



Self-Study Modules On Tuberculosis



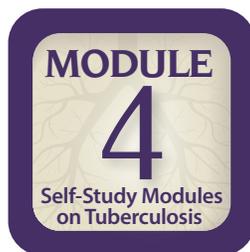
MODULE 4

Treatment of Latent Tuberculosis Infection and Tuberculosis Disease



Centers for Disease Control and Prevention
National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention

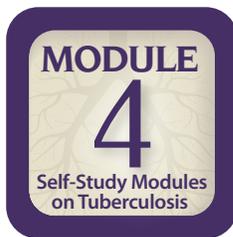




Treatment of Latent Tuberculosis Infection and Tuberculosis Disease

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control and Prevention
National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Division of Tuberculosis Elimination

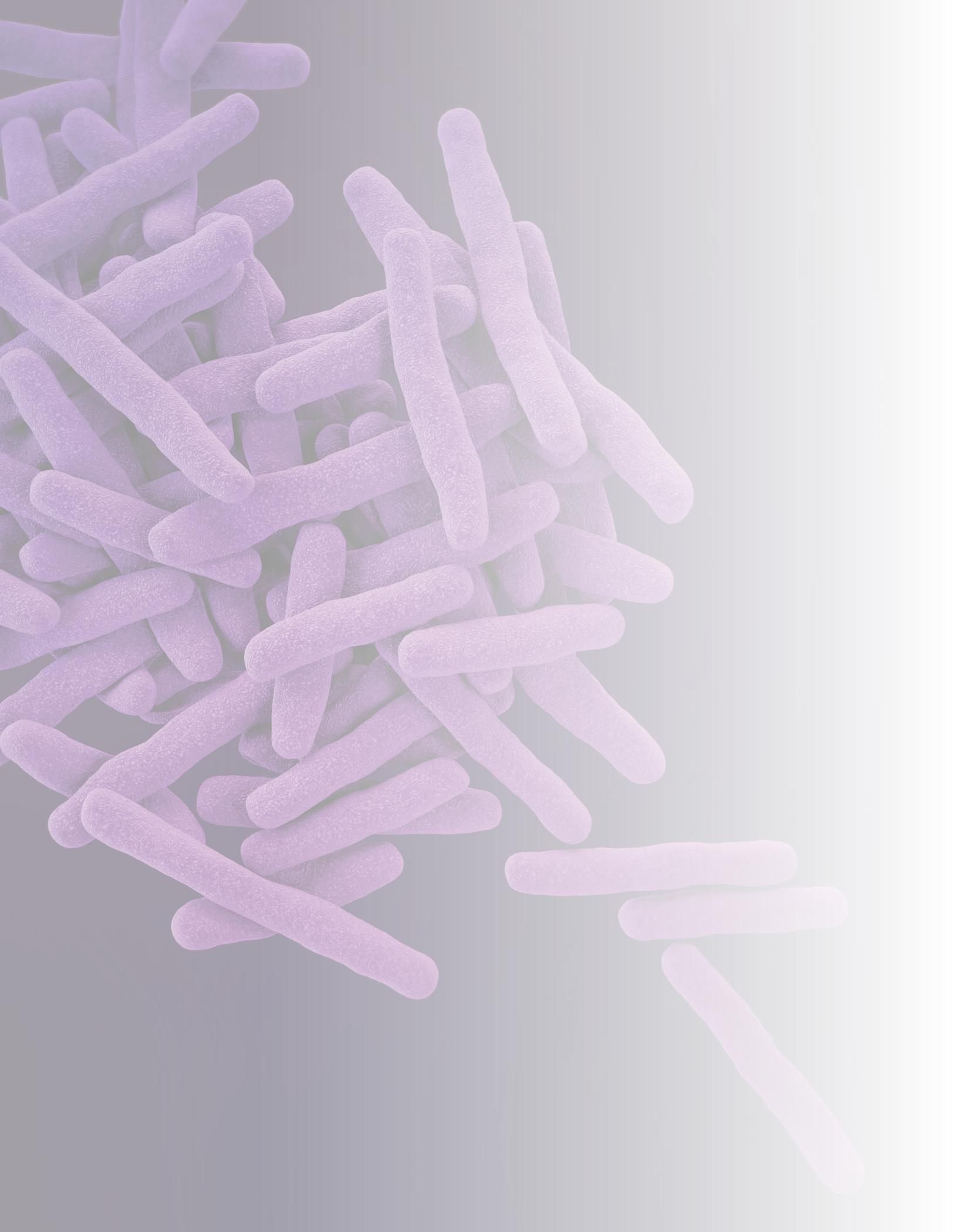
Atlanta, Georgia
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Treatment of Latent Tuberculosis Infection and Tuberculosis Disease

CONTENTS

Background.....	1
Objectives.....	1
New Terms.....	2
Treatment of Latent TB Infection (LTBI).....	4
Treatment of TB Disease.....	20
Additional Resources.....	41
Answers to Study Questions.....	43
Case Study Answers.....	51



Background

In this module, you will learn about the principles of treating latent TB infection (LTBI) and TB disease. A person with LTBI is treated to prevent them from progressing to TB disease. Some people with LTBI are at very high risk of developing TB disease, and they should receive high priority for LTBI treatment. Patients with LTBI who do not complete treatment as prescribed can develop TB disease.

TB disease is treated to cure the patient and to stop the spread of TB. As a health care worker, you may be responsible for ensuring that TB patients take their medications as prescribed. This is very important because patients with TB disease who do not complete treatment as prescribed may become infectious and spread TB to others or develop drug-resistant TB.

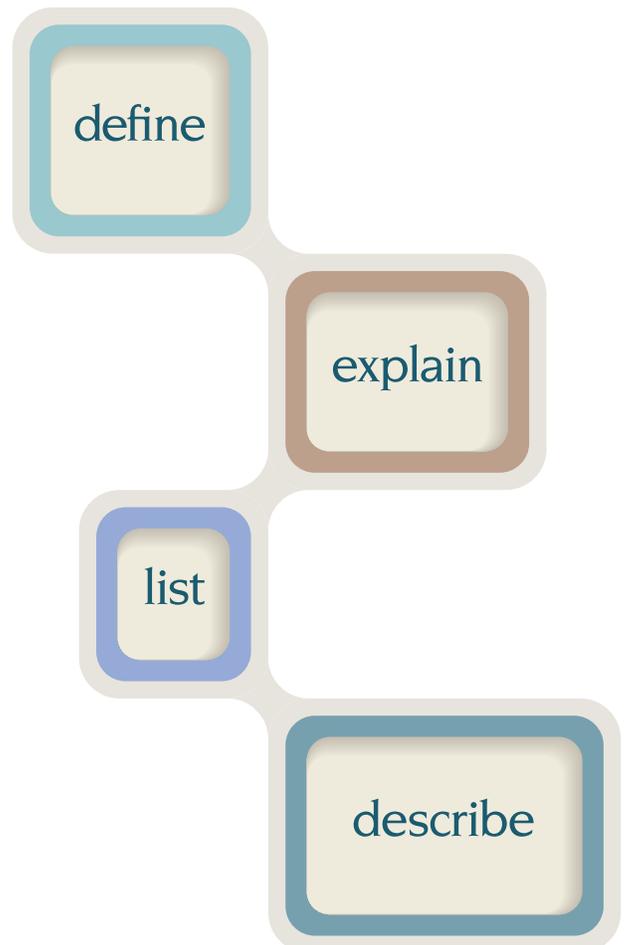
This module also explains the possible side effects of the drugs used to treat LTBI and TB disease. If you work with TB patients, it is important to be aware of the signs and symptoms of these side effects.

Note: The Self-Study Modules on Tuberculosis are a series of educational modules designed to provide information about TB in a self-study format. The target audiences include outreach workers, nurses, physicians, administrators, health educators, and students from a variety of settings. The Modules should not be used as a substitute for guidelines and should not be used for patient care decisions.

Objectives

After working through this module, you will be able to

1. List the groups of people who should receive high priority for LTBI treatment.
2. Describe treatment regimens for LTBI.
3. Describe treatment regimens for TB disease.
4. Describe the principles of preventing drug resistance.
5. Describe patient monitoring during LTBI and TB disease treatment.
6. Describe TB treatment adherence strategies.
7. List the common adverse reactions to the drugs used to treat LTBI and TB disease.





Doctor reviewing a chest x-ray.

New Terms

New terms introduced in this module are included below. These terms appear in bold in the module text.

adherence to treatment—following the recommended course of treatment by taking all the prescribed medications for the entire recommended time

adverse reaction—negative side effect resulting from the use of a drug (for example, hepatitis, nausea, headache)

antiretroviral therapy (ART)—a lifelong combination drug treatment to suppress HIV and improve the quality and length of life for a person living with HIV/AIDS

case management—a strategy health departments can use to manage patient care and help ensure patients successfully complete treatment

clinical evaluation—an evaluation done to find out whether a patient has symptoms or signs of TB disease or is responding to treatment; also done to check for adverse reactions to TB medications

continuation phase—the period after the first 8 weeks of TB disease treatment, during which tubercle bacilli that remain after the intensive phase are treated with at least two drugs

daily regimen—a treatment schedule in which the patient takes a dose of each prescribed medication every day

directly observed therapy (DOT)—a strategy devised to help patients adhere to treatment; a designated person watches the TB patient swallow each dose of the prescribed drugs to ensure adherence to and tolerability of the regimen

electronic directly observed therapy (eDOT)—DOT that is delivered remotely (e.g., over a smartphone, tablet, or computer). eDOT can either be real-time or recorded.

ethambutol (EMB)—a drug used to treat TB disease; may cause vision problems. Ethambutol should be used cautiously in children who are too young to be monitored for changes in their vision.

extensively drug-resistant TB (XDR TB)—a type of MDR TB that is resistant to isoniazid and rifampin, plus resistant to any fluoroquinolone and at least one of three injectable anti-TB drugs (such as amikacin, kanamycin, or capreomycin)

hepatitis—inflammation of the liver, causing symptoms such as nausea, vomiting, abdominal pain, fatigue, and brown urine; hepatitis can be caused by several drugs used to treat LTBI or TB disease

intensive phase—the first 8 weeks of TB disease treatment, during which most of the tubercle bacilli are killed

intermittent therapy—a treatment schedule in which the patient takes each prescribed medication one, two, or three times weekly at the appropriate dosage

isoniazid (INH)—a drug that is used for treating LTBI and TB disease; although cheap and relatively safe, it may cause hepatitis and other adverse reactions in some patients

liver function tests—tests done to detect injury to the liver, such as hepatitis

LTBI treatment—medication that is given to people who have latent TB infection to prevent developing TB disease

multidrug-resistant TB (MDR TB)—TB that is resistant to at least the drugs isoniazid and rifampin; MDR TB is more difficult to treat than drug-susceptible TB

peripheral neuropathy—damage to the sensory nerves of the hands and feet, causing tingling, numbness, or pain in the hands and feet

pyrazinamide (PZA)—first-line drug for the treatment of TB disease, may cause hepatitis and other adverse reactions in some patients

pyridoxine—another name for vitamin B6; it is given to prevent peripheral neuropathy; should always be given to pregnant and breastfeeding women on isoniazid; and to patients with diabetes or HIV

rifabutin—a drug used to treat TB disease; used as a substitute for rifampin (RIF) in the treatment of all forms of TB

rifampin (RIF)—a key drug used to treat TB disease; also used for LTBI treatment. Rifampin has several possible side effects (for example, hepatitis, turning body fluids orange, drug-drug interactions, and flu-like symptoms).

rifapentine (RPT)—a drug used to treat TB disease; also used in the 12-dose regimen to treat LTBI

Treatment of Latent TB Infection (LTBI)

Why is LTBI treated?

LTBI is treated with medication to prevent the development of TB disease. Treatment of LTBI is essential for controlling and eliminating TB disease in the United States.

LTBI is treated with medication to prevent the development of TB disease.

It is estimated that up to 13 million people in the United States have LTBI. While not everyone with LTBI will develop TB disease, about 5–10% of infected people will develop TB disease if not treated.

Who should be tested for LTBI?

Some groups of people are at higher risk for TB than others (see *Module 2, Epidemiology of Tuberculosis*). These groups can be divided into two categories:

- People who are at higher risk for exposure to or infection with *M. tuberculosis*
- People who are at higher risk for developing TB disease once infected with *M. tuberculosis*

People in these groups should be identified through contact investigations or targeted testing programs. People who are diagnosed with LTBI with a positive tuberculin skin test (TST) or blood test (interferon-gamma release assay [IGRA]) should receive high priority for treatment of LTBI. Before starting LTBI treatment, it is very important to exclude TB disease.

People in certain groups should receive high priority for LTBI treatment if they have a positive TST or IGRA result.

Before starting LTBI treatment, it is very important to exclude TB disease.

The criteria for determining who should receive high priority for LTBI treatment are listed in the following table (Table 4.1).

People without any risk factors should generally not be tested for TB infection. Testing should be targeted to groups at high risk for LTBI and TB disease (see *Module 3, Targeted Testing and the Diagnosis of Latent Tuberculosis Infection and Tuberculosis Disease*). However, if a person without any risk factors is tested and has a positive IGRA result or a TST reaction that is 15 mm or more, they should be evaluated for LTBI treatment.



A provider sharing materials.

Table 4.1 – High-Priority Candidates for LTBI Treatment Using a TST or IGRA.

<p>People in these groups should be given high priority for LTBI treatment if they have a positive IGRA result or a TST reaction that is <u>5 or more millimeters</u></p>	<p>People in these groups should be given high priority for LTBI treatment if they have a positive IGRA result or a TST reaction that is <u>10 or more millimeters</u></p>
<ul style="list-style-type: none"> • Recent contacts of people with infectious TB disease • People living with HIV • People with chest x-ray findings suggestive of previous TB disease • Patients with organ transplants • Other immunosuppressed patients (for example, patients on prolonged therapy with corticosteroids equivalent to/greater than 15 mg per day of prednisone for one month or more or those taking TNF-alpha antagonists) 	<ul style="list-style-type: none"> • People born in countries where TB disease is common • People who abuse drugs • People who live or work in high-risk congregate settings (for example, nursing homes, correctional facilities, homeless shelters, hospitals, or other health care facilities) • People who work in mycobacteriology laboratories • People with medical conditions that increase the risk for TB disease (for example, silicosis, diabetes mellitus, severe kidney disease, certain types of cancer, and certain intestinal conditions) • Children younger than 5 years of age • Infants, children, and adolescents exposed to adults in high-risk groups

See *Module 3, Targeted Testing and the Diagnosis of Latent Tuberculosis Infection and Tuberculosis Disease*, for information on interpreting a TST or IGRA result. In certain circumstances, people may be given LTBI treatment even if they do not have a positive TST or IGRA result (see the Special Considerations for LTBI Treatment section in this Module).

Before starting treatment for LTBI, patients should receive a medical evaluation to exclude TB disease.

Patient Medical Evaluation

Patient Medical Evaluation

All persons being considered for LTBI treatment should receive a medical evaluation. One reason for this evaluation is to exclude TB disease. Treating TB disease with an LTBI treatment regimen can lead to drug resistance (see the Preventing Drug Resistance section in this Module). To rule out TB disease, clinicians should determine whether the patient has symptoms of TB disease and evaluate the patient with a chest x-ray. People who are diagnosed with TB disease based on symptoms of TB disease, sputum specimens positive for acid-fast bacilli, or chest x-ray findings suggestive of TB disease, should be given treatment for TB disease, not LTBI.

All persons being considered for LTBI treatment should receive a medical evaluation.

TB disease should be excluded before starting LTBI treatment.

It is also important to determine whether the patient has ever been treated for LTBI or TB disease. In general, people who have been adequately treated should not be treated again. Neither the TST nor IGRA can determine whether a patient has received treatment for LTBI or TB disease. This is because most people who have a positive TST or IGRA result will have a positive result for the rest of their lives, regardless of whether they have received treatment. Furthermore, there are currently not enough data on the ability of either test to detect re-infection after treatment for both LTBI and TB disease. Thus, some people may require re-treatment if they are at risk of becoming re-infected and progressing to TB disease. Persons who complete LTBI treatment should be given documentation of completion.

It is also important to determine whether the patient has ever been treated for LTBI or TB disease.

Another reason for the medical evaluation is to find out whether the patient has other medical problems that may complicate therapy or require more careful monitoring during therapy. These patients include:

- People living with HIV
- People with a history of liver disorder or disease
- People who use alcohol regularly
- Women who are pregnant or just had a baby (within 3 months of delivery)
- People who are taking other medications that may increase the risk of **hepatitis**

For these patients, baseline laboratory **liver function tests** are recommended before starting LTBI treatment.

It is also important to find out if the patient has ever had any **adverse reactions** to drugs used for LTBI treatment or if they are currently on medications that may interact with LTBI treatment medications.

It is important to find out if the patient is on other medications or has any medical problems that may complicate therapy.

Finally, conducting a medical evaluation provides the health care worker an opportunity to build and establish rapport with the patient. Health care workers should highlight the important aspects of treatment, such as:

- Benefits of treatment
- Importance of **adherence to treatment**
- Possible adverse reactions
- Establishing a follow-up plan

Medical evaluation allows health care providers to build and establish rapport with patients.

Because of the interaction between TB and HIV, health care workers should also recommend that patients undergo HIV counseling and testing.

Health care workers should recommend that patients undergo HIV testing and counseling.

Regimens for LTBI Treatment

Four regimens are approved for the treatment of LTBI (Table 4.2). While all the regimens are effective, health care providers should prescribe shorter regimens when possible. Patients are more likely to complete shorter treatment regimens. For more detailed information on treating LTBI, please refer to the CDC *Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection* guidelines and *Update of Recommendations for Use of Once-Weekly Isoniazid-Rifapentine Regimen to Treat Latent Mycobacterium tuberculosis Infection*, available from the CDC website (www.cdc.gov/tb).

Isoniazid and Rifapentine Regimen (12-Dose Regimen)

The 12-dose regimen is a combination of isoniazid (INH) and rifapentine (RPT) given in 12 once-a-week doses. The 12-dose regimen of INH and RPT is sometimes referred to as “3HP.” The 12-dose regimen of INH and RPT can be given under **directly observed therapy (DOT)** or self-administered therapy (SAT). Health care providers should choose the mode of administration (DOT or SAT) based on local practice, individual patient attributes and preferences, and other considerations including risk of progression to severe forms of TB disease.

The regimen is recommended for patients 2 years of age or older, including people with HIV/AIDS who are taking antiretroviral medications that have acceptable drug-drug interactions with rifapentine, such as efavirenz and raltegravir.

The 12-dose regimen of isoniazid and rifapentine is recommended for people 2 years of age or older, including people with HIV/AIDS who are taking antiretroviral medications that have acceptable drug-drug interactions with rifapentine.

The 12-dose regimen of isoniazid and rifapentine is NOT recommended for:

- Children younger than 2 years of age,
- People with HIV/AIDS who are taking antiretroviral medications with clinically significant or unknown drug interactions with once-weekly rifapentine,
- People presumed to be infected with isoniazid or rifampin-resistant *M. tuberculosis*, and
- Pregnant women or women expecting to become pregnant during the 12-week regimen.

Rifampin

Rifampin (RIF) is also recommended for people with a positive TST or IGRA result, especially if they have been exposed to isoniazid-resistant TB. LTBI treatment with rifampin should be given daily for 4 months to both adults and children. Rifampin should not be used in HIV-infected persons being treated with some combinations of **antiretroviral therapy (ART)**. In situations where rifampin cannot be used, sometimes another drug, **rifabutin**, may be substituted.

LTBI treatment with rifampin should be given daily for 4 months.

Isoniazid – 9 Month Regimen

Nine months of isoniazid for LTBI treatment is very effective in preventing the development of TB disease in both people infected with HIV and those not infected with HIV.

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Isoniazid – 6 Month Regimen

Six months of isoniazid is another treatment option, and may be preferred by some clinicians from a cost-effectiveness standpoint and because some patients may find it easier to adhere to a shorter treatment regimen. However, it is important to note that 9 months of isoniazid is more effective than 6 months.

Since isoniazid for LTBI treatment is not always effective when it is given for less than 6 months, every effort must be made to ensure that patients receive it for at least 6 months.

The 6-month treatment regimen is not recommended for people living with HIV, children, and people with chest x-ray findings suggestive of previous TB disease.

The 6-month isoniazid treatment regimen is not recommended for people living with HIV, children, and people with chest x-ray findings suggestive of previous TB disease.

Rifampin and Pyrazinamide

The previously used LTBI treatment regimen of rifampin and **pyrazinamide (PZA)** should no longer be used due to reports of severe liver injury and death.

The combination of rifampin and pyrazinamide should NOT be used.

Table 4.2 – LTBI Treatment Regimens.

Drugs	Duration	Dose	Frequency	Total Doses	Comments
Isoniazid* and Rifapentine[†]	3 months	Adults and Children 12 years of age and over: Isoniazid: 15 mg/kg rounded up to the nearest 50 or 100 mg; 900 mg maximum Rifapentine: 10.0–14.0 kg 300 mg 14.1–25.0 kg 450 mg 25.1–32.0 kg 600 mg 32.1–49.9 kg 750 mg ≥50.0 kg 900 mg maximum Children aged 2–11 years: Isoniazid: 25 mg/kg; 900 mg maximum Rifapentine: as above	Once weekly [‡]	12	Not recommended for children younger than 2 years of age, HIV-infected patients taking antiretroviral medications with clinically significant or unknown drug interactions with once-weekly rifapentine, patients with presumed isoniazid or rifampin resistant <i>M. tuberculosis</i> , pregnant women, or women expecting to become pregnant within the treatment period DOT or SAT may be used
Rifampin[§]	4 months	Adult: 10 mg/kg Children: 15–20 mg/kg [¶] Maximum dose: 600 mg	Daily	120	Recommended for patients who have isoniazid-resistant, rifampin-susceptible LTBI Not recommended for HIV-infected patients on certain combinations of ART; rifabutin may be used instead
Isoniazid	9 months	Adult: 5 mg/kg Children: 10–20 mg/kg [¶] Maximum dose: 300 mg	Daily	270	The preferred isoniazid regimen is daily treatment for 9 months
		Adult: 15 mg/kg Children: 20–40 mg [¶] Maximum dose: 900 mg	Twice weekly [‡]	76	DOT must be used with twice-weekly dosing
Isoniazid	6 months	Adult: 5 mg/kg Children: Not recommended Maximum dose: 300 mg	Daily	180	Not recommended for people with HIV, children, and people with chest x-ray findings suggestive of previous TB disease
		Adult: 15 mg/kg Children: Not recommended Maximum dose: 900 mg	Twice weekly [‡]	52	DOT must be used with twice-weekly dosing

*Isoniazid is formulated as 100 mg and 300 mg tablets.

[†]Rifapentine is formulated as 150 mg tablets in blister packs that should be kept sealed until use.

[‡]Intermittent isoniazid regimens must be provided via directly observed therapy (DOT), that is, a health care worker observes the ingestion of medication. DOT or SAT may be used for the 12-dose regimen of isoniazid and rifapentine.

[§]Rifampin (rifampicin; RIF) is formulated as 150 mg and 300 mg capsules.

The American Academy of Pediatrics acknowledges that some experts use rifampin at 20–30 mg/kg for the daily regimen when prescribing for infants and toddlers (American Academy of Pediatrics. Tuberculosis. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:829–853).

[¶]The American Academy of Pediatrics recommends an isoniazid dosage of 10–15 mg/kg for the daily regimen and 20–30 mg/kg for the twice-weekly regimen.



Study Questions 4.1 – 4.4

- 4.1 Which statement is true about the purpose of LTBI treatment?**
- A.** It is given to people who have LTBI to prevent them from testing positive on future tests for TB infection
 - B.** It is given to people who have LTBI to prevent them from developing TB disease
 - C.** It is given to people who have TB disease to prevent the disease from getting worse
 - D.** It is given to people who have TB disease to prevent them from becoming infectious
- 4.2 Which groups of people should receive high priority for LTBI treatment if they have a positive IGRA result or a TST reaction with an induration that is 5 millimeters or larger? Name five.**
- 4.3 Which groups of people should receive high priority for LTBI treatment if they have a positive IGRA result or a TST reaction with an induration that is 10 millimeters or larger? Name seven.**
- 4.4 List the four regimens that are approved for the treatment of LTBI.**

Answers to study questions are on pages 43–50

Special Considerations for LTBI Treatment

Directly Observed Therapy (DOT)

DOT for LTBI treatment should be considered for persons who are at especially high risk for TB disease (e.g., young children) and are either taking an intermittent regimen or are suspected of nonadherence. DOT is a strategy used to help patients adhere to treatment. It means that a health care worker or another designated person watches the patient swallow each dose of the prescribed drugs to ensure adherence to and tolerability of the regimen. Because of the importance of each dose, DOT is recommended for patients on isoniazid regimens given twice weekly. For more information on DOT, see the Adherence to Treatment section of this module.

DOT is a strategy used to help patients adhere to treatment.

Contacts

Contacts are people who have been exposed to someone with infectious TB disease. Contacts should be quickly identified, located, and assessed for TB disease and LTBI. If a contact's TST or IGRA result is positive and TB disease is excluded, he or she should be considered high priority for LTBI treatment. If a contact's TST or IGRA is negative, he or she should be retested if it has been less than 8 to 10 weeks after his or her last exposure to infectious TB disease. This is because it can take 2 to 8 weeks after being infected with *M. tuberculosis* for the body's immune system to mount a response detectable by the tests. If the result of the repeat test is positive, and TB disease is excluded, the contact should be classified as recently infected and followed-up and treated appropriately.

In general, contacts with a positive TST or IGRA and a documented history of completion of LTBI treatment do not need to be retreated. However, retreatment may be necessary for persons who are at high risk of becoming re-infected and progressing to TB disease (for example, immunocompromised persons). In complicated situations, a TB expert should be consulted.

Contacts at High Risk for Rapid Development of TB Disease

Sometimes LTBI treatment is given to people who have a negative TST or IGRA result. For example, some contacts at high risk for rapidly developing TB disease should start LTBI treatment even if they have a negative test and less than 8 to 10 weeks have passed since they were last exposed to TB. These contacts include

- Children who are younger than 5 years of age (some TB programs may have different age cutoff guidelines)
- People living with HIV

Some contacts may start taking LTBI treatment if they have a negative TST or IGRA result but less than 8 to 10 weeks have passed since they were last exposed to TB.

Once TB disease is ruled out, these contacts should start LTBI treatment to prevent them from rapidly developing TB disease. They also should be retested 8 to 10 weeks after they were last exposed to TB. If the contact has a positive TST or IGRA result, he or she should continue to take LTBI treatment. Contacts living with HIV may be given a full course of LTBI treatment even if their second TST or IGRA result is negative.

TB contacts living with HIV may be given a full course of LTBI treatment even if their second TST or IGRA result is negative.

Expert consultation should be sought to determine if contacts with immunocompromised states other than HIV infection (e.g., contacts taking immunosuppressive therapies, diabetic patients) could benefit from treatment even if they have a negative TST or IGRA result. Offering treatment for presumed *M. tuberculosis* infection may be considered if the likelihood of infection is high, based on the circumstances of the exposure and prevalence of TB infection among other contacts.

Infants and Children

Because of their age, infants and young children with a positive TST reaction must have been infected recently and are at high risk of rapidly developing TB disease. Infants and young children are also more likely than older children and adults to develop life-threatening forms of TB disease.

Once TB disease has been ruled out, children who are younger than 5 years of age who have been exposed to TB should receive LTBI treatment, even if they have a negative TST result. This is because they are at high risk of rapidly developing TB disease and because they may have a false-negative TST reaction (see *Module 3, Targeted Testing and the Diagnosis of Latent Tuberculosis Infection and Tuberculosis Disease*). Because they are at high risk for rapidly developing TB disease, DOT should be considered for children taking LTBI treatment. Children should be retested 8 to 10 weeks after they were last exposed to TB.

Children who are younger than 5 years of age and who have been exposed to TB should start taking LTBI treatment, even if they have a negative TST result.

Children younger than 5 years of age should continue taking LTBI treatment until ALL of the following conditions are met:

- The child is at least 6 months of age
- The second TST is negative
- The second TST was done at least 8 weeks after the child was last exposed to a person with infectious TB disease

The 12-dose regimen of isoniazid and rifampine is not currently recommended for children younger than 2 years of age.

Contacts of Isoniazid-Resistant TB

If a person is a contact of a patient with isoniazid-resistant but rifampin-susceptible TB, a 4-month regimen of daily rifampin may be recommended. In situations where rifampin cannot be used, rifabutin may be substituted.

Contacts of Multidrug-Resistant TB

If a person is a contact of a patient with **multidrug-resistant (MDR) TB**, the risk for developing TB disease should be considered before recommending LTBI treatment. MDR TB contacts may be treated for 6 to 12 months or they can be observed for signs and symptoms of disease without treatment.

If a person is a contact of a patient with MDR TB, the risk for developing TB disease should be considered before recommending LTBI treatment.

If treating an MDR TB contact for LTBI, an alternative regimen of drugs to which the *M. tuberculosis* isolate is known to be susceptible should be used. Immunocompromised contacts (such as persons living with HIV) should be treated for 12 months. All persons with suspected MDR LTBI should be followed and observed for signs and symptoms of TB disease for 2 years, regardless of the treatment regimen. An expert in the treatment of MDR TB should also be consulted.

Pregnant Women

For most pregnant women with LTBI, treatment can be delayed until after delivery, even though isoniazid has NOT been shown to have harmful effects on the fetus. If the woman does not have any high risk factors for developing TB disease, treatment should be given after she has delivered her baby, so she can avoid having to take anti-TB medications during pregnancy. If the pregnant woman is a recent contact or is HIV-infected, immediate treatment should be considered. The preferred LTBI treatment regimen for pregnant women is 9 months of isoniazid with **pyridoxine** (vitamin B6). For women in the postpartum period (within 3 months of delivery), baseline liver function tests should be conducted.

Pregnant women should not be given LTBI treatment until after delivery, unless they have certain medical conditions.

The 12-dose regimen of isoniazid and rifapentine is not currently recommended for pregnant women or women expecting to be pregnant during the treatment regimen.

Breastfeeding Women

Breastfeeding is not contraindicated for women taking isoniazid or rifampin. The amount of isoniazid or rifampin found in the breast milk is not harmful to the infant. Additionally, the concentration of drugs found in the breast milk is not considered effective treatment for the infant. Breastfeeding women who are taking isoniazid must be given a vitamin B6 supplement. Women who are taking rifampin may notice a normal orange discoloration of body fluids, including breast milk.

Currently, there is not enough data to indicate whether the 12-dose regimen of isoniazid and rifapentine is safe for women to take while breastfeeding.

People with HIV Infection

The 12-dose regimen of isoniazid and rifapentine is recommended for people with HIV infection who are taking antiretroviral medications that have acceptable drug-drug interactions with rifapentine, such as efavirenz and raltegravir. The 12-dose regimen of isoniazid and rifapentine is not recommended for people with HIV infection who are taking antiretroviral medications with clinically significant or unknown drug interactions with rifapentine.

People with HIV infection can also be treated with a 9-month regimen of isoniazid. For people with HIV infection who cannot tolerate isoniazid or who have been exposed to isoniazid-resistant *M. tuberculosis*, an alternative treatment is 4 months of rifampin. However, rifampin should not be used for people with HIV who are being treated with certain combinations of ART. In these cases, dose-adjusted rifabutin may be given.

As new research occurs, guidelines may change. Expert consultation should be sought for the care and treatment of HIV-infected persons who have LTBI.



Study Questions 4.5 – 4.8

- 4.5** What LTBI treatment regimen may be recommended for people with a positive TST or IGRA result who have been exposed to isoniazid-resistant TB? Select one.
- A. Isoniazid and rifapentine once a week for 12 weeks
 - B. Rifampin daily for 4 months
 - C. Rifapentine once a week for 6 months
 - D. Ethambutol daily for 6 months
- 4.6** In what circumstances may LTBI treatment be given to people who have a negative TST or IGRA result?
- 4.7** What conditions must be met to stop LTBI treatment for children who are 5 years old or younger and have been exposed to TB?
- 4.8** When should pregnant women be treated for LTBI and for how long?

Answers to study questions are on pages 43–50



Case Study 4.1

You are sent to visit the home of a TB patient who was admitted to the hospital last week and diagnosed with infectious TB disease. Living in the home are his wife and his 1-year-old daughter. Neither one has symptoms of TB disease. You give them both a tuberculin skin test and return 2 days later to read the results. You find that the wife has 14 mm of induration, but the daughter has no induration.

- Should either one receive further evaluation for LTBI or TB disease? Should either one start LTBI treatment? Explain.

Answers to case study questions are on pages 51–54

Adverse Reactions and Patient Monitoring

Adverse Reactions

Many health care providers have concerns about treating patients for LTBI. These concerns are generally related to the length of treatment and adverse reactions, or negative side effects. As many as 10% to 20% of people treated with isoniazid will have some mild, abnormal liver function tests results (tests done to detect injury to the liver) during treatment. In most people, these test results return to normal even when isoniazid treatment is continued. As with any treatment, the risks and benefits must be weighed for each individual. For example, isoniazid may cause hepatitis, or inflammation of the liver. Hepatitis prevents the liver from functioning normally, causing symptoms such as:

- Nausea
- Vomiting
- Abdominal pain
- Fatigue
- Brown urine (patients taking rifampin or rifapentine will notice a different and normal orange-red discoloration of body fluids, including urine and tears).

A risk of isoniazid and rifampin is hepatitis (inflammation of the liver).

Isoniazid can cause hepatitis in anyone; however, hepatitis occurs in less than 1% of people taking isoniazid. Many things can cause hepatitis, including various viruses and other medications. There are certain risk factors that increase the risk of serious isoniazid hepatitis, such as alcoholism and older age. Although rare, there have been some cases of severe and fatal hepatitis.

Some factors, such as older age and alcoholism, increase the risk that isoniazid will cause serious hepatitis.

Isoniazid can also damage the sensory nerves of the hands and feet. This is called **peripheral neuropathy**. The main symptom of peripheral neuropathy is a tingling sensation, a weakened sense of touch, or pain in the hands, palms, soles, and feet. Some conditions, such as HIV, alcoholism, diabetes, and malnutrition increase the risk for peripheral neuropathy. People with these conditions should be given vitamin B6.

Isoniazid can damage the sensory nerves of the hands and feet.

Patients taking either rifampin, rifapentine, or rifabutin should also be aware of possible adverse effects. Some infrequent side effects from these drugs can include:

- Rash
- Gastrointestinal symptoms (nausea, anorexia, and abdominal pain)
- Orange discoloration of body fluids (e.g., urine, saliva, tears, or breast milk); soft contact lenses may be permanently stained
- Interaction with many other drugs, such as birth control pills and implants, warfarin, some HIV drugs, and methadone
- Hypersensitivity

Rifapentine may also cause flu-like symptoms.

Rifabutin may cause:

- Eye inflammation
- Joint pain
- Lower white blood cell count

All persons taking LTBI treatment should be educated about the symptoms caused by adverse reactions.

Patient Monitoring

All persons receiving LTBI treatment should be evaluated at least monthly during therapy for:

- Adherence to the prescribed regimen
- Signs and symptoms of TB disease
- Adverse reactions (such as signs and symptoms of hepatitis)

All persons receiving LTBI treatment should be evaluated at least monthly during therapy for signs and symptoms of TB disease and adverse reactions.

During each monthly evaluation, patients should be asked whether they have nausea, abdominal pain, or any of the other symptoms that may be caused by adverse reactions. In addition, health care workers should examine patients for signs of these adverse reactions. Patients should be instructed to stop taking medications and contact their health care provider immediately if they have any signs or symptoms of hepatitis (Table 4.4) or other severe adverse reactions.

In general, baseline laboratory testing is not recommended unless the person is at high risk for hepatitis. People at greatest risk for hepatitis should have baseline liver function tests before starting LTBI treatment and during therapy. This includes:

- People living with HIV
- People with a history of liver disorder or disease
- People who drink alcohol regularly
- Women who are pregnant or just had a baby (within 3 months of delivery)
- People who are taking other medications that may increase the risk of hepatitis

People at greatest risk for hepatitis should have liver function tests before starting isoniazid or rifampin and every month during therapy.

For all patients, isoniazid, rifampin, or rifapentine should be stopped if the results of liver function tests are three times higher than the upper limit of the normal range and the patient has symptoms, or if the results are five times higher than the upper limit of the normal range and the patient is asymptomatic. Expert consultation should be sought for difficult cases.

Treatment Follow-up

Patients should receive documentation of TST or IGRA results, regimens, and treatment completion dates. The patient should be told to present this document any time they are required to be tested for TB. Patients should also be re-educated about the signs and symptoms of TB disease. For detailed information on the treatment of LTBI, please refer to the CDC *Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection guidelines* and *Update of Recommendations for Use of Once-Weekly Isoniazid-Rifapentine Regimen to Treat Latent Mycobacterium tuberculosis Infection*, available from the CDC website (www.cdc.gov/tb).

All patients should receive documentation upon completion of LTBI treatment.



Study Questions 4.9 – 4.13

- 4.9** Name four reasons why patients should receive a medical evaluation before starting LTBI treatment.
- 4.10** Why is it important to exclude the possibility of TB disease before giving a patient LTBI treatment?
- 4.11** Which of the following are symptoms of hepatitis? Select the correct answer(s).
- A. Nausea
 - B. Weight gain
 - C. Vomiting
 - D. Brown urine
- 4.12** Who is at greatest risk for hepatitis? What special precautions should be taken for these patients?
- 4.13** How often should patients be evaluated for signs and symptoms of adverse reactions during LTBI treatment?

Answers to study questions are on pages 43–50



Case Study 4.2

A 65-year-old man is prescribed LTBI treatment with isoniazid because he is a contact of a person with infectious TB and he has an induration of 20 mm to the tuberculin skin test. His baseline liver function tests are normal, but he drinks a six-pack of beer every day.

- What kind of monitoring is necessary for this patient while he is taking isoniazid?

Answers to case study questions are on pages 51–54

Treatment of TB Disease

Treating TB disease benefits both the person who has TB and the community. It helps the patient because it prevents disability and death and restores health; it benefits the community because it prevents the further transmission of TB.

TB disease must be treated for **at least 6 months**; in some cases, treatment lasts longer. Most of the actively multiplying tubercle bacilli are killed during the first 8 weeks of treatment (the **intensive phase**). However, some bacilli survive longer. Therefore, treatment with at least two drugs must be continued for several more months to kill or control these remaining bacilli (the **continuation phase**). If treatment is not continued for a long enough time, the surviving bacilli may cause TB disease in the patient at a later time (**relapse**).

***TB disease must be treated for at least 6 months;
in some cases, treatment lasts longer.***

TB treatment regimens must contain multiple drugs to which the organisms are susceptible. Treatment with a single drug can lead to the development of drug-resistant TB. The intensive phase for treating drug-susceptible TB disease should include the following four drugs (Figure 4.1):

- Isoniazid (INH)
- Rifampin (RIF)
- Pyrazinamide (PZA)
- Ethambutol (EMB)

***TB disease must be treated with multiple drugs
to which the bacilli are susceptible.***

***The intensive phase for treating drug-susceptible TB disease should
include four drugs: isoniazid, rifampin, pyrazinamide, and ethambutol.***

When the drug susceptibility results are available, clinicians may change the regimen accordingly. For detailed information on the treatment of TB, please refer to the *Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis*, available from the CDC website (www.cdc.gov/tb).

Preventing Drug Resistance

Drug resistance can develop when patients are prescribed an inappropriate regimen for treatment. TB disease must be treated with multiple drugs to which the bacilli are susceptible. Using only one drug to treat TB disease can select a population of tubercle bacilli resistant to that drug. When multiple drugs are used together, each drug helps prevent the emergence of bacilli that are resistant to the other drugs. When a patient is not improving in response to a prescribed regimen, adding a single drug to that regimen may have the same effect as using only one drug for treatment: it can lead to drug resistance.

Drug resistance can also develop when patients do not follow treatment regimens as prescribed — in other words, if they do not take all of their pills or they do not take their pills as often as prescribed. When this happens, the patients may expose the bacilli to a single drug.

Drug resistance can develop when patients are prescribed an inappropriate regimen for treatment or when patients do not follow treatment regimens as prescribed.

Following are factors that increase the chance of a patient having or developing drug-resistant TB:

- Patient does not take their medicine regularly and completely
- Patient comes from an area of the world where drug-resistant TB is common
- Malabsorption of drugs
- Patient is a contact to someone with drug-resistant TB
- Failure to improve on drug-susceptible regimen
- Patient develops TB disease again after having taken TB medicine in the past

For more information on the development of drug-resistant TB, see *Module 1, Transmission and Pathogenesis of Tuberculosis*.

Treatment Regimens

The recommended treatment regimens are described in Table 4.3. This table is provided for you to use as a reference. For detailed information on TB treatment, please refer to the *Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis* available from the CDC website (www.cdc.gov/tb).



Figure 4.1 Example of pills used to treat TB disease. From left to right: isoniazid, rifampin, pyrazinamide, and ethambutol.

Table 4.3 – Drug Regimens for Pulmonary TB Caused by Drug Susceptible Organisms in Adults.*

Regimen	Intensive Phase Drugs ¹	Intensive Phase Interval and Doses ² (minimum duration)	Continuation Phase Drugs	Continuation Phase Interval and Doses ^{2,3} (minimum duration)	Range of total doses (Intensive and Continuation phases, combined)	Comments ^{3,4}	Regimen effectiveness
1	INH RIF PZA EMB	7 days/week for 56 doses (8 weeks) or 5 days/week for 40 doses (8 weeks)	INH RIF	7 days/week for 126 doses (18 weeks) or 5 days/week for 90 doses (18 weeks)	182 to 130	This is the preferred regimen for patients with newly diagnosed pulmonary TB.	 <p>greater</p> <p>lesser</p>
2	INH RIF PZA EMB	7 days/week for 56 doses (8 weeks) or 5 days/week for 40 doses (8 weeks)	INH RIF	3 times weekly for 54 doses (18 weeks)	110 to 94	Preferred alternative regimen in situations in which more frequent DOT during continuation phase is difficult to achieve.	
3	INH RIF PZA EMB	3 times weekly for 24 doses (8 weeks)	INH RIF	3 times weekly for 54 doses (18 weeks)	78	Use regimen with caution in patients with HIV and/or cavitary disease. Missed doses can lead to treatment failure, relapse, and acquired drug resistance.	
4	INH RIF PZA EMB	7 days/week for 14 doses then twice weekly for 12 doses ⁵	INH RIF	Twice weekly for 36 doses (18 weeks)	62	Do not use twice-weekly regimens in HIV-infected patients or patients with smear positive and/or cavitary disease. If doses are missed then therapy is equivalent to once weekly, which is inferior.	

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

* For dosing information, refer to the *Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis*.

¹ Other combinations may be appropriate in certain circumstances; additional details are provided in the *Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis*.

² When DOT is used, drugs may be given 5 days per week and the necessary number of doses adjusted accordingly. Although there are no studies that compare 5 with 7 daily doses, extensive experience indicates this would be an effective practice. DOT should be used when drugs are administered less than 7 days per week.

³ Based on expert opinion, patients with cavitation on initial chest radiograph and positive cultures at completion of 2 months of therapy should receive a 7-month (31-week) continuation phase.

⁴ Pyridoxine (vitamin B6), 25–50 mg/day, is given with INH to all persons at risk of neuropathy (e.g., pregnant women; breastfeeding infants; persons with HIV; patients with diabetes, alcoholism, malnutrition, or chronic renal failure; or patients with advanced age). For patients with peripheral neuropathy, experts recommend increasing pyridoxine dose to 100 mg/day.

⁵ Alternatively, some U.S. TB control programs have administered intensive-phase regimens 5 days per week for 15 doses (3 weeks), then twice weekly for 12 doses.

Note: Use of once-weekly therapy with INH 900 mg and rifapentine 600 mg in the continuation phase is not generally recommended. In uncommon situations where more than once-weekly DOT is difficult to achieve, once-weekly continuation phase therapy with INH 900 mg plus rifapentine 600 mg may be considered for use only in HIV uninfected persons without cavitation on chest radiography.



Study Questions 4.14 – 4.17

4.14 Why must TB disease be treated for at least 6 months?

4.15 Which drugs are recommended for the intensive phase of treatment for TB disease? Select the correct answer(s).

- A. Isoniazid (INH)
- B. Rifapentine (RPT)
- C. Rifampin (RIF)
- D. Pyrazinamide (PZA)
- E. Ethambutol (EMB)

4.16 Why should multiple drugs be used to treat TB disease?

4.17 What factors can lead to drug resistance? Select the correct answer(s).

- A. The patient is prescribed an inappropriate treatment regimen
- B. The patient does not follow the treatment regimen as prescribed
- C. The patient follows an appropriate treatment regimen
- D. Malabsorption of TB drugs

Answers to study questions are on pages 43–50

Special Considerations

People Living with HIV

For HIV-infected TB patients receiving antiretroviral therapy (ART), the recommended treatment of drug-susceptible TB disease is a 6-month daily regimen consisting of:

- An intensive phase of isoniazid, rifampin, pyrazinamide, and ethambutol for 2 months
- A continuation phase of isoniazid and rifampin for 4 months.

The management of HIV-infected TB patients can be complex and therefore expert consultation should be sought for the care and treatment of these patients and to discuss alternative treatment regimens if necessary.

To improve treatment outcomes for HIV-infected TB patients, ART should be initiated during TB treatment. For patients with CD4 cell counts less than 50/mm³, ART should ideally be initiated within the first 2 weeks of TB treatment. For patients with CD4 cell counts greater than or equal to 50/mm³, ART should ideally be initiated by 8 to 12 weeks of TB treatment. However, for HIV-infected patients with TB meningitis or TB involving the central nervous system, ART should NOT be initiated during the first 8 weeks of TB treatment. Additionally, it is important to be aware of the interaction of rifampin with some ART drugs. Rifabutin has fewer drug interaction problems and may be used as a substitute for rifampin in some situations.

If an HIV-infected patient is NOT receiving ART during TB treatment, it is recommended to prolong the patient's treatment to 9 months (the continuation phase can be extended to 7 months).

DOT and other adherence promoting strategies should be used in all HIV-infected TB patients. The use of intermittent TB treatment regimens has been associated with high rates of relapse and the development of drug-resistance and therefore it is recommended that TB treatment be given daily in both the intensive and continuation phase for HIV-infected TB patients. As with all patients, HIV-infected TB patients should be closely monitored for their response to treatment.

***HIV-infected TB patients should be closely monitored
for their response to treatment.***

If any patient does not seem to be responding to treatment, the patient should be reevaluated and the continuation phase can be increased to 7 months (a total of 9 months of treatment) if necessary. Because of the potential for drug-drug interactions, side effects, immune reconstitution inflammatory syndrome (worsening of TB symptoms), and the possibility of TB treatment failure or relapse, expert consultation should always be sought when treating HIV-infected TB patients.

Pregnant Women

Treatment should not be delayed for pregnant women who have TB disease; rather, it should begin as soon as TB is diagnosed. The treatment regimen should consist of at least isoniazid, rifampin, and ethambutol. Adding pyrazinamide to the treatment regimen for pregnant women is controversial in the United States. Therefore, expert consultation should be sought to evaluate the risks and benefits of prescribing pyrazinamide on a case-by-case basis. If pyrazinamide is not included in the treatment regimen, treatment should last for at least 9 months. Streptomycin, a second-line TB drug, should NOT be used because it has been shown to have harmful effects on the fetus. Vitamin B6 supplementation is recommended for all pregnant women who are taking isoniazid.

Treatment for pregnant women who have TB disease should begin as soon as TB is diagnosed.

Breastfeeding

Women being treated with the first-line TB drugs should not be discouraged from breastfeeding. Only a small concentration of the drugs is found in the breast milk and it is not harmful to the infant. The concentration of drugs found in breast milk is not considered effective treatment for LTBI or TB disease for the nursing infant. Vitamin B6 supplementation is recommended for all women who are taking isoniazid and are breastfeeding.

Children and Adolescents

TB treatment in infants and children younger than 5 years of age should be started as soon as the diagnosis is suspected. As with adults, it is recommended that children be treated for 6 months.

TB treatment in infants and children younger than 5 years of age should be started as soon as the diagnosis is suspected.

Children can be treated with the preferred four-drug regimen (isoniazid, rifampin, pyrazinamide, and ethambutol) for 2 months followed by a two-drug (isoniazid and rifampin) regimen for 4 months. However, children receiving ethambutol should be monitored for vision changes. Some clinicians use a three-drug regimen (isoniazid, rifampin, and pyrazinamide) in the intensive phase for children who are too young to have their vision monitored, who are not infected with HIV, have no prior TB treatment history, and are not at risk for having drug-resistant TB. When possible, it is preferred to treat children daily. However, children who are not infected with HIV may be treated two or three times a week during the continuation phase. Expert consultation should be sought if needed. Pills given to children may have to be crushed or given in a liquid form.

People with Extrapulmonary TB

In general, regimens that are used for treating pulmonary TB are also effective for treating extrapulmonary TB. Thus, 6 months of treatment is recommended for treating TB involving any site with the exception of the meninges or central nervous system, for which a 9 to 12-month regimen is recommended, or bone and joint TB, for which a 6 to 9 month regimen is recommended. Extending treatment should be considered for patients with TB in any site that is slow to respond.

Alternative Regimens for Treating Drug-Resistant TB

Alternative regimens should be used for treating drug-resistant TB. The treatment of drug-resistant TB should always be done with expert consultation from a physician who is familiar with the treatment of drug-resistant TB.

The treatment of drug-resistant TB should always be done with expert consultation from a physician who is familiar with the treatment of drug-resistant TB.

People with Isoniazid-Resistant TB

Isoniazid-resistant TB can be treated with the recommended 6-month, three-drug regimen (rifampin, ethambutol, and pyrazinamide).

People with TB Resistant to Isoniazid and Rifampin (MDR TB)

It is more difficult to treat MDR TB than it is to treat drug-susceptible TB. More drugs are required to treat MDR TB, and these drugs are less effective and more likely to cause adverse reactions. When TB is resistant to isoniazid and rifampin, treatment is usually for 18 to 24 months after culture conversion. As a last resort, some patients with MDR TB may undergo surgery to remove part of the infected site.

When TB is resistant to isoniazid and rifampin, treatment can last 2 years or longer.

People with Extensively Drug-Resistant TB (XDR TB)

Extensively drug-resistant TB (XDR TB) is a rare type of MDR TB. XDR TB is defined as TB that is resistant to isoniazid and rifampin, plus any fluoroquinolone and at least one of three injectable anti-TB drugs (such as amikacin, kanamycin, or capreomycin).

Because XDR TB is resistant to first-line and second-line drugs, patients are left with less effective treatment options. XDR TB is difficult to treat and successful outcomes for the patient depend greatly on the extent of drug resistance, the severity of the disease, and whether the patient's immune system is compromised.



Study Questions 4.18 – 4.19

4.18 What treatment regimen should be used for HIV-infected TB patients?

4.1 In what situations should treatment for TB disease last longer than 6 months?

Answers to study questions are on pages 43–50



Case Study 4.3

An 18-month-old girl is admitted to the hospital because of meningitis. Doctors discover that her grandmother had pulmonary TB and was treated with a 6-month regimen. The medical evaluation of the child confirms the diagnosis of TB meningitis.

- For how long should the child be treated? Why?

Answers to case study questions are on pages 51–54

Treatment and Monitoring Plan

For each patient with newly diagnosed TB, a specific treatment and monitoring plan should be developed in collaboration with the local health department. This should be done within one week of the suspected diagnosis. This plan should include:

- A description of the treatment regimen
- Methods of monitoring for adverse reactions
- Methods of assessing and ensuring adherence to the treatment
- Methods for evaluating treatment response

Each TB patient should have a specific treatment and monitoring plan developed in collaboration with the local health department.

For detailed information on treating TB, refer to the *Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis*, available from the CDC website (www.cdc.gov/tb).

Monitoring for Adverse Reactions

Before starting treatment, patients should have certain baseline blood and vision tests to help detect any problems that may complicate treatment. For example, patients who are taking ethambutol should have baseline visual acuity testing and testing of color discrimination.

Before starting treatment, patients should have baseline tests to help detect any problems that may complicate treatment.

Follow-up tests should be done periodically if the results of the baseline tests indicate abnormalities or if the patient has symptoms that may be due to adverse reactions. For example, liver function tests and symptoms should be closely monitored for patients taking isoniazid who have pre-existing liver disease or patients who develop abnormal liver function. Patients taking ethambutol should have monthly color discrimination tests and be asked about vision changes.

As with patients receiving LTBI treatment, all patients being treated for TB disease should be educated about the symptoms that are caused by adverse reactions to the drugs they are taking (Table 4.4). Patients should be warned about minor side effects such as nausea or orange-red discoloration of urine, as well as the symptoms of potentially serious side effects, such as vomiting, abdominal pain, or loss of appetite. Patients should be instructed to seek medical attention immediately if they have symptoms of a serious side effect.

All patients being treated for TB disease should be educated about the symptoms caused by adverse reactions to the drugs they are taking.

All patients should be seen by a clinician at least monthly during treatment and evaluated for response and for possible adverse reactions. Monitoring for adverse reactions must be individualized, depending on the drugs the patient is taking and the patient's risk for adverse reactions.

All patients should be seen by a clinician at least monthly during treatment and evaluated for response and for possible adverse reactions.

During this evaluation, clinicians should ask patients whether they have any of the symptoms that may be due to adverse reactions and examine patients for signs of possible adverse reactions. Clinicians should also monitor patients for response to treatment.

Public health workers who have regular contact with patients should ask patients about adverse reactions at every visit. If a patient has symptoms of a serious adverse reaction, the public health worker should:

- Instruct the patient to stop the medication
- Report the situation to a clinician and arrange for a medical evaluation right away
- Note the symptoms on the patient's form

Table 4.4 – Common Adverse Reactions to TB Drugs.

Caused by	Adverse Reaction	Signs and Symptoms	Significance of Reaction*
Any drug	Allergic	<ul style="list-style-type: none"> • Skin rash 	May be serious or minor
Ethambutol	Eye damage	<ul style="list-style-type: none"> • Blurred or changed vision • Changed color vision 	Serious
Pyrazinamide Isoniazid Rifampin	Hepatitis (liver toxicity)	<ul style="list-style-type: none"> • Abdominal pain • Abnormal liver function test results • Brown urine, light colored stool • Fatigue • Fever for 3 or more days • Flu-like symptoms • Lack of appetite • Nausea • Vomiting • Yellow skin or eyes 	Serious
Isoniazid	Nervous system damage	<ul style="list-style-type: none"> • Dizziness • Tingling or numbness around the mouth 	Serious
	Peripheral neuropathy	<ul style="list-style-type: none"> • Tingling sensation, numbness, or pain in hands and feet 	Serious
Pyrazinamide	Stomach upset	<ul style="list-style-type: none"> • Stomach upset, vomiting, lack of appetite 	May be serious or minor
	Gout	<ul style="list-style-type: none"> • Abnormal uric acid level • Joint aches 	Serious
Rifampin	Bleeding problems due to low platelets	<ul style="list-style-type: none"> • Easy bruising • Slow blood clotting 	Serious
	Discoloration of body fluids	<ul style="list-style-type: none"> • Orange urine, sweat, or tears • Permanently stained soft contact lenses 	Minor
	Drug interactions	<ul style="list-style-type: none"> • Interferes with many medications, such as birth control pills or implants, blood thinners, some HIV medicines, and methadone 	May be serious or 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.



Study Questions 4.20 – 4.22

4.2 What should be included in each patient's treatment plan?

4.3 Name the drug(s) that may cause each of the following symptoms or adverse reactions.

- Nervous system damage:
- Hepatitis:
- Eye damage:
- Orange discoloration of the urine:

4.4 How often should patients be monitored for adverse reactions to TB drugs?

Answers to study questions are on pages 43–50



Case Study 4.4

You are assigned to deliver medications to TB patients as part of the DOT program where you work. When you visit Mr. Jackson's house, you ask him how he is feeling. He tells you that he was up all night vomiting.

- What are the possible causes? What should you do?

Answers to case study questions are on pages 51–54



Case Study 4.5

Ms. Young, a patient who started treatment for TB disease last week, calls the TB clinic to complain that her urine has changed to an odd color.

- Name two possible causes, and explain how each would affect the color of the urine.

Answers to case study questions are on pages 51–54

Adherence to Treatment

Treatment for TB disease lasts longer and requires more drugs than treatment for most other infectious diseases. In order to cure TB and prevent drug resistance, patients with TB disease must follow the recommended course of treatment. This is called adhering to treatment. However, ensuring that patients adhere to treatment can be difficult because many patients are reluctant to take several different medications for many months.

In order to cure TB and prevent drug resistance, patients with TB must adhere to treatment.

There are many ways to encourage patients to adhere to treatment. The most effective strategy is **directly observed therapy (DOT)**. DOT means that a health care worker or another designated person watches the TB patient swallow each dose of the prescribed drugs to ensure adherence to and tolerability of the regimen. This method of treatment should be considered for **all patients** because there is no way to reliably predict which patients will adhere to treatment. DOT should be done at a time and a place that are convenient for the patient. For example, health care workers can meet TB patients at work, at home, or in other locations to provide DOT.

DOT should be considered for all patients because there is no way to reliably predict which patients will adhere to treatment.

Electronic DOT (eDOT) is an alternative method to in-person DOT in which a patient is remotely observed (e.g., over a smartphone, tablet, or computer) taking his or her TB medication. eDOT can be either real-time or recorded. During a real-time eDOT visit, the health care worker and the patient schedule a specific day and time to meet virtually, and the health care worker watches the patient take his or her medication. In contrast, recorded eDOT is when the health care worker and the patient do not set a specific time to meet, and the patient records himself or herself taking the medications. For more information on eDOT, please refer to *Implementing an Electronic Directly Observed Therapy (eDOT) Program: A Toolkit for Tuberculosis (TB) Programs*, available on the CDC website (www.cdc.gov/tb).

DOT should be used for all children and adolescents. Even when drugs are given under DOT, tolerance of the medications must be monitored closely. Parents should not be given the responsibility of supervising DOT. DOT is also highly recommended for patients on intermittent regimens (e.g., patients receiving treatment three times a week). Other persons who should be considered a high priority for receiving DOT include:

- Patients with drug-resistant TB
- Patients with positive sputum smears
- Patients with delayed culture conversion
- Patients with treatment failure or relapse
- Patients with HIV infection
- Persons at high risk for nonadherence, such as
 - ▢ Homeless or persons with unstable housing
 - ▢ Persons who abuse alcohol or use illicit drugs
 - ▢ Persons who are unable to take pills on their own due to mental, emotional, or physical disabilities
 - ▢ Children and adolescents
 - ▢ Persons with a history of nonadherence
- Residents at correctional or long-term care facilities
- Patients who have been previously treated for TB disease or LTBI

Another way to improve patient adherence is to offer incentives or enablers. Incentives are rewards given to patients to encourage them to take their own medicines or to keep their DOT or clinic appointments. For example, patients may be given food, restaurant coupons, clothing, or other items as an incentive. Enablers are things that help the patient receive treatment, such as bus tokens 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.

Another way to improve patient adherence is to offer incentives or enablers.

An important part of helping patients take their medicine is to educate them about TB. This means talking to them about the cause of TB, the way TB is spread, the methods of diagnosing TB, and the specific treatment plan.

Health care providers should take the time to clearly explain to patients when the medication should be taken, how much, and how often, especially if the patient is not receiving DOT. Written instructions should also be provided. Patients who understand these concepts are more likely to adhere to treatment.

An important part of helping patients take their medicine is to educate them about TB.

In summary, in order to prevent relapse and drug resistance, clinicians must prescribe an adequate regimen and make sure that patients adhere to treatment. For more information on treatment adherence, refer to *Module 6, Managing Tuberculosis Patients and Promoting Adherence*.

Monitoring Patients' Adherence to Therapy

Patients who are not receiving DOT (i.e., self-administered therapy) should be monitored carefully for adherence to treatment. This can be done in at least four ways:

- Check to see whether the patient is reporting to the clinic as scheduled, and ask the patient about adherence
- Ask the patient to bring the prescribed medications to each clinic visit and count the number of pills to determine how many have been taken
- Use special urine tests to detect the presence of the prescribed medication in the urine
- Assess the patient's clinical response to treatment

Patients who are not receiving DOT should be monitored carefully for adherence to treatment.

None of these methods can be used to prove that a patient is taking every dose of the prescribed medication. The best way to ensure adherence to treatment is to use DOT.

The best way to ensure adherence to treatment is to use DOT.

Evaluating Patients' Response to Treatment

Clinicians use three methods to determine whether a patient is responding to treatment. First, they can check to see whether the patient still has symptoms of TB (**clinical evaluation**). Although each patient responds to treatment at a different pace, most patients' 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.

Clinicians can evaluate a patient's response to treatment by checking to see whether the patient still has symptoms of TB.

Patients whose symptoms do not improve during the first 2 months of treatment, or whose symptoms worsen after improving initially, should be reevaluated.

Public health workers who have regular contact with patients should pay attention to improvement in symptoms. If a patient has worsening symptoms of TB or serious adverse reactions, the health worker should report the situation to the clinician, advise the patient to stop taking the medication, and arrange for a medical evaluation right away. The health worker should also note the symptoms on the patient's forms.

Second, clinicians can check a patient's response to treatment by obtaining sputum or other specimens for acid fast bacilli (AFB) smear and culture. Specimens should be examined at least every month until the culture results have converted from positive to negative. Any patient whose culture results have not become negative after 2 months of treatment, or whose culture results become positive after being negative, should be carefully reevaluated for treatment failure, relapse, or acquired drug resistance.

Sputum specimens should be examined every month until the culture results have converted from positive to negative.

Third, clinicians can use chest x-rays to monitor a patient's response to treatment. Repeated chest x-rays are not as helpful as monthly bacteriologic and clinical evaluations. However, a chest x-ray taken at the end of treatment can be compared with any follow-up x-rays taken subsequently should symptoms recur. Chest x-rays are also useful for patients who have negative culture results before treatment. In these patients, the bacteriological response may be difficult to assess, and the clinician may have to rely on the clinical and x-ray responses.

Patients should have a chest x-ray at the end of treatment so that it can be compared with any chest x-rays given later on.

The TST or IGRA cannot be used to determine whether a patient is responding to treatment. This is because the TST or IGRA measures the immune response to TB infection and, therefore, most people with a positive result will remain positive if they are tested later in their lives, regardless of whether they have received treatment.

The TST or IGRA cannot be used to determine whether a patient is responding to treatment.

Treatment completion is defined by the number of doses that a patient takes within a specific time frame. The length of therapy depends on the drugs used, the drug susceptibility test result, and the patient's response to therapy.

Reevaluating Patients Who Do Not Respond to Treatment or Who Relapse

Patients should be reevaluated promptly if:

- Symptoms do not improve during the first 2 months of therapy
- Symptoms worsen after improving initially
- Culture results have not become negative after 2 months of treatment
- Culture results become positive after being negative
- Chest x-rays show worsening

Reevaluating the patient means obtaining a new (sputum) specimen for TB culture and (if positive) for drug susceptibility testing, assessing whether the patient has been taking medication as prescribed, reviewing symptoms, performing a clinical examination, and repeating chest x-rays.

Any patient who has not responded to treatment after 2 months or who has relapsed should be reevaluated promptly.

The treatment of TB can be complicated, especially in patients who fail to respond to treatment, who relapse, have drug-resistant TB, or have serious adverse reactions to medications. A new regimen may be required, and treatment may last longer. Clinicians who do not have experience with these situations should consult a TB expert.



Study Questions 4.23 – 4.27

- 4.5 Name four ways by which clinicians can assess whether a patient is adhering to treatment.
- 4.6 What is the best way to ensure that a patient adheres to treatment?
- 4.7 How can clinicians determine whether a patient is responding to treatment? Select the correct answer(s).
- A. Do bacteriologic evaluations
 - B. Repeat tuberculin skin test
 - C. Do clinical evaluations
 - D. Use special urine tests
- 4.8 Under what circumstances should patients be reevaluated?
- 4.9 What does reevaluating the patient mean?

Answers to study questions are on pages 43–50



Case Study 4.6

Mr. Vigo was diagnosed with smear-positive pulmonary TB disease in January. He was treated with isoniazid, rifampin, and pyrazinamide by his private physician. He visited his physician again in March. His drug susceptibility test results were not available at the time of this appointment. Nevertheless, the physician discontinued his prescription of pyrazinamide and gave Mr. Vigo refills of isoniazid and rifampin. Mr. Vigo visited his physician again in April. He had a persistent cough, and his sputum smear was found to be positive.

- What should be done next?

Answers to case study questions are on pages 51–54

What Is the Role of the Public Health Worker in TB Treatment?

Successful TB treatment is the responsibility of the medical providers and health care workers, not the patient. Public health workers in TB programs and other facilities play an important role in helping patients complete LTBI or TB treatment.

A strategy that may be used to ensure patients complete TB treatment is **case management**. The strategy's goal is to provide patient-centered care for completion of treatment and to ensure all public health activities related to stopping TB transmission are completed. Patient-centered care can help ensure successful treatment outcomes because it emphasizes tailoring treatment to address both the patient's clinical and social concerns.

Case management is a strategy that can be used to ensure that patients complete TB treatment.

In case management, a health department employee is assigned responsibility for the management of specific patients. This person is held accountable for ensuring that each of their patients is educated about TB treatment and that their therapy is appropriate and continuous.

Many public health workers provide DOT, eDOT, or have regular contact with TB patients in clinics, nursing homes, drug treatment centers, or other facilities. At each visit with a patient, public health workers should look for signs and symptoms of adverse reactions to the medication. For this reason, public health workers must be familiar with the signs and symptoms of serious and minor adverse reactions to the drugs commonly used to treat TB. If a patient has symptoms of an adverse reaction, the public health worker should:

- Instruct the patient to stop the medication
- Report the situation to a clinician and arrange for a medical evaluation right away
- Note the symptoms on the patient's form

At each visit with a TB patient, public health workers should look for signs and symptoms of adverse reactions to the medication.

Also, public health workers can help monitor a patient's response to treatment for TB disease by looking for symptoms of TB disease. Patients receiving treatment for pulmonary TB disease usually have symptoms at the beginning of therapy, such as productive cough, fevers, heavy night sweats, weight loss, and sometimes chest pain or coughing up blood. These symptoms should gradually improve and eventually go away. At each visit with a patient, public health workers should pay attention to the patient's improvement.

Public health workers can help monitor a patient's response to treatment for TB disease by looking for symptoms of TB disease.

In addition to providing DOT, public health workers may be responsible for locating patients who have missed DOT visits or clinic appointments and helping them return to treatment. They may also educate patients and their families about TB, serve as interpreters, arrange and provide transportation for patients, and refer patients to other social services as needed. Finally, in many areas public health workers work with physicians in private practice (physicians who do not work in the health department) to make sure that their TB patients complete an adequate regimen for TB treatment. For more information on case management, please refer to *Module 6, Managing Tuberculosis Patients and Improving Adherence*.



Study Questions 4.28 - 4.29

4.10 What is the goal of TB case management?

4.11 What should a public health worker do if he or she notices that a patient has symptoms of an adverse reaction?

Answers to study questions are on pages 43–50



Case Study 4.7

Ms. DeVonne began treatment for pulmonary TB disease 2 months ago, at the beginning of September. You have been supervising her eDOT. During the first few weeks of therapy, you noticed that Ms. DeVonne's symptoms were improving a little. However, during an eDOT session in October, you see that Ms. DeVonne is coughing up blood, and she tells you that she feels like she has a fever.

■ What should you do?

Answers to case study questions are on pages 51–54

Additional Resources

1. American Academy of Pediatrics (AAP). Tuberculosis. In: Red Book 2018: Report of the Committee on Infectious Diseases. Itasca, IL: AAP; 2018. <https://redbook.solutions.aap.org/chapter.aspx?sectionid=88187262&bookid=1484>.
2. Borisov AS, Bamrah Morris S, Njie GJ, et al. Update of Recommendations for Use of Once-Weekly Isoniazid-Rifapentine Regimen to Treat Latent *Mycobacterium tuberculosis* Infection. MMWR 2018; 67:723–726. https://www.cdc.gov/mmwr/volumes/67/wr/mm6725a5.htm?s_cid=mm6725a5_w.
3. CDC. Controlling Tuberculosis in the United States Recommendations from the American Thoracic Society, CDC, and the Infectious Diseases Society of America. The Americas, 2005. MMWR 2005;54(No. RR–12):1-81. www.cdc.gov/mmwr/preview/mmwrhtml/rr5412a1.htm.
4. CDC. Fatal and Severe Hepatitis Associated With Rifampin and Pyrazinamide for the Treatment of Latent Tuberculosis Infection – New York and Georgia, 2000. MMWR 2001;50(No. 15):289-291. www.cdc.gov/mmwr/preview/mmwrhtml/mm5015a3.htm.
5. CDC. Guidelines for the Investigation of Contacts of Persons with Infectious Tuberculosis: Recommendations from the National Tuberculosis Controllers Association and CDC. The Americas, 2005. MMWR 2005;54(No. RR–15, 1–37):1-47. www.cdc.gov/mmwr/preview/mmwrhtml/rr5415a1.htm.
6. CDC. Implementing an Electronic Directly Observed Therapy (eDOT) Program: A Toolkit for Tuberculosis (TB) Programs. Atlanta, GA: Department of Health and Human Services, CDC; 2017. www.cdc.gov/tb/publications/guidestoolkits/tbedottoolkit.htm.
7. CDC. Notice to Readers: Updated Guidelines for the Use of Rifamycins for the Treatment of Tuberculosis Among HIV–Infected Patients Taking Protease Inhibitors or Nonnucleoside Reverse Transcriptase Inhibitors. The Americas, 2004. MMWR 2004;53(No. 2):37. www.cdc.gov/mmwr/preview/mmwrhtml/mm5302a6.htm.
8. CDC. Provisional CDC Guidelines for the Use and Safety Monitoring of Bedaquiline Fumarate (Sirturo) for the Treatment of Multidrug-Resistant Tuberculosis, 2013. MMWR 2013;62: 1-12. www.cdc.gov/mmwr/preview/mmwrhtml/rr6209a1.htm?s_cid=rr6209a1_e.
9. CDC. Recommendations for Use of an Isoniazid-Rifapentine Regimen with Direct Observation to Treat Latent *Mycobacterium tuberculosis* Infection. MMWR 2011; 60 (48): 1650– 1653. www.cdc.gov/mmwr/preview/mmwrhtml/mm6048a3.htm?s_cid=mm6048a3_w
Errata (February 3, 2012) <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6104a7.htm>.

10. CDC. Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection. The Americas, 2000. MMWR 2000;49(No. RR-6):1-51. www.cdc.gov/mmwr/preview/mmwrhtml/rr4906a1.htm.
11. CDC. Update: Adverse Event Data and Revised American Thoracic Society/CDC Recommendations Against the Use of Rifampin and Pyrazinamide for Treatment of Latent Tuberculosis Infection. The Americas, 2003. MMWR 2003;52(No. 31):735-739. www.cdc.gov/mmwr/preview/mmwrhtml/mm5231a4.htm.
12. CDC. Update: Fatal and Severe Liver Injuries Associated with Rifampin and Pyrazinamide for the Treatment of Latent Tuberculosis Infection, and Revisions in American Thoracic Society/CDC Recommendations – United States, 2001. MMWR 2001; 50 (No. 34):733-735. www.cdc.gov/mmwr/preview/mmwrhtml/mm5034a1.htm.
13. Curry International Tuberculosis Center and California Department of Public Health. Drug-Resistant Tuberculosis: A Survival Guide for Clinicians, 3rd edition, 2016. www.currytbcenter.ucsf.edu/products/cover-pages/drug-resistant-tuberculosis-survival-guide-clinicians-3rd-edition.
14. Nahid P, Dorman SE, Alipanah N, Barry PM, Brozek JL, Cattamanchi A, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines. Treatment of Drug-Susceptible Tuberculosis. Clinical Infectious Diseases. 2016; 63(7): 853-867. <https://academic.oup.com/cid/article/63/7/853/2197067>.
15. Reichman L, Tanne JH. Timebomb: The Global Epidemic of Multi-Drug Resistant Tuberculosis. United States of America: McGraw-Hill; 2002.



Answers to Study Questions

4.1 Which statement is true about the purpose of LTBI treatment?

- A. It is given to people who have LTBI to prevent them from testing positive on future tests for TB infection
- B. It is given to people who have LTBI to prevent them from developing TB disease**
- C. It is given to people who have TB disease to prevent the disease from getting worse
- D. It is given to people who have TB disease to prevent them from becoming infectious

The correct answer is B. The purpose of LTBI treatment is to prevent people with LTBI from developing TB disease.

4.2 Which groups of people should receive high priority for LTBI treatment if they have a positive IGRA result or a TST reaction with an induration that is 5 millimeters or larger? Name five.

- Recent contacts of people with infectious TB disease
- People living with HIV
- People with chest x-ray findings suggestive of previous TB disease
- Patients with organ transplants
- Other immunosuppressed patients (for example, patients on prolonged therapy with corticosteroids equivalent to/greater than 15mg per day of prednisone or those taking TNF-alpha antagonists)

4.3 Which groups of people should receive high priority for LTBI treatment if they have a positive IGRA result or TST reaction with an induration that is 10 millimeters or larger? Name seven.

- People who have come to the U.S. from areas of the world where TB is common (for example, Asia, Africa, Eastern Europe, Russia, or Latin America)
- People who abuse drugs
- People who live or work in high-risk congregate settings (for example, nursing homes, correctional facilities, homeless shelters, hospitals, or other health care facilities)
- People who work in mycobacteriology laboratories
- People with medical conditions that increase the risk for TB disease (for example, silicosis, diabetes mellitus, severe kidney disease, certain types of cancer, and certain intestinal conditions)
- Children younger than 5 years of age
- Infants, children, and adolescents exposed to adults in high-risk groups



Answers to Study Questions (Continued)

4.4 List the four regimens that are approved for the treatment of LTBI.

- Isoniazid and rifapentine once a week for 12 weeks
- Rifampin for 4 months
- Isoniazid for 9 months
- Isoniazid for 6 months

4.5 What LTBI treatment regimen may be recommended for people with a positive TST or IGRA result who have been exposed to isoniazid-resistant TB? Select one.

- A. Isoniazid and rifapentine once a week for 12 weeks
- B. Rifampin daily for 4 months
- C. Rifapentine once a week for 6 months
- D. Ethambutol daily for 6 months

The correct answer is B. Treatment with rifampin for 4 months may be recommended in this situation.

4.6 In what circumstances may LTBI treatment be given to people who have a negative TST or IGRA result?

Some contacts may start taking LTBI treatment even if they have a negative skin test and less than 8 to 10 weeks have passed since they were last exposed to TB. These contacts include

- Children who are 5 years of age or younger (some TB programs may have different age cutoff guidelines)
- People living with HIV

Once TB disease is ruled out, these contacts should start LTBI treatment to prevent them from rapidly developing TB disease. They also should be retested 8 to 10 weeks after they were last exposed to TB. If the contact has a positive TST or IGRA result, he or she should continue to take LTBI treatment. Contacts living with HIV may be given a full course of LTBI treatment even if their second TST or IGRA result is negative.

Expert consultation should be sought to determine if contacts with immune impairments other than HIV infection (e.g., contacts taking immunosuppressive therapies) could benefit from treatment even if they have a negative TST or IGRA result. Offering treatment for presumed *M. tuberculosis* infection may be considered if the likelihood of infection is high, based on the circumstances of the exposure and prevalence of TB infection among other contacts.



Answers to Study Questions (Continued)

4.7 What conditions must be met to stop LTBI treatment for children who are 5 years old or younger and have been exposed to TB?

Children 5 years and younger who have been exposed to TB should start taking LTBI treatment, even if they have a negative TST. Children should be retested 8 to 10 weeks after they were last exposed to TB. LTBI treatment can be stopped if all of the following conditions are met:

- The child is at least 6 months of age
- The second TST is negative
- The second TST was done at least 8 weeks after the child was last exposed to an adult with infectious TB disease

4.8 When should pregnant women be treated for LTBI and for how long?

For most pregnant women with TB infection, LTBI treatment can be delayed until after delivery. If the pregnant woman is a recent contact or HIV-infected, immediate treatment should be considered. The preferred LTBI treatment regimen for pregnant women is 9 months of isoniazid with a vitamin B6 supplement.

4.9 Name four reasons why patients should receive a medical evaluation before starting LTBI treatment.

All patients being considered for LTBI treatment should receive a medical evaluation in order to:

- Exclude the possibility of TB disease
- Determine whether they have ever been treated for TB infection or disease
- Identify any medical problems that may complicate therapy or require more careful monitoring
- Establish and build rapport with patient

4.10 Why is it important to exclude the possibility of TB disease before giving a patient LTBI treatment?

It is important to exclude the possibility of TB disease because treating TB disease with a LTBI treatment regimen can lead to drug resistance.

4.11 Which of the following are symptoms of hepatitis? Select the correct answer(s).

- A. Nausea
- B. Weight gain
- C. Vomiting
- D. Brown urine

The correct answers are A, C, and D. Symptoms of hepatitis include nausea, vomiting, and brown urine. Other symptoms include abdominal pain and fatigue.



Answers to Study Questions (Continued)

4.12 Who is at greatest risk for hepatitis? What special precautions should be taken for these patients?

The people at greatest risk for hepatitis are:

- People living with HIV
- People with a history of liver disorder or disease
- People who drink alcohol regularly
- Women who are pregnant or just had a baby (within the last 3 months)
- People who are taking other medications that may increase the risk of hepatitis

These patients should have liver function tests before starting LTBI treatment, and during therapy.

4.13 How often should patients be evaluated for signs and symptoms of adverse reactions during LTBI treatment?

All persons receiving LTBI treatment should be evaluated at least monthly during therapy for signs and symptoms of adverse reactions. During each monthly evaluation, clinicians should ask patients whether they have nausea, abdominal pain, or any of the other symptoms that may be caused by adverse reactions. In addition, they should examine patients for signs of these adverse reactions.

4.14 Why must TB disease be treated for at least 6 months?

TB disease must be treated for at least 6 months; in some cases, treatment lasts even longer. Most of the tubercle bacilli are killed during the first 8 weeks of treatment (the intensive phase). However, some bacilli survive. Therefore, treatment must be continued for several more months to kill or control these remaining bacilli (the continuation phase). If treatment is not continued for a long enough time, the surviving bacilli may cause TB disease in the patient at a later time (relapse).

4.15 Which drugs are recommended for the intensive phase of treatment for TB disease? Select the correct answer(s).

- A. Isoniazid (INH)
- B. Rifapentine (RPT)
- C. Rifampin (RIF)
- D. Pyrazinamide (PZA)
- E. Ethambutol (EMB)

The correct answers are A, C, D, and E. The intensive phase should include isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB). When the drug susceptibility results are available, clinicians may change the regimen accordingly.



Answers to Study Questions (Continued)

4.16 Why should multiple drugs be used to treat TB disease?

Using only one drug to treat TB disease can select a population of tubercle bacilli that is resistant to that drug. When multiple drugs are used together, each drug helps prevent the emergence of bacilli that are resistant to the other drugs.

4.17 What factors can lead to drug resistance? Select the correct answer(s).

- A. The patient is prescribed an inappropriate treatment regimen
- B. The patient does not follow the treatment regimen as prescribed
- C. The patient follows an appropriate treatment regimen
- D. Malabsorption of TB drugs

The correct answers are A, B, and D. Drug resistance can develop when patients are prescribed an inappropriate regimen for treatment, when patients do not follow treatment regimens as prescribed, or malabsorption of TB drugs.

4.18 What treatment regimen should be used for HIV-infected TB patients?

For HIV-infected TB patients receiving ART, the recommended treatment of drug-susceptible TB disease is a 6-month daily regimen consisting of:

- An intensive phase of isoniazid, rifampin, pyrazinamide, and ethambutol for 2 months
- A continuation phase of isoniazid and rifampin for 4 months

ART should be initiated during TB treatment. For patients with CD4 cell counts less than 50/mm³, ART should ideally be initiated within the first 2 weeks of TB treatment. For patients with CD4 cell counts greater than or equal to 50/mm³, ART should ideally be initiated by 8 to 12 weeks of TB treatment. However, for HIV-infected patients with TB meningitis or TB involving the central nervous system, ART should NOT be initiated during the first 8 weeks of TB treatment.

Additionally, it is important to be aware of the interaction of rifampin with some ART drugs. Rifabutin has fewer drug interaction problems and may be used as a substitute for rifampin in some situations.

DOT and other adherence promoting strategies should be used in all HIV-infected TB patients.



Answers to Study Questions (Continued)

4.19 In what situations should treatment for TB disease last longer than 6 months?

- HIV-infected TB patients should receive a minimum of 6 months of treatment and be closely monitored for their response to treatment. If an HIV-infected patient is NOT receiving ART during TB treatment, it is recommended to prolong the patient's treatment to 9 months (the continuation phase can be extended to 7 months). Also, as with any patient, if they do not seem to be responding to treatment, they should be reevaluated and the continuation phase can be increased to 7 months (a total of 9 months of treatment) if necessary.
- Pregnant women with TB disease should receive at least 9 months of treatment
- Persons with TB disease of the meninges or central nervous system should receive a 9 to 12-month regimen
- Persons with bone or joint TB disease should receive a 6 to 9-month regimen
- Extending treatment should be considered for patients with TB disease in any site that is slow to respond
- Treatment for multidrug-resistant TB disease can last 18 to 24 months

4.20 What should be included in each patient's treatment plan?

This plan should include:

- A description of the treatment regimen
- Methods of monitoring for adverse reactions
- Methods of assessing and ensuring adherence to the treatment
- Methods for evaluating treatment response

4.21 Name the drug(s) that may cause each of the following symptoms or adverse reactions.

- Nervous system damage: isoniazid
- Hepatitis: isoniazid, pyrazinamide, rifampin
- Eye damage: ethambutol
- Orange discoloration of the urine: rifampin



Answers to Study Questions (Continued)

4.22 How often should patients be monitored for adverse reactions to TB drugs?

All patients should be seen by a clinician at least monthly during treatment and evaluated for possible adverse reactions. During this evaluation, clinicians should ask patients whether they have any of the symptoms that may be due to adverse reactions and examine patients for signs of possible adverse reactions. Also, public health workers who have regular contact with patients should ask patients about adverse reactions at every visit.

4.23 Name four ways by which clinicians can assess whether a patient is adhering to treatment.

- Check to see whether the patient is reporting to the clinic as scheduled
- Ask the patient to bring the prescribed medications to each clinic visit and count the number of pills to determine how many have been taken
- Use special urine tests to detect the presence of the prescribed medication in the urine
- Assess the patient's clinical response to therapy

4.24 What is the best way to ensure that a patient adheres to treatment?

The best way to ensure adherence to therapy is to use directly observed therapy (DOT). DOT means that a health care worker or another designated person watches the patient swallow each dose of the prescribed drugs. This method of treatment should be considered for all patients, because there is no way to predict reliably which patients will adhere to treatment.

4.25 How can clinicians determine whether a patient is responding to treatment? Select the correct answer(s).

- A. Do bacteriologic evaluations
- B. Repeat tuberculin skin test
- C. Do clinical evaluations
- D. Use special urine tests

The correct answers are A and C. To determine whether a patient is responding to therapy, clinicians should do clinical evaluations and bacteriologic evaluations during therapy. Clinicians may also use x-rays to monitor a patient's response to treatment, especially in patients who have negative culture results before treatment or who have certain types of extrapulmonary TB.



Answers to Study Questions (Continued)

4.26 Under what circumstances should patients be reevaluated?

Patients should be reevaluated promptly if their

- Symptoms do not improve during the first 2 months of therapy
- Symptoms worsen after improving initially
- Culture results have not become negative after 2 months of treatment
- Culture results become positive after being negative
- Chest x-rays show worsening

4.27 What does reevaluating the patient mean?

Reevaluating the patient means obtaining a new (sputum) specimen for TB culture and (if positive) for drug susceptibility testing, assessing whether the patient has been taking medication as prescribed, reviewing symptoms, performing a clinical evaluation, and repeating chest x-rays.

4.28 What is the goal of TB case management?

The goal of TB case management is to provide patient-centered care for completion of treatment and to ensure all public health activities related to stopping TB transmission are completed.

4.29 What should a public health worker do if he or she notices that a patient has symptoms of an adverse reaction?

The public health worker should:

- Instruct the patient to stop the medication
- Report the situation to a clinician and arrange for a medical evaluation right away
- Note the symptoms on the patient's form



Case Study Answers

4.1 You are sent to visit the home of a TB patient who was admitted to the hospital last week and diagnosed with infectious TB disease. Living in the home are his wife and his 1-year-old daughter. Neither one has symptoms of TB disease. You give them both a tuberculin skin test and return 2 days later to read the results. You find that the wife has 14 mm of induration, but the daughter has no induration.

■ **Should either one receive further evaluation for LTBI or TB disease? Should either one start LTBI treatment? Explain.**

Yes, both should receive further evaluation for LTBI or TB disease. The wife is a contact of someone with infectious TB disease, and she has a positive skin test (greater than or equal to 5 mm for contacts). Therefore, after receiving a medical evaluation (to rule out TB disease, determine whether she has ever been treated for TB infection or disease, and identify any medical problems that may complicate therapy), she should complete an entire course of LTBI treatment, regardless of her age.

The daughter is also a contact. Currently, she has a negative skin test. However, only 1 week has passed since she last spent time with her infectious father. It is possible that not enough time has passed for her to be able to react to the tuberculin skin test. At this point, it is impossible to determine whether she has TB infection. In addition, because she is a young child, she may develop TB disease very quickly after infection.

For these reasons, the daughter should start LTBI treatment now and be retested 8 to 10 weeks after she last spent time with her father. If she has a negative TST result on the repeat test, she may stop taking the medicine. If she has a positive TST result, she should complete an entire course of LTBI treatment.



Case Study Answers (Continued)

4.2 A 65-year-old man is prescribed LTBI treatment with isoniazid because he is a contact of a person with infectious TB disease and he has an induration of 20 mm to the tuberculin skin test. His baseline liver function tests are normal, but he drinks a six-pack of beer every day.

■ **What kind of monitoring is necessary for this patient while he is taking isoniazid?**

Even though his liver function tests are normal, this man is at high risk of isoniazid-associated hepatitis because he abuses alcohol and older persons are at higher risk for hepatitis. He should be educated about the symptoms of adverse reactions to isoniazid and be instructed to seek medical attention immediately if these symptoms occur. Furthermore, once a month, he should be seen by a clinician. The clinician should ask him about his symptoms, examine him for signs of adverse reactions, and consider performing liver function tests.

4.3 An 18-month-old girl is admitted to the hospital because of meningitis. Doctors discover that her grandmother had pulmonary TB disease and was treated with a 6-month regimen. The medical evaluation of the child confirms the diagnosis of TB meningitis.

■ **For how long should the child be treated? Why?**

The child should be treated for 9 to 12 months because she has TB meningitis.

4.4 You are assigned to deliver medications to TB patients as part of the DOT program where you work. When you visit Mr. Jackson's house, you ask him how he is feeling. He tells you that he was up all night vomiting.

■ **What are the possible causes? What should you do?**

His vomiting may be a symptom of hepatitis (caused by isoniazid, rifampin, and pyrazinamide) or of stomach upset due to pyrazinamide. You should advise Mr. Jackson to stop his medication and report the situation to the clinician immediately. Mr. Jackson should receive a medical evaluation right away.



Case Study Answers (Continued)

4.5 Ms. Young, a patient who started treatment for TB disease last week, calls the TB clinic to complain that her urine has changed to an odd color.

- **Name two possible causes, and explain how each would affect the color of the urine.**

One possible cause is the discoloration of body fluids, a common side effect of rifampin. This would cause Ms. Young's urine to turn orange. The clinic nurse, physician, or public health worker should explain to Ms. Young that orange urine and other body fluids is a side effect of rifampin and that this is NOT a serious condition.

Another possible cause is hepatitis, which can be caused by isoniazid, rifampin, or pyrazinamide. Hepatitis, a serious condition, would cause Ms. Young's urine to turn dark. If Ms. Young's urine is dark, the situation should be reported to the clinician and Ms. Young should receive a medical examination right away.

4.6 Mr. Vigo was diagnosed with smear-positive pulmonary TB disease in January. He was treated with isoniazid, rifampin, and pyrazinamide by his private physician. He visited his physician again in March. His drug susceptibility test results were not available at the time of this appointment. Nevertheless, the physician discontinued his prescription of pyrazinamide and gave Mr. Vigo refills of isoniazid and rifampin. Mr. Vigo visited his physician again in April. He had a persistent cough, and his sputum smear was found to be positive.

- **What should be done next?**

Mr. Vigo's persistent cough and positive sputum smear indicate that he is not responding to therapy. The most likely explanations are:

- He is not taking his medications as prescribed,
- He has drug-resistant TB and the regimen he has been prescribed is not adequate to treat his TB, or
- A combination of the two factors listed above.

The initial drug susceptibility test results should be located, and susceptibility tests should be repeated on a recent sputum specimen. In addition, his adherence should be evaluated, and he should be given DOT if possible.



Case Study Answers (Continued)

4.7 Ms. DeVonne began treatment for pulmonary TB disease 2 months ago, at the beginning of September. You have been supervising her eDOT. During the first few weeks of therapy, you noticed that Ms. DeVonne’s symptoms were improving a little. However, during an eDOT session in October, you see that Ms. DeVonne is coughing up blood, and she tells you that she feels like she has a fever.

■ **What should you do?**

Coughing up blood and feeling feverish are symptoms of TB disease. You should report Ms. DeVonne’s symptoms to the clinician and arrange for her to receive a medical evaluation right away. Also, you should note Ms. DeVonne’s symptoms on her form.

The fact that Ms. DeVonne’s TB symptoms got worse after improving initially indicates that she is not responding to therapy. Because she is receiving eDOT, Ms. DeVonne is probably taking her medications as prescribed. Therefore, the most likely explanation is that she has drug-resistant TB and the prescribed regimen is not adequate to treat the TB.

Ms. DeVonne’s initial drug susceptibility test results should be located, and drug susceptibility tests should be repeated on a recent sputum specimen.





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