods. If RIF cannot be used, rifabutin may be used for daily therapy, but requires dose adjustment; seek expert consultation. Concomitant use of ART with rifamycins is complex; consult an HIV expert and refer to hivinsite.ucsf.edu/InSite for updated recommendations and information on drug-drug interactions; monitoring serum drug concentrations may be necessary.

DRUG	PATIENT WEIGHT[2]	SUGGESTED DOSAGE		ADVERSE REACTIONS	COMMENTS
		Daily	3x/wk[3]		
Pyrazinamide PZA	40-55 kg	1000 mg	1500 mg	Hepatitis, GI intolerance, rash, arthralgias, hyperuricemia, gout (rare), photosensitivity	In patients with creatinine clearance <30 mL/minute or on hemodialysis, reduce dose interval to 3x/wk (using standard doses). Use of PZA in pregnant women in the US is controversial (see Special Situations panel). Carefully monitor elderly patients for adverse events, drug interactions, or intolerance. If PZA is omitted for any reason, extend treatment duration to 9 months.
	56-75 kg	1500 mg	2500 mg		
	76-90 kg	2000 mg	3000 mg		
Ethambutol EMB	40-55 kg	800 mg	1200 mg	Optic neuritis	In patients with creatinine clearance <30 mL/minute or on hemodialysis, reduce dose interval to 3x/wk (using standard doses).
	56-75 kg	1200 mg	2000 mg		
	76-90 kg	1600 mg	2400 mg		

1. TB fixed-dose combinations (FDCs) may be used, if available.
2. INH and RIF dosing may be based on actual body weight for non-obese patients; PZA and EMB dosing is based on estimated lean body weight. Optimal doses for obese patients have not been established; consult Table 3 in ATS/CDC/IDSA guidelines.
3. Consult ATS/CDC/IDSA guidelines for dosages when other intermittent regimens are used.

PREFERRED REGIMENS FOR CULTURE-POSITIVE DRUG-SUSCEPTIBLE PULMONARY TB

- Daily dosing with case management and DOT is preferred throughout treatment. During the continuation phase, intermittent dosing using thrice-weekly DOT is a reasonable option for HIV-uninfected patients.
- Pyridoxine (vitamin B6) is given with INH to all persons at risk of neuropathy and those with peripheral neuropathy (see previous table for details).

INTENSIVE PHASE		
4-Drug Combination	**Interval & Doses (Minimum Duration) with DOT**	**Recommendation**
INH **RIF** **PZA** **EMB**[2]	**Daily:**[1] 7 d/wk for minimum of 56 doses (8 wks) **OR** 5 d/wk for minimum of 40 doses (8 wks)	**Preferred**
	OR	May be considered in certain patients: **HIV-uninfected** with low risk of relapse (known drug-susceptible TB that is noncavitary and smear-negative at start of treatment).
	Intermittent:[3] 3x/wk for minimum of 24 doses (8 wks)	

CONTINUATION PHASE[4]		
2-Drug Combination	**Interval & Doses (Minimum Duration) with DOT**	**Recommendation**
INH/RIF	**Daily:**[1] 7 d/wk for minimum of 126 doses (18 wks) **OR** 5 d/wk for minimum of 90 doses (18 wks)	**Preferred**
	OR	Acceptable alternate regimen for **HIV-uninfected** patients.
	Intermittent:[3] 3x/wk for minimum of 54 doses (18 wks)	

1. Follow your TB program policy for the definition of daily dosing. Many programs that use 5 d/wk DOT to meet the definition of daily dosing also elect to provide 2 additional doses through self-administered therapy (SAT), though SAT doses are not included when counting total number of doses provided. In complicated cases, some experts prefer the maximum number of doses listed above for daily therapy.
2. EMB may be omitted from the regimen as soon as a drug susceptibility test (DST) demonstrates that the isolate is susceptible to INH and RIF.
3. Other intermittent dosing options may be used in specific circumstances. See Recommended Treatment Regimens section of ATS/CDC/IDSA guidelines. Twice-weekly dosing is generally **not** recommended, as missed doses result in the equivalent of once-weekly dosing, which is inferior. However, twice-weekly dosing may be used in the continuation phase if programmatic conditions exist to address missed doses.
4. In certain circumstances (including patients with cavitation on initial CXR and positive cultures at 2 months of therapy), the continuation phase should be extended to 7 months of daily dosing, for a total of 9 months (31 weeks) of therapy (see Special Situations panel).

RECOMMENDED MONITORING FOR PATIENTS TREATED WITH FIRST-LINE TB MEDICATIONS

		BASELINE EXAMINATION		FOLLOW-UP MONITORING	
		Initial	**Comment**	**Monthly**	**Comment**
Clinical Assessment	**Height and Weight**	✓	Consider nutritional supplement for significant weight loss.	✓	Weight gain is a marker of clinical improvement. Adjust medication dosage based on weight as needed.
	Symptom and Adherence Review	✓	In patients with extrapulmonary TB, infectious pulmonary TB should be excluded for public health reasons. Evaluate for possible extrapulmonary sites of TB in patients with pulmonary TB (TB meningitis and bone, joint, or spinal TB require extension of therapy).	✓	Assess adherence using DOT log. Monitor improvement in symptoms and development of adverse drug effects (e.g., anorexia, nausea, vomiting, abdominal pain, malaise, arthralgias, neuropathy, fever, rash, jaundice, or dark urine).
	Vision Assessment	✓	**For patients on EMB:** Color discrimination/Ishihara plates (available online) and visual acuity tests.	✓	**For patients on EMB:** Inquire about visual disturbance and perform color discrimination testing.
Microbiology	**Sputum Smear and Culture**	✓	At least one initial specimen should be tested using rapid molecular test/nucleic acid amplification (NAA) assay.	✓	**At least monthly UNTIL two consecutive specimens are culture-negative.** Ensure sputum collection at 2 months to document culture conversion, which has implications for length of therapy. May be used more frequently early in treatment as needed for infection control purposes or clinical management.
	Drug Susceptibility Testing (DST)*	✓	Obtain DST for INH, RIF, EMB, PZA. Molecular resistance testing should be performed for patients at risk for drug resistance, or for all patients if resources are available.		Repeat if culture-positive after 3 months of treatment.
Laboratory Assessment	**AST, ALT, Bilirubin, Alkaline Phosphate**	✓	Elevation may occur with extensive TB disease and may not require medication adjustment. Advise patients to avoid excessive acetaminophen use due to additive hepatotoxicity.		**Periodic LFTs are indicated for patients with:** – Current viral hepatitis – Alcoholism – HIV infection – Abnormalities at baseline – Other potentially hepatoxic medications – Symptoms consistent with hepatotoxicity – Prior drug-induced liver injury – History of liver disease 1. Medications should be withheld and patients evaluated if transaminase levels are >3 times upper limit of normal (ULN) with symptoms or >5 times ULN in asymptomatic patients. 2. Use of an alternate liver-sparing regimen may be necessary. 3. When LFTs are <2 times ULN, a systematic re-challenge process can be initiated, with expert consultation.
	Platelet Count	✓	For all patients.		As clinically indicated.
	Creatinine	✓	For all patients.		As clinically indicated.
	HIV Testing	✓	For all patients (CD4 & HIV RNA load if HIV-infected).		Continue regular monitoring in coordination with HIV care provider.
Imaging	**Chest X-Ray (CXR)**	✓	CXR should be obtained for all patients, including those with extrapulmonary TB.		Experts recommend obtaining CXR at 2 months to evaluate response to therapy and at completion of treatment to provide a baseline against which subsequent examinations can be compared.
	Other Imaging	✓	As needed for extrapulmonary sites or extensive pulmonary disease (e.g., CT, MRI).		As needed for monitoring of extrapulmonary disease based on site of disease and adequacy of clinical response.

* Molecular DST (MDDR service) is available from CDC through state or city public health laboratories.

Additional Laboratory Testing for Specific Circumstances

- Perform baseline screening for Hepatitis B and C for patients with risk factors for these viruses (e.g., current or former injection drug use, HIV infection, birth in Asia and Africa, or birth between 1945 and 1965).
- Perform baseline fasting glucose or hemoglobin A1c for patients with risk factors for diabetes (age >45 years, BMI >25 kg/m^2, first degree relative with diabetes, race/ethnicity of African American, Asian, Hispanic, American Indian/Alaska Native, or Hawaiian Native/Pacific Islander), or for all patients, if resources permit.
- Carefully evaluate patients with persistently positive cultures after 3 months of treatment to identify cause of delayed response (e.g., secondary or unrecognized drug resistance, malabsorption, or DOT issues). Those with positive cultures after 4 months are considered to have failed treatment; seek expert consultation.
- Consider therapeutic drug monitoring (TDM) for patients with delayed response to therapy or patients with medical conditions or potential drug interactions suspected of causing sub-therapeutic or supra-therapeutic drug concentrations (e.g., HIV infection, GI abnormalities, diabetes, or impaired renal clearance).

TREATMENT IN SPECIAL SITUATIONS

Expert consultation is strongly recommended for complicated cases or special situations.

NEED FOR EXTENSION OF THERAPY

- The continuation phase should be extended by an additional 3 months for a total of 9 months of therapy in patients with:
  - Drug-susceptible pulmonary TB with cavitation on initial CXR who remain culture-positive after 2 months of therapy.
  - **EITHER** cavitation on initial CXR **OR** positive culture at 2 months **AND** one or more of the following conditions: diabetes, extensive disease on CXR, immunosuppressing condition, smoking, or >10% below ideal body weight.
  - HIV infection when patients are not on antiretroviral therapy (ART) (see below).
  - PZA resistance or intolerance (including patients with *M. bovis*) which results in PZA discontinuation before the intensive phase is completed, or in whom PZA is not used (e.g., pregnant women).
- 6-9 month regimens containing INH and RIF are effective for most sites of extrapulmonary TB; most experts recommend 12 months of treatment for TB meningitis and 9-12 months for many forms of bone, joint, and spinal TB.

HIV

Expert consultation is strongly recommended for treatment of TB/HIV as management of these patients can be complex; some ART agents have potential drug interactions with rifamycins, requiring drug and/or dosage changes. Immune reconstitution inflammatory syndrome (IRIS) may warrant additional evaluation and treatment. Dosing frequency less than 5 d/wk is not recommended for HIV-infected patients.

Treatment of TB in HIV-infected patients:

- Standard 6-month daily regimen is adequate for most patients with drug-susceptible pulmonary TB on ART.
- Extend continuation phase by 3 months for drug-susceptible pulmonary TB in uncommon situations where patients are not on ART.

Antiretroviral Therapy Initiation:

- For HIV-infected patients not on ART, risk-benefit analysis favors initiation of ART early in TB regimen:
  - Begin ART within 2 weeks for CD4 <50 cells/µL.
  - Begin ART within 8-12 weeks for CD4 ≥50 cells/µL.
- ART should not be initiated within the first 8 weeks of anti-TB therapy for patients with HIV infection and CNS TB (e.g.,TB meningitis or tuberculomas) due to risk of IRIS.

CULTURE-NEGATIVE TB

- 4-month regimen (2-month intensive phase followed by 2-month continuation phase) is adequate for treatment of HIV-uninfected adult patients with noncavitary pulmonary TB disease that is AFB smear and culture-negative, in cases where adequate specimens were obtained at start of therapy. Consult an expert if there is is a concern about drug resistance.
- Monitor clinical and radiographic response; CXR should be performed after 2 months and at completion of therapy.
- Extension to 6 months of therapy may be considered in certain situations.

TB IN PREGNANT OR BREASTFEEDING WOMEN

- Pregnant women should be treated for TB disease. PZA is usually omitted from the regimen in the US, but may be used on a case-by-case basis when benefit outweighs risk. If PZA is omitted, extend treatment to 9 months and consider expert consultation.
- Breastfeeding is encouraged for non-infectious mothers receiving first-line anti-TB agents. For women on appropriate TB therapy who are not yet deemed non-infectious, discuss risks and benefits of breastfeeding with patient and a TB expert. In this case, infection control measures must be in place and the infant should be on treatment for TB disease, if indicated, or on window prophylaxis.
- Pregnant women on INH should receive 25-50 mg/day vitamin B6; all exclusively breast-fed infants should receive 1-2 mg/kg/day B6 when the mother is on INH, regardless of the infant's treatment status.

RESOURCES

Official 2016 ATS/CDC/IDSA *Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis* is available at:

cdc.gov/tb/publications/guidelines/pdf/clin-infect-dis.-2016-nahid-cid_ciw376.pdf

Additional information, guidelines, and resources on drug-susceptible and other forms of TB are available at: cdc.gov/tb/education/professionaltools.htm

Updated HIV recommendations and information on drug-drug interactions with antiretroviral agents are available at: hivinsite.ucsf.edu/InSite

Consult your TB program or seek expert consultation for guidance in the following situations:

- Drug resistance
- Patients who are persistently culture-positive
- Treatment failure
- Significant treatment interruptions
- Severe adverse drug reactions or drug-drug interactions
- TB/HIV
- Severe liver disease
- Transplant patients
- Pericardial TB, CNS TB, severe bone or joint TB, or rare forms of extrapulmonary TB
- Social or behavioral circumstances requiring additional expertise or resources

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