

TUBERCULOSIS AND HIV DISEASE



Tuberculosis (TB) is caused by a bacterium called *Mycobacterium tuberculosis*. It usually infects the lungs, but it can also enter the blood and infect almost any part of the body. This includes the liver, kidneys, stomach and gut, bones, skin, breasts, brain and spinal cord. TB in these places is more common in children and people with weak immune systems, including people living with HIV.

A PUBLICATION FROM

PROJECT
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Information,
Inspiration and
Advocacy for People
Living With HIV/AIDS

NOVEMBER 2004

TB is spread when a person with active TB disease coughs, sneezes or spits. Tiny droplets of fluid from the lungs are carried in the air and if other people breathe in these droplets they can get infected. TB can also pass from a mother to her unborn child before and after birth. However, it's more common for a baby to catch it after birth, due to close contact with its mother.

If you or someone you live with has TB, you are all at risk for TB infection and TB screening is recommended for the whole family. Depending on your health and the health of people you live with, TB preventive therapy might be recommended for others in your household.

You are not likely to catch TB from a stranger coughing on a bus. Even if a healthy person spends 24 hours a day for two months with someone with active disease, there's still only a 50% chance that he or she will catch TB, though certainly people with weakened immune systems are more at risk.

TB infection and disease

TB infection is not the same as having TB disease. For most people who are exposed to TB bacteria and become infected, the immune system can stop the bacteria from growing. Nine out of ten people with healthy immune systems who are infected with TB do not get

active disease. They feel well and cannot spread TB to others. This is also true for people who have active TB disease but not in their lungs. Most people with active disease can no longer pass on TB after about three weeks of treatment.

TB disease develops when the immune system cannot fight off the infection. People with HIV are ten times more likely to develop active TB than HIV-negative people. For this reason, routine TB screening and appropriate preventive therapy and treatment, when needed, is critical for people living with HIV.

TB is an ever-increasing concern for people with HIV. In some parts of the world, TB is the leading cause of death of people with HIV. In the U.S., TB prevention and control efforts have been strengthened. However, in environments with crowded living conditions and poor ventilation, such as homeless shelters, nursing homes and prisons, TB is more common. Young children, seniors and people of color are also at an increased risk of developing active TB disease. In addition, the following factors put a person at an increased risk for developing active TB disease: pregnancy, HIV, diabetes, long-term kidney failure, poor nutrition, alcohol and/ or injection drug use.

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What are the symptoms?

Not all people with TB have symptoms unless they have active disease. The most common place for active TB is in the lungs and symptoms include a prolonged cough (lasting over 2 weeks), pain in the chest and coughing up fluid (sometimes with blood). A chart of symptoms is shown in the box below. Children infected with TB near their time of birth may have TB in many organs. They may have difficulty breathing or feeding and fail to grow at the normal rate.

Some symptoms of TB disease are similar to symptoms of other common HIV-related infections like toxoplasmosis, *Pneumocystis carinii* pneumonia (PCP) and *Mycobacterium avium* complex (MAC). Therefore, it's important to make sure that when symptoms appear they are appropriately diagnosed and treated the right way.

TB and HIV disease

For many people, TB is the first sign of immune dysfunction associated with HIV infection, and active TB is an AIDS-defining illness. One in ten people living with HIV will get active TB within a year of being diagnosed with HIV. It can occur early in HIV disease when CD4+ cell counts are relatively high, in the 300–400 range. In early HIV infection, TB usually infects and affects just the lungs. As CD4+ cell counts drop, however, TB is more likely to appear in other organs too.

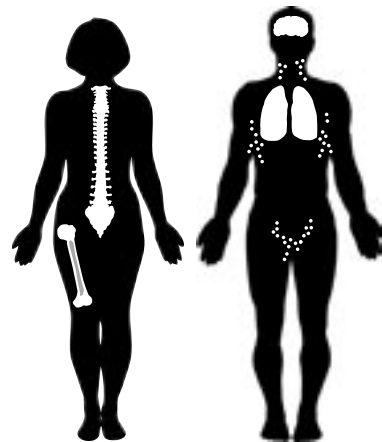
When the immune system responds to TB it can cause HIV levels to increase, and HIV disease may then progress more quickly. This, in turn, increases the risk of other opportunistic infections. The good news is that TB treatment leads to lower HIV levels in people with both infections.

It's very important for people with HIV to be screened regularly for TB. TB testing is recommended to begin when a person is first diagnosed with HIV, then yearly after that. Also, when starting anti-HIV therapy, a TB test is also recommended. Finally, for people living with HIV who come into contact with someone with active TB, a TB test is recommended.

Whether you have TB infection or active TB disease, it's extremely important to get treated right away. If you are diagnosed with TB and HIV at the same time, you may not want to start treating both at the same time. It might be easier to stick to your regimens if you start the anti-TB treatment first and wait awhile before starting anti-HIV therapy. This might not always be possible, but it's something to discuss with your doctor.

symptoms of active TB disease

BODY LOCATION	SYMPTOMS
General	Feeling tired and/or weak, loss of appetite, nausea, weight loss, fever and chills, night sweats
Lungs	Cough lasting over 2 weeks, chest pain, coughing up fluid (sometimes with blood)
Spinal cord/brain (meninges)	Headache, coma
Lymph nodes	Lymph node swelling
Bone marrow	Anemia
Back/vertebrae (Pott's disease)	Back pain, paralysis



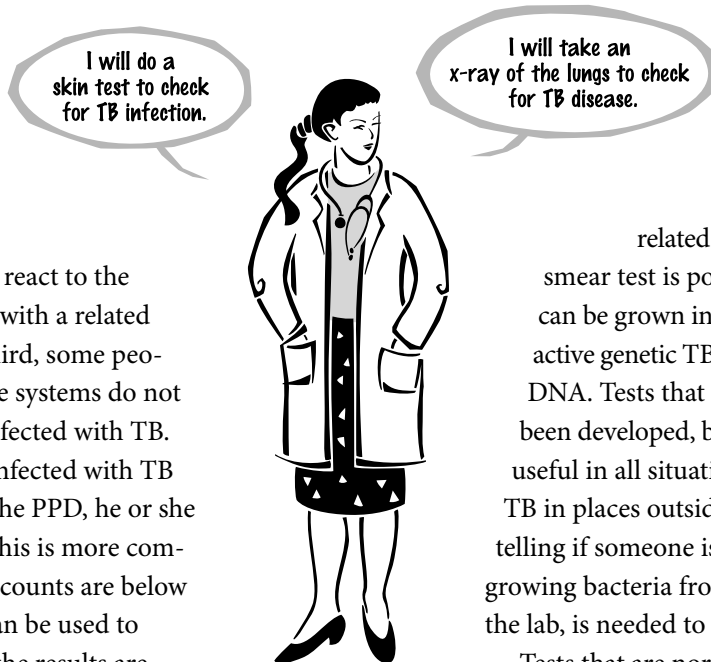
How does a doctor diagnose TB infection?

A PPD skin test is used to detect TB infection. A small amount of liquid (called PPD Tuberculin) is injected under the skin of the arm. After 48–72 hours, a nurse or doctor reads the test. A hard swelling at the site larger than 10mm means that the person is infected with TB. A smaller swelling of 5mm is used to detect TB infection in people with HIV. This is because people with HIV might not have a strong immune response resulting in the more pronounced swelling seen in people who are HIV-negative and otherwise healthy.

Unfortunately, the PPD test is not 100% accurate for three main reasons. First, the reaction is caused by an immune response, and this may take awhile to develop. There actually may be no reaction within the first 10–12 weeks after infection.

Second, a person may react to the test if they're infected with a related bacteria like MAC. Third, some people with weak immune systems do not react even if they're infected with TB.

When a person is infected with TB but does not react to the PPD, he or she is said to be *anergic*. This is more common when CD4+ cell counts are below 200. A different test can be used to check for anergy, but the results are not very reliable in people living with HIV. Anergy testing is not routinely used, but it may be helpful in certain cases. So, a negative PPD test result does not always mean that a person is free of TB. For this reason, routine testing is very important.



How does a doctor diagnose TB disease?

Chest x-rays are used to detect active TB disease and to check for damage in the lungs. During or after active TB, x-rays will show lumps, holes or scars in the lungs. Chest x-rays may provide misleading or confusing results, however, because a chest x-ray may look unusual due to HIV or other HIV-related complications, including PCP and MAC. This is especially true for people with CD4+ cell counts below 200. This can make TB more difficult to diagnose in people living with HIV.

The best proof that a person has TB is to find the actual bacteria. In a TB smear test, a sample of sputum

is studied under a microscope to see if it contains the bacteria. Unfortunately, it cannot tell the difference between TB and

related bugs like MAC. If the smear test is positive, then the sputum can be grown in a lab to see if it contains active genetic TB material, called TB DNA. Tests that detect TB DNA have been developed, but are not routinely useful in all situations, such as diagnosing TB in places outside the lungs or definitely telling if someone is TB-negative. Also, growing bacteria from a sputum sample, in the lab, is needed to test for drug resistance.

Tests that are normally used to look for active TB in other organs include scans of the head, chest or abdomen; spinal tap; biopsy of lymph nodes or bone marrow; and urine culture.

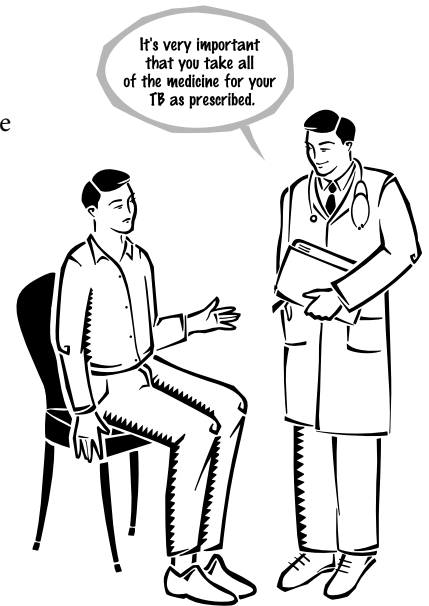
Treating active TB

The effectiveness of anti-TB treatment is quite good, regardless of HIV infection. However, it is vital that people take the full course of drugs in order to kill all the TB and to prevent the development of anti-TB drug resistance or recurrence of active TB disease. People on anti-TB drugs are generally encouraged to see their doctors at least once a month and maybe more often at the start of treatment. This is to check whether the drugs are working, to identify adherence problems (problems with taking the drugs as prescribed), and to monitor for side effects or reactions.

Treating TB in the lungs and other organs is the same and usually lasts for six months, although widespread TB may require taking anti-TB therapies for a longer period of time. Treating TB in the brain (*meninges*), bones or joints might require at least nine months of therapy. If anti-TB treatment doses are missed for any reason, longer courses of treatment are likely necessary. Also, people who don't respond quickly to the normal course of therapy might need to continue on anti-TB for nine months or longer.

Symptoms of active TB disease usually ease off 3–4 weeks after starting anti-TB treatment. When a person has had three negative smear tests, he or she is considered to be non-infectious, or not likely to be able to infect others with TB. This usually occurs 2–3 months after starting anti-TB treatment.

The first line treatment for TB disease is a combination of four drugs that includes isoniazid (Nydrazid) 300mg/day, rifampin (Rifadin, Rimactane) 450–600mg/day, pyrazinamide (Tebrazid) 20–30mg/kg/day, and ethambutol (Myambutol) 15–25mg/kg/day or streptomycin sulfate 15mg/kg/day. These five drugs are given and resistance testing is performed. If the resistance test shows that the TB can be killed by isoniazid and rifampin, then the ethambutol or streptomycin can be stopped. The US Public Health guidelines recommend that people with HIV taking isoniazid also take pyridoxine (Vitamin B6) because they are at higher risk for developing peripheral neuropathy.



six-month treatment plans for TB

standard plan

- 4 drugs daily for 2 months, then isoniazid + rifampin daily for 4 months

modified plans

- 4 drugs daily for 2 months, then isoniazid + rifampin 2-3 times a week for 4 months (preferred for children); or
- 4 drugs daily for 2 weeks, then 4 drugs 2-3 times a week for 6 weeks, then isoniazid + rifampin 2 times a week for 4 months; or
- 4 drugs 3 times a week for 6 months

(Doses must be increased if they're given less often than once a day.)

first line anti-TB drugs

DRUG	SIDE EFFECTS	POTENTIAL INTERACTIONS	NOTES
ethambutol (Myambutol)	rash, joint pain, gut upset, fever, headache, dizziness, eyesight problems	antacids	Check eyesight often. Drug assistance program: 1-800-859-8586.
isoniazid (Nydrazid)	gut upset, loss of appetite, fever, rash, liver problems, peripheral neuropathy	phenytoin, antacids, alcohol, steroids	Take on an empty stomach. Take pyridoxine (vitamin B6) to prevent peripheral neuropathy. Monitor liver function.
pyrazinamide (Tebrazid)	gut upset, fever, rash, joint pain, hepatitis, gout, light sensitivity	protease inhibitors, NNRTIs, <i>azole</i> antifungal drugs, oral contraceptives, methadone, dapsone	Monitor liver function.
rifampin (Rifadin, Rimactane)	gut upset, rash, fever, orange urine/tears/saliva, light sensitivity, liver problems, acute renal failure		Take on an empty stomach.

second line anti-TB drugs

DRUG	SIDE EFFECTS	POTENTIAL INTERACTIONS	NOTES
amikacin (Amikin)	inner ear damage, kidney problems, joint pain	some antibiotics, diuretics	Must be injected. Contraindicated for pregnant women.
capreomycin (Capastat)	inner ear damage, kidney problems	some antibiotics	Must be injected. Contraindicated for pregnant women.
ciprofloxacin (Cipro)	nausea, diarrhea, stomach cramps, headache, rash, seizures, allergic reaction	antacids, caffeine	Drug assistance program: 1-800-998-9180.
clofazimine (Lamprene)	gut upset with severe cramps, rash, eye irritation, coloring of skin and body fluids		Take with food.
cycloserine (Seromycin)	dizziness, headache, mood changes, seizures, neuropathy	alcohol, ethionamide, isoniazid	
ethionamide (Trecator)	gut upset, rash, loss of appetite, liver problems		
kanamycin	inner ear damage, kidney problems		Contraindicated for pregnant women.
levofloxacin (Lеваquin)	gut upset, sleep problems, headaches	antacids, insulin	
ofloxacin (Floxin)	gut upset, rash, dizziness, sleep problems, anxiety, headache, seizures, allergic reaction, thrush	antacids	
para-aminosalicylic acid	gut upset, liver problems		
rifabutin (Mycobutin)	gut upset, rash, eye inflammation, blood cell changes, joint pain, orange urine/tears/saliva, liver function changes, fever	protease inhibitors, fluconazole, oral contraceptives, steroids, methadone	Avoid wearing soft contact lenses as they can become discolored.
rifapentine (Priftin)	gut upset, rash, hepatitis, orange urine/tears/saliva, light sensitivity, acute renal failure, fever	alcohol, protease inhibitors, oral contraceptives	Long-acting form of rifampin taken once or twice a week. Drug assistance program: 1-800-221-4025.
streptomycin	nausea, rash, inner ear damage, kidney problems	some antibiotics	Monitor hearing. Contraindicated for pregnant women. Drug assistance program: 1-800-254-4445.

Using rifampin and rifabutin with anti-HIV drugs

Rifampin interacts with protease inhibitor (PI) and non-nucleoside reverse transcriptase inhibitor (NNRTI) drugs. So people taking these classes of drugs should use rifabutin (Mycobutin, a treatment for MAC) rather than rifampin for treating TB.

There are a few exceptions to this general rule including when a person is taking 1) efavirenz and two nucleoside analogues (NRTIs); 2) ritonavir and one or two NRTIs; or 3) ritonavir, saquinavir and a NRTI. However, if it is taken with ritonavir, the dose of rifabutin has to be dropped to 150mg 2–3 times a week. Lower doses may also be needed with other PIs. If rifabutin is used with efavirenz, its dose should be raised to 450–600mg daily, or 600mg 2–3 times a week.

The bottom line is that drug interactions are a concern with anti-HIV therapies and some anti-TB drugs. Ask your doctor and pharmacist about the safety and appropriateness of taking your therapies together and if any dose modifications are needed because of drug interactions.

For people taking both PIs and NNRTIs, it may be hard to predict what effect rifabutin will have. If you're taking these drugs, it's wise to be checked often by your doctor for drug levels and side effects.

Unusual reactions to treatment

Some people find that their TB gets worse when they start treatment. This more often happens when people are starting anti-HIV therapies for the first time. As HIV levels drop and the immune system starts to work better due to anti-HIV treatment, the immune system begins to respond to the TB and this can cause physical symptoms like fever, swelling of lymph nodes and even worsening of chest x-rays. This effect often doesn't last very long and switching anti-TB or anti-HIV drugs is probably not necessary. In some instances, however, the symptoms may get severe and might even require hospitalization. A short course of steroids may help control the symptoms.

Side effects

The list of side effects for anti-TB drugs shown in the charts on page 5 is not complete. It's important to discuss all possible side effects with your doctor as well as discuss any other drugs you take. For example, people with HIV may be more likely to get peripheral neuropathy when using isoniazid (Nydrazid). You may also have more skin problems from these drugs.

drug i.d. chart

TRADE NAME	GENERIC NAME
Protease inhibitor	
Agenerase	amprenavir
Aptivus	tipranavir
Crixivan	indinavir
Invirase	saquinavir hgc
Kaletra	lopinavir+ritonavir
Lexiva	fosamprenavir
Norvir	ritonavir
Prezista	darunavir
Reyataz	atazanavir
Viracept	nelfinavir
Nucleoside (NRTI) and nucleotide (NtRTI) analogue reverse transcriptase inhibitor	
Combivir	3TC+AZT
Emtriva	emtricitabine (FTC)
Epivir	lamivudine (3TC)
Epzicom	3TC+abacavir
Retrovir	zidovudine (AZT)
Trizivir	3TC+AZT+abacavir
Truvada	FTC+tenofovir
Videx	didanosine (ddI)
Videx EC	didanosine enteric-coated (ddI EC)
Viread	tenofovir
Zerit	stavudine (d4T)
Ziagen	abacavir
Non-nucleoside reverse transcriptase inhibitor (NNRTI)	
Rescriptor	delavirdine
Sustiva	efavirenz
TMC-125	etravirine
Viramune	nevirapine
NRTI + NNRTI	
Atripla	Emtriva+Sustiva+Viread
Entry inhibitor	
Fuzeon	enfuvirtide (T20)
Selzentry	maraviroc
Integrase inhibitor	
Isentress	raltegravir

Coping with treatment

Anti-HIV therapy requires the use of many pills. Adding multi-drug anti-TB regimens on top of anti-HIV therapy can be daunting. Some people find it difficult to cope with taking the large number of pills, daily, required for treating both HIV and TB. There are options to explore that might help to make this easier:

- ▶ short-course anti-TB treatments
- ▶ anti-TB regimens that are taken 2–3 times per week rather than daily
- ▶ combination pills (one pill that includes two or more drugs), like Rifamate (rifampin/isoniazid) or Rifater (rifampin/isoniazid/pyrazinamide)
- ▶ use of long-acting drugs, like rifapentine (Priftin), that require less frequent dosing
- ▶ use of reminders, rewards and practical support, like childcare and transportation
- ▶ directly observed therapy (DOT)

DOT is advised for all people living with both HIV and TB. DOT involves receiving drugs daily from a healthcare worker who gives you the medication and watches you take it. DOT is intended to help people adhere to medication, decrease the risk of developing resistance, decrease recurrence of TB disease and hopefully contain the spread of TB.

How to reduce the spread of TB

Steps can be taken to stop the spread of active TB. People with active disease are often isolated until they are no longer infectious. This sometimes includes staying in hospital rooms with special airflow,

called negative airflow, where air is circulated out of the room with new air constantly coming in to reduce the risk of TB in the air. Some low income and residential hotels and shelters are remodeling to include negative airflow devices to help contain the spread of TB. Also, to prevent spreading TB, someone with active TB can take simple precautions such as covering their nose and mouth when coughing or sneezing. Also, health-care workers and caretakers can use disposable breathing masks to reduce their risk of contagion.



For more treatment information, call Project Inform's toll-free National HIV/AIDS Treatment Information Hotline at 1-800-822-7422.

Drug resistance

Over the past decade there has been an increase in the appearance of strains of TB that are resistant to two or more anti-TB drugs. These strains are called multi-drug resistant TB, or MDR-TB. Resistance can occur if someone does not take a full course of treatment or if an extra drug is merely added to an already failing anti-TB therapy regimen. Once someone has developed drug-resistant TB they can transmit that TB to others, leaving those newly infected with fewer treatment options. Drug-resistant TB is more difficult to treat and more likely to cause death as a consequence.

In 1997, over 7% of TB strains were resistant to at least isoniazid, and 1.3% were resistant to at least isoniazid and rifampin. People with HIV are six times more likely to have MDR-TB than HIV-negative people. MDR-TB is three times more likely than drug-sensitive TB to cause active disease in HIV-positive people.

Below shows treatment plans for TB resistant to either rifampin or isoniazid. If there is resistance to both, at least three new potent drugs should be used. Treatment may take up to 24 months, and sometimes seven or more drugs are needed.

Treating MDR-TB usually includes the use of an aminoglycoside (amikacin [Amikin], capreomycin [Capastat], etc.) and a fluoroquinolone (ciprofloxacin [Cipro], ofloxacin [Zagam], etc.). Aminoglycosides (streptomycin, kanamycin and amikacin) should not be used during pregnancy because it can harm the unborn baby. Other drugs include rifabutin, cycloserine (Seromycin), ethionamide (Trecator-SC), clofazamine (Lamprene) and para-aminosalicylic acid. After treatment has finished, patients are encouraged to see their doctor every four months for two years to check for TB recurrence.

In more severe cases of TB, surgery may be used to remove infected tissue. Steroids are sometimes used to reduce inflammation and control tissue damage, as is the case when TB affects the brain.

Preventing active disease

People with TB infection can take drugs to help prevent them from developing active disease. This is called TB prevention or prophylaxis. People living with HIV are encouraged to consider TB preventive therapy if TB skin testing has come back positive, if there has been contact with someone with active TB disease or if it's determined that a prior episode of TB disease was not treated properly.

It's important that a doctor make sure that a person does not have active TB before starting TB preventive therapy. This is because preventive therapy is less intensive than TB treatment for active disease and if active disease is present but not yet expressing itself fully, resistance to TB drugs could rapidly develop due to sub-optimal treatment. Isoniazid is the most common TB preventive therapy. It has few side effects and is cheap. It is usually taken daily or twice a week for nine months.

Studies also show that a two-month course of rifampin (600mg once a day) plus pyrazinamide (20mg/kg once a day) prevents active disease as well as 12 months of isoniazid. There is no difference in the amount of side effects between the two. The two-month course is also useful if the TB is thought to be resistant to isoniazid.

Preventive TB therapy is not usually given to people thought to be anergic (see page 3 for description). However, if someone who is anergic is determined to be at high risk for TB infection, they may be given TB preventive therapy. Pregnant women with TB infection are advised to start isoniazid preventive therapy right away, even in the first trimester. Children who need preventive therapy should take isoniazid for twelve months.

If the TB strain is resistant to both isoniazid and rifampin, preventive therapy may be difficult. In this case, options include pyrazinamide plus one of ethambutol, ofloxacin or ciprofloxacin daily for six months. Preventive therapy using three drugs has been tested but is not often used due to side effects.

Is there a vaccine for TB?

The BCG vaccine is used in some countries for TB prevention but is not common in the US. It is 80% effective at best. BCG should not be given to people with weak immune systems.

For more information about TB, contact the American Lung Association, 1740 Broadway, New York, NY 10019. Call them at 212-315-8700 or email at info@lungusa.org. Their website is www.lungusa.org.

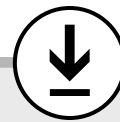
treatment plans for resistant TB

rifampin-resistant TB

- isoniazid, streptomycin, pyrazinamide + ethambutol (daily for 8 weeks or daily for 2 weeks + twice a week for 6 weeks)
- isoniazid, streptomycin + pyrazinamide 2–3 times a week for 7 months

isoniazid-resistant TB

- rifampin/rifabutin, pyrazinamide + ethambutol daily for at least 2 weeks
- the same three drugs twice a week for 6–9 months



the bottom line on TB

- Get screened for TB as early as possible and then every year after.
- If you have symptoms that might be TB, get tested right away.
- If you are diagnosed with or suspect you might have TB, try to find a doctor experienced in treating both HIV and TB.
- If you have active TB, start treatment as soon as possible.
- If you are on preventive TB therapy, visit your doctor at least once a month.
- Ask your doctor about side effects and interactions between the drugs for TB and HIV.
- Take every dose at the right time, and finish your full course of drugs.
- Learn about how you can prevent spreading TB to others.