Section 2: Virology, HIV and viral load

2.1 Introduction to Section 2

The second section provides 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 reading section 2, advocates will have a basic understanding of:

- The definition of HIV.
- The difference between different causes of illness: viruses, bacteria, fungi and parasites.
- Viral load in early and chronic infection and the natural history of HIV.
- The impact of coinfections on viral load.
- Viral load tests and their accuracy.
- Viral load in relation to whether or not you are taking HIV treatment (ART).
- The HIV viral life cycle.
- A basic theory of resistance.
- CD4 count and viral load graphs and how to superimpose them.
2.3 Definition of HIV

**HIV stands for Human Immunodeficiency Virus.**

- Human – means it is a virus that infects humans.
- Immunodeficiency – means it reduces the immune system.
- Virus – means that the infection is a virus!

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

**Viral infections that affect people with HIV** include hepatitis A, B and C, herpes (HSV-1 and HSV-2), cytomegalovirus (CMV), and human papilloma virus (HPV).

**HIV** belongs to a family of viruses called **retroviruses**. This is why **HIV drugs** are called **antiretrovirals (or ARVs)**.

A retrovirus is a type of virus that needs to make a ‘backward step’ in order to reproduce – hence ‘retro’.

2.4 Other causes of illness

**As well as viruses, other things can affect your health. This includes bacteria, fungi, parasites and protozoa.**

Different types of drugs are used for each infection. For example, antibiotics work against bacteria but do not work against viruses.

The difference between viral, bacterial and fungal infections is not always clear.

However, sometimes drugs designed to treat one kind of infection also work against another type. This is complicated because it applies only to individual drugs for specific infections.

**Bacteria**

Bacteria are single-cell microorganisms. Some bacteria are healthy and help your body. Some bacteria are dangerous and 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**

Fungi are parasitic organisms that include moulds, mildews, mushrooms and yeast. **Antifungal drugs** are used to treat fungal infections.

Examples of fungal infections that affect people with HIV include candida (thrush) and cryptococcosis.

**Parasites and protozoa**

A parasite is an animal or plant that gets nutrients and support from another species. This includes protozoa which are single-celled animals that are larger and more complex than bacteria.

Examples of parasite-related infections are cryptosporidium and microsporidium. An example of an illness cause by protozoa is toxoplasmosis.
2.5 HIV and infection: key facts

- The risk of HIV transmission is related to how much virus is in the blood or infectious fluids. The risk is highest when the viral load is high. Levels of HIV are measured using viral load tests.
- HIV is not infectious in saliva, spit, tears, urine or faeces.
- Outside the body, HIV in blood or other bodily fluids is thought to die within a minute or so.
- HIV is a difficult virus to catch from sexual exposure. But only one exposure is needed to become HIV positive. This is just good or bad luck.
- HIV is much easier to catch from sharing infected needles or other IV drug taking equipment. This is because there is direct blood-to-blood contact.
- HIV enters the blood by broken skin or through cells that are close to the surface of the skin. This can include contact with mucous membranes (the type of tissue that lines the inside of the vagina, rectum and inner foreskin).
- Without testing, many people with HIV do not know they are HIV positive.
- Without treatment (ART), some people (less than 5%) will become ill within 1-2 years. A few people (also less than 5%) can go for 15 years without symptoms.
- Although a lot of information about your health and HIV comes from blood tests, less than 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 load in early and chronic infection

The natural history of any illness describes the pattern of a disease if it is not treated.

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

Natural history of HIV

The natural history of HIV infection has several different stages. These stages include infection, seroconversion, primary infection, chronic infection and late-stage illness.

HIV treatment (ART) prevents progression of HIV disease.

Infection

This is the point when HIV infects the first cells. It then takes several hours for these newly infected cells to carry HIV to the lymph nodes. During the next few days or weeks, HIV continues to multiply in the lymph nodes. Lymph nodes are packed with CD4 cells, which HIV uses to reproduce.

Seroconversion

After building up in the lymph nodes, the nodes burst sending HIV into the blood. This sends HIV throughout the body. HIV levels (viral load) become detectable in blood and reach very high levels (often millions of copies/mL).

As viral load increases, this high level of viral activity produces symptoms in up to 80% people. HIV can cause a range of symptoms that include night sweats, fevers, weakness and tiredness and, more rarely, mouth ulcers.

The immune system reacts to viral load in the blood by producing antibodies to fight HIV. It usually takes 1-3 months after infection for antibodies to HIV to be strong enough to be detected on an HIV antigen test. Occasionally it can take longer.

Primary (HIV) infection – PHI

PHI is also called early infection or acute infection. Primary infection describes the first six months after infection.

Chronic infection

Chronic infection describes HIV infection after the first six months. Chronic infection can last for many years. It can take from 2-10 years until the majority of people get symptoms from having a damaged immune system. With ART, chronic infection can be life-long – ie 20, 30, or 40 or more years after infection.

Late stage infection

Late stage infection is the most serious stage. Late stage HIV is now more rare. It is only seen in people who do not have access to treatment, who are only diagnosed very late. It is also seen when treatment has stopped working because HIV has become resistant to drugs. Late stage HIV used to be called AIDS, but the term AIDS is now rarely used.
Effect of ARVs on viral dynamics of HIV infection

After starting ART, viral load should go down by at least 90% (1 log) within the first week – mostly in the first few days.

After staring ART, viral load should then become undetectable (less than 50 copies/mL) within three months. Some people become undetectable after only a month. For some people this takes longer.

How quickly viral load becomes undetectable depends on three main factors.

1. How high viral load is when ART is started.
2. How good someone is at taking their meds and not missing doses.
3. Which HIV drugs are in the combination. Integrase inhibitors reduce viral load quicker than other types of HIV drugs.

- A few weeks after infection, HIV viral load shoots up to very high levels. This is when someone is most infectious.
- Then your body fights back. Viral load drops to much lower levels in most people.
- Without ART, over the next 2-10 years viral load increases slowly. Viral load usually becomes very high (around 50,000-200,000 copies/mL) by the time the CD4 count drops to 350 cells/mm³.
- In 2015, most guidelines recommend ART for all HIV positive people – at any CD4 count.
- ART stops HIV reproducing once viral load becomes undetectable.

After ART brings viral load down to less than 50 copies/mL, treatment can last for many years.
2.7 Reinfection with HIV

Reinfection describes when someone who is already HIV positive becomes infected with a new strain of HIV. Sometimes this is referred to as HIV superinfection.

There have been many reports of cases of HIV reinfection. This was controversial because 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 reinfection occurs, or what the risk factors for reinfection are. Most studies suggest that the risk of reinfection are likely to be similar to the original risk of infection. Viral load is probably the most important risk factor for reinfection, with very high viral loads having the highest risk.

Although reinfection was first reported in early infection, cases have also been reported in chronic infection. They include examples where someone on treatment has been reinfected by someone with drug resistant HIV, and where the treatment then stopped working.

Drug resistance is the major risk from 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.

If two HIV-positive people have the same virus and the same resistance, then reinfection is unlikely to directly affect either their health or the effectiveness of treatment. If one of the partners develops drug resistance on treatment, this risk would change.

Further reading
Link to page of questions and answers about reinfection:
http://i-base.info/qa/category/reinfection-with-hiv

2.8 What is a viral load test

A viral load test is a measurement of the amount of HIV virus in a sample of blood. This is usually reported as the number of copies per millilitre (copies/mL). Information about units of measure for blood tests: i-Base.info/qa/factssheets/units-of-measure

Even though less than 2% of HIV is in your blood, viral load is a good marker of how much HIV is in your body. Blood tests are also easier than trying to test lymph nodes or other body tissues.

Viral load tests can also check the amount of HIV in other kinds of sample like genital fluid, semen or spinal fluid.

Types of viral load test

There are three main types of viral load tests:

- **PCR** – polymerase chain reaction (written as PCR RNA). This is the most widely used type of test.
- **bDNA** – branched DNA
- **NASBA** – nucleic acid sequence based amplification

These tests work in slightly different ways. PCR is the most widely used viral load test. PCR technology is also used to measure levels of HIV DNA in some circumstances.
How viral load tests work

Viral load tests multiply virus found in a small sample of blood many times so that it can be counted more easily. But this means that the individual results from any one test are not very accurate.

Viral load tests can have a 3-fold margin of error. So, if your viral load result is 30,000, the real result could be anywhere between 10,000 and 90,000 copies/mL.

- Each viral load test has a sensitivity cut off. This is the lowest level of HIV that the test can measure. It is a measure of how sensitive the test is.
- The main cut-off limit for viral load tests is less than 50 copies/mL. Many tests now have a lower cut-off of 20 copies/mL.
- Special tests can measure down to 5 copies/mL or even to 1 copy/mL. These are only used in research.

Using viral load and CD4 count to monitor HIV

Used together, CD4 counts and viral load results will tell a doctor nearly everything about the risk to your health from HIV. These tests also show how well treatment is working.

Viral load test results can be used together with CD4 counts to monitor HIV infection. As with CD4 counts, it is important to look at the trend of viral load 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.
- When using HIV treatment, viral load is important, not CD4 count, because not getting viral load below 50 copies/mL will limit how long treatment will work.

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

In some countries, viral load and CD4 tests cost much more than the drugs. New research is 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 count and viral load change.

2.9 History of viral load tests

Without viral load tests combination therapy might never have been developed or understood.

In 1995 viral load tests could only measure down to 10,000 copies/mL. By 1996-7 the next generation of tests could measure down to 400 or 500 copies/mL. Since 1998 the most routinely used tests can measure down to 40 or 50 copies/mL.

Tests used for research are even more sensitive (down to 5 or even 1 copy/mL).

In the 1990s, viral load tests were a new technology being developed as a research tool.

Before viral load could be measured, most doctors thought that HIV had a dormant period.

Viral load tests showed that HIV is not a dormant infection. It is a gradually progressive viral infection that is always active.

Viral load tests also provided doctors and researchers with a direct marker for the impact of each new drug. Before viral load tests, everything was dependent on either CD4 counts or progression to symptoms.
Before viral load tests were first developed many doctors thought that it would be impossible to measure the progress of a disease on an individual patient level. Viral load tests now allow a high level of individual care.

2.10 Impact of co-infections on viral load

Other infections can increase HIV viral load.

- Having another virus can increase HIV viral load.
- Some sexually transmitted infections (STIs) increase levels of HIV in genital fluids, but only by relatively small amounts. These STIs include herpes, gonorrhoea and syphilis. The higher viral load will make HIV slightly more infectious. This is one reason why having other STIs are related to a higher risk of HIV transmission.
- Luckily, the results from the PARTNER study did not report HIV transmissions when a positive partner had an undetectable viral load in blood, even though some people had STIs that might have increased viral load a little. Link: i-base.info/partner-study/
- Viral infections like the flu can increase your viral load while the infection is active. If you get a high viral load result when you have flu or a cold, you should retest when you feel better.
- Malaria can increase your viral load while the infection is active.
- Some vaccinations may also increase viral load temporarily.
- HIV can also increase the levels of other viruses in someone who has HIV and another infection.

2.11 Compartments and sanctuary sites

Several places in the body have barriers that limit both HIV and HIV drugs from moving freely. These are called compartments or sanctuary sites.

Viral load in compartment sites can differ from viral load in your blood.

These compartments include the genital tract, the fluid that circulates around the brain and spinal column (called cerebral spinal fluid, or CSF), and the brain itself.

- HIV can develop independently 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.
- People who keep their viral load undetectable (below 40 or 50 copies/mL) in their blood have a very high chance of having undetectable viral load in their CSF.
- About 10% of people with an undetectable viral load in their blood have a detectable viral load in other compartments, including genital fluids. This difference seems to fluctuate within different people at different times.
- Luckily, the results from the PARTNER study did not report HIV transmissions when a positive partner had an undetectable viral load in blood, even though some people are likely to have had detectable viral load in genital fluids.

This makes HIV a very complicated illness.
Current research suggests that the direction of infection is lymph → blood → compartments. But because HIV can develop independently in a compartment, there is also a concern that infection can travel in both directions. For example if resistance developed in a compartment site this might then cause resistance in the rest of your body.

In practice, because blood is used for most tests, you are unlikely to know exactly what is going on in other compartments. For most people (approximately 90%) an undetectable viral load in blood means undetectable viral load in other compartments.

Reducing HIV in blood and lymph nodes seems to stop HIV related complications in other compartments (eg in the brain) even if HIV drugs don’t penetrate these parts of the body. This is a complex area of research because testing viral load accurately in compartments besides the blood is difficult.

2.12 Viral load on and off treatment

Viral load when not on HIV treatment (ART)

When not on ART, your CD4 count is more important than viral load.

Even though ART is now recommended for everyone, the CD4 count still gives an indication of the urgency to start.

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

The one exception may be if your viral load is very high. This is because some HIV drugs are not recommended if your viral load is higher than 100,000 copies/mL.

Viral load when on treatment

If you are taking ART, viral load is more important than CD4 count.

This is because on ART, your CD4 count is probably already increasing.

Your viral load when on treatment is the best measure of how long you can expect treatment to last.

If viral load gets to less than 50 copies/mL then ART is likely to last for many years. When viral load is this low, resistance usually only develops if you are late or miss taking your medication.

If viral load only gets down to a low level like 500 copies/mL, there is still enough HIV reproducing each day for resistance to develop to the drugs in your combination.

Viral load usually goes down by at least 90% (1 log) within the first few days of treatment, even though it is rarely measured this early. It usually drops by 99% (2 logs) within the first month. Most people reach undetectable (less than 50 copies/mL) within three months.

How quickly viral load becomes undetectable depends:

1. How high viral load is when you start ART.
2. How good you are at taking all your meds.
3. What drugs are in your combinations. Integrase inhibitors reduce viral load more quickly than other types of HIV drugs.
How often to use viral load tests? What happens if you do not have access?

How often viral load should be tested varies in different guidelines.

UK and US guidelines historically recommended viral load testing every 3-6 months when not on treatment, and every 3 months when on treatment. They also recommend a viral load test 1 month after starting or changing treatment.

More recently, in someone who has a high CD4 count and who is not on treatment, guidelines have recommended viral load testing every 6-12 months.

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.

Not having access to viral load tests should not be used as a reason to not use ART. Many countries do not have viral load tests in routine use, but still provide treatment effectively.

2.13 Viral life cycle, drug resistance and adherence

Viral life cycle: copies, mistakes and mutations

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

When you are not taking ART, the virus probably produces every single possible mutation. But there is no reason for any particular mutations to develop because:

- Mutations are usually weaker than the original (wild-type) HIV.
- Wild-type HIV and mutations compete to reproduce – and the stronger virus wins!

When you are taking ART, drug mutations can develop that stop a drug from working. This is called drug resistance.

- With drug resistance, the resistant virus is more effective at reproducing than non-resistant virus.
- Resistant mutations that continue to reproduce eventually become the major type of HIV in your body.
- Mutations resistant to a drug in one class are often resistant to other similar drugs in the same. For example, resistance to one NNRTI or to one integrase inhibitor can stop other NNRTIs or integrase inhibitors from working. This is called cross-resistance.

Resistance, treatment and viral load

Having drug resistant mutations means HIV drugs do not work as well. Sometimes they stop working completely.

- The higher your viral load when you are on treatment, the more likely that you will develop resistance.
- This is why treatment guidelines emphasise that it is 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

The mutations that occur when you have low concentrations of your drugs in your body can stop the drugs working.

Adherence is therefore critical.

Adherence means taking HIV drugs on time in the right way every day.

Taking one or more of your drugs late – or missing doses altogether – will increase the risk of drug resistance. This is because drug levels become too low to control the virus.

To get the best levels, meds need to be taken exactly as they are prescribed. This includes special instructions on whether ART needs to be taken with food or on an empty stomach.

- Drug interactions can also affect the levels of ARV drugs.
- HIV drugs can interact with other HIV and OI medications (especially with treatment for TB).
- HIV drugs 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.

Drug levels and resistance

Taking drugs at the exact same time makes sure that you keep the drug in the body above the lowest level needed to keep HIV under control.

Each time you take a drug, the level of the drug stays above the lowest level needed to keep HIV under control.

If you are late with a dose, or miss one altogether, the drug levels fall below the lowest level needed to keep HIV under control. Resistance can then develop.

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.**

**Further reading**

i-Base have developed a more detailed online training course of drug resistance.

http://i-base.info/home/hiv-and-drug-resistance/

This online course is a learning resource for HIV advocates who want to learn about HIV and resistance.

Each module should take 30–60 minutes. It was published in February 2011.

### 2.14 How CD4 and viral load are related

**Although the CD4 and viral load tests measure different things, the pattern of results between each test is usually related.**

- **When viral load is low, CD4 counts will be high.**
- **When CD4 counts are low, viral load will be high.**

A few weeks after infection, HIV viral load is very high, and the CD4 count drops. Then as the immune system brings viral load down, CD4 counts go back up again.

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

- **After starting HIV treatment (ART) viral load drops very quickly. The CD4 count only increases slowly (often over several months).**
- **If treatment fails and the viral load level starts to rebound, the CD4 count may take a while before it starts to fall.**
- **As viral load gets higher, the CD4 count will nearly always start to fall within a few weeks.**

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

**CD4 count and viral load without ART**
After infection, viral load levels are very high. Then your body fights back and it drops to much lower levels. Over time though, usually over several years, viral load increases again. Viral load continues to rise and the CD4 count continues to fall.

When the CD4 count is very low, the immune system is no longer strong enough to fight off infections. This causes serious illnesses. Some of these infections can be fatal.

Without ART, for nearly everyone, HIV is likely to be fatal.

**Effect of ARVs on CD4 count and viral load**

After starting treatment, viral load falls quickly and CD4 counts rise slowly.

**If ART brings viral load down to less than 50 copies/mL, then treatment can last for many years.**
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 drug 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**
test that look at the amount of virus. This is usually in a small sample of blood, but viral load test can also be used to check viral levels in other compartments like genital fluid, semen or spinal fluid

**virus**
infectious organism that can only reproduce inside the cell of another plant or animal

2.15 Questions: Section 2

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. List four 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 (i.e. 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.

**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?