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# viral load & CD4

seventh edition 2007



## acknowledgements

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

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# viral load & CD4

**This booklet focuses on blood tests called viral load and CD4 counts. These tests are crucial in helping you decide when to start treatment, and to monitor the effects of your treatment. This booklet is not intended to replace discussion with your doctor about your treatment or test results. However, it may help you to decide what questions to ask your doctor about any course of treatment you may be considering.**

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## What is the CD4 count?

CD4 cells, or T-helper cells, are white blood cells which organise the immune system's response to some microorganisms, including bacteria, fungal infections and viruses.

The CD4 count is the measurement of the number of CD4 cells, in a cubic millimetre of blood (not the whole of your body). This is sometimes written as CD4 cells/mm<sup>3</sup>.

CD4 counts can vary considerably between individuals; women usually have higher CD4 counts than men, for example. The CD4 count of a person who is not infected with HIV may be anywhere between 500 and 1200.

While the CD4 cells play an important role in fighting viruses, HIV has the ability to infect CD4 cells and use them to produce more HIV copies. Even while a person with a HIV feels well and has no symptoms, millions of CD4 cells are infected by the virus and destroyed each day, and millions more CD4 cells are produced to replace them. HIV can also cause a high turnover of CD4 cells indirectly, through general activation of the immune system.

## What CD4 counts predict

Most people with HIV find that their CD4 count gradually declines over a number of years.

A CD4 count between 500 and 200 indicates that some damage to the immune system has occurred. If your CD4 count drops below 350, or starts falling rapidly, your doctor should talk with you about whether you need to start anti-HIV treatment.

If your CD4 count falls below 250-200 you are recommended to start treatment with anti-HIV drugs because this is the level at which the risk of AIDS-related illness is greatly increased.

The most important information that your CD4 count can give you is the overall trend of your immune system's health - whether it is declining or improving.

## **Changes in the CD4 count**

Your CD4 count can go up and down in response to infections, stress, smoking, exercise, the menstrual cycle, the contraceptive pill, the time of day and even the seasons of the year. Different methods of counting CD4 cells also give different readings.

This is why it is important to monitor a trend over time, rather than to focus too much on individual test results. It's also best to have your CD4 count measured at the same clinic and at roughly the same time of day wherever possible. If you have an infection like flu or herpes it is best to delay having a CD4 count until you are feeling better.

If you have a relatively high CD4 count, no symptoms and you are not taking anti-HIV drugs, you only need to measure your CD4 count once every three months.

However, if your count has been falling rapidly, or you are taking part in a clinical trial, or you have just started new treatment, your doctor may suggest that your count should be monitored more often.

If you are experiencing very wide variations in your CD4 count then it could be because your overall white blood cell count has changed, possibly in response to an infection. In these

circumstances your doctor may look at other test results which give an indication of the state of the immune system, such as the CD4/CD8 ratio or CD4 percentage, to decide if the wide variation in CD4 count is important.

### **CD4 percentages**

Instead of counting the number of CD4 cells per  $\text{mm}^3$ , doctors sometimes assess what proportion of all white blood cells are CD4 cells. This is called the CD4 cell percentage; in HIV-negative people, a normal result is about 40%. CD4 percentages, along with CD4 cell counts, could be of benefit in helping patients decide when to start antiretroviral

therapy. A CD4 percentage below about 20% is thought to reflect the same risk of becoming ill because of HIV as a CD4 count of about 200. Some doctors argue that the CD4 percentage is potentially the most accurate CD4 test, although it is not very sensitive to small changes.

Viral load is the term used to describe the amount of HIV in your blood. The more HIV in your blood, the faster your CD4 cells are likely to disappear, and the greater your risk of developing symptoms or further illness within the next few years.

## **What is the viral load test?**

Viral load tests estimate the number of HIV particles in the liquid, or plasma part of the blood. They do this by looking for HIV's genetic material, which is called HIV RNA.

The result of a viral load test is described as the number of copies of HIV RNA per millilitre.

There are several different viral load tests available. Each test uses a different technique to measure the number of HIV particles, but all the tests are equally reliable at determining whether your viral load is low, medium or high.

In the past, some tests had difficulty picking up specific types of HIV which were common in Africa and Asia. Today, the most commonly used viral load tests are now equally accurate at measuring these strains of HIV.

However, HIV strains in different parts of the world are always changing and mixing with one another, and there is a risk that the tests will be unable to pick

up new strains of HIV. If your viral load result does not seem right (for example, low when your CD4 count is also low), several different viral load tests may be used to get a more accurate picture.

### **Natural variations**

Viral load measurements can rise and fall from one blood sample to the next but this may have no long-term impact on the health of the person being tested.

Researchers have investigated viral load changes in people not on treatment and found that two separate tests on the same sample of blood can give results which differ by as much as three fold.

For example, this means that you shouldn't necessarily be worried if your viral load goes up from 5,000 to 15,000 at a time when you are not on treatment.

Similarly, a rise from 50,000 to 100,000 if you aren't on treatment may not be significant, although it may seem like a big increase. Viral load appears to have doubled, but it's within the margins of error for this test.

Your viral load should ideally only be measured when you are well. If you have an infection or have recently had a vaccination, your viral load could temporarily increase.

## Significant changes

When viral load results seen over several months show an upward trend, or when the increase is greater than threefold, there may be cause for concern.

For example, a rise from 5,000 to 25,000 is significant. It represents a fivefold increase in the amount of virus in your blood since your last viral load test.

However, it is still best to confirm this trend on a repeat test.

## The effects of vaccinations and infections

If you currently have an infection or have recently received a vaccination, you may have a temporary increase in your viral load. In these cases it is best to avoid having a viral load test for at least one month after a vaccination or illness.

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# Why do I need to know my viral load and CD4 count?

## **If you are not currently taking anti-HIV treatment**

If you are not taking anti-HIV drugs, your viral load can provide information on the likely course of HIV infection if left untreated.

A study of viral load levels in untreated people suggests that, in combination with your CD4 count, they may help you to predict your risk of developing symptoms in the future.

Among people with the same CD4 count, research shows that those with higher viral load tend to develop symptoms more quickly than those with lower viral load.

Among people with the same viral load, those with lower CD4 counts tend to develop symptoms more quickly.

As the table on the following page shows, taken together, both CD4 count and viral load provide valuable information to predict the likelihood of developing AIDS in the short to medium term (assuming there is no treatment).

If you look at the column for people whose CD4 counts were between 351 and 500, there is a big difference in the risk of disease progression, depending on their viral load.

**Predicting progression****% of people who develop AIDS within 3 years (assuming no treatment)**

Viral load	CD4				
	below 200	201-350	351-500	501-750	above 750
below 1,500	**	**	**	3.7	0
1,500-7,000	**	**	2.0	2.0	2.0
7,000-20,000	**	8.1	8.1	8.1	3.2
20,000-55,000	40.1	40.1	16.1	16.1	9.5
above 55,000	85.5	64.4	42.9	32.6	32.6

\*\* indicates lack of data

Researchers have also looked at the risk of developing AIDS or dying for people taking treatment. Monitoring a very large number of people over a number of years they found that people who did less well on anti-HIV therapy tended to have the following characteristics when they started anti-HIV therapy:

- A CD4 count below 200.
- A viral load above 100,000 copies.
- Age over 50 years.
- Being an injecting drug user.
- Already had an AIDS defining illness.

It is possible to calculate individual disease progression risk by visiting

[www.art-cohort-collaboration.org](http://www.art-cohort-collaboration.org) and entering individual characteristics such as CD4 count, viral load, age, drug use history and past HIV-related illnesses.

## **Deciding whether to start treatment**

The level of your viral load, along with other indicators, may help you to decide whether to start anti-HIV treatment.

At the moment, research evidence which helps doctors make decisions about when people with established (more than six months) HIV infection should start treatment places emphasis on CD4 count rather than viral load. It is

recommended that people start treatment before their CD4 count falls below 200, as people who start treatment with a CD4 count below 200 face a greater risk of death, in the short-term, than those who start before their CD4 count drops below this level.

At higher CD4 counts the picture is less clear, current guidelines suggest that in these circumstances timing will depend on the level of viral load, the speed at which CD4 count is falling, the likelihood of achieving good adherence, the presence of symptoms, and the patient's wishes.

However, evidence is mounting that starting treatment earlier, at CD4 cell counts of around 350 cells/mm<sup>3</sup>, may have benefits.

Serious non-AIDS defining illnesses (like heart disease, serious kidney disease, liver cirrhosis and some non-AIDS defining cancers) occur more frequently than AIDS-defining illnesses in patients with higher CD4 cell counts. Studies have shown that earlier treatment may help to reduce the risk of some of these occurring.

Other evidence shows that the CD4 cell rise seen with anti-HIV therapy is predicted by the level of damage already

caused, before treatment has started, and by the nadir (lowest ever) CD4 cell count reached during chronic infection. There is also evidence from the UK that people with a CD4 count between 200 and 250 when taking treatment are around five times more likely to develop an AIDS-related illness than people on treatment with a CD4 count above 650.

Together, these findings suggest that starting treatment earlier may result in a better CD4 increase, and greater protection from illness.

Current guidance has not been changed in light of these studies but is being reviewed to weigh up the costs and benefits of earlier initiation of treatment.

People who are advised to start treatment, but decide not to, should review their decision regularly, and have their CD4 and viral load monitored more regularly.

### **Viral load in women**

When HIV-positive women and men with the same CD4 cell counts are compared, women tend to have slightly lower viral load on average. However, this doesn't translate into any differences in response to treatment.

## CD4 counts and viral load in children

Normal CD4 counts tend to be much higher in very young children than adults. On average the CD4 cell count in a six-month old baby is about 3,000, and is about 1,500 in one year olds and often over 1,000 in infants under six. However, CD4 cell counts stabilise at similar levels to those seen in adults when a child is aged between about six and twelve.

In HIV-positive babies, HIV viral load can rise to very high levels (over 1 million copies/ml) within a few weeks and gradually decline over the first few

years of life. The exact reason for this is not known.

## The effect of treatment

Effective anti-HIV treatment results in a reduction in viral load. If you start anti-HIV treatment your doctor will test your viral load after four to twelve weeks of treatment to see by how much your viral load has gone down.

Changes in viral load are sometimes expressed using a logarithmic (log) scale.

### EXAMPLE

- If your viral load falls from 100,000 to 10,000, this is a 1 log reduction.

## EXAMPLE

- If your viral load falls from 100,000 to 1,000, this is a 2 log reduction.

## EXAMPLE

- If your viral load falls from 100,000 to 100, this is a 3 log reduction.

## What is undetectable viral load?

All viral load tests have a cut-off point below which they cannot reliably detect HIV. This point is called the limit of detection (LOD) and varies from one testing kit to another.

However, just because the level of HIV is too low to be measured by these tests, it does not necessarily mean that the virus has disappeared entirely. The virus may still be present in your blood, but in amounts too low for the test to pick it up. Viral load tests only measure the amount of HIV in the blood. Even if you have an undetectable viral load this does

not mean that your viral load in other parts of your body, such as your lymph nodes, is undetectable.

## What are the limits of detection of current tests?

For tests used in the past, the lower limit of detection was 400 or 500 copies. However, ultra-sensitive tests are now available that measure down to 50 copies and are routinely used. Some clinics use tests that can measure down to 40 copies. Boosted tests can measure much lower levels but these are mainly used in research.

## The value of having undetectable viral load

Having undetectable viral load is desirable for two reasons:

- A very low risk of developing AIDS.
- A very low risk of developing resistance to the drugs you are taking now.

Doctors now think that undetectable viral load (below 50 copies) is the aim of treatment.

It may be the case that the quicker your viral load falls below 50 copies, the longer it should stay there, providing you keep taking the drugs as instructed. Some people take three to six months to

reach this point, while others go below the limit of detection within four to twelve weeks, and others may never achieve this goal.

After six months on a first-line combination, your viral load should ideally have gone below 50 copies. Some people do not respond this well, however.

If your viral load is not reduced to undetectable levels after three months on a new combination of drugs, some doctors will recommend changing your combination or adding another drug (after they have done a resistance test and found that this drug will work). However, doctors differ in their view of

how quickly treatment should be changed and this also depends on the number of HIV treatments you have taken previously. Some favour switching 'early' to reduce the risk of resistance. Others argue that this approach may cause you to stop treatments from which you were still benefiting.

People taking anti-HIV drugs for the first time are more likely to reduce their viral load to these very low levels than those who have taken treatment previously.

## **Viral load blips**

People with undetectable viral load are likely to experience small blips in their viral load from time to time. Typically,

viral load may rise from below 50 copies to above 100 or 200 copies on a single test, and be undetectable on the next test. This is common and does not necessarily indicate that your treatment is failing. Most viral load blips seem to be due to testing errors at the laboratory.

However, if viral load continues to rise on each test, or if it stays above 50 copies without rising above 500 copies, this indicates that your treatment may fail and you may develop resistance.

At this point you should discuss switching treatment with your doctor. The longer that your viral load remains detectable while you take your current

drug combination, the more likely you are to develop resistance to the drugs.

If a second combination seems very likely to reduce your viral load to undetectable levels, then an earlier switch will offer the least possible risk of resistance developing. If you have fewer drug options available, you may be more inclined to switch later. However, if it is possible to switch early with higher CD4 counts and a lower viral load, this is recommended.

## Developing resistance

If HIV develops resistance to the drugs you are taking, this means that they will be unable to suppress HIV efficiently, and viral load usually begins to rise.

Keeping viral load below the level of detection is associated with a very low risk of developing resistance to the anti-HIV drugs you are taking.

This is because the chance of developing resistance when you are taking anti-HIV drugs depends on the amount of HIV which is still being produced in your body.

The lower your viral load, the lower your risk of developing resistance to the drugs you are taking.

So, suppressing viral load to undetectable levels (below 50 copies) is likely to delay the development of resistance for longer, hopefully indefinitely.

## Cross-resistance

HIV that has developed resistance to one drug that you are taking may also be resistant to some other similar drugs which you have not taken yet. This is called cross-resistance.

Cross-resistance can limit the range of drugs you can take in the future. In order to keep as many options open as possible, some doctors argue that treatment should always aim for undetectable viral load.

However, other doctors take the view that if you switch drugs every time your viral load rises above the limit of detection, you may run out of drugs relatively quickly. If it is possible to switch early with higher CD4 counts and a lower viral load, this is recommended. For more information, see another NAM booklet in this series, *Resistance*.

# Viral load and HIV transmission

If you have high levels of HIV in the blood, you may also have high levels of HIV in semen or vaginal fluid. People with high viral load are likely to be more infectious.

Anti-HIV treatment that reduces viral load in the blood usually also reduces HIV levels in semen and in vaginal fluid. However, even if the viral load in your blood becomes undetectable after treatment, this doesn't mean that HIV has disappeared from your semen or vaginal fluid. You still risk passing on the virus during sexual intercourse if you aren't using a condom with your partner. Untreated sexually transmitted

infections, most notably gonorrhoea, can increase viral load in sexual fluids and mean that the risk of passing on HIV to your partner is greater if you are not using a condom.

Anti-HIV treatment has been proven effective in reducing mother-to-baby HIV transmission. If you are pregnant or planning to conceive, discuss your treatment options with your doctor. If you have undetectable viral load whilst pregnant, the risk of passing HIV to your baby will be very low.

## How often should I have my viral load tested?

### **If you are not on treatment**

As the table 1 (shown previously) indicates, there's a big difference in the risk of developing AIDS between having a low viral load of 5,000 compared with a high viral load of 50,000, even when you have a CD4 count above 500.

If your CD4 cell count is between 350 and 200 and is falling quickly, you should attend your clinic every month or possibly weekly for closer monitoring, because a fast decline in CD4 cell count indicates a higher risk of AIDS-related illness.

Even if your CD4 count is currently above 500, it is a good idea for you to attend your clinic for viral load testing

every three to six months, and to get the results back quickly.

### **If you are about to start treatment**

Get two 'baseline' viral load measurements before starting, so that later you will be able to see just how well your treatment has worked.

### **If you have started treatment**

It is possible to get an indication of how well your combination therapy is working by testing your viral load after a month or so, and again after three months of treatment. Subsequent tests should occur every twelve weeks.

Additional tests may be needed from time to time, for example if you develop symptoms. You should get these results within a week if they are to provide an accurate picture of the current effect of your treatment. The level your viral load has reached at these points usually predicts how long this particular combination will keep your viral load low, or undetectable.

The initial fall in viral load after four months is also an accurate indicator of how much benefit you'll get from this combination in the next few years, in terms of a reduced risk of developing AIDS or further illness. The greater the

fall in viral load at this point, the better your outlook in the medium to long term.

### **If you have just had an increase in viral load on treatment**

Another test should be carried out within two to four weeks to confirm this result. You should always have viral load and CD4 counts tested at the same time.

- Your CD4 cell count gives an impression of the health of your immune system.
- Monitoring your CD4 cell count can help you and your doctor decide when you need to start HIV treatment.
- Viral load is the term used to describe the amount of HIV in your blood.
- CD4 cell counts and viral load can vary naturally - you should look at trends, not single results.
- The aim of anti-HIV treatment for people who have never taken HIV drugs before is a viral load below 50 copies, this is usually called an undetectable viral load.

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

**cross-resistance** The mechanism by which HIV that has developed resistance to one drug may also be resistant to other similar drugs.

**gene** A DNA sequence which determines the structure of a protein.

**immune system** The body's mechanisms for fighting infections and eradicating infections and eradicating dysfunctional cells.

**resistance** A drug resistant HIV strain is one which is less susceptible to the effects of one or more anti-HIV drugs because of its genotype.

**strain** A variant characterised by a specific genotype.

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

**viral load rebound** An increase in viral load, often from below the level of detection on a viral load test.

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