Chapter 6
Treatment of Tuberculosis Disease

Table of Contents

Chapter Objectives

After working through this chapter, you should be able to

- Describe tuberculosis (TB) disease treatment adherence strategies;
- Identify anti-TB drugs;
- Describe treatment regimens for TB disease;
- Describe patient monitoring; and
- List common adverse drug reactions to TB medications.

Introduction

The major goals of treatment for TB disease are to

- Cure the individual patient;
- Minimize risk of death and disability; and
- Reduce transmission of *M. tuberculosis* to other persons.

To ensure that these goals are met, TB disease must be treated for at least 6 months and in some cases even longer. Most of the bacteria are killed during the first 8 weeks of treatment; however, there are persistent organisms that require longer treatment. If treatment is **not** continued for a long enough duration, the surviving bacteria may cause the patient to become ill and infectious again, potentially with drug-resistant disease.

There are several options for daily and intermittent therapy, but the goal of treatment for TB disease should be to provide the safest and most effective therapy in the shortest period of time. Given adequate treatment, almost all patients will recover and be cured.

Regimens for the treatment of TB disease must contain multiple drugs to which the bacteria are susceptible. The standard of care for initiating treatment of TB disease is four-drug therapy. Treatment with a single drug can lead to the development of a bacterial population resistant to that drug. Likewise, the addition of a single drug to a failing anti-TB regimen can lead to additional resistance. When two or more drugs to which in vitro susceptibility has been demonstrated are given together, each helps prevent the emergence of tubercle bacilli resistant to the others.

> **The standard of care for initiating treatment of TB disease is four-drug therapy. Treatment with a single drug can lead to the development of a bacterial population resistant to that drug.**

Study Questions

6.1 **The major goals for treatment of TB disease include which of the following?**

    A. Curing the individual patient

    B. Minimizing risk of death and disability

    C. Reducing transmission of *M. tuberculosis* to other persons

    D. A, B, and C are all correct.

    E. Only A and B are correct.

Are the following statements about TB treatment true or false?
(Choose the one best answer and write the letter for the correct answer on the line next to the question number.)

Statements	True or False
_____ **6.2** Most of the TB bacteria are killed during the first 8 weeks of treatment. However, some persistent organisms require longer treatment.	**A.** True **B.** False
_____ **6.3** Regimens for the treatment of TB disease need to only contain one drug to which the bacteria are susceptible.	
_____ **6.4** Treatment that is **not** continued for a long enough time allows the surviving bacteria to cause the patient to become ill and infectious again.	
_____ **6.5** Treatment with a single drug cannot lead to the development of a bacterial population resistant to that drug.	
_____ **6.6** When two or more drugs to which in vitro susceptibility has been demonstrated are given together, each helps prevent the emergence of tubercle bacilli resistant to the other drugs(s).	
_____ **6.7** Given adequate treatment, almost all patients will recover and be cured.	

Treatment and Monitoring Plan

For each patient with newly diagnosed TB disease, a specific treatment and monitoring plan should be developed in collaboration with the local TB control program within 1 week of the presumptive diagnosis. This plan should include:

- Description of the TB treatment regimen;
- Methods of assessing and ensuring adherence to the TB treatment regimen;
- Methods to monitor for adverse reactions; and
- Methods for evaluating treatment response.

Study Question

6.8   Which of the following should NOT be included in a treatment and monitoring plan?
(choose the one best answer)

   A. Description of the TB treatment regimen

   B. Methods of assessing and ensuring adherence to the TB treatment regimen

   C. Methods to monitor for adverse reactions

   D. Methods to prevent a patient returning to work when noninfectious

   E. Methods for evaluating treatment response

Adherence Strategies

To treat TB disease and prevent acquired drug resistance, clinicians must ensure that their patients with TB disease follow the recommended course of treatment. However, ensuring that patients adhere to treatment can be difficult because patients are often unable or reluctant to take multiple medications for several months. Nonadherence to treatment is a major problem in TB control. Inadequate treatment can lead to

- Treatment failure;
- Relapse;
- Ongoing transmission; and
- Development of drug resistance.

Responsibility for successful treatment is assigned to the health-care provider, **not** the patient. Health-care professionals should consult their health department's TB control program to ensure their TB patients are able to adhere to a prescribed treatment regimen. The TB control program should assist the health-care professional in evaluating patient barriers to adherence and recommend directly observed therapy (DOT) and the use of incentives and enablers that may assist the patient in completing the recommended therapy.

Inadequate treatment can lead to treatment failure, relapse, ongoing transmission, and the development of drug resistance.

Responsibility for successful treatment is assigned to the health-care provider, not the patient.

If these efforts are unsuccessful, the TB control program should take more restrictive action. The TB program should consider court-ordered DOT or, if all other measures fail, the involuntary isolation of a patient who is unwilling or unable to complete treatment. This is necessary to protect the general public from patients who are infectious, at risk of becoming infectious, or at risk for developing drug-resistant TB disease. A patient may be involuntarily isolated, but the patient **cannot** be forced to swallow anti-TB drugs. Involuntary isolation should only be pursued as a last resort after all less-restrictive measures have failed.

Patient Education

Educating patients about TB disease helps ensure their successful completion of therapy. Health-care providers must take the time to explain clearly to patients what medication should be taken, how much, how often, and when. Patients should be clearly informed about possible adverse reactions to the medications they are taking and when to seek necessary medical attention. Providing patients with the knowledge they need regarding the consequences of **not** taking their medicine correctly is very important. In addition, patients should be educated about infection control measures and potential need for isolation (Table 6.1). HIV testing and counseling is recommended for all patients with TB disease in all health-care settings. The patient must first be notified that testing will be performed. The patient has the right to decline HIV testing and counseling (opt-out screening).

Table 6.1
Patient Education

Topics to Include When Educating Patients
• What medication should be taken, how much, how often, and when
• Possible adverse reactions to the medications
• When to seek necessary medical attention
• Consequences of not taking their medicine correctly
• TB infection control measures and potential need for isolation

HIV testing and counseling is recommended for all patients with TB disease in all health-care settings.

Case Management

Case management is a strategy used to ensure that patients complete treatment for TB disease. There are three elements of case management:

1. Assigning responsibility;
2. Conducting a regular systematic review; and
3. Developing a plan to address barriers to adherence.

Case managers are health department employees, usually nurses or public health professionals, who are assigned primary responsibility for the management of specific patients. Case managers are held accountable for ensuring that each patient is educated about TB and treatment, ensuring that therapy is continuous and complete, and confirming that all contacts are evaluated according to CDC/National Tuberculosis Controllers Association guidelines. Some specific responsibilities may be assigned to other persons such as clinic supervisors, outreach workers, health educators, social workers, and human service workers. Case management is a patient-centered strategy. Whenever possible, a worker who has the same cultural and linguistic background as the patient should be assigned as case manager, to be able to help develop an individualized treatment adherence plan with the patient.

> **Case managers are held accountable for ensuring that each patient is educated about TB and treatment, ensuring that therapy is continuous and complete, and confirming that all contacts are evaluated according to CDC/ National Tuberculosis Controllers Association guidelines.**

Directly Observed Therapy (DOT)

DOT is a component of case management that helps ensure patients adhere to therapy. It is the method whereby a trained health-care worker or another trained designated person watches a patient swallow each dose of anti-TB drugs and documents it. DOT is the preferred core management strategy recommended by CDC for treatment of TB disease and, if resources allow, for latent tuberculosis infection (LTBI) treatment. DOT can reduce the development of drug resistance, treatment failure, or relapse after the end of treatment. Good case management, which includes establishing a relationship with the patient and addressing barriers to adherence, facilitates successful DOT.

> **DOT is the preferred core management strategy recommended by CDC for treatment of TB disease and, if resources allow, for latent tuberculosis infection (LTBI) treatment.**

Nearly all the treatment regimens for drug-susceptible TB disease can be given intermittently if they are directly observed. Using intermittent regimens reduces the total number of doses a patient must take, as well as the total number of encounters with the health-care provider or outreach worker, making these regimens more cost-effective. Drug-resistant TB disease should always be treated with

a daily regimen and under direct observation. There are **no** intermittent regimens for treatment of multidrug-resistant (MDR) TB. If anti-TB drugs for the treatment of MDR TB need to be given twice daily, then DOT should be provided twice daily as well.

Nearly all the treatment regimens for drug-susceptible TB disease can be given intermittently if they are directly observed.

Drug-resistant TB disease should always be treated with a daily regimen and under direct observation. There are no intermittent regimens for treatment of multidrug-resistant (MDR) TB.

It is important that DOT be carried out at times and in locations that are as convenient as possible for the individual patient (Figures 6.1 and 6.2). Therapy may be directly observed in a medical office or clinic setting, but can also be observed by an outreach worker in the field (e.g., patient's home, place of employment, school, or other mutually agreed-upon place). In some situations, staff of correctional facilities or drug treatment programs, home health-care workers, maternal and child health staff, or designated community members may provide DOT. In general, family members should **not** be the providers of DOT.

Figure 6.1
Conducting DOT in a Clinic Setting

Figure 6.2
Conducting DOT in a Location Convenient for the Patient

DOT should be used for all children and adolescents with TB disease. Even when drugs are given by DOT, adherence to and tolerability of the regimen must be monitored closely. Parents should **not** be relied on to supervise DOT.

Incentives and Enablers

Incentives and enablers should be used to ensure adherence to therapy (Figure 6.3). Incentives are small rewards given to patients to encourage them to take their medicines and to keep DOT or clinic appointments. Enablers are things that help the patient receive treatment, such as bus fare to get to the clinic. Incentives and enablers should be chosen according to the patient's needs, and they are frequently offered along with DOT.

Figure 6.3
Incentives and Enablers

Fixed-Dose Combination Drugs

Although there is no evidence indicating that fixed-dose combination medications are superior to individual drugs, expert opinion suggests that these formulations should be used when DOT is given daily or when DOT is **not** possible. The use of fixed-dose combination capsules or tablets facilitates DOT administration by minimizing the chance for error through the use of fewer tablets and may reduce the risk of acquired drug resistance since one medication cannot be selectively taken. In the United States, the Food and Drug Administration (FDA) has approved fixed-dose combinations of isoniazid and rifampin (Rifamate®) and of isoniazid, rifampin, and pyrazinamide (Rifater®). Clinicians should become familiar with the management of TB disease using these fixed-dose combination drugs.

> **The use of fixed-dose combination capsules or tablets facilitates DOT administration by minimizing the chance for error through the use of fewer tablets and may reduce the risk of acquired drug resistance since one medication cannot be selectively taken.**

Self-Administered Therapy

Patients on self-administered therapy should be asked routinely about adherence at follow-up visits. Pill counts should be performed consistently, and urine or blood tests can be used periodically to check for the presence of urine drug metabolites or appropriate blood serum level of the drugs. In addition, the response to treatment should be monitored closely for all patients. If culture results have not become negative after 2 months of treatment, the patient should be reevaluated and DOT should be considered for the remainder of treatment.

Study Questions

6.9 **Inadequate treatment can lead to which of the following?**
(choose the one best answer)

    A. Treatment failure

    B. Relapse

    C. Ongoing transmission

    D. Development of drug resistance

    E. A, B, C, and D are all correct.

6.10 **The responsibility for successful treatment is assigned to which of the following?**
(choose the one best answer)

    A. The patient

    B. The health-care provider

    C. The family of the patient

    D. A, B, and C are all correct.

    E. Only A and B are correct.

6.11 **What should be included when educating a patient about TB treatment?**
(choose the one best answer)

    A. How to take the medication

    B. Adverse reactions to the medications

    C. Consequences of not taking the medication correctly

    D. TB infection control measures

    E. A, B, C, and D are all correct.

6.12 What is case management?
(choose the one best answer)

A. Includes assigning responsibilities, conducting a regular systematic review of the case, and developing a plan to address barriers to adherence.

B. Can be used to ensure that patients complete treatment for TB disease.

C. Can be used to identify all cases of TB from a source case.

D. A, B, and C are all correct.

E. Only A and B are correct.

6.13 What is DOT?
(choose the one best answer)

A. A supervisor watches a health-care worker give a patient a bottle of prescribed pills.

B. A physician sees the patient once a month and counts the remaining pills in the medication bottles.

C. A health-care worker or another designated person watches the patient swallow each dose of the prescribed drugs.

D. The nurse uses special urine tests to detect the presence of medicine in the patient's urine.

6.14 Which of the following statements about DOT is true?
(choose the one best answer)

A. Is the preferred core management strategy for treatment of TB disease.

B. Can reduce the development of drug resistance, treatment failure, or relapse after the end of treatment.

C. Parents can always be relied upon to give DOT to their children.

D. A, B, and C are all correct.

E. Only A and B are correct.

6.15 Which of the following statements about intermittent treatment regimens and DOT is true? (choose the one best answer)

A. Reduces the total number of doses the patient must take.

B. Reduces the total number of encounters with the health-care provider.

C. Are always used for drug-resistant TB disease.

D. A, B, and C are all correct.

E. Only A and B are correct.

6.16 DOT should always be used for all children and adolescents with TB disease.
(circle the one best answer)

A. True

B. False

TB Disease Treatment Regimens

Current Anti-TB Drugs

Currently, there are 10 drugs approved by the U.S. Food and Drug Administration (FDA) for the treatment of TB disease (Table 6.2). In addition, the fluoroquinolones (levofloxacin, moxifloxacin, and gatifloxacin), although **not** approved by the FDA for TB disease, are commonly used to treat TB disease caused by drug-resistant organisms or for patients who are intolerant of some first-line drugs. Rifabutin, approved for use in preventing *Mycobacterium avium* complex disease in patients with HIV infection but **not** approved for TB disease, is useful for treating TB disease in patients concurrently taking drugs that interact with rifampin (e.g., certain antiretroviral drugs). Amikacin and kanamycin, nearly identical aminoglycoside drugs used in treating patients with TB disease caused by drug-resistant organisms, are **not** approved by the FDA for treatment of TB.

Of the approved drugs, isoniazid (INH), rifampin (RIF), ethambutol (EMB), and pyrazinamide (PZA) are considered first-line anti-TB drugs and form the core of standard treatment regimens (Figure 6.4) (Table 6.2). Rifabutin (RBT) and rifapentine (RPT) may also be considered first-line drugs under certain circumstances. RBT is used as a substitute for RIF in the treatment of all forms of TB caused by organisms that are known or presumed to be susceptible to this agent. RBT is generally reserved for patients for whom drug-drug interactions preclude the use of rifampin. Streptomycin (SM) was formerly considered to be a first-line drug and, in some instances, is still used in the initial treatment regimen. However, an increasing prevalence of resistance to SM in many parts of the world has decreased its overall usefulness. The remaining drugs are reserved for special situations such as drug intolerance or resistance.

INH, RIF, PZA, and EMB are considered first-line anti-TB drugs and form the core of standard treatment regimens.

Figure 6.4
First-line Anti-TB Agents
From left to right: INH, RIF, PZA, and EMB
form the core of initial treatment regimens.

Table 6.2
Anti-TB Drugs Currently Used in the United States

Drug Classes	Anti-TB Drugs	Comments
First-line drugs	Isoniazid (INH)	INH, RIF, PZA, and EMB form the core of initial treatment regimen.
	Rifampin (RIF)	
	Pyrazinamide (PZA)	
	Ethambutol (EMB)	
	Rifabutin* (RBT)	May be used as a substitute for RIF in the treatment of all forms of TB caused by organisms that are known or presumed to be susceptible to this agent.
	Rifapentine (RPT)	May be used once weekly with INH in the continuation phase of treatment for HIV-negative patients with noncavitary, drug-susceptible pulmonary TB who have negative sputum smears at completion of the initial phase of treatment.
Second-line drugs	Streptomycin (SM)	• SM was formerly considered to be a first-line drug and in some instances, is still used in initial treatment. • Increasing prevalence of resistance to SM in many parts of the world has decreased its overall usefulness.
	Cycloserine	These drugs are reserved for special situations such as drug intolerance or resistance.
	Capreomycin	
	ρ-Aminosalicylic acid	
	Levofloxacin*	
	Moxifloxacin*	
	Gatifloxacin*	
	Amikacin/Kanamycin*	
	Ethionamide	

* **Not** approved by the U.S. Food and Drug Administration for use in the treatment of tuberculosis.

Rating System for TB Disease Treatment Recommendations

The recommended treatment regimens are based, in large part, on evidence from clinical trials and are rated on the basis of a system developed by the U.S. Public Health Service (USPHS) and the Infectious Diseases Society of America (IDSA) (Table 6.3).

TB Disease Treatment Regimens

There are four basic treatment regimens recommended for treating adults with TB disease caused by organisms that are known or presumed to be susceptible to INH, RIF, PZA, and EMB. Each treatment regimen consists of an initial 2-month treatment phase followed by a continuation phase of either 4 or 7 months (Table 6.5). The 4-month continuation phase is used for the majority of patients. Although these regimens are broadly applicable, there are modifications that should be made under specified circumstances (Tables 6.3 and 6.4).

> **There are four basic treatment regimens recommended for treating adults with TB disease caused by organisms that are known or presumed to be susceptible to INH, RIF, PZA, and EMB. Each treatment regimen consists of an initial 2-month treatment phase followed by a continuation phase of either 4 or 7 months.**

Initial Phase

The initial phase of treatment is crucial for preventing the emergence of drug resistance and determining the ultimate outcome of the regimen. Four drugs—INH, RIF, PZA, and EMB—should be included in the initial treatment regimen until the results of drug-susceptibility tests are available. Each of the drugs in the initial regimen plays an important role. INH and RIF allow for short-course regimens with high cure rates. PZA has potent sterilizing activity, which allows further shortening of the regimen from 9 to 6 months. EMB helps to prevent the emergence of RIF resistance when primary INH resistance is present. If drug-susceptibility test results are known and the organisms are fully susceptible, EMB need **not** be included. For children whose clarity or sharpness of vision cannot be monitored, EMB is usually not recommended except when the risk of drug resistance is high or for children who have "adult-type" (upper lobe infiltration, cavity formation) TB disease.

Continuation Phase

The continuation phase of treatment is given for either 4 or 7 months. The 4-month continuation phase should be used in patients with uncomplicated, noncavitary, drug-susceptible TB, if there is documented sputum conversion within the first 2 months. The 7-month continuation phase is recommended only for

- Patients with cavitary or extensive pulmonary TB disease caused by drug-susceptible organisms and whose sputum culture obtained at the time of completion of 2 months of treatment is positive;
- Patients whose initial phase of treatment did **not** include PZA; or
- Patients being treated with once-weekly INH and RPT and whose sputum culture at the time of completion of the initial phase (i.e., after 2 months) is positive.

Table 6.3
Drug Regimens for Pulmonary TB in Adults Caused by
Drug-Susceptible Organisms*

Initial Phase			Continuation Phase			
Regimen	Drugs	Interval and Doses± §	Regimen	Drugs	Interval and Doses± §	Range of Total Doses
1	INH RIF PZA EMB	7 days/week for 56 doses (8 weeks) **or** 5 days /week for 40 doses (8 weeks)¶	1a	INH RIF	7 days/week for 126 doses (18 weeks) **or** 5 days/week for 90 doses (18 weeks)	182–130 (26 weeks)
			1b#	INH RIF	2 days/week for 36 doses (18 weeks)	92–76 (26 weeks)
			1c**	INH RPT	1 day/week for 18 doses (18 weeks)¶	74–58 (26 weeks)
2	INH RIF PZA EMB	7 days/week for 14 doses (2 weeks), then 2 days/week for 12 doses (6 weeks) **or** 5 days/week for 10 doses (2 weeks),¶ then 2 days/week for 12 doses (6 weeks)	2a#	INH RIF	2 days/week for 36 doses (18 weeks)¶	62–58 (26 weeks)
			2b**	INH RPT	1 day/week for 18 doses (18 weeks)¶	44–40 (26 weeks)
3	INH RIF PZA EMB	3 times weekly for 24 doses (8 weeks)	3a	INH RIF	3 times weekly for 54 doses (18 weeks)¶	78 (26 weeks)
4	INH RIF EMB	7 days/week for 56 doses (8 weeks) **or** 5 days/week for 40 doses (8 weeks)¶	4a	INH RIF	7 days/week for 217 doses (31 weeks) **or** 5 days/week for 155 doses (31 weeks)¶	273–195 (39 weeks)
			4b#	INH RIF	Twice weekly for 62 doses (31 weeks)¶	118–102 (39 weeks)

INH = isoniazid   RIF = rifampin   PZA = pyrazinamide   EMB = ethambutol   RPT = rifapentine

* For more information on strength of recommendation and quality of supporting evidence, refer to treatment of tuberculosis guidelines. *MMWR* 2003; 52 (No.RR-11).

± When DOT is used, drugs may be given 5 days/week and the necessary doses adjusted accordingly.

§ Patients with cavitation on initial chest x-ray and positive cultures at completion of 2 months of therapy should receive a 7-month continuation phase.

¶ Patients on regimens given less than 7 days a week should receive DOT.

Regimens given less than 3 times a week are **not** recommended for HIV-infected patients with CD4+ counts less than 100

** Used only for HIV-negative patients with negative sputum smears at completion of 2 months of therapy and who do **not** have cavitation on initial chest x-ray. For patients started on this regimen and found to have positive culture from the 2-month specimen, treatment should be extended an extra 3 months.

Table 6.4
Dosage Recommendations for the Treatment of TB in Adults and Children[1]

Drug	Adults/Children[2]			Dose in mg/kg (maximum dosage in parentheses)			
				Daily	1 time/week[3]	2 times/week[3]	3 times/week[3]
INH	Adults			5 mg/kg (300 mg)	15 mg/kg (900 mg)	15 mg/kg (900 mg)	15 mg/kg (900 mg)
	Children			10–15 mg/kg (300 mg)		20–30 mg/kg (900 mg)	
RIF	Adults			10 mg/kg (600 mg)		10 mg/kg (600 mg)	10 mg/kg (600 mg)
	Children			10–20 mg/kg (600 mg)		10–20 mg/kg (600 mg)	
RBT	Adults			5 mg/kg (300 mg)		5 mg/kg (300 mg)	5 mg/kg (300 mg)
	Children			Appropriate dosing for children unknown			
RPT	Adults				10 mg/kg (600 mg) (continuation phase)		
	Children			This drug is **not** approved for use in children			
PZA	Adults	weight	40–55 kg	18.2–25 mg/kg (1000 mg)		36.4–50 mg/kg (2000 mg)	27.3–37.5 mg/kg (1500 mg)
			56–75 kg	20–26.8 mg/kg (1500 mg)		40–53.6 mg/kg (3000 mg)	33.3–44.6 (2500 mg)
			76–90 kg	22.2–26.3 mg/kg (2000 mg)		44.4–52.6 mg/kg (4000 mg)	33.3–39.5 mg/kg (3000 mg)
	Children			15–30 mg/kg (2000 mg)		50 mg/kg (2000 kg)	
EMB[4]	Adults	weight	40–55 kg	14.5–20 mg/kg (800 mg)		36.4–50 mg/kg (2000 mg)	21.8–30 mg/kg (1200 mg)
			56–75 kg	16–21.4 mg/kg (1200 mg)		37.3–50 mg/kg (2800 mg)	26.7–35.7 mg/kg (2000 mg)
			76–90 kg	17.8–21.1 mg/kg (1600 mg)		44.4–52.6 mg/kg (4000 mg)	26.7–31.6 mg/kg (2400 mg)
	Children			15–20 mg/kg (1000 mg)		50 mg/kg (2500 mg)	

INH= isoniazid   RIF= rifampin   RBT= rifabutin   RPT= rifapentine   PZA= pyrazinamide   EMB= ethambutol

[1] Although these regimens are broadly applicable, modifications may be needed for certain circumstances (patients on antiretroviral therapy [ART]). For more information, refer to treatment of tuberculosis guidelines. *MMWR* 2003; 52 (No.RR-11).

[2] For purposes of this document, adult dosing begins at age 15 years. Children weighing more than 40 kg should be dosed as adults. Adjust doses as the patient's weight changes.

[3] All patients prescribed an intermittent regimen should be given DOT.

[4] Ethambutol should be used with caution in young children since it is difficult to monitor their vision. However, if they have TB that is resistant to INH or RIF, a dose of 15 mg/kg per day can be used.

Treatment Completion

Treatment completion is defined primarily as the ingestion of the total number of doses prescribed within the specified time frame. The duration of therapy depends on the drugs used, the drug-susceptibility test results of the isolate, and the patient's response to therapy (see Chapter 4, Drug-Susceptibility Testing). Most patients with previously untreated pulmonary TB disease can be treated with either a 6-month or a 9-month regimen, although the 6-month regimen is used for the majority of patients. All 6-month regimens must contain INH, RIF, and initially, PZA. The goal is to complete all doses within 1 year (Table 6.5).

> **The duration of therapy depends on the drugs used, the drug susceptibility test results of the isolate, and the patient's response to therapy.**

> **Most patients with previously untreated pulmonary TB disease can be treated with either a 6-month or a 9-month regimen, although the 6-month regimen is used for the majority of patients.**

Table 6.5
TB Treatment Phases

Phase	Purpose	Treatment
Initial phase	• Kills most of the tubercle bacilli during the first 8 weeks of treatment, but some bacilli can survive longer • Prevents the emergence of drug resistance • Determines the ultimate outcome of the regimen	Initial 2-month treatment regimen • Includes four drugs in the treatment (usually INH, RIF, PZA, and EMB) • Each of the drugs plays an important role for short-course regimens with high cure rates • Multiple drugs are needed to prevent the development of drug-resistant TB disease

Continuation phase	• Kills remaining tubercle bacilli (after initial phase)
	
	• If treatment is **not** continued long enough, the surviving bacilli may cause TB disease in the patient at a later time
		An addition of either 4 or 7 months of treatment
		
		• 4 months is used for majority of patients
		
		• 7 months is recommended only for persons
		
		  » Who have drug-susceptible cavitary or extensive pulmonary TB disease and whose sputum culture obtained at the time of completion of 2 months of treatment is positive
		
		  » Whose initial phase of treatment did **not** include PZA
		
		  » Who are treated with once-weekly INH and RPT and whose sputum culture at the time of completion of the initial phase is positive

Treatment completion	Defines the number of doses ingested within a specified time frame Duration depends on • Drugs used • Drug susceptibility test results of the isolate • Patient's response to therapy	Most patients with previously untreated pulmonary TB disease can be treated with either • 6-month regimen (preferred) containing INH, RIF, and initially PZA or • 9-month regimen containing INH and RIF

Follow-Up After Treatment

Routine follow-up after treatment is **not** necessary for patients who have had a satisfactory response to a 6- or 9-month regimen with both INH and RIF (Table 6.6). Patients whose organisms were fully susceptible to the drugs being used should be instructed to promptly report the development of any symptoms, particularly prolonged cough, fever, or weight loss. Patients with resistance to both INH and RIF should be monitored for 2 years post-treatment. For patients with organisms resistant to INH or RIF, follow-up evaluation must be individualized.

Table 6.6
Follow-Up After Treatment

| Patients	Type of Follow-Up
Have a satisfactory response to 6- or 9- month regimen with both INH and RIF	Routine follow-up after treatment is **not** necessary
Have organisms that were fully susceptible to drugs being used	Patients should promptly report any of the following symptoms: • Prolonged cough • Fever • Weight loss
Have organisms resistant to INH and RIF	Patients should be monitored for 2 years post-treatment
Have organisms resistant to INH or RIF	Follow-up must be individualized

Treatment Interruptions

Interruptions in the treatment of TB disease are common. Health-care providers are responsible for deciding whether to restart a complete course of treatment or to continue as intended. These decisions should be based on when the interruption occurred and the duration of the interruption.

Treatment Interruption During Initial Phase

If the interruption occurred during the initial phase, the following guidelines apply (Figure 6.5) (Table 6.7):

- Lapse is ≥14 days– restart treatment from the beginning
- Lapse is <14 days– continue treatment to complete planned total number of doses (as long as all doses are completed within 3 months)

Figure 6.5
Algorithm for Management of
Initial Phase Treatment Interruptions
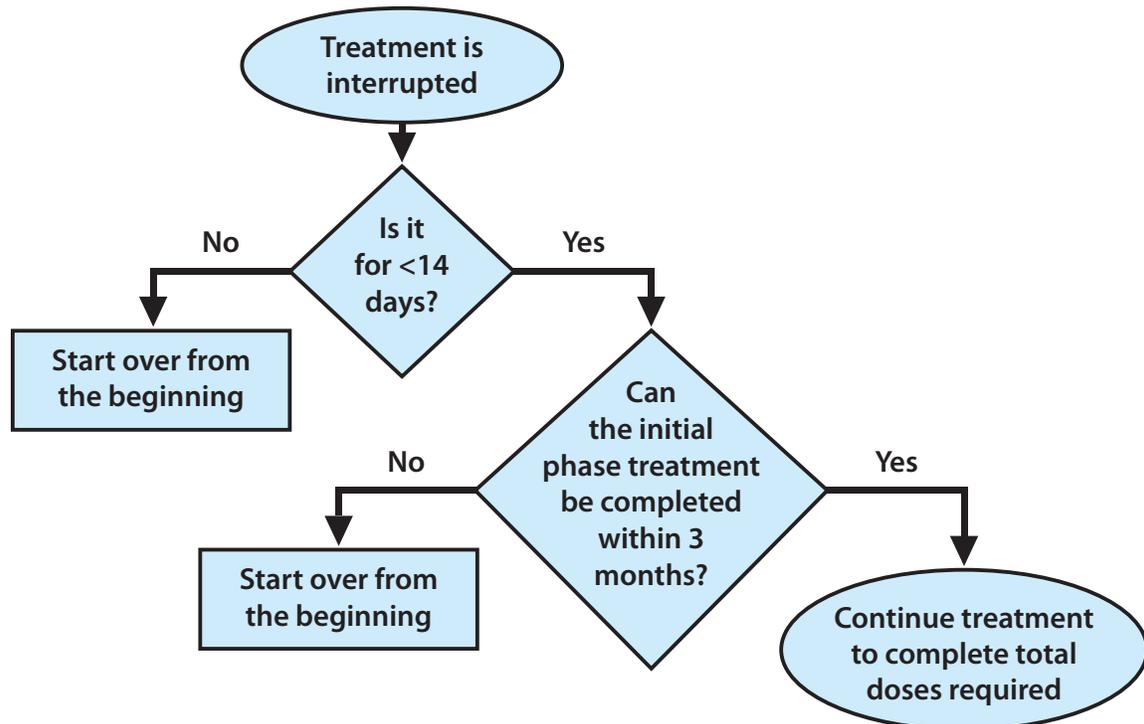
Treatment Interruption During Continuation Phase

If the interruption occurred during the continuation phase, the following guidelines apply (Figure 6.6) (Table 6.7). If the patient received:

- ≥80% of doses, and sputum was acid-fast bacilli (AFB) smear negative on initial testing– further therapy may **not** be necessary;
- ≥80% of doses, and sputum was AFB smear positive on initial testing– continue therapy;
- <80% of doses, and lapse is less than 3 months in duration– continue therapy until all doses are completed (full course); or
- <80% of doses, and lapse is greater than 3 months in duration– restart therapy from the beginning of initial phase.

Figure 6.6
Algorithm for Management of
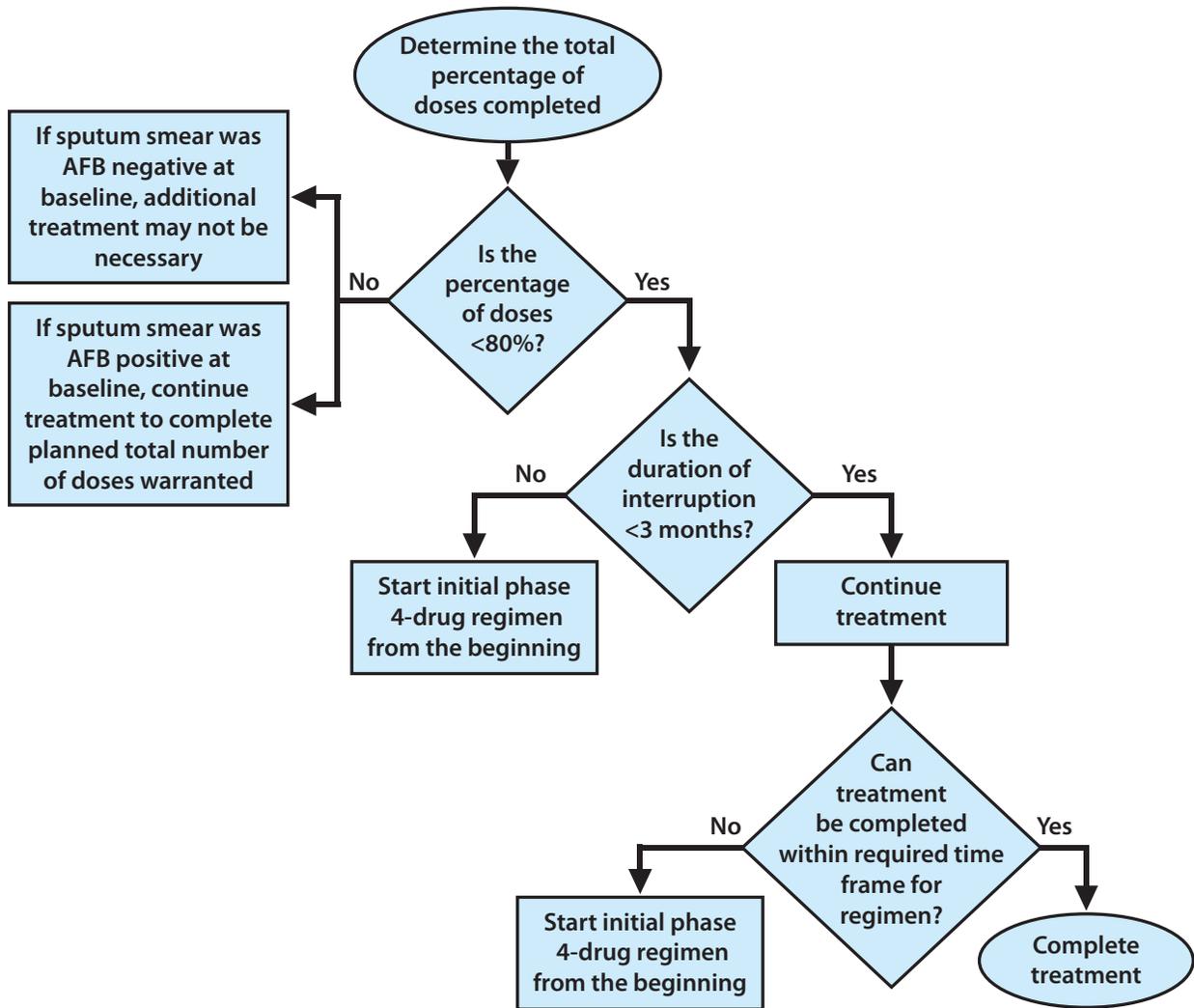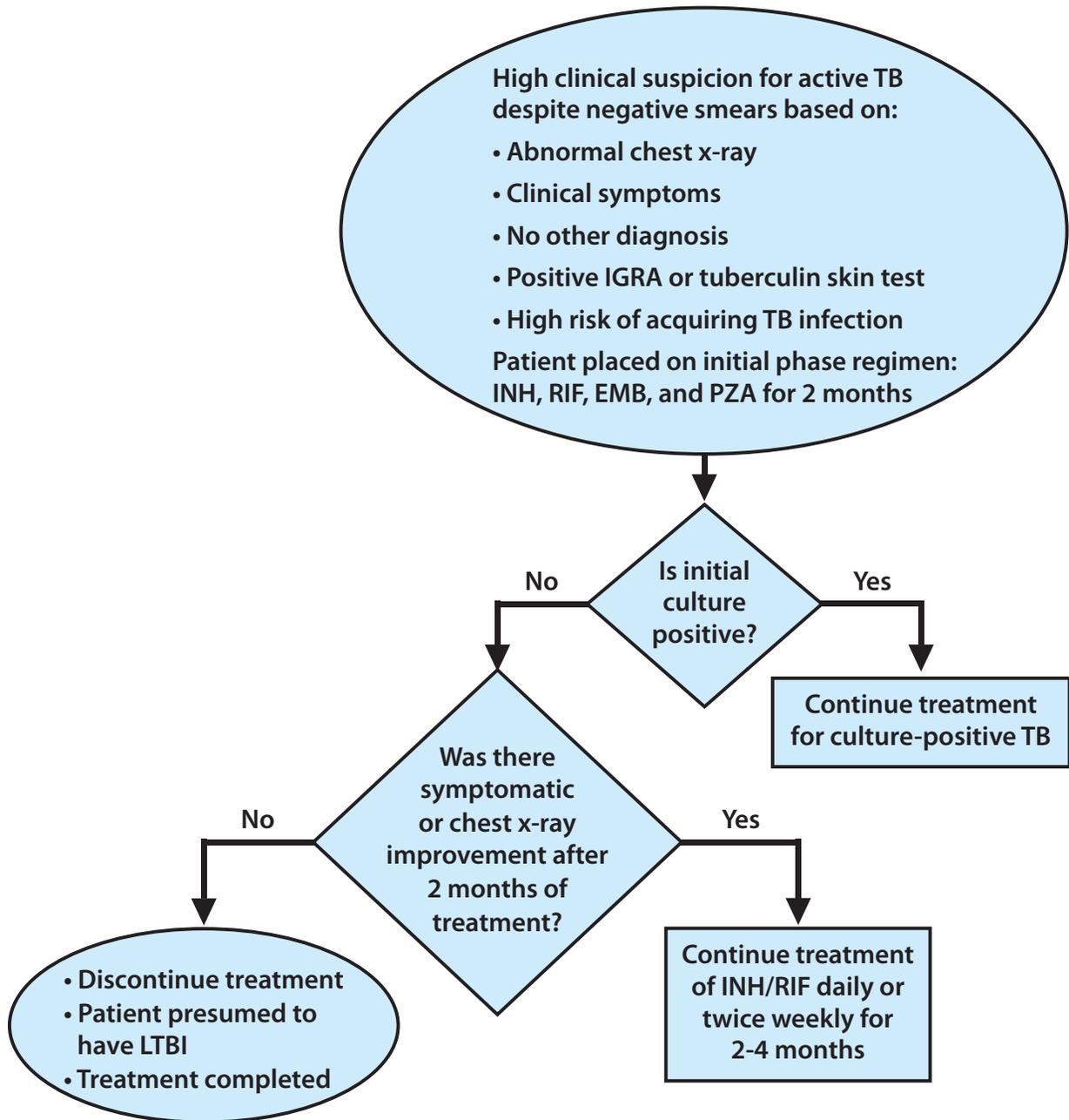## Continuation Phase Treatment Interruptions

Determine the total percentage of doses completed

Is the percentage of doses <80%?

No → **If sputum smear was AFB negative at baseline, additional treatment may not be necessary**

→ **If sputum smear was AFB positive at baseline, continue treatment to complete planned total number of doses warranted**

Yes → **Is the duration of interruption <3 months?**

No → **Start initial phase 4-drug regimen from the beginning**

Yes → **Continue treatment**

Can treatment be completed within required time frame for regimen?

No → **Start initial phase 4-drug regimen from the beginning**

Yes → **Complete treatment**

Table 6.7
Treatment Interruptions

When Interruption Occurs	Situation	Guidelines
During initial phase	Lapse is <14 days in duration	Continue treatment to complete planned total number of doses (as long as all doses are completed within 3 months)
	Lapse is ≥14 days in duration	Restart treatment from the beginning
During continuation phase	Received ≥80% of doses and sputum was AFB smear **negative** on initial testing	Further therapy may **not** be necessary
	Received ≥80% of doses and sputum was AFB smear **positive** on initial testing	Continue therapy until all doses are completed
	Received <80% of doses and lapse is <3 months in duration	Continue therapy until all doses are completed (full course) If treatment cannot be completed within recommended timeframe for regimen, restart therapy from the beginning
	Received <80% of doses and lapse is ≥3 months in duration	Restart therapy from the beginning, new initial and continuation phase

Decision to Treat Culture-Negative TB Disease

Alternative diagnoses must be considered carefully with appropriate diagnostic studies undertaken in patients who have what appears to be culture-negative pulmonary TB disease. Patients who, based on careful clinical and radiographic evaluation, are thought to have pulmonary TB disease should have treatment initiated with INH, RIF, PZA, and EMB even when the initial sputum smears are negative. Figure 6.7 provides an algorithm for treatment of culture-negative TB.

Figure 6.7
Algorithm to Guide Treatment of Culture-Negative TB

High clinical suspicion for active TB despite negative smears based on:

- **Abnormal chest x-ray**
- **Clinical symptoms**
- **No other diagnosis**
- **Positive IGRA or tuberculin skin test**
- **High risk of acquiring TB infection**

Patient placed on initial phase regimen: INH, RIF, EMB, and PZA for 2 months

Is initial culture positive?

No → **Yes** → **Continue treatment for culture-positive TB**

Was there symptomatic or chest x-ray improvement after 2 months of treatment?

No →
- **Discontinue treatment**
- **Patient presumed to have LTBI**
- **Treatment completed**

Yes → **Continue treatment of INH/RIF daily or twice weekly for 2-4 months**

Study Questions

Indicate whether the following statements about the initial phase of treatment are true or false. (Choose the one best answer and write the letter for the correct answer on the line next to the question number.)

Statements about Initial Phase of Treatment	True or False
_____ **6.17** Consists of 2 months of treatment.	**A.** True
_____ **6.18** Is crucial for preventing the emergence of drug resistance.	**B.** False
_____ **6.19** Treatment regimen usually consists of 6 drugs.	

Indicate whether the following statements about the continuation phase of treatment are true or false. (Choose the one best answer and write the letter for the correct answer on the line next to the question number.)

Statements about Continuation Phase of Treatment	True or False
_____ **6.20** Consists of either 4 or 7 months of treatment.	**A.** True
_____ **6.21** The 4-month continuation phase is used in the majority of patients.	**B.** False
_____ **6.22** The 7-month continuation phase is usually only used for patients with extrapulmonary TB.	

6.23 Treatment completion is defined primarily as the ingestion of the total number of doses prescribed within the specified time frame.
(choose the one best answer)

A. True

B. False

6.24 The duration of therapy depends on which of the following?
(choose the one best answer)

A. Drugs used

B. Drug-susceptibility test results of the isolate

C. Patient's response to therapy

D. A, B, and C are all correct.

E. Only A and B are correct.

6.25 Which of the following statements about follow-up after treatment is true?
(choose the one best answer)

A. Follow-up evaluation must be individualized for patients with organisms resistant to INH or RIF or both.

B. Routine follow-up after treatment is **not** necessary for patients who have had a satisfactory response to a 6- or 9-month regimen with both INH and RIF.

C. Follow-up evaluation is **not** needed for patients with continued positive cultures.

D. A, B, and C are all correct.

E. Only A and B are correct.

The following patients have had an interruption in treatment. Match the patient with the treatment decision.
(Choose the one best answer and write the letter for the correct answer on the line next to the question number.)

Patient	Treatment Decision
_____ **6.26** During the initial phase of treatment, Perry has had a lapse in therapy that was less than 14 days.	**A.** Restart treatment from the beginning
_____ **6.27** During the initial phase of treatment, Walter has had a lapse in therapy that was greater than 14 days.	**B.** Continue treatment to complete planned total number of doses (as long as all doses are completed within 3 months)
_____ **6.28** During the continuation phase of treatment, Desiree has had a lapse in therapy after receiving more than 80% of doses. She had a negative smear on initial testing.	**C.** Further treatment may not be necessary
_____ **6.29** During the continuation phase of treatment, Maurine has had a lapse in therapy for cavitary TB after receiving less than 80% of doses. Her lapse is more than 3 months in duration.	**D.** Continue therapy until all doses are completed
_____ **6.30** During the continuation phase of treatment, Ratcliff had a lapse in therapy after receiving more than 80% of doses. His sputum was AFB smear positive on initial testing.	
_____ **6.31** During the continuation phase of treatment, Alex has had a lapse in therapy after receiving less than 80% of doses. His lapse is less than 3 months in duration.	

TB Disease Treatment Regimens for Specific Situations

TB disease treatment regimens for specific situations require special management and should be administered in consultation with a TB expert. Specific situations include the following people:

- Pregnant women
- Breast-feeding women
- Infants and children
- HIV-infected persons

> **TB disease treatment regimens for specific situations require special management and should be administered in consultation with a TB expert.**

Pregnant Women

Untreated TB disease represents a greater hazard to a pregnant woman and her fetus than does its treatment. Because of the risk of TB to the fetus, treatment of TB in pregnant women should be initiated whenever the probability of maternal disease is moderate to high. The initial treatment regimen should consist of INH, RIF, and EMB. Although all of these drugs cross the placenta, they do **not** appear to have teratogenic effects. Streptomycin is the only anti-TB drug documented to have harmful effects on the human fetus (congenital deafness) and should **not** be used. Although detailed teratogenicity data are **not** available, PZA can probably be used safely during pregnancy and is recommended by the World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease (IUATLD). If PZA is **not** included in the initial treatment regimen, the minimum duration of therapy is 9 months.

> **Untreated TB disease represents a greater hazard to a pregnant woman and her fetus than does its treatment.**

> **Streptomycin is the only anti-TB drug documented to have harmful effects on the human fetus (congenital deafness) and should not be used.**

For pregnant women with MDR TB, treatment should only be done in consultation with an MDR TB expert. Many of the medications currently used for treatment of MDR TB may be harmful to the fetus.

Breast-feeding

Breast-feeding should **not** be discouraged for women being treated with first-line anti-TB drugs, because the small concentrations of these drugs in breast milk do **not** produce toxicity in the nursing newborn. Conversely, drugs in breast milk should **not** be considered to serve as effective treatment for TB disease or for LTBI in a nursing infant. Pyridoxine (vitamin B$_6$) supplementation (25 mg/day) is recommended for all women taking INH who are either pregnant or breast-feeding. The amount of pyridoxine in multivitamins is variable, but generally less than the needed amount.

Infants and Children

Infants and children with TB disease should be treated with the regimens recommended for adults, with the exception that EMB is **not** used routinely in children. For children whose clarity or sharpness of vision cannot be monitored, EMB is usually not recommended except when the risk of drug resistance is high or for children who have "adult-type" (upper lobe infiltration, cavity formation) TB disease. In infants, TB is much more likely to disseminate; therefore, treatment should be started as soon as the diagnosis is suspected. Children commonly develop primary TB disease which generally affects the middle and lower lung. Children should be treated with three (rather than four) drugs in the initial phase (INH, RIF, and PZA). In general, extrapulmonary TB in children can be treated with the same regimens as pulmonary disease. Exceptions are disseminated TB and tuberculous meningitis, for which there are inadequate data to support 6-month therapy; thus 9 to 12 months of treatment is recommended.

> **In infants, TB is much more likely to disseminate; therefore, treatment should be started as soon as the diagnosis is suspected.**

HIV-Infected Persons

Management of HIV and TB coinfection is complex, and the clinical and public health consequences associated with the failure of treatment and other negative outcomes are serious. HIV-infected patients are on numerous medications, some of which interact with anti-TB drugs. **It is therefore strongly recommended that experts in the treatment of HIV-related TB be consulted.** The treatment regimens listed in Table 6.3 are effective for people living with HIV, with two exceptions due to increased risk of developing acquired drug resistance:

- Once-weekly administration of INH and RPT in the continuation phase should **not** be used in any HIV-infected patient; and
- Patients with advanced HIV (CD4 counts less than 100) should be treated with daily or three times weekly therapy in both the initial and continuation phase.

Every effort should be made to use a rifamycin-based regimen for the entire course of therapy in coinfected patients. The key role of the rifamycins in the success of TB disease treatment mandates that the drug-drug interactions between the rifamycins and antiretroviral drugs be managed appropriately, rather than using TB treatment regimens that do **not** include a rifamycin or by withholding antiretroviral therapy until completion of anti-TB therapy.

Of particular concern is the interaction of rifamycins with antiretroviral agents and other anti-infective drugs. Rifampin can be used for the treatment of TB with certain combinations of antiretroviral agents. Rifabutin, which has fewer drug-drug interactions due to its decreased induction of the cytochrome P450 system, may also be used in place of rifampin and appears to be equally effective, although the doses of the rifabutin and antiretroviral agents may require adjustments and should be administered with expert consultation.

Therefore, patients with HIV-related TB disease should be treated with a regimen including a rifamycin for the full course of TB disease treatment, unless the isolate is resistant to the rifamycins or the patient has a severe side effect that is clearly due to the rifamycins.

> **HIV-infected patients are on numerous medications, some of which interact with anti-TB drugs. It is therefore strongly recommended that experts in the treatment of HIV-related TB be consulted.**

Treatment Duration

Six months should be considered the minimum duration of treatment for HIV-infected adults, even for patients with culture-negative TB disease. If there is evidence of a slow or suboptimal response (e.g., cultures are still positive after 2 months of therapy), the continuation phase should be prolonged to 7 months (a total of 9 months of treatment). DOT and other adherence- promoting strategies should be used in all patients with HIV-related TB disease.

Predicting Drug Interactions Involving Rifampin

Much is known about the interactions of antiretroviral agents and RIF. In addition, knowledge of the mechanisms of drug interactions can help predict the likelihood of an interaction, even if that specific combination of drugs has **not** been formally evaluated. A major concern in treating TB disease in HIV-infected persons is the interaction of RIF with certain antiretroviral agents (some protease inhibitors [PIs] and nonnucleoside reverse transcriptase inhibitors [NRTIs]). Rifabutin, another rifamycin that has fewer drug-drug interactions, may be used as an alternative to RIF.

As new antiretroviral agents and more pharmacokinetic data become available, these recommendations are likely to be modified. For more information, see Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis at: www.cdc.gov/tb/publications/guidelines/TB_HIV_Drugs/default.htm

Pregnancy in HIV-Infected Women

A number of issues complicate the treatment of the HIV-infected pregnant woman who has TB disease. Pregnancy alters the distribution and metabolism of a number of drugs, including antiretroviral drugs (there is very little information on whether the metabolism of anti-TB drugs is altered during pregnancy). Notably, the serum concentrations of protease inhibitors are decreased during the latter stages of pregnancy. There are no published data on drug-drug interactions between anti-TB and antiretroviral drugs among pregnant women. However, it is likely that the effects of RIF on protease inhibitors are exacerbated during pregnancy.

HIV-Infected Children

HIV-infected children with TB disease are at greater risk for severe, life-threatening manifestations (e.g., disseminated disease, meningitis). There are very limited data on the absorption, metabolism, and elimination of anti-TB drugs among children, particularly among very young children (< 2 years of age). For more information, please see Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis at: www.cdc.gov/tb/publications/guidelines/TB_HIV_Drugs/specialpop.htm

> **HIV-infected children with TB disease are at greater risk for severe, life-threatening manifestations (e.g., disseminated disease, meningitis).**

Persons with Additional Treatment Considerations

A number of medical conditions or disease characteristics require additional treatment considerations and TB treatment decisions should be made in consultation with a TB expert. These include:

- Renal insufficiency/end-stage renal disease
- Hepatic disease
- Extrapulmonary TB disease
- Drug-resistant TB disease
- Culture-negative TB disease

Renal Insufficiency and End-stage Renal Disease

Renal insufficiency complicates the management of TB disease because some anti-TB drugs are cleared by the kidneys. Alteration in dosing of anti-TB drugs is commonly necessary in patients with renal insufficiency and end-stage renal disease (ESRD) requiring hemodialysis. The dosage of anti-TB drugs should **not** be decreased because the peak serum concentrations may be low and smaller doses may decrease drug efficacy. Instead, the dosing interval of anti-TB drugs should be increased. Based on creatinine clearance, most anti-TB drugs can be given three times a week immediately after hemodialysis. Consultation with the patient's nephrologist is advised.

> **Renal insufficiency complicates the management of TB disease because some anti-TB drugs are cleared by the kidneys.**

> **Alteration in dosing of anti-TB drugs is commonly necessary in patients with renal insufficiency and end-stage renal disease (ESRD) requiring hemodialysis.**

Hepatic Disease

The treatment of TB disease in patients with unstable or advanced liver disease is problematic for several reasons:

- The likelihood of drug-induced hepatitis is greater;
- The implications of drug-induced hepatitis for patients with marginal hepatic reserve are potentially serious, even life-threatening; and
- Fluctuations in the indicators of liver function related to the pre-existing liver disease can confound monitoring for drug-induced hepatitis.

Thus, clinicians may consider regimens with fewer potentially hepatotoxic agents in patients with advanced or unstable liver disease. Expert consultation is advisable in treating such patients. It should be noted that TB disease itself may involve the liver, causing abnormal liver function; thus, **not** all abnormalities in liver function tests noted at baseline should be attributed to causes other than TB disease. The hepatic abnormalities caused by TB disease will improve with effective treatment.

> **Clinicians may consider regimens with fewer potentially hepatotoxic agents in patients with advanced or unstable liver disease. Expert consultation is advisable in treating such patients.**

Extrapulmonary TB Disease

As a general rule, the principles used for the treatment of pulmonary TB disease also apply to extrapulmonary forms of the disease. A 6-month treatment regimen is recommended for patients with extrapulmonary TB disease, unless the organisms are known or strongly suspected to be resistant to the first-line drugs. If PZA cannot be used in the initial phase, the continuation phase must be increased to 7 months. The exception to these recommendations is central nervous system TB, for which the optimal length of therapy has **not** been established but some experts recommend 9 to 12 months. Most experts do recommend corticosteroids to be used as additional therapy for patients with TB meningitis and pericarditis. Consultation with a TB expert is recommended.

> **As a general rule, the principles used for the treatment of pulmonary TB disease also apply to extrapulmonary forms of the disease. A 6-month treatment regimen is recommended for patients with extrapulmonary TB disease, unless the organisms are known or strongly suspected to be resistant to the first-line drugs.**

Drug-Resistant TB Disease

Drug-resistant TB disease can develop in two different ways, called primary and secondary resistance. Primary resistance occurs in persons who are initially exposed to and infected with resistant organisms. Secondary resistance, or acquired resistance, develops during TB therapy, either because the patient was treated with an inadequate regimen or because the patient did **not** take the prescribed regimen appropriately or because of other conditions such as drug malabsorption or drug-drug interactions leading to low serum levels (see Chapter 2, Transmission and Pathogenesis of Tuberculosis).

Drug-resistant TB disease can develop in two different ways:
- **Primary resistance**
  - » **Occurs in persons who are initially exposed to and infected with resistant organisms**
- **Secondary resistance, or acquired resistance**
  - » **Develops during TB therapy because of**
    - – **patient being treated with an inadequate regimen,**
    - – **patient not taking prescribed regimen appropriately,**
    - – **drug malabsorption, or**
    - – **drug-drug interactions leading to low serum levels**

Drug resistance in a patient with newly diagnosed TB disease may be suspected on the basis of previous treatment, contact with a known drug-resistant case, or time spent in a region in which drug resistance is common. Drug resistance can be proven only by drug-susceptibility testing (see Chapter 4, Diagnosis of Tuberculosis Disease).

Patients with strains of *M. tuberculosis* resistant to both INH and RIF (multidrug-resistant) are at high risk for

- Treatment failure;
- Relapse;
- Further acquired resistance; or
- Death.

These patients must be referred immediately to an expert in the management of drug-resistant TB disease; or consultation should be obtained from specialized treatment centers.

Patients with strains of *M. tuberculosis* resistant to both INH and RIF (multidrug-resistant) are at high risk for treatment failure, relapse, further acquired resistance, or death. These patients must be referred immediately to an expert in the management of drug-resistant TB disease; or consultation should be obtained from specialized treatment centers.

Management of patients with drug-resistant TB disease is based on the following guidelines:

- A single new drug should never be added to a failing regimen;
- In patients with MDR organisms resistant to first-line drugs in addition to INH and RIF, regimens employing four to six drugs that are new to the patient and to which the isolate shows in vitro susceptibility appear to be associated with better results;
- Patients with multidrug-resistant organisms should receive the highest priority for DOT, which should be administered either in the hospital, home, or other facility;
- The use of drugs to which there is demonstrated in vitro resistance is **not** encouraged because there is little or no efficacy of these drugs and alternative medications may be available;
- Resistance to RIF is associated in nearly all instances with cross-resistance to rifabutin and rifapentine (RPT);
- There is no cross-resistance between SM and the other injectable agents, amikacin, kanamycin, and capreomycin (although resistance to all may occur as independent events); cross-resistance between amikacin and kanamycin is not universal but frequently seen;
- Resistance to PZA is uncommon in the absence of resistance to other first-line drugs; if monoresistance to PZA is observed, consideration must be given to the possibility that the disease is caused by *M. bovis*, **not** *M. tuberculosis*; and
- Intermittent therapy should **not** be used in treating TB disease caused by drug-resistant organisms, except perhaps for injectable agents after the initiation phase (usually 2 to 3 months) of daily therapy.

Table 6.8 provides information on drug classes for TB, types of drug-resistant TB, and appropriate anti-TB drugs for treatment.

Table 6.8
Drug Classes for TB

Drug Classes	Anti-TB Drugs	Drug-Susceptible TB	Multidrug-Resistant TB (MDR TB)	Extensively Drug Resistant TB (XDR TB)
First-line oral drugs • Standard treatment for drug-susceptible TB • Four drugs for 6–9 months • Safe, effective, inexpensive • 95% cure • Based on solid scientific evidence from ~30 years of drug discovery and controlled clinical trials, 1943–72	INH	Susceptible	Resistance by definition	Resistance by definition
	RIF	Susceptible	Resistance by definition	Resistance by definition
	PZA	Susceptible	Resistance possible or likely	Resistance possible or likely
	EMB	Susceptible	Resistance possible or likely	Resistance possible or likely
Second-line drugs • Treatment based on laboratory drug-resistance testing and epidemiological information • Four to six drugs for 2 years	Aminoglycosides and Capreomycin	N/A	Resistance possible	Resistance by definition
	Quinolones	N/A	Resistance possible	Resistance by definition
	Thioamides	N/A	Resistance possible	Resistance possible or likely
	Cycloserine	N/A	Resistance possible	Resistance possible or likely
	ρ-Aminosalicylic Acid	N/A	Resistance possible	Resistance possible or likely

Culture-Negative TB Disease

Failure to isolate *M. tuberculosis* from appropriately collected specimens in persons who, because of clinical or radiographic findings, are suspected of having pulmonary TB disease does **not** exclude a diagnosis of TB disease. Low bacillary populations, temporal variations in the number of bacilli being expelled, and errors in specimen processing all may result in failure to isolate organisms from patients who have TB disease. It should be emphasized that alternative diagnoses must be considered carefully and appropriate diagnostic studies undertaken in patients who have what appears to be

culture-negative TB disease. At a minimum, patients suspected of having pulmonary TB disease should have three sputum specimens (using sputum induction with hypertonic saline if necessary) for AFB smear and culture as part of the diagnostic evaluation prior to or coincident with treatment initiation. Depending on the clinical features and differential diagnosis, other diagnostic testing, such as bronchoscopy with bronchoalveolar lavage and biopsy, should be considered before making a presumptive diagnosis of culture-negative TB disease.

> **Failure to isolate *M. tuberculosis* from appropriately collected specimens in persons who, because of clinical or radiographic findings, are suspected of having pulmonary TB disease does not exclude a diagnosis of TB disease.**

Patients who, on the basis of careful clinical and radiographic evaluation, are thought to have a high likelihood of having pulmonary TB disease should have treatment initiated with INH, RIF, PZA, and EMB even when the initial sputum smears are negative. If *M. tuberculosis* is isolated in culture, treatment for TB disease should be continued. Patients who have negative cultures but who still are presumed to have pulmonary TB disease should have a thorough follow-up clinical and radiographic evaluation at the time 2 months of therapy has been completed to determine whether there has been a response that can be attributed to anti-TB treatment. If there is either clinical or radiographic improvement and **no** other etiology is identified, treatment should be continued for TB disease. A 4-month INH and RIF regimen for culture-negative TB disease has been demonstrated to be successful. However, because the results of cultures may **not** be known for 3 to 8 weeks and because of the possibility of drug resistance, use of two-drug therapy with INH and RIF alone is **not** recommended in the initial phase of treatment (i.e., first 2 months) while culture results are pending. The continuation phase can be shortened to 2 months using INH and RIF for HIV-negative patients once it is known that cultures are negative. However, HIV-infected patients with culture-negative pulmonary TB should be treated for a minimum of 6 months (total). Figure 6.7 provides an algorithm for treatment of culture-negative TB.

> **Patients who, on the basis of careful clinical and radiographic evaluation, are thought to have a high likelihood of having pulmonary TB disease should have treatment initiated with INH, RIF, PZA, and EMB even when the initial sputum smears are negative.**

On occasion, patients who are being evaluated for pulmonary TB disease will be found to have positive AFB smears, but negative cultures. There are several potential explanations for this occurrence, including the possibilities that the acid-fast organisms are nontuberculous and difficult to culture, that they are nonviable tubercle bacilli, or that there was laboratory error. The approach taken in such cases should be individualized on the basis of clinical and radiographic findings. If suspicion of TB disease is high and the patient has positive AFB smears, even with negative cultures, the patient should be treated as if culture positive, using one of the recommended regimens.

Study Questions

6.32 Which drug is harmful to the fetus and should NOT be used with pregnant women during the initial treatment phase?
(choose the one best answer)

   A. Isoniazid

   B. Rifampin

   C. Ethambutol

   D. Streptomycin

6.33 Which of the following statements about infants and children is true?
(choose the one best answer)

   A. Anti-TB drugs in breast milk can be considered effective treatment for TB disease or for LTBI in a nursing infant.

   B. EMB is routinely used to treat children for TB disease.

   C. Young children should be treated with three (rather than four) drugs in the initial phase.

   D. TB disease is less likely to disseminate in children than in adults.

6.34 For HIV-infected patients, which of the following statements is true?
(choose the one best answer)

   A. The minimum duration of treatment of TB disease for HIV-infected adults is 6 months.

   B. If there is evidence of a slow or suboptimal response, the continuation phase should be prolonged to 7 months (a total of 9 months of treatment).

   C. DOT and other adherence promoting strategies should be used in all patients with HIV-related TB disease.

   D. A, B, and C are all correct.

   E. Only A and B are correct.

TB patients can have additional medical problems or presentations. Match the problem or presentation with the appropriate type of TB disease treatment.
(Choose the one best answer and write the letter for the correct answer on the line next to the question number.)

Additional Medical Problems or Presentations	Type of Treatment
_____ **6.35** End-stage renal disease _____ **6.36** Hepatic disease _____ **6.37** Extrapulmonary TB disease	**A.** Consider a regimen with fewer potentially hepatotoxic agents. **B.** Alteration in dosing anti-TB drugs is commonly necessary. Do not decrease dose of anti-TB drugs. Dosing interval should be increased to 3 times a week. **C.** Use the same principles as for pulmonary TB disease. A 6-month treatment regimen is recommended, unless the organisms are known or strongly suspected to be resistant to the first-line drugs.

6.38 Drug resistance in a patient with newly diagnosed TB disease may be suspected on the basis of which of the following?
(choose the one best answer)

A. Time spent in a region in which drug resistance is common

B. Contact with a known drug-resistant case

C. Previous TB treatment

D. A, B, and C are all correct.

E. Only A and B are correct.

6.39 Joanne has an *M. tuberculosis* strain that is resistant to both isoniazid and rifampin. What is Joanne at high risk for?
(choose the one best answer)

A. Treatment failure

B. Relapse

C. Further acquired resistance

D. A, B, and C are all correct.

E. Only A and B are correct.

Patient Monitoring

Adverse reactions to anti-TB drugs are relatively rare, but in some patients they may be severe. Clinicians who treat TB disease should be familiar with the methods of monitoring for adverse reactions and patients' response to treatment. In some situations (drug-resistant TB disease, pregnancy, HIV-infected patients), expert consultation should be sought.

Baseline Monitoring

Before starting treatment, adult patients should have certain baseline blood and vision tests to help detect any underlying problems that may complicate treatment. For children, only vision tests are necessary unless there are other medical conditions that may complicate treatment. Recommended examinations for baseline monitoring are included in Table 6.9.

> **Before starting treatment, adult patients should have certain baseline blood and vision tests to help detect any underlying problems that may complicate treatment.**

> **For children, only vision tests are necessary unless there are other medical conditions that may complicate treatment.**

Table 6.9
Recommended Examinations for Baseline Monitoring

Patient	Recommended Test
All patients	Measure aminotransferases (i.e., AST, ALT), bilirubin, alkaline phosphatase, and serum creatinine and a platelet count
Patients at risk for hepatitis B or C (e.g., injection drug user, born in Asia or Africa, or HIV infected)	Conduct serologic tests
Patients who are taking EMB	Test visual acuity (Snellen chart) and color vision (Ishihara)
HIV-infected patients	Obtain CD4+ lymphocyte count

Monitoring During Treatment

Patients with TB disease should have clinical evaluations at least monthly to identify possible adverse reactions to medications and to assess adherence (Table 6.10).

As a routine practice, it is **not** necessary to monitor liver or renal function or platelet count for patients being treated with first-line anti-TB drugs unless there were abnormalities at baseline or there are clinical reasons to obtain measurements. Patients who have stable abnormalities of hepatic or renal function at baseline should have repeat measurements early in the course of treatment, then less frequently to ensure that conditions have **not** worsened.

Monthly repeat testing of visual acuity (Snellen) and color vision (Ishihara) is recommended for patients receiving an EMB dose exceeding 15– 20 mg/kg (the recommended range) and for patients receiving EMB for more than 2 months. Patients receiving EMB should be questioned regarding visual disturbances at monthly intervals. Patients should be educated regarding the possible visual side effects of EMB and should be instructed to immediately report vision changes to their health-care provider.

Table 6.10
Monitoring During Treatment

Patient	Recommended Test
All patients	Repeat at least monthly clinical evaluations to • Identify possible adverse reactions to medications • Assess adherence
Patients who are taking EMB	• Question monthly regarding visual disturbances • Repeat monthly testing for visual acuity (Snellen chart) and color vision (Ishihara) for patients whose dose exceeds 15– 20 mg/kg and those who have been receiving EMB for >2 months
Patients who have extrapulmonary TB disease	Evaluation depends on • Sites involved • Ease with which specimens can be obtained

Study Questions

6.40 **For baseline monitoring, children only need vision tests unless there are other medical conditions that may complicate treatment.**
(circle the one best answer)

  A. True

  B. False

Match the patient with the type of monitoring that should occur during treatment.
(Choose the one best answer and write the letter for the correct answer on the line next to the question number.)

Patients	Monitoring During Treatment
_____ **6.41** Pauline is being treated with first-line anti-TB drugs. She had no abnormalities at baseline and no clinical problems.	**A.** Repeat measurements early in the course of treatment, then less frequently to ensure that condition does not worsen.
_____ **6.42** Don had stable abnormalities of hepatic function at baseline.	**B.** Repeat visual acuity and color vision.
_____ **6.43** Percy has been on first-line anti-TB drugs that include ethambutol for greater than 2 months.	**C.** Not necessary to monitor liver or renal function or platelet count.

Evaluating Response to Treatment

It is important for clinicians to evaluate a patient's response to treatment to determine the efficacy of the treatment and to identify any adverse reactions. Clinicians use three methods to determine whether a patient is responding to treatment:

1. Clinical evaluation
2. Bacteriological examination
3. Chest radiograph

> **It is important for clinicians to evaluate a patient's response to treatment to determine the efficacy of the treatment and to identify any adverse reactions.**

Clinical Evaluation

Patients should have clinical evaluations at least monthly to

- Identify possible adverse reactions to medications;
- Assess adherence; and
- Determine treatment efficacy.

Although each patient responds to treatment at a different pace, all TB symptoms should gradually improve and eventually go away. Patients whose symptoms do **not** improve during the first 2 months of treatment, or whose symptoms worsen after improving initially, should be reevaluated for adherence issues and development of drug resistance.

Adverse Reactions to Anti-TB Drugs

In addition to the microbiological evaluations, it is essential that patients have clinical evaluations to identify possible adverse effects of the anti-TB drugs (Table 6.11). Monitoring for adverse reactions must be individualized. The type and frequency of monitoring should depend on the drugs used and the patient's risk for adverse reactions (e.g., age or alcohol use). At minimum, patients should be seen monthly during therapy and questioned by health-care providers concerning adverse reactions, even if no problems are apparent.

Adverse reactions to anti-TB drugs are relatively rare, but in some patients they may be severe. Mild adverse effects can generally be managed with symptomatic therapy. The drug or drugs must be discontinued for more severe effects. It is important that first-line drugs **not** be stopped without adequate justification. Proper management of serious adverse reactions often requires expert consultation.

Patients should be specifically instructed to look for symptoms associated with the most common reactions to the medications they are taking. They should also be instructed to seek medical attention immediately should these symptoms occur. All patients receiving INH, RIF, or PZA should immediately report any symptoms suggestive of hepatitis (nausea, loss of appetite, vomiting, persistently dark urine, yellowish skin or eyes, malaise, unexplained elevated temperature for more than 3 days, or abdominal tenderness). If the symptoms suggest adverse reactions, the patient should be instructed to stop the medication, and appropriate laboratory testing should be performed.

> **Patients should be specifically instructed to look for symptoms associated with the most common reactions to the medications they are taking. They should also be instructed to seek medical attention immediately should these symptoms occur.**

Table 6.11
Common Adverse Reactions to TB Drugs

Caused by	Adverse Reaction	Signs and Symptoms	Significance of Reaction*
Any drug	Allergic	• Skin rash	May be serious or minor
EMB	Eye damage	• Blurred or changed vision • Changed color vision	Serious
INH PZA RIF	Hepatic toxicity	• Abdominal pain • Abnormal liver function test results • Dark urine • Fatigue • Fever for 3 or more days • Flu-like symptoms • Lack of appetite • Nausea • Vomiting • Yellowish skin or eyes	Serious
INH	Nervous system damage	• Dizziness; tingling or numbness around the mouth	Serious
	Peripheral neuropathy	• Tingling sensation in hands and feet	Serious
PZA	Stomach upset	• Stomach upset • Vomiting • Lack of appetite	May be serious or minor
	Gout	• Abnormal uric acid level** • Joint aches	Serious
RIF	Bleeding problems	• Easy bruising • Slow blood clotting	Serious
	Discoloration of body fluids	• Orange urine, sweat, or tears • Permanently stained soft contact lenses	Minor
	Drug interactions	• Interferes with certain medications such as birth control pills, birth control implants, and methadone treatment	May be serious or minor
	Sensitivity to the sun	• Frequent sunburn	Minor

* Patients should stop medication for serious adverse reactions and consult a clinician immediately. Patients can continue taking medication if they have minor adverse reactions.

** Asymptomatic elevated uric acid levels are expected with PZA treatment. Acute gouty arthritis, which is rare without preexisting gout, is a contraindication to PZA use.

Common Adverse Reactions to TB Disease Treatment

The items listed below are common adverse reactions to TB treatment:

- Gastrointestinal problems
- Hepatitis
- Rash
- Drug fever

Gastrointestinal Problems

Gastrointestinal reactions to the anti-TB drugs are common, particularly in the first few weeks of therapy. These reactions include:

- Upset stomach
- Nausea
- Poor appetite
- Abdominal pain

In the presence of gastrointestinal symptoms, measure

- Serum aminotransferases (i.e., AST, ALT) and
- Bilirubin

Hepatic Toxicity

Liver injury can be caused by three of the first-line TB disease drugs, INH, RIF and PZA. Significant liver toxicity is indicated by AST ≥3 times the upper limit of normal in the presence of symptoms, or ≥5 times the upper limit of normal in the absence of symptoms (Table 6.12). If the AST and ALT are <5 times the upper limit of normal, toxicity can be considered mild; an AST or ALT of 5–10 times normal defines moderate toxicity; and >10 times normal is severe. In addition to elevation of the AST and ALT, occasionally there are disproportionate increases in bilirubin and alkaline phosphatase. This pattern is more consistent with RIF hepatotoxicity.

Table 6.12
Hepatic Toxicity

AST and ALT Level	Levels of Toxicity
AST and ALT <5 times the upper limit of normal	Mild
AST or ALT 5–10 times the normal limit	Moderate
AST or ALT >10 times the normal limit	Severe

Rash

All drugs used in treating TB disease can cause a rash. The response to a patient with a rash depends upon its severity. The rash may be minor, affecting a limited area or being predominantly manifested as itching. In this case, antihistamines should be given for symptomatic relief, but all TB disease medications can be continued.

All drugs used in treating TB disease can cause a rash.

Drug Fever

Recurrence of fever in a patient who has been receiving therapy for several weeks should suggest drug fever, especially if the patient is showing microbiologic and radiographic improvement. It should be noted, however, that fever from TB may persist for as long as 2 months after therapy has been initiated.

Bacteriologic Examination

Important treatment decisions concerning the continuation-phase regimen are based on the microbacteriological status at the end of the initial phase of treatment (i.e., at least 2 months). Patients whose cultures have **not** become negative after 3 months of therapy should be reevaluated for potential drug-resistant disease, as well as for potential failure to adhere to the regimen. Patients who have positive cultures after 4 months of treatment should be considered as having failed treatment and managed accordingly.

Patients whose cultures have not become negative after 3 months of therapy should be reevaluated for potential drug-resistant disease, as well as for potential failure to adhere to the regimen.

Positive Sputum Cultures Prior to Treatment

For patients whose sputum culture is positive prior to treatment, the best way to measure the efficacy of therapy is to obtain specimens for culture at least monthly until two consecutive specimens are negative on culture (Table 6.13). Patients with multidrug-resistant TB should have sputum AFB smears and cultures performed monthly for the entire course of treatment.

Negative Sputum Cultures Prior to Treatment

For patients with negative sputum cultures prior to treatment for pulmonary disease, the major indicators of response to therapy are the chest radiograph and the clinical evaluation (Table 6.13). The intervals at which chest radiography should be repeated depend on the clinical circumstances and the differential diagnosis that is being considered. If the radiograph does **not** improve after the patient has received 2 months of treatment, the abnormality may be the result of either previous (**not** current) TB disease or another reason.

Table 6.13
Response to Treatment for Pulmonary TB Disease

Bacteriologic Status	Recommendations for Response to Treatment
Positive sputum cultures prior to treatment	• Obtain specimens for culture at least monthly until two consecutive specimens are negative on culture • Perform monthly sputum AFB smears and cultures on MDR TB patients for entire course of treatment • A repeat chest radiograph after 2 months of treatment may be useful but is **not** essential
Negative sputum cultures prior to treatment	• Repeat chest radiograph at intervals based on clinical circumstances and differential diagnosis • If radiograph does not improve after patient has received 2 months of treatment, abnormality may be due to 　» Previous (not current) TB disease 　» Another reason
Cultures have **not** become negative after 3 months of therapy	Reevaluate for • Potential drug-resistant disease • Potential failure to adhere
Cultures are still positive after 4 months of treatment	Consider as having failed treatment and manage accordingly

Chest Radiograph

For patients with positive cultures at diagnosis, a repeat chest radiograph at completion of 2 months of treatment may be useful, but is **not** essential. For patients with culture-positive TB, a chest radiograph at completion of treatment provides a baseline for comparison with any future films. For patients with cultures that are initially negative, a chest radiograph is necessary after 2 months of treatment, and a radiograph at completion of treatment is desirable. Generally, follow-up after completion of therapy is **not** necessary.

For patients with cultures that are initially negative, a chest radiograph is necessary after 2 months of treatment, and a radiograph at completion of treatment is desirable.

Study Questions

6.44 How often should patients have clinical evaluations to identify possible adverse reactions to medications and to assess adherence and to determine treatment efficacy?
(circle the one best answer)

    A. Weekly

    B. Twice a month

    C. Once a month

    D. Every 6 weeks

6.45 LaRue has been receiving TB treatment for 2 months. She is experiencing nausea, vomiting, abdominal pain, malaise, and persistently dark urine. What could be the cause?
(circle the one best answer)

    A. TB disease has spread to her abdomen.

    B. She has hepatic toxicity due to adverse reaction to TB medications.

    C. She has an adverse reaction to EMB.

Match the characteristic of an adverse reaction to TB therapy with the type of adverse reaction.
(Choose the one best answer and write the letter for the correct answer on the line next to the question number.)

Characteristic	Adverse Reaction
_____ **6.46** Can be caused by three of the first-line TB drugs.	**A.** Gastrointestinal problems **B.** Hepatic toxicity
_____ **6.47** Can cause a recurrence of fever in a patient who has been receiving therapy for several weeks.	**C.** Rash **D.** Drug fever
_____ **6.48** Is common particularly in the first few weeks of therapy.	
_____ **6.49** Can be caused by all drugs used in treating TB disease.	

Match the patient with the type of measures that should be taken to determine how the patient is responding to treatment.

(Choose the one best answer and write the letter for the correct answer on the line next to the question number.)

Patients	Measures for Determining the Patient's Response to Treatment
_____ **6.50** Carol had a positive sputum cultures prior to treatment and has multidrug-resistant TB disease.	**A.** Obtain specimens for culture at least monthly until 2 consecutive specimens are negative on culture.
_____ **6.51** Tom's culture has not become negative after 3 months of treatment.	**B.** Repeat chest radiographs at intervals based on clinical circumstances and the differential diagnosis.
_____ **6.52** Roxanne had negative sputum cultures prior to treatment.	**C.** Perform sputum AFB smears and cultures monthly for the entire course of treatment.
_____ **6.53** Burl had positive sputum cultures prior to treatment.	**D.** Reevaluate for potential drug-resistant TB disease, as well as for potential failure to adhere to the regimen.
_____ **6.54** Mike had positive sputum cultures after 4 months of treatment.	**E.** Consider as having failed treatment and manage accordingly.

Chapter Summary

The major goals for treatment of TB disease include

- Cure the individual patient;
- Minimize risk of death and disability; and
- Reduce transmission of *M. tuberculosis* to other persons.

To ensure that these goals are met, TB disease must be treated for at least 6 months or longer. Most of the bacteria are killed during the first 8 weeks of treatment; however, there are persistent organisms that require longer treatment. If treatment is **not** continued for a long enough duration, the surviving bacteria may cause the patient to become ill and infectious again.

There are several options for daily and intermittent therapy, but the goal of treatment for TB disease should be to provide the safest and most effective therapy in the shortest period of time. Given adequate treatment, almost all patients will recover and be cured.

Regimens for the treatment of TB disease must contain multiple drugs to which the bacteria are susceptible. The standard of care for initiating treatment of TB disease is a four-drug regimen. Treatment with a single drug can lead to the development of a bacterial population resistant to that drug. Likewise, the addition of a single drug to a failing anti-TB regimen can lead to additional resistance. When two or more drugs to which in vitro susceptibility has been demonstrated are given together, each helps prevent the emergence of tubercle bacilli resistant to the others.

Responsibility for successful treatment is assigned to the health-care provider, **not** the patient. Health-care professionals should consult their health department's TB control program to ensure their TB patients are able to adhere to a prescribed treatment regimen. The TB control program should assist the health-care professional in evaluating patient barriers to adherence and recommend directly observed therapy (DOT) and the use of incentives and enablers that may assist the patient in completing the recommended therapy.

Currently, there are 10 drugs approved by the U.S. FDA for the treatment of TB disease. In addition, the fluoroquinolones (levofloxacin, moxifloxacin, and gatifloxacin), although **not** approved by the FDA for TB disease, are commonly used to treat TB disease caused by drug-resistant organisms or for patients who are intolerant of some first-line drugs. Rifabutin, approved for use in preventing *Mycobacterium avium* complex disease in patients with HIV infection but **not** approved for TB disease, is useful for treating TB disease in patients concurrently taking drugs that interact with rifampin (e.g., certain antiretroviral drugs). Amikacin and kanamycin, nearly identical aminoglycoside drugs used in treating patients with TB disease caused by drug-resistant organisms, are not approved by the FDA for treatment of TB.

Of the approved drugs, INH, RIF, EMB, and PZA are considered the first-line anti-TB drugs and form the core of standard treatment regimens. RBT and RPT may also be considered first-line drugs under certain circumstances. RBT is used as a substitute for RIF in the treatment of all forms of TB caused by organisms that are known or presumed to be susceptible to this agent. The drug is generally reserved for patients who have intolerance to RIF or for whom drug-drug interactions preclude the use of rifampin. SM was formerly considered to be a first-line drug and, in some instances, is still used in the initial treatment regimen. However, an increasing prevalence of

resistance to SM in many parts of the world has decreased its overall usefulness. The remaining drugs are reserved for special situations such as drug intolerance or resistance.

There are four basic treatment regimens recommended for treating adults with TB disease caused by organisms that are known or presumed to be susceptible to INH, RIF, PZA, and EMB. Each treatment regimen consists of an initial 2-month treatment phase followed by a continuation phase of either 4 or 7 months. The 4-month continuation phase is used for the majority of patients. Although these regimens are broadly applicable, there are modifications that should be made under specified circumstances.

Adverse reactions to anti-TB drugs are relatively rare, but in some patients they may be severe. Clinicians who treat TB disease should be familiar with the methods of monitoring for adverse reactions and patients' response to treatment. In some situations (drug-resistant TB disease, pregnancy, HIV-infected patients), expert consultation should be sought.

References

CDC. Controlling tuberculosis in the United States: Recommendations from the American Thoracic Society, CDC, and the Infectious Diseases Society of America. *MMWR* 2005; 54 (No. RR-12). www.cdc.gov/mmwr/preview/mmwrhtml/rr5412a1.htm

CDC. National action plan to combat multidrug-resistant tuberculosis. *MMWR* 1992; 41 (RR-11): 1–48. www.cdc.gov/mmwr/preview/mmwrhtml/00031159.htm

CDC. Notice to Readers: Updated guidelines on managing drug interactions in the treatment of HIV-related tuberculosis. *MMWR* 2008; 57 (04): 98. www.cdc.gov/mmwr/preview/mmwrhtml/mm5704a4.htm?s_cid=mm5704a4_e

CDC. Treating opportunistic infections among HIV-exposed and infected children. *MMWR* 2004; 53 (No. RR-14). www.cdc.gov/mmwr/preview/mmwrhtml/rr5314a1.htm

CDC. Treating opportunistic infections among HIV-infected adults and adolescents. *MMWR* 2004; 53 (No. RR-15). www.cdc.gov/mmwr/preview/mmwrhtml/rr5315a1.htm

CDC. Treatment of tuberculosis. American Thoracic Society, CDC, and Infectious Diseases Society of America. *MMWR* 2003; 52 (No. RR-11). www.cdc.gov/mmwr/preview/mmwrhtml/rr5211a1.htm

   Errata (January 7, 2005)
   www.cdc.gov/MMWR/preview/MMWRhtml/mm5351a5.htm