Self-Study Modules on Tuberculosis

Treatment of Latent Tuberculosis Infection and Tuberculosis Disease

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**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. 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 helping 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 or develop drug-resistant TB; patients with LTBI who do not complete treatment as prescribed can unnecessarily develop TB disease.

This module also explains the possible side effects of the drugs used to treat LTBI and TB disease. If you have regular contact with TB patients, you should be aware of the signs and symptoms of these side effects. If a patient has symptoms of a serious side effect, you should notify a clinician immediately.

**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.
6. Describe TB treatment adherence strategies.
7. List the common adverse reactions to the drugs used to treat LTBI and TB disease.
NEW TERMS

Look for the following new terms in this module and in the glossary.

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

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

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

case management – a system in which a specific health department employee is assigned primary responsibility for the patient, systematic regular review of patient progress is conducted, and plans are made to address any barriers to adherence

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

continuation phase – the period after the first 8 weeks of TB disease treatment, during which most of the tubercle bacilli are killed

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

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 rare type of MDR TB which is resistant to isoniazid and rifampin, plus resistant to any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin)

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

initial 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 two or three times weekly at the appropriate dosage

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

liver function tests – tests done to detect injury to the liver

LTBI treatment – medication that is given to people who have TB infection to prevent them from developing TB disease

multidrug-resistant TB (MDR TB) – TB that is resistant to isoniazid and rifampin; more difficult to treat than drug-susceptible TB
peripheral neuropathy – damage to the sensory nerves of the hands and feet, causing a tingling sensation or a weakened sense of touch in the hands and feet

primary TB – primary TB generally affects the mid and lower lung; in children this form of TB is much more common

pyridoxine – another name for vitamin B6; it is given to prevent peripheral neuropathy; should always be given to pregnant and breastfeeding women on isoniazid

reactivation (post-primary) TB – TB that generally affects upper lobes; sometimes with cavities and is usually found in adults. Sometimes called adult-type TB

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 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 interactions)

rifapentine – a drug used to treat TB disease; used once weekly with isoniazid during the continuation phase with selected HIV negative patients

XDR TB – see extensively drug resistant TB
Treatment of Latent TB Infection (LTBI)

Why is LTBI treated?

LTBI is treated to prevent people who have TB infection from developing TB disease. LTBI is treated with medication.

Who should receive LTBI treatment?

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

- People who are at higher risk for becoming infected with *M. tuberculosis*
- People who are higher risk for developing TB disease once infected with *M. tuberculosis*

People in these groups should be identified through targeted testing programs. Once identified, people in these groups should receive high priority for treatment of LTBI if they have a positive tuberculin skin test (TST) or a QuantiFERON-TB Gold® (QFT-G) test (see Module 3, Targeted Testing and the Diagnosis of Latent Tuberculosis Infection and Tuberculosis Disease).

The criteria for determining who should receive high priority for LTBI treatment are listed in the following table (Table 4.1).
### Table 4.1
High-Priority Candidates for LTBI Treatment Using a TST or QFT-G*

<table>
<thead>
<tr>
<th>People in these groups should be given high priority for LTBI treatment if they have a positive QFT-G result or a TST reaction* that is 5 or more millimeters</th>
<th>People in these groups should be given high priority for treatment of LTBI if they have a positive QFT-G result or a TST reaction that is 10 or more millimeters</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Recent close contacts of people with infectious TB disease**</td>
<td></td>
</tr>
<tr>
<td>▪ People living with HIV**</td>
<td></td>
</tr>
<tr>
<td>▪ People with chest x-ray findings suggestive of previous TB disease</td>
<td></td>
</tr>
<tr>
<td>▪ Patients with organ transplants</td>
<td></td>
</tr>
<tr>
<td>▪ Other immunosuppressed patients (such as patients on prolonged therapy with corticosteroids, equivalent to taking 15 mg or more of prednisone, or those taking TNF-alpha antagonists)**</td>
<td></td>
</tr>
<tr>
<td>▪ People who have come to the U.S. within the last 5 years from areas of the world where TB is common (for example, Asia, Africa, Eastern Europe, Russia, or Latin America)</td>
<td></td>
</tr>
<tr>
<td>▪ People who inject illegal drugs</td>
<td></td>
</tr>
<tr>
<td>▪ People who live or work in high-risk facilities (for example, nursing homes, correctional facilities, homeless shelters, hospitals, or other health care facilities)</td>
<td></td>
</tr>
<tr>
<td>▪ People who work in mycobacteriology laboratories</td>
<td></td>
</tr>
<tr>
<td>▪ People with medical conditions that appear to increase the risk for TB disease (silicosis, diabetes mellitus, severe kidney disease, certain types of cancer, and certain intestinal conditions)</td>
<td></td>
</tr>
<tr>
<td>▪ Children younger than 4 years old</td>
<td></td>
</tr>
<tr>
<td>▪ Infants, children, and adolescents exposed to adults in high-risk groups**</td>
<td></td>
</tr>
</tbody>
</table>

*See Module 3, Targeted Testing and the Diagnosis of Latent Tuberculosis Infection and Tuberculosis Disease, for information on interpreting a TST or QFT-G result.

**In certain circumstances, people in these categories may be given LTBI treatment even if they do not have a positive TST or QFT-G result (see the Special Considerations for LTBI Treatment section in this Module).
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 QFT-G result or TST reaction that is 15 mm or more, they should be evaluated for LTBI treatment. It is necessary to make sure that the person does not have active TB disease before starting LTBI treatment.
Study Questions 4.1 – 4.3

4.1 What is the purpose of LTBI treatment?

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

Answers to study questions are on pages 52 – 58.
Regimens for LTBI Treatment

There are several treatment regimens available for LTBI (Table 4.2). The drug isoniazid (also known as INH), is usually used alone to treat LTBI. For more detailed information on treating LTBI, please refer to the CDC Targeted Tuberculin Testing and Treatment of Latent TB Infection guidelines.

Isoniazid – 9 Month Regimen

The preferred regimen for LTBI treatment is isoniazid given daily for 9 months. 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.

Isoniazid – 6 Month Regimen

Six months of isoniazid can also provide protection, 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, 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. Moreover, 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. These people should always receive isoniazid for 9 months.

Alternative Regimens for LTBI Treatment

Rifampin

In some situations, drugs other than isoniazid may be used for LTBI treatment. For example, the drug rifampin (RIF) is recommended for people with a positive TST or QFT-G result who cannot tolerate isoniazid or 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 (ARV) therapy. In situations where rifampin cannot be used, another drug, rifabutin, may be substituted.
The combination of rifampin and pyrazinamide should **NOT** be used for either people with or without HIV infection.

**Rifampin and Pyrazinamide**

Due to the reports of severe liver injury and death, CDC advises **NOT** using the combination of rifampin and pyrazinamide (PZA) for 2 months for LTBI treatment for either people with or without HIV infection.

Table 4.2

**LTBI Treatment Regimens**

<table>
<thead>
<tr>
<th>Drug/Dose</th>
<th>Duration (months)</th>
<th>Interval</th>
<th>Minimum Doses</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>9</td>
<td>Daily</td>
<td>270</td>
<td>The preferred regimen is daily treatment for 9 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Twice weekly</td>
<td></td>
<td>Recommended regimen for people with HIV, children, and people with chest x-ray findings suggestive of previous TB disease</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>6</td>
<td>Daily</td>
<td>180</td>
<td>Not recommended for people with HIV, children, and people with chest x-ray findings suggestive of previous TB disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Twice weekly</td>
<td>52</td>
<td>DOT should be used with twice-weekly dosing</td>
</tr>
<tr>
<td>Rifampin</td>
<td>4</td>
<td>Daily</td>
<td>120</td>
<td>Recommended for patients who have isoniazid-resistant, rifampin-susceptible LTBI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Alternative for people who cannot tolerate isoniazid</td>
</tr>
<tr>
<td>Rifampin/Pyrazinamide</td>
<td></td>
<td></td>
<td></td>
<td>Not recommended for HIV-infected patients on certain combinations of ARV therapy; rifabutin may be used instead</td>
</tr>
</tbody>
</table>

* For more detailed information on LTBI treatment, please refer to Targeted Tuberculin Testing and Treatment of Latent TB Infection — MMWR 2000; 49 (No. RR–6). See “Additional Reading” for more information.
Study Questions 4.4 – 4.5

4.4  What is the preferred LTBI treatment regimen?

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

Answers to study questions are on pages 52 – 58.
Special Considerations for LTBI Treatment

Directly Observed Therapy (DOT)
For people who are especially at high risk for TB, or who are suspected to be more likely to be non-adherent, directly observed therapy (DOT) for LTBI should be considered. 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. Patients on regimens given once or twice weekly may be more likely to miss doses, thus DOT is recommended for patients on intermittent therapy. For more information on DOT, see the Adherence to Treatment section of this module, page 39.

Close Contacts
Close contacts include people who have had recent or prolonged exposure to a person with known or suspected infectious TB. These people should be evaluated immediately for TB disease and LTBI. If their TST or QFT-G result is positive, they should be given high priority for LTBI treatment. If their TST or QFT-G is negative, the contacts should be retested in 8 to 10 weeks. This is due to the fact that it can take 2 to 8 weeks after TB infection for the body’s immune system to be able to react to tuberculin and for the infection to be detected by the TST.

Sometimes LTBI treatment is given to people who have a negative TST or QFT-G result. For example, some close contacts at high risk for developing TB disease may start taking LTBI treatment if they have a negative skin test but less than 8 to 10 weeks have passed since they were last exposed to TB. These contacts include:

- Children who are 5 years old or younger (some TB programs may have different age cutoff guidelines)
- People living with HIV
- Other immunocompromised persons who may develop TB disease quickly after infection

These contacts may be infected with *M. tuberculosis* but have a false-negative TST reaction because less than 8 to 10 weeks have passed since they were last exposed to TB. (see Module 3, Targeted Testing and the Diagnosis of Latent Tuberculosis Infection and Tuberculosis Disease).
Once active 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 they have a negative TST or QFT-G, they can stop taking the LTBI treatment. If they have a positive TST or QFT-G result, they should continue to take LTBI treatment. Contacts living with HIV or others with a weakened immune system may be given a full course of LTBI treatment regardless of their second TST or QFT-G result.

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

**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 6-12 months or they can be observed for signs and symptoms of disease without treatment.

If treating an MDR TB contact for LTBI, an alternative regimen of drugs to which the infecting organism is known to be susceptible should be used. Immunocompromised contacts (such as, persons who are HIV-infected) 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.
Infants and Children

Because of their age, infants and young children with a positive TST reaction are known to 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.

Children who are 5 years old and younger who have been exposed to TB should start taking 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).

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 second TST is negative.
- The second TST was done 8 to 10 weeks after the child was last exposed to TB.
- The child is at least 6 months old.

Currently, there are limited data on diagnosing TB infection using QFT-G in children younger than 17.
Pregnant women should not be given LTBI treatment until after delivery, unless they have certain medical conditions.

**Pregnant Women**

For most pregnant women with TB infection, 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 unnecessary medications during pregnancy. If the pregnant woman is HIV-infected or a recent contact, immediate treatment should be considered. The preferred LTBI treatment regimen for pregnant women is 9 months of isoniazid with a vitamin B6 supplement (also known as pyridoxine).

**Breastfeeding Women**

Women who are breastfeeding can take isoniazid, but they should also be given a vitamin B6 supplement. The amount of isoniazid found in the breast milk, however, is not enough to be considered as treatment for the infant.

**People with HIV Infection**

People with HIV infection should be treated with a 9-month regimen of isoniazid. Rifampin should not be used for an HIV-infected person who is being treated with a certain combination of antiretroviral therapy (ARV). In these cases, rifabutin may be given instead.
Study Questions 4.6 – 4.8

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

4.7 What conditions must be met to stop LTBI treatment for children, 5 years and younger, who were exposed to TB?

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

Answers to study questions are on pages 52 – 58.
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 be evaluated for LTBI treatment?

- Why or why not?

Answers to case study questions are on pages 59 – 62.
Treatment of Latent Tuberculosis Infection and Tuberculosis Disease

Patient Medical Evaluation and Monitoring for LTBI Treatment

Patient Medical Evaluation

All persons being considered for LTBI treatment should receive a medical evaluation. One reason for this evaluation is to exclude the possibility of TB disease. Treating TB disease with a LTBI treatment regimen (usually a single drug) can lead to drug resistance (see the Preventing Drug Resistance section in this Module, page 24). To rule out the possibility of TB disease, clinicians should determine whether the patient has symptoms of TB disease, and they should evaluate the patient with a chest x-ray. People with symptoms of TB disease or chest x-ray findings suggestive of TB disease should be given treatment for TB disease, not LTBI.

It is also important to determine whether the patient has ever been treated for TB infection or disease. In general, people who have been adequately treated should not be treated again. The TST or QFT-G cannot be used to determine whether a patient has received treatment for TB infection or disease. This is because most people who have a positive TST reaction will have another positive reaction if they are skin tested later in their lives, regardless of whether they have received treatment. Furthermore, there is currently not enough data on the ability of the QFT-G 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 (for example, immunocompromised people). Persons who complete LTBI treatment should be given documentation.

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

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

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

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 drugs.

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
- Establishment of a follow-up plan

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

**Adverse Reactions to Isoniazid**

Many health care providers have concerns about treating patients for LTBI. These concerns are generally related to the length of the treatment and the fact that sometimes medications cause adverse reactions, or negative side effects. As many as 10%-20% of people treated with isoniazid will have some mild, abnormal liver function tests results (tests done to detect damage 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 of LTBI treatment 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
- Dark urine

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

Isoniazid can damage the sensory nerves of the hands and feet. This is called peripheral neuropathy. The main symptom of peripheral neuropathy is a tingling sensation or a weakened sense of touch in the hands and feet. Some conditions, such as alcoholism, diabetes, and malnutrition, increase the risk for peripheral neuropathy. People with these conditions should be given vitamin B6, also known as pyridoxine. Vitamin B6 should also be given to pregnant or breastfeeding women who are taking isoniazid.

Patients taking rifampin should also be aware of possible adverse effects. Hepatitis is more likely to occur when rifampin is combined with isoniazid. Some other side effects from rifampin include:

- Rash
- Gastrointestinal symptoms (nausea, anorexia, and abdominal pain)
- Orange discoloration of urine, saliva, and tears; soft contact lenses may be permanently stained
- Increased sensitivity to the sun
- Interaction with other drugs, such as birth control pills and implants, warfarin, and methadone

**Patient Monitoring**

All patients taking LTBI treatment should be educated about the symptoms that are caused by adverse reactions to isoniazid and rifampin. These patients should be instructed to stop taking the medication and seek medical attention immediately if serious symptoms occur (Table 4.5).
All persons receiving LTBI treatment should also be evaluated at least monthly during therapy for:

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

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 providers immediately if they have any signs or symptoms of hepatitis (Table 4.5).

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 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 all patients, isoniazid 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.

**Treatment Follow-up**

Patients should receive documentation of TST or QFT-G 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 TB Infection* guidelines.
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 What are the symptoms of hepatitis?

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 52 – 58.
Case Study 4.2
A 65-year-old man is prescribed isoniazid LTBI treatment because he is a close 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 59 – 62.
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 even longer. Most of the tubercle bacilli are killed during the first 8 weeks of treatment (the initial phase). However, a few bacilli can survive. Therefore, treatment with at least two drugs must be continued for several more months to kill 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 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 initial regimen for treating TB disease should include the following four drugs (Figure 4.1):

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

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 ATS, CDC, and IDSA Treatment of Tuberculosis guidelines.
Drug resistance can develop when patients are prescribed an inappropriate regimen for treatment. TB disease must be treated with at least two drugs to which the bacilli are susceptible. Using only one drug to treat TB disease can create a population of tubercle bacilli resistant to that drug. When two or more 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, if they do not take their pills as often as prescribed, or both. When this happens, the patients may expose the bacilli to a single drug.

Drug resistance is more common in people who have spent time with someone with active drug resistant TB disease. Following are factors that increase the chance of a patient having or developing drug-resistant TB.

- Patient does not take their medicine regularly
- Patient does not take all of their medicine, as told by their health care provider
- Patient develops active TB disease again, after having taken TB medicine in the past
- Patient comes from areas of the world where drug-resistant TB is common

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

There are several options for daily and intermittent therapy. The recommended regimens are described in Table 4.3; the recommended dosages for the most common drugs are listed in Table 4.4. These tables are provided for you to use as a reference. For detailed information on TB Treatment, please refer to the ATS, CDC, and IDSA Treatment of Tuberculosis guidelines.

Figure 4.1 Drugs 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*

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Drugs</th>
<th>Interval and Doses(^\ddagger)</th>
<th>Interval and Doses(^{\ddagger})§</th>
<th>Range of Total Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>INH RIF PZA EMB</td>
<td>7 days/week for 56 doses (8 weeks) or 5 days/week for 40 doses (8 weeks)(^\ddagger)</td>
<td>7 days/week for 126 doses (18 weeks) or 5 days/week for 90 doses (18 weeks)(^\ddagger)</td>
<td>182-130 (26 weeks)</td>
</tr>
<tr>
<td>1a</td>
<td>INH RIF</td>
<td>7 days/week for 126 doses (18 weeks) or 5 days/week for 90 doses (18 weeks)(^\ddagger)</td>
<td>92-76 (26 weeks)</td>
<td></td>
</tr>
<tr>
<td>1b(^#)</td>
<td>INH RIF</td>
<td>2 days/week for 36 doses (18 weeks)(^\ddagger)</td>
<td>74-58 (26 weeks)</td>
<td></td>
</tr>
<tr>
<td>1c(^**)</td>
<td>INH RPT</td>
<td>1 day/week for 18 doses (18 weeks)(^\ddagger)</td>
<td>44-40 (26 weeks)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>INH RIF PZA EMB</td>
<td>7 days/week for 14 doses (2 weeks), then 2 days/week for 12 doses (6 weeks) or 5 days/week for 10 doses (2 weeks),(^\ddagger) then 2 days/week for 12 doses (6 weeks)</td>
<td>2 days/week for 36 doses (18 weeks)(^\ddagger)</td>
<td>62-58 (26 weeks)</td>
</tr>
<tr>
<td>2a(^#)</td>
<td>INH RIF</td>
<td>2 days/week for 36 doses (18 weeks)(^\ddagger)</td>
<td>44-40 (26 weeks)</td>
<td></td>
</tr>
<tr>
<td>2b(^**)</td>
<td>INH RPT</td>
<td>1 day/week for 18 doses (18 weeks)(^\ddagger)</td>
<td>44-40 (26 weeks)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>INH RIF PZA EMB</td>
<td>3 times weekly for 24 doses (8 weeks)</td>
<td>3 times weekly for 54 doses (18 weeks)(^\ddagger)</td>
<td>78 (26 weeks)</td>
</tr>
<tr>
<td>3a</td>
<td>INH RIF</td>
<td>3 times weekly for 54 doses (18 weeks)(^\ddagger)</td>
<td>78 (26 weeks)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>INH RIF EMB</td>
<td>7 days/week for 56 doses (8 weeks) or 5 days/week for 40 doses (8 weeks)(^\ddagger)</td>
<td>7 days/week for 217 doses (31 weeks) or 5 days/week for 155 doses (31 weeks)(^\ddagger)</td>
<td>273-195 (39 weeks)</td>
</tr>
<tr>
<td>4a</td>
<td>INH RIF</td>
<td>7 days/week for 217 doses (31 weeks) or 5 days/week for 155 doses (31 weeks)(^\ddagger)</td>
<td>(118-102) (39 weeks)</td>
<td></td>
</tr>
<tr>
<td>4b(^#)</td>
<td>INH RIF</td>
<td>Twice weekly for 62 doses (31 weeks)(^\ddagger)</td>
<td>(118-102) (39 weeks)</td>
<td></td>
</tr>
</tbody>
</table>

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

*For more information on strength of recommendation and quality of supporting evidence, refer to ATS, CDC, and IDSA MMWR Treatment of Tuberculosis Guidelines.

\(^\ddagger\) When DOT is used, drugs may be given 5 days/week and the necessary doses adjusted accordingly.

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

\(^\ddagger\) Patients on regimens given less than 7 days a week should receive DOT.

\(^\#\) Regimens give less than 3 times a week are not recommended for HIV-infected patients with CD4+ counts less than a 100.

\(^**\) Used only for HIV-negative patients with negative sputum smears at completion of 2 months of therapy and who do not have cavitation on initial chest x-ray. For patients started on this regimen and found to have positive culture from the 2-month specimen, treatment should be extended an extra 3 months.
### Table 4.4
Dosage Recommendations for the Treatment of TB in Adults and Children

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adults/Children²</th>
<th>Daily</th>
<th>1 time/week³</th>
<th>2 times/week³</th>
<th>3 times/week³</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH</td>
<td>Adults</td>
<td>5 mg/kg (300 mg)</td>
<td>15 mg/kg (900 mg)</td>
<td>15 mg/kg (900 mg)</td>
<td>15 mg/kg (900 mg)</td>
</tr>
<tr>
<td></td>
<td>Children</td>
<td>10-15 mg/kg (300 mg)</td>
<td>20-30 mg/kg (900 mg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RIF</td>
<td>Adults</td>
<td>10 mg/kg (600 mg)</td>
<td>10 mg/kg (600 mg)</td>
<td>10 mg/kg (600 mg)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Children</td>
<td>10-20 mg/kg (600 mg)</td>
<td>10-20 mg/kg (600 mg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RBT</td>
<td>Adults</td>
<td>5 mg/kg (300 mg)</td>
<td>5 mg/kg (300 mg)</td>
<td>5 mg/kg (300 mg)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Children</td>
<td>Appropriate dosing for children unknown</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RPT</td>
<td>Adults</td>
<td>10 mg/kg (600 mg) (continuation phase)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Children</td>
<td>This drug is not approved for use in children</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PZA</td>
<td>Adults</td>
<td>40-55 kg</td>
<td>18.2-25 mg/kg (1000 mg)</td>
<td>36.4-50 mg/kg (2000 mg)</td>
<td>27.3-37.5 mg/kg (1500 mg)</td>
</tr>
<tr>
<td></td>
<td>56-75 kg</td>
<td>20-26.8 mg/kg (1500 mg)</td>
<td>40-53.6 mg/kg (3000 mg)</td>
<td>33.3-44.6 (2500 mg)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>76-90 kg</td>
<td>22.2-26.3 mg/kg (2000 mg)</td>
<td>44.4-52.6 mg/kg (4000 mg)</td>
<td>33.3-39.5 mg/kg (3000 mg)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Children</td>
<td>15-30 mg/kg (2000 mg)</td>
<td>50 mg/kg (2000 mg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMB²</td>
<td>Adults</td>
<td>40-55 kg</td>
<td>14.5-20 mg/kg (800 mg)</td>
<td>36.4-50 mg/kg (2000 mg)</td>
<td>21.8-30 mg/kg (1200 mg)</td>
</tr>
<tr>
<td></td>
<td>56-75 kg</td>
<td>16-21.4 mg/kg (1200 mg)</td>
<td>37.3-50 mg/kg (2800 mg)</td>
<td>26.7-35.7 mg/kg (2000 mg)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>76-90 kg</td>
<td>17.8-21.1 mg/kg (1600 mg)</td>
<td>44.4-52.6 mg/kg (4000 mg)</td>
<td>26.7-31.6 mg/kg (2400 mg)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Children</td>
<td>15-20 mg/kg (1000 mg)</td>
<td>50 mg/kg (2500 mg)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

¹Although these regimens are broadly applicable, modifications may be needed for certain circumstances (patients on ARVs). For more information, refer to the ATS, CDC, and IDSA MMWR Treatment of Tuberculosis Guidelines.

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

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

⁴Ethambutol should be used with caution in young children since it is difficult to monitor their vision. However, if they have TB that is resistant to INH or RIF, dose of 15 mg/kg per day can be used.
Study Questions 4.14 – 4.17

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

4.15 Which four drugs are recommended for the initial treatment of TB disease?

4.16 Why should at least two drugs be used to treat TB disease?

4.17 Name two factors that can lead to drug resistance.

Answers to study questions are on pages 52 – 58.
Special Considerations

People Living with HIV
The management of HIV-infected TB patients can be complex and therefore medical experts should be involved in the care and treatment of the patients. The treatment regimens listed in Table 4.3 are also effective for people living with HIV with two exceptions:

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

HIV-infected TB patients should receive a minimum of at least 6 months of treatment and be closely monitored for their response to treatment. 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.

DOT should be used in all HIV-infected TB patients. If the HIV-infected TB patient is on ARVs, it is important to be aware of the interaction of rifampin with some ARV drugs. Rifabutin has fewer drug interaction problems and may be used as a substitute for rifampin.

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 preferred initial regimen for pregnant women who have TB is isoniazid, rifampin, and ethambutol for at least 9 months. In most cases, pyrazinamide should NOT be used because there is not enough information about how this drug affects the fetus. Streptomycin, a second-line TB drug, should NOT be used because it has been shown to have harmful effects on the fetus. Vitamin B6 supplements are recommended for all pregnant women who are taking isoniazid.
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 should not be considered to be effective treatment for LTBI or TB disease for the nursing infant. Vitamin B6 supplements are recommended for all women who are taking isoniazid and are breastfeeding.

Children and Adolescents
TB treatment in infants and children younger than 4 years of age should be started as soon as the diagnosis is suspected. It is recommended that children be treated for 6 months. Children commonly develop primary TB. Primary TB generally affects the mid and lower lung. Children should be treated with 3 (rather than 4) drugs in the initial phase (isoniazid, rifampin, and pyrazinamide). Ethambutol is generally not recommended for children, unless there is an increased chance of either isoniazid-resistance TB or TB that is consistent with reactivation TB (see New Terms, p.3). Pills given to children may have to be crushed or given in a liquid form. It is not recommended to treat children three times a week.

People with Extrapulmonary TB
In general, regimens that are used for treating pulmonary TB are also effective for treating extrapulmonary TB. However, infants and children with miliary TB, bone and joint TB, or TB meningitis should receive at least 9-12 months of treatment.
Alternative Regimens

Alternative regimens should be used for treating drug-resistant TB. The treatment of drug-resistant TB should always be done under the supervision of a medical expert 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). It can also be treated with rifampin and ethambutol for 12 months.

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 can last 2 years or longer. As a last resort, some patients with MDR TB undergo surgery to remove part of the infected site.

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 which is resistant to isoniazid and rifampin, plus resistant to any fluoroquinolone and at least one of three injectable second-line drugs (i.e., 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 regimens should be used for HIV-infected TB patients?

4.19 In what special situations should treatment for TB disease last longer than the usual course of treatment?

Answers to study questions are on pages 52 – 58.
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 the child should be treated?

Answers to case study questions are on pages 59 – 62.
Each TB patient should have a specific treatment and monitoring plan developed in collaboration with the local health department.

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

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 possible adverse reactions.

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

For detailed information on treating TB, refer to the ATS, CDC, and IDSA *Treatment of Tuberculosis* guidelines.

Monitoring for Adverse Reactions

Before starting treatment, adult patients should have certain baseline blood and vision tests to help detect any problems that may complicate treatment. For children, only vision tests are necessary unless there are other medical conditions 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.

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 4.5). The patients should be warned about the symptoms of insignificant (minor) side effects, such as the orange discoloration of the urine from rifampin, as well as the symptoms of potentially serious side effects, such as vomiting or abdominal pain. Patients should be instructed to seek medical attention immediately if they have symptoms of a serious side effect.

All patients should be seen by a clinician at least monthly during treatment and evaluated 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.
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. If a patient has symptoms of a serious adverse reaction, the public health worker should

- Instruct the patient to stop the medication if the symptoms are serious (before working with TB patients, public health workers should be educated about which symptoms are serious)
- Report the situation to a clinician and arrange for a medical evaluation right away
- Note the symptoms on the patient’s form
### Table 4.5
**Common Adverse Reactions to TB Drugs**

<table>
<thead>
<tr>
<th>Caused by</th>
<th>Adverse Reaction</th>
<th>Signs and Symptoms</th>
<th>Significance of Reaction*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any drug</td>
<td>Allergic</td>
<td>Skin rash</td>
<td>Serious</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Eye damage</td>
<td>Blurred or changed vision, Changed color vision</td>
<td>Serious</td>
</tr>
<tr>
<td>Isoniazid Pyrazinamide Rifampin</td>
<td>Hepatitis</td>
<td>Abdominal pain, Abnormal liver function test results, Dark urine, Fatigue, Fever for 3 or more days, Flulike symptoms, Lack of appetite, Nausea, Vomiting, Yellowish skin or eyes</td>
<td>Serious</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Nervous system damage</td>
<td>Dizziness, Tingling or numbness around the mouth</td>
<td>Serious</td>
</tr>
<tr>
<td></td>
<td>Peripheral neuropathy</td>
<td>Tingling sensation in hands and feet</td>
<td>Serious</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Stomach upset</td>
<td>Stomach upset, vomiting, lack of appetite</td>
<td>Serious</td>
</tr>
<tr>
<td></td>
<td>Increased uric acid</td>
<td>Abnormal uric acid level, Joint aches, Gout (rare)</td>
<td>Serious</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Bleeding problems</td>
<td>Easy bruising, Slow blood clotting</td>
<td>Serious</td>
</tr>
<tr>
<td></td>
<td>Discoloration of body fluids</td>
<td>Orange urine, sweat, or tears, Permanently stained soft contact lenses</td>
<td>Minor</td>
</tr>
<tr>
<td></td>
<td>Drug interactions</td>
<td>Interferes with certain medications, such as birth control pills, birth control implants, and methadone treatment</td>
<td>May be Serious or Minor</td>
</tr>
<tr>
<td></td>
<td>Sensitivity to the sun</td>
<td>Frequent sunburn</td>
<td>Minor</td>
</tr>
</tbody>
</table>

*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

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

4.21 Name the drug or drugs that may cause each of the following symptoms or adverse reactions.

Nervous system damage:

Hepatitis:

Eye damage:

Orange discoloration of the urine:

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

Answers to study questions are on pages 52 – 58.
Case Study 4.4
You are assigned to deliver medications to TB patients as part of the directly observed therapy 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?

Answers to case study questions are on pages 59 – 62.

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 a funny color.

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

Answers to case study questions are on pages 59 – 62.
In order to cure TB and prevent drug resistance, patients with TB must adhere to treatment.

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

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.

---

**Adherence to Treatment**

Treatment for TB disease lasts longer and requires more drugs than treatment for other infectious diseases. In order to cure TB and prevent drug resistance, patients with TB 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.

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. This method of treatment should be considered for all patients because there is no way to predict reliably 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 used for all children and adolescents. Even when drugs are given under DOT, tolerance of the medication must be monitored closely. Parents should not be relied on to supervise DOT.

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

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

Patients who are not receiving directly observed therapy should be monitored carefully for adherence to treatment.

The best way to ensure adherence to treatment is to use directly observed therapy.

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.

In summary, in order to prevent relapse and drug resistance, clinicians must prescribe an adequate regimen and make sure that patients adhere to treatment.

**Monitoring Patients’ Adherence to Therapy**

Patients who are not receiving directly observed therapy (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

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 directly observed therapy. For more information on patient adherence, please refer to *Self Study Modules on Tuberculosis, 6-9.*
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, all 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.

Public health workers who have regular contact with patients should pay attention to the patients’ improvement. If a patient has symptoms of TB (or of serious adverse reactions), they should report the situation to the clinician and arrange for a medical evaluation right away. They should also note the symptoms on the patient’s forms.

Second, clinicians can check a patient’s response to treatment by doing a bacteriologic examination of the sputum or other specimens. 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.

Third, clinicians can use x-rays to monitor a patient’s response to treatment. Repeated x-rays are not as important as monthly bacteriologic and clinical evaluations. However, an x-ray taken at the end of treatment can be compared with any follow-up x-rays taken subsequently should symptoms recur. 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.
The TST or QFT-G cannot be used to determine whether a patient is responding to treatment. This is because most people who have a positive TST result will have a positive result again if they are skin tested later in their lives, regardless of whether they have received treatment. Currently, there is not enough information on the use of QFT-G to determine treatment response (see Module 3, Targeted Testing and the Diagnosis of Latent Tuberculosis Infection and Tuberculosis Disease).

Treatment completion is defined by the number of doses that 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 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

Reevaluating the patient means checking for drug resistance by repeating the drug susceptibility tests and assessing whether the patient has been taking medication as prescribed.

The treatment of TB can be complicated, especially in patients who fail to respond to treatment, who relapse, or who have drug-resistant TB or 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 medical expert.
Study Questions 4.23 – 4.27

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

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

4.25 How can clinicians determine whether a patient is responding to treatment?

4.26 Under what circumstances should patients be reevaluated?

4.27 What does reevaluating the patient mean?

Answers to study questions are on pages 52 – 58.
Mr. Vigo was diagnosed with smear-positive pulmonary TB 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 him 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 59 – 62.
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**. There are three elements of case management:

- Assignment of a health department employee to manage specific patients
- Systematic regular review of each patient’s treatment progress
- Plans to address barriers to adherence

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 continuous.

Many public health workers provide directly observed therapy (DOT) 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 if the symptoms are serious (Before working with TB patients, public health workers should be educated about which symptoms are serious)
- Report the situation to a clinician and arrange for a medical evaluation right away
- Note the symptoms on the patient’s form
Public health workers can help monitor a patient’s response to treatment for TB disease by looking for symptoms of TB disease. 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 TB disease usually have symptoms at the beginning of therapy, such as coughing, fatigue, and fever. 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.

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 Self Study Modules on Tuberculosis, 6-9.
Study Question 4.28-4.29

4.28 What are the three elements of case management?

4.29 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 52–58.
Case Study 4.7

Ms. DeVonne began treatment for pulmonary TB disease 2 months ago, at the beginning of September. You have been giving her directly observed therapy. During the first few weeks of therapy, you noticed that Ms. DeVonne’s symptoms were improving a little. However, at a visit 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 59 – 62.
**SUMMARY**

LTBI treatment is medication that is given to people who have TB infection to prevent them from developing TB disease. Some people with LTBI are at higher risk of developing TB disease, and they should be evaluated and receive higher priority for LTBI treatment if they have a positive TST or QFT-G result. All patients being considered for LTBI treatment should receive a medical evaluation 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
- Determine if patient is taking a medication which may interact with LTBI treatment drugs

Generally, people who have already completed treatment for LTBI or TB disease do not need to be retreated again for LTBI.

The usual regimen for LTBI treatment is isoniazid given daily for 9 months for both adults and children. Sometimes LTBI treatment is given to people who have a negative TST or QFT-G result, such as high-risk contacts and children younger than 6 months old who have been exposed to TB.

Patients should be evaluated every month for signs of hepatitis and other adverse reactions to isoniazid. They should also be educated about the symptoms caused by serious adverse reactions to isoniazid and instructed to seek medical attention immediately if these symptoms occur. In addition, people at greatest risk for hepatitis should have liver function tests before starting LTBI treatment and during therapy.

Patients should be given documentation of LTBI treatment upon completion.

TB disease must be treated for at least 6 months; in some cases, treatment lasts even longer. The initial regimen for treating TB disease should include four drugs: isoniazid, rifampin, pyrazinamide, and ethambutol. When the drug susceptibility results are available, clinicians may change the regimen accordingly. The TB treatment regimen must include at least two drugs to which the bacilli are susceptible. Using only one drug to treat TB disease can create a population of tubercle bacilli that is resistant to that drug. Drug resistance can also develop when patients do not take treatment as prescribed. Thus, to prevent relapse and drug resistance, clinicians must prescribe an adequate regimen and make sure that patients adhere to treatment. The best way to ensure that patients adhere to treatment is to use directly observed therapy.

There are several options for daily and intermittent therapy. Treatment may last longer or involve different regimens for children with certain types of extrapulmonary TB, pregnant women, people living with HIV, or people with drug-resistant TB. For people living with HIV and people with drug-resistant TB, treatment should be provided under the supervision of a medical expert who is familiar with the treatment.
All patients being treated for TB disease should be educated about the symptoms caused by adverse reactions to the drugs they are taking and instructed to seek medical attention immediately if they have symptoms of a serious side effect. Patients should be seen by a clinician at least monthly during treatment and evaluated for possible adverse reactions. In addition, before starting treatment, patients should have baseline tests to help clinicians detect any abnormalities that may complicate treatment.

Patients who are not receiving directly observed therapy should be carefully monitored for adherence to treatment. However, the only way to ensure adherence to treatment is to use directly observed therapy.

To determine whether a patient is responding to treatment, clinicians should do clinical evaluations and bacteriologic evaluations during treatment. Patients should be carefully reevaluated if their

- Symptoms do not improve during the first 2 months of treatment
- Symptoms worsen after improving initially
- Culture results have not become negative after 2 months of treatment
- Culture results become positive after being negative

In certain situations, clinicians may also use chest x-rays to monitor a patient’s response to treatment.

The treatment of TB can be complicated, especially in patients who fail to respond to treatment, who relapse, or who have drug-resistant TB or adverse reactions to medications. Clinicians who do not have experience with these situations should consult a medical expert.

Successful TB treatment is the responsibility of the medical providers and the health care workers, not the patient. Case management is a strategy that can be used to ensure patients complete TB treatment. At each visit with a patient, public health workers should look for signs and symptoms of adverse reactions to the medication. If a patient has symptoms of a serious adverse reaction, the public health worker should

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

Also, public health workers should pay attention to the patient’s improvement. If a patient has symptoms of TB, public health workers should

- Report the situation to a clinician and arrange for a medical evaluation right away
- Note the symptoms on the patient’s form
Additional Reading


CDC. Interactive Core Curriculum on Tuberculosis [online course]. Atlanta, GA: Department of Health and Human Services, CDC; 2004.  www.cdc.gov/tb


4.1 **What is the purpose of LTBI treatment?** (page 4)
The purpose of LTBI treatment is to prevent people with latent TB infection from developing TB disease.

4.2 **Which groups of people should receive high priority for LTBI treatment if they have a positive QFT-G result or TST reaction with an induration that is 5 millimeters or larger? Name four.** (page 5)
- People with HIV infection
- Recent close contacts of people with infectious TB disease
- People with chest x-ray findings suggestive of previous TB disease
- Patients with organ transplants
- Other immunosuppressed patients (such as patients on prolonged therapy with corticosteroids, equivalent to taking 15 mg or more of prednisone for at least 1 month, or those taking TNF-alpha antagonists)

4.3 **Which groups of people should receive high priority for LTBI treatment if they have a positive QFT-G result or TST reaction with an induration that is 10 millimeters or larger? Name seven.** (page 5)
- People who have come to the U.S. within the last 5 years from areas of the world where TB is common (for example, Asia, Africa, Eastern Europe, Russia, or Latin America)
- People who inject illegal drugs
- People who live or work in high-risk facilities (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 appear to increase the risk for TB disease (silicosis, diabetes mellitus, severe kidney disease, certain types of cancer, and certain intestinal conditions)
- Children younger than 4 years old
- Infants, children, and adolescents exposed to adults in high-priority groups

4.4 **What is the preferred LTBI treatment regimen?** (page 8)
The preferred regimen for LTBI treatment is isoniazid given daily for 9 months. 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.
4.5 What LTBI treatment regimen may be recommended for people with a positive TST or QFT-G result who have been exposed to isoniazid-resistant TB? (page 8)
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 QFT-G result? (pages 11-12)
Some close contacts may start taking LTBI treatment if they have a negative skin test but less than 8 to 10 weeks have passed since they were last exposed to TB. These contacts include:

- Children who are 5 years old or younger (some TB programs may have different age cutoff guidelines)
- People living with HIV
- Other immunosuppressed persons who may develop TB disease quickly after infection

Because less than 8 to 10 weeks have passed since they were last exposed to TB, these contacts may be infected with *M. tuberculosis* but have a false-negative TST reaction (see Module 3, Targeted Testing and the Diagnosis of Latent Tuberculosis Infection and Tuberculosis Disease). Once active TB disease is ruled out, they should start LTBI treatment to prevent them from rapidly developing TB disease. These contacts should be retested 8 to 10 weeks after they were last exposed to TB. If they have a negative TST or QFT-G, they can stop taking the LTBI treatment. If they have a positive TST or QFT-G result, they should continue to take LTBI treatment. HIV-infected contacts or others with a weakened immune system may be given a full course of LTBI treatment regardless of their TST or QFT-G result.

4.7 What conditions must be met to stop LTBI treatment for children, 5 years and younger, who were exposed to TB? (page 13)
Children 5 years and younger who have been exposed to TB should start taking the LTBI treatment, even if they have a negative skin test or QFT result. The children should be retested 8 to 10 weeks after they were last exposed to TB. The LTBI treatment can be stopped if all of the following conditions are met:

- The second skin test is negative.
- The second skin test was done 8 to 10 weeks after the child was last exposed to TB.
- The child is at least 6 months old.

4.8 When should pregnant women be treated for LTBI and for how long? (page 14)
For most pregnant women with TB infection, LTBI treatment can be delayed until after delivery. If the pregnant woman is HIV-infected or a recent contact 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. (page 17-18)
All patients being considered for LTBI treatment should receive a medical evaluation 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? (page 17)
It is important to exclude the possibility of TB disease because treating TB disease with a LTBI treatment regimen (usually a single drug) can lead to drug resistance.

4.11 What are the symptoms of hepatitis? (page 18)
The common symptoms of hepatitis are nausea, vomiting, abdominal pain, fatigue, and dark urine.

4.12 Who is at greatest risk for hepatitis? What special precautions should be taken for these patients? (page 20)
The people at greatest risk for hepatitis are
- 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 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 isoniazid LTBI treatment, and during therapy.

4.13 How often should patients be evaluated for signs and symptoms of adverse reactions during LTBI treatment? (page 20)
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? (page 23)
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 initial phase). However, a few bacilli can survive. Therefore, treatment must be continued for several more months to kill 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 four drugs are recommended for the initial treatment of TB disease? (page 23)
The initial regimen for treating TB disease should include isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB). When the drug susceptibility results are available, clinicians may change the regimen accordingly.

4.16 Why should at least two drugs be used to treat TB disease? (page 24)
Using only one drug to treat TB disease can create a population of tubercle bacilli that is resistant to that drug. When two or more drugs are used together, each drug helps prevent the emergence of bacilli that are resistant to the other drugs.

4.17 Name two factors that can lead to drug resistance. (page 24)
Drug resistance can develop when patients are prescribed an inappropriate regimen for treatment or when patients do not follow treatment regimens as prescribed.

4.18 What treatment regimens should be used for HIV-infected TB patients? (page 29)
The treatment regimens for HIV-infected TB patients are generally the same as for TB patients without HIV-infection with two exceptions:
- Once weekly administration of isoniazid and rifapentine in the continuation phase should not be used in any HIV-infected patient.
- Patients with advanced HIV (CD4 counts less than 100) should be treated with daily or three times weekly therapy in both the initial and continuation phase

HIV-infected TB patients should receive a minimum of at least 6 months of treatment and be closely monitored for their response to treatment. 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.

DOT should be used in all HIV-infected TB patients. If the HIV-infected TB patient is on ARVs it is important to be aware of the interaction of rifampin with some ARV drugs. Rifabutin has fewer drug interaction problems and may be used as a substitute for rifampin.
4.19 In what special situations should treatment for TB disease last longer than the usual course of treatment? (pages 29-31)

- HIV-infected TB patients should receive a minimum of at least 6 months of treatment and be closely monitored for their response to treatment. 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 should receive at least 9 months of treatment, if PZA is not used.
- Infants and children with miliary TB, bone and joint TB, or TB meningitis should receive at least 9-12 months of treatment.
- Treatment for isoniazid-resistant TB can last 12 months when a regimen of rifampin and ethambutol is used; treatment for multidrug-resistant TB can last 2 years or longer.

4.20 What should be included in each patient’s treatment plan? (page 34)

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

4.21 Name the drug or drugs that may cause each of the following symptoms or adverse reactions. (page 36)

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

4.22 How often should patients be monitored for adverse reactions to TB drugs? (page 34)

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. (page 40)

- 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? (page 39)

The best way to ensure adherence to therapy is to use directly observed therapy. Directly observed therapy 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? (pages 41)

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.

4.26 Under what circumstances should patients be reevaluated? (pages 42)

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

4.27 What does reevaluating the patient mean? (page 42)

Reevaluating the patient means checking for drug resistance by repeating the drug susceptibility tests and assessing whether the patient has been taking medication as prescribed.
4.28 What are three elements of case management? (page 45)
A strategy that may be used to ensure patient’s complete TB treatment is case management. There are three elements of case management
- Assignment of a health department employee to manage specific patients
- Systematic regular review of each patient’s treatment progress
- Plans to address barriers to adherence

4.29 What should a public health worker do if he or she notices that a patient has symptoms of an adverse reaction? (page 45)
The public health worker should
- Instruct the patient to stop the medication if the symptoms are serious (before working with TB patients, public health workers should be educated about which symptoms are serious)
- Report the situation to a clinician and arrange for a medical evaluation right away
- Note the symptoms on the patient’s form
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 start LTBI treatment?**
  Yes, both should start LTBI treatment.

- **Why or why not?**
  The wife is a close contact of someone with infectious TB disease, and she has a positive skin test (5 mm for close 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 close 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. In other words, her TST reaction may be a false-negative. 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 8-10 weeks after she last spent time with her father. If she has a negative TST or QFT-G result on the repeat test, she may stop taking the medicine. If she has a positive TST or QFT-G result, she should complete an entire course of LTBI treatment (9 months for children).
4.2 A 65-year-old man is prescribed isoniazid LTBI treatment because he is a close 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?**

  Even though his liver function tests are normal, this man is at high risk of isoniazid-associated hepatitis because he is older than 35 and abuses alcohol. 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 and was treated with a 6-month regimen. The medical evaluation of the child confirms the diagnosis of TB meningitis.

- **How long should the child be treated?**

  Infants and children with miliary TB, bone and joint TB, or TB meningitis should be treated for at least 12 months.

4.4 You are assigned to deliver medications to TB patients as part of the directly observed therapy 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?**

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

  - [ ] That he is not taking his medications as prescribed,
  - [ ] That 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 directly observed therapy if possible.
Ms. DeVonne began treatment for pulmonary TB disease 2 months ago, at the beginning of September. You have been giving her directly observed therapy. During the first few weeks of therapy, you noticed that Ms. DeVonne’s symptoms were improving a little. However, at a visit 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 directly observed therapy, 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.