Before you begin this unit, please take the corresponding test at the end of the book to assess your knowledge of the subject matter. You should redo the test after you’ve worked through the unit, to evaluate what you have learned.

**Objectives**

When you have completed this unit you should be able to:
- List the goals of antiretroviral treatment.
- Describe the three classes of antiretroviral drugs.
- Describe the actions of antiretroviral drugs.
- Define multi-drug treatment of HIV.
- Give the advantages of standardised regimens.
- List the first- and second-line drug combinations.
- Describe how antiretroviral drugs should be taken.
- Recognise common and serious side effects of antiretroviral drugs.

**INTRODUCTION TO ANTI-RETROVIRAL TREATMENT**

### 4-1 What is antiretroviral treatment?

Antiretroviral treatment (ART) is the use of drugs (i.e. medicines) to treat patients with HIV infection.

**NOTE** In 1996 Dr David Ho of New York presented the results of a landmark study showing that multi-drug antiretroviral treatment was successful in stopping viral replication and controlling the immune damage of HIV.

### 4-2 How does antiretroviral treatment work?

Antiretroviral drugs prevent HIV from multiplying (making copies of itself) in the CD4 lymphocytes. This reduces the number of viruses in the body and, thereby, allows the damaged immune system to recover. Antiretroviral treatment results in an improvement of the clinical disease.

Antiretroviral treatment stops HIV from multiplying in the body.

### 4-3 What are the goals of antiretroviral treatment?

The goals are to:

1. Prevent the multiplication (replication) of HIV and, thereby, suppress the viral load and keep it suppressed.
2. Prevent the further destruction of CD4 cells and allow the immune function to recover.
3. Improve the quality of life and general health by decreasing the clinical signs and symptoms of HIV infection.
4. Manage the side effects of antiretroviral treatment.
5. Reduce the occurrence of HIV-associated infections.
6. Reduce the risk of death due to AIDS.
The main goals of antiretroviral treatment are to improve the quality of life and reduce mortality due to AIDS.

4-4 At what sites in the CD4 lymphocytes do antiretroviral drugs act?
1. At the stage where the virus gives instructions to produce new viruses.
2. At the stage where new viruses are manufactured and released into the body.

CLASSES OF ANTI-RETROVIRAL DRUGS

4-5 What are the classes of antiretroviral drugs?
Most drugs used fall into one of three classes:
1. Nucleoside reverse transcriptase inhibitors and nucleotide reverse transcriptase inhibitors, are also known as ‘nucs’ (pronounced as ‘nukes’). They act at the stage where the virus infects CD4 lymphocyte and gives instructions to these cells to produce new viruses.
2. Non-nucleoside reverse transcriptase inhibitors are commonly called ‘non-nucs’. They also act at the stage where the virus gives instructions to the CD4 cells to produce new viruses but the method of action is different from the ‘nucs’.
3. Protease inhibitors (‘PIs’). They act at the final stage where the CD4 cell manufactures new viruses.

NOTE Nucleoside reverse transcriptase inhibitors (NRTIs) and nucleotide reverse transcriptase inhibitors (NtRTIs) are also known as nucleoside and nucleotide reverse transcriptase antagonists. Two new classes of antiretrovirals (intergrase inhibitors and entry inhibitors) may be available in the next few years. NRTIs were the first group of antiretroviral drugs available.

4-6 What are common examples of ‘nucs’?
1. AZT (zidovudine)
2. 3TC (lamivudine)
3. FTC (emtricitabine)
4. d4T ( stavudine)
5. ddI (didanosine)
6. TDF (tenofovir)

These are the generic (common) names of the drugs. For each generic drug there are one or more different trade names for the same drug manufactured by different companies. This makes it difficult to remember all the trade names. Therefore, it is best to remember the generic names and only the commonly used trade names of the frequently used antiretroviral drugs. If possible, use the generic names rather than the trade names.

NOTE NRTIs mimic (look like) natural nucleosides (DNA building blocks, e.g. thymidine) and thereby block the function of the reverse transcriptase enzyme. They act as false building blocks for HIV DNA and prevent the HIV instructions being inserted into the DNA of the CD4 cells.

4-7 Can different ‘nucs’ be used together?
‘Nucs’ are generally used in pairs, e.g. d4T and 3TC or AZT and ddI. However, AZT and d4T should not be used together as they compete with each other. AZT and 3TC can be combined as Combivir. TDF is usually given with 3TC or FTC.

AZT and d4T should never be used together as they compete with one another.

NOTE TDF together with FTC is sold as Truvada.

4-8 What are common trade names for the ‘nucs’?
Common ‘nucs’ are:
1. AZT is sold as Retrovir.
2. 3TC is simply called 3TC.
3. d4T is sold as Zerit.
4. ddI is sold as Videx.
5. TDF is sold as Viread.

NOTE TDF together with FTC is sold as Truvada.
4-9 What are examples of 'non-nucs'?

Common 'non-nucs' are:
1. Nevirapine
2. Efavirenz

'Non-nucs' are particularly powerful inhibitors of HIV multiplication. However, HIV rapidly becomes resistant to 'non-nucs' if they are used alone. Therefore, they are usually used with a pair of 'nucs'.

**NOTE** NRTIs directly inhibit the reverse transcriptase enzyme by binding to it and thereby prevent the formation of DNA containing the HIV genetic code in the CD4 lymphocytes.

4-10 What are common trade names for the 'non-nucs'?

- Nevirapine is called Viramune.
- Efavirenz is called Stocrin.

4-11 What are examples of 'PIs'?

1. Ritonavir
2. Lopinavir

The common trade name for ritonavir is Norvir. Sometimes two 'PIs' (protease inhibitors) are put together in a single preparation such as Aluvia (a trade name for lopinavir combined with ritonavir). Using two 'PIs' together allow a lower dose of both with fewer side effects.

There are a large number of other 'PIs'. They are easy to recognise as their generic names all end in 'avir' such as ritonavir.

**NOTE** A low dose of ritonavir is used to boost the effect of lopinavir.

4-12 Can antiretroviral drugs be taken by mouth?

Yes. The common antiretroviral drugs in all classes can be taken by mouth.

It is very important that all antiretroviral drugs are taken at the same time every day.

4-13 Should a number of antiretroviral drugs be used together?

Yes. With antiretroviral treatment it is essential to use a number of drugs together. This is called multi-drug treatment. It is important to use multi-drug treatment as it is more effective and also reduces the chance of the HIV becoming resistant to the drugs. The same advantages of multi-drug therapy apply to the treatment of TB. Except for the prevention of mother-to-child transmission and post-exposure prophylaxis, single or double drug treatment of HIV infection should never be used.

**Multi-drug treatment should be used to treat HIV.**

**NOTE** Multi-drug treatment of HIV infection in 1995 showed dramatic results following earlier disappointing results with single drug treatment.

4-14 What is HAART?

Highly active antiretroviral treatment (HAART) is another name for antiretroviral treatment (ART). It is the use of multiple drugs to treat HIV infection. Three or more drugs are always used together for antiretroviral treatment.

**Three or more antiretroviral drugs are always used to provide antiretroviral treatment.**

**NOTE** Sometimes one drug (monotreatment) or two drugs (dual treatment) are used in short-course prophylactic treatment to prevent the transmission of HIV from mother to child during pregnancy and delivery. One or two drugs are only appropriate in HIV prophylaxis.

4-15 Can antiretroviral treatment cure HIV infection?

Unfortunately not. However, antiretroviral treatment can dramatically improve the symptoms and clinical signs of HIV infection and allow the patient to remain healthy for...
many years. Antiretroviral treatment is the most important advance in the management of HIV infection. Antiretroviral treatment can change the outcome of HIV infection from a rapidly fatal disease into a manageable chronic illness.

### STANDARDISED REGIMENS FOR ANTIRETROVIRAL TREATMENT

4-16 What is a standardised regimen for treating HIV infection?

The choice of which antiretroviral drugs to use can be based on either an individualised or a standardised approach. Initially an individualised approach was used where the most appropriate drugs were chosen to meet the needs of each patient. More recently a standardised approach has been used where all patients are started on the same combination, as is done with TB treatment.

4-17 What are the advantages of using a standardised regimen?

1. The standardised approach is safer, easier and simpler.
2. It is also affordable and effective.
3. Both healthcare workers and patients can learn how to use these drugs correctly and which side effects to be aware of. The education and training of healthcare workers and patients are much easier.
4. It limits the number of drugs that are used and makes it possible to monitor patterns of drug use and resistance. Monitoring for side effects is simplified.
5. It is easier to buy and distribute a limited range of drugs.
6. Fixed doses are used in the standardised approach.

### Antiretroviral treatment is the most important advance in the management of HIV infection and has changed the course from a rapidly fatal disease into a manageable chronic illness.

A standardised regimen consists of a specific combination of antiretroviral drugs where the risk of drug interactions and side effects are low. The drug combination should target at least two sites in the lifecycle of HIV (i.e. important stages in the viral replication).

4-18 What are the disadvantages of an individualised approach?

Using combinations of antiretroviral drugs is very complicated as each combination has its own risk of drug interactions. Some drugs counteract each other (block the function of the other drug). Other drug combinations have a high risk of serious side effects. Therefore, a wide knowledge and experience of these drugs is essential if the individual approach is to be used. This ability is usually only available at antiretroviral clinics where particularly difficult management problems are referred.

4-19 What is a first-line combination?

This is the combination of drugs which is routinely used when patients first start antiretroviral treatment.

4-20 What is the first-line combination commonly used in South Africa?

When treating adults with HIV infection in South Africa, the first-line combination is usually two ‘nucs’ together with a ‘non-nuc’.

The currently recommended South African combination is TDF plus 3TC plus either efavirenz or nevirapine. Unless contraindicated, all patients should be started on this regimen. AZT can be used if there are...
contraindications to TDF. Some old regimes still use d4T instead of TDF.

**NOTE** Sometimes TDF is combined with FTC. The combination is called Truvada.

In South Africa antiretroviral treatment is usually started with TDF and 3TC or FTC plus either efavirenz or nevirapine.

This combination is chosen for its effectiveness and availability, few serious side effects and low cost.

**4-21 What is a second-line combination?**

Patients who fail to respond to the first-line combination, despite good adherence, are changed to a second-line combination of antiretroviral drugs.

**NOTE** Unfortunately there is no standardised third-line combination of drugs available in the public sector in South Africa. This will change when new drugs are introduced in the future.

**4-22 What common second-line combination is used in South Africa?**

Usually two ‘nucs’ plus a combination of two ‘PIs’. The common second-line combination in South Africa is AZT plus 3TC plus ritonavir and lopinavir together. TDF can be used if the failed first-line combination included AZT.

The previous second-line combination is sometimes still used.

Therefore both the first- and second-line combinations include two ‘nucs’. However, only the first-line combination includes a ‘non-nuc’ while only the second-line combination includes ‘PIs’.

In South Africa the new second-line combination is AZT plus 3TC plus ritonavir and lopinavir together.

**4-23 When are other combinations of antiretroviral drugs used?**

Sometimes changes to the first- or second-line combinations are made:

1. When there are serious side effects to only one drug in a standardised regimen.
2. In patients who have previously been exposed to one or more antiretroviral drugs, e.g. nevirapine in labour.

These changes (swaps) should only be made by an experienced doctor at an antiretroviral clinic. Using individualised combinations reduce the future options of treatment.

**NOTE** Patients who have failed to respond to both first- and second-line combinations, despite good adherence, may be offered ‘salvage treatment’ with new drugs.

**ANTIRETROVIRAL MEDICATION**

**4-24 What are the practical implications of taking antiretroviral treatment?**

The following questions must be considered:

1. Which medications are taken?
2. How many tablets or capsules are taken at a time?
3. When and how often is the medication taken?
4. Should the medication be taken with or without food?
5. Can all the drugs be taken together at the same time?

**4-25 How should tenofovir be taken?**

TDF (generic name tenofovir) is a ‘nuc’ (trade name is Viread). One TDF 300 mg tablet is taken daily, usually at night, with or without food.

Some patients on an older regime may still receive d4T (generic name stavudine). D4T is also a ‘nuc’ (trade name is Zerit). One 30 mg capsule is taken twice a day (12-hourly).
Capsules can be taken with or without food. However, taking d4T with food reduces nausea. More recent guidelines do not include d4T.

**NOTE** Initially d4T may be well tolerated but in the long term 20% of patients will have side effects. These may include serious complications such as peripheral neuropathy, pancreatitis, hepatitis, lipodystrophy and lactic acidosis due to mitochondrial DNA depletion. The risk of these side effects is particularly high with d4T, and further increased if d4T is taken together with ddI or if the patient is a woman, obese or pregnant.

d4T must not be given with ddI.

**4-26 How should 3TC be taken?**

3TC is also a ‘nuc’ (generic name lamivudine while trade name is also 3TC). One 150 mg tablet is taken twice a day (12-hourly) with or without food. However, 300 mg 3TC is taken as a once-daily dose. 3TC is well tolerated and has very few side effects. Mild nausea, headache and diarrhoea may occur.

3TC is well tolerated with few side effects.

**4-27 How should AZT be taken?**

AZT (generic name zidovudine) is a ‘nuc’ (trade name is Retrovir). One 300 mg tablet is taken twice daily (12-hourly). Tablets can be taken with or without food. However, nausea may be less if taken with food. AZT has many short term minor side effects such as fatigue, nausea and vomiting, headache, muscle pains and altered taste. These are common at the start of treatment and are worse with higher doses. However, they become less after a few weeks. AZT may also discolour the nails. The most important side effect of AZT is anaemia. This usually occurs in the first few months of treatment.

AZT may cause anaemia.

**NOTE** Serious complications of AZT are anaemia, neutropenia and lactic acidosis.

**4-28 How should ddI be taken?**

ddI (generic name didanosine) is a ‘nuc’ (trade name is Videx). Usually four tablets (100 mg each) are taken once a day on waking, giving a total dose of 400 mg. All four tablets are dissolved in water (about 30 ml) and taken immediately. Only water or clear apple juice must be used to dissolve the tablets. Unlike other antiretroviral drugs, ddI tablets should not be taken with meals as food reduces absorption of the drug. ddI should be taken at least an hour before a meal or not less than two hours after a meal. The more recent South African guidelines minimise the use of ddI.

**NOTE** The most common side effects of ddI are gastrointestinal symptoms. Serious side effects include pancreatitis, peripheral neuropathy and lactic acidosis due to interference with mitochondrial metabolism. If d4T is still being used, these side effects may be worsened if ddI is given with d4T.

ddI tablets must be dissolved in water.

**4-29 How should nevirapine be taken?**

Nevirapine is a ‘non-nuc’. One nevirapine 200 mg tablet (trade name is Viramune) is taken at night to start with. After 14 days the dosage is increased to one tablet twice daily (12-hourly). If there is a mild rash or raised liver enzymes, do not increase the dose to twice a day until the liver enzymes have dropped and the rash has cleared. A mild rash is common, usually during the first six weeks of treatment. A severe rash may also occur with nevirapine. The drugs must be stopped immediately if a severe rash appears.

**NOTE** Serious complications of nevirapine include blistering rash with mucosal involvement, hepatitis and fever due to a hypersensitivity reaction.

Nevirapine may cause early, serious side effects.
4-30 How should efavirenz be taken?
Efavirenz is also a ‘non-nuc’ and is very similar to nevirapine.

One efavirenz 600 mg capsule (trade name Stocrin) is taken at night. Efavirenz has the advantage of the patient only needing a single dose a day.

A rash may occur. However this side effect is less common and not as severe as with nevirapine. Efavirenz commonly causes mild emotional symptoms for the first few weeks (mood changes, abnormal dreams, insomnia and dizziness). These are reduced if efavirenz is taken on an empty stomach in the evening. When side effects have cleared efavirenz should be taken with meals.

**NOTE** The absorption of efavirenz is greater if it is taken with meals. This may make side effects worse during the first weeks of treatment.

4-31 Who should not take efavirenz?
Efavirenz must not be taken during the first trimester of pregnancy, if pregnancy is planned or if reliable contraception is not being used as it may cause fetal abnormalities (birth defects). People who cannot use contraception reliably should take nevirapine rather than efavirenz. Injectable contraception plus condoms are recommended.

**Efavirenz should not be used in a woman who is at risk of falling pregnant.**

4-32 How should ‘Pis’ be taken?
Usually lopinavir 400 mg and ritonavir 100 mg (LPV/r) are taken in combination as Kaletra or Aluvia (trade names). Three capsules of Kaletra are taken twice daily (12-hourly) with food (i.e. a total of six capsules a day) or two tablets of Aluvia twice a day (12-hourly) with or without food. Nausea and diarrhoea are common for the first few weeks, especially with Kaletra. These side effects can be reduced if the drug is taken with food. Unlike Kaletra, Aluvia need not be kept in a fridge or cool place. The dosages of many drugs have to be altered if they are used together with lopinavir and ritonavir.

**NOTE** Protease inhibitors may cause lipodystrophy with abnormal fat distribution. Lipodystrophy may be associated with insulin resistance and hyperlipidaemia. Protease inhibitors may also affect the metabolism and breakdown of many drugs (ritonavir inhibits cytochrome P450 and thereby increases the blood level of lopinavir and a wide range of other drugs). A small dose of ritonavir therefore boosts the effect of lopinavir.

The dose of lopinavir/ritonavir must be increased if used with efavirenz or rifampicin. Expert advice should be asked for.

4-33 Which antiretroviral drugs should not be taken with a meal?
It is important that ddI is taken on an empty stomach as food decreases the absorption of the drug. In addition, the side effects of efavirenz are less if the drug is taken on an empty stomach in the evenings. Therefore it is best if efavirenz is taken without food for the first few weeks. However, most other antiretroviral drugs can be taken twice a day with meals.

**ddI must be taken on an empty stomach.**

With the first-line combination all three drugs can be taken with meals, except efavirenz for the first few weeks.

If the previous second-line combination is used, AZT and lopinavir/ritonavir are best taken with meals, but ddI must be taken on an empty stomach. Take ddI at least an hour before or two hours after a meal.

**It is important to know which drugs should be taken with meals and which drugs must be taken on an empty stomach.**

4-34 Which drugs must be kept cool?
Kaletra should be kept in a fridge if possible. If a fridge is not available, keep Kaletra in a cool place (less than 25 °C).
SIDE EFFECTS OF ANTIRETROVIRAL DRUGS

4-35 Do all antiretroviral drugs have side effects?
Side effects to antiretroviral drugs are common and usually mild, but they can sometimes be severe. Remember that drugs used to treat HIV-associated infections also cause side effects, which may be similar to the clinical symptoms and signs of HIV infection. Most side effects can be easily managed.

Side effects can be graded into mild (grade 1), moderate (grade 2), severe (grade 3) and potentially life threatening (grade 4).

All antiretroviral drugs may have side effects.

4-36 Should patients be warned about side effects?
It is very important that patients know the common side effects of the antiretroviral drugs that they are taking. It is also important that patients know which side effects to look out for and which can be serious. If side effects are mild, patients should not stop the antiretroviral drugs. With severe side effects they should report immediately to the clinic. Educating patients about side effects is an important part of care. All patients on antiretroviral treatment must be able to monitor themselves for side effects.

Patients should be educated about side effects.

4-37 What are the common side effects of antiretroviral drugs?
Tiredness, nausea and vomiting, headaches and diarrhoea are common and may be caused by all classes of antiretroviral drugs. These side effects are not serious and usually settle after the first few days or weeks. It is important that patients continue with their antiretroviral drugs in spite of mild side effects. Sometimes other medication can be taken to help relieve these symptoms (paracetamol for headache and antiemetics for nausea and vomiting). Taking antiretroviral treatment with food often helps reduce side effects. Side effects, no matter

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<td>lopinavir/ritonavir</td>
<td>Aluvia</td>
<td>3 capsules</td>
<td>Twice daily</td>
<td>Yes</td>
</tr>
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* Twice daily doses are best taken 12 hours apart e.g. 7 am and 7 pm
* Only one tablet of nevirapine daily at night for the first two weeks of treatment
** Efavirenz is best taken on an empty stomach for the first few weeks
how mild, must always be reported to the staff. Fortunately, most side effects are mild. Most patients will not experience side effects.

**Most patients have no side effects.**

**Note** Severe vomiting or diarrhoea may cause dehydration as well as reduce absorption of medication.

4-38 When do most side effects occur?

Most side effects occur in the first six weeks of starting antiretroviral treatment. They usually get better on their own after one to two months. However, some serious side effects may occur at any time that antiretroviral drugs are taken.

4-39 What serious side effects may occur with antiretroviral drugs?

1. Rash
2. Hepatitis
3. Anaemia
4. Peripheral neuropathy
5. Renal failure
6. Wasting and accumulation of fat (lipodystrophy)
7. Pancreatitis
8. Lactic (metabolic) acidosis
9. Severe vomiting or diarrhoea

4-40 What rashes occur commonly with antiretroviral drugs?

1. Mild rashes are common and include a localised or generalised erythematous (pink), maculopapular (measles-like) or urticarial rash with no other symptoms.
2. Severe rashes include any rash with blistering, peeling or involvement of the mucous membranes of the mouth and conjunctivae. A severe rash may also present together with fever, a fast pulse or abdominal pain (due to hepatitis).
Severe rashes are due to a hypersensitivity reaction and can be fatal.

Rashes are common with antiretroviral treatment and usually are caused by ‘non-nucs’, especially nevirapine. These rashes almost always occur in the first six weeks of treatment.

**Nevirapine commonly causes skin rashes.**

Remember that HIV infection itself and drugs used to treat HIV-associated infections (especially co-trimoxazole) also commonly causes rashes. Therefore the rash may not be due to the antiretroviral drugs.

**Note** Severe rashes due to a hypersensitivity reaction may result in Stevens-Johnson syndrome and toxic epidermal necrolysis (TEN). Constitutional symptoms such as fever are also present and warn of a dangerous side effect. Always look for hepatitis with severe drug rashes.

4-41 How should skin rashes be managed?

Nevirapine must always be started at half doses (i.e. 200 mg once daily) for the first 14 days as this reduces the risk of a rash. Continue treatment if the rash is mild. Do not increase the dose of nevirapine until any rash has settled.

All patients with a severe rash must be referred to an antiretroviral clinic urgently. If this cannot be done on the same day, stop all three antiretroviral drugs immediately and send the patient to an antiretroviral clinic as soon as possible. Usually nevirapine is swapped for a ‘PI’. These patients must never be given a ‘non-nuc’ again (i.e. neither nevirapine nor efavirenz should ever be prescribed again).

**All antiretroviral drugs must be stopped immediately if a severe rash occurs.**

**Note** Steroids and antihistamines do not help most sensitivity rashes caused by nevirapine.

4-42 Which antiretroviral drugs cause hepatitis?

All classes of antiretroviral drugs can cause hepatitis. However, nevirapine is the drug which is usually associated with hepatitis. Efavirenz can also cause hepatitis but less commonly.
Hepatitis due to nevirapine is most common in patients, especially women, who have a high CD4 count before the start of treatment. Liver function tests (ALT, i.e. alanine amino transferase) should be done on all patients when nevirapine is started and then repeated after two weeks, four weeks and eight weeks of treatment as hepatitis usually occurs during the first weeks of treatment.

**Hepatitis is usually caused by nevirapine.**

*Note* Nevirapine causes asymptomatic hepatitis in 10% and clinical hepatitis in 1% of patients. Nevirapine plus TB treatment increases the risk of severe rash and hepatitis. d4T and co-trimoxazole may also cause hepatitis with raised enzymes. Nucleoside reverse transcriptase inhibitors may cause a fatty liver (steatosis).

**4-43 What are the clinical signs of hepatitis?**

Hepatitis may be clinical (nausea, loss of appetite, jaundice, enlarged liver, itching and abdominal pain) or asymptomatic (when it is diagnosed by finding raised liver enzymes in the blood without any clinical signs of hepatitis). An ALT level above three times normal (normal< 40 iu/l) indicates an increased risk of hepatitis.

*Note* Liver damage can be severe and permanent, but rarely fatal.

**4-44 What is the management of a patient with hepatitis?**

Patients with asymptomatic hepatitis and only mildly raised liver enzymes (up to five times normal) can be followed clinically without stopping the drugs. The hepatitis usually resolves. Using a low dose of nevirapine (200 mg daily) for the first two weeks lowers the risk of hepatitis (and rash).

Patients with clinical hepatitis or asymptomatic hepatitis with markedly raised liver enzymes should be urgently referred to an antiretroviral clinic where stopping all treatment may be considered.

**4-45 Is anaemia a common problem with antiretroviral drugs?**

Anaemia (Hb below 10 g/dl) is seen in few patients receiving AZT. These patients may appear pale and feel weak and dizzy. Anaemia is usually mild and the AZT need not be stopped.

A full blood count should be done when AZT is started and then be repeated at four weeks, eight weeks, 12 weeks and 24 weeks. Patients with a haemoglobin concentration (Hb) below 8 g/dl due to AZT should be referred to an antiretroviral clinic. It is important to monitor the Hb in patients receiving AZT.

**Anaemia is a side effect of AZT.**

*Note* With severe anaemia (haemoglobin less than 6.5 g/dl) it is important to stop AZT and replace with TDF. A blood transfusion may be needed. Patients with an Hb between 6.5 and 8 g/dl should be closely followed. AZT also causes neutropenia but does not lower the platelet count.

**4-46 What is peripheral neuropathy?**

This is a problem which affects the peripheral nerves, especially in the legs. It presents with pain, numbness and abnormal sensation in a ‘glove and stocking’ distribution. Most patients with peripheral neuropathy present with painful feet at night.

Peripheral neuropathy is usually caused by ‘nucs’ which have a ‘d’ in their names, e.g. ddi and d4T. These drugs should not be used together as this increases the risk of peripheral neuropathy. Depending on the severity of the neuropathy, the drugs may have to be changed, after consultation with an HIV clinic, as the peripheral neuropathy can become worse if the drug is continued. The symptoms of peripheral neuropathy usually slowly improve after the drugs have been stopped. Other drugs, such as INH and alcohol may also cause peripheral neuropathy.

*Note* d4T and ddi are associated with peripheral neuropathy and should not be used together.
**4-47 What is lipodystrophy?**

This is an abnormal distribution of subcutaneous fat resulting in a change in body shape. Fat is lost (fat atrophy) from the face and limbs and gained (accumulated) over the abdomen, back of the neck and breasts. Unfortunately lipodystrophy is not usually corrected when the antiretroviral drugs are changed. Many patients gain weight when antiretroviral treatment is started. Lipodystrophy is usually caused by the 'PIs', but also by ddI, d4T and efavirenz.

**Lipodystrophy is a redistribution in body fat and is usually associated with 'PIs'.**

**NOTE** Lipodystrophy with central obesity and peripheral wasting may be associated with insulin resistance and fasting hyperlipidaemia with a raised plasma cholesterol and triglyceride concentration (the lipodystrophy syndrome). Marked hypertriglyceridaemia can cause pancreatitis while a raised serum cholesterol increases the risk of coronary heart disease.

**4-48 Which drugs may cause lactic acidosis?**

Lactic acidosis is a rare but serious and potentially fatal side effect of 'nucs', particularly d4T and ddI. Therefore these drugs must never be used together. It usually only occurs more than six months into treatment when patients have responded well and are clinically improving with good adherence. It is most common in women who are overweight or pregnant. Patients with lactic acidosis present with a gradual onset of tiredness, weight loss and abdominal complaints (nausea, vomiting, abdominal pain or discomfort). Always suspect lactic acidosis if patients, who have been well and gaining weight for months, start to lose weight.

Lactic acidosis is a rare but serious side effect of 'nucs' and occurs after months of good response to treatment. Patients with suspected lactic acidosis must be immediately taken off all treatment and urgently referred to an HIV treatment centre for investigation and management.

**NOTE** Hyperlactataemia (serum lactate above 2 mmol/l) and lactic acidosis often with hepatic steatosis (fatty liver), liver failure, pancreatitis or peripheral neuropathy, are due to mitochondrial damage as 'nucs' also interfere with the replication of mitochondrial DNA. Asymptomatic hyperlactaemia (without acidosis) is common (up to 20%) while symptomatic hyperlactaemia (without acidosis) occurs in 1% and hyperlactataemia with lactic acidosis in 0.1% of patients on 'nucs.' The risk is lower with TDF and AZT than d4T. TDF and 3TC are relatively safe and can be started once the lactate has returned to normal.

**4-49 Which drugs cause pancreatitis?**

Pancreatitis (inflammation of the pancreas) is another severe complication of d4T and ddI, especially when they are used together. Alcohol abuse may increase the risk of pancreatitis.

Pancreatitis presents with vomiting, abdominal pain and tenderness. The drugs must be stopped immediately and the patient urgently referred. Abdominal pain or discomfort is an important symptom in patients on antiretroviral treatment as it may be due to hepatitis, lactic acidosis or pancreatitis.

**NOTE** The serum amylase and lipase levels are raised in pancreatitis.

**4-50 What is the management of severe vomiting or diarrhoea?**

Some antiretroviral drugs cause nausea and vomiting or diarrhoea. The problem is usually mild and settles after a few weeks. However, vomiting may be severe (especially with AZT) while diarrhoea may also be severe (especially with d4T). This can lead to dehydration. Taking
medicine with food and anti-nausea medication may help reduce vomiting. Efavirenz should be taken without food if it causes vomiting.

Oral rehydration solution will help prevent or correct dehydration. Patients with signs of severe dehydration should be urgently referred to hospital. The sudden onset of severe vomiting after weeks of treatment may indicate lactic acidosis.

4-51 Should antiretroviral drugs rather not be used because of their side effects?
No. Antiretroviral drugs are a very important part in the treatment of HIV infection and the only way of managing AIDS. Like most other drugs, they have side effects. Usually side effects are mild and the antiretroviral drugs need not be stopped. Most patients have no or only mild side effects. However, both patients and health workers should know the symptoms and signs of severe side effects. If these appear the drugs must be stopped immediately and the patient referred urgently to an antiretroviral clinic for assessment.

The advantages of antiretroviral drugs far outweigh the side effects.

4-52 When do side effects occur?
1. They may occur early during the initiation of treatment (the first few weeks or months of treatment).
2. They may occur later when treatment is stabilised (after many months).

4-53 Which side effects occur during early treatment?
Minor side effects are common, e.g. nausea, vomiting, diarrhoea, headaches, muscle pains, sleeplessness, minor rashes. However, serious side effects such as serious rashes and hepatitis may also occur early and need to be looked out for.

To reduce early side effects, some drugs (e.g. nevirapine) are started at half doses. The doses of other drugs may have to be reduced for a while. Most minor side effects during the initiation of antiretroviral treatment get better over time without any treatment.

Peripheral neuropathy may also occur early in treatment.

4-54 Which side effects occur during later treatment?
1. Lipodystrophy and fat wasting
2. Lactic acidosis
3. Peripheral neuropathy

NOTE Some other metabolic disorders can occur later in treatment (with or without lipodystrophy) including high cholesterol and glucose levels.

4-55 Do patients lose weight on antiretroviral treatment?
Normally patients feel better and gain weight when antiretroviral treatment is started. Therefore weight loss on antiretroviral treatment is an important danger sign. It may be due to common early side effects such as nausea, vomiting or diarrhoea. However, weight loss in patients who have previously been well may also indicate the development of lactic acidosis.

Many patients on antiretroviral treatment complain of hunger once their immune system starts to recover. This may be a problem in poor people who cannot afford to buy more food.

4-56 Should one drug be stopped if side effects are severe?
It may be necessary to stop an antiretroviral drug if severe side effects occur, e.g. severe rash or clinical hepatitis. If this is done, all drugs must be stopped together. Stopping one drug will lead to resistance of the remaining two drugs. The drug combination must be carefully examined as the problem drug may have to be swapped or a different combination may be needed. Changing drugs must always be done at an antiretroviral clinic by an HIV expert. HIV infection must never be treated with only one or two drugs. A full combination of three drugs is always needed.
If necessary, stop all antiretroviral drugs and not just one drug.

### CASE STUDY 1

A patient with HIV infection, who has been treated with AZT alone for two weeks by a general practitioner, is referred to an HIV clinic. The patient complains of headache, nausea and feeling generally unwell since the treatment was started.

1. **Do you agree with AZT alone as acceptable treatment for AIDS?**

   One or two drugs alone should never be used to treat HIV. Three drugs are always used together (multi-drug therapy), e.g. AZT, 3TC and lopinavir/ritonavir.

2. **What is the advantage of using multiple drugs?**

   There is a higher rate of successful treatment with less drug resistance.
3. Why is this patient complaining of headache, nausea and feeling unwell?

These are common side effects of AZT. Mild side effects of antiretroviral treatment usually settle on their own after a few weeks. Unless the side effects are serious, treatment should not be stopped. Mild side effects can be treated symptomatically.

4. What is an important side effect of AZT?

Anaemia. Therefore the haemoglobin concentration should be monitored in patients receiving antiretroviral treatment which includes AZT.

5. What class of drug is AZT?

TDF, AZT, 3TC, d4T and ddI are ‘nucs’. They all block an important enzyme and thereby prevent HIV from infecting CD4 lymphocytes. ‘Nucs’ are used in most multi-drug regimens to treat HIV.

6. What are the main goals of antiretroviral treatment?

To suppress the multiplication of HIV. This will allow the immune system to recover (increased CD4 count), improve the patient’s clinical condition and decrease the risk of death.

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**CASE STUDY 2**

A young woman who has HIV infection presents at an HIV clinic with the hope of being cured. She wants to start a family as soon as she is well again.

1. Can antiretroviral treatment cure HIV infection?

Unfortunately not. However, it can markedly improve the patient’s health and make HIV infection a chronic but manageable disease.

2. What treatment should she receive?

She should be given a standardised regimen. Once she has been prepared for treatment, a first-line combination using nevirapine will be started.

3. What is a standardised regimen?

This is a fixed combination of antiretroviral drugs. There are many advantages to a standardised regimen over an individualised regimen. With an individualised regimen each patient is given their own combination of antiretroviral drugs.

4. What are the advantages of a standardised regimen?

It is simpler, safer and cheaper to use with fewer side effects and drug interactions. The education and training of both patients and staff is much easier. Tuberculosis is also treated with a standardised fixed combination of drugs.

5. What first-line regimen is used in South Africa?

TDF or AZT plus 3TC (‘nucs’) plus either efavirenz or nevirapine (‘non-nucs’).

6. Which ‘non-nuc’ would you choose for this woman?

Nevirapine, as she plans to start her family when she is well. Efavirenz has fewer serious side effects than nevirapine, but may cause congenital abnormalities in the unborn infant. Efavirenz should only be used in women who are on reliable contraception, and therefore unlikely to fall pregnant, and men.

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**CASE STUDY 3**

A patient has recently started on a first-line regimen with nevirapine. Three weeks after starting antiretroviral treatment he develops a fever and feels ill with a generalised blistering skin rash which also involves his mouth.
1. Are skin rashes common with nevirapine?

Yes. They are usually mild and the patient does not feel generally unwell. With continued antiretroviral treatment most mild skin rashes caused by nevirapine will disappear.

2. Would you be concerned about this patient’s skin rash?

Yes, because this is a serious rash and the patient is ill with a fever. Any blistering skin rash, especially if it involves the mouth, is serious. All drugs must be stopped immediately and the patient should be referred urgently to hospital. Nevirapine will have to be replaced (swapped) with a ‘PI’ such as Aluvia.

3. Should this patient be given efavirenz instead of nevirapine?

No. This patient must never again be given a ‘non-nuc’ (either nevirapine or efavirenz) as the severe reaction is likely to recur.

4. What other serious side effect may be caused by nevirapine?

Hepatitis. Clinical hepatitis presents with nausea and vomiting, abdominal pain and jaundice. A rash and hepatitis may occur together. Patients with any signs of hepatitis must be urgently referred to hospital. Severe hepatitis can be fatal.

5. How can the risk of side effects with nevirapine be reduced?

By starting with a smaller dose for the first two weeks of treatment (one tablet at night only).

6. Should patients be warned about side effects?

It is very important that patients be well educated about the symptoms and signs of the common side effects before antiretroviral treatment starts. They should immediately report any side effects.

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**CASE STUDY 4**

During preparation for antiretroviral treatment a group of patients is fully informed about the drugs they are going to take. One patient is afraid of starting treatment when he learns about the possible side effects. A friend of his developed very painful legs after antiretroviral treatment was started.

1. **What information about the antiretroviral drugs should patients be given?**

They must know the names and appearances of the drugs in the first-line combination. They must know how many drugs to take and when they should be taken.

2. **How many times a day are antiretroviral drugs taken?**

Some drugs in the first-line combination (AZT and 3TC) are taken twice a day (12-hourly) while TDF and Efavirenz are taken once a day. Nevirapine is taken once a day to start, but later is also taken twice a day. 300 mg 3TC can also be taken once a day.

3. **Should antiretroviral drugs be taken with meals?**

Most antiretroviral drugs in the first-line combination should be taken with meals as this reduces the risk of side effects. For the first few weeks efavirenz should be taken on an empty stomach. Second-line drugs are also taken with meals, except ddI which must be dissolved with water and taken on an empty stomach, one hour before a meal or two hours after a meal.

4. **Should patients who are afraid of the side effects rather not take antiretroviral drugs?**

No. Antiretroviral drugs are the only way to effectively treat patients with HIV. Without antiretroviral treatment they will die. Most patients have no or only mild side effects.
5. Which antiretroviral drugs cause painful legs?

Pain and numbness of the hands and feet are due to peripheral neuropathy. This is usually caused by d4T or ddl. Therefore, these two drugs should never be used together as this increases the risk of peripheral neuropathy. Other drugs such as INH and alcohol may also cause peripheral neuropathy.

CASE STUDY 5

After failing treatment with the first-line combination of antiretroviral treatment a patient is started on the second-line combination. She feels much better on the new treatment. However, after a few months she notices that her face is becoming wasted and she is gaining weight around her abdomen.

1. What antiretroviral drugs are used in the second-line combination?

Usually AZT and 3TC plus lopinavir/ritonavir.

2. What class of drugs are these?

AZT and 3TC are ‘nucs’. As with the first-line combination, ‘nucs’ are an important part of the multi-drug regimen. Kaletra and Aluvia (trade names) are a combination of two ‘PIs’ (ritonavir and lopinavir). The second-line combination therefore includes ‘PIs’ but not ‘non-nucs’.

3. How should lopinavir/ritonavir be taken?

Twice a day with meals.

4. What are common minor side effects with lopinavir/ritonavir?

Nausea and loose stools. These are less troublesome if the medication is taken with meals.

5. Why is this patient developing wasting of the face?

Unfortunately peripheral wasting of the face and limbs and central fat accumulation over the stomach and back of the neck may occur with ‘PIs’. This change of body shape due to the redistribution of fat does not always resolve when the ‘PIs’ are stopped.

6. What is the name of this condition?

Lipodystrophy.