

HIV i-Base



treatment training

for advocates

Sections 1-8: HIV Basics

- The immune system and CD4 count
- Virology, HIV and viral load
- Introduction to ARVs
- Side effects of ARVs
- OIs and co-infections
- HIV and pregnancy
- Drug users and ARVs
- Science Support modules

HIV i-Base



Treatment training for advocates

Sections 1-8

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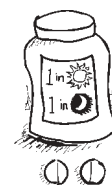
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Introduction to this resource

This training resource uses eight work units for the basic course.

The format is very simple.

Other units can be added if they are more appropriate to different situations.

This resource is part of a copyright-free project that will be available on the i-Base website to download in various formats, or to work online. As with other treatment information produced by i-Base we encourage translations into other languages.

It is written for people who do not have a scientific background or any medical training. People who already have a basic understanding of the way HIV and treatment works may want to start with the intermediate course.

Some of the sessions are very short, and have simple questions. This is so that anyone can start to learn about treatment, and in turn pass that information on to others.

Even if you are not very academic, and this training is difficult, you can still be a very good and effective advocate and activist. It will help though if you can understand these sessions.

The training material has been written in a way that makes it easier for you to then explain the information again to other people without a medical background.

As community advocates and trainers, it is important to understand and explain things that people may not be initially very interested in. And explain them in a way that makes the new information relevant to getting better care.

Most people don't want to know about science - they just want to get on with their lives.

But this often involves explaining the science behind how things work. It means getting people to believe in things that they can't see, and getting them to trust in things that are too small to see with their own eyes.

We can't see a virus, or a CD4 cell or any of the things that are tested in blood with the naked eye. We can't see whether one pill or another will work better or at all.

But understanding a bit about how treatment works does empower people to have more control over their treatment and their choices.

This course is written by treatment advocates who have had no formal medical training and who are mostly HIV-positive – and we've tried to remember the biggest surprises that we found as we developed our own treatment knowledge.

Sometimes it's the surprises that keep you learning – because they show how different things are to how you imagined them.

Hopefully some of these will be helpful in developing your own treatment interest – once you start, you realise there is always more to learn.

Introduction to course programme

Sessions 1-8 – Basics of HIV and treatment

The first six sessions are to introduce the most important aspects of treatment to a basic standard.

The aim for each section is to provide a general understanding for each area. This will form the structure for more advanced training and your own research in the future.

Understanding and completing this would enable a good grasp of 90% of the issues involved in HIV and treatment.

Although this course presents a structure for what you need to learn about HIV, the approach to learning will be more practical than just reading or taking notes.

Advocacy is based on a problem solving approach to new information.

You will never reach a point where you suddenly know everything.

You will always need to use research to confirm the things you think that you know, and to find out new things that you don't.

This is also because information itself changes very quickly.

Each section then has around 15-20 questions that you should be able to answer.

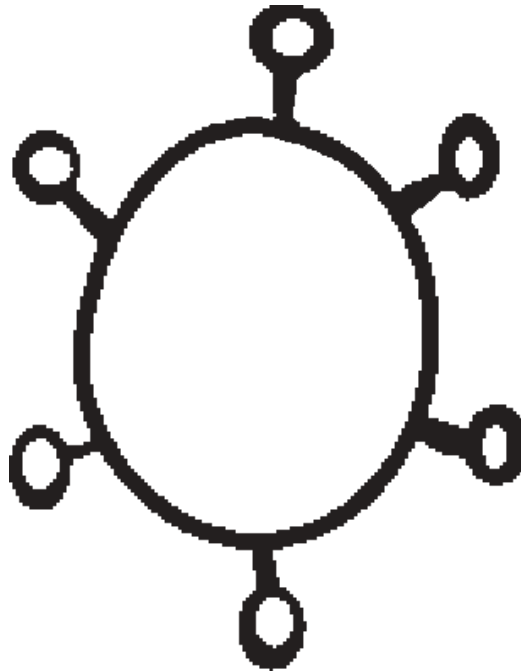
The aim for the first section of basic training is to get familiar with the most important terms and concepts.

You do not need to know everything about each area in detail, and it will be too much to deal with if you try to learn everything straight away.

These first eight sections are to provide the basic structure to build on.



Section I: the immune system and CD4 count



I.1 Introduction

If you understand CD4 counts and viral load test you will be able to understand:

- the risk for HIV-related illnesses
- when and why treatment is recommended at different times, and
- whether treatment is working properly.

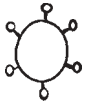
The first session starts with your body and the way that it fights infections using the immune system. For example HIV is a virus and you need to know how your body reacts to a virus. HIV is a virus that attacks the immune system – so you need to understand how your body is damaged.

Sections 2 links closely to Section 1.

I.2 Aims for Section I

After reading and completing this section, advocates will have a basic understanding of:

- the ways a scientist or doctor understands the immune system
- CD4 cells and CD4 tests and what they mean
- how the CD4 count is used to monitor HIV infection
- use of CD4 count in treatment decisions and guidelines



1.3 Definition of AIDS

AIDS stands for Acquired Immune Deficiency Syndrome

Acquired	⊕	because it is largely an infection that people catch
Immune	⊕	because it relates ^{relates} to your immune system
Deficiency	⊕	because it reduces ^{reduces} your immune system
Syndrome	⊕	because it describes a collection of different infections and illness caused by the HIV virus

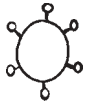
Learning about HIV will involve learning lots of new terms that you do not already know. Every time you see a word you don't understand, write it down and find out the meaning. After a while you will find you have learnt things you would never have expected. For many HIV-positive people the meaning of the words that make up AIDS do not mean very much until they are explained clearly.

1.4 Basic organs in the body

It is easy to know the bits on the outside of your body, but most people don't know where their thymus, or kidneys or lungs are, or what these organs do.

Understanding treatment is much easier if you know the way the major systems in your body work.

Heart - The heart is between the two lungs. The heart muscles continually circulate blood around your body. You know your heart is working because you can feel your heart beat and you can feel the blood at your pulse. The heart pumps oxygen to every part of your body and pumps the oxygen-depleted blood back through the lungs to be re-oxygenated.



Lungs - your lungs are sponge-like organs and every time you breath they filter oxygen from the air where it passes through tiny vessels into the blood - and is then carried to the heart to be pumped round your body. The lungs filter carbon dioxide from your body when you breath out.

Liver - your liver is the organ below the lungs that acts like a filter for the blood. Chemicals and impurities - such as drugs and medications - are filtered out by the liver. Important other activities occur in the liver including production and processing of many body fats. The liver is the only internal organ that can regrow.

Kidneys - the kidneys also act like a filter. Some drugs are filtered more by the kidneys than the liver. Waste products are filtered by the kidneys and leave the body as urine. You have two kidneys and they are at the back of your body. Any blockage to your kidneys is extremely painful and can cause permanent damage. Although you are born with two kidneys, many people survive very well with just one.

Stomach and intestines - The stomach is where food, drink and oral medications is starts to be broken down and processed in the body. Nutrients and drugs are absorbed through the stomach and small intestine walls. The small intestines are about 5 metres long. The large intestines are about 1.5 metres long.

Thymus - this is a small gland high in the chest where CD4 cells and other lymphocytes develop. CD4 cells are sometimes called T-cells ('Thymus-cells'). The thymus is very active in children and adolescents, and becomes much less active as you grow older.

Pancreas - your pancreas is a pistol shaped gland below the liver that releases digestive enzymes into the small intestine and hormones that control sugar levels in your blood. You can live without a pancreas but you need to take insulin to regulate blood sugar levels and take supplementary digestive enzymes.

Skin - your skin is the largest organ in the body and makes up 16% of your body weight. It stops your body from drying out and is the main barrier against infection.

Bone - your bones are a living material and about 10% of bone cells die and are replaced each year. If bone cells are not replaced quickly enough, bones becomes brittle and break more easily.

Bone marrow is the soft tissue inside bones and is the source of all blood cells.

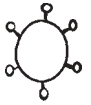
Blood is the fluid pumped by your heart to deliver oxygen and nutrients to every part of your body and carries waste products away. Blood contains cells (red cells, white cells, platelets etc) and plasma.

Plasma is the fluid part of blood that contains nutrients, glucose, proteins, minerals, enzymes, and other substances (i.e. without the blood cells).

Lymph is a clear fluid that contains white blood cells and antibodies and is distributed around your body through a series of lymph vessels nodes and organs. The lymph system supports the blood in removing waste products from the body.

Although a lot of information about your health and HIV comes from blood tests, only 2% of the HIV in your body is in your blood. Most of the other 98% is in the lymph system.

Lymph nodes are the little lumps that sometimes get enlarged in your neck, under your arms and in the crease between your legs and your body.

**Web resources:**

There are hundreds of sites on the internet that explain basic biology, immunology and other medical terms.

The following sites may be useful:

In the US, a 39-year-old man on death row donated his body to science after he was executed. His body was frozen, cut into one-millimetre-thick slices, and photographed. The data were made available in 1994 on the Internet by the US National Library of Medicine.

To view two- and three-dimensional representations of the human body based on these data, visit these sites:

http://www.nlm.nih.gov/research/visible/visible_human.html

BodyQuest - a site designed to explain human anatomy to students ages 11–16. Try starting with the tour, which gives you an overview of the human body and allows you to find more detailed information:

<http://library.thinkquest.org/10348/?tqskip1=1&tqtime=0326>

The Atlas of the Body - An interactive exploration of muscles, internal organs, and skeleton of the human body from the American Medical Association.

<http://www.ama-assn.org/ama/pub/category/7140.html>



1.5 How the immune system works (before HIV infection)

Some ways of protection from infection are straight forward:

- Your skin is a major barrier for example

If your skin is damaged - for example through a tiny cut or tear in the skin (in the case of a virus like HIV) or is breathed in (in the case of TB) then your body uses different cells to attack and break down this new infection.

Two medical words are often used when talking about the immune system:

- Antigen is a word for small particles of infectious material broken down in the body, that is recognised by the immune system.
- Antibody is a type of protein made by certain white blood cells in response to a foreign substance (antigen). Each antibody can bind to only a specific antigen. The purpose of this binding is to help destroy the antigen. Some antibodies destroy antigens directly. Others make it easier for white blood cells to destroy the antigen

Cellular and humoral immunity

There are two main ways that your body deals with different infections

- Humoral immune responses are based on antibodies.

HIV is routinely diagnosed using an antibody test that looks for the bodys response to HIV. This usually takes 2-3 weeks to develop, but can take several months and occasionally longer.

- Cellular immunity is based on CD4 and CD8 responses

T-cells are a type of white blood cell (lymphocyte). The two main types of T-cells are CD4 cells and CD8 cells.

CD4 cells are sometimes called helper cells because they help the immune response by sending signals to CD8 cells.

CD8 cells are sometimes called killer cells because they recognise and kills cells that are infected with a virus

Sometimes these processes and functions overlap

Generally your body uses cellular immunity to fight viruses, and to fight HIV.

Macrophages are another type of larger white blood cell that engulf or swallow up infectious organisms or waste material from dead cells.

They also signal other cells in the immune system.



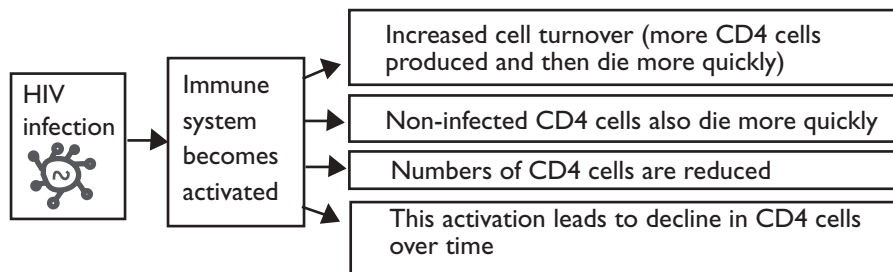
I.6 How HIV interacts with the immune system

HIV is an especially difficult virus for the body to deal with.

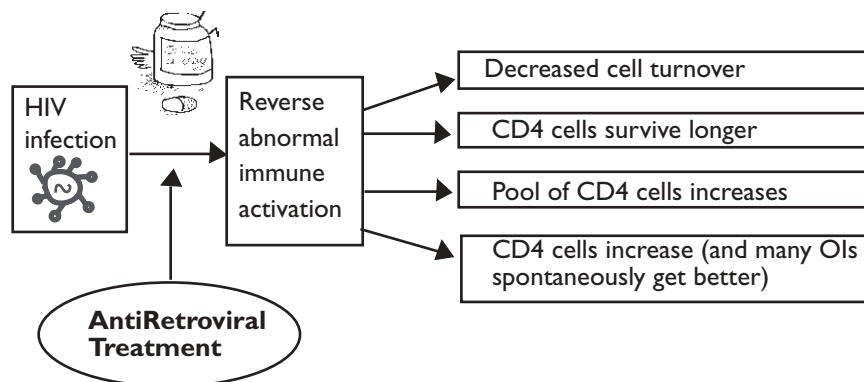
This is because the cells that the virus uses to reproduce itself are the cells that the body uses to fight infection. HIV infection makes infected cells die more quickly, and it also makes infected cells signal to other cells to die more quickly.

These two factors are like a dog chasing its tail!

- HIV infection makes the body produce more CD4 cells to fight this new virus.
- These new cells provide more target cells for HIV to infect and reproduce
- The body responds by making more cells to fight the new virus



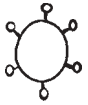
After a while the HIV-specific T cells get worn out and disappear (in most people within 6 months after infection). After many years the body gets very tired and the rest of the immune system is worn down.



This is a difficult page to understand. The main point is that HIV makes the immune system go into overdrive - producing more and more cells.

These cells also die very quickly though and over time the immune system loses out. This is why your CD4 cells, as measured by your CD4 count, drops.

ARV treatment blocks HIV from reproducing as quickly, and returns your immune system back to an almost normal state.



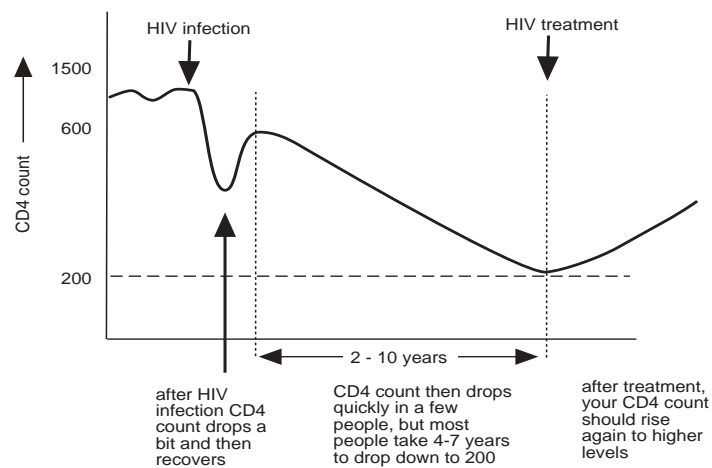
1.7 CD4 count as 'surrogate marker'

Pattern of CD4 count after HIV infection without treatment.

The CD4 count (full name: CD4+ T-lymphocyte count, but also called CD4+ T-cell or T4 count) is the result of a blood test that tells you how many of these cells are in a cubic millimetre of blood.

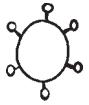
The CD4 count is a very good 'surrogate marker' for how much HIV has damaged your immune system. It can tell you your risk of infections and when you need to start treatment.

The average CD4 count for an HIV-negative person is usually between 600 and 1600 - but a few people have naturally lower or higher levels than this.



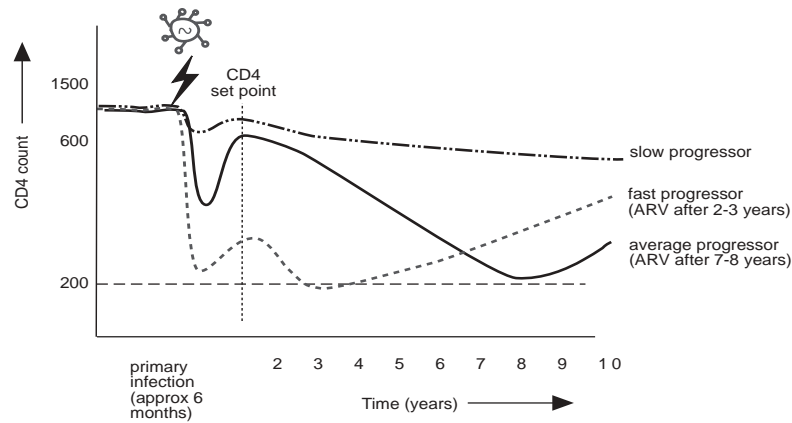
- A few weeks after infection with HIV the CD4 count usually falls
- Then as the body's immune system begins to fight back, it goes back up again - though not to the levels that it was before HIV infection.
- This level is sometimes called the CD4 set point and usually take about 3- 6 months after infection to stabilise, but it can take much longer
- Then the trend for the CD4 count is to gradually go down over several years. The average rate that CD4 counts fall is about 50 cells/mm³ every year. In some people this will be much faster and in some people much slower.

Most people's immune system controls HIV very successfully without needing drugs for many years.



I.8 How quickly does HIV progress in different people

The time it takes for someone's CD4 count to drop (for example to 200 cells/mm³) varies a lot between different people



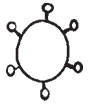
Approximate time for CD4 counts to drop to 200 cells/mm³:

- <5% people take 1-2 years (fast progressors)
- 10% people will take 3-4 years
- 70% people will take 5-9 years
- 10% people will take 10-12 years
- <5% people will not see any drop in their CD4 count even after 10-15 years (long term slow progressors)

Sometimes people who have very serious illness when they are first infected (during seroconversion) will lose CD4 cells more quickly.

There is no way of telling how quickly someone will progress, other than by monitoring their CD4 count over time.

People who progress more quickly, and who lose CD4 counts more quickly will still get as good and as strong a response to treatment when they use it as people who progress more slowly.



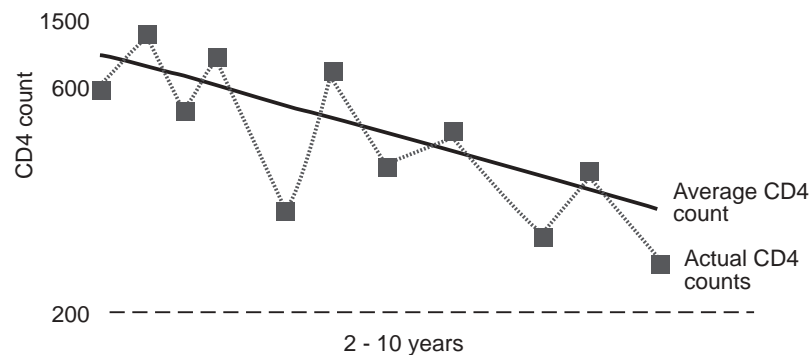
I.9 Interpreting CD4 results: CD4 count and CD4 percentage

A single CD4 count doesn't mean very much. You really need to get several results over time to see what the trend is.

When you have several results you can see whether the trend is going up or down and how quickly it is changing - or whether it is generally stable.

CD4 counts can go up and down depending on the time of day, whether you have eaten a fatty meal, if you have just been running up and down stairs, whether you have other infections or even if there were just more or fewer cells in that sample of blood.

This is why the trend looks at the average results.



Each point on the dotted line shows an individual 'absolute' CD4 count. This is the number of CD4 cells in a cubic millimetre (cells/mm³) or microlitre (cells/uL) of blood. In scientific papers this is sometimes written as 'cells × 10⁶/L'.

The solid line shows the average of these results - and shows that in this example the trend shows the CD4 count falling over time.

If you ever get an unexpectedly high or low count, then if possible this should always be confirmed with a second test.

The CD4 percentage (CD4%) is sometimes a more stable indication of whether there has been a change in the immune system. It is the percentage of total lymphocytes that are CD4 cells.

A CD4% of 12-15% is about the same as a count of under 200 cells/mm³.

A CD4% of 29% is about the same as a count of over 500 cells/mm³, but there is a wider range for higher values.

An HIV-negative person has a percentage of about 40%.

Absolute CD4 counts are not used for children, who are monitored by CD4%.

I.10 Differences between adults and children

- Children generally have much higher CD4 counts than adults.
- Babies have higher CD4 counts than children.
- Over time, and as we age our CD4 count drops gradually.
- Because the differences are so much higher in children though, children with HIV are monitored by CD4% rather than absolute CD4 count.



1.1.1 Different stages of infection

Stages of HIV infection are described in slightly different ways by different organisations like the WHO and the US medical system etc. Now that there are effective treatments, these stages are less important. The WHO definition relies on symptoms only and not test results. The US-based definition relies on symptoms and lab results.

WHO staging categories:

The WHO categories do not include CD4 counts. A list of the related symptoms are included in Appendix II. These symptoms are used with the following performance stages:

Performance Stage 1: asymptomatic, normal activity

Performance Stage 2: symptoms, but nearly fully ambulatory

Performance Stage 3: in bed more than normal but < 50% of normal daytime during the previous month

Performance Stage 4: in bed > 50% of normal daytime during previous month

US CDC staging categories:

Clinical categories are determined with the letters A, B and C.

CD4 count is determined by numbers: 1, 2 or 3.

	Clinical categories		
	A	B	C
CD4 count	No symptoms, inc primary infection	Symptoms (if not A or C) *	AIDS-defining infections **
1 = 500 or over	A1	B1	C1
2 = 200-499	A2	B2	C2
3 = less than 200	A3	B3	C3

* Less serious or early symptoms include: candida (thrush) in the mouth, or vagina if not responding to treatment, fever (over 38.5 °C) or diarrhoea lasting >1 month, cervical abnormalities or cancer, pelvic inflammatory disease (PID)

** AIDS defining infections include all the most serious infections including: oesophageal candida, CMV disease, many active lymphoma, pulmonary TB, KS, MAI, PCP, weight loss >10%, bacterial pneumonia, PML, toxoplasmosis. See Appendix I for a full list.

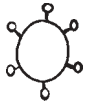
In the US (but not Europe) a CD4 count under 200 cells/mm³ is an AIDS diagnosis.

Before there were effective treatments, people were categorised based on how ill they were and their life expectancy. This system is used less now where treatment is available.

People did not generally get better, so that the progression through stages A, B and C was a 'one-way' direction.

For more information on classification of HIV see:

<http://hivinsite.ucsf.edu/InSite?page=kb-01-01#S3X>



1.12 CD4 level cut-offs for opportunistic infections

An 'opportunistic infection' or OI is the name given to HIV-related illnesses that your body would normally be able to fight off, but which take advantage of the fact that your immune system is damaged.

The lower a person's CD4 count, the higher the risk that they will develop HIV-related illnesses.

This is why monitoring of CD4 levels is important when you are not on treatment.

You can still be well and healthy with a CD4 count that is below 200, below 100, below 50 or even below 10 - but it is much more likely that you will have serious health-related problems.

Different illnesses become more likely at different CD4 counts. Many serious and life threatening illnesses become a risk when the CD4 count drops to under 200 cells/mm³.

When the count drops below 300:

Diarrhoea from microsporidia and cryptosporidia

Skin problems - candida (thrush), dry skin etc

When the count drops below 200:

PCP (pneumonia) and chest infections

Toxoplasmosis - parasitic infection that commonly causes brain lesions

When the count drops below 100:

MAI / MAC - bacterial infections similar to TB

Cryptococcus infection - fungal infection that can cause meningitis in the brain and PCP-like symptoms in the lungs

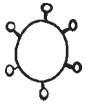
When the count drops below 50:

CMV (cytomegalovirus) - a viral infection that can cause permanent vision loss and blindness

More detailed information on these opportunistic infections are given later in the course.

The main point is that the lower your CD4 count the higher the risk of these and other illnesses.

When your CD4 count increases after starting HIV treatment, your immune system is often able to deal with these infections by itself again.



1.13 Use of CD4 count in guidelines for starting therapy

The main use of the results from CD4 tests is to know when to start HIV treatment.

If HIV drugs were perfect - with no side effects and no resistance - then everyone would use treatment as soon as they were diagnosed.

However, they are not perfect.

This means you need to decide when the risk of not using treatment becomes outweighed by the risk of using treatment. Or when the benefits of treatment are greater than the risks of treatment.

In general, people are unlikely to have HIV-related illnesses when their CD4 count is over 200 cells/mm³.

Several large studies have also shown that people who start treatment with a CD4 count of 200 compared to people starting at 350 or above, get the same benefit.

WHO and UK treatment guidelines therefore recommend starting treatment in people who have no other symptoms, before the CD4 count falls below 200.

US treatment guidelines recommend starting treatment before CD4 counts falls below 350. Several years ago both UK and US treatment guidelines recommended starting at higher levels, and they may change again in the future - especially if better and easier to tolerate drugs become available.

If you have any HIV related symptoms or illnesses, then treatment is recommended, even if your CD4 count is over 350.

Remember that any one count is just a general figure. It doesn't matter very much whether you start treatment at 180 or 220 - but generally around 200 is better than waiting much longer.

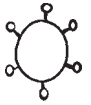
In practice, many people start treatment at much lower levels - and they will still do very well.

Many people are only diagnosed with HIV when they have HIV-related illness and CD4 counts that are under 200.



I.14 Glossary: Section I

acute infection	early infection (first few months with HIV)
antibody	cells in your immune system that recognise antigens
antigen	infectious material produced by a virus or bacteria
TB	tuberculosis - bacterial infection that commonly infections the lungs but which can affect other organs
CD4 cell	cell (lymphocyte) in your immune system that signals CD8 cells to destroy a virus. CD4 cells are also used by HIV as factories to reproduce in
CD8 cell	cell (lymphocyte) in your immune system that kills cells that are infected with HIV
chronic infection	established infection (everything after the first 6 months)
CMV	cytomegalovirus - infection that can produce permanent loss of sight. Occurs mainly with CD4 count under 50. Can also affect other organs.
immune system	different parts of your body used to fight infections
MAC / MAI	bacterial infection similar to TB called MAI in Europe and MAC in the US
opportunistic infections	also called 'OIs' - infections that occur after your immune system has been damaged by HIV
prophylaxis	a drug that you take in order to prevent a future illness
surrogate marker	an indirect measure for something else that can not be easily measured directly (i.e. a CD4 count is an indirect marker for HIV disease)
toxoplasmosis (toxoplasma)	infection that affects the brain (can cause fits and memory loss). Risk increases with CD4 under 100. Co-trimoxazole (Septrin) can protect from toxo.
WHO	World Health Organisation



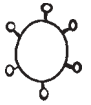
1.15 Questions: Section I

I. Immune system and immunology basics

Give simple explanations:

1. What does AIDS stand for?
2. What is a CD4 T cell?
3. What is a CD8 T cell?
4. What is the 'normal range' of a CD4 count for an adult?
5. Give other names for each of these cells
6. What is CD4% and when is it used?
7. What is the difference between cellular and humoral immune responses, which are used by the body to fight HIV?
8. What is a 'surrogate marker'?
9. How often should a CD4 test be done? (describe several different circumstances)
10. How does CD4 test results relate to when to start treatment?
11. Describe the general pattern of what happens to your CD4 after HIV infection, in early infection and through chronic infection?
12. Draw a graph to show this.
13. Which OI's become more likely after your CD4 count falls below these levels: 300, 200, 100, 50?
14. What is the main difference between children's and adults CD4 counts?
15. What is an antigen?
16. What is an antibody?

Now write 1000 words about the immune system including this and other information you learnt about CD4 cells and CD4 cells counts. (i.e. a basic leaflet that you would send to someone who wanted to know about this).



1.16 Course evaluation. I

Please take a few minutes to complete this evaluation. Any comments are appreciated, including on the usefulness of the evaluation as we can develop this into an online resource.

Session One:

How much of the information was new? None 1 2 3 4 5 All

How useful was the source material? Very 1 2 3 4 5 Not

How much support time did you need in 1-2-1 questions?

Were you given enough support for this section?

Did you find better internet sites for information, if so, which ones?

Did the questions relate to the information you found yourself?

What was your pass rate?

Sit the test again in one week to see how much you remember.

Did your pass rate improve?

Section 2: virology, HIV and viral load



2.1 Introduction

The second section provide information about HIV as a virus: what kind of infection is HIV; what happens after you are infected and how is the virus monitored.

2.2 Aims for Section 2

After this section you should understand:

- Definition of HIV
- Difference between different causes of illness: viruses, bacteria, fungal and parasitic.
- Viral dynamics of early and chronic infection (the natural history of HIV)
- Impact of co-infections on viral load.
- Brief history of viral load technology and accuracy.
- Importance of viral load on treatment and off treatment.
- Viral lifecycle.
- Basic theory of resistance.
- Recap CD4 and viral load graphs and superimpose them.

2.3 Definition of HIV

HIV stands for Human Immunodeficiency Virus.

Immunodeficiency means 'reduced immunity'

A virus is genetic organism that can only reproduce *inside cells* of another living organism. Some viruses are harmless and others can cause illness. *Antiviral* drugs are used to treat viral infections.

Examples of viral infections that affect people with HIV include hepatitis A, B and C; cytomegalovirus (CMV); herpes (HSV);



2.4 Other causes of illness

Other causes of illness include bacteria, fungal parasites and protozoa - and different types of treatment are used for each cause. For example, antibiotics do not work against a viral infection. Sometimes this is complicated though because the differences are not always clear.

Bacteria - bacteria are single-cell micro-organisms. Some bacteria are healthy and help your body and some cause disease. Antibiotic drugs are used to treat bacterial infections.

Examples of bacterial infections that affect people with HIV include tuberculosis, bacterial pneumonia, sinusitis, gonorrhoea and some skin infections.

Fungi - fungal infections

Examples of fungal infections that affect people with HIV include candida (thrush); cryptococcosis. Anti fungal drugs are used to treat fungal infections.

Parasites - Parasite-related infections: cryptosporidium, microsporidium and protozoa like toxoplasmosis.

2.5 HIV and infection

HIV is actually a difficult virus to catch, but at the same time people can become HIV-positive after only one exposure to the virus.

HIV dies within a minute or so in blood and other bodily fluids once they are outside the body. HIV is not infectious in saliva.

Levels of HIV are measured using viral load tests and these are discussed in more detail later in this chapter in Section 2.5.

The risk of catching HIV is related to the risk of the virus coming into contact with broken skin or through cells that are close to the surface of the skin. The risk is highest when viral load levels are high.

The majority of people with HIV stay well for many years after they are infected.

Some people (less than 5%) will become ill within a few years and a few people (also less than 5%) can go for 15 years or more before they need treatment.

Although a lot of information about your health and HIV comes from blood tests, only 2% of the HIV in your body is in your blood.

Most HIV is in your lymph system and lymph nodes. These are the little lumps that sometimes get enlarged in your neck, under your arms and in the crease between your legs and your body).

2.6 Viral dynamics of early and chronic infection

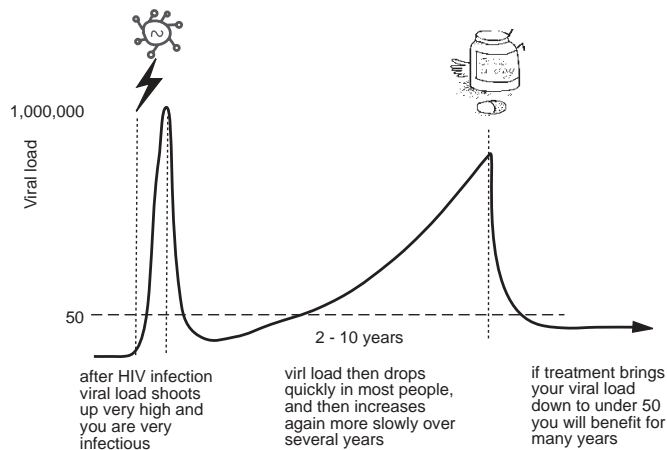
The 'natural history' of any illness is the term to describe how that illness normally progresses if left untreated.

It is very important to understand the natural history of HIV.

With HIV infection there are several different periods including infection, seroconversion, primary infection, chronic infection and late-stage illness.



Fig. 1: What happens to your viral load after infection



Infection - this is the point when the virus infects the first cells. It then takes several hours for these newly infected cells to be carried, with the virus, to the lymph nodes.

During the new few days or weeks the virus continues to multiply. Over this time the levels of viral load will be going up very high very quickly.

Seroconversion - as viral load increases, and this high level of viral activity produces symptoms in 50-80% people that include sweating, fevers, temperature, weakness and tiredness etc.

The body produces an immune reaction to this new infection, and starts to produce antibodies to fight the virus. It can take 1-3 months after infection for this immune response (antibodies to HIV) to be strong enough to be detected on an HIV-antigen test.

Primary HIV Infection (PHI) - also called early infection or acute infection. Primary infection is usually used to describe the first six months after infection.

Chronic infection - chronic infection is the term given to HIV infection after the first six months. Chronic infection can last for many years. It can take anything from 2 - 10 years until the majority of people need treatment. With treatment, chronic infection can be lifelong - ie 20, 30, or 40 or more years.

Late stage infection - AIDS - this is the term used to describe the most serious stage.

This is usually in people who do not have access to treatment, who are only diagnosed very late, or whose treatment has stopped working.

2.7 Reinfection with HIV

There have been several recent reports of cases of reinfection with HIV.

This is where someone who is already diagnosed with HIV, is exposed to, and infected with, a second different strain of HIV.

The reason that this is controversial, is that for many years it was assumed that once you had been infected with HIV, reinfection was not a risk.

It is not clear how often this occurs, or the risk factors for reinfection.

Some recent studies have not indicated that the risk is very high, but the fact it has been reported is something to be aware of.

Many of these case reports have included people in early infection.

They have also included examples where someone whose treatment was working effectively has been reinfected by someone with drug resistant HIV, and where the treatment then stopped working.

This is the real risk of reinfection.

Two people with the same non-resistant virus, or with the same resistant virus would not risk the same difficulties from reinfection, as someone who is reinfected with drug-resistant virus.



2.8 What is a viral load test

A viral load test measures how much HIV is in a sample of blood.

After infection, viral load levels are very high, but then your body fights back and it drops to much lower levels. Over time though, usually over several years, the levels of virus increases again. It is usually very high (around 50,000 - 200,000 copies/mL) by the time that your CD4 count drops to around 200 cells/mm³.

A viral load test is used after starting treatment to check that the drugs are working.

If ARV treatment brings viral load down to less than 50 copies/mL, then treatment can last for many years.

These tests are used in many countries but are difficult to get in many others.

In some countries, viral load and CD4 tests cost much more than the drugs. New research is also looking at developing new tests that will be just as good but which are not so expensive or difficult to run.

Even if you do not have access to these tests, it makes a difference that you understand how CD4 and viral load change.

These two tests tell any doctor 95% of what they need to know about the risk of HIV to your health and how well your treatment is working.

2.9 History of viral load technology

Without viral load tests it is possible that combination therapy would never have been developed or understood. This was a new technology that was only being developed as a research tool during the 1990s.

Viral load tests showed that HIV was never a dormant infection. It is a gradually progressive viral infection that is always active.

There are three main types of viral load tests:

- i) PCR - polymerase chain reaction (written as PCR RNA)
- ii) bDNA - branched DNA
- iii) NASBA

These tests multiply a small sample of virus many times so that it can be more easily counted. But this means that the individual results from any *one* test are not very accurate and can have a 3-fold margin of error.

So, if your viral load result is 30,000 - the real result could potentially be anywhere between 10,000 and 90,000 copies/mL.

As with CD4 test results, it is important to look at the trend of results over several tests to get a picture of whether there is any change.

- Never make any treatment decision based on the result of one test.
- Different tests are also sensitive down to different minimum levels.
- For example the first tests in 1995 could only measure down to 10,000 copies/mL. By 1996-7 the next tests were able to measure down to 400 or 500 copies/mL. Since 1998 the most routinely used tests now measure down to 50 copies/mL although some tests used for research are even more sensitive (down to 5 copies).

When viral load tests were first developed many doctors thought that it would be impossible to measure the progress of a disease on an individual level.

2.10 Impact of co-infections on viral load

Other infections can have an impact on HIV viral load.

Sexually transmitted infections like herpes, gonorrhoea and syphilis increase the levels of HIV in sexual fluids (semen and vaginal fluids).

Viral infections like the 'flu can increase your viral load while the infection is active.

Responses to some vaccinations may also increase viral load temporarily.



2.11 Compartments and sanctuary sites

Although we measure viral load in blood, which is one compartment, several other important places in the body have barriers that limit both HIV and HIV drugs from moving freely.

These are sometimes referred to as compartments or sanctuary sites.

They include the genital tract, the CSF - Cerebral Spinal Fluid - the fluid that circulates around the brain and spinal column, and the brain itself.

HIV can develop differently in these compartments. Some drugs get into these compartments better than others.

Resistance can be different in different compartments - it will usually develop in one compartment but can then travel to other sites. Viral load levels can be different in each compartment.

This makes HIV a very complicated illness - although in practice, because blood is used for most tests, you are unlikely to know exactly what is going on in other compartments.



2.12 Importance of viral load on-treatment and off-treatment

When not on-treatment:

When not taking ARVs, then the CD4 count is more important than viral load.

Viral load tests are still useful, but they are not as important at predicting the risk of infections or when you should start treatment.

The one exception may be if your viral load is very high. If your viral load is over 100,000 or perhaps over 500,000, this would be seen as a reason to start treatment at a higher CD4 count than 200.

When on-treatment:

If you are using HIV treatment, then viral load tests are probably more important than a CD4 test. This is because on treatment, your CD4 count is probably already increasing.

Your viral load when on-treatment is a good measure of how long you can expect treatment to last. Sometimes viral load tests are used to check adherence.

If your viral load goes to below 50 copies/mL then treatment can last for many years. When viral load is this low, resistance usually only develops if you are late or miss taking your medication.

If it is reduced, but only gets down to for example 500 copies/mL, then there is enough HIV reproducing each day for resistance to develop to the drugs in your combination.

If you do not have access to a viral load test, then your doctor will manage you based either on CD4 tests or on clinical symptoms.

Viral load is higher in children than in adults when not using ARV treatment, but it is just as important for children on treatment to reduce their viral load to less than 50 copies/mL.

It is not clear how often you need to have your viral load tested. UK and US guidelines recommend a viral load test every 3-6 months when not on treatment, and every 3 months when on treatment. They also recommend a viral load test one month after starting treatment or after making any treatment change.

2.13 Viral lifecycle, drug resistance and adherence

Everyone who is HIV-positive and not on-treatment produces several billion new HIV infected cells every day. In making this vast number of copies of itself, the virus also makes lots of very small mistakes. These are called mutations.

When you are not taking treatment there is no reason for any particular mutation to be produced because they are usually not as strong as the original wild-type HIV.

However, when you are on treatment, some mutations that develop will not be affected by drugs you are taking. These resistant mutations will continue to reproduce and eventually become the major type of your HIV. You then become more resistant to these drugs, as well as to other similar drugs. This is called cross-resistance.

The higher your viral load when you are on treatment, the more likely that you are developing resistance. This is why it is so important to get your viral load as low as possible, as quickly as possible, and ideally below 50 copies/mL.

Resistance and adherence are closely related. If you miss, or are late, taking one or all of your drugs, you increase the chance of developing resistance. This is because drug levels fall below a minimum safe level during this period.

Drug interactions can also affect the levels of ARV drugs.

ARVs can interact with other HIV and OI medications (especially with treatment for TB).

They can also interact with some recreational drugs, and complementary and herbal drugs.

Always tell your doctor and pharmacist about any other medications or treatments that you are taking.

If you have to take your ARV drugs with food or on an empty stomach this is important to make sure that you get the correct concentrations of each drug.

The mutations that occur when you only have low concentrations of your drugs can stop the drugs working. Adherence is therefore critical.

Resistance and adherence are discussed in detail in Section 3.



2.14 How CD4 and viral load are related

Although they measure completely different things, the pattern of viral load and CD4 results are usually related:

- Generally when viral load is low, CD4 counts will be high.
- In a similar way, when CD4 counts are low, viral load will be high.

A few weeks after infection when HIV levels go up to very high levels, CD4 counts drop. Then as the immune system brings viral load levels down, CD4 counts go back up again.

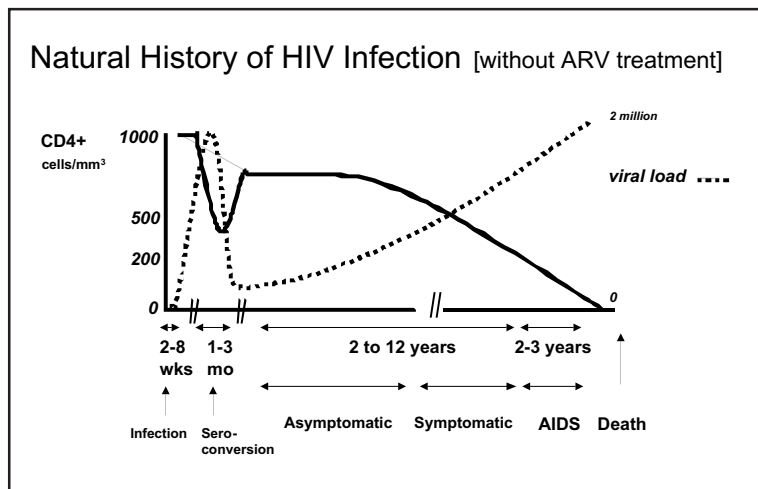
There is sometimes a lag period between viral load and CD4 changes:

- after starting treatment viral load drops very quickly, but CD4 counts sometimes take several months before they start to increase
- if treatment fails and viral load levels start to rebound, CD4 count may still continue to rise for a while, although as viral load gets higher CD4 count then usually starts to fall.

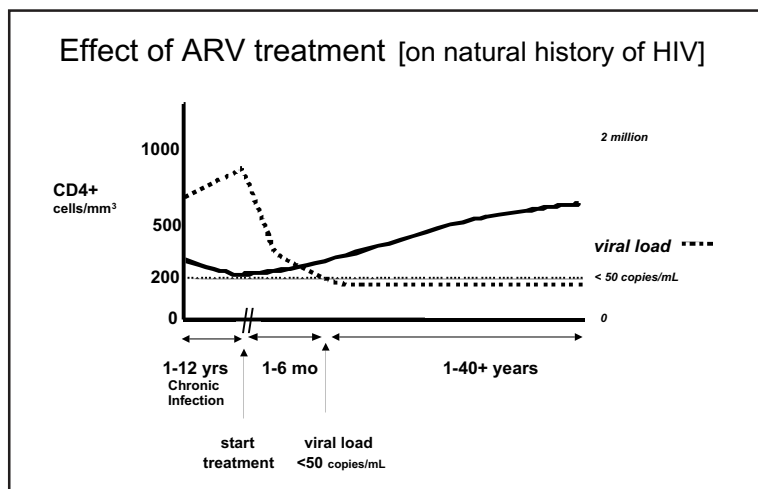


You can now see how the CD4 count and viral load curves fit together.

Firstly without treatment:



And then when on treatment:



2.14 Glossary for Section 2

ARV	antiretroviral - a drug used to treat a retrovirus (i.e. anti-HIV drug)
bacteria	single-cell micro-organisms without a nucleus
lymph system	vessel, nodes, organs and clear fluid, that are part of the immune system
natural history	the pattern a disease takes if it is not treated
nucleus	the central part of some cells that contains DNA
parasite	an animal or plant that get nutrients and support from another species
protozoa	single-cell creatures with a nucleus, with similar characteristics to animals
resistance	when the genetic structure of an organism changes in ways that stops a from working
seroconversion	the period when the body generates an immune response to HIV (usually 2-3 weeks after infection, occasionally much longer)
viral load test	blood test that look at the amount of virus in a small sample
virus	infectious organism that can only reproduce inside the cell of another plant or animal



2.15 Questions for Section 2: Virology, HIV and viral load

1. What is HIV, what does HIV stand for?
2. What percentage of HIV virus is circulating in the blood?
3. Where is the rest?
4. Why are blood tests used for CD4 and viral load?
5. What are 'sanctuary sites' ?
6. How can viral load behave differently in these sites?
7. Describe 4 main causes of infections and illness
8. Explain the viral dynamics of early and chronic infection, with approximate ranges for viral load levels and times (ie 2 weeks, 2 month, 2 years after infection) and after treatment (after 1 week, 1 month, 6 months).
9. Draw a simple graph for the answer to question 8.
10. Give a brief history of viral load technology and levels of sensitivity.
11. Name three types of viral load tests
12. What is the margin of error for viral load tests?
13. What is the importance of viral load results for someone who is taking HIV treatment?
14. What is the importance of viral load results for a patient who is not yet taking HIV treatment?
15. Explain in simple language how HIV can become resistance to treatment.



2.16 Course evaluation for Section 2

Please take a few minutes to complete this evaluation. Any comments are appreciated, including on the usefulness of the evaluation as we can develop this into an online resource.



Section 2:

How much of the information was new? None 1 2 3 4 5 All

How useful was the source material? Very 1 2 3 4 5 Not

How much support time did you need in 1-2-1 questions?

Were you given enough support for this section?

Did you find better internet sites for information, if so, which ones?

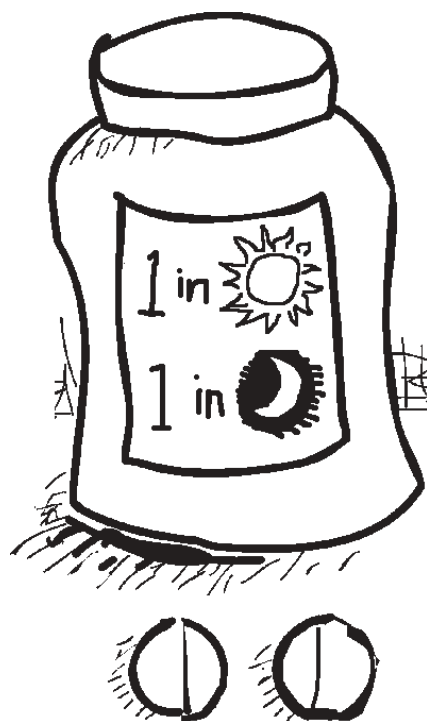
Did the questions relate to the information you found yourself?

What was your pass rate?

Sit the test again in one week to see how much you remember.

Did your pass rate improve?

Section 3: Introduction to ARVs



3.1 Introduction to Section 3

The third section is a basic introduction to treatment of HIV infection.

It includes information about the medical approach to treatment as well as how to approach this as an HIV-positive person.

Combination therapy with ARVs is more complicated than many other medical conditions, and every person starting treatment needs to understand something about this if they are to have the best chance of long term benefit.

3.2 Aims for Section 3

After completing this section you should have a basic understanding of:

- How ARV drugs work
- Treatment guidelines - using 3 or more drugs and getting viral load undetectable
- Main drugs that are used and generic combinations
- Treatment choice and side effects
- Adherence and drug levels: including practical aspects (late with dose, missed dose, being sick, tips to remember, importance of good habits etc).
- Resistance and failing treatment

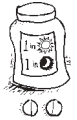
3.3 What is combination therapy?

Combination therapy is the term for using three or more ARV drugs to treat HIV.

ARV stands for Antiretroviral. This is because HIV is a retrovirus.

It is also called triple therapy, 'potent' or 'effective' therapy, or HAART (Highly Active Anti-Retroviral Therapy).

The treatment only works because there are three different drugs all fighting the virus. If you miss doses or are late taking them, then they may not work at all, or will only work for a few months. HIV is a difficult disease to treat.



3.4 Do the drugs really work?

Yes! In every country that uses ARVs, AIDS-related deaths and illnesses drop dramatically.

Treatment works for women, men and children. It works no matter how you were infected with HIV. Whether this was sexually, through IV drug use, or by blood transfusion.

Taking HIV drugs, exactly as prescribed, will reduce the virus in your body to tiny amounts. This then lets your immune system recover and get stronger by itself.

Now that there are treatments for HIV, this is an important reason to know whether you are HIV-positive.

Generic drugs work as well as brand-name drugs and sometimes they are available in formulations that are easier to take.



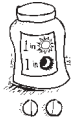
3.5 How HIV drugs work - main types of drugs

Like everything that is living, HIV has to be able to reproduce itself. It does this inside CD4 cells. This involves many different stages, and HIV drugs work by interfering with some of these stages.

There are four main parts of the HIV life-cycle where different HIV drugs work.

The four families of drugs are:

- Nucleoside Reverse Transcriptase Inhibitors (NRTIs) - 'nucleosides' or 'nukes'
- Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)
- Protease Inhibitors (PIs)
- Entry Inhibitors (EIs)



HIV uses CD4 cells as factories to make hundreds of copies of itself. Different

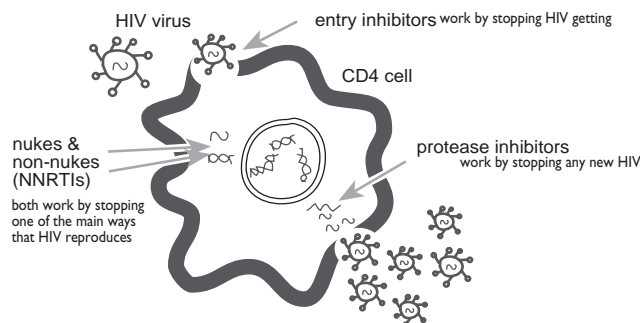


Fig 1: HIV drugs work in different ways



3.6 Treatment guidelines

Many countries already have guidelines for how treatment should be used. They include guidelines for treatment of adults, but also separate documents for treating children for treatment during pregnancy, for TB or hepatitis co-infection, for adherence, and for treating opportunistic infections.

Guidelines are only useful though if they are up-to-date - so always look at the date first.

Many guidelines are also available online. They are generally written for doctors in a more technical language. They present a consensus guidelines for example on when to start treatment, which drugs to use, how to manage side effects etc and updated regularly.

WHO guidelines:

http://www.who.int/3by5/publications/documents/arv_guidelines/en/

US guidelines (for prevention, treatment, OIs, children and pregnancy):

<http://www.hivatis.org/>

UK guidelines are updated every two years.

<http://www.bhiva.org>

3.7 When to start treatment

There are several areas to consider before starting treatment.

- i) Firstly - someone has to be ready to start treatment.

This involves:

- understanding that treatment will help your health
- understanding that 100% adherence means taking every dose
- understanding that 100% adherence means following any food recommendations
- understanding that side effects will usually be mild and can be managed

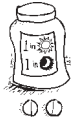
All these 'non-medical' aspects are very important.

Someone has to want to actively be committed to treatment before they start.

Otherwise adherence will not be good, resistance will develop and treatment will fail.

- ii) Secondly, anyone with any HIV-related symptoms is usually recommended to start treatment (at any CD4 count).
- iii) Thirdly, people with or without symptoms are recommended to start before their CD4 count falls to below 200 cells/mm³.

See section 1 for more details about CD4 counts and starting treatment.



3.8 Why three or more drugs are used

When HIV drugs were first developed, people used each drug by itself, or used them in combinations of two drugs.

In both these cases the benefit from treatment only lasted a few months, perhaps a year or two at the most, and resistance to the drugs developed quickly.

Three or more drugs are used in HIV combinations, because none of the drugs are powerful enough to use on their own.

Some combination therapies include three drugs in a single pill - but it is important to remember that there are three drugs involved.

3.9 Reducing viral load to less than 50 copies/mL

Although people start treatment to improve their health, and to stay healthy, one of the main goals of treatment in most guidelines is to reduce viral load to undetectable levels (less than 50 copies/mL).

Combinations using 3 or more drugs are able to do this for 50-80% of people starting treatment for the first time - even if resistance tests are not available to test this..

If you get viral load this low, and you take all the drugs on time, you are unlikely to develop resistance. You can then use the same drugs for many years.

3.10 Treatment choice

There are over 20 HIV drugs, but not all drugs are available in every country.

Lists of WHO-approved drugs and all licensed drugs in Europe and the USA are included in Appendices IV and V.

Also, although there are many hundreds of possible combinations with these individual drugs, there are a few combinations that are recommended in treatment guidelines.

This usually involves either:

2 x NRTIs (nukes) plus an NNRTI or

2 x RTIs (nukes) plus a PI (preferably a PI boosted with ritonavir)

The WHO recommends four similar NNRTI-based combinations:

3TC + d4T + nevirapine

3TC + d4T + efavirenz

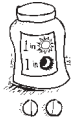
3TC + AZT + nevirapine

3TC + AZT + efavirenz

Fixed Dose Combinations (FDCs) are where these three drugs are combined into one pill. Generic manufacturers produce combination treatments that are not available to all countries.

There are different advantages and disadvantage of each combination:

- nevirapine-based combinations are preferred in women who are pregnant.
- efavirenz-based combinations are preferred in people who need TB treatment at the same time.
- efavirenz-based combinations are used if people are intolerant to, or have side effects with nevirapine.
- efavirenz-based combinations should not be used by women who want to become pregnant.
- d4T-based combinations are generally recommended because this is a very inexpensive drug - but if you get side effects like neuropathy, the d4T needs to be changed to AZT.
- d4T-based combinations are generally recommended in people who develop AZT-related side effects.
- AZT-based combinations are not recommended if you have anaemia.



3.11 Side effects

Everyone is worried about side effects before they start treatment.

In practice though, most people manage to lead a very normal life when taking medication. If side effects occur, they are often easy to manage:

- Most side effects are usually mild.
- They can often be reduced with other medication that is easy to use.
- There is a small risk of more serious side effects, but these should be picked up by routine monitoring from your doctor. More information about these side effects is included below.

Many people however also put up with side effects when they could change to another treatment and that is not good.

If you experience any side effects contact your doctor as soon as possible.

You have to make sure that your doctor understands exactly how the side effects affect you.

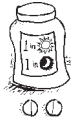
More serious side effects can usually be avoided by changing to alternative drugs.

Before starting treatment, learn about the side effects that can occur with the drugs you are going to use.

Ask your doctor, nurse or HIV pharmacist about how likely they are to occur. Ask how many people stop treatment because of them (usually very few). Even rough estimates will give you a good idea of what is involved.

This way you will know what to look out for.

The most common side effects associated with drugs recommended in the WHO first-line combinations are included in detail in Section 4: Side effects with ARVs.



3.12 Can I change treatments?

If your first combination is too difficult to follow, or if any initial side effects have not improved after the first few weeks or months then there may be an alternative drug or combination that you can change to.

If this is your first combination, you have more choice. You should not put up with difficult side effects for months on end.

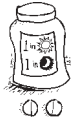
3.13 Can I take a break in my treatment?

Once you start treatment it is best not to take any break or interruption unless your doctor recommends this.

To benefit from HIV treatment you need to take every dose on time. The longer you stay on treatment the longer the benefit should continue.

If you get a very good response to treatment and start to feel better, it is still important to continue taking every dose of treatment on time.

- Stopping treatment for any short period is not recommended. Levels of HIV in your blood - your viral load - can increase again very quickly (from undetectable to several thousand in as little as a few days). Each interruption of treatment also carries a risk of developing drug resistance.
- An interruption may be reasonable if you have a very strong CD4 count or have very difficult side effects.
- If you want to take a treatment break, it is essential you talk to your doctor first. Some drugs have to be stopped all together, and others need to be stopped at different times. Nevirapine, efavirenz and 3TC all stay in the blood for longer than d4T or AZT. They are also easy drugs to develop resistance to. Stopping all three drugs at the same can give the virus several weeks to develop resistance.



3.14 Recreational drugs, alcohol and complementary therapy

Some HIV drugs interact with recreational drugs, street drugs, methadone and complementary or traditional herbal therapies.

The interactions can be complicated.

Sometimes the interactions will increase the amount of recreational drugs found in blood to dangerous levels.

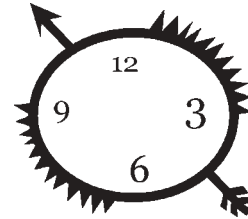
Some recreational drugs can reduce the levels of ARVs, increasing the risk for resistance.

It is therefore very important that your doctor and pharmacist know about any other drugs or supplements that you use. Even if you use them rarely. Your doctor should treat this information in confidence.

Alcohol does not interact with HIV medications. However, heavy alcohol use, as with recreational drug use, may reduce adherence. It would help if your healthcare workers know about this.

3.15 Adherence - and why it is so important

See the 'Science Support' section 3: 'What happens when you take a drug' and 'Science Support' section 4: 'Drug levels, drug activity and side effects'.



What is adherence?

Adherence is a word to describe taking your drugs exactly as prescribed. This includes taking them at the right time. It also includes following any special diet restrictions.

This ensures that you have a constant minimum level of each drug - 24 hours a day, 7 days a week, 365 day a year! Every time that the levels of a drug fall below this minimum level, you are at risk of the virus developing resistance to the drugs in your combination.

It is important that you develop a routine. Treatment for HIV involves a complicated daily schedule. You may need some support to get used to the changes it makes in your life. Adherence can be very difficult.

This is the most important thing you have to think about when you start taking a new combination.

Start treatment when you can give yourself the extra time and space you may need to adjust.

During the first few weeks, nothing else should take priority over getting your treatment right.

Many treatment centres now have an adherence clinic or an adherence nurse.

How much is enough?

Taking medication exactly on time is very important.

However, there is usually a window period of about an hour that is still okay. Some drugs, and some people, have a wider window period than others.

Because of this variation, it is still better to aim for the same time each day.

Diet restrictions are very important. Ignoring these can be like only taking half a dose. You will not absorb enough of the drug for it to work. Resistance is then more likely to occur.

The next question is: 'exactly how close to perfect adherence do you have to get?'

Unfortunately, the answer is 'almost 100%'...

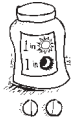
Many studies have shown that even missing one or two doses a week can have a big impact on the chances of a successful treatment.

One early study showed that even with 95% adherence only 81% people achieved undetectable viral load. That is only one in every 20 doses that was missed or late. [1]

Adherence rates	% of people undetectable
over 95%	81%
90-95%	64%
80-90%	50%
70-80%	25%
under 70%	6%

Adherence also directly impacts HIV-related mortality. In another study of 950 people starting treatment for the first time, for every 10% decrease in adherence there was a 16% increase in HIV-related death. [2]

On the other hand, a US study of people in prison who took every dose showed much better results. [3]



Because these patients were in prison, every dose was supervised. All had viral loads below 400 copies/ml after a year and 85% were below 50 copies/ml.

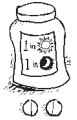
This result was more impressive than nearly every clinical trial. Most of these people had already failed previous treatments and so were even less likely to get a good result.

The point is not that you need to be in prison. It is that if you find a way to take all your drugs as prescribed, you will get good results.

- Be strict with yourself in assessing how adherent you are through a regular week.
- If it's not looking so good, you need more support. You will need to ask.
- Talk to your doctor!

References:

1. Paterson DL et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern Med* 133-21-30 (2000).
2. Hogg RS et al. Non-adherence to triple combination therapy is predictive of AIDS and death in HIV-positive men and women. 7th CROI, 2000. Abstract 73.
3. Fischl M et al. Impact of Directly Observed Therapy (DOT) on outcomes in clinical trials. 7th CROI, 2000. Abstract 71.



3.16 Tips to help adherence...

The following tips will be helpful in different situations:

- Choice of treatment.
 - Get all the information on what you will need to do before you start treatment:
 - How many tablets? How big are they?*
 - How often do you need to take them?*
 - How exact do you have to be with timing?*
 - Are there food or storage restrictions?*
 - Can they be taken with any other current medications?*
 - Are there easier choices?*
- Use a daily chart to plan your timetable and use it to get used to the routine. For the first few weeks mark off each dose and the time that you took it.
- Make sure that you contact your hospital or clinic if you have difficulties with side effects. They can prescribe additional medication to help. They can also change the treatment if necessary.
- Divide up your day's drugs each morning and use a pillbox. Then you can always check if you think you have missed a dose.
- Use a pill beeper or alarm watch. Use it for both morning and evening doses.
- Take extra drugs if you go away for a few days.
- Keep a small supply where you may need them in an emergency. This can be in a cool place in your car, at work or at a friend's house.
- Get friends to help you remember difficult dose times. Ask them to remind you when you are out at night.
- Ask friends who are already on treatment what they do. Ask them how well they are managing. Ask your treatment centres if you can talk to someone who is already taking the same treatment if you think this will help.
- Ask your doctor for a supply of medications to control nausea and diarrhoea. These side effects are the most common when starting therapy.
- Most combinations are twice-daily regimens. This usually means taking them every 12 hours. However, several drugs only need to be taken once a day. This usually means taking them every 24 hours.
- Completely missing a once-daily dose may be more serious than forgetting a dose from a twice-daily regimen. Adherence is especially important with once daily regimens.

3.17 What if I forget to take my pills?

Almost everyone will forget or be late with their drugs at some time. There is a difference though between occasionally missing a dose, and regularly forgetting on a daily or weekly basis. You need to aim to take all your doses at approximately the right time.

You may be regularly taking them late or missing doses completely. If this is the case it may be better to talk to your doctor about stopping treatment altogether.

This would at least limit your risk of resistance. You can restart treatment later when you are more able to cope with the regimen.

There may be an easier combination that you can use. Some people hate lots of pills. Some hate fatty foods or having to eat breakfast. Some people will always have trouble with taking medicine at work during the day.

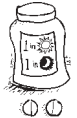
All these things are important in deciding which combination will suit you best.

You have to follow your regimen everyday. This includes both during the weekend, and in the different situations involved in life.

Taking days off your regimen is a very dangerous way of using treatment.

There are always things that can help you to avoid missing doses, whatever your lifestyle.

If you realise you have missed a dose; take it as soon as you remember. BUT, if you only realise when you're going to take your next dose, do not take a double dose.



3.18 Resistance to ARVs

What is resistance?

Resistance to ARVs occurs when the structure of the virus makes tiny changes. These changes are called mutations. This can mean that the drugs no longer work as well or even at all.

You can also be infected with a strain of HIV that is already resistant to some or all HIV drugs.

How does resistance occur?

Mutations that lead to drug resistance are generally only produced when you continue taking a treatment with a detectable viral load.

If your viral load is still above 400 copies/ml after 2-3 months, or above 50 copies/ml after 6 months you may need to change your treatment.

Your doctor should look closely at why the results are not as good as they could be. They will want to discuss how you are managing adherence and side effects. They should also test for resistance and possibly drug levels.

Resistance can develop even at low viral load levels between 50 and 500 copies/ml.

Ideally, it is recommended to have a viral load test four weeks after starting or changing treatment. This should then be checked at least every 3 months when on treatment.

Get the results when they are ready (usually after two weeks). Don't just wait until your next visit.

What is cross-resistance?

Some drugs are cross-resistant to others. This means that if you become resistant to one drug you will also be resistant to other similar drugs, even if you have never taken them before. This is particularly true of drugs in the same class.

There are also varying degrees of cross-resistance.

Sometimes you may still get some benefit from the second drug but the response is less likely to be as strong or as durable.

What are resistance tests

Resistance tests can show if you have these resistance mutations. These tests are not available in every country. Because some drugs are very vulnerable to resistance - such as nevirapine, efavirenz and 3TC.

If you have a detectable viral load on these treatments, or your viral load rebounds to levels above 2000 copies/mL, you would assume that you have resistance to one or more ARV drugs in your combination.

How do I avoid resistance?

Avoiding resistance is one of the most important conditions for using combination therapy. You need to use a combination that is potent enough to minimise the risk of getting resistance to any of the drugs you take.

The best chance you have of stopping resistance involves reaching and maintaining undetectable on viral load tests that measure down to 50 copies/ml.



3.19 Treatment failure

Treatment failure is defined in different ways, and sometimes this relates to the different treatments that are available in a country.

Virological failure

If viral load levels never reach undetectable, or rebound and become detectable, this is called 'virological failure'.

The drugs are not working to suppress the virus.

With virological failure, you will not necessarily feel more ill in the short term.

Clinical failure

Clinical failure is when you get symptoms - ie other illnesses mean that the drugs are not preventing you from getting ill.

How to manage treatment failure depends on the choice of alternative drugs that are available in any country.

Virological failure usually occurs first - and it can sometimes take months or even years for this to lead to clinical failure.

This is why management of treatment failure depends on which treatments are available.

- For people who have several good options for a new regimen, virological failure is used to decide when to change treatment.
- For people who have limited options for a new regimen, clinical failure is used to decide when to change treatment.

Low level increases in viral load (up to 2000) often are just 'blips' and often go down by themselves.

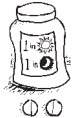
Before making any decision to change treatment it is important to identify why the treatment failed.

It may be for a simple reason that the person has stopped taking treatment altogether, or that they have not been taking treatment on time, or in the way prescribed.

It may be because of resistance or because the treatment was not potent enough, or because the drugs were being poorly absorbed.

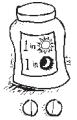
When there are new treatment options, then changing all 3 drugs to a new regimen is recommended when it is confirmed that the viral load has rebounded and it is not a 'blip'.

Management of treatment failure is a specialised area, and approaches changes based on new research.



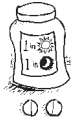
3.20 Glossary for Section 3

adherence	the term to describe taking medication exactly as it is prescribed - both at the right time and following any special diet recommendations
DNA	genetic material inside every living cell that contains the information and code for how that cell grows, functions and reproduces
EI	entry inhibitor - family of drugs that target HIV before it enters a cell
HAART	Highly Active Anti-Retroviral Therapy - a term for HIV combination therapy using at least three drugs
lactic acidosis	life threatening side-effect, mainly associated with d4T when it is used in combination with ddl (didanosine)
lipoatrophy	side effect that reduces subcutaneous fat on the arms, legs or face
lipodystrophy	name for a set of side effects relating to the way your body processes fats and sugars. Symptoms include lipoatrophy, fat accumulation and increased blood cholesterol and triglycerides
NRTI	Nucleoside Reverse Transcriptase Inhibitor - family of anti-HIV drugs that work when HIV is in the cell, but before it is integrated into the cells DNA
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor - family of anti-HIV drugs, similar to NRTIs, that work when HIV is in the cell, but before it is integrated into the cells DNA
PI	Protease inhibitor - family of anti-HIV drugs that work stops new virus being cut into manageable portions and preventing it leaving the cell
peripheral neuropathy	this is a term for damage to the nerves in your hands and feet, and which starts in your fingers and toes. It can be caused by HIV, and is also a common side effect of some ARVs. It starts with tingling or numbness, or increased sensitivity. If allowed to continue it can become very painful and debilitating if it is allowed to progress.



3.21 Questions for Section 3: Introduction to ARVs

1. What does ARV stand for?
2. How many drugs are usually used in ARV combination therapy?
3. Name four families of drugs
4. Which drug family is active before HIV enters a CD4 cell?
5. How many drugs are approved in the US to treat HIV?
6. How many combinations are recommended as first-line treatment by the WHO?
7. Name the individual drugs used in the WHO combinations
8. Give at least three reasons to delay starting treatment
9. What can affect the levels of ARVs in the blood?
10. What is adherence?
11. Give six examples of things that could help with adherence.
12. What is resistance?
13. What is clinical failure?
14. What is virological failure?
15. How low does viral load need to go to prevent resistance developing?
16. Write 500 words about adherence?
17. Suggest four examples of ways you could make adherence easier.
18. What is drug resistance?



3.22 Course evaluation for Section 3

Please take a few minutes to complete this evaluation. Any comments are appreciated, including on the usefulness of the evaluation as we can develop this into an online resource.

Section 3:

How much of the information was new? None 1 2 3 4 5 All

How useful was the source material? Very 1 2 3 4 5 Not

How much support time did you need in 1-2-1 questions?

Were you given enough support for this section?

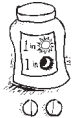
Did you find better internet sites for information, if so, which ones?

Did the questions relate to the information you found yourself?

What was your pass rate?

Sit the test again in one week to see how much you remember.

Did your pass rate improve?



Section 4: Side effects of ARVs



4

*Regular blood tests will check for some side effects.
If you have any difficulties make sure your doctor takes
these seriously...*

Nausea and fatigue can be very serious...

4.1 Introduction

This is one of the most important sections of the training resource.

Treatment for most people can become an easy routine part of life so long as any side effects are managed effectively. This can involve treatment for the side effect, dose adjustments or changing to alternative HIV drugs.

To get this you need to take your quality of life seriously, and may need to become active in your own care.

A minority of side effects can be extremely serious, and it is important to be able to know which of these are associated with different drugs.

4.2 Aims for section five

This section will provide an overview of the following areas:

- overview of risk of side effects
- difference between major and minor side effects
- how to reduce side effects, including switching treatment
- main side effects linked to WHO combinations

4.3 General questions

What are side effects?

Drugs are generally tested on, and licensed, to help with specific illnesses. When they affect the body in other ways, these are called side effects. They are also called adverse events (a/e's) or drug toxicity.

In this booklet we will focus on unwanted side effects of HIV treatments.

It is important to realise that many of the symptoms of side effects are similar to symptoms of illnesses. Different treatment are needed when related to illnesses.

Why do side effects occur?

Although drugs are designed to work against specific illnesses, they sometimes interfere with other ways that your body works.

It is difficult enough to develop a drug that works against HIV, and any drug that reaches the market has undergone a lot of research trying to minimise toxicity. Often, very promising drugs have their development stopped because of toxicity. The aim is always to develop safer and more tolerable, as well as better drugs.

Most people – people living with HIV, doctors and researchers – recognise that the current drugs available to treat HIV are far from perfect and hopefully new drugs in the future will be easier to tolerate.



Do all drugs have side effects?

Most drugs have side effects of some sorts, although in the majority of cases they are mild and easily manageable.

Sometimes side effects are so mild that they are rarely noticed. Sometimes they only affect a small proportion of people that use the drug.

Sometimes side effects only become apparent after the drugs have been licensed and approved, when many more people use them over a much longer period than the original studies.

All drugs have side effects, but not all people taking drugs will experience the same effects and to the same extent.

The leaflet included in the packaging with your drugs (called the Summary of Product Characteristics, SPC) lists all the reported range of possible side effects associated with each drug. This booklet also includes other useful information including how the drug needs to be taken, possible interactions with other medications, etc.

How are side effects for drugs reported?

When drugs are first studied, every side effect that occurs is recorded, even if it only affects a few people, and even if it cannot be directly linked to the drug being studied. This means that if you look at the SPC leaflet you usually find a long list of potential side effects.

Side effects that are serious or occur most frequently are also usually discussed in more detail.

If side effects only become apparent after the drug has been approved, as with lipodystrophy, the SPC may not have this information and the leaflet will usually be changed later to reflect this.

Starting treatment for the first time?

Risk of side effects can be a big worry if you are about to start HIV treatment for the first time. It will help if you know what to expect from different drugs before choosing your combination.

Ask for information about each of the drugs you might take, including the likelihood of side effects occurring. For example, what percentage of people had side effects related to those drugs and how serious they were?

You may be asked to consider entering a study looking at side effects in different combinations and these studies are important to define the extent of side effects in different combinations.

Can I change drugs easily?

If starting treatment for the first time, you will usually have a lot of flexibility in choosing and changing drugs until you find a combination that works and is tolerable.

There are already 20 approved ARV drugs, and while you can't quite mix and match them all, you have a lot of choice. If one or more of the drugs in your combination are difficult to tolerate, you can change it for another.

Often people are not given a choice when starting treatment. However, the fewer drugs you have used previously, the more choice you have to change.

If you change a drug because of tolerability, you can usually go back and use it later if you need to. Just because you used a drug once, doesn't mean you have 'used up your option' of using it again in the future. The only drug you can not do this with is abacavir. If you have a hypersensitivity reaction to abacavir you must never take it again.

Sometimes side effects improve after the first few weeks or months, but sometimes they don't. Read the sections on individual side effects for more recommendations for how long you should put up with them before changing.

You do not have to continue with a drug to prove anything to yourself or to please your doctor. If you know something is wrong, ask your doctor to change it to something else. Some drugs are just not for everyone.

Can I predict the side effects I may get?

Generally you cannot predict how difficult or easy you will find it to take any particular drug beforehand. Sometimes, if you already have similar symptoms related to the side effects, these may make the risk of side effects greater.

For example, if results of routine liver tests show that you have raised liver enzymes, this may increase higher still if you use nevirapine. If you have high cholesterol or triglycerides before treatment, these are more likely to increase if you use protease inhibitors.

Are side effects different in men and women?

Many trials in the past enrolled far too few women to be able to study differences adequately. Sometimes differences in side effects between men and women are reported later.

Women have shown higher rates of side effects in some nevirapine studies (both liver toxicity and rash), which highlights the importance of careful monitoring.

With lipodystrophy (fat loss in your arms, legs or face; or fat gain in abdomen, breasts, and shoulders), women are more likely to report symptoms of fat accumulation rather than fat loss.



What about side effects and adherence?

Whether you are starting your first treatment or have been using HIV drugs for a long time, your doctor should have talked to you about the importance of adherence.

This is the term that describes taking the meds in your combination exactly as they are prescribed - ie on time and following any diet advice. There is special section about adherence and side effects on page 12.

Getting your doctor to do something...

Unfortunately it is true that:

- some doctors generally think that their patients **overestimate** side effects.

Doctors generally think that their patients exaggerate side effects, and that they are not really as bad as their patients say.

It is also true that:

- most patients actually **underestimate** side effects. Patients generally say that side effects are less inconvenient or less difficult than they really are, or often forget to mention them at all.

This means there can be a big difference between what is actually going on and what doctors think is going on – and this is why side effects are often under treated.



What happens if side effects persist?

If the first treatment you are given to help with a side effect does not work, there are usually others that you can use that may be more tolerable.

This is why we have listed a range of options, including alternative treatments, for each of the main symptoms. If one doesn't work – try the other options.

Changing or stopping treatment are important options that you can discuss with your doctor.

4.4 General side effects

Nausea (feeling sick), diarrhoea and tiredness are the most common general side effects.

These often become easier after the first few weeks. Very rarely, nausea and tiredness can be very serious. This is why you should tell your doctor of any problems.

Ask your doctor or pharmacist for anti-nausea and diarrhoea medications when you first start therapy so you can use these if you need them.

If these medications aren't effective, ask your clinic for stronger or more effective drugs.

If this still doesn't help you may be able to change to a different treatment.

4.5 Side effects associated with WHO combinations

The following pages detail on more detail with the more serious side effects associated with the combinations recommended as first-line treatment by WHO.

These are summarised in the table below, and more detail is provided in the text afterwards.

Table 1: Serious side effects from main WHO drugs

Symptoms in bold are urgent to describe to your doctor.

Drug Name	Side Effect	Symptoms
d4T (stavudine)	Peripheral neuropathy (PN)	Loss of feeling (numbness) OR pain in fingers and/or toes
	Lactic acidosis	Feeling sick, vomiting, no appetite, extreme tiredness
	Lipoatrophy	Loss of fat in face, arms, legs or buttocks. Veins become more prominent.
3TC (lamivudine)	Hair loss (rare)	Hair thinning or falling out
	PN (rare)	Loss of feeling (numbness) OR pain in fingers and/or toes
AZT (zidovudine)	Anaemia	Feeling tired or weak
	Lipoatrophy	Loss of fat in face, arms, legs or buttocks. Veins become more prominent.
nevirapine	Liver toxicity	Feeling sick, vomiting, poor appetite, yellow eyes or skin, light coloured stool or dark coloured urine, tenderness or swelling in your liver
	Rash	Redness or small rash on skin
	Severe rash	Any rash over more than 10% of body, any broken skin
efavirenz	CNS side effects	Mood changes, feeling disorientated or anxious, vivid or disturbing dreams, change in sleep pattern. If severe then urgent to see doctor.
	Liver toxicity	Feeling sick, vomiting, poor appetite, yellow eyes or skin, light coloured stool or dark coloured urine, tenderness or swelling in your liver
	Rash	Redness or small rash on skin
	Severe rash	Rash over more than 10% of body, any broken skin



- **Liver toxicity: nevirapine, efavirenz**

Although liver toxicity with nevirapine (or efavirenz) is not very common it can be very serious and life-threatening if it does occur. Less than 5% people have to change treatment for this reason, but because nevirapine is included in Fixed Dose Combinations (FDCs) it is very important to know about these symptoms.

If you have a rash with nevirapine, it is important that you have a blood test to check whether your liver is being affected. These tests are usually for levels of liver enzymes called ALT or AST.

If this is not available, other symptoms include:

- Feeling sick (nausea) or being sick (vomiting)
- Poor appetite
- If your eyes or skin looks more yellow
- Light coloured stool or dark coloured urine
- Tenderness or swelling in your liver - your liver is just below your stomach

If you have any of these symptoms, you should contact your doctor straight away.

Liver toxicity usually occurs in the first 6 weeks of treatment, but can also occur later. If you are co-infected with hepatitis then the risk of liver toxicity is much higher, and another choice of drug would be more appropriate.



- **Rash: nevirapine**

About 10-15% people who use nevirapine or efavirenz get a low level rash that is not serious, and about 5% people discontinue the drug because of this.

However, 2-3% people can be at risk of a much more serious rash, especially using nevirapine.

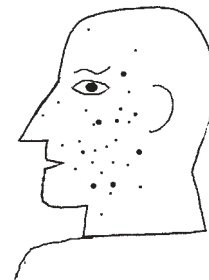
Nevirapine should be given at a reduced dose of 200mg once-daily for the first two weeks that it is used. If there is no rash at the end of these two weeks then the dose increases to 200mg every 12 hours.

The nevirapine dose should NEVER be increased if you still have a rash.

If the rash covers more than 10% of your body or breaks the skin at all, you must see your doctor immediately. In these rare cases, nevirapine has to be stopped very quickly to reduce the risk of a severe reaction that can be fatal.

The staggered dose does not always happen with Fixed Dose Combinations.

This is something you should check and ask your doctor about.



- **Peripheral neuropathy: d4T, rarely 3TC**

Peripheral neuropathy is the term for damage to the nerves in your hands or feet. Sometimes this starts as a tingling or numbness, but if it is allowed to develop it can become very painful and permanent and move up your limbs.

Although it is sometimes caused by HIV, it can also be a side effect from some HIV drugs. It is also more likely if you start treatment with a very low CD4 count. The main drugs linked to neuropathy are ddC (which is rarely used), d4T, ddI and to a lesser extent, 3TC.

d4T is one of the drugs in Triomune, and d4T is currently recommended in first-line therapy in many countries.

This means that you have to be very aware of any tingling or pain in your hands or feet and report this to your doctor.

Because there is no cure for neuropathy, the best choice is to stop using d4T and change it to another drug.

Many people are also able to reduce the dose of just the d4T part of your combination. Triomune for example comes with a dose of either 30mg or 40mg of d4T. If you can get each drug prescribed separately, then you may be able to reduce to dose even further to 20mg twice a day.

Reducing the dose of d4T can be enough to stop further nerve damage.

If neuropathy continues and there are no other treatment choices, then it may be better to stop your treatment for a period. You could only do this if you are doing well now and your lowest ever CD4 count never dropped much below 200 cells/mm³. You could restart treatment later if you need it again or when an alternative ARV becomes available..

Neuropathy can reverse by itself when you stop the drug that is causing it, but only if you stop the drug before serious damage has been caused. You and your doctor should manage this important side effect very carefully.



• **Lipodystrophy: d4T, AZT, nevirapine, efavirenz, protease inhibitors**

Lipodystrophy refers to changes in fat cells and the distribution of body fat. This can result in losing fat from your arms, legs and face or gaining fat in your abdomen, breasts or shoulders. It also includes changes in blood fat and blood sugar levels.



Different drugs may be responsible for fat gain than those responsible for fat loss. Fat accumulation, to the stomach or breasts and/or across the shoulders, has been more linked to protease inhibitors and NNRTIs. Fat loss, from arms, legs, face and buttocks, has been linked mainly to d4T, and to a lesser extent to AZT.

d4T and AZT are both drugs that are included in recommended first line therapy in the WHO guidelines.

We do not know what causes lipodystrophy. Symptoms can occur rarely in HIV-positive people who are not on treatment. Lipodystrophy usually, but not always, develops slowly over many months or years.

Early symptoms may reverse if you switch to different HIV drugs. Exercise and dietary changes can also help. Careful body measurements by a dietician, by DEXA scan, or photographs can monitor changes.

Regular blood tests will check for other side effects. If you have any difficulties, make sure your doctor takes them seriously and does something about it.



- **Mood changes, paranoia, strange dreams, nervousness: efavirenz**

Efavirenz is linked to one set of side effects that are different to all the other drugs. This is because it can affect your mood and feelings. You may feel disorientated or anxious when you start taking efavirenz and you may have vivid or disturbing dreams. This is a side effect of this drug.



Most people get some changes when they first start to take efavirenz, but this also reduces after the first few weeks, and is much easier to manage.

However, some people get very serious problems and should contact their doctor to switch to another drug. Efavirenz can make your worries or depression worse and you need to be aware of this if you start a combination that includes this drug.

- **Anaemia: AZT**

Anaemia is a shortage of oxygen-carrying red blood cells whose symptoms are extreme tiredness, and it is caused by AZT's effect on bone marrow.

Lower doses of AZT may be just as effective against HIV, but this is not possible in the currently available Fixed Dose Combinations.

If you are using AZT and become extremely tired or weak, you need to see your doctor who should perform a blood test or change this treatment.



- **Lactic acidosis: d4T, ddl, AZT**

Lactic acidosis is a term for a dangerous build up of lactate in the blood. The symptoms include feeling sick and/or very tired and muscle weakness. The risk of lactic acidosis is much higher when d4T is used with ddl - and these two drugs are not recommended to be used together in most guidelines.

If you have these symptoms, it is essential to contact your doctor.

4.6 Other side effects

This booklet has focused on the more serious side effects that also occur more rarely. However anything that makes you feel unwell - even if they are not classed as serious is something you should tell your doctor about.

If you are using drugs that are not included in the WHO first line recommended combinations then use the internet to find out information about the drugs you will be using. Sites with good information (in English) on other drugs include:

Basic easily explained factsheets on every drug

www.aidsinfonet.org

More detailed factsheets:

www.tpan.com/publications/drug_guide/drug_guide_2004.html

Website of the European regulatory agency. This site is very difficult to navigate but it includes the full prescribing information for every EU-approved drug in different European languages.

www.emea.eu.int

4.7 How to report side effects

If you want your doctor to be able to understand your side effects and how they are affecting you, you will need to be able to describe them very clearly.

This will be important for your doctor to check for other causes (ie that diarrhoea is not related to food poisoning or low sex drive to low testosterone levels).

The best way to do this is to keep a side effects diary from when you start a new treatment until you next see your doctor.

Information about how to describe symptoms is given in detail in the following sections. It generally includes information about the following areas:

Frequency:

- How often do you get symptoms?
- Once or twice a week? Once every day, or 5 – 10 times a day etc?
- Do they occur at night as well as during the day?

Duration:

- How long do the symptoms last?
- If you feel sick or get headaches, do they last for 20 minutes or for 3 – 4 hours, or for different times?
- Is there a pattern to when they occur – ie when you take your medications or at a regular time afterwards?

Severity:

- How bad are the symptoms?
- Often it helps to rate them on a scale (from 1 for very minor to 10 for very severe).
- A scale is a useful tool for describing anything that involves pain.
- Recording how severe side effects are when they occur is better than recording them later.
- Have you noticed anything that helps to reduce or stop them.

Quality of life:

This can really help your doctor understand how difficult the side effects are for you. Many people put up with chronic diarrhoea without explaining to their doctor that it stops them ever going to the pub or the cinema.

If you are feeling more anxious or nervous, are not sleeping properly, have a lower sex drive, have experienced taste changes, or are too nauseous to eat proper meals, it is important that your doctor understands this.

Symptoms of lipodystrophy are difficult to evaluate. Although minor changes may not be a problem, some people find that more severe symptoms can change their whole outlook on life, and become a cause for underlying depression.

If side effects are affecting adherence (ie you are not taking all your meds at the correct time) and how you take your treatment, you must tell your doctor about this.

A side effects diary is included in Section 4.10.

Use this for any changes that you notice after you start treatment.

Take this diary with you when you see your doctor at your next appointment.



4.8 How side effects are graded

Most information about the risk of side effects comes from the original studies when the drugs were first being developed. This is why it is very important to report to your doctor all side effects if you take part in any trials.

These studies collect information about frequency and severity of all side effects – although studies for new HIV drugs generally only use small groups of people for relatively short periods of time.

Some side effects only become apparent after the drugs have been approved and have been used by thousands more people over a longer period of time.

Knowing what the risk of side effects are for a particular drug – ie what percentage of people get these side effects – can help you to make an informed decision about which drugs to choose. Where a side effect is very common, knowing what percentage of people who needed to change therapy because of it, is useful too.

More accurate information may be provided by your doctor, or from a community treatment organisation. It is usually also included in the information that you should get with all HIV drugs.

Although there are slightly different details for reporting the severity of each side effect, they are graded from 1 to 4. Grade 1 is very mild and grade 4 is very serious – life threatening or requiring hospitalisation.

GRADE 1 (Mild): Transient (goes away after a short time) or mild discomfort; no limitation in activity; no medical intervention/therapy required.

GRADE 2 (Moderate): Your daily activity is affected mild to moderately – some assistance may be needed; no or minimal medical intervention/therapy required.

GRADE 3 (Severe): Your daily activity is markedly reduced – some assistance usually required; medical intervention/therapy required, hospitalisation or hospice care possible.

GRADE 4 (Potentially life threatening): Extreme limitation to daily activity, significant assistance required; significant medical intervention/therapy, hospitalisation or hospice care very likely.

A general indication of grading (based on US NIH Division of AIDS) is shown below together with specific details for some of the most common side effects.



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Side effect	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhoea	3–4 loose stools a day OR mild diarrhoea lasting less than one week	5–7 loose stool a day OR diarrhoea lasting more than one week	Bloody diarrhoea OR over 7 loose stools a day OR needing IV treatment OR feeling dizzy when standing	Hospitalisation required (possible also for Grade 3)
Fatigue	Normal activity reduced by less than 25%	Normal activity reduced by 25–50 %	Normal activity reduced by over 50 %; cannot work	Unable to care for yourself
Liver toxicity: AST or ALT levels	1.25–2.5 Upper Limit Normal	>2.5–5.0 ULN	5.0–7.5 ULN	> 7.5 ULN
Mood disturbance	Mild anxiety, able to continue daily tasks	Moderate anxiety/disturbance, interfering with ability to work, etc	Severe mood changes requiring medical treatment Unable to work	Acute psychosis, suicidal thoughts
Nausea	Mild OR transient reasonable food intake	Moderate discomfort OR intake decreased for less than 3 days	Severe discomfort OR minimal food intake for more than 3 days	Hospitalisation required
Rash	Redness or itchy skin on part or whole body	Rash that breaks skin, hard or soft pimples OR light peeling/scaling	Blistering, open ulcers, wet peeling, serious rash over large areas	Severe rash, Stevens Johnson syndrome. Severe broken skin, etc
Vomiting	2–3 episodes a day OR mild vomiting for less than one week	4–5 episodes a day OR mild vomiting for more than one week	Severe vomiting of all food and fluids over 24 hours OR needing IV treatment OR feeling dizzy when standing	Hospitalisation for IV treatment (possibly also for Grade 3)

4.9 Side Effects Diary

Use this page to record any changes in your health that could be related to side effects.

You may not get any side effects but if you do, then this diary will be useful. The most common side effects are listed below but include others even if they are not listed here.

- | | | | | | |
|---|--------------------------------|----|------------------------------|----|--------------------------|
| 1 | Tingling or pain in hands/feet | 9 | Stomach pains | 17 | Vivid dreaming |
| 2 | Pain in hands/feet | 10 | Hair loss | 18 | Feeling anxious/nervous |
| 3 | Nausea/vomiting | 11 | Body shape changes | 19 | Changes to your eyesight |
| 4 | Headache | 12 | Weight gain | 20 | Mood swings |
| 5 | Feeling tired | 13 | Weight loss | 21 | Feeling depressed |
| 6 | Dry skin | 14 | Changes in taste or appetite | 22 | Other(s) specify |
| 7 | Rash | 15 | Sexual problems | | |
| 8 | Diarrhoea | 16 | Sleep disturbance | | |

Side effect symptom	Day	Time(s)	Scale: 1 = very mild 5 = very bad				
			1	2	3	4	5
			1	2	3	4	5
			1	2	3	4	5
			1	2	3	4	5
			1	2	3	4	5
			1	2	3	4	5
			1	2	3	4	5
			1	2	3	4	5
			1	2	3	4	5
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			1	2	3	4	5
			1	2	3	4	5
			1	2	3	4	5
			1	2	3	4	5
			1	2	3	4	5
			1	2	3	4	5
			1	2	3	4	5
			1	2	3	4	5
			1	2	3	4	5



Other comments and questions to ask your doctor:

4.10 Glossary for Section 4

anaemia	low or reduced red blood cells - this reduces the amount of oxygen distributed to the body
ALT	alanine transaminase - a liver enzyme which if it becomes raised can be an indication of liver disease or liver toxicity
AST	aspartate transaminase - a liver enzyme which if it becomes raised can be an indication of liver disease or liver toxicity
CNS	Central Nervous System. Consists of the brain and the spinal cord - the parts of the body that process and conduct sensory information
DEXA scan	Dual Energy X-ray Absorptiometry, is a type of X-ray that can measure the proportion of fat, muscle and bone in a body and can also measure bone mineral density
liver toxicity	side effects that damage the liver or reduce liver function
side effects	secondary effect of a drug other than the reason it is prescribed. Side effects are usually related to negative effects. Some side effects can be positive and lead to new uses for that drug
SPC	Summary of Product Characteristics - the leaflet included in the packaging with your drugs
Stevens Johnson syndrome (SJS)	Severe life-threatening skin reaction
toxicity	harmful effects of a substance
ULN	Upper Limit of Normal



4.11 Questions for Section 4

1. What are side effects?
2. Are side effects different in men and women?
3. Should you stop your treatment, or change it because of side effects? Give examples of each situation.
4. Which are the mildest and the most serious grades for side effects?
5. What is the difference between lipodystrophy and lipoatrophy?
6. What is peripheral neuropathy?
7. Which drug/drugs are most commonly associated with peripheral neuropathy?
8. Which is the medication from the ARVs that is most common associated with anaemia?
9. Which drug/drugs are most commonly associated with liver toxicity?
10. Name two symptoms associated with liver toxicity.
11. Which drug/drugs are most commonly associated with serious rash?
12. How is a 'severe rash' defined?
13. Give an example of any two grade 4 side effects.
14. When is the risk of lactic acidosis higher?
15. Which medication is associated with mood changes, paranoia and strange dreams?



4.12 Course evaluation for Section 4

Please take a few minutes to complete this evaluation. Any comments are appreciated, including on the usefulness of the evaluation as we can develop this into an online resource.

Session One:

How much of the information was new? None 1 2 3 4 5 All

How useful was the source material? Very 1 2 3 4 5 Not

How much support time did you need in 1-2-1 questions?

Were you given enough support for this section?

Did you find better internet sites for information, if so, which ones?

Did the questions relate to the information you found yourself?

What was your pass rate?

Sit the test again in one week to see how much you remember.

Did your pass rate improve?



Section 5: Opportunistic Infections (OIs) and important co-infections

OIs

OIs

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5.1 Introduction

This section provides an overview of the most common opportunistic infections and co-infections related to HIV.

Opportunistic Infections (OIs) are the illness that take advantage of the reduced immune system caused by HIV, when your CD4 count is low.

The information is just an introduction. You will need to research more detailed information yourself after you have understood these basic notes.

5.2 Aims for Sections 5: Opportunistic infections and co-infections

To understand the main symptoms and ways to prevent and treat the following infections and co-infections:

- Candida and other skin problems
- GI infections: giardia, cryptosporidia/microsporidia
- PCP
- TB
- MAI and MAC
- Hepatitis C
- CMV
- Toxoplasmosis
- Cryptococcal meningitis
- Cancer: lymphoma and sarcoma, including NHL, KS
- Wasting and weight loss

5.3 Approach to each OI

There are about 10 main OIs that advocates should know about.

There are at least another 10 others that are less common but which are still important. The full list of AIDS-defining infections is included in Appendix I.

All AIDS-defining OIs are potentially fatal, but the majority also improve dramatically when ARVs are available.

For basic training you should learn about the OIs that are most common in your country.

For each OI aim to know:

- Type of infection: whether viral, bacterial etc, how it is contracted and avoided and whether it is infectious to other people.
- Main symptoms: how you or your doctor might diagnose this OI - note that many symptoms overlap for many of these infections. This is further complicated by the fact that most OIs can cause primary disease in a wide range of organs.
- Diagnosis: how is the infection confirmed. Sometimes this involves either testing blood, saliva or sputum (fluid from the lungs) or trying to grow a culture from one of these samples (which can take several weeks).
Sometimes symptoms alone are sufficient to start treatment, based on a 'best guess'.
Sometimes a definite diagnosis is difficult or even impossible to confirm, and you only know afterwards that the suspected illness was the right one if you respond to treatment.
- Treatment: which drugs or choices of drugs can be used to treat and the success rate for each one. Can treatment be stopped afterwards? Most OIs, but not all of them, resolve after successful ARV treatment for HIV has enabled CD4 counts to raise to higher levels.
- Prophylaxis: whether treatment is appropriate in order to prevent infection in the first place. Secondary prophylaxis is where you continue a treatment after the illness has been treated in order to prevent it occurring again in the future. At what CD4 count can prophylaxis treatment be stopped (after ARV treatment)?
- Future research: are better tests or drugs being developed that could help in the future?

This structure will help you build your knowledge of HIV-related complications.

The summaries in this section of the training course on each OI are very brief.

You will need to undertake further reading and research to get more detailed information on each of these infections. There are many sources of information on these OIs on the internet, because they were the first focus of HIV research, before ARV drugs were available.

The recommendations in Appendix VI for further reading are internet resources available in English.

They provide more detail on the full range of OIs in both simple, intermediate and advanced levels of medical detail.

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5.4 GI infections: giardia, cryptosporidia and microsporidia

- Type of infection:** weight loss can be caused by many factors and illnesses. Giardia, cryptosporidia and microsporidia are tiny parasites (protozoa) that can cause stomach upset and severe diarrhoea. Diarrhoea and weight loss after often linked because the body is less able to absorb food and nutrition. Severe diarrhoea can also reduce absorption of medication.

Weight loss in HIV-positive people, that is not explained by a change in diet, can be very serious. Unexplained weight loss of 10% over a year is an AIDS-defining illness. Several studies have suggested that unexplained weight loss of 5% over a shorter period is predictive of 10% weight loss later, and therefore any weight loss should be taken seriously.
- Main symptoms:** persistent diarrhoea that does not resolve within a few weeks. Microsporidia can also cause inflammation in other parts of the body including the lungs, bladder, bowel, sinuses, ears, eyes, brain and pancreas.
- Diagnosis:** Laboratory analysis of a stool sample can look for causes of diarrhoea, but sometimes the cause of diarrhoea is difficult to identify.

Infection is almost always the result of drinking unfiltered water, swallowing contaminated water when swimming or eating raw vegetables that were contaminated by infected or infested food handlers.

Cryptosporidia infections may also result from drinking unpasteurised milk and exposure to diapers, daycare facilities, pets, livestock, and other people must be considered as well.
- Treatment:** In people with strong immune systems (HIV-negative people, or HIV-positive people with CD4 counts over 300) the body usually flushes out these parasitic causes of diarrhoea without treatment within a few weeks. In people with CD4 counts under 300 this doesn't always happen and diarrhoea can become chronic.

There are no universally effective treatments for these infections, although albendazole and thalidomide have been used to treat some kinds of microsporidia. HIV treatment with ARVs to increase CD4 count is likely to be the most effective direct treatment.

It is important to drink plenty of fluids to help prevent dehydration caused by diarrhoea.
- Prophylaxis:** Ways to minimise risk of these infections for HIV-positive people with lower CD4 counts is to drink bottled water, to wash vegetables carefully and cook meat thoroughly, and not to eat foods washed in unbottled water. Hygiene (especially washing your hands) is important to reduce the risk of becoming infected or spreading infection. Many parasites that cause GI (gastro-intestinal) upset are linked to pet or human faeces, and so hygiene when caring for children is especially important if you are HIV-positive.

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5.5 Candida (candidiasis) and other skin problems

Minor skin problems can be one of the first symptoms of HIV and are an indication that CD4 counts is less than 300 cells/mm³.

Sometimes these can be relatively minor, like dry skin, and sometimes it can be the result of an infection that your immune system is no longer strong enough to fight effectively.

Candida is also called thrush and it is very common in people with CD4 counts under 300, and it becomes more common the lower the CD4 count.

- **Type of infection:** Candida is a fungal yeast infection that commonly affects the mouth and throat (oral candida), gullet (oesophagus), sinuses, genital organs and much more rarely, the brain
- **Main symptoms:** Oral thrush appears as white and sometimes red patches (especially in the mouth) that can sometimes be scraped off, and sometimes includes cracks at the corners of the mouth. In the sinuses this can cause headaches, difficulty breathing and build up of mucus. Oesophageal candida can make eating difficult and result in vomiting.
- **Diagnosis:** Visual examination (for oral candida) or swap biopsy for candida in other areas.
- **Treatment:** Some diet approaches include reducing or cutting down on foods that contain refined sugars and wheat.

Live unpasteurised yoghurt that contains lactobacillus bacteria can be eaten or applied directly to the vagina.

Anti-fungal medications are available in different formulations - as creams, lozenges (pastilles), syrup, patches and tablets.

These include:

- co-trimoxazole lozenges
- nystatin or itraconazole syrup
- fluconazole oral solution
- miconazole patch (for the inside of the mouth)
- ketaconazole, fluconazole and itraconazole tablets (fluconazole may be better if using rifampicin for TB treatment).

Anti-HIV treatment (HAART) should increase CD4 counts and reduce the occurrence of candida.

- **Prophylaxis:** the possible benefit from prophylaxis has to be balanced against the risk of developing resistance
- **Future research:** Several experimental treatments are in development, and these would help people who develop resistance to existing anti-fungals

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5.6 PCP

- **Type of infection:** PCP stands for *Pneumocystis carinii* which is a form of pneumonia. PCP is caused by a relatively common organism that behaves more like a fungi than a protozoa (this is an area of recent research).

As with other opportunistic infections, PCP only becomes a problem in people who have a damaged immune system. A CD4 count of under 200 cells/mm³ puts you at higher risk of PCP, which rarely occurs at higher counts. Most cases of PCP occur in people with a CD4 count under 100.

- **Main symptoms:** PCP is predominantly a lung infection and symptoms include difficulty breathing (shortness of breath), dry cough, tightness in the chest, fatigue, fever and weight loss. The organisms can sometimes grow in other area of the body like the lungs, bones and eye, though this is much more rare.
- **Diagnosis:** Symptoms in an HIV-positive person with a low CD4 count are often sufficient to start treatment. Analysis of sputum from either bronchoscopy or 'induced' sputum - after breathing salty mist which brings up fluid from deeper in the lungs - is used for definite diagnosis.
- **Treatment:** First-line treatment for PCP is with Co-trimoxazole (*Septtrin, Bactrim, TMP-SMX*). Co-trimoxazole is made up of two the drugs trimethoprim (TMP) and sulphamethoxazole (SMX). Standard doses are TMP 15-20 mg/kg/day and SMX 75 mg/kg/day by continuous drip or injection (three to four injections daily) for 3-4 days, and then switch to tablet.

Other treatments include trimethoprim plus dapsone, pentamidine, trimetrexate, atovaquone and clindamycin plus primaquine.

- **Prophylaxis:** Prophylaxis against PCP is routinely recommended for anyone with a CD4 count below 200 cells/mm³ whether or not they are using ARVs, at lower doses that used for treatment. Co-trimoxazole (*Septtrin or Bactrim*) at 960mg/day is the most widely used prophylaxis, with other treatments below largely used when co-trimoxazole causes side effects or if resistance has developed.

Dapsone is often associated with side effect in people who cannot tolerate co-trimoxazole. Other treatments used as prophylaxis include aerosolised pentamidine (with treatment every 2-4 weeks), atovaquone, sulphadiazine plus pyrimethamine and dapsone plus pyrimethamine.

Prophylaxis for PCP with TXP-SMX provides protection against other infections including toxoplasmosis. Prophylaxis can usually be safely stopped after CD4 counts rise over 200 cells/mm³ after successful response to ARV treatment.

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5.7 TB

TB and HIV are closely linked in many parts of the world. Where there is a high rate of one infection this is often driven by a high rate of the other.

TB infection is more serious and more common and harder to treat in HIV-positive people. TB can also make HIV progress more quickly.

- **Type of infection:** TB (Tuberculosis) is a bacteria infection that is most widely known as an infection of the lungs (pulmonary TB). It can more rarely affect other parts of the body including the brain, lymph nodes, stomach, liver, bones and even muscles. The majority of people are exposed to TB in childhood, when the spores are breathed in, but then stay dormant, usually in the lungs for many years. The risk of TB becoming active again is less than 10% over the lifetime of an HIV-negative adult, but is about 10% *per year* in an HIV-positive person who does not have access to ARVs.

TB is transmitted from someone with active infection when they sing, shout, sneeze (without covering their mouth) and people can have active infection for 1-2 years before they develop symptoms.

- **Main symptoms:** Symptoms of pulmonary TB include chronic productive cough, shortness of breath, fatigue, fever, night sweats and weight loss. Symptoms of TB in other part of the body are different (ie TB in the brain leads to confusion etc).
- **Diagnosis:** The distinction between active and inactive disease is very important to understand. Inactive disease is not infectious but diagnosis of latent (inactive) TB is not straight-forward. Skin tests that show previous exposure to TB are not accurate or effective in HIV-positive people who have a CD4 count under 400 cells/mm³.

Active TB can be grown in the lab from a sample of spit or blood and is accurate if the result is positive, but not if the result is negative as infection can be missed in these tests. Pulmonary TB will show on X-ray. There is currently no simple blood test for TB.

- **Treatment:** TB treatment requires a 2-month course of a combination of four antibiotics (i.e. isoniazid, rifampicin, pyrazinamide and ethambutol), followed by a 4-month course of a combination of two antibiotics (i.e. isoniazid and ethambutol). Adherence is so critical that TB treatment is often given in DOT (Directly Observed Therapy) where a nurse or other healthcare worker is responsible for seeing you take every dose. Even though you will feel better after a few weeks, the whole six month course needs to be completed, otherwise:
 - i) infection will return
 - ii) resistance to these drugs will develop

TB that is resistant to TB medication requires longer treatment (sometimes for two years) and selection of different, usually less effective drugs.

Is HIV treatment the same for people with TB coinfection?

HIV treatment is recommended for anyone who also has active TB infection, even if the CD4 count is higher than 200.

Because of the interaction between rifampicin-based TB treatment and ARVs, different HIV drugs are recommended.

The dose of efavirenz is higher (800mg rather than 600mg) when using TB treatment, although a recent study in Thailand suggested that the dose change may

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not be needed in people who have a lower body weight (less than 50 kg).

HIV only	HIV + TB
nevirapine +2 RTIs	efavirenz + 2 RTIs
	abacavir + 2 RTIs
	saquinavir+ritonavir + RTIs

Efavirenz should not be used in pregnant woman (who should use pyrazinamide in their TB regimen) or in women who may become pregnant. Children with low weight are recommended to use abacavir + 2 RTIs.

Summary of drug interactions

- rifampicin should not be taken with any PI or nevirapine because rifampicin reduces these drugs to very low levels
- rifabutin should not be taken with ritonavir, saquinavir or nevirapine
- rifabutin interacts with indinavir, nelfinavir, amprenavir, saquinavir (*Fortovase* and *Invirase*) and efavirenz, but dose appropriate dose adjustments can be made.
- rifabutin levels are increased by PIs
- rifampicin may also interact with other drugs taken by people with HIV
- risk of neuropathy with isoniazid is likely to be increased in people using d4T as an ARV to treat HIV

When to use ARVs with active TB infection

There are very few trials of how to treat TB in HIV coinfection, so recommendations are based on expert guidelines.

People with a CD4 count under 100, can start TB meds for 2-3 weeks and then start ARVs.

People with a CD4 count between 100 - 200, can usually wait until after the first 2 months TB treatment before starting ARVs.

People whose CD4 count is over 200 can usually finish the 6-month course of TB treatment before starting ARVs.

A serious side effect of the TB-drug isoniazid is peripheral neuropathy (PN). PN can also be caused by HIV and by ARV drugs including d4T, ddI, and 3TC - and this risk increases when both isoniazid and these ARVs are used over the same period.

Sometimes ARV treatment for HIV, especially in people with very low CD4 counts, can cause an immune response that complicates the management of TB (such as IRIS disease). This requires specialist management.

- **Prophylaxis:** Prophylaxis treatment for TB is usually only recommended in specific circumstances, usually where people share the same confined living or working space - ie family members will often receive treatment if a member of their family is diagnosed with active TB. Secondary prophylaxis, to prevent either TB coming back, or reinfection with a new strain of the virus, is rarely recommended. This is mainly because treatment is difficult to tolerate, and the risk of resistance is high.
- **Future research:** There is an urgency for new accurate tests for TB and these may become available in the future. This would dramatically improve management and care of HIV-positive people co-infected with TB.

Other antibiotics and regimens are also being studied.

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5.8 MAI/MAC

- **Type of infection:** *Mycobacterium avium* and *Mycobacterium intracellulare* are two bacterial organisms closely related to *Mycobacterium tuberculosis* which causes TB. Illness from these bacteria are generally called MAI in Europe and MAC in the US, but they are the same.

MAI can spread throughout the body, and can affect almost any organ, especially the blood, lymph nodes, liver, spleen and bone marrow. The cells infected by these bacteria include macrophages (the cells that engulf infectious material).

- **Route of infection:** Infection comes from soil, dust or contaminated water, but is not infectious between individuals. Like other OIs, MAI only become a problem in people with suppressed immune systems. If your CD4 count is under 100 cells/mm³ you are at risk for MAI. As your count goes lower still your risk increases.
- **Symptoms:** Symptoms include fever, night sweats, weight loss, loss of appetite and weakness. MAI in the gut can cause diarrhoea and abdominal pain due to ulcers. In the lymphatic system, MAI will cause swollen lymph nodes, liver and spleen. Blood tests can show low levels of red blood cells and platelets (anaemia, neutropenia).
- **Diagnosis:** MAI can be confirmed by growing culture from blood or biopsy samples (from the affected organ or gland), but this can take up to four weeks. An 'acid smear' test is much quicker but cannot differentiate between bacteria that cause MAI and TB.
- **Treatment:** Treatment involves a combination of two or more antibiotics in order to reduce the risk of resistance; usually clarithromycin or azithromycin, plus ethambutol. People who develop resistance to clarithromycin will have cross resistance to azithromycin and vice versa. Other drugs used in combinations include rifabutin (see section on interactions with HIV drugs in the section on TB), rifampicin, gentamicin, amikacin, ciprofloxacin and sparfloxacin.

Treatment is lifelong, unless ARV treatment for HIV has increased CD4 count back above 100 cells/mm³, in which case MAI treatment can be safely stopped after a year.

- **Prophylaxis:** Whether prophylaxis treatment in people with CD4 counts under 50 cells/mm³ is not clear, although the risk of developing resistance to these antibiotics means that in many countries prophylaxis is not used. If ARV drugs are available they are likely to be more protective from MAI illness but increasing CD4 to a safer level than using MAI prophylaxis.

Azithromycin may also help protect against toxoplasmosis.

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5.9 Hepatitis

- **Type of infection:** Hepatitis is a name for any infection that causes liver infirmation or damage. Three main causes of liver infection are Hepatitis A (HAV), Hepatitis B (HBV) and Hepatitis C (HCV). These are all very different viruses with different treatment. This section mainly deals with HBV (which is contracted sexually including through saliva) and HCV (contracted by blood contact through infected needles, and more rarely sexually). In the context of HIV these are considered co-infections rather than OIs.
- **Main symptoms:** Some of the symptoms of acute (early) or active liver infection include nausea, vomiting, fatigue, diarrhoea, jaundice (yellow eyes or skin) are similar for any viral infection to the liver, but not everyone will get symptoms of infection or even know they are infected. Hepatitis C can take 20-25 years in HIV-negative people to progress to liver damage (scarring/cirrhosis and liver cancer). HCV progresses over 10-15 years in people co-infected with HIV. Intolerance to fatty foods or alcohol, a swollen or tender liver, or 'liver spots' on the skin are other symptoms of hepatitis. Chronic HCV is also associated with mental difficulties and depression.
- **Diagnosis:** Blood tests can screen for either previous exposure to viral hepatitis (many people clear the virus without knowing they were infected, and produced antibodies) or active infection. The symptoms listed above should prompt a doctor to test for these infections. Viral load (PCR) tests for hepatitis are used similar to HIV viral load tests, and can confirm an infection when immunological tests are either negative or unclear.
- **Treatment:** Treatment for coinfection with hepatitis and HIV requires specialist care from a doctor with experience in both infections.

HBV: Several oral ARV drugs used to treat HIV also are active against HBV. These include adefovir (not now used for HIV), 3TC, tenofovir and FTC. Interferon was an early treatment for HBV that is used less frequently now because oral drugs are easier to tolerate. Adefovir, tenofovir and FTC are the most active oral drugs, with the least risk of developing hepatitis resistance.

These treatments have to be used very carefully in coinfection with HIV. Because of the risk of HIV resistance, 3TC, tenofovir and FTC should only be used in HIV-positive people in triple ARV combinations. Adefovir can be used as single treatment if ARV treatment is not needed. Resistance to HIV and HBV are different and occur independently.

HBV can be successfully treated in many people. If lifelong treatment is needed, there is a serious risk of reactivation, and severe or fatal liver toxicity if the drugs providing an anti-HBV activity are stopped in someone who has not cleared the infection. This is a specialist area of disease management.

HCV: Treatment of HCV/HIV infection is also highly specialised. Combination HCV treatment with interferon or PEG interferon, plus ribavirin, for 48-weeks is current standard of care, but people with HIV/HCV coinfection may require longer treatment. Response rates to permanently clear HCV vary from 30% for people with HCV genotype 1 or 4 to 60-70% with genotype 2 or 3. Response rate after 12 weeks may be an early indication of the effectiveness of treatment. Even if HCV is not cleared, treatment may improve liver damage and delay disease progression.

- **Prophylaxis:** Effective vaccinations are available for Hepatitis A and Hepatitis B, there is no vaccination against Hepatitis C.
- **Future research:** HCV treatment for longer than one year may be more effective for some people. There is extensive research into drugs that work in other ways and which have less side effects than interferon, including oral drugs. It is hoped that some of these compounds will become new drugs in the next 5-10 years.

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5.10 CMV (cytomegalovirus)

- **Type of infection:** CMV is a viral infection that only becomes serious when CD4 levels drop below 50. So although it is widespread (over 50% general population, over 60% in IDU and over 90% in gay men), it only becomes a problem when the immune system is reduced - mainly people with HIV or having an organ transplant.
- **Main symptoms:** CMV infection can affect many different organs. CMV retinitis can cause progressive and permanent loss of sight. Early symptoms include floaters, blind-spots, blurred or dark area of vision, flashing lights or any vision loss. Sometimes active disease can affect peripheral vision without this being clear so it is essential that everyone with a CD4 count under 50 has regular eye examinations (every 1-3 months).

CMV can affect other organs: GI tract, stomach, bowel, rectum (all of which can cause diarrhoea and bleeding); lungs (often with PCP); brain and the central nervous system.

- **Diagnosis:** CMV retinitis is diagnosed by eye examination. CMV in other organs usually requires diagnoses from a biopsy sample.
- **Treatment:** With CMV retinitis, immediate treatment is essential, as damage to the eyes is permanent. The three main treatments are ganciclovir, foscarnet and cidofovir, usually given by slow IV delivery, twice-daily, started on the day of diagnosis. Ganciclovir and foscarnet are first line options. Local treatment (ie to the affected eye) can be given by a direct injection into the eye or slow delivery implants. Valganciclovir is available in an oral formulation, which is replacing the previous oral formulation of ganciclovir.

ARV treatment for HIV that brings CD4 counts back over 50 cells/mm³ is the best medium and long-term treatment. Once the CD4 count has been raised over 100 cells/mm³ (perhaps even over 50) for several months, CMV treatment can usually be safely stopped. Otherwise this difficult treatment is lifelong.

Sometimes ARV treatment for HIV can cause an immune response that complicates the management of CMV. This requires specialist management.

The same IV and oral formulations are used to treat CMV in other organs.

- **Prophylaxis:** There may be a role for primary or secondary prophylaxis with oral valganciclovir (valganciclovir) in people with CD4 counts under 50 cells/mm³ who are not responding to HIV treatment. This has to be balanced against the side effects of the drugs and the risk of developing resistance.
- **Future research:** Several other compound are in development for treating CMV, but much of the urgency of this research dropped because of the huge impact that ARVs to treat HIV had on reducing the incidence of CMV retinitis.

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5.11 Toxoplasmosis

- **Type of infection:** Toxoplasmosis ('toxo') is an illness caused by a protozoa. It is mainly transmitted by eating raw or under cooked meat, or through exposure to cat faeces. Although many adults have been exposed it the serious risk of illness only usually occurs if your CD4 count falls below 200 cells/mm³.
- **Main symptoms:** Toxoplasmosis most commonly causes lesions in the brain. Symptoms include fever, headache, disorientation, confusion, memory loss and vision loss. If this progresses it can lead to behaviour change. If untreated toxo can be fatal.
- **Diagnosis:** Diagnosis is difficult because blood tests for antibodies, and even viral load tests in CSF (cerebrospinal fluid) are not always positive. MRI or CT brain scans can highlight any damaged to the brain, but rarely provide sufficient information to diagnose the cause of the damage.

Symptoms are often sufficient to start treatment, and if symptoms improve within a two weeks then toxoplasmosis will have been the cause. Lesions should start to reduce on an MRI or CT scan by three weeks.

- **Treatment:** Treatment is effective and usually straight forward using antibiotics pyrimethamine plus sulphadiazine, usually in oral tablet, sometimes IV in severe disease. Other antibiotics - clindamycin, clarithromycin or azithromycin can be used if there is a reaction against sulphadiazine, but they are not as effective.

After a successful response to treatment (usually three weeks) maintenance therapy is continued with low dose pyrimethamine plus either sulphadiazine or clindamycin.

Treatment is lifelong as long as your CD4 count remains below 200. As with many other OIs, a successful response to ARV treatment for HIV which brings CD4 count back over 200, means that treatment for toxo can usually be stopped, as long as long as it stays above this level.

- **Prophylaxis:** Prophylaxis with co-trimoxazole (trimethoprim plus sulfamethoxazole) - Bactrim, Septrin - in people with CD4 counts under 200 is widely used - mainly because this is the same prophylaxis used to prevent PCP. In people who can not tolerate co-trimoxazole, either atovaquone or dapsone can be used as prophylaxis against both toxoplasmosis and PCP.
- **Future research:** Alternative antibiotics including atovaquone, azithromycin and doxycycline are the subject of future research.

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5.12 Cryptococcal meningitis

- **Type of infection:** Cryptococcus is a fungal infection found in soil from bird droppings, that can be breathed in as dust. It can not be passed in the air from one infected person to another. Infection can be dormant for many years. As with other OIs this only becomes a problem as an active disease if your CD4 count drops to below 100 cells/mm³. Smokers and people who work out of doors have higher risk of cryptococcus.
- **Main symptoms:** If cryptococcus infects the blood it can cause cryptococcal meningitis which can be very serious. Symptoms of cryptococcal meningitis include headache, neck-ache, nausea, fever, confusion and disorientation, sensitivity to light and can lead to stroke and coma. In the lungs, symptoms can be similar to PCP and include coughing and shortness of breath, fever and fatigue.
- **Diagnosis:** Diagnosis is made by testing spinal fluid or blood either for antigens, or by growing the fungus in culture. A successful response to treatment is confirmed using the same tests. Spinal fluid is more difficult to test and requires a lumbar puncture or 'spinal tap'.
- **Treatment:** Moderate to severe initial infection (when there are brain-related symptoms) is treated with amphotericin B, or liposomal (fat-coated) amphotericin B. Treatment is through a central line (Hickman or Portacath) into a deep vein. This is a more complicated and difficult and can last up to six weeks. Oral fluconazole or itraconazole are active against cryptococcus but are not as effective, and are only used in cases of mild infection. If the meningitis has caused high pressure in the spinal fluid this may also be drained periodically as part of treatment to reduce the risk of brain damage. Once the infection is cleared a second stage of maintenance treatment (secondary prophylaxis) is essential to prevent the infection returning. This is with oral fluconazole capsules at 400 mg/day for the first eight weeks, reduced to 200 mg/day for as long as CD4 count remains below 100-200. Maintenance therapy can be stopped after a successful response to ARV treatment that increases CD4 levels above 100. As with other maintenance therapy, if CD4 counts drop again in the future, secondary prophylaxis should be restarted.
- **Prophylaxis:** If you are in a country where the incidence of cryptococcus is high, then prophylaxis with fluconazole (200mg/day) or itraconazole if you have a CD4 count under 100 may protect you from infection. This has to be balanced against the risk of resistant infections and cost. ARV therapy to raise your CD4 count to a safer level would be much better value if this is available.

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5.13 Lymphoma, including Kaposi's Sarcoma (KS), Non-Hodgkins Lymphoma (NHL), Hodgkins Disease (HD)

Several important cancers are linked to HIV, and are listed as AIDS-defining illnesses. These include NHL, KS and cervical cancer.

Even though many other cancers occur more frequently in HIV-positive individuals compared to the general population (i.e. anal cancer, lung cancer, Hodgkins Disease) they have not been categorised as AIDS-defining. This may change in the future.

Some cancers (i.e. breast cancer) do not appear to occur at higher rates in HIV-positive people.

The definition of cancer is a disease caused by uncontrolled growth and spread of abnormal cells. Benign (or 'in situ') cancers are contained to the original cells and as long as they do not spread, they are not dangerous. Malignant cancers spread to other parts of the body and are much more serious. If the spread is not controlled, they can be fatal.

Lymphoma are cancers that develop in the lymphatic system. The most common type of lymphoma is Hodgkins Disease (HD). All other lymphomas are called non-Hodgkins lymphomas (NHL).

Sarcoma are cancers of the bone, cartilage, fat, muscle, blood vessels, skin or other connective or supportive tissue. The most common Sarcoma associated with HIV is Kaposi's Sacroma (KS).

Carcinoma is the name for a form of cancer that develops in tissues covering or lining organs of the body, such as the skin, the uterus, the lung, or the breast.

Each cancer has different characteristics, symptoms and treatment. All cancers have a better prognosis if the earlier they are detected.

Apart from KS, in general, HIV-related cancers are the one type of illnesses that do not dramatically improve and resolve as a response to ARV therapy. This is why screening and early monitoring is so important.

Recent research has linked many HIV-related cancers to other viral infections:

- KS is skin cancer that can also affect other organs and is associated with HHV-8 (Human Herpes Virus-8).
- Cervical and anal cancer are both linked to HPV (Human Papilloma Virus). HPV is a large family of viruses that also cause genital and anal warts. Some strains (16, 18, 31, 33, 35) have a stronger link to cancer than others.
- Epstein-Barr virus is associated with NHL.
- Liver cancer is associated with Hepatitis C virus (HCV).

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5.14 HIV-related weight loss and HIV-related wasting

Weight loss can be a symptom of many infections, including HIV itself. It may be caused by more than one factor, and may need more than one approach to diagnose and treat.

Severe weight loss or wasting is a life threatening, that usually reverses if ARV treatment are used. Even people using ARV treatment can have difficulty regaining and maintaining higher weight.

In someone with diarrhoea and weight loss, the cause of the diarrhoea needs to be found. The same is true if nausea or vomiting are factors.

As well as treating the cause of weight loss, you need to look at diet changes to reduce diarrhoea and improve nutrition if this is a factor, treatment to reduce diarrhoea. Often the best long term response is to get effective ARV treatment.

With nausea and vomiting, anti-nausea and anti-sickness medication should be prescribed.

- **Type of illness:** Weight loss is a symptom of most of the other OIs discussed in this section. It can also be a side effect of any illness or treatment that reduces your appetite. Weight loss or wasting are also caused by HIV itself, because the energy that you generate from nutrition (food and drink) is being used by the virus to over-activate your immune system. The amount of energy from diet that your body needs to function even when just sitting or lying down (called Resting Energy Expenditure, REE) is higher in HIV-positive people. It becomes higher still as HIV disease progresses. Other infections and illnesses also increase the amount of energy the body needs in order to fight infection.
- **Main symptoms:** Weight loss is general reduction in weight.
HIV-related wasting specifically includes muscle wasting and specifically lean body mass. Food is basically a source of energy. If you eat less calories each day than your body needs to do the things it needs to, then the extra energy is taken from stores of body fat. If body fat levels are already low, then this extra energy will be taken from protein that is used to build and maintain muscle.
- **Diagnosis:** Diagnosis of weight loss is easy and straight-forward because it only requires a pair of scales. Weight loss of 10% from normal body weight that can not be explained by other factors (ie change of diet, increased exercise, other infections or medications) becomes an AIDS-defining illness.
Unexplained weight loss of 5% of body weight over six months is predictive of continued loss to 10%, and therefore should be taken seriously.
Loss of subcutaneous fat as a side effect of ARV drugs (called lipoatrophy or lipodystrophy) is different, although when lipoatrophy and wasting can occur in the same person making this more complicated.
- **Treatment:** In very simple terms, regaining weight should just be a matter of increasing the amount of calories that you get in your daily diet. Achieving this can be more complicated though. Depending on the cause of weight loss, things that may seem common sense - like eating more high calorie foods may not always be appropriate. For example, increasing high calorie fatty foods in someone with diarrhoea, will increase the diarrhoea and reduce the likelihood that any nutrition will be absorbed by the body. Special dietary advice should always be sought.
If the cause of diarrhoea, nausea and vomiting are other OIs, the ARV treatment should help these symptoms improve. Also, people starting ARV treatment generally put on weight as they find they have a stronger appetite and more energy.
If oral or oesophageal thrush or mouth ulcers had made eating difficult or painful,

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then ARVs will similarly help resolve those problems.

Steroid use (with exercise), testosterone replacement (for both men and women) and appetite stimulants like Dronabinol (medicinal marijuana) are often used to help regain weight.

- Prophylaxis: If you are HIV-positive and not using ARVs, it is easier to lose weight than it is to put weight back on again. Earlier interventions are easier and more successful.

5.15 Summary table of OIs and effect of ARV treatment

This table summarises the OIs and co-infections discussed in this section, together with the impact of ARV treatment.

Infection/OI	CD4 risk level (cells/mm ³)	Prophylaxis	Protection returns after ARV increases CD4
Gut infections: giardia, cryptosporidia/microsporidia	Under 300	None, care with food and water etc	Yes
Candida and other skin problems. Herpes.	Under 300	None *	Yes
PCP	Under 200	Yes	Yes
TB (pulmonary)	Under 500	Not generally *	No
MAI / MAC	Under 100	Not generally *	Yes
Hepatitis B and C	Any CD4	None	No, but response to HCV treatment is stronger
CMV	Under 50	Not generally	Yes
Toxoplasmosis	Under 200	Yes	Yes
Cryptococcal meningitis	Under 100	Sometimes *	Yes
Cancer: lymphoma and sarcoma	Varies. Can be at any CD4 NHL usually under 200	No	Varies depending on lymphoma, KS can resolve on ARV treatment alone
Wasting syndrome	Usually under 300	No	Yes

* Although drugs can be used as prophylaxis, the risks or side effects and developing resistance usually outweigh the benefit of protection for infection.

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5.16 Glossary for Section 5

biopsy	The removal of cells or tissues for examination under a microscope.
bronchoscopy	This test uses a thin, flexible lighted tube called a bronchoscope to look inside your lungs.
cirrhosis	Chronic injury to the liver can result in scar tissue. This scarring distorts the normal structure and regrowth of liver cells. The flow of blood through the liver from the intestine is blocked and the work done by the liver, such as processing drugs becomes much more difficult. Cirrhosis is Stage 4 on Metavir and Knodell disease staging and Stage 6 on Ishak score.
CSF (cerebrospinal fluid)	A clear, colourless fluid surrounding the central nervous system.
GI (gastro intestinal)	The gastro-intestinal system includes the stomach, bowel and colon.
prophylaxis	Taking a drug to prevent an infection or before it occurs. This is most important at lower CD4 counts and/or when they is no access to ARV medication. Secondary prophylaxis is when you continue take medication are an illness has already been treated, often at a lower dose, in order to reduce the risk of re-infection or re-activation.
protozoa	Small parasites that can cause upset stomach and serious diarrhoea.
vaccination	A low dose, or inactivated version of an infectious organism that is given as an injection to stimulate the body to produce antibodies. These anitbodies provide protection against future infection. It is important that HIV-positive poeple are not generally given vaccinations that are made or live viruses. Inactivated alternatives are available and should be used if you are HIV-positive.

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5.17 Questions for Section 5

1. What are protozoa? Name three that cause gastric infections.
2. At what CD4 count are you at greater risk for gastric infections?
3. Name three ways to minimise the risk of gastric infections?
4. What is candida?
5. What are the main symptoms of candida?
6. Name three anti-fungal medications.
7. What is PCP?
8. At what CD4 are you more at risk for PCP?
9. What is used as prophylaxis?
10. What is first-line treatment?
11. What other treatments can be used for PCP?
12. What is TB?
13. What is the difference between active and inactive TB?
14. What is the first-line treatment for TB
15. What ARVs should not be taken with rifampicin?
16. When is TB prophylaxis recommended?
17. What is MAI/MAC?
18. What treatment is recommended?
19. What is hepatitis?
20. How long does hepatitis C take to progress to liver damage in HIV negative people?
21. What is the treatment for hepatitis B?
22. Below what CD4 count does the risk of CMV become active dramatically increase?
23. How is CMV diagnosed?
24. How is toxoplasmosis transmitted?
25. How long does toxoplasmosis need to be treated?
26. Which are the main AIDS-defining cancers?
27. Do cancers improve with ARV treatment?
28. What cancer is associated with hepatitis C?
29. What is AIDS wasting?

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5.18 Course evaluation for Section 5

Please take a few minutes to complete this evaluation. Any comments are appreciated, including on the usefulness of the evaluation as we can develop this into an online resource.

Session 5

How much of the information was new? None 1 2 3 4 5 All

How useful was the source material? Very 1 2 3 4 5 Not

How much support time did you need in 1-2-1 questions?

Were you given enough support for this section?

Did you find better internet sites for information, if so, which ones?

Did the questions relate to the information you found yourself?

What was your pass rate?

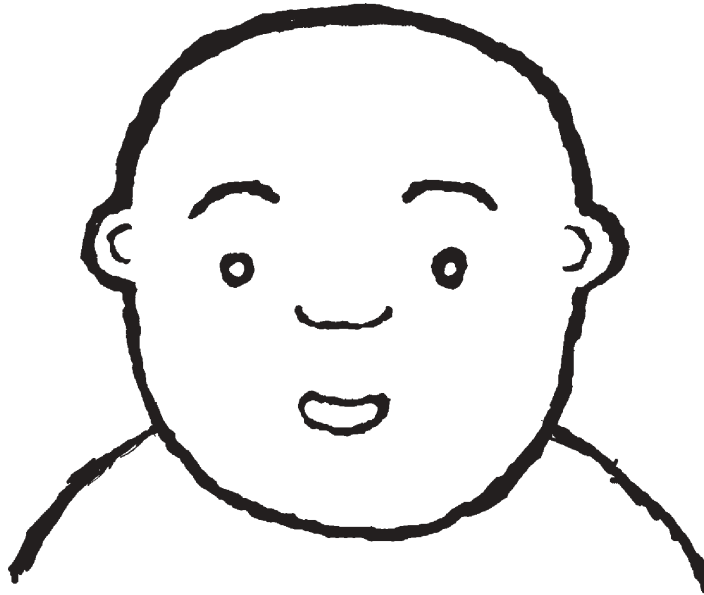
Sit the test again in one week to see how much you remember.

Did your pass rate improve?

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Section 6: HIV and pregnancy



6.1 Introduction

Section 6 provides an overview of HIV and pregnancy.

This section is particularly important as over half of new HIV diagnoses are in young women and many will want to have children in the future.



6.2 Aims for section 6

After completing this section you should have a basic understanding of:

- Why maternal health is important for a healthy baby.
- Where treatment in pregnancy differs from that for non-pregnant adults.
- Which HIV drugs are safest to use in pregnancy for the mother's and baby's health.
- Some treatment strategies for different situations.
- Resistance, monitoring and other tests.
- Choices for delivery and use of C-section.
- Baby's diagnosis.
- Feeding the baby.

6.3 General Questions

Can HIV-positive women safely become mothers without risks to their babies?

Yes. Using antiretroviral (ARV) drugs, an HIV positive woman can safely become pregnant with very little risk of transmitting the virus to her baby.

Many thousands of women have taken therapy during pregnancy without complications to their babies.

This has resulted in many HIV-negative babies.

How is HIV transmitted to a baby?

Without treatment, about 25% of babies born to HIV-positive women will be HIV-positive.

The exact way that transmission from mother to baby happens is still unknown. However, the majority of transmissions occur near the time of or during labour and delivery when the baby is being born. It can also occur through breastfeeding.

Certain risk factors seem to make transmission during labour much more likely. The strongest of these is the mother's viral load. If a woman has a high viral load the risk of transmission to her baby is much greater than if it is very low or "undetectable", so the aim of the HIV drugs is to make sure that her viral load is as low as possible, particularly at the time of delivery. This will also give the most benefit to the mother herself if she needs treatment for her own HIV.

Other risk factors include premature birth, lack of prenatal HIV care and the time between when the mothers waters' break and the actual delivery. This time is called 'duration of ruptured membranes'.

- The mother's health directly relates to the HIV status of the baby.
- Whether the baby's father is HIV-positive will not affect whether the baby is born HIV-positive.

Do HIV drugs protect the baby?

Reducing the risk of a baby becoming HIV-positive was an early benefit of ARVs.

PACTG 076 is the name of a famous HIV trial. This was the first study to show that using the drug AZT could protect the baby from HIV. Mothers took AZT before and during labour. The baby received AZT for six weeks after birth. This reduced the risk of the baby becoming HIV-positive from 25% to 8%.

From 1994, this strategy was recommended for all HIV-positive pregnant women in Western Europe and North America. But, even further advances have been made over the last few years. Transmission rates with combination therapy of three or more drugs are now less than 1%.



6.4 Mother's health and pregnancy

A mother's own health (and her own treatment) is the most important consideration to ensure a healthy baby. Overall treatment for an HIV positive pregnant woman will be the same as for any HIV positive adult differences in treatment strategies will be discussed later in this section.

It is important that the mother receives support from an experienced healthcare team during her pregnancy. Some discrimination still exists against HIV-positive people deciding to have children but although situations vary throughout the world things are generally better than they used to be.

- **HIV** - Pregnancy does not make a woman's own health related to HIV get any worse. It will not make HIV progress any faster.
- **CD4** - Pregnancy may cause a drop in a woman's CD4 count. This is usually about 50 cells/mm³ but it can vary a lot. This drop is only temporary. Her CD4 count will normally return to her pre-pregnancy level soon after the baby is born.
This is not a concern unless her CD4 falls below 200 cells/mm³. Below this level, she is at a higher risk from opportunistic infections. These infections could affect both the mother and the baby.
- **OIs** - In general, pregnant women need the same treatment to prevent opportunistic infections as people who are not pregnant (see Section 6.10 and all of Section 5).

6.5 Prenatal care and treatment

Prenatal or antenatal care is all the extra care that you receive during your pregnancy in preparation for your baby's birth.

Treatment in pregnancy - Recommendations will vary depending on the mother's situation and her own treatment needs when she becomes pregnant.

Most guidelines now recommend treating adults at around a CD4 count of 200 cells/mm³. This is one situation where using anti HIV drugs is different for pregnancy than for other HIV positive adults.

This is because even with mothers who have low viral loads that are less than 1000 copies/ml before they start treatment there is a risk of transmission. Transmission drops from almost 10% in untreated women to less than 1% in women treated with anti HIV drugs.

We will look at different situations and treatment strategies:

i) **If a woman is pregnant and does not need HIV treatment for her own health:**

In this situation a woman will most likely be offered a short course of triple combination therapy after the second trimester (6 months into pregnancy) at 24 to 28 weeks OR to use AZT monotherapy to mother and baby - as in the 076 study - and have an elective Caesarean or C-section (see Section 6.12). She will need to carefully consider these two options.

- Using three drugs will be more likely to reduce her viral load to undetectable levels. This has shown the lowest transmission risk to date.



- Using three drugs will also protect her from the possibility of developing resistance. This will protect her options for future treatment.
- C-sections are major surgery. They can carry risks for the mother.
- The baby will be exposed to a greater number of drugs with combination therapy.
- The risk of the mother developing resistance is higher using AZT monotherapy than triple combination therapy.

ii) If a woman is HIV-positive and needs treatment for her own HIV?

If someone is diagnosed during pregnancy and needs treatment for her own HIV she should be prescribed appropriate combination therapy.

If she is diagnosed early on in her pregnancy, she may wish to delay starting treatment until the end of the first trimester. This is the first 12 to 14 weeks from her last missed period. She may also want to delay treatment if she already knows her HIV status but has not yet started treatment.

There are two main reasons for delaying treatment.

- The baby's main organs develop in the first 12 weeks in the womb. This is called organogenesis. The baby may therefore be vulnerable to any effects the medicines could have during this time.
- Nausea or 'morning sickness' in the early stage of pregnancy. This is very normal. But symptoms of morning sickness are very similar to the nausea that can occur when starting HIV treatment.

If she wants to begin treatment immediately, or her need to start is urgent because she has a low CD4 count, your doctor will recommend it.

iii) If she discovers she is HIV-positive late in pregnancy

Even late in pregnancy, there is still a benefit to using treatment. Even after 36 weeks, it will reduce the mother's viral load to very low levels.

Even treatment for one week with combination therapy will reduce her viral load very quickly by a large amount.

iv) If she is already using HIV treatment when she becomes pregnant

Many women decide to have a baby when they are already using HIV treatment.

Unless there are very particular circumstances she should remain on her treatment (see Section 6.4).



6.6 Safety of HIV drugs in pregnancy

Which drugs to use:

- As with all treatment decisions there are no hard and fast rules.
- AZT is the only drug licensed for use in pregnancy and there is much experience with its use so it is likely that it will be recommended as part of her combination.
- The second NRTI is likely to be 3TC as there is also much experience with this drug in pregnancy.
- The third drug will be either a protease inhibitor - and there is most experience with nelfinavir - or an NNRTI such as nevirapine – but there are some cases where this drug would not be appropriate.

Drugs and situations where drugs are not recommended:

- Efavirenz is not recommended in pregnancy and the caution is strongest during the first trimester (12 weeks), because of possible risk to the baby. If someone finds that she is pregnant and using efavirenz she will need to have some extra tests, After the first trimester there is no point in switching efavirenz.
- Nevirapine is not recommended for women with high CD4 counts above 250 cells/mm³ (not just during pregnancy), because of risk of liver toxicity to the mother. It is very safe for women with CD4 counts below 250 cells/mm³.
- There is a strong warning against using d4T and ddI - the 'd' drugs – together. There have been several reports of fatal side effects in pregnant women using these drugs together. d4T is no longer recommended for first line therapy in Western Europe and North America.



6.7 Side effects and pregnancy

Side effects should be carefully monitored in pregnancy. These are a few important points about side effects in pregnancy (see also Section 4: Side effects of ARVs)

Similar to non-pregnant adults - Approximately 80% of pregnant women using combination therapy with ARVs will experience some side effects. This is similar to the percentage of people using ARVs who are not pregnant.

Usually minor - Most side effects are minor and include nausea, feeling tired and diarrhoea. Sometimes, but more rarely, they can be very serious.

ARV side effects and pregnancy changes - Some effects of HIV medicines are very similar to the changes in that happen during pregnancy e.g. morning sickness and the nausea caused by ARVs. This can make it harder to tell whether treatment or pregnancy is the cause.

Anaemia (low red blood cells) can cause tiredness. It is a very common side effect of both AZT and pregnancy. A simple blood test checks for this. If someone has anaemia they may need to take iron supplements.

Diabetes - There is a risk of developing diabetes during pregnancy. And women taking protease inhibitors in pregnancy may have a higher risk of this common complication. They should have glucose levels monitored and be screened for diabetes during pregnancy.

Lactic acidosis -Pregnancy may be an additional risk factor for raised levels of lactic acid. Your liver normally regulates this. Lactic acidosis is a rare but potentially fatal side effect of nucleoside analogues. Using d4T and ddI together in pregnancy appears to be particularly risky. This combination is now not recommended in pregnancy.

6.8 Resistance in pregnancy

Resistance is an important issue during pregnancy.

Some strategies to reduce mother-to-child transmission can also easily lead to resistance.

Using only one drug (monotherapy) or two drugs (dual therapy) is not as good as the minimum treatment for an HIV-positive person. Of these strategies, AZT used alone is less likely to induce resistance than AZT plus 3TC or nevirapine alone.

Resistance can also develop when a person's viral load is detectable with three or more drugs. This will affect their long-term health. Viral load at time of delivery is also strongly linked with risk of transmission from mother to child.

It is also possible to transmit resistant virus. The expectation for outcome of a baby born with drug resistant HIV virus is very poor as their HIV will be much harder to treat.

See also Section 3.19 on Resistance to ARVs.



6.9 Other screening and tests

HIV care in pregnancy should include screening for hepatitis, syphilis and other sexually transmitted diseases, anaemia and TB. Sexually transmitted diseases and vaginal infections can increase HIV transmission.

Screening for toxoplasmosis and CMV may also be necessary. These are two common viruses that can be transmitted to a baby. The tests should be performed as early as possible in pregnancy, and treated if necessary.

A clinic should provide a gynaecological check up. This will include a cervical smear. This is particularly important if a woman's CD4 is below 200 cells/mm³.

Tests to be avoided by HIV-positive pregnant women

Generally HIV-positive pregnant women are advised to avoid the following tests unless they are essential:

- Amniocentesis
- Chorionicvillus sampling
- Fetal scalp sampling
- Cordocentesis
- Percutaneous umbilical cord sampling
- Internal fetal labour monitoring (external ultrasound and fetal monitoring are perfectly okay).

6.10 Other infections

Treatment and prophylaxis for most opportunistic infections (OIs) during pregnancy is broadly similar to that for non-pregnant adults. Only a few drugs are not recommended.

PCP, MAC, TB - Prophylaxis and treatment of pneumocystis carinii pneumonia (PCP), mycobacterium avium complex (MAC) and tuberculosis (TB) infections are recommended if necessary during pregnancy.

CMV -Prophylaxis against cytomegalovirus (CMV), candida infections, and invasive fungal infections is not routinely recommended because of drug toxicity. Treatment of very serious infections should not be avoided because of pregnancy.

Herpes - A large number (about 75%) of women with HIV also have genital herpes. HIV-positive mothers are far more likely to experience an outbreak of herpes during labour than negative mothers. To reduce this risk prophylaxis treatment for herpes with acyclovir is often recommended.

Herpes is very easily transmitted from mother to child. Even if HIV viral load is below detection on ARVs, herpes sores contain high levels of HIV.

The herpes virus can also be released from the sores during labour. This will put the baby at risk from neonatal herpes and at increased risk of HIV.

Prophylaxis and treatment with acyclovir is safe to use during pregnancy



6.11 Drugs and the baby's health

Today, even children who were first exposed to AZT monotherapy during their mothers' pregnancy will not be older than fifteen. Children first exposed to combination therapy will not be more than six years old now.

So this is the limit of long-term follow up of children of mothers who have used these drugs in pregnancy. But careful follow-up of children exposed to AZT has not shown any differences to other children so far.

However, the biggest risk, to a baby born to a mother with HIV, is HIV itself. Combination therapy can prevent this.

Prematurity - There was initial caution over the use of protease inhibitors. This was over possible links to prematurity (delivery before 37 weeks) and low birth rate.

Abnormality - No particular abnormality in children has so far been linked to exposure to HIV treatments.

Development - So far no adverse effects on these children's development have been reported either.

Mitochondrial toxicity - There have been a small number of reports that the use of 3TC and AZT in pregnancy may be linked to mitochondrial damage in children.

Mitochondria are the 'energy producing factories' that live within our cells.

But a large study failed to show evidence of fatal mitochondrial damage in children exposed to these drugs during their mothers' pregnancy.

6.12 Choices for delivery and use of C-section

Caesarean or C-section is a procedure to deliver a baby that involves making a cut through the abdominal wall to surgically remove the infant from the uterus.

The way a baby is born and whether to have a vaginal birth or Caesarean section is controversial for HIV-positive women.

Several early studies showed that an elective Caesarean (or C-) section significantly reduced mother-to-child transmission compared to vaginal birth.

But these studies were before combination therapy and viral load testing were routinely used. Whether or not elective Caesarean delivery offers any benefit to babies born to mothers using combination therapy is unknown.

The operation must be carried out before the onset of labour and ruptured membranes. This is called 'elective' or 'scheduled' C-section.

Complications, particularly infections, are more common in woman having C-sections than woman having vaginal delivery.

There is such a low risk of transmission if a woman's viral load is undetectable associated with either mode of delivery that it may never be possible to show an advantage in transmission risk either way.

Interestingly, HIV transmission to the baby is rare among mothers who are taking ARV triple therapy, even when their viral load is greater than 50 copies/mL.

It is very important that a woman makes her own informed decision in association with her healthcare team concerning mode of delivery.



6.13 When the baby is born

The baby's diagnosis

Babies born to HIV-positive mothers will always test HIV-positive at first. This is because they have their mother's immune system and share her antibodies. If a baby is not infected with HIV these will gradually disappear. This can sometimes take as long as 18 months.

The best test for HIV in babies is very similar to a viral load test. This is an HIV PCR DNA test. It looks for virus in the baby's blood rather than at immune responses.

To check the baby is HIV negative:

- HIV PCR DNA is a polymerase chain reaction (PCR) test is a highly sensitive test that detects tiny amounts of HIV DNA in blood plasma.
- The test will "amplify" or multiply the DNA so that it can be more easily detected.

Good practice is to test babies the day they are born, and when they are one month and three months old.

It will be possible to show that the baby no longer has the mother's antibodies when he or she is 18 months old. This is called seroreversion.

If all these tests are negative, and she is not breast-feeding your baby, then the baby is not HIV-positive.

The baby's treatment

A baby will need to take HIV drugs for probably four to six weeks following his or her birth.

This is most likely to be AZT, which must be taken either two or four times a day. In a few cases a baby may be given another drug or combination therapy.

6.14 Breastfeeding

The risk of transmitting HIV from mother-to-baby via breast milk can be as high as 28%.

HIV-positive mothers living in industrialised countries can easily avoid this by using bottles and formula milk.

Bottle-feeding is currently strongly recommended for all HIV-positive mothers.

It is very strongly recommended that a woman does not breastfeed occasionally. In fact one study showed that 'mixed feeding' may carry an even higher transmission risk than exclusive breastfeeding.



6.15 Mother's health after the baby is born

A mother's own adherence after the baby is born is critical. New mothers often neglect their own health. Many women have excellent adherence during their pregnancy. After the baby is born it is easy to forget her own health.

Having a new baby can be a huge shock. In serious cases, women can have postnatal depression. So she will need lots of extra support from her family, friends and healthcare team. She may also find a community group very helpful.

Many mothers find the best way to remember to take their own medication is if they link it to the dosing schedule of their new baby.

6.16 Other useful information

i-Base pregnancy booklet

<http://www.i-Base.info>

International Community of Women (ICW)

<http://www.icw.org>

WORLD

<http://www.womenhiv.org>

Project Inform

<http://www.projinf.org>

British (BHIVA) pregnancy and treatment guidelines

<http://www.bhiva.org/>

US pregnancy guidelines

<http://www.aidsinfo.nih.gov/guidelines/>

Pregnancy registry

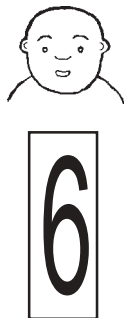
<http://www.apregistry.com>

So far, the registry has not seen any increase in the type or rate of birth defects.



6.17 Glossary for Section 6

Caesarean or C-section	A procedure to deliver a baby that involves making a cut through the abdominal wall to surgically remove the infant from the uterus. This can be either a planned or scheduled C-section or an emergency C-section. An emergency C-section offers no reduction in transmission to women receiving no therapy or monotherapy.
Mother-to-child-transmission	Transmission of HIV is when the virus passes from one person to another. When this is from mother to baby it is called mother-to-child transmission (MTCT) or perinatal or vertical transmission.
Pre-natal	The period before a baby is born during which the foetus (developing baby) develops and grows in the uterus.
Post-natal	The period after a baby is born.
Prophylaxis	When you take a drug to prevent an infection or reinfection before it occurs.
“Treat as non-pregnant adult”	– This is a very commonly used phrase. This means that generally your HIV is treated as if you are not pregnant. There are some exceptions- particularly when you do not need treatment for your own HIV and concerning some of the commonly used HIV drugs.



6.18 Questions for Section 6

1. What percentage of babies will be born HIV-positive if their mothers receive no treatment?
2. What is the most important factor in preventing mother to child transmission?
3. Does the father's HIV status relate to the baby being born HIV positive?
4. Does pregnancy influence the CD4 count of the pregnant woman? If yes, how?
5. What are the risks for the mother if she uses only AZT monotherapy for reducing mother to child transmission?
6. What is the current mother to child transmission rate when a pregnant woman receives a combination therapy of three or more drugs?
7. What should be the advice to an HIV positive pregnant woman who does not need ARVs for her own HIV infection yet?
8. List the pros and cons of the C-section as a means of delivery for an HIV positive pregnant woman.
9. Which ARVs, combinations of ARVs are not recommended in pregnancy or in particular circumstances in pregnancy. List them and explain why.
10. To which conditions can pregnancy contribute?
11. Which tests should an HIV-positive pregnant woman avoid?
12. When would you recommend prophylaxis with acyclovir during pregnancy?
13. What is acyclovir used to treat?
14. When and how should the baby's HIV status be checked?
15. Can an HIV-positive women breastfeed? Please explain?
15. For how long after they are born is it recommended that the baby should take ARVs ?
16. What is particularly important for an HIV positive woman to remember after her baby is born?



6.19 Course evaluation for Section 6

Please take a few minutes to complete this evaluation. Any comments are appreciated, including on the usefulness of the evaluation as we can develop this into an online resource.

Session 6

How much of the information was new? None 1 2 3 4 5 All

How useful was the source material? Very 1 2 3 4 5 Not

How much support time did you need in 1-2-1 questions?

Were you given enough support for this section?

Did you find better internet sites for information, if so, which ones?

Did the questions relate to the information you found yourself?

What was your pass rate?

Sit the test again in one week to see how much you remember.

Did your pass rate improve?



Session 7: Drug users and ARVs

“Access to HIV treatment should not be artificially restricted due to political or social constraints. Specifically there should be no categorical exclusion of injection drug users from any level of care. All patients who meet eligibility criteria and want treatment should receive it, including IDUs, sex-business workers and other populations.”

WHO's 2004 Protocols for HIV/AIDS

7.1 Introduction

Transmission of HIV through injecting drug use accounts for the majority of new infections in: Russia, Ukraine, Central Asia, most of Eastern Europe, South East Asia, North Africa, Iran, Afghanistan, Pakistan, Nepal, Indonesia, Portugal and the Southern Cone of Latin America. People at risk of becoming HIV positive through injection drug use are often among the poorest and most marginalised sections of society: ethnic minorities, unemployed, youth, migrants and sex workers.

Additionally - although there has been little or no research to address this - there are potential interactions between injection and non-injection recreational drugs and substitution therapies and ARVs,



7.2 Aims for Section 7

This section provides an overview of three key areas:

- Beliefs and realities around treatment for drug users with HIV.
- Known and potential interactions between recreational drugs and ARVs.
- Known and potential interactions with methadone.

7.3 General Questions

Why are drug users sometimes excluded from ARV treatment programmes?

In many countries drug users are routinely excluded from ARV treatment programmes due to widespread belief that they are less likely to be adherent to treatment and less likely to have a good response to treatment.

Reluctance to offer ARV to drug users includes not only injection drug users (IDUs), but also those on medically prescribed substitution treatment such as methadone, users of non-injection drugs, and former drug users.

Is this appropriate?

No. Beliefs that drug users are non-adherent and untreatable are based on prejudice rather than science. However, several studies suggest that drug users—particularly when HIV treatment is delivered with adherence, social and medical support—can achieve high levels of adherence and benefit from treatment just like any other group of people with HIV.

- A large Western European study of people receiving ARVs found no significant difference between IDUs and non-drug users in CD4 or treatment response.
- Another study in Canada found that drug users who were adherent to treatment gained the same increases in CD4 count as adherent non-drug users.
- In an American mobile syringe exchange programme, 77% of drug users offered peer support along with ARVs achieved reduction of viral load to less than 400 copies/ml and a 25% increase in CD4 after six months.
- A French study of people receiving ARVs found that those also receiving buprenorphine achieved higher levels of adherence (78.1%) than either former drug users (65.5%) or active IDUs not on buprenorphine (42.1%).



7.4 Comprehensive and accessible care

Including as many health and social services as possible at a single site has been shown to improve both adherence and treatment outcomes for IDUs.

Drug users are often unwilling to come forward, and there is a need for appropriate support. Services need to be located somewhere accessible to IDUs and within the HIV clinic setting.

Comprehensive, multi disciplinary services should include:

- Access to ARVs
- Access to substitution therapy: methadone or buprenorphine
- OI prophylaxis and treatment
- Accessible, non-judgemental healthcare team
- Needle exchange
- Adherence support and counselling
- Strong links with community based programmes
- Food programmes and public transport
- Outreach strategies

7.5 Interactions between recreational drugs and antiretrovirals

There is much research and information about interactions between antiretrovirals and other prescribed medications, but little reliable information about interactions between ARVs recreational drugs.

In 1996 a young HIV positive British man died after taking ecstasy while using ritonavir. His death was caused by an overdose, and the level of ecstasy in his blood was nearly ten times the level that is expected to cause serious toxic effects, ie roughly the level after taking 22 ecstasy tablets (although he had only taken a normal amount of ecstasy).

The patient had previously taken ecstasy before with no such ill effects. This was the first time that he had taken ecstasy since adding ritonavir – taken full dose ie 600mg twice daily – to his ARV combination, which is why his doctors concluded that this interaction was the culprit.

Following interventions by activists, the company – Abbott - produced some theoretical interaction information for ritonavir and commonly used recreational drugs.

Predicted interactions with ritonavir and street drugs:

- 2 to 3 fold increase in ecstasy levels
- About 50% decrease in blood levels of heroin
- 2 to 3 fold increase in levels of amphetamines
- No serious interactions with cocaine

Note: this information was based on using full dose ritonavir; this drug is now most commonly used to boost other protease inhibitors.



7.6 Why this theoretical information is not as useful as controlled interaction studies in humans

Because these drugs are illegal, predicted interactions are not based on studies in humans but based on theory, experiments in test tubes (in vitro) or animal studies. There are a number of difficulties both with conducting proper studies and using the theoretical information:

- Clinical trials using illegal drugs would require permission from the (American) government, which has been exceedingly reluctant to allow such studies for fear of being perceived as “soft on drugs”.
- Finding supplies of pure drugs would, in some cases, be difficult. There are no approved versions of drugs such as cocaine. For legal and ethical reasons, drug companies are unwilling to manufacture test versions of such drugs in their own laboratories, even if the government granted permission.
- Illegal drugs are seldom pure, are often contaminated by other substances, and may contain very little or none of the actual ingredient.
- Illegal drugs rarely have standardised doses: what could be a relatively minor interaction at one dose could be serious at another.
- There is little financial incentive for drugs companies to do this work.
- Some protease inhibitors have been found to have effects in real life opposite to those predicted in the test tube (eg, there have been instances of decreased methadone levels in human users where test tube experiments had predicted such levels would increase).
- Manufacturers are concerned about legal liability should they offer advice based on uncertain or potentially incomplete information

7.7 Interactions with other ARVs

All protease inhibitors are processed by the body in a similar way to ritonavir, as is the NNRTI efavirenz, so there is potential for interaction with any of these drugs.

A comprehensive overview summarising interactions between ARVs and recreational drugs (and methadone) lists the following potential interactions and observed interactions from case studies and makes recommendations. See Table 1 in Section 7.9.

- Ecstasy -** Potential for an interaction with PIs or efavirenz. Advised to take appropriate precautions: use 25% of the usual amount of ecstasy, take breaks from dancing, ensure rave or party has medical team on site, drink lots of water and avoid combining with alcohol.
- Other amphetamines** – Potentially dangerous interactions with ritonavir and this combination should be avoided if possible.
- GHB** Potential interaction with PIs (especially ritonavir) and possibly efavirenz.
- KETAMINE** There are no studies or reports describing interactions between ketamine and antiretroviral agents. People using PIs may be at risk for ketamine toxicity due to drug accumulation.
- PCP (angel dust)** Potential that use of PCP with PIs, and possibly efavirenz may result in elevated PCP concentrations and resultant toxicity. People using PCP who are also receiving treatment with ARVs should be cautioned to use less than what they would normally use given the potential for a drug interaction.
- LSD** It is not very clear how this drug works therefore anticipating drug interactions with LSD is extremely difficult. People who use LSD recreationally and who use ARVs should be warned about the possibility of an interaction and to be familiar with signs of LSD toxicity, and perhaps consider using a smaller amount than normal.
- Cocaine** Interactions between cocaine and antiretrovirals have not been described. It is thought that interactions with nevirapine or efavirenz may possible increase the risk of liver toxicity but there is no research to support this.
- Heroin** There may be concern that heroin is more rapidly metabolized producing symptoms of withdrawal when used with PIs and efavirenz.

7.8 Interactions with methadone

There have been more studies of interactions between ARVs and methadone.

- People using methadone and efavirenz or nevirapine will have a reduced dose of methadone (of up to 60% in blood concentration) and may require an increase in their methadone dose to overcome symptoms of methadone withdrawal.
- There was a decrease of methadone of 36% in a human study of interaction with ritonavir. This was interesting as a previous study in the test tube found a 30% increase in methadone.
- Reduced concentrations of methadone have been found with PIs nelfinavir and lopinavir/ritonavir. Some people may need a dose increase of methadone.
- AZT concentrations are increased by approximately 2-fold and so a dose reduction of 50% of this drug is recommended with methadone.
- In contrast methadone appears to decrease concentrations of d4T and ddI – there are currently no guidelines for dose adjustment.

Reduced methadone concentrations are not always accompanied by symptoms of withdrawal.

It can be difficult to distinguish between symptoms of ARV toxicity and symptoms of withdrawal (eg nausea, vomiting). It is likely that symptoms that develop within 2-3 days may be due to ARV toxicity, and those that develop after 6 days are more likely to be associated with withdrawal.

7.9 Table I – Interactions Between Antiretrovirals and Rave Drugs

Drug	Metabolism	Actual/Theoretical Interaction	Potential Significance	Recommendation
Amphetamines	CYPD6	Possible _ concentration with ritonavir	Hypertension, hyperthermia, seizures, arrhythmias, tachycardia, tachypnea	Avoid combination with ritonavir if possible; alternatively, start with _ - _ of initial amount of amphetamine used
GHB	Expired breath as CO ₂ : first pass metabolism	Possible _ concentrations/prolonged effect with antiretrovirals, especially ritonavir	1 case of GHB toxicity with ritonavir/saquinavir: myoclonic or seizure activity, bradycardia, respiratory depression, loss of consciousness	Use cautiously with CYP450 inhibitors (i.e. PIs, delavirdine, efavirenz,); become aware of signs/symptoms of GHB toxicity
Ketamine	CYP2B6 (main) 3A, 2C9 (both to lesser extent)	Possible _ concentration with antiretrovirals, especially ritonavir, nelfinavir and efavirenz	Respiratory depression, loss of consciousness, hallucinations	Use cautiously with CYP450 inhibitors, especially ritonavir nelfinavir, and efavirenz; become aware of signs/symptoms of ketamine toxicity
LSD	Unknown	Possible _ LSD concentration	Hallucinations, agitation, psychosis, flashbacks	Use cautiously with CYP450 inhibitors; become aware of signs/symptoms of LSD toxicity
MDMA, Ecstasy	CYP2D6 (main) 1A2, 2B6, 3A4 (to lesser extent)	Possible _ with ritonavir, other PIs, efavirenz	1 death reported; hyponatremia, hyperthermia, arrhythmias, tremor, hyperreflexia, sweating, seizures, tachycardia, rhabdomyolysis	Avoid combination with ritonavir if possible; alternatively use _ - _ of usual amount and watch for signs of MDMA toxicity; stay well hydrated, avoid alcohol
PCP	CYP3A, CYP2C11, inhibits CYP2B1	Possible _ concentrations with antiretrovirals	Seizures, hypertension, rhabdomyolysis, hyperthermia	Use cautiously with CYP450 inhibitors; become aware of signs/symptoms of PCP toxicity

From: T Antoniou and A Lin-in Tseng. Interactions Between Recreational Drugs and Antiretroviral Agents. The Annals of Pharmacotherapy. 2002, October; Volume 36

7.10 Questions for Section 7

1. Why are drug users frequently excluded from ARV treatment?
2. Is this based on scientific evidence?
3. What treatment and services would be ideally included in a system of comprehensive care for IDU?
4. Is there an interaction between ritonavir and ecstasy?
5. Is there an interaction between ritonavir and heroin?
6. Is there an interaction between efavirenz and methadone?
7. What is dose changes, if any, are recommended in each case?
8. Is there an interaction between efavirenz and AZT?
9. What is recommended?
10. How could you distinguish between symptoms caused by ARVs toxicity and symptoms of drug withdrawal?

7.11 Course evaluation of Section 7

Please take a few minutes to complete this evaluation. Any comments are appreciated, including on the usefulness of the evaluation as we can develop this into an online resource.

Session 7

How much of the information was new? None 1 2 3 4 5 All

How useful was the source material? Very 1 2 3 4 5 Not

How much support time did you need in 1-2-1 questions?

Were you given enough support for this section?

Did you find better internet sites for information, if so, which ones?

Did the questions relate to the information you found yourself?

What was your pass rate?

Sit the test again in one week to see how much you remember.

Did your pass rate improve?

7

Session 8: Science support modules

8.1 Introduction

The following 2-page sections provide summaries of some of the technical, medical or scientific aspects related to HIV and treatment.

If you want to be able to review results from studies - either to see whether a treatment is appropriate, or to follow latest research, then you will find this easier if you can understand the terms involved.

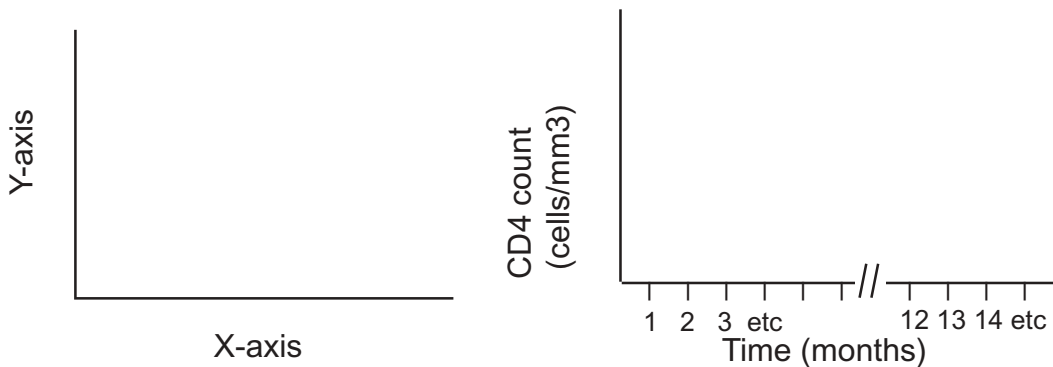


Science support 1: How to read a graph

This short section explains how to read and understand information from a graph.

A graph is a way of showing complicated information in a clear easy to understand way. They are used to summarise complicated results.

A graph usually has two axis - vertical (y-axis) and horizontal (x-axis), and anything can be measured on either axis.



If time is one of the variables that is being compared, then 'time' is always measured on the x-axis. Each axis need to be clearly marked with what is being measured: ie Time, CD4 count etc. All graphs should have a clear title.

If the graph is being used to show data rather than just a general trend or idea, then the units being measured need to be included: ie hours or years for time and cells/mm³ for CD4 counts. This scale needs to be shown in even measurements. If all the results cannot be fitted on the same scale, then the axis can be broken as in the second graph above, and the scale shown on each section.

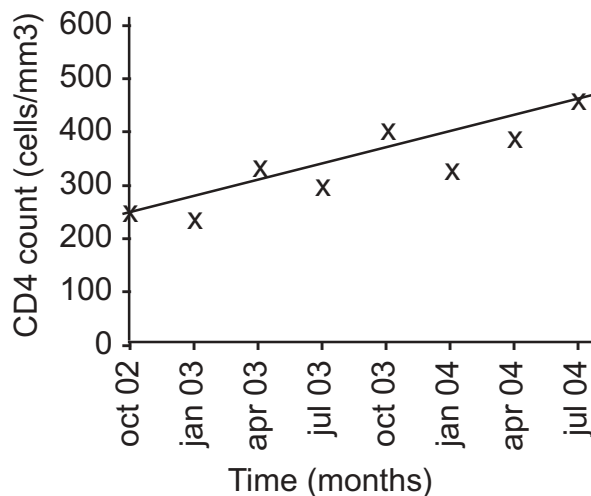
An example of how one persons CD4 results after starting treatment could be plotted is shown in Figure 1.

To make results clearer, a line showing an 'average' of the results is often added to make the general trend appear more clearly.

Although the actual counts go up and down a lot, the average trend in the example above shows CD4 count increasing by about 200 copies/mm³ over 18 months.

You can also plot the average results of much larger amounts of data. For example the 'average' CD4 counts of a group of 100 people after treatment could look exactly the same.

Figure 1: CD4 count changes in Patient A after starting treatment in October 2002



The only difference in a graph that is showing more than one set of results, is that the numbers of people at each time point should also be included underneath each time. See Figure 2.

'N' is the mathematical term for 'number'

Although the results are for a group of 100 people, in this example either not all the people have completed the study and it is an early analysis, or some people have dropped out of the study.

Graphs should also really show the variation within a group (see also the next module on scientific terms and averages).

They show this by vertical lines that go up from and down from the average result that is plotted - see Figure 3.

The top and bottom of these lines often have a small horizontal line to make this clearer

This can either show:

- i) the full range of the results
- ii) the range of the middle 50% (called the Inter-Quartile Range: IQR); or
- iii) the middle 95%.

The graph should state which range is being shown.

Figure 2: Average (median) CD4 count change in 100 patients after starting treatment in Oct 2002

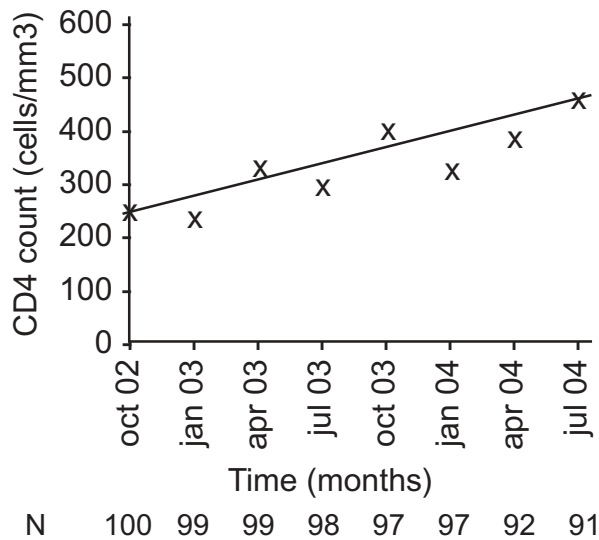
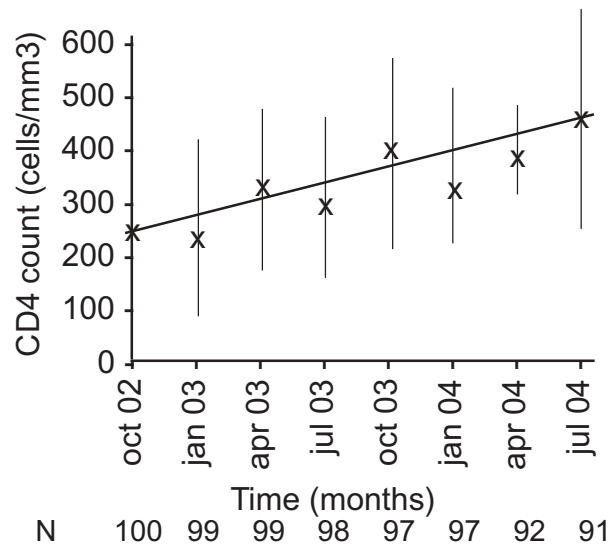


Figure 3: Median CD4 count and IQR change in 100 patients after starting treatment in Oct 2002



Caution: Just as graphs can make information much clearer they can also be used to show make things look better or worse than they really are.

- i) Scales - always check the scale on a graph. If it doesn't start at zero, then the change shown may look more impressive than it really is.
- ii) Numbers of people or results at any time point. If a study started with 100 people, then any average results plotted in a graph should be an average of all 100 people. If early or preliminary results of a study are being shown, the numbers at each time point may much lower after further time points.



Further reading: Caroline Sabin- Statistics part I

<http://www.i-Base.info/ukcab>

Science support 2: What is an 'average'?

Study results are nearly always based on finding a pattern from lots of individual observations. In order to see any trend the average results are then presented.

The average can be used to be able to generalise results for larger groups of people or larger sets of results.

You always need to remember when looking at average results that some results will have been higher and lower than the average. This is especially important when looking at studies related to healthcare.

There are two most commonly used ways to calculate the average, that can give very different results.

Mean average - this is where all the results are added together, and then divided by the number of results.

ie CD 4 increases after 6 months treatment in 10 people could be:
+20 +40 +15 -20 -5 +120 +250 +30 +50 +100

Most people had increase but some people's count was lower after 6 months.

The mean average from these results would be $20 + 40 + 15 - 20$ etc divided by 10 people:
ie $600 / 10 = 60$.

Median average - this is where the results are all arranged in numerical order and the most of the results in the centre is taken as the median. In the same example this would be:

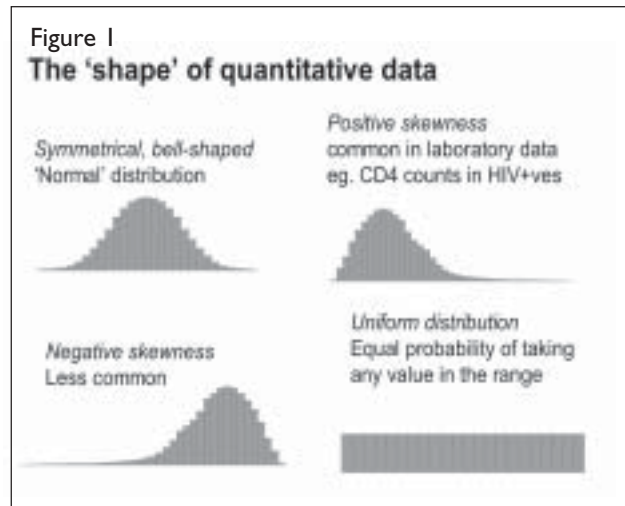
-20 -5 +15 +20 +30 +40 +50 +100 +120 +250

The median CD4 increase would be the middle point - ie half way between the 5th and 6th result - ie an increase of +35.

'Even distribution' is a term to describe data where most results are in the middle and a roughly similar number of results fall either side. It is also called a bell-shaped distribution. If results are evenly distributed then the mean average is appropriate,

When the results are not evenly distributed this is called a skewed distribution. For example the majority of results may be higher or lower than the middle range and skewed to the right or the left, then it is important to use the median average. (see Figure 1).

In the example above, the result of one person that was much higher than the rest (+250) had a disproportionate effect on the mean average.



8

When thinking about averages, you also need to know how much variation there is in any collection of results. This will help you decide how much you want to rely on the results.

For example the mean of $48 + 49 + 50 + 50 + 51 + 52$ is $300/6 = 50$

But the mean of $0 + 25 + 50 + 50 + 75 + 100$ is also $300/6 = 50$

You can see that completely different patterns of results give you the same mean average. Different ways to show variation are used depending on whether the results are evenly or unevenly distributed.

If distribution is even and you are using the mean average, then variation is usually calculated as being twice the 'standard deviation' - and shown in brackets with a +/- sign in front of the result.

One x standard deviation gives you the middle range of 50% of the results.

Two x standard deviations give you the middle range of 95% of the results.

If the results are not evenly distributed - like the example of CD4 counts earlier - then the median average is used.

Variation with the median average is easier to understand, and is shown in two main ways:

i) either the full range of results - ie the lowest and the highest

ie for the same example:

-20 -5 +15 +20 +30 +40 +50 +100 +120 +250

Median = 35 (range -20, +250)

ii) or the middle section of results - called the Inter Quartile Range (IQR)

The Inter-Quartile Range is sometimes given instead of the full range, to reduce the impact of very high or very low results. This is the range of the middle 50% of result with the highest 25% and lowest 25% not included.

The IQR for the above example would be midway between -5 and +15 = 10 for the lowest 25% and midway between 100 and 120 for the highest 25% = 110.

The median and IQR for the same results would be shown as:

Median = 35 (IQR 10, 110)

Further reading:

Caroline Sabin- Statistics part 2

<http://www.i-Base.info/ukcab>



Science support 3: What happens when you take a drug

If you understand what happens when you take a drug through the following graphs, you will understand the science behind adherence.

When you take a drug, it can be absorbed by your body into the blood in different ways depending on how it is taken.

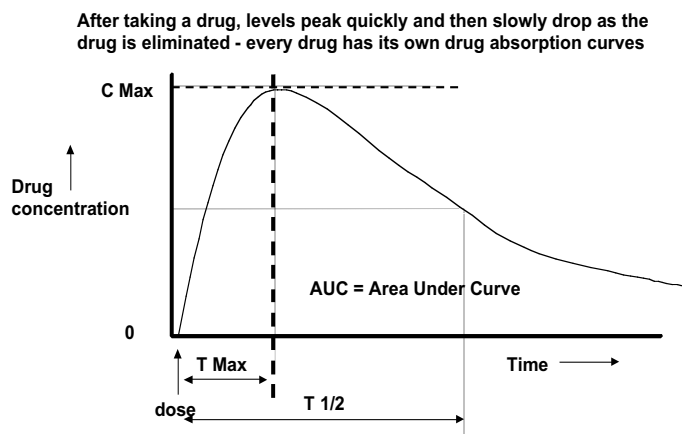
- A pill is usually absorbed through the stomach walls after it is swallowed - these can become active in a few minutes but usually take an hour or two to reach the highest concentration in the blood.
- IV drugs are injected directly into the blood work much faster - sometimes in seconds or minutes.

However a drug is taken though, it will reach a peak level and then these levels will go down as the body breaks down the active ingredients, usually as the circulating blood is filtered by the liver or kidneys.

This basic process happens with every drug - alcohol, nicotine, aspirin, HIV drugs....

Drugs are always absorbed more quickly than the body can break them down, so the highest concentration is reached relatively quickly, and then it takes longer to leave the body.

Figure 1: Drug absorption



The maximum concentration is called the Cmax.

The total exposure to drug over the dosing period is called the Area Under the Curve (AUC)

The time taken to get to the maximum concentration is called the Tmax



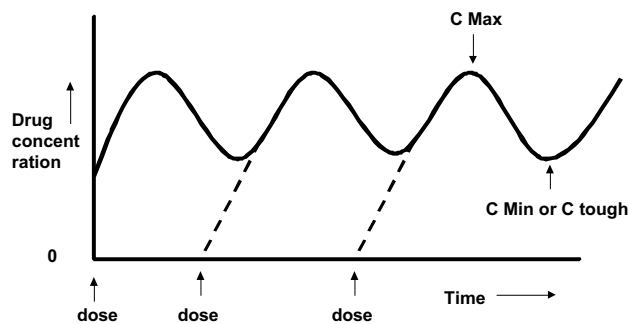
The time taken to reduce the maximum concentration by half (by 50%) is called a drug's 'half-life' or $T_{1/2}$.

It takes approximately 5 = half life for a drug to be cleared to negligible levels, but in theory, tiny quantities can be in the system for much longer.

When a drug is taken routinely as treatment, the minimum concentration just before the next dose is called the C_{min} or C_{tough} (trough level).

Figure 2: Drug absorption after multiple doses

Each dose taken on time makes sure that you keep above a minimum level



- Remember that all these results are 'averages'.
- Some people absorb drugs more quickly or more slowly than the average.
- Some people clear drugs more quickly or more slowly than the average.

These results are usually only calculated in blood and blood levels do not always relate to how active a drug is.

With nucleoside analogues, the level on the active drug inside the cell is more important than blood levels. The graphs showing drug levels inside cells would follow a similar pattern.

Pharmacokinetics is the name for ways that drugs are absorbed and eliminated by the body. Although drug levels can behave in different compartments: blood, brain, genital fluids, inside different cells etc the basic principles of absorption and elimination are often very similar.

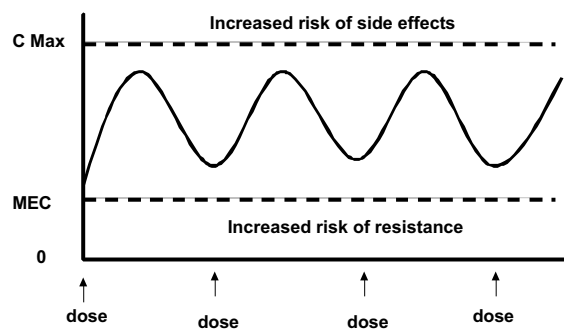
Science support 4: Drug levels, drug activity and side effects

On a very basic level, if drug levels are too low, then the drug will not be active enough to have any effect.

If drug levels are too high, then the risk of some side effects is likely to be higher.

Figure 1: Drug levels and resistance

Taking drugs at the exact time makes sure that you keep above a minimum level



- Doses of a drug and how often you need to take a medication are designed to keep you in this target range.
- Different drugs have different target ranges.
- Drugs that leave your body quickly have to be taken more frequently and drugs that are processed more slowly can have longer dosing intervals.
- Some drugs - including HIV drugs, TB drugs, antibiotics and anti-fungal drugs have to be above a certain concentration, so that resistance doesn't occur (see next section for more on this).

It is important to remember that there is often a very wide range of variability between different people who take the same dose of a drug.

Some people will process the drug more quickly and get lower than average drug levels.

Some people will process drugs more slowly and get higher than average levels.

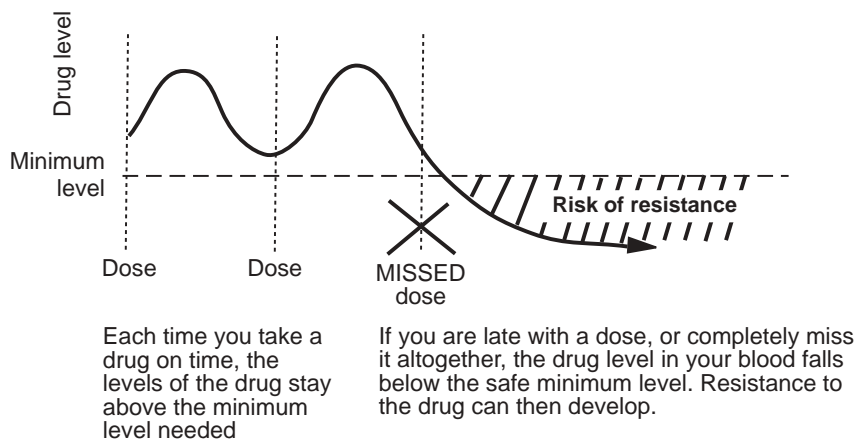
Just to make things even more complicated, there can be differences in drug levels in the same person, even if the levels are measured at the same time after each dose. Some drug levels are different 12 hours after a morning dose compared to 12 hours after an evening dose.



Again, although the details are complicated the simple picture is important to grasp: you are aiming to have a constant safe levels on drug whenever you are on treatment.

You can see that a graph of drug levels can give you information about adherence and what happens if you are late with a dose or if you miss a dose completely.

If you remember that average figure involve a range of higher and lower actual concentrations, that people who absorb lower levels of drugs are at higher risk of resistance if they are late or miss a dose.



Occasionally missing or being late with a dose (say once a month) may not make very much difference.

If you are missing or being late with a dose even once a week though, this will increase the time the virus has to develop resistance, and will increase the chance you will develop resistance over time.

Adherence is not about doing things on time just because your doctor says so. It is about keeping minimum levels of each drug in your body 100% of the time that you are on treatment.

Appendix I

Conditions included in the 1993 CDC AIDS surveillance case definition

- Candidiasis of bronchi, trachea, or lungs
- Candidiasis, esophageal (thrush)
- Cervical cancer, invasive
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (greater than 1 month's duration)
- Cytomegalovirus disease (CMV) (other than liver, spleen, or nodes)
- Cytomegalovirus retinitis (CMV) (with loss of vision)
- Encephalopathy, HIV-related
- Herpes simplex: chronic ulcer(s) (greater than 1 month's duration); or bronchitis, pneumonitis, or esophagitis
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (greater than 1 month's duration)
- Kaposi's sarcoma (KS)
- Lymphoma, Burkitt's (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- Mycobacterium avium complex or *M. kansasii*, disseminated or extrapulmonary
- Mycobacterium tuberculosis (TB), any site (pulmonary or extrapulmonary)
- Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
- Pneumocystis carinii pneumonia (PCP)
- Pneumonia, recurrent
- Progressive multifocal leukoencephalopathy (PML)
- Salmonella septicemia, recurrent
- Toxoplasmosis of brain
- Wasting syndrome due to HIV

Source:

<http://www.cdc.gov/mmwr/preview/mmwrhtml/00018871.htm>

Appendix II: WHO Classification System for HIV Infection

Clinical Stage 1

1. Asymptomatic infection
2. Persistent generalized lymphadenopathy
3. Acute retroviral infection

Performance Stage 1

Asymptomatic, normal activity

Clinical Stage 2

4. Unintentional weight loss <10% body weight
5. Minor mucocutaneous manifestations (e.g. dermatitis, prurigo, fungal nail infections, angular cheilitis)
6. Herpes zoster within previous 5 years
7. Recurrent upper respiratory tract infections

Performance Stage 2

Symptoms, but nearly fully ambulatory

Clinical Stage 3

8. Unintentional weight loss >10% body weight
9. Chronic diarrhea >1 month
10. Prolonged fever >1 month (constant or intermittent)
11. Oral candidiasis
12. Oral hairy leukoplakia
13. Pulmonary tuberculosis within the previous year
14. Severe bacterial infections
15. Vulvovaginal candidiasis

Performance Stage 3

In bed more than normal but <50% of normal daytime during the previous month

Clinical Stage 4

16. HIV wasting syndrome
17. Pneumocystis carinii pneumonia
18. Toxoplasmosis of the brain
19. Cryptosporidiosis with diarrhea > 1 month
20. Isosporiasis with diarrhea > 1 month
21. Cryptococcosis, extrapulmonary
22. Cytomegalovirus disease of an organ other than liver, spleen or lymph node
23. Herpes simplex virus infection, mucocutaneous
24. Progressive multifocal leukoencephalopathy
25. Any disseminated endemic mycosis (e.g., histoplasmosis)
26. Candidiasis of the esophagus, trachea, bronchi, or lung
27. Atypical mycobacteriosis, disseminated
28. Non-typhoid Salmonella septicemia
29. Extrapulmonary tuberculosis
30. Lymphoma
31. Kaposi's sarcoma
32. HIV encephalopathy

Performance Stage 4

In bed > 50% of normal daytime during previous month

Source: HIV InSite Knowledge Base

<http://hivinsite.ucsf.edu/InSite?page=kb-01-01>

Appendix III: OIs listed by disease type

Bacterial Infections

- Mycobacterium Avium Complex (MAI / MAC)
- Mycobacterium Kansasii
- Salmonellosis
- Syphilis & Neurosyphilis
- Tuberculosis (TB)

Malignancies (Cancers)

- Anal Dysplasia/Cancer
- Cervical Dysplasia/Cancer
- Kaposi's Sarcoma (KS)
- Lymphomas

Viral Infections

- Cytomegalovirus (CMV)
- Hepatitis C
- Herpes Simplex Virus (oral & genital herpes)
- Herpes Zoster Virus (shingles)
- Human Papilloma Virus (HPV, genital warts, anal/cervical dysplasia/cancer)
- Molluscum Contagiosum
- Oral Hairy Leukoplakia (OHL)
- Progressive Multifocal Leukoencephalopathy (PML)

Fungal Infections

- Aspergillosis
- Candidiasis (thrush, yeast infection)
- Coccidioidomycosis
- Cryptococcal Meningitis
- Histoplasmosis

Protozoal Infections

- Cryptosporidiosis
- Isosporiasis
- Microsporidiosis
- Pneumocystis Carinii Pneumonia (PCP)
- Toxoplasmosis

Neurological Conditions

- AIDS Dementia Complex (ADC)
- Peripheral Neuropathy

Other Conditions and Complications

- Aphthous Ulcers (Canker Sores)
- Thrombocytopenia (low platelets)
- Wasting Syndrome

Source: <http://www.aidsmeds.com>

Appendix IV: Drugs and doses of WHO combinations

The following table is a reference for different names of drugs, dosing, total pill count and brief details of food restrictions. Alternative doses are required for some combinations. Some drugs (ritonavir, nevirapine) start at lower doses for the first 1 or 2 weeks.

Name Brand & other names	Dosing	Total daily pills	Food restrictions
REVERSE TRANSCRIPTASE INHIBITORS (RTIs)			
d4T, Zerit, stavudine	1 capsule, twice daily	2	none
AZT, Retrovir, zidovudine	1 capsule, twice daily	2	none
ddl Videx, didanosine 100mg,	4 tablets, once daily	4	do not eat for 2 hours before and 1 hour after (2 hours after for EC)
200mg 'Reduced mass' ddl	2 tablets, once daily	2	
ddl/EC 'Enteric coated' formula	1 capsule, once daily	1	take on empty stomach
3TC (150mg) Eпивir, lamivudine	1 tablet, twice daily	2	none
3TC (300mg) Eпивir, lamivudine	1 tablet, once daily	1	none
abacavir, Ziagen	1 tablet, twice 2 daily	2	none
tenofovir, Viread	1 tablet, once daily	1	take with food
FTC. emtricitabine	1 capsule, once daily	1	none
Multi-nuke FDCs			
AZT+3TC together (ie Combivir)	1 tablet, twice daily	2	none
AZT+3TC+abacavir (ie Trizivir)	1 tablet, twice daily	2	none
NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIs)			
efavirenz, Sustiva	1 x 600mg tablet once daily	1	not with high-fat meal
OR	3 x 200mg capsules, once daily	3	not with high-fat meal
nevirapine, Viramune	1 tablet, twice daily	2	none
DUAL & BOOSTED PROTEASE COMBINATIONS [the most used doses]			
lopinavir/r, Kaletra	3 capsules, twice daily	6	take with food
indinavir/ritonavir			
400mg/400mg, 1xIDV / 4xRTV twice daily		10	none
800mg/200mg, 2xIDV / 2xRTV, twice daily		8	none
800mg/100m, 2xIDV / 1xRTV, twice daily		6	none
saquinavir/ritonavir			
400mg/400mg, 2xSQV / 4xRTV, twice daily		12	food reduces side effects
1000mg/100mg, 5xSQV / 1xRTV, twice daily		12	food reduces side effects
<i>[Invirase, hard gel formulation of saquinavir can be used instead of Fortovase soft gel capsule when using ritonavir. Invirase is a smaller pill with less side effects]</i>			
atazanavir*/ritonavir	300mg/100mg	2xATV/ 1 x RTV, once daily	3 none
fosamprenavir*/ritonavir	700mg/100mg	1xFosAPV / 1xRTV, once or twice daily	none
SINGLE PROTEASE INHIBITORS (PIs)			
indinavir, Crixivan	2 capsules, 3 times daily	6	2 hrs after food and 1 hr before
nelfinavir, Viracept (film coated)	5 tablets, twice daily	10	take with meal
atazanavir, Reyataz	2 capsules, once daily	2	take with food
ENTRY INHIBITORS (Fusion inhibitors)			
enfuvirtide, T-20, Fuzeon subcutaneous injection, twice daily			none

CREDITS: Not-for-profit copying is encouraged. Written by S Collins, HIV i-Base. Drawings: B Higgins.

Appendix V: Drugs and doses of European licensed ARVs

The following table is a reference for different names of drugs, dosing, total pill count and brief details of food restrictions. Alternative doses are required for some combinations. Some drugs (ritonavir, nevirapine) start at lower doses for the first 1 or 2 weeks. An asterisk * is for a drug which may be available on an expanded access programme and/or which is expected to be licensed shortly. All combinations and doses should be discussed with your doctor.

Name	Brand & other names	Dosing	Total daily pills	Food restrictions
REVERSE TRANSCRIPTASE INHIBITORS (RTIs)				
d4T	Zerit, stavudine	1 capsule, twice daily	2	none
AZT	Retrovir, zidovudine	1 capsule, twice daily	2	none
ddl 100mg	Videx, didanosine	4 tablets, once daily	4	do not eat for 2 hours before and 1 hour after (2 hours after for EC)
ddl 200mg	'Reduced mass' ddl formula	2 tablets, once daily	2	
ddl/EC	'Enteric coated' formula	1 capsule, once daily	1	
3TC (150mg)	Epivir, lamivudine	1 tablet, twice daily	2	none
3TC (300mg)	Epivir, lamivudine	1 tablet, once daily	1	none
abacavir	Ziagen, 1592	1 tablet, twice daily	2	none
Combivir	(AZT/3TC together)	1 tablet, twice daily	2	none
Trizivir	(AZT/3TC/abacavir together)	1 tablet, twice daily	2	none
tenofovir	Viread	1 tablet, once daily	1	take with food
FTC	emtracitabine	1 capsule, once daily	1	none
NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIs)				
efavirenz	Sustiva	1 tablet (600mg), once daily	1	not with high-fat meal
nevirapine	Viramune	1 tablet, twice daily	2	none
delavirdine *	Rescriptor	6 tablets, twice daily	12	none
DUAL & BOOSTED PROTEASE COMBINATIONS <i>[the most used doses - individual monitoring (TDM) of drug levels is recommended]</i>				
lopinavir/r	Kaletra, ABT-378/r	3 capsules, twice daily	6	take with food
indinavir/ritonavir	400mg/400mg	1xIDV / 4xRTV twice daily	10	none
	800mg/200mg	2xIDV / 2xRTV, twice daily	8	none
	800mg/100mg	2xIDV / 1xRTV, twice daily	6	none
saquinavir/ritonavir	400mg/400mg	2xSQV / 4xRTV, twice daily	12	food reduces side effects
saquinavir/ritonavir	1000mg/100mg	5xSQV / 1xRTV, twice daily	12	food reduces side effects
<i>[Invirase, hard gel formulation of saquinavir can be used instead of Fortovase soft gel capsule when using ritonavir. Invirase is a smaller pill with less side effects]</i>				
fosamprenavir*/ritonavir	700mg/100mg	1xFosAPV / 1xRTV, twice daily (once-daily possible)		none
atazanavir/ritonavir	300mg/100mg	2xATV/ 1 x RTV, once daily	3	none
tipranavir/ritonavir	500mg/200mg	2xTPV/ 2 x RTV, twice daily	8	food reduces side effects
SINGLE PROTEASE INHIBITORS (PIs) <i>[Some PIs are used without ritonavir boosting. This is not generally recommended.]</i>				
indinavir	Crixivan	2 capsules, 3 times daily	6	2 hours after food and 1 hour before
nelfinavir	Viracept (film coated)	5 tablets, twice daily	10	take with meal
atazanavir	Reyataz	2 capsules, once daily	2	take with food
ENTRY INHIBITORS (Fusion inhibitors)				
enfuvirtide	T-20, Fuzeon	subcutaneous injection, twice daily		none
OTHER DRUGS USED IN HIV TREATMENT				
Interleukin-2 (IL-2)	<i>Experimental immune treatment used with combination therapy to boost CD4 counts. IL-2 is given by injection for five days every 2 months and heavy flu-like side effects are expected during each five-day course.</i>			

Appendix VI: Resources and further reading

The following resources in English provide further information at a range of different levels.

Basic and intermediate

New Mexico AIDS Infonet

The most comprehensive range of basic factsheets covering a wide range of HIV-related subjects, including information on tests and monitoring, side effects, OIs and each HIV drug. Available in English and Spanish. This information is revised monthly, and is one of the few websites that do not keep out-dated information online.

<http://www.aidsinfonet.org/topics.php>

HIV i-Base treatment guides

Each of these guides is written in a similar format to this training manual. Emphasis is on non-technical language and up-to-date information. Produced by an HIV-positive led activist organisation. Material is copyright-waived and free to copy or translate.

Starting treatment: Introduction to combination therapy

<http://www.i-base.info/pub/guides/combo903/index.html>

Changing treatment: guide to second-line and salvage therapy

<http://www.i-base.info/pub/guides/salv1103/index.html>

Guide to avoiding and managing side effects

<http://www.i-base.info/pub/guides/side802/index.html>

HIV, pregnancy and womens health

<http://www.i-base.info/pub/guides/pregnancy03/index.html>

Advanced and reference

HIV Treatment Bulletin

Monthly bulletin that includes reviews of medical journals and conference reports with an emphasis on clinical care. Distributed free in print, online and pdf format. Technical language but produced from an HIV-positive activist organisation.

<http://www.i-Base.info>

aidsmap

UK based website with extensive information. All treatment information is referenced. Useful for overview of individual drugs and illnesses. Check the date for non-technical factsheets.

<http://www.aidsmap.com>

HIV inSite Knowledge Base

Extensive online reference manual with chapters on every aspect of HIV treatment. Very technical site. New chapters are added or updated on a monthly basis, but check the last modified date at the top of information.

<http://hivinsite.ucsf.edu/>

Medscape

Professional website, with many aspects of specialist care, including HIV. Free one-time online registration. Includes conference reports and free access to selected journal papers.

<http://www.medscape.com>

Treatment guidelines

WHO guidelines:

http://www.who.int/3by5/publications/documents/arv_guidelines/en/

US guidelines (for prevention, treatment, OIs, children and pregnancy):

<http://www.hivatis.org/>

UK guidelines are updated every two years.

<http://www.bhiva.org>

Internet sites with treatment information in Russian

<http://www.aids.ru>

<http://www.positivenet.ru>

<http://www.infospid.ru>

<http://www.spid.ru>

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