Anti-HIV therapy

Aims

This section reviews why antiretrovirals are used to treat HIV, and looks at the practicalities of using anti-HIV therapy. It summarises the different types of treatments currently available, how individual treatment decisions might be reached, current views on when to start and change therapy, how to avoid drug resistance, and why adherence to treatment is so important in HIV.

Through completing this module, participants will also gain an understanding of drug side-effects, and an overview of current WHO guidelines on the use of antiretrovirals.

It is preferable that participants should have completed the Introduction to HIV and AIDS module before this module. It may also be helpful to use the section on the HIV lifecycle within the module “The Immune System and HIV”

Target audience

- This section is a basic introduction to antiretroviral therapy for:
- Doctors new to HIV care
- Clinical officers
- Nurses
- Health care workers involved in the support of people with HIV
- Community treatment workers
- Non-medical audiences
Topics covered

- Introduction to anti-HIV therapy (I-II).
- Basics of Antiretroviral Therapy.
- Side-effects of Antiretroviral Treatment.
- Resistance.
- Adherence.
- Side-effects.
What is antiretroviral therapy?

Antiretroviral therapy (ART) is treatment with drugs that attack HIV itself. The medical term for anti-HIV drugs is antiretrovirals. By reducing the amount of HIV in a person's body with antiretrovirals (ARVs), some of the damage that HIV causes to the immune system can be slowed, prevented or even reversed. The aim of antiretroviral therapy (ART) is to stop the progression of HIV disease.

HIV makes millions of copies of itself every day, so the drugs must be taken every day to keep the virus under control. The drugs cannot eliminate all traces of the virus from the body, because HIV can hide inside cells.

Treatment aims to reduce the levels of virus in the blood below the limits of tests that look for HIV, called viral load tests. This gives the best chance for treatment to succeed, because it limits the risk that resistance to the drugs will develop. Although viral load tests are not yet available in most resource-limited settings, we know that if taken correctly, ART is able to reduce viral load below the limits of detection in the majority of people who take it.
What is antiretroviral therapy? (2)

- ART is not a cure
- If treatment is stopped, the virus will come back
- Treatment:
  - Controls HIV
  - Allows the body to recover its ability to fight infections
  - Reduces the chance that a mother will pass HIV to her baby during pregnancy, birth or breastfeeding
Rules for success

There are a few rules that apply no matter where ART is taken, and which greatly increase the likelihood that ART will control HIV for a number of years.

These include:

- Taking all doses as prescribed
- Taking at least three drugs
- Avoiding the use of medications that could reduce the level of ARVs in the blood
- Choosing drugs with few serious side effects

Starting treatment before levels of HIV in the blood become too high (this is more difficult because it is not possible to monitor virus levels in most people with HIV; indeed, most people with HIV do not know that they are infected until they become sick)

In the past, doctors prescribed anti-HIV drugs one at a time (monotherapy). By mid-1996, it was discovered that these drugs are far more effective when three or more are taken at the same time. This is because triple combination therapy attacks HIV at two different points in its life cycle at the same time, greatly reducing the chance that viruses with resistance to one drug will be able to carry on copying themselves.

Since the introduction of triple combination therapy, the widespread use of ART in many well-resourced countries has led to a dramatic decline in the number of AIDS-related deaths. Studies have shown that ART can improve health and prolong life of people with HIV when used in resource-limited settings as well.
Reasons treatment may fail (1)

Treatment fails if:

- The drugs are not strong enough to control the virus (most likely in very sick patients) or the patient has many other infections
- The drugs are not taken every day as prescribed (poor adherence)
- Other medicines stop the ARVs from working
- The patient cannot tolerate the ARVs due to side effects

Reasons that treatment may fail

However, these drugs are not a cure.

In some patients treatment may start too late. This may be because they have very high levels of HIV in their blood, and the drugs are not strong enough to control HIV. Or it may be because they have several serious infections which cannot be treated successfully. Although ART helps the immune system recover, it may be too late to stop some infections or conditions such as cancers.

If a person stops taking the drugs, HIV levels will rise again. ART controls HIV by stopping the virus from making new copies of itself. ART cannot kill the virus when it is “hiding” in cells. If treatment is stopped, these “hidden” viruses will form the new “seed corn” that quickly restores high levels of the virus throughout the body.

HIV can also become resistant to the drugs that then stop working, particularly, if doses are missed or if the medications are not taken properly. Everyone has a role to play in making sure that patients are able to take their medication – doctors, nurses, other community health care workers, family and friends.

Resistance not only reduces the benefits of the current combination — it may limit any future treatment options. Furthermore, resistant virus can be transmitted to uninfected people, limiting the effectiveness of available treatments for others and for the prevention of mother-to-child transmission.
 Reasons treatment may fail (2)

Too sick
- The patient may have several serious infections which are not treatable

Poor adherence
- If the drugs are not taken every day, drug levels fall and HIV becomes resistant
- Missing more than three doses a month increases the risk that treatment will fail
- Encouraging good adherence is vital
- Everyone has a part to play in good adherence, not just the patient – doctor, nurse, other clinic staff, community health workers, family, friends

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Reasons treatment may fail

Interactions with other drugs can also reduce the effects of ART, by reducing drug levels. Other drugs may stop the antiretrovirals from being processed properly in the body. One example is the TB medication rifampicin, which can reduce the levels of some ARVs.

This problem concerns not only the medicines prescribed by doctors, but any traditional herbal remedies too. The effects of many of the herbal medicines used by traditional healers on levels of antiretrovirals is still unknown, and it is possible that some could either reduce ARV levels or raise ARV levels in such a way that the patient suffers dangerous side effects.

It is important that any efforts to provide ART in a community involve traditional healers, who need to know about the possible risks of prescribing traditional herbal medicines to people taking ARVs.

In some patients, antiretroviral drugs can have toxic side effects that can be life threatening. For example, liver damage and nerve damage can be so serious that a patient must stop ART. If suitable replacement ARVs are not available, the patient may no longer benefit from ART.
The patient cannot tolerate the available drugs

- Liver damage and nerve damage, anaemia are possible serious side effects
- Diarrhoea, nausea and vomiting caused by the drugs may sometimes be too much to bear
- Treatment may have to be stopped if these side effects become serious and replacement drugs are not available
Exercise: What are the key reasons for the success or failure of ARV treatment?

Objectives
To help participants review reasons for potential treatment failure, and key information needed to prevent treatment failure.

To prepare participants for the probability that a proportion of very sick patients will experience failure of antiretroviral therapy, and that this should not be seen as a sign that ART is ineffective for all.

Equipment
Paper and pen

Time
10 mins for small groups, 15 mins for review

Actions
Divide into small groups

Ask the groups to summarise the key reasons why treatment succeeds or fails.

Feedback to the group to review the key learning points
How long will treatment keep people alive?

Many important questions relating to the best use of ART remain unanswered, including, for example, when is the best time to start therapy, and which are the best drugs to use. Nonetheless, the prognosis for people with HIV who have access to ART is significantly better than for those who do not. In Europe and North America, the majority of those who started taking ART in 1996 and who have taken it ever since are still alive.

In the developing world, ART is still very new. Although early signs are promising, we do not know whether it will be possible to sustain the same level of success as in the richer nations. This is because patients in the richer nations have usually taken several combinations of drugs since starting ART. When one combination fails, another is available to replace it. This will be less easy in the developing world, because the cost of ARVs which can be used as ‘second line’ treatment is much higher than the cost of drugs used as first-line treatment.

It is important that where second line drugs are not easily available, people with HIV and the communities in which they live are prepared for the possibility that treatment may fail. Although taking medication is the responsibility of the patient, everyone is responsible for helping people with HIV to take medication successfully. We are all working together to make the best use of limited resources!

It is important that everyone involved in the care and support of people understands that people with HIV who experience difficulties in taking medication need help and support, not blame and control.
WHO SHOULD RECEIVE TREATMENT?

World Health Organisation recommends

- Everyone with AIDS
- Everyone with symptoms of immune system damage (with CD4 count below 350)
- Children with AIDS, or with symptoms and CD4 % below 20

Who should receive treatment?

The World Health Organisation has recommended that all adults with AIDS should receive ART.

Also, anyone with symptoms of immune system damage and a CD4 cell count below 200 should receive treatment. A CD4 cell count is a measure of the health of the immune system.

Children with AIDS or children with symptoms of immune system damage and a CD4 percentage below 20% should receive treatment.

Identifying who is eligible for treatment is covered in more detail in Preparing people for treatment. This section explains in detail how to recognise conditions at each of the clinical stages of HIV infection.

The section also explains monitoring the immune system with CD4 cell counts in more detail.
The basics of anti-HIV therapy

Antiretrovirals do not directly kill the virus. Instead, the drugs interfere with the way the virus reproduces or infects new cells. By controlling the virus, antiretroviral treatment preserves the immune system from further damage and allows the immune system to recover its ability to fight infections.

The anti-HIV drugs that are currently in use fall into three main categories that each interfere in a different way with a stage of the HIV infection and reproduction process:

- Reverse transcriptase inhibitors
- Non-nucleoside reverse transcriptase inhibitors
- Protease inhibitors

Not all of the following drugs are available in every country. The drugs in each class are listed below by common name (generic name) followed by the most common brand names.
Reverse transcriptase inhibitors

Once HIV has invaded the cell, part of the virus, an enzyme called reverse transcriptase (RT) translates HIV’s genetic material into a form compatible with DNA, the building blocks of human cells. This viral DNA can then become part of the cell’s DNA and transform the cell into a factory for making more HIV.

There are two different classes of anti-HIV drug that target reverse transcriptase.

The first class are commonly called nucleoside analogues. A newer type of drug, nucleotide analogues, inhibits RT in exactly the same way but has a different chemical structure. Both types of drug act as decoys for genetic material that can deceive reverse transcriptase and defeat its attempts to construct viral DNA. Both types of NRTIs, or ‘nukes,’ are often combined in pairs. The combination of two NRTIs is considered the ‘backbone’ of antiretroviral therapy.

The nucleoside analogues are:

- ddi (didanosine, Videx, Dinx, Virosine, Aspen-Didanosine)
- 3TC (lamivudine, Epivir, Lamivir, Virovlam, Aspen-Lamivudine, Heptavir)
- d4T (stavudine, Zerit, Stavir, Virostav, Stag, Aspen-Stavudine)
- abacavir (Ziagen, Virol, Abavir)
- ddC (zalcitabine, Hivid)
- tenofovir (Viread), the nucleotide analogue
- FTC (emtricitabine, Emtriva)
Non-nucleoside reverse transcriptase inhibitors

The other class of drugs that interferes with reverse transcriptase are non-nucleoside reverse transcriptase inhibitors, which are also known as NNRTIs. Like NRTIs, they also attack reverse transcriptase, but in a very different way. These drugs bind to the enzyme so that it cannot move and work. The NNRTIs currently available do not work against HIV-2 or HIV-1 subtype O because the shape of the binding site differs for those viruses:

- nevirapine (Viramune, Nevimune, Nevirex, Nevivir, Nevipan, Aspen-Nevirapine)
- efavirenz (Stocrin, Efavir, Efferven, Estiva)
- delavirdine (Rescriptor).
Co-formulated reverse transcriptase inhibitors

A number of reverse transcriptase inhibitors and NNRTIs have been formulated into one pill. They are listed below by common names and then brand names or generic brand names where applicable.

- **AZT/3TC** (Combivir, Generic Brands: Duovir, Virocomb, Zidolam)
- **D4T/3TC** (Lamivir-S, Viro LIS, Lamistar)
- **Abacavir/AZT/3TC** (Trizivir or Trisivir, Generic Brands: Virol LZ)
- **Nevirapine/d4T/3TC** (Generic Brands: Triomune, Viro LNS, Nevilast)
- **Nevirapine/AZT/3TC** (Generic brand: Duovir-N)
- **Efavirenz/ddI/3TC** (Generic brand: Odivir Kit)
Protease inhibitors

The protease is a different HIV enzyme. Once HIV has taken control of a cell, its machinery begins to produce chains of viral protein to be packaged into new virus particles. New HIV particles are not infectious until the protease enzyme cuts each protein chain into smaller functional proteins. By binding protease, protease inhibitors prevent an infected cell from producing more infectious virus.

The protease inhibitors that are in current use are:

- indinavir (Crixivan, Indivan, Virodin)
- ritonavir (Norvir, Ritovir)
- nefifarnavir (Viracept, Nelvir, Nelfin)
- saquinavir (Invirase, Fortovase, Saquin)
- lopinavir/ritonavir (ABT-378/r, Kaletra)
- amprenavir (Agenerase).
- atazanavir (Reyataz)
Rules for combining ARVs

Where resources permit, anti-HIV therapy should be individualised, taking account of a person’s HIV disease status, treatment history and preferences. However, in most resource-limited settings, a limited number of drug combinations will be available for use.

This section looks at the main points doctors and health care workers must know about the frequently used drug combinations recommended by the World Health Organisation.

Use of drug combinations not listed in this section should only be initiated by doctors experienced in prescribing antiretrovirals.

This is because there are some important rules for combining drugs and using them in people with HIV infection:

- It is better to combine drugs of different types or classes, because they can interfere with new virus production in several different ways at once, increasing the chance that viral load levels will fall and stay low.
- It is essential to use three drugs because two drugs will not be powerful enough to control HIV replication. A combination of two drugs usually has short-term health benefits, at best.
- Some antiretroviral drugs can’t be combined because they interact with each other in a negative way (for example, AZT and d4T).
- In patients with TB and HIV, it is important to use antiretrovirals that do not reduce the levels of the TB drugs.
- Some drugs have been found effective in preventing mother-to-child transmission (AZT, 3TC, nevirapine), whilst others, such as efavirenz, should not be used during pregnancy.
- Certain drugs work especially well in combination because one boosts the effects of the other (for example, taking low doses of ritonavir can increase the effectiveness of most of the other protease inhibitors).
Pill burdens, the number of doses taken per day, and dietary requirements vary between different combinations. For example, some drugs (eg ddI, isoniazid) must be taken on an empty stomach. Other drugs can be taken once a day (eg efavirenz). These are important considerations since patients must adhere to these requirements as long as treatment is taken.

All drugs are associated with side effects, which may be more or less significant to different individuals or populations.

Some drugs penetrate the central nervous system (CNS) better than others, and so may be more active against HIV disease in the brain.

These are the basic rules that have influenced the choices of first-line treatment for HIV throughout the world.
Recommended first-line treatment

WHO recommends that treatment programmes set up in resource-limited settings choose one potent first-line anti-HIV regimen with which to start treatment in the majority of patients.

Since a number of ART regimens seem to be equally potent, the choice of the initial regimen should be guided by:

- Its side-effect profile
- Its potential for drug interactions (with TB drugs for instance)
- Its potential effect on co-infections such as TB and hepatitis
- The preservation of second-line options should the first-line regimen fail
- Its cost and availability.

Of almost 20 anti-HIV drugs approved in the US, 12 have been included on the WHO’s List of Essential Medicines for use in three or four drug combinations.

WHO recommends that regimens contain a dual nucleoside analogue backbone combined with a ‘cornerstone’ drug, either an NNRTI, a PI or abacavir (which is a particularly potent nucleoside analogue).

When available, the WHO recommends using fixed-dose combination drugs because of the simplified regimens encourage better adherence.

For group O HIV-1 subtype or HIV-2 infections, only the triple NRTI and PI-based regimens should be used because of the inherent resistance of these viruses to the NNRTI class of compounds.

The ART Backbone:
Of the possible nucleoside backbones that could be included in the first-line regimen, the WHO prefers zidovudine/lamivudine (AZT/3TC) because of its safety and efficacy profile, and also because it is available in a fixed-dose combination pill (Combivir, Lamivir).
However, some countries and programmes prefer stavudine/lamivudine (d4T/3TC) because of the risk of anaemia associated with zidovudine. Stavudine/lamivudine is becoming increasingly available in a generic fixed-dose combination pill, sometimes combined with nevirapine too.

Other nucleoside backbones with good efficacy and safety profiles include stavudine/lamivudine (d4T/3TC), zidovudine/didanosine (AZT/ddI), and didanosine/lamivudine (ddI/3TC), although WHO says that there are less data on the use of the latter combination.

Stavudine/didanosine (d4T/ddI) is included as an equally potent nucleoside backbone, but WHO notes it may have greater potential to cause lactic acidosis (particularly in pregnant women), liver toxicity and peripheral neuropathies.

Zalcitabine (ddC) has not been recommended because it must be dosed three times daily and causes severe peripheral neuropathy in many patients.

WHO recommends that abacavir be reserved for use as a cornerstone for ART regimens.

Zidovudine and stavudine should never be used together because they block each others’ activity inside cells.

A third ‘cornerstone’ drug must be added to the ‘backbone’ to form a potent ART regimen: either an NNRTI; abacavir; or a protease inhibitor, with or without the addition of low-dose ritonavir (see below).

**NNRTI-based regimens**

NNRTIs are very potent against HIV-1 but do not work against HIV-2 (largely confined to West Africa) or HIV-1 group O subtype (very rare, confined to Cameroon)

WHO recommends using either efavirenz (EFZ) or nevirapine (NVP).

NVP should be considered the NNRTI of choice in women of childbearing age unless effective non-oral contraception is used. Efavirenz should not be used in women who are pregnant or who wish to become pregnant because it may cause birth defects. Nor should it be used with oral contraceptives because it can diminish their effectiveness.

**Triple NRTI-based regimens**

The potency of abacavir makes it potentially useful as a cornerstone drug.

Abacavir has no effect on rifampicin blood levels and so may be particularly appealing in patients on TB medication.

There is a risk of potentially fatal ABC hypersensitivity that may affect up to 5% of patients starting on the medication. This may complicate its use in regions with a high incidence of illnesses such as malaria and tuberculosis that could hinder accurate diagnosis of this potentially fatal side effect.

ABC has mostly been used with AZT/3TC but WHO believes it could also be used with other nucleoside backbones. Abacavir should not be combined with tenofovir and lamivudine in a triple combination, and more evidence is needed before it is safe to recommend the use of abacavir and tenofovir together.

A fixed-dose combination (Trizivir) containing ABC/AZT/3TC is an appealing choice from the standpoint of adherence (one pill taken twice daily). It is also stable at room temperature, which is important in settings without access to refrigeration.

However, ABC/AZT/3TC may not be as effective as NNRTI or PI based regimens in patients with advanced disease (high viral loads), and is less effective than AZT/3TC/efavirenz in all patients.
Recommended first-line treatment

The guidelines also note that the nucleotide analogue, tenofovir disoproxil fumarate (TDF), can be used as part of the nucleoside analogue backbone in an initial drug combination. There are more data on the use of tenofovir and lamivudine with efavirenz, and 2 year follow-up of a large study shows that this is a safe and highly effective combination.

Do not use triple combinations of ddI, 3TC and tenofovir or abacavir, 3TC and tenofovir. These show very high failure rates.

Do not use dual nucleoside therapy by itself. It is substandard treatment!
Protease inhibitors in resource-limited settings

Possible choices:
- Nelfinavir
  - Least potent?
- Kaletra (Lopinavir/ritonavir)
  - Most potent?
- Indinavir/ritonavir
  - High number of pills
- Saquinavir/ritonavir
  - Can be used with rifampicin
- Atazanavir
  - Once daily, small number of pills, expensive and no generic version yet available

- Best reserved for second-line use
- Ritonavir and Kaletra need long term refrigerated storage
- All very expensive compared to first-line therapy

Protease inhibitors in resource-limited settings

WHO suggests four protease inhibitors as possible cornerstones: nelfinavir, indinavir combined with low-dose ritonavir (IDV/r), lopinavir combined with ritonavir (LPV/r), and saquinavir combined with low-dose RTV (SQV/r). Each has its advantages and disadvantages. Ritonavir, used to boost blood levels of indinavir, lopinavir and saquinavir, must be refrigerated to remain stable beyond 30 days. This can be a problem in some areas without access to adequate refrigeration.

Nelfinavir does not require refrigeration but has a significant pill burden, commonly causes diarrhoea and cannot be combined with rifampicin. Data suggest that it is not as potent as the ritonavir-boosted PIs. Nelfinavir must be taken with food, so combining it with ddl is awkward, since ddl must be taken on an empty stomach.

IDV/r is potent but has a significant pill count as well. Its use in tropical climates is a concern because of refrigeration problems and because it must be taken with plenty of fluids to prevent drug-related kidney stones. It is also incompatible with rifampicin.

LPV/r is also potent and is a convenient co-formulation. However, it must not be kept out of the refrigerator for more than thirty days. There is limited experience of its use in pregnancy. It should not be taken with rifampicin.

SQV/r, is a PI option that has been reported to be compatible with rifampicin. The hard-gel formulation appears to be associated with a lower rate of diarrhoea and nausea.

The protease inhibitors are best reserved for second-line treatment, and are generally much more expensive than the other classes of drugs. Guidelines in the United States prefer Kaletra as the most potent protease inhibitor.
Exercise: combining drugs

Objectives
To help participants review the key learning points on the use of recommended drug combinations
To help participants relate this knowledge to local recommendations for first-line treatment, and to help them understand why the choice has been made.

Timing
Up to 30 minutes

Cards with backbones
- AZT/3TC
- d4T/3TC
- d4T/ddI
- ddI/3TC

Cards with cornerstones
- D4T
- ddl
- AZT
- 3TC
- Efavirenz
- Nevirapine
- Abacavir
- Nelfinavir
anti-HIV therapy:

- Lopinavir/ritonavir
- Saquinavir/ritonavir
Questions to the group

- Which of the possible cornerstones should not be used with the backbones? Can you say why?
- Which of the cornerstones should not be used in pregnancy?
- Which of the cornerstones is best used in patients receiving TB treatment?
- Which of the backbones may have a higher risk of serious side effects?
- Which combination(s) is recommended for local use?

Trainer notes

The cornerstones ddI, d4T, AZT and 3TC should not be used with the backbones because they are nucleoside analogues; d4T may block AZT; nelfinavir must be taken at the same time as food whereas ddI must be taken on an empty stomach, so a ddI/nelfinavir combination would require the patient to take medication three times in one day

Efavirenz should not be used in pregnancy because it may harm the unborn child

Efavirenz, abacavir or saquinavir/ritonavir are best used in TB patients because they are not affected by rifampicin

ddI/d4T has a high risk of nerve damage, pancreatitis and lactic acidosis; d4T/3TC may have a higher risk of nerve damage

Check local protocols
Resistance

What is resistance?
HIV reproduces itself very quickly, making billions of new copies every day. Because the virus often makes mistakes when copying itself, each new generation differs slightly to the one before. These tiny differences are called mutations.

Some mutations occur in the parts of HIV that are targeted by anti-HIV drugs. This can result in strains of HIV that can still copy themselves when the drug is present in the body. These HIV strains are called drug-resistant.

Drug-resistant HIV strains vary: some may be highly resistant to anti-HIV drugs, while others may be less so. When an anti-HIV drug is started, HIV that is fully sensitive to that drug disappears rapidly, leaving behind drug-resistant viruses. These viruses continue to reproduce themselves despite the drug’s presence.

Resistance is an important reason why anti-HIV treatment can fail. Viral load, which should drop in a person when he or she starts a new drug combination, may rebound if a population of drug resistant HIV is able to emerge. A drop in CD4 cells and clinical illness usually follows if a person’s treatment regimen is not switched.

Resistance is an important reason why many anti-HIV drugs have only limited or short-term effects. Whenever HIV is still able to reproduce in the body of someone who is taking anti-HIV drugs, it is extremely likely that resistant strains will eventually emerge, and the viral load will increase. This increase is sometimes called viral load rebound.
Cross-resistance
Single mutations or patterns of mutations in HIV can produce resistance to several different anti-HIV drugs. This means that once resistance to one drug has emerged, this HIV may also be resistant to drugs not yet taken. This is called cross-resistance.

Cross-resistance may affect all currently available anti-HIV drugs to a greater or lesser extent. So resistance to one nucleoside analogue will affect the choice of other nucleoside analogues, resistance to an NNRTI drug will affect the choice of other NNRTIs, and resistance to a protease inhibitor will affect the choice of other protease inhibitors.

New classes of anti-HIV drugs are in development, but these too may well be affected by cross-resistance.
Reducing the risk of resistance

**Suppress viral load**
Resistance can emerge whenever HIV continues to reproduce whilst anti-HIV drugs are being taken. HIV can develop resistance to all available anti-HIV drugs, but if they are taken together in a combination, resistance can be delayed. This is because together, the drugs are able to exert a much more powerful effect on HIV, and because it's much more difficult for an HIV population to emerge which is resistant to all of the drugs in a combination, rather than to only one drug.

People whose viral load falls and remains below 50 copies when they start treatment are at a lower risk of developing resistance than people whose viral load does not fall that low. The current standard is for anti-HIV treatment to use three drugs.

In the absence of viral load tests, the signs that treatment is failing will be:
- Falling CD4 cell count (where CD4 testing is available)
- Return of symptoms, indicating that the immune system is declining once again

**Take care when changing to new drugs**
Merely adding a single new drug to a combination which is not keeping viral load fully suppressed can allow resistance to that drug to emerge rapidly, because the impact of that one drug is unlikely to be enough to stop HIV reproducing. It wastes that drug. If a combination is unable to fully suppress HIV, the patient should be switched to a regimen with all new drugs, if possible to give the best chance that the new combination will work.

Where resources allow, the replacement drugs should be chosen with help from a test to detect whether the virus is resistant to particular drugs. There is more about this issue in the later section, called Resistance tests.

If drugs are being switched because of side effects, and the patient’s viral load is suppressed, this does not present the same risk of resistance emerging. In this situation, doctors may change just a single drug.
Switch early
The speed at which resistance develops to different anti-HIV drugs is variable. HIV needs only one mutation to become fully resistant to 3TC, to efavirenz and to nevirapine. This simple change (just a single mutation) can happen easily, even at quite low levels of viral load rebound.

Full resistance to the other drugs may require a particular pattern of several mutations to emerge. This will take a little longer and will happen only if these drugs are taken while there is ongoing HIV reproduction. In other words, this will be more of a risk if a patient continues to take the drugs while their viral load is rebounding. The higher the viral load rebounds, the greater the risk that a drug-resistant pattern of mutations will develop.

For this reason, a rising viral load should signal the need to consider changing to a new combination, so long as there are options to switch to. However, regular viral load monitoring may not be possible in some settings. See Making Treatment Decisions later in this chapter.
The effect of missed doses

Anti-HIV drugs are prescribed at doses that will maintain an effective level of drug in the bloodstream. If a dose is missed, taken late, or with the wrong type of food, the blood level dips and the virus will be more able to reproduce itself. While the blood levels of drugs are low, viruses that have some natural resistance to the drugs being taken will reproduce easily. If these viruses gain a foothold, then even if a person starts taking drugs regularly again, enough drug-resistant viruses may already have emerged to cause treatment to fail.

Following drug regimens to the letter (taking pills exactly as they were prescribed) is called adherence (and sometimes also compliance). Unlike treatments used in many other chronic diseases, anti-HIV drug therapy requires an extremely high level of adherence if it is not to fail: some say, a level of at least 95%. Increasingly, researchers are recognising that adherence is perhaps the most important factor in successful HIV treatment, and that people taking anti-HIV drugs need support in sticking with their treatment in the long-term.
Infection with drug-resistant HIV

With the widespread use of anti-HIV drugs in many parts of the world and the accompanying problem of drug resistance, it’s become more common for people who contract HIV to be infected with a drug-resistant strain. This can happen either through sexual transmission, through contact with infected blood (for example through injecting drugs), or from an HIV-positive mother to her baby.

Becoming infected with a drug-resistant strain may seriously limit a person’s treatment options in the same way as developing resistance while taking treatments, narrowing down the range of drugs that he or she might benefit from.

Whether someone who is already HIV-positive can become infected a second time with a drug-resistant strain is much less clear. Though there is some evidence that it may occur, it’s difficult to know how great the risk is.

In the regions where ART use has been widespread, the transmission of drug-resistant HIV is on the increase. With time, and the greater use of multiple classes of HIV drugs, the transmission of HIV that is multi-drug resistant (resistant to a number of drugs and therefore more difficult to treat) is becoming more common.
True or false? Why?

Objectives
To help participants review their understanding of resistance and the reason for high adherence to treatment

Equipment
Paper and pen

Actions
This exercise can be conducted with the whole group or in small groups. If in small groups, divide into pairs and ask people to review the questions for no more than 6-8 minutes. Then review the answers in the whole group.

True or false? Why?

1. HIV cannot make errors when it copies itself
2. Resistance means that a drug does not work against HIV
3. There is less risk of resistance if a person takes all three drugs in a combination
4. The chance of developing resistance increases if people do not take medication as prescribed
5. A virus which is resistant to a drug cannot be passed onto another person
6. Resistance is only a problem for nevirapine and 3TC
Answers

1. **False.**  
   HIV makes billions of copies each day, and makes many errors

2. **True.**  
   When a virus is resistant to a drug, this means that it has changed shape and the drug cannot work in the correct way.

3. **True.**  
   Combination therapy with at least three drugs will interfere with HIV’s ability to copy itself in three ways at once.

4. **True.**  
   When drug levels fall low, viruses which have changes, or mutations, will get the chance to copy themselves before any other viruses. Every time this happens, it encourages the growth of viruses with a bit more resistance.

5. **False.**  
   Drug resistant viruses can be passed to others through sexual intercourse, breastfeeding, during birth or pregnancy, and through infected blood.

6. **False.**  
   Resistance to all drugs can happen. However, resistance to these drugs is more likely to happen first.
**Exercise: our own experience of taking medicines**

**Objectives**
To help participants review their own experience of starting a course of treatment

To help participants think about the need for preparing patients for treatment

**Actions**
Divide the group into pairs.

Each pair should take turns to discuss a past experience of taking a course of treatment. This may be, for example, a prescribed course of antibiotics or other medication, or a daily vitamin or other supplement.

- Each person should speak for up to three minutes, and then the listening partner should briefly sum up what they have heard their partner say.

- Discussion should focus on participants’ recollection of how easy it was to find information about how to take the medication, whether this advice was followed, and what influenced how easy or hard it was to do so.

- Remind the group of their confidentiality agreement, and that if participants share information with their partner which they would rather not be fed back to the larger group, then they should tell their partner this at the time.

- After each person has had a turn (allow about six minutes), resume the group and invite participants to share some of the information they had told their partner about themselves. This should be an open discussion where nobody should feel under pressure to disclose information.
Exercise: practice taking ARVs

Adherence exercise suitable for multi-day course

Objective
This exercise is designed to raise awareness of the issues involved in adhering to HIV treatment by inviting participants to take a dummy anti-HIV drug regimen for one day.

Equipment
Sweets (or something similar) which will be used to represent anti-HIV drugs.

Written pill schedules for a range of anti-HIV drug regimens TO BE CREATED

Time
This exercise is completed over the course of a day, and requires participants to be prepared and supplied with appropriate materials in advance. This may make it particularly suitable for awareness-raising within office environments, or for use within a two day HIV treatment training course. An optional feedback session of around 40 minutes can be added the following day in suitable settings.

If this exercise is to be part of a one-day course, participants will need to be prepared prior to the course starting.

Steps
- Each participant should make a written pill schedule for an anti-HIV drug regimen. A number of these are supplied within this Manual. Try to use a range of schedules.
- In addition, each participant will need a supply of sweets (or something similar, such as vitamin tablets, nuts, fruit) which will substitute for the actual drugs in the regimen described on their pill schedule. There should be enough for several day’s doses.
- Use a different sweet for each drug.
For example, a regimen of d4T/3TC/efavirenz would require two orange sweets for d4T (one pill, twice daily); two white sweets for 3TC (one pill, twice daily); and three yellow sweets for efavirenz (three pills, once daily).

Participants should be advised that they must aim to adhere to their regimen perfectly, by spacing doses correctly, and by observing any food or liquid restrictions. The aim is to simulate taking anti-HIV therapy as accurately as possible (remembering that some participants may already have done so and may wish to preserve their confidentiality).

Issues such as confidentiality, and therefore who observes your pill-taking, can be assigned as important for some participants. The trainer may choose to hand out cards to some participants instructing them of the need to take pills privately. The trainer can also determine how much discussion of pill taking is allowed to take place by setting rules such as:

- Participants must pretend that they are a community which is not doing an exercise on pill taking
- Participants must choose who to tell about their ‘medication’ and what to tell people
- The trainer should not remind people to take medication unless discussion arises spontaneously within the group and a reminder is agreed as a strategy for helping people take medication
- If the setting allows, such as within a two or three day training course, divide participants into small groups to discuss their experiences. Each group should record which factors acted as barriers to following their regimen, and which acted as enablers. Allow 15 minutes and then reform the group for a twenty minute feedback session.
- Remember that enablers and barriers vary between individuals, and that where several different regimens are available, a drug combination which is easy to manage for one person may be inappropriate for another.
- This exercise can still be a useful experiential task when undertaken outside the group setting, and without the feedback session. Encourage participants to think for themselves about barriers and enablers to adherence.
- In addition, people who are considering beginning an anti-HIV drug regimen are often encouraged to perform a dummy run such as this for a longer period. You may like to invite members of the group to do this where appropriate.
Adherence: issues for those on therapy

People beginning treatment must understand that treatment is a long-term commitment – it cannot be stopped and started. This is because combination therapy cannot eradicate the virus from the body completely. Instead combination ARV therapy stops almost all the reproduction of the virus, and stops the virus from infecting new cells in the body. When the drugs are stopped, the small amounts of virus left in the body will rapidly spread and newly infected cells will begin to make millions of copies of HIV.

People beginning treatment must also understand that treatment must not be stopped if they start to feel better. Improved health is a sign that the drugs are working, but to do the job of keeping a person alive, the drugs must continue to be taken every day.

There are a number of reasons why people stop taking medicines.

Sometimes when people are depressed and isolated they will stop taking ARVs because they feel that life is no longer worth living, or they do not have the strength to continue. If patients appear depressed, they should be questioned for signs of depression and treated accordingly.

If people believe the drugs are doing harm or might do them harm, they are more likely to miss doses. For example, if people hear stories that the drugs have harmful long-term effects, they may decide not to take them any more, or may take fewer doses because they believe this will reduce the risk of long-term harm.

People may also miss doses in an attempt to control side effects such as nausea, vomiting and diarrhoea. If doses are being missed for this reason, the side effects causing problems should be identified and the health care worker should work with the patient to identify ways of controlling the side effects. Side effects are covered in more detail later in this training course.
If the drugs are inconvenient to take, they will not be taken with any regularity in the long-term. For example, if a person finds that a drug combination that is supposedly taken twice a day in fact requires pills to be taken at three points during the day because one drug must be taken on an empty stomach and the others must be taken at meal times, this will become difficult. Inconvenient dosing is likely to be a particular problem if drugs for treatment of TB must also be taken, because rifampicin is best taken on an empty stomach to combat nausea, whilst the ARV zidovudine is best taken on a full stomach to avoid nausea.

This is why fixed dose combinations that do not rely on food are recommended by the World Health Organisation. These fixed dose ARVs can be taken twice or once a day.

If the patient does not understand when, why and how the drugs should be taken, the drugs will not be taken properly. It is essential that when preparing the patient for treatment, all these things are explained. At each visit to the clinic the health care worker should check that the patient still understands the rules for taking the drugs, and that the patient is following them.
Adherence: issues for those on therapy

Health care workers should discuss with each patient their plan for taking treatment. This will involve identifying times of day when it is suitable to take the pills. If possible, the patient should practice taking the act of taking pills for a week or two, using sweets, fruit, nuts, grains or some other small item of food that is easy to carry around. The patient should follow the plan that has been agreed, and then report back on any problems that arose so that the patient and his/her health care worker can discuss ways of solving the problems.

Membership of a support group or contact with other people with HIV already taking ARVs will also help in adherence to treatment. Encourage membership of a support group after starting treatment in order to share experiences with other people taking ARVs. Other people living with HIV will be a great source of support during this period.

Support from family members and/or friends will also be helpful. Disclosure to another person who will help in taking treatment can be helpful.

Patients should be encouraged to seek help quickly if they have problems in taking pills. They should know who they can contact for advice and support if problems arise.
Adherence: issues for healthcare workers

- Don’t make assumptions about patient adherence – ask questions and discuss solutions.

- **BEFORE TREATMENT:**
  - Do you know that the medicines must be taken for the rest of your life? Your life depends on taking them every day at the right times.
  - If you stop, you will become ill (not immediately, but after months or years).
  - Do you know that you should not share these medicines with family or friends?
  - Have you told anyone that you are HIV-positive? Telling someone else who can help you take your medicines every day will help you.
  - Check the patient’s clinic attendance – ask about reasons for missed appointments.
  - How far do you have to travel to the clinic, and do you think you can keep regular appointments here?

- Adherence: issues for healthcare workers
  - Don’t make assumptions about patient adherence – ask questions and discuss solutions.
  - Before beginning treatment, the healthcare worker should make sure that the patient understands the following points:
    - Do you know that the medicines must be taken for the rest of your life? Your life depends on taking them every day at the right times.
    - If you stop, you will become ill (not immediately, but after months or years).
    - Do you know that you should not share these medicines with family or friends?
    - Have you told anyone that you are HIV-positive? Telling someone else who can help you take your medicines every day will help you.
    - How far do you have to travel to the clinic, and do you think you can keep regular appointments here?
    - Check if the patient has missed any clinic appointments, and find out the reason for missed appointments. Poor clinic attendance may be a sign that the patient will also have difficulty in taking ARVs.
Adherence: issues healthcare workers

- After starting treatment it is important to check adherence at every clinic visit.
- Ask questions in a respectful and non-judgmental way. Ask in a way that makes it easier for patients to be truthful:
  - “Many patients have trouble taking their medications. What trouble are you having?”
  - “Can you tell me when and how you take each pill?”
  - “When is it most difficult for you to take the pills?”
  - “It is sometimes difficult to take the pills every day and on time. How many have you missed in the last 4 days (insert agreed time period)?”
- Ask about stigma related to taking the pills.
- Count pills.
- How many pills forgotten yesterday, last 3 days, last month?
Possible reasons for poor adherence

The most common reason stated by patients for failing to take pills is ‘I forgot’. Always try to discover the reason for forgetting. For example, was the patient too busy, or does their work schedule make it difficult to take the pills at the right time? Did the patient forget to take the pills once, or several times? Is there a pattern? Is the patient having problems remembering the plan for pill taking that was agreed before starting treatment?

Many people with HIV have learnt to find ways around the difficulties of pill taking. Always remind patients that they are not alone in facing these difficulties, and that membership of a support group may help in adjusting to taking medication, and maintaining very high adherence to treatment.

Other possible reasons may include:

- Difficulties in taking pills around others – if this is the case, discuss ways of taking pills privately, or identifying whether it may be necessary to disclose HIV status to a specific person who is often present when pills must be taken.
- Misunderstanding about how to take pills – review the information given about pill taking at each visit to ensure that the patient still understands correctly.
- Scheduling problems because of special events – work, travel, family events. Discuss ways of dealing with these sort of events and changes in living pattern in the future.
- Ran out of pills. Examine why this happened – was it because the patient missed an appointment to pick up new supplies, or because the clinic ran out of drug supplies, or because the patient was away from home and had not taken enough medication with them? Discuss ways of dealing with travel away from home.
- Depressed. If depression arises as a reason for failing to take medication, refer for counselling and to doctor for treatment if possible.
- Excess alcohol use. If a pattern exists, refer for counselling and to a doctor for treatment if possible.
Exercise: discussion

Objectives
To review participant understanding of reasons for non-adherence and adherence difficulties, and of procedures that should be implemented to teach and monitor adherence

To develop participants’ skills in discussing adherence with patients and helping patients to solve adherence problems

Time
35-45 minutes (20-25 minutes small group work and 10-15 minutes group feedback)

Trainer actions
Divide into smaller groups if the group is large enough

Present the questions and ask the groups to review each in turn, asking the groups to identify the most common problems they think will arise when patients try to take medication.

- How do we respond to each of the common reasons for missing doses?
- How can we help patients with future pill taking?

Feedback key points
Review the points in previous adherence slides with the group when receiving feedback.

This exercise may be most productive if the previous exercise on pill taking has been done by the group.

Remember to emphasise the importance of preparing the patient for treatment.
Understanding why side-effects occur

In addition to their potential benefits, virtually every drug carries the risk of some unwanted side effect in a proportion of patients.

Side effects are sometimes referred to as adverse drug reactions (ADRs), adverse effects (AEs), or simply toxicities.

Side effects are variable, unpredictable and a subjective experience. They are also one of the most common reasons for missing doses of anti-HIV drugs. This can affect the overall efficacy of treatment.

Before starting ART, people should be warned about the potential side effects of the drugs that they will be receiving. Such counselling can enhance adherence and encourages the early identification of serious toxicities.

Some of these side effects will go away after the first few weeks of therapy. Others may be severe, even life-threatening and warrant a change in therapy. The side effects of most drugs are well established. However, some of the drugs used by people with HIV are rather new, and have been released onto the market after only a relatively small number of people have taken them for a relatively short period. This means that their longer term or rare side effects may not be fully understood, particularly in resource-limited settings. The emergence of metabolic and fat disorders (lipodystrophy) associated with anti-HIV therapy, demonstrates that some side effects take months or years to be identified.
Types of side effects

Side effects can be divided into two main types:

- Allergic side-effects.
- Side effects due to the direct effects of the drug.

Allergic side effects occur when the immune system reacts to a drug or its metabolites (the chemicals into which a drug is broken down in the body), by causing symptoms such as a rash or fever. This is unpredictable: some people can take a drug without developing an allergy, while others suffer severe reactions to it. Sometimes allergies take time to develop.

If the patient is allergic to a drug, he or she will probably experience this type of side effect no matter what dose is taken. However, it is sometimes possible to desensitise the immune system by starting to take the drug at a very low dose, then gradually building up to the correct dose over time. This strategy has worked well for many people who are allergic to co-trimoxazole (Septrin), the commonest form of PCP prophylaxis, but must always be done under medical supervision.

Similarly, nevirapine treatment must be started at half dose for the first 14 days because of the risk that the patient will develop a serious rash.

Other side effects may be caused directly by unwanted effects of the drug itself, rather than by the immune system’s response. For example, some drugs damage the cells in the bone marrow that are responsible for producing new blood cells, so may lead to blood abnormalities such as anaemia (low red blood cell count).

Side effects are often dose-related; the more of a drug that is taken, the greater the risk and/or the severity of the side effects. So a drug may cause side effects in only a small proportion of people who take the usual dose, but in a larger proportion when it is given at a higher dose.
Some people may be vulnerable to unusual or unpredictable side effects because of inherited conditions. The most common cases are among people whose genetic make-up means that they produce unusually low levels of certain enzymes. For example, people who are lacking an enzyme called glucose-6-phosphate dehydrogenase (G6PD) are more likely to suffer blood toxicities from antibiotics such as dapsone, because the lack of this enzyme allows toxic by-products of the drug to accumulate in the body. In some settings, at-risk groups can be tested for these genetic deficiencies.

Others may be at particular risk because of other infections or health problems. For example, people with liver damage due to hepatitis viruses may be more vulnerable to liver toxicities than others.

**Timing of Side Effects**

Most side effects occur within the first few weeks of starting a drug, then may lessen or disappear.

Side effects such as nausea, vomiting, diarrhoea, bloating, abdominal discomfort, headache and dizziness tend to be associated with the time at which drug levels reach their peak in the blood. This is why side effects may occur regularly at certain times of day. It may be possible to minimise the inconvenience by adjusting the time at which the particular medications are taken, although this may also depend on a person’s eating schedule and the need to take medications with food or on an empty stomach. Doses of anti-HIV drugs must be spaced regularly, so patients should not alter the timing of pill taking without consulting their doctor first.

During the first few weeks of treatment, especially high levels of the drug may be present in the bloodstream. After this time the peaks and troughs in blood levels of the new drug become less pronounced, and side effects wear off. This is why some treatments, such as nevirapine, are dose escalated.

It may be easier for patients to put up with a side effect if they know that it will just be a temporary problem. During this period, they may need to take other treatments to deal with the side effects, such as anti-nausea or anti-diarrhoea medicines.

For a few drugs, the risk of side effects depends on the cumulative dose taken. In other words, the patient may experience few or no side effects during the first weeks or months of treatment, but once the total amount of drug taken passes a certain level, the risk of side effects increases.
Common side-effects

In resource-limited settings, it is particularly important to be aware of the side effects and serious adverse events that may occur on anti-HIV therapy because medical attention is not as readily available as in well-resourced regions. Patients experiencing side effects on treatment should be urged to report any unusual symptoms to their health care provider or caseworker at the earliest possible opportunity to reduce the risk of serious health problems. Many of the side effects can be managed with other medications, but in some cases, the anti-HIV regimen may have to be switched.

Detailed advice on managing side effects of specific drugs within a combination is covered in the training module on Recommended ARV combinations.

Trainers note: Commentary in this section will need to be tailored to the locally recommended drug combinations.

Anaemia

Anaemia means a shortage of red blood cells. Red blood cells transport oxygen around the body, so anaemia can cause symptoms of tiredness and breathlessness. Laboratory monitoring of patients should include haemoglobin counts where possible.

Anaemia can be caused by opportunistic infections, and is common in the population due to poor iron intake in food. It can also be caused or made worse by AZT treatment. Anaemia is best avoided by either reducing the dose or changing to an alternative drug that does not cause anaemia. If anaemia returns when a full dose of AZT is restored, it is best to switch to another drug. People with severe anaemia may need blood transfusions to top up their red blood cells, but blood transfusions should be used sparingly because of the risk of complications.
Diarrhoea

Diarrhoea is a common side effect of all the protease inhibitors, ddl and abacavir, as well as a number of antibiotics used by people with HIV. With some drugs, diarrhoea goes away after the first few weeks or months of treatment; however for some people it becomes a permanent feature of living with the drug.

The severity of the diarrhoea varies. Severe diarrhoea, involving several trips to the toilet each day, large, uncontrollable liquid bowel movements, and feelings of weakness and dizziness as a result of the loss of fluids and electrolytes is experienced by about a quarter of people starting treatment with nelfinavir and a fifth of people starting saquinavir (Fortavase soft gel capsule formulation). Similar levels have been reported in people taking amprenavir, lopinavir, ritonavir and indinavir. Many more people taking protease inhibitors experience less serious diarrhoea.

Changes in diet have little effect on protease inhibitor and other drug-related diarrhoea. However a variety of treatments are available to doctors to try and control diarrhoea caused by drugs. These include: imodium (loperamide), calcium supplements, and oat bran tablets. In the absence of these treatments, local non-herbal remedies for diarrhoea should be used, such as rice water. More fibre in the diet (or other stool binding agents) may help with nelfinavir diarrhoea, although this goes against typical advice for managing diarrhoea with other causes.

In some cases, it might be necessary a change to a different anti-HIV drug regimen.

There are many infections that commonly cause diarrhoea amongst people with HIV, also, particularly those with a low CD4 count. If diarrhoea does not settle down within a few days or is severe, patients should be advised to contact their health care provider to determine the cause and proper treatment of their condition.

Nausea & Vomiting

Many anti-HIV drugs are associated with nausea (the feeling of wanting to vomit or be sick). It is a common symptom, which most people with HIV experience at some time. Nausea and vomiting are common side effects of antiretroviral drugs but may also be caused by a variety of different causes such as other infections, pregnancy or anxiety. If nausea is accompanied by other symptoms, the underlying cause needs to be investigated and treated. If it is due to drug side effects then the dose and frequency may need to be altered or the drug discontinued. Some drugs, e.g. AZT, can be taken with food in order to limit nausea. Anti-nausea medication (sometimes called anti-emetics), taken as either tablets or injections, can help manage symptoms. This can be particularly important when starting a new treatment, such as anti-HIV combination therapy, which is associated with a high risk of nausea and vomiting during the first few weeks. Adequate anti-nausea medication can make adjusting to the new regimen easier.

If anti-nausea medications are not available, drinking ginger tea or chewing ginger root may relieve nausea. Other local, non-herbal remedies for nausea should also be investigated.
Common side-effects

**Fatigue**
People with HIV may use a lot of energy because they are constantly battling the virus, so fatigue may slowly develop as a consequence of HIV itself. Often, taking anti-HIV therapy slows HIV production in the body, and thus many people have more energy after taking anti-HIV drugs. However, some anti-HIV medications may also cause fatigue, especially in the first few weeks of therapy.

If fatigue does not improve, and is accompanied by breathlessness, it may be a symptom of anaemia, especially in AZT-treated patients.

If fatigue is accompanied by weakness, abdominal pain, nausea and loss of appetite, it could signify either liver toxicity or lactic acidosis. If this pattern of symptoms appears, the patient should seek medical advice as soon as possible.

**Hepatitis**
Some anti-HIV drugs, particularly ritonavir and nevirapine, and other prescription medication can cause the liver to become inflamed, particularly when the health of the liver has already been compromised by the viruses hepatitis A, B and C. Severe liver damage can increase the chances of developing liver cancer, which can prove fatal. In rare cases, liver toxicity can be life threatening.

Typical symptoms of liver problems include extreme tiredness, a feeling of general poor health, weight loss, loss of appetite, nausea and vomiting, abdominal pain, itchy skin, and an enlarged or tender liver. Jaundice may also develop. This is easily noticeable as the skin and whites of the eyes turn yellow, urine becomes dark and stools pale. Liver function is should be monitored by blood tests amongst people taking anti-HIV drugs.
Common side-effects

Mental Health Problems
It is known that the anti-HIV drug efavirenz (Stocrin) can cause psychological disturbances. Some people have difficulty sleeping, or vivid dreams or nightmares. Other people have reported depression without any other apparent cause. Others may experience psychotic episodes and suicidal tendencies. These side effects are more common in patients with a history of mental illness or recreational drug use. Usually, the milder psychological disturbances resolve within a few months on treatment, but for a small number of patients the effects may worsen in severity and be long lasting. Efavirenz may have to be discontinued. In some cases, antidepressant drugs, which relieve the symptoms of depression by altering chemicals in the brain which influence mood and behaviour, may need to be taken.

Neuropathy
Neuropathy is damage to the nerves. Nerves transmit signals within the brain and spinal cord (the central nervous system or CNS), and extend from the CNS to the muscles, skin and organs. The nerves that are outside the CNS are called the peripheral nervous system (PNS). They detect sensations, such as pain, and control movement. Peripheral neuropathy usually involves damage to the nerves in the feet or, less commonly, the hands. The symptoms can range from mild tingling and numbness through to excruciating pain that makes it impossible even to wear a pair of socks. Usually both sides of the body are affected equally. Neuropathy can be caused by a shortage of vitamin B12, or by infections such as cytomegalovirus (CMV) or HIV itself. However, neuropathy is commonly caused by several anti-HIV drugs – in particular, ddC, ddl, d4T (stavudine) and, to a lesser extent, 3TC. It can also be caused by other drugs prescribed for people with HIV, such as the antibiotics dapsone and the anti-TB drug isoniazid, among others. The risk of developing neuropathy may be increased if more than one of these drugs is being taken. Those with a history of neuropathy caused by something else, such as HIV itself, may be more likely to develop neuropathy while on antiretrovirals. Treatment may have to be discontinued and/or the dosage reduced. Certain treatments can also reduce the pain, such as carbamazepine or amitriptyline, and in severe cases, strong painkillers.
Common side-effects

**Rash and Hypersensitive Allergic Reactions**

Anti-HIV drugs, particularly NNRTI’s can cause skin rashes. Most are usually mild and disappear as the body gets used to the drug.

A very small number of people (0.1 – 0.5%) develop a life-threatening reaction called Stevens Johnson Syndrome (SJS). Toxic epidermal necrosis (TEN) is another severe skin condition. Serious skin reactions such as SJS and TEN may cause severe rash, crusting or ulcers of the mouth or genitals, burning skin and large layers of skin to flake off (exfoliative dermatitis). If these symptoms develop within two weeks of starting a drug, treatment should be stopped immediately.

A rare life-threatening allergic reaction can also occur on abacavir. Sometimes this reaction is accompanied by a rash, but it more commonly begins with a flu-like illness. If a confirmed case of abacavir hypersensitivity reaction occurs, abacavir should be stopped and it must not be taken again.
Common side-effects

Neutropenia
Neutropenia means a shortage of blood cells called neutrophils. Neutrophils are white blood cells that mainly attack bacteria and fungi, so people who have neutropenia are at increased risk from these infections. The most common cause is drugs such as AZT, the anti-CMV drug ganciclovir or drugs used to treat cancers and tumours. Neutropenia can be treated by reducing the dose or stopping the drug which is causing it.

New bacterial infections in people whose health has begun to improve may indicate neutropenia. Symptoms may include:

- Fever, aches, pains, chills and sweating
- Sores in the mouth or gums
- Chest infections – cough producing lots of green mucus
- Very sore throat and fever
- Ear ache and fever
- Discharge from the genitals
- Sudden swelling around cuts or sores on the skin
Common side-effects

**Thrombocytopenia (low platelet count)**
Platelets are cells in the blood that help the blood to clot. If you do not have enough platelets you may bleed more often and it can be difficult to stop the bleeding. If thrombocytopenia becomes severe, blood loss may become serious, or internal bleeding may occur. This is a rare but serious side effect of AZT. A platelet count below 10 million per ml indicates serious thrombocytopenia.

Where it is not possible to carry out a complete blood count that includes a platelet count, signs of developing thrombocytopenia include:

- Nose bleeds
- Frequent bruising
- Small pinpoint red spots
- Blood in the stools or urine
- More severe: coughing up blood
- Switching treatment from AZT is recommended if this is the likely cause.
Common side-effects

Lactic Acidosis
Lactic acidosis is a very rare but serious side effect of the nucleoside analogue class of anti-HIV drugs. Although extremely rare when it does occur there is a high chance of death even if it is treated immediately. Lactic acidosis may occur in conjunction with a severely enlarged liver.

Lactate or lactic acid is a by-product of sugar (glucose) processing by cells. Little organs inside each human cell called mitochondria process glucose to provide energy for the cell. Lactate is a by-product of this process. Lactic acidosis occurs when there is an over-accumulation of lactate in the body that the liver is unable to clear.

Nucleoside analogues disrupt mitochondria function inside the cell. This could cause excessive lactate production, which could lead to lactic acidosis is the liver is not functioning properly. Many of the other side-effects of nucleoside analogues may also be associated with damage to mitochondria including peripheral neuropathy (numbness or pain in the feet and hands); bone marrow suppression; pancreatitis (inflammation of the pancreas); hepatic steatosis (accumulation of fat in the liver); and myopathy (muscle damage).

Between 30-60% of people taking nucleoside analogues have elevated levels of lactate in their body, but levels are rarely high enough to induce the symptoms of lactic acidosis. These symptoms include general gastrointestinal symptoms such as nausea (feeling sick), vomiting, bloating, abdominal pain and lack of appetite, as well as malaise, and difficulty in breathing. Of course, these symptoms can also occur for many other reasons. In people who have lactic acidosis, the liver may be swollen and tender (hepatomegaly), and liver enzymes, which are measured by a liver function test, may be abnormally high.

Lactic acidosis may be more common in those who have been taking nucleoside analogues for an extended period, especially d4T containing regimens. Other risk factors for developing lactic acidosis include pregnancy, obesity and women may be at greater risk than men. There is some evidence of a link with severe infection and malnutrition.

If there is evidence of lactic acidosis, then treatment with nucleoside analogues should be stopped immediately.
Group exercise: side-effects

How can we relieve side effects, and when should patients seek medical attention?

Note: if a local protocol already exists for when patients should be referred for medical attention, it is important to highlight the contents as part of this training session

Objectives
To help participants review the information on drug side effects
To help participants identify local resources that may assist in the management of side effects

Equipment
Paper and pen for each group, flip chart for group feedback

Time
Up to 10 minutes for introductory discussion, 30 minutes for small group discussion and 20 minutes feedback to main group (dependent on overall size of the group)

Steps

- Identify the main ARVs used in the locality with the whole group (refer to local protocols if a limited set of combinations will be prescribed). List on a flipchart.
- Divide into groups of four
- List the main side effects of ARVs used in the locality
Divide side effects into two groups
  ■ Serious and life threatening
  ■ Side effects which can be relieved

Brain storm local remedies that might relieve less serious side effects

Feed back to the main group – maintain two lists – one of the serious side effects that require medical attention, the other of local remedies. Establish consensus on each and highlight any absences or potential issues with drug interactions where local remedies are used.
Key side-effects by drug or drug class

The more common side effects of ART are described below by drug or drug class. It should be noted that the incidence of the following side effects have been determined largely by studies conducted in the US and Europe. Side effects may be more or less common among populations living in resource-limited settings.

Nucleoside analogue reverse transcriptase inhibitors:

Class-specific: lactic acidosis
Lactic acidosis, is the accumulation of dangerously high levels of lactic acid in the blood stream. It is a very rare syndrome, but if it goes unrecognised, mortality can be high. Patients experiencing it may complain of weakness, abdominal pain, nausea and vomiting, shortness of breath, fatigue and hypotension. It is more common in women, those with high body mass, prolonged NRTI use (in particular d4T), and, possibly, pregnancy. The initial symptoms are variable; an early clinical syndrome may include generalized fatigue and weakness. These may be observed as soon as one month or as late as 20 months after starting therapy. All drugs should be stopped at once because the longer a patient is on therapy the more symptoms worsen.

Abacavir is well tolerated by most patients. However, in developed countries, approximately 3-5% of adults and children who have taken abacavir develop a potentially fatal hypersensitivity syndrome.

Abacavir Hypersensitivity syndrome: The reaction appears to produce a wide variety of symptoms that appear suddenly and grow worse with each dose of abacavir. These include fever, nausea, vomiting, diarrhoea, abdominal pain, malaise, fatigue, sore throat, cough and shortness of breath. There is often no rash to speak of. Although these symptoms can be present with a lot of other illnesses, the sudden onset of both respiratory and gastrointestinal symptoms after starting abacavir is suggestive of a hypersensitivity reaction. Patients who have recently started abacavir who experience these symptoms should seek medical care as soon as possible. Abacavir treatment should be stopped immediately and never restarted if the health care provider suspects hypersensitivity. Death can occur within hours of restarting abacavir therapy.

Didanosine. The most common symptoms associated with ddI are diarrhoea, nausea, vomiting and/or abdominal pain, with an incidence of 5-18%. Two of the more serious side effects are peripheral neuropathy and pancreatitis.
Peripheral neuropathy is damage to the peripheral nervous system. The symptoms range from tingling, or burning sensations to severe pain usually in the feet, legs and sometime in the arms and hands. Numbness and muscle weakness can also occur. Peripheral neuropathy has been reported in 6-15% of patients taking ddl, but it may be more common (and severe) in patients taking other neurotoxic drugs such as d4T. Symptoms usually resolve within a few weeks of stopping drug.

Pancreatitis. Inflammation of the pancreas has been reported in about 1-7% of the patients taking ddl, and it can be fatal. Symptoms include nausea, vomiting and abdominal pain. Blood tests may find elevated levels of pancreatic enzymes. The incidence is dose related, underscoring the need to dose ddl properly by body weight, and is increased in patients who have had pancreatitis or gallstones in the past. Other risk factors include alcohol and obesity. ddl should be permanently discontinued if pancreatitis is confirmed.

Lamivudine is fairly well tolerated. Patients may experience transient headache, fatigue and gastrointestinal upset. The major serious reported toxicities are pancreatitis, primarily in children with advanced disease who are receiving treatment, and peripheral neuropathy. On rare occasions, the drug may cause toxicity to the liver and neutropenia (a drop in the levels of a type of blood cell that fights bacterial infections).

Stavudine's most significant toxicity is peripheral neuropathy. As with ddl, this condition is dependent upon dose, duration of therapy and the use of other neurotoxic drugs such as ddl. Symptoms usually resolve within 2-3 weeks after the discontinuation of d4T. d4T may also be more frequently associated with lactic acidosis and liver toxicities.

Zidovudine's most common side effects are blood related: severe anaemia and/or low white blood cell counts occur in over 5-10% of patients. These side effects are dose-related and more common in patients with advanced HIV disease. Medications such as ganciclovir and hydroxyurea may aggravate the condition. Fatigue, headache and nausea occur in 5-10% of zidovudine-treated patients but are usually temporary, going away after a few weeks on continued therapy. Zidovudine can also cause reversible muscle pain, weakness and wasting in about 17% of patients.

Non-nucleoside reverse transcriptase inhibitors

Class-specific: rash and hepatitis
Rash and liver toxicity can occur on either nevirapine or efavirenz. However, these drugs do not appear to cause rash and hepatitis in the same manner. Patients who experience rash or liver toxicity on nevirapine can probably be safely switched to efavirenz, unless the toxicity on nevirapine was very severe.

Efavirenz's most serious adverse effects are to the central nervous system and to the fetus when taken by pregnant women.

Efavirenz CNS effects: Possibly half of patients on efavirenz experience some neuroligical side effects ranging from altered senses, dizziness, headache, insomnia, depression, impaired concentration, agitation, nightmares, and drowsiness. Some of these symptoms may be manageable by taking the drug before bedtime. A minority of patients experience severe psychiatric symptoms including delusions, manic episodes and severe depression. They may even become suicidal and require anti-psychotic medication. This is particularly common in people with a history of mental illness or recreational drug abuse.

Efavirenz-associated birth defects: Efavirenz caused significant birth defects in primates exposed to it in utero. Efavirenz is particularly dangerous during the first trimester, so pregnancy should be avoided by women taking the drug. Women who may become pregnant while on ART should be advised to use a different drug, if possible.
Nevirapine most commonly causes a skin rash, though in some patients it can cause hepatitis and a life-threatening hypersensitivity reaction (see below). In developed countries, about 17% of the patients appear to develop a rash on nevirapine, the rash can be severe leading about 6-8% of patients to quit treatment. It may occur more often in women and in persons of Asian descent. The rash most commonly appears on the body and arms, usually within the first month of therapy, although occasionally it may start a few weeks later. Nevirapine should be stopped if the rash is severe or effects the mucosa, or if there are symptoms consistent with hypersensitivity syndrome.

Steven’s-Johnson syndrome is a life-threatening hypersensitivity syndrome that has been reported in about 0.3% of the patients who have taken nevirapine. Symptoms include fever, swelling, pain in the muscles and joints, and hepatitis all of which occur before the rash, and sometimes without a rash even developing. Nevirapine treatment should be stopped as such as reaction can prove fatal.

Nevirapine-associated hepatitis can occur in about 13-17% of patients, severe hepatitis may occur in 1-9%. It may be more common in patients with a history of alcohol abuse, coinfection with hepatitis B or C and in patients who are older or are women.

Protease inhibitors

Class-specific: insulin resistance/diabetes:
Insulin resistance occurs in up to 40% of patients treated with PIs, and hyperglycaemia (high blood sugar), new cases of diabetes mellitus and worsening of pre-existing diabetes mellitus have also been reported. High blood sugar has been reported in 3-17% of patients receiving PIs; about 1% of these patients develop clinical evidence of diabetes. Patients receiving PIs should be advised about the warning signs of hyperglycaemia, such as excessive thirst, excessive urination, and excessive appetite. Hyperglycaemia resolves in some but not all patients after the discontinuation of therapy. Most experts, however, would continue ART with supportive therapy (oral hypoglycaemic drugs or insulin) in the absence of severe diabetes.

Class-specific: hyperlipidaemia:
(elevated triglycerides and/or cholesterol) have been linked to treatment with all the PIs, although the increases tend to be higher in patients receiving ritonavir. Whether this will lead to a higher rate of cardiovascular disease or pancreatitis, is unclear.

Class-specific: lipodystrophy:
(changes in body fat distribution) have been reported in as many as 80% of patients receiving PIs. They have also been described in connection with nucleoside analogue therapy (particularly d4T-containing regimens). These changes are gradual and generally not apparent until months after the initiation of therapy.

Class-specific: increased bleeding episodes in haemophiliacs:
have been reported in patients with haemophilia A or B who are receiving PIs. They may develop skin hematomas (a swelling of clotted blood caused by a broken blood vessel). Serious bleeding in the gastrointestinal tract or within the skull has been reported rarely. Bleeding episodes usually begin to occur about three weeks after the initiation of PI therapy.

Class-specific: hepatitis:
All PIs can cause liver inflammation, though ritonavir has been more frequently associated with severe liver toxicity. Elevated liver enzymes in the blood can occur at any time during PI treatment. Liver toxicity is more common in patients who: drink too much alcohol; had high liver enzymes on blood tests when treatment started; use other medication that can cause toxicity to the liver such as d4T; or are coinfected with hepatitis B or C.
Class-specific: bone disorders (weakening and destruction of bone and cartilage) have been reported in adults and children on ART. The risk appears higher in patients receiving PIs than in those on regimens that do not contain PIs.

Amprenavir: The most common side effects associated with amprenavir are headache, nausea, rash, diarrhoea, vomiting and tingling around the mouth. The incidence of nausea and vomiting may be significantly increased when amprenavir is used together with zidovudine (AZT).

Indinavir: kidney stones/and elevated bilirubin

The most serious side effect of indinavir in adults and children is the formation of kidney stones, seen in about 9% of patients; it may be more frequent in hot climates. Temporary abnormal kidney function, including acute kidney failure, and inflammation have been observed in some patients with nephrolithiasis. The condition may be signalled by severe pain beneath the ribs with or without blood in the urine. Indinavir may need to be interrupted for a few days. The condition may recur in have of the patients if indinavir is restarted. Patients taking indinavir must drink plenty of fluids — at least 1.5 litres of water daily and more in hot weather.

Elevated bilirubin has been seen in about 10% of patients receiving indinavir; in most cases the maximum bilirubin elevation was observed after one or more weeks of treatment; jaundice (yellowing of the skin) and elevations in liver enzymes have been reported only rarely.

Indinavir may also cause dry skin, bald patches in the hair, dry lips and ingrown toe or finger nails. About three percent of patients develop acid reflux.

Lopinavir/ritonavir (Kaletra) most commonly causes diarrhoea, weakness, and elevations in cholesterol and triglycerides. Pancreatitis has been reported in adults, possibly due to high triglyceride levels.

Nelfinavir: The most common adverse effects on nelfinavir are diarrhoea, abdominal pain, flatulence and rash.

Saquinavir: The primary toxicities are mild gastrointestinal disturbances, such as nausea, diarrhoea and abdominal pain; headache; and reversible elevations in liver enzymes. Nausea and diarrhoea are more common with the soft-gel formulation than with the hard-gel formulation.
Symptoms of lipodystrophy

Whilst many side effects develop in the first few weeks on new medication, some do not emerge until the medication has been used over the longer term.

As more information becomes available about the mechanisms that cause long-term side effects, it will be more possible to develop effective interventions to prevent and treat these side effects. Of the side effects to emerge over the past few years, ART-associated metabolic disturbances have caused the greatest concern in developed countries. The metabolic changes may be responsible for serious side effects such as lactic acidosis, diabetes, the body fat changes known as lipodystrophy, and potentially heart disease.

Metabolism disorders— the basics
Antiretroviral treatment seems to have complex effects upon metabolism in people with HIV. Metabolism is a general term for the breakdown of food and production of energy within the body. Sugar and fat are sources of energy. Abnormalities in sugar and fat levels or abnormalities in the processing of fats and sugars may indicate metabolic disorders and cause physical symptoms.

A number of metabolic disorders have been reported among people taking anti-HIV therapy. These include hyperlipidemia (high levels of fat in the blood); diabetes, high blood sugar (hyperglycemia); and insulin resistance; and high levels of lactate (a by-product of sugar metabolism in the body) and elevated ALT (a liver enzyme).

Cholesterol and triglycerides
The general term for body fats is lipids. There are two main types of lipids: cholesterol and triglycerides. Cholesterol is made in the liver from saturated fats in food and is essential for the production of the sex hormones, as well as the repair of cell membranes. To move around the body, cholesterol joins up with special proteins to form ‘lipoproteins’ which are carried in the blood. There are two kinds of lipoproteins; low-density lipoproteins (LDL), which carry cholesterol from the liver to the cells and high-density lipoproteins (HDL), which return excess cholesterol to the liver. One may often hear cholesterol described as ‘good’ and ‘bad’. HDL, or ‘good’ cholesterol clears cholesterol from the arteries to the liver, where it is removed from the body. LDL or ‘bad’ cholesterol is associated with hardening of the arteries (atherosclerosis). This can lead to angina, heart attack and stroke.
Fatty substances in the blood like LDL and HDL cholesterol are often grouped together with triglycerides and called blood lipids. Triglycerides are one of the basic building blocks from which fats are formed.

Lipid abnormalities were seen among HIV-positive people prior to the introduction of ART. People with AIDS often had raised LDL cholesterol and declining HDL cholesterol. People on protease inhibitor therapy have been shown to have higher levels of lipids compared to people not on protease inhibitors. Rises in cholesterol and triglycerides may put someone at increased risk of heart disease particularly if they smoke, are overweight or have high blood pressure. If tryglyceride levels are extremely high, there is a risk of acute necrotising pancreatitis, a potentially fatal but very rare condition.

**Diabetes, hyperglycemia and insulin resistance**
Diabetes mellitus is a condition caused by the inability to use sugar in the blood properly. Low levels of insulin, a hormone used to regulate sugar in the blood, and insulin resistance are often causes of diabetes. Insulin resistance means the body is not able to use insulin properly to process blood sugar and can lead to high levels of sugar in the blood. A high level of blood sugar (hyperglycemia) is thus a sign of diabetes. Diabetes due to protease inhibitors seems to be a relatively rare metabolic side effect. A family history of diabetes may increase a person’s risk of developing diabetes on ART.

**Heart disease**
ART-related changes in the body's metabolism, such as high HDL cholesterol levels, could increase the risk of heart disease. Some studies have shown thickening of and damage to the arteries among people taking protease inhibitors. Other risk facts such as smoking, high blood pressure or diabetes, pre-existing heart conditions, and age also play roles in the development of heart disease. Male sex may also play a role: the risk of coronary heart disease in men occurs ten years earlier than in women. As medical developments improve the prognosis for people with HIV, general health conditions such as heart disease, which more commonly affects middle aged or older people, are likely to grow in importance for people with HIV.
What causes lipodystrophy

Lipodystrophy is the medical name used to describe body fat changes. Three patterns of body fat changes are being seen in people with HIV who are taking HAART. These are:

- Gaining fat on the abdomen/ belly (central fat), or between the shoulder blades, or around the neck, or in the breasts (mostly in women)
- Losing fat from under the skin, which becomes most obvious in the arms, legs, buttocks and face; this can result in facial wasting, shrunken buttocks and prominent veins on the arms and legs
- A mixture of both fat gain and fat loss

The fat gain is not sub-cutaneous fat (the soft fat directly under the skin). Central fat gain is within the abdomen. This makes the belly feel harder. Some people have described it as feeling taut, like a football or like pregnancy. This fat accumulation may also interfere with food intake.

The majority of people who develop these changes experience a mixture of both types of body fat change. These fat changes are often referred to as “fat redistribution”.

The body fat changes can be accompanied by metabolic changes (rises in levels of fats and sugar in the blood).

A few people will also develop small, unusual fat deposits on other parts of the body. These are called lipomas.

Who will develop body fat changes?
People taking protease inhibitors and nucleoside analogues (NRTIs) together seem more likely to develop some or all of these changes than people taking these agents alone.
There is some evidence to suggest that the following might increase the risk further if in those taking combination therapy:

- Research shows that the longer a person takes combination therapy, the more likely he or she is to have changes in body fat. Studies in well-resourced countries have shown that after three years on a combination of nucleoside analogues and a protease inhibitor, 30 to 40% of people will develop body fat changes. It is not yet clear whether the risk carries on growing after this point, or whether most people who will eventually get lipodystrophy can expect to do so within three years of starting treatment with a protease inhibitor and NRTIs.
- People who are overweight are more likely to complain of an increase in central fat.
- Fat loss is more commonly reported in men than women, although women with average or low body weight are more likely to observe loss of fat than women who are overweight.
- Older people are more likely to report both central fat gain and fat loss from the arms, legs, and face. Some of these changes could be being confused with the usual body fat changes that occur with ageing; because the syndrome is new, it will take time to be sure.
- The extent of immune system damage before starting, and the recovery after, treatment also seems to influence the risk of body fat changes. A large CD4 cell rise and a past CD4 cell count below 200 have been associated with more severe fat redistribution (but this may be an indication of very successful treatment or the length of time a person has been on treatment, both of which have been suggested as causes of the body fat changes).
- Body fat changes have been less common in children, but tend to become more noticeable in teenagers.

**ART and body fat changes**

The causes of body fat changes in people with HIV are still unknown. This makes it very difficult to give clear advice about how to avoid lipodystrophy and how to treat the problem.

At first, people with HIV and doctors thought protease inhibitors caused body fat changes. In fact, the changes have also been seen in people who have never taken protease inhibitors, but not as often.

It is hard to tell whether particular drugs are more likely to cause fat wasting, or fat gain. This is because none of the studies conducted so far has been large enough or carefully enough designed to show whether one drug or another is more closely linked to body fat changes.

Until studies can be designed and carried out which address all these problems, it will not be possible to say for sure whether any specific drugs are more likely to cause body fat changes than others.

Nevertheless, we do know that some protease inhibitors cause changes in the body's handling of fats and sugar when they are given to people without HIV. This shows that in HIV-positive people, it is the drugs themselves, and not just the disease or the effects of the drugs on the immune system, which are contributing to the problem.

It is not clear how nucleoside analogues (NRTIs), such as AZT, d4T, 3TC, abacavir and ddI contribute to the problem. However, fat loss has been seen at a lower rate in people who just took two nucleoside analogues with no protease inhibitor, in people who took a protease inhibitor and a non-nucleoside reverse transcriptase inhibitor with no NRTIs, and in people who took protease inhibitors with no other drugs.

In other words, the most likely conditions for getting lipodystrophy seem to be when taking nucleosides and protease inhibitors together.
Are body fat changes dangerous or harmful?

Body fat changes alone do not appear to substantially contribute to poor future health. However, they may be stigmatising, uncomfortable, or embarrassing and so worry many people when they occur. Persistent changes in fat and sugar metabolism, together with central fat increases however, could increase the risk of heart disease if a someone also has other risk factors for heart disease (such as smoking or a family history).

Body fat changes may nevertheless have a serious effect on a patient's quality of life.
HAART and the heart

- Some HIV drugs, especially PIs, can increase fats and sugar levels which may increase heart disease risk.
- Several large studies have found no relationship between increased fats and sugars and heart disease risk.
- The DAD study found the longer you are on HAART, the higher the risk of heart disease.
- Still fairly low risk, and benefits of HAART outweigh risks, in short term.
- Stop smoking, eat healthily, and exercise more.