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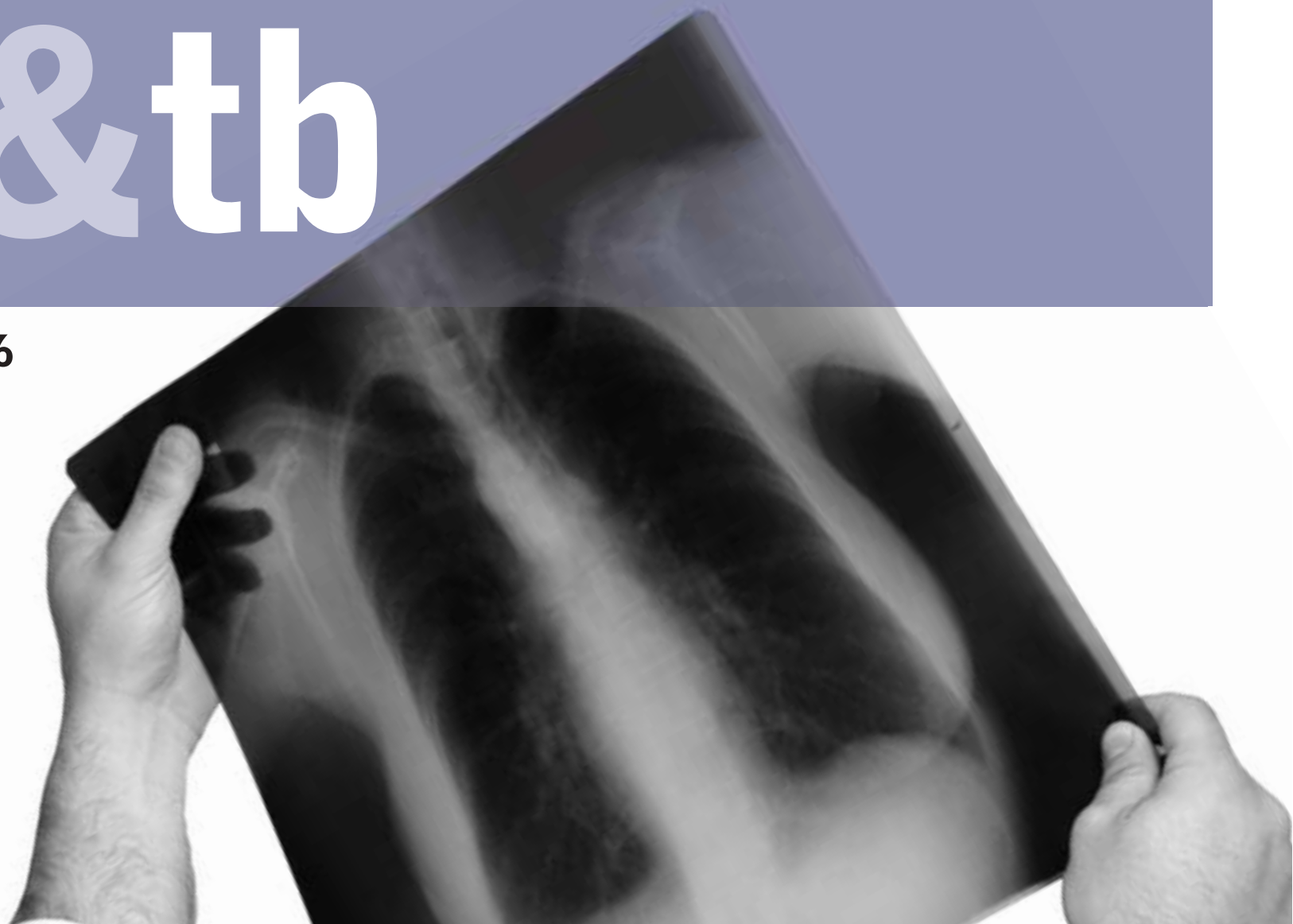

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Written by Michael Carter
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NAM is a charity that publishes information for people affected by HIV and those working with them. We believe information helps people to make decisions about, and be in control of, their lives, health and treatment options.

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This booklet provides introductory information about tuberculosis (TB), the leading cause of AIDS deaths around the world. It includes information on the disease TB, why people with HIV can be more vulnerable to TB, how TB can be treated and prevented, and on interactions between anti-TB and anti-HIV drugs. A summary can be found on page 27, and a glossary on page 28. This booklet is not intended to replace discussion with your doctor. However, it may help you decide what questions to ask your doctor.

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What is tuberculosis? 1

A disease of the past?

Tuberculosis (TB) is caused by a very small bacterium called Mycobacterium tuberculosis and has been causing illness and death in people for thousands of years. Symptoms of TB include cough, fever, night sweats, and rapid weight loss – the disease used to be called "consumption" because of this. TB is still one of the leading causes of death worldwide, mainly affecting the poor, the very young and old, and people who have been weakened by other diseases or by not having enough to eat.

The number of cases of TB fell dramatically in countries like the UK thanks to improved standards of living, better general health, effective anti-TB drugs, and TB vaccination programmes. In fact, progress against the disease was so successful that, by the 1980s, many countries, such as the UK and USA, became confident that they could eradicate TB.

However, since then the number of cases of TB has increased worldwide, partly because of HIV. TB and HIV are seen as the major threats to world health in the 21st century.

TB is an AIDS-defining illness. Worldwide, TB is now the leading cause of death among people with HIV and is the most common AIDS-defining illness in the UK.

2 TB - the basics

Many people are exposed to TB as children, when they breathe in TB germs that have been expelled into the air from the lungs of a person infected with TB.

TB can have a number of phases.

The TB germs multiply in the lungs, cause inflammation, and move to the lymph glands – the command centres of the immune system - in the lungs. This phase is called primary TB. The TB can spread and grow and cause disease. In most HIV-negative people, the body's immune system contains the TB by forming a wall of scar tissue around it. Although a person may not feel ill because of TB, the TB germ can remain alive within this contained area for many years, even decades, causing illness at a later time. This type of TB is usually called latent TB.

In HIV-positive people, TB may not get walled off by scar tissue and spread, causing disease.

TB that is causing illness is called active TB.

TB that resurfaces from scar tissue and causes illness after a period of time is called reactivation TB.

In people who are HIV-negative, the lifetime risk of latent TB becoming active is about one in ten. However, in untreated

people with HIV, the risk increases to between five and ten per cent per year, giving a lifetime risk of 50% or more.

Unlike most other opportunistic infections (so called because they take the opportunity of the body's weakened immune defences to develop) seen in people with HIV, TB can occur in people with relatively high CD4 cell counts and can be transmitted to other HIV-positive and HIV-negative people.

4 Transmission

People who have active TB (TB that the immune system has not been able to control) in the lungs can transmit the disease to other people. TB is spread through the air when a person with active TB coughs.

Rarely, TB can affect the larynx, and active TB here can be spread when a person coughs, shouts, or sneezes. Occasionally, TB can be spread from open wounds.

However, not everybody who has active TB is infectious.

You need to have close contact with TB in an enclosed space, such as an aeroplane or stuffy room, for at least eight hours to run a substantial risk of becoming infected with TB.

In the UK, there have been cases of HIV-positive people becoming infected with TB on hospital wards. This happened before it was realised that TB was a major health concern for people with HIV, and it is now standard practice for HIV-positive people with TB to be cared for in single rooms rather than wards, and for these rooms to have "negative pressure" meaning that the air is gently sucked out of the room and expelled outside the building so it cannot escape into the rest of the hospital.

In very rare cases, TB can cause ulcers to develop on the skin, and these can be infectious.

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There is some evidence that having active TB leads to a fall in CD4 cell count and a rise in viral load which does not drop even after the TB has been treated, unless anti-HIV drugs are given.

However, people who have had TB and been successfully treated are just as likely to benefit from potent combination anti-HIV treatments (often called highly active antiretroviral therapy, or HAART for short), experiencing the same fall in viral load and increase in CD4 cell count as HIV-positive people who have never had the disease, and living just as long.

6 Symptoms

The normal symptoms of TB in the lungs (often called pulmonary TB) are a cough that won't go away, which produces phlegm or mucus which can be bloody. Weight loss, chills and fevers followed by sweats, fatigue, night sweats, and occasionally pain in the chest, are also common symptoms of TB. Other diseases that can affect people with HIV also cause similar symptoms.

In HIV-positive people with very severe immune damage, TB can spread from the lungs into any part of the body but especially the lymph nodes, causing them to swell, or into the stomach, causing severe diarrhoea, or into the liver, causing inflammation, or into the brain, causing meningitis with symptoms of confusion, loss of vision and paralysis.

Diagnosing TB

Active TB

Because the symptoms of TB can resemble those of other diseases seen in people with HIV, doctors will often carry out a number of tests to see if it is TB or something else causing illness. Also, symptoms of TB can come on very slowly, often over a period of months, and it can be hard for either the person with TB or their doctor to recognise them.

Chest x-rays are the standard test. TB can show up in a number of ways:

- Active TB can cause small white patches to show up on the x-ray. These can have holes or cavities in the middle of them.
- If the immune system is mounting an aggressive response to TB, then a pleural effusion may form. This is fluid on the lung and it shows up as a white mass at the bottom of the lung.

Samples of phlegm can be checked for TB germ. If these are present it shows that a person has active TB and they that they could potentially infect other people with TB.

Sometimes the lung is examined with a tiny camera that is put down the nose, often under local anaesthetic. This procedure is called a bronchoscopy and will only be conducted if doctors are uncertain what is causing the illness.

Samples of tissue (a biopsy) from the lungs, liver, or lymph nodes may be taken for examination under a microscope. Again, this should only be performed if doctors cannot diagnose the cause of illness using methods which are less intrusive and less painful.

Latent TB

Tests are also available to see if a person has latent TB - TB that is not causing illness.

Chest X-rays can be used to diagnose latent TB. The scar tissue around the TB shows as a "shadow."

Another test is called a PPD (purified protein derivative) or tuberculin test. This involves injecting a small amount of purified TB protein into the skin. After a few days, the area of injection may show a reaction by reddening or hardening. The larger the size of this reaction, the more

likely it is that a person has been infected with TB in the past and has either active TB or latent infection.

However, a lack of a reaction does not prove that a person does not have TB, and this is particularly the case in people who have very weakened immune systems. What's more, the PPD test does not provide very accurate results if a person received the BCG TB vaccination which used to be given to most school children in the UK.

A new, more reliable and quicker blood test, called T SPOT-TB test, has recently been developed. It looks for key immune cells called T-cells that the body produces in response to infection with TB. There is some evidence to show that it can be better at detecting TB in people with weakened immunity due to HIV than the PPD test.

10 Preventing TB

Vaccination

In the UK and many other European countries, schoolchildren aged 12-14 were given a BCG vaccination against TB. However, this vaccination does not offer complete protection against TB, and there have been many cases of people who received the BCG jab as a child developing TB.

People who are HIV-positive should not be given the BCG jab, as it is a live vaccine and can cause a TB-like illness.

Preventing TB - Improving the immune system with anti-HIV treatment

One of the best ways of preventing TB in people with HIV is to improve the immune system. Treatment with potent combinations of effective anti-HIV drugs boosts the immune system, enabling it to fight TB and other infections.

Preventing TB - taking anti-TB drugs (prophylaxis)

People with latent TB are sometimes given an anti-TB drug or drugs to prevent the TB becoming active. The drug normally used is called isoniazid, which is given for six at least months. It is recommended that HIV-positive people who come from communities that have high levels of TB, including Africans and those from the Indian sub-continent, are given it if they are PPD-positive. It is also recommended that HIV-positive people who have been in close contact with people with active TB should receive this treatment.

However, there are concerns about the safety of this approach, as it could lead to the development of drug-resistant TB if the latent TB is really active TB that has not been correctly diagnosed. Also, isoniazid can cause side-effects and interact with some anti-HIV medicines, particularly ddI (didanosine, *Videx*) and d4T (stavudine, *Zerit*).

Isoniazid can also be harmful to the liver, and you will need to have your liver's function monitored closely as long as you are taking isoniazid.

Isoniazid can also be used to prevent TB from recurring in people who have been ill from it. However, this is not recommended.

There are concerns about side-effects and there are questions about how effective it really is when used in this situation.

Helping yourself

Eating well, getting an adequate amount of sleep and living in dry, well-ventilated housing will help you avoid infection with TB or stay well if you have been exposed to it or if you have latent TB. The booklet *Nutrition,* which is also produced by NAM in this series, gives some tips on healthy eating. If you cannot afford to eat properly or have housing problems help may be available to you. Try contacting THT Direct whose contact details are provided at the back of this booklet. They should be able to put you into contact with somebody who can provide you with advice, help and information.

If you come into contact with somebody with TB, such as a family member, housemate or friend, then you should go to your HIV clinic as soon as possible for tests to see if you have been infected.

Treating TB

Antibiotics to treat TB have been available since the 1950s, and when used correctly they can cure TB in people with HIV.

However, like HIV, treating TB means taking a combination of drugs at the right time and in the right way. Treatment is often for six months but may last for nine months in some cases. Many people either don't take their treatment properly or stop taking their pills once they start to feel better. This can lead to TB becoming resistant to some or all of the drugs used to treat it, and multidrug-resistant TB is a growing problem worldwide. In some parts of the world doctors have given people with TB inadequate therapy in the first place, which has also caused drug resistance.

Anti-TB drugs can also interact with some drugs, including those used to treat HIV, and can have unpleasant side-effects.

Anti-TB drugs

- **Clarithromycin.** This drug is an antibiotic used for the treatment of the AIDS-defining illness MAI, but is also sometimes used to treat TB.
- **Dapsone.** An antibiotic used to treat the AIDS-defining illnesses PCP and MAI, which is also sometimes used to treat TB, particularly drug-resistant TB.

- **Ethambutol.** An anti-mycobacterial antibiotic which, in combination with other drugs, is used as part of standard treatment TB.
- **Isoniazid.** An antibiotic drug which, in combination with other drugs, is a standard treatment for TB. It is also sometimes used by itself as TB prophylaxis.
- **Pyrazinamide.** A first-line drug for the treatment of TB in combination with other drugs.
- **Rifampicin.** An anti-mycobacterial drug which is included in standard anti-TB combinations.
- **Rifabutin.** This drug is used against the AIDS-defining illness MAI and is sometimes used as an alternative to rifampicin in anti-TB combinations.
- **Streptomycin.** The first effective anti-TB drug. It is now rarely used except in cases of multidrug-resistant TB. Administered by injection.
- **Combinations pills.** To help reduce the number of pills you need to take, some anti-TB drugs are available combined together in a single tablet. The following are available in the UK: *Rifater* (contains rifampicin, pyrazinamide and isoniazid), *Rifinah* (contains rifampicin and isoniazid), and *Rimactazid* (contains rifampicin and isoniazid).

Table – Commonly used anti-TB drugs

drug name	side-effects	tips on taking it	drug interactions
clarithromycin	Liver inflammation and should not be taken by people with a history of liver problems, upset stomach, rash and gout. Stomach upset, nausea and headache.		Rifabutin reduces levels of clarithromycin in the blood, and clarithromycin increases levels of rifabutin.
dapsone	Nausea and rash.	Take with food to reduce the risk of nausea.	Should be taken two hours before ddI.
ethambutol	Inflammation of the optic nerve, distorted vision, fever and rash. If you develop sight problems whilst taking ethambutol, contact your doctor immediately. Risk of allergic reaction. Can cause ear problems and kidney damage.	Take with food to reduce the risk of nausea.	

drug name	side-effects	tips on taking it	drug interactions
isoniazid	Rare risk of psychosis or hepatitis. Fever, rash, peripheral neuropathy, and hepatitis. Taking vitamin B-6 (pyridoxine) reduces the risk of peripheral neuropathy and not drinking alcohol may reduce the risk of hepatitis.	Take on an empty stomach, a minimum of 30 minutes to one hour before eating.	Care is needed when taking with anti-HIV drugs that can cause peripheral neuropathy, particularly d4T and ddI.
pyrazinamide	Liver inflammation (hepatitis) and should be used with caution by people with a history of liver problems, can also cause upset stomach, rash and gout.	Drinking plenty of water helps reduce the risk of upset stomach.	Should be taken two hours before ddI.

drug name	side-effects	tips on taking it	drug interactions
rifabutin	Rash, fever, nausea, liver inflammation, leukopenia (shortage of white blood cells), thrombocytopenia (shortage of platelets in the blood) and inflammation around the eye when used with clarithromycin and ethambutol.	Can be taken with or without food.	Can have significant interactions with protease inhibitors and NNRTIs. The anti-fungal drug fluconazole increases blood levels of rifabutin. Clarithromycin increases levels of rifabutin.
rifampicin	Rash, fever, stomach problems and orange discolouration of the skin, urine, stools and tears (do not wear contact lenses when taking rifampicin).	Take on an empty stomach, 30 minutes to one hour before food.	Reduces levels of protease inhibitors and NNRTIs in the blood. Reduces blood levels of atovaquone (used to treat PCP). Can reduce blood levels of methadone by up to 50%. It is also possible that it reduces the amount of the anti-fungal drug ketaconazole.
streptomycin	Risk of allergic reaction. Can cause ear problems and kidney damage.	Injected.	

Treating active TB

In the UK, the TB treatment of choice is a combination of four antibiotics that work against TB. The treatment lasts for at least six months. For the first two months, four anti-TB drugs are used. These are isoniazid, rifampicin, pyrazinamide and ethambutol. If tests have shown that all the main drugs can treat your TB you may only require treatment with three drugs. These will be isoniazid, rifampicin and pyrazinamide.

Treatment with two drugs, normally isoniazid and rifampicin, then continues for a further four months. Some people take these two drugs for up to seven months. Everybody should also take a vitamin supplement called pyridoxine to stop to painful side-effect involving nerve damage in the lower legs and feet (and sometimes the hands) developing.

In some cases it may be necessary to take two drug treatment for seven months. This is particularly likely if you did not take pyrazinamide during the first two months of treatment or if TB germs can still be detected in your sputum at the end of the initial two month phase of treatment.

It is normal to take all the drugs as tablets, once daily.

As TB comes under control, normally after a week or two of treatment, you will feel a lot better, and if you have infectious TB

you will stop being able to pass on the disease to others as long as you take anti-TB medication.

However, it is vital to go on and complete the full course of anti-TB treatment. Failure to do this can cause the TB to come back, or drug resistance to emerge. If you would like more information on why taking medicines properly is important and some tips on how you can improve your chances of taking your medicines properly, read the booklet in this series called *Adherence.*

Directly observed therapy

Because of concerns about drug-resistant TB, it might be recommended that a healthcare worker visits you at home every day to make sure that you take your medication. This is called Directly Observed Therapy (DOT for short), and although it is standard practice in some countries, it is only used in exceptional circumstances in the UK, one of which is multidrug-resistant TB (see page 24).

Treat TB first or TB and HIV together?

There are potential interactions between some protease inhibitors and non-nucleoside analogue reverse transcriptase inhibitors (NNRTIs) and rifampicin, a key drug included in many anti-TB combinations.

Because of this, many doctors recommend either delaying HIV treatment until the TB has been controlled, or even stopping or changing anti-HIV medication if a person develops TB whilst taking it.

If you have a low CD4 cell count, and start anti-HIV drugs immediately after finishing your TB treatment, you may be at risk of developing what is called immune restoration syndrome. This is when your strengthening immune system is stimulated to attack TB again. This can make you very unwell and cause unpleasant symptoms, particularly fever and an enlargement of the lymph nodes.

The British HIV Association (BHIVA), the professional body for doctors who care for people with HIV, recommends that TB should be treated first if your CD4 cell count is above 200.

If your CD4 cell count is between 100 and 200, then BHIVA recommends that you start your HIV drugs two months after starting your TB drugs. If you have a very weak immune system, with a CD4 cell count below 100, BHIVA recommends that you start anti-HIV treatment as soon as possible after starting TB drugs. Some doctors recommend waiting up to two months to limit the risks of side-effects, drug interactions, and the occurrence of immune reconstitution syndrome.

TB treatment for HIV-positive women who are pregnant

UK doctors make special recommendations for the treatment of TB in HIV-positive pregnant or breastfeeding women.

Because of the risk of TB to the developing baby, it is important that pregnant women with active TB take anti-TB treatment. Women with latent-TB are also recommended to take isoniazid treatment if it is thought that they have a reasonable risk of becoming ill with TB.

TB treatment in pregnant women should consist of four drugs – rifampicin, isoniazid, pyrazinamide and ethambutol for the first two months and then two drugs – rifampicin and isoniazid – for a further seven months. Pyridoxine (vitamin B-6) should also be taken to prevent isoniazid causing nerve damage.

Pregnant women are also recommended to take anti-HIV treatment to prevent mother-to-child transmission of HIV. The exact type of treatment will depend on the health of the mother and the stage during pregnancy when HIV was diagnosed. An additional factor for women with TB is the risk of an interaction between some anti-TB drugs and some anti-HIV medicines. Because of this it is extremely

important that doctors providing ante-natal care and TB treatment are very knowledgeable about HIV and TB and work very closely together.

Because of the risk of mother-to-child transmission, HIV-positive women in the UK should never breastfeed.

For more information on HIV and pregnancy and mother-to-child transmission of HIV see the booklets in this series, *HIV and women* and *HIV and children.*

Interactions between TB drugs and anti-HIV drugs

Many anti-HIV drugs and TB drugs can work well and safely together. However, as mentioned above, there can be interactions. It is not recommended to use certain anti-TB and HIV drugs together or adjust the dose of either the TB or HIV drug.

Rifampicin can cause large reductions in the amount of protease inhibitors in the blood, even if they are "boosted" by ritonavir, making them ineffective and increasing the chance that resistance to anti-HIV drugs will develop. Because of this, rifampicin should not be used with many of the protease inhibitors and NNRTI drugs.

Rifabutin can interact with protease inhibitors and NNRTIs, causing the amount of antiretrovirals in the bloodstream to fall and the amount of rifabutin to increase.

Because of these interactions it is very important that your doctor is skilled in the treatment of both TB and HIV.

TB drugs and anti-HIV drugs: side-effects

Hepatitis (inflammation of the liver) has also been seen in a numbers of people taking HAART who are also taking isoniazid or rifampicin. Isoniazid can also cause painful nerve damage called peripheral neuropathy, and it is recommended that it is used with extreme caution if given at the same time as d4T or ddI which also cause this side-effect. Taking a daily dose of vitamin B-6 (pyridoxine) can help prevent isonaizid causing peripheral neuropathy, but does not prevent peripheral neuropathy caused by anti-HIV drugs.

There can be other complex interactions between anti-TB and anti-HIV drugs. This is another reason why your doctor should be experienced at treating both HIV and TB.

24 Multidrug-resistant TB

TB that is resistant to isoniazid, rifampicin, and to other drugs as well, is becoming more and more common. This is called multidrug-resistant TB and cases have been seen in HIV-positive people.

Unlike normal drug-sensitive TB, which is normally cured, the risk of dying from multidrug-resistant TB is very high, unless you very quickly receive treatment consisting of anti-TB drugs that still work.

In the early 1990s there were outbreaks of multidrug-resistant TB that caused deaths on HIV wards in two UK hospitals.

To help control the spread of multidrug-resistant TB, it is often necessary for a person with it to stay in hospital in isolation, until treatment has started to be effective. Thanks to such measures, there has not been an outbreak of multidrug resistant TB in a UK hospital for many years.

Treating multidrug-resistant TB is much harder than treating normal drug-sensitive TB. People who have it need to take more anti-TB drugs for longer. Treatment for up to two years or more may be required. Drugs used to treat multidrug-resistant TB include streptomycin, kanamycin, clarithromycin, amikacin, capreomycin, and flouroquinolone.

Some of these drugs can also interact with anti-HIV medication or have unpleasant side-effects and close monitoring is needed.

Multidrug-resistant TB should only be treated by an expert doctor.

26 Immune reconstitution syndrome

After starting HAART and experiencing an improvement in their immune system, about 25% of people who have had TB experience a temporary worsening of TB. A chest x-ray might show worsening of TB in the lung. Symptoms include fever and swollen glands, which can turn into pus-filled abscesses. These need expert management.

It is not normally necessary to change HIV treatment or to restart anti-TB therapy.

It seems that people who started HIV treatment with a CD4 cell count below 100, and within two months of starting an anti-TB drug combination, are at greatest risk.

Summary

- TB is the most common AIDS-defining illness worldwide.
- People with HIV can get TB when their CD4 cell count is at any level and pass it on to other people.
- TB can be active, causing illness, or latent, which could cause illness in the future.
- TB can be treated, but it is necessary to take the drugs properly over many months.
- TB drugs can interact with anti-HIV drugs, meaning that the doses of both the anti-HIV and the anti-TB drugs you take may need to be adjusted.
- Some strains of TB are multidrug-resistant. This type of TB is harder to treat.
- TB in people with HIV needs expert management.
- People who have been successfully treated for TB respond just as well to HAART.

28 Glossary

abscess A collection of pus formed as the result of infection.

antibiotic A drug that affects bacteria.

bacteria A single-celled micro-organism.

biopsy A small sample of tissue that can be examined for signs of disease.

bronchoscopy A medical procedure using a flexible tube that enables examination and biopsy of the lungs.

CD4 A molecule on the surface of some cells onto which HIV can bind. The CD4 cell count roughly reflects the state of the immune system.

hepatitis Inflammation of the liver.

immune system The body's mechanism for fighting infection and eradicating dysfunctional cells.

leukopenia Fewer than normal white blood cells, usually due to bone marrow damage.

lymph nodes Special areas in the body where white blood cells and other important immune cells are found. Also known as glands.

meningitis Inflammation of the outer lining of the brain.

NNRTI Non-nucleoside reverse transcriptase inhibitor, the family of antiretrovirals which includes efavirenz, nevirapine and delavirdine.

NRTI Nucleoside analogue reverse transcriptase inhibitor, the family of antiretrovirals which includes AZT, ddI, 3TC, d4T, ddC, abacavir, and FTC.

opportunistic infection Specific infections which cause disease in someone with a damaged immune system.

peripheral neuropathy Damage to the nerves of the hands and/or feet, causing symptoms ranging from numbness to excruciating pain.

protease inhibitor Family of antiretrovirals which target the protease enzyme. Includes amprenavir, fosamprenavir, indinavir, opinavir, ritonavir, saquinavir, nelfinavir, and atazanavir.

pulmonary Affecting the lungs.

regimen A drug or treatment combination and the way it is taken.

strain A variant characterised by its genotype.

thrombocytopenia A decreased number of specific cells (responsible for clotting) in the blood.

tuberculosis A disease caused by the bacterium *Mycobacterium tuberculosis*.

viral load Measurement of the amount of virus in a sample. HIV viral load indicates the extent to which HIV is reproducing in the body.

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opening hours Monday-Friday, 10am-10pm
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