

Chapter VI: Treatment and Follow-up for Suspect and Active TB Disease

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A. Recommended Treatment Regimens

There are four recommended regimens for treating adults with tuberculosis caused by organisms susceptible to INH, RIF, PZA, and EMB. Children, depending on the circumstances, may not receive EMB in the initial phase of a 6-month regimen, but otherwise, the regimen for children and adults are identical. Each regimen has an initial phase of 2 months followed by a continuation phase of either 4 or 7 months. Because of the high proportion of adult patient with tuberculosis caused by organisms resistant to INH, four drugs are necessary in the initial phase to prevent the development of drug resistance.

1. Six-Month Regimen

The current minimally acceptable duration of treatment for all children and adults with culture-positive tuberculosis is 6 months (26 treatment weeks). A treatment week consists of 7 doses of a daily treatment regimen when given 7 days a week self-administered or by directly observed therapy (DOT) in a hospital or other institutional setting. Five day-a-week drug administration by DOT is considered to be equivalent to 7 day-a-week administration; thus, either may be considered “daily”. A DOT treatment week in the outpatient setting is usually composed of 5 doses of a daily treatment regimen, 2 doses of a twice-weekly regimen, 3 doses of a thrice-weekly regimen, or one dose of a once-weekly regimen.

DOSES*OF FIRST-LINE ANTITUBERCULOSIS DRUGS FOR ADULTS AND CHILDREN†‡

Drug	Preparation	Adults/children	Doses			
			Daily	1x/wk	2x/wk	3x/wk
INH	Tablets (50 mg, 100 mg, 300 mg); elixir (50 mg/5 ml); aqueous solution (100 mg/ml) for intramuscular injection¶	Adults (max.)	5 mg/kg (300 mg)	15 mg/kg (900 mg)	15 mg/kg (900 mg)	15 mg/kg (900 mg)
		Children (max.)	10–15 mg/kg (300 mg)	—	20–30 mg/kg (900 mg)	—
RIF	Capsule (150 mg, 300 mg); powder may be suspended for oral administration; aqueous solution for intravenous injection	Adults† (max.)	10 mg/kg (600 mg)	—	10 mg/kg (600 mg)	10 mg/kg (600 mg)
		Children (max.)	10–20 mg/kg (600 mg)	—	10–20 mg/kg (600 mg)	—

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Drug	Preparation	Adults/children	Doses			
			Daily	1x/wk	2x/wk	3x/wk
RFB	Capsule (150 mg)	Adults† (max.)	5 mg/kg (300 mg)	—	5 mg/kg (300 mg)	5 mg/kg (300 mg)
		Children	Appropriate dosing for children is unknown			
RPT	Tablet (150 mg, film coated)	Adults	—	15 mg/kg (continuation phase) (900 mg)	—	—
		Children	This drug is not approved for use in children	This drug is not approved for use in children	This drug is not approved for use in children	This drug is not approved for use in children
PZA	Tablet (500 mg, scored)	Adults	See Table 5	—	See Table 5	See Table 5
		Children (max.)	15–30 mg/kg (2.0 g)	—	50 mg/kg (2.0 g)	—
EMB	Tablet (100 mg, 400 mg)	Adults	See Table 6	—	See Table 6	See Table 6
		Children§ (max.)	15–20 mg/kg daily (1.0 g)	—	50 mg/kg (2.5 g)	—

Definitions of abbreviations: EMB = ethambutol; FDA = Food and Drug Administration; INH = isoniazid; PZA = pyrazinamide; RFB = rifabutin; RIF = rifampin; RPT = rifapentine.

* Dose per weight is based on ideal body weight. Children weighing more than 40 kg should be dosed as adults.

† For the purposes of this document, adult dosing begins at the age of 15 years.

¶ INH is used, but not FDA-approved, for intravenous administration. For intravenous use of INH, please consult with *CDPHE's TB Nurse Consultant* at 303-692-2565

‡ Dose may need to be adjusted when there is concomitant use of protease inhibitors or nonnucleoside reverse transcriptase inhibitors.

§ The drug can likely be used safely in older children but should be used with caution in children less than 5 years of age, in whom visual acuity cannot be monitored. In younger children, EMB at the dose of 15 mg/kg per day can be used if there is suspected or proven resistance to INH or RIF.

Source: ATS, CDC, IDSA. Treatment of tuberculosis. *MMWR* 2003;52(No. RR-11):4.

The initial 8-week phase of a 6-month regimen for adults should consist of a 2-month period of INH, RIF, PZA, and EMB and may be given as follows:

- Daily for 8 treatment weeks (*40 total doses*)
- Daily for 2 treatment weeks (10 doses) followed by twice weekly for 6 treatment weeks (12 doses) (*22 total doses*)
- Daily for 3 treatment weeks (15 doses) followed by twice weekly for 5 treatment weeks (10 doses) (*25 total doses*)

Patients should receive a minimum of 2 daily treatment weeks (10 doses) followed by 6 treatment weeks of intermittent (twice-weekly or thrice-weekly) dosing.

For patients with HIV-infection, particularly with CD4 counts under 200 and other patients with more severe disease, defined as having positive sputum smears or cavitary disease, the daily phase of treatment should be at least 3 treatment weeks (15 doses) followed by 5 treatment weeks of thrice-weekly dosing.

For patients with the most severe disease, particularly those who are underweight and/or have diffuse bilateral lung involvement, continuing daily therapy throughout the 8 weeks of the initiation phase may be indicated.

A 4-drug regimen is initially used based on the current proportion of new TB cases caused by organisms that are resistant to INH. If therapy is being initiated after drug susceptibility test results are known for an organism that is susceptible to INH and RIF, and the treatment will be given daily for the first 8 weeks, EMB is not required during the initial phase of treatment. EMB may also be discontinued in patients at low risk of treatment failure or relapse who are being treated with intermittent regimens. Data are inadequate to recommend this for all patients treated with intermittent dosing.

The continuation phase of treatment should consist of INH and RIF given for a minimum of 4 months (18 treatment weeks). Patients should be treated until they have received the specified number of treatment weeks for the treatment regimen. The continuation phase may be given daily, twice-weekly, or three-times-weekly.

 For more information on DOT treatment weeks, see section A., “Directly Observed Therapy” in *Chapter VII: Practical Aspects of Treatment*.

2. Nine-Month Regimen

If PZA cannot be included in the initial regimen, or if the isolate is determined to be resistant to PZA (an unusual circumstance, except for *Mycobacterium bovis* and *M. bovis* var.BCG), a regimen consisting of INH, RIF, and EMB should be given for the initial 2 months followed by INH and RIF for 7 months given either daily, twice, or thrice weekly. Selected patients at low-risk for relapse may take once-weekly INH plus rifapentine for treatment completion.

Extension of treatment to 9 months is also recommended for patients at high risk for relapse based on radiological, bacteriological, and/or body-weight responses.

 For more information, see section D., “Patients at Increased Risk of Relapse” in this chapter.

3. Alternative Regimens

Patients who are HIV-negative, with non-cavitary TB, and who have negative sputa AFB smears at completion of the initial phase of treatment may be treated with once-weekly INH and rifapentine in the continuation phase for 4 months. If the 2-month sputum culture is positive, the continuation phase of once-weekly INH and rifapentine should be extended to 7 months.

In some cases, the above-described regimens cannot be used. Because of intolerance or drug resistance, in these instances, an alternative regimen may be required. When INH cannot be used or the organisms are resistant to INH, a 6-month regimen of RIF, PZA, and EMB is nearly as efficacious as a regimen containing INH although it is not well-tolerated. Alternatively, RIF and EMB for 12 months may be used, preferably with PZA during at least the initial 2 months. If RIF is not used, INH and EMB should be given for a minimum of 12-18 months with PZA during at least the initial 2 months. A fluoroquinolone may be useful in alternative regimens, but its potential role and optimal length of therapy has not been defined.

 For more information, see *Chapter IX: Management of Relapse, Treatment Failure, and Drug Resistance*.

B. Baseline Tests

The following tests should be ordered for all patients with active TB disease. Results from an outside lab may be used if the tests have been done within the past month.

- Complete blood cell (CBC) count, including platelets
- Chemistry panel (at a minimum: ALT, total bilirubin, creatinine, and alkaline phosphatase)
- Weight
- HIV (should be performed regardless of age).

The following tests should be ordered in certain situations.

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CD4+ lymphocyte count	HIV-infected patients should have a CD4+ lymphocyte count within the past 3 months. Often this can be obtained from their HIV care provider.
Pregnancy testing	Female patients should be asked whether they might be pregnant. Women with menses more than two weeks late should be referred for pregnancy testing or, if testing is available, be tested in the TB Clinic. Women receiving rifampin should be advised that hormonal contraception may not be effective and to use another method of birth control.
Thyroid-stimulating hormone (TSH)	If p-aminosalicylic acid (PAS) or ethionamide will be used
Visual acuity exam and Ishihara's test for color blindness	If ethambutol is used
Baseline audiogram	If an aminoglycoside (amikacin, kanamycin, streptomycin) or capreomycin will be used for longer than 2 months

Note: If any of the above tests are needed, please contact CDPHE's TB Program. Additional tests need prior approval from the TB Program if the patient does not have insurance. CDPHE is the payer of last resort.

C. Follow-up Evaluations

1. Clinical Evaluations

It is essential that patients have clinical evaluations with a nurse at least monthly to identify possible adverse effects of the anti-tuberculosis medications and to assess adherence. The following tests should be done as needed depending on patients' status and the medications they are taking.

- Weight: should be recorded monthly
- Temperature: if the patient is febrile whether documented or not
- Vision: Patients receiving EMB should be questioned regarding visual disturbances at monthly intervals. Monthly repeat testing of visual acuity and color vision is recommended for patients receiving an EMB dose exceeding 15-20 mg/kg (the recommended range) and for patients receiving the drug for more than 2 months.
- Hearing: Patients receiving an aminoglycoside or capreomycin should undergo an audiogram, vestibular testing, and Romberg testing if there are symptoms of eighth nerve toxicity such as hearing loss, tinnitus, or vertigo.

2. Chest X-Ray

a. Positive culture at diagnosis

For patients with positive cultures at diagnosis, a repeat chest x-ray at the end of therapy is important in order to provide a baseline to compare subsequent examinations.

Additional repeat chest x-rays may be obtained after completion of the initial 8 weeks of treatment or at intervals after treatment as clinically indicated. Routine 8-week chest x-rays are not required in all cases.

b. Negative initial sputum culture

A 2-month chest x-ray is particularly important for individuals with negative cultures because the clinical diagnosis of tuberculosis is based on clinical or radiological improvement while on treatment. Patients who show no clinical or radiological improvement after 2 months of treatment should be reevaluated for other diagnoses including latent TB infection, inactive TB, or other conditions. In patients with negative initial sputum cultures who are classified as clinical cases, a chest x-ray at completion of therapy should be done to provide a new baseline for future comparisons.

3. Mycobacteriology

Follow-up bacteriologic examinations are important for assessing the patient's infectiousness and response to therapy. Culture conversion is the most important objective measure of response to treatment and is used to determine the length of treatment. Obtaining sputa specimens to document the time of culture conversion and whether it occurs by the end of the initial 8 weeks is critical.

During treatment of patients with pulmonary and renal tuberculosis, a sputum and/or urine specimen for AFB smear and culture should be obtained at monthly intervals until 2 consecutive specimens are negative on culture.

For patients who had positive AFB smears at the time of diagnosis, follow-up smears and cultures may be obtained at more frequent intervals (e.g., every 2 weeks until 2 consecutive specimens are negative) to provide an early assessment of the response to treatment, especially for patients in situations in which the risk of transmission is high.

If release from isolation is dependent on sputa smear status, sputa samples may be collected more frequently. Please refer to Isolation Procedures in Chapter 12.

Drug susceptibility tests should be repeated on isolates from patients who have positive cultures after 3 months of treatment. Patients who have positive cultures after 4 months of treatment should be considered as having failed treatment and should be managed accordingly.

4. Laboratory Tests – CBC, Chemistry Panel, TSH

For patients under 35 years of age without risk factors, clinical reasons, or baseline abnormalities, it is not necessary to monitor liver enzymes, renal function (creatinine), or platelet count when treating with first-line drugs.

Lab tests should be monitored at 2-week to 3-month **intervals** during active TB treatment for patients with the following risk factors:

Risk Factor	Lab Tests
Chronic Hepatitis B or C and an abnormal baseline	ALT, consider bilirubin, albumin, alkaline phosphatase
HIV infection	ALT, bilirubin, albumin, alkaline phosphatase Complete blood count (CBC), platelets and CD4 lymphocyte count by HIV care provider as clinically indicated
Cirrhosis	ALT, bilirubin; consider alkaline phosphatase, prothrombin time CBC with platelets
Current alcoholism with or without hepatitis	ALT
≤3 months postpartum	ALT
Abnormal baseline lab tests	Whatever labs were abnormal at baseline as clinically indicated
Current intravenous drug user (IDUs)	ALT
Patients on PAS or ethionamide	TSH
Patients ≥35 years old on treatment for active TB with first-line drugs	ALT at 2-4 week intervals during the first 8 weeks then every 1 to 3 months during the continuation phase
When rifampin hypersensitivity is suspected (hematuria, back pain, severe febrile reaction, petechiae, bruising)	CBC with platelets Comprehensive Metabolic Panel (CMP)
Patients who have stable abnormalities of hepatic or renal function at baseline	ALT, bilirubin creatinine

Note: If any of the above tests are needed, please contact CDPHE’s TB Program. Additional tests need prior approval from the TB Program if the patient does not have insurance. CDPHE is the payer of last resort.

D. Completion of Therapy

Treatment for a defined duration without accounting for the number of doses taken can result in under-treatment. Therefore, the determination of whether or not treatment has been completed is based on the total number of treatment weeks received—not solely on the duration of therapy.

In some cases, either because of drug toxicity or non-adherence to the regimen, the specified number of doses cannot be administered within the targeted time period. Every effort should be made to complete treatment on schedule because having to extend treatment for more than a month is associated with poor treatment outcomes.

 *Treatment of Tuberculosis, 2003 (ATS/CDC/IDSA)* gives the number of doses for daily dosing and for once, twice, and three times per week dosing for the initial and continuation phases of each regimen option. <http://www.cdc.gov/mmwr/pdf/rr/rr5211.pdf>

F. Interruptions in Therapy

Interruptions in therapy are common in the treatment of tuberculosis. When interruptions occur, the person responsible for supervision must decide whether to restart a complete course of treatment or simply to continue as intended originally. This decision depends in part on whether the interruption occurred during the initial or the continuation phase of therapy. In general, the earlier the break in treatment occurs and the longer its duration, the more serious the effect and the greater the need to restart treatment from the beginning.

Continuous treatment is more important in the initial phase of therapy when there is the highest bacillary population and the chance of developing drug resistance is greatest. During the continuation phase, the number of bacilli is much smaller and the goal of therapy is to kill the persisting organisms. The duration of the interruption and the bacteriological status of the patient before and after the interruption are also important considerations.

If the interruption occurs during the initial phase of treatment and the lapse is 2 treatment weeks or more in duration, treatment may need to be restarted.

After any treatment interruption, sputa smears and cultures as well as a chest x-ray may be helpful for deciding whether to restart a new course, resume the previous course, or monitor the patient while not receiving therapy. Patients who are culture-positive after an interruption should have drug susceptibility performed and should be restarted on a multi-drug regimen which may include the addition of 2 new drugs (e.g., a fluoroquinolone and an injectable) when there is a concern about acquired drug resistance. Again therapy should always be given by DOT. Patients who failed to complete an adequate initial course but have negative sputum cultures on re-evaluation can often be re-treated with a 4-month course including a 2-month initiation.

Additionally, legal action (isolation, civil arrest, travel restrictions) should be taken to ensure completion of treatment.

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¹ ATS, CDC, IDSA. Treatment of tuberculosis. *MMWR* 2003;52(No. RR-11):4.