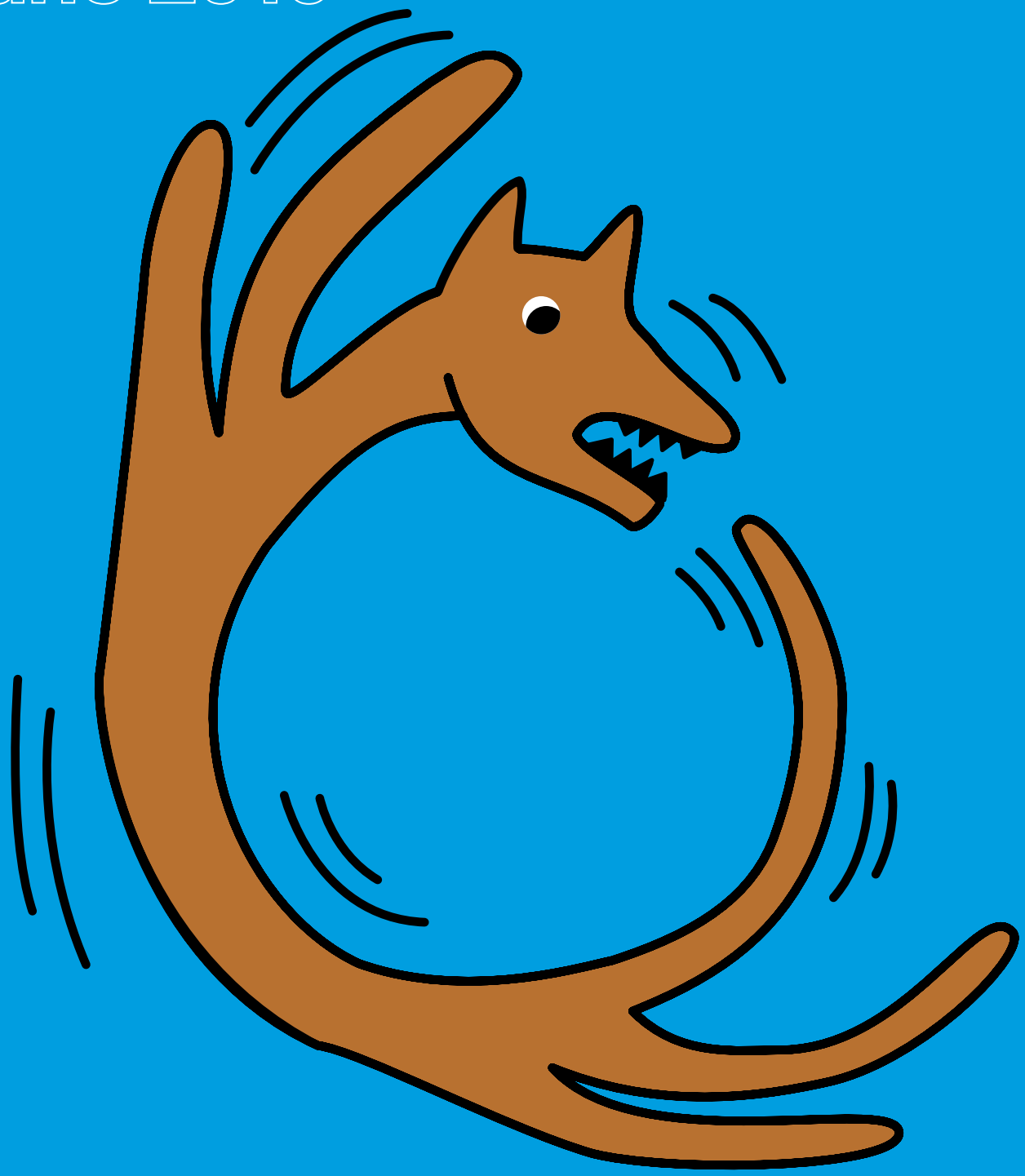
3rd edition

i-base
0808 800 6013

ART in pictures

HIV treatment explained

June 2019



Contents

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1. John Walter, *HIV Capsid*, laser cut card and glue, 2015.

2. John Walter, *Popcorn Fannypack is Confused at How Green Trimminz can Wear His Blinkers without Fear of Transmission as he Treads the Astroturf Labyrinth,* (detail), Ink and watercolour on paper, 2015.

3. John Walter, *Wayne Gibbous Stands Guard Against the Virus in the Intestine Corridor*, (detail), Ink and watercolour, 2015.

Thanks to MAC AIDS Fund for funding i-Base this publication.

This booklet explains some of the ideas and science behind HIV and treatment.

- It is easy to read.
- Each section includes a picture and summary notes.
- Additional text in each section tells a more detailed story.

The resource was developed as an advocacy course for HIV positive people.

Glossary

ART: antiretroviral treatment (HIV drugs).

ARV: antiretroviral – an HIV drug.

CCR5 inhibitor: an HIV drug that blocks HIV from attaching to a CD4 cell (for example, maraviroc).

Confirmatory test: a second test to double-check the results of a previous one.

Cross-resistance: where resistance to one drug is also resistant to similar drugs in the same class.

Expanded access: a way to use a drug before it is fully approved. This is for people who need them urgently. It is also called "early access" or "named-patient".

Fusion inhibitor: an HIV drug that stops HIV attaching to a CD4 cell (e.g. T-20).

Genotype: relating to the genetic structure of an organism.

mAb: monoclonal antibody (also bnAbs - broadly neutralising monoclonal antibodies) - biological compounds that are being studied for HIV treatment, prevention and cure.

Integrase inhibitor: a type of HIV drug that stops HIV from integrating into the DNA in a cell (for example, raltegravir, elvitegravir, dolutegravir, bictegravir and cabotegravir).

Mutation: a change in the structure of HIV that can stop a drug working.

NNRTI: non-nucleoside reverse transcriptase inhibitor – a type of HIV drug (for example, nevirapine, efavirenz, rilpivirine, etravirine and doravirine).

NRTI: nucleoside reverse transcriptase inhibitor (also called nucleoside analogue) – a type of HIV drug (for example, AZT, 3TC, FTC and abacavir). Tenofovir-DF and TAF are nucleo*tide* RTIs and work in a similar way.

PI: protease inhibitor – a type of HIV drug (for example atazanavir, darunavir, lopinavir, and tipranavir).

Second-line therapy: the combination used after your first treatment has failed.

Treatment-experienced: someone who has previously used HIV treatment.

Treatment-naive: someone who has never taken HIV treatment before. People who are treatment naive can still be resistant to HIV drugs if they were infected with drug resistant HIV.

Viral tropism: the type of coreceptor used by HIV in order to attach (and then infect) a cell. HIV can use CCR5 (R5 tropic), CXCR4 (R4 tropic), or both (dual or mixed tropic).

Viral load test: a blood test to measure the amount of HIV in your blood. Each test has a cut-off (usually 50 copies/mL). Results below this cut-off are called undetectable.

Viral rebound: when current treatment fails and viral load starts to rise again.

Wild-type virus: HIV that has no drug resistance mutations. This is usually the virus that you are first infected with.

Introduction

Nearly everyone who is HIV positive has a question about HIV that has never been answered – by your doctor, your friends or general reading.

This is a shame because nearly everything is easy to explain.

Although finding out you are positive can be difficult, it does get easier. The experience of coming to terms with HIV can even become very positive and life-changing.

Understanding your own health and treatment can help you feel more confident when talking to your doctor. It can also help you feel more in control when other things in life might be difficult. Supporting other people as an advocate can also be a positive experience.

HIV treatment (ART) is one of the most important successes of modern medicine. The science behind ART can be exciting.

ART has changed the outlook for HIV positive people

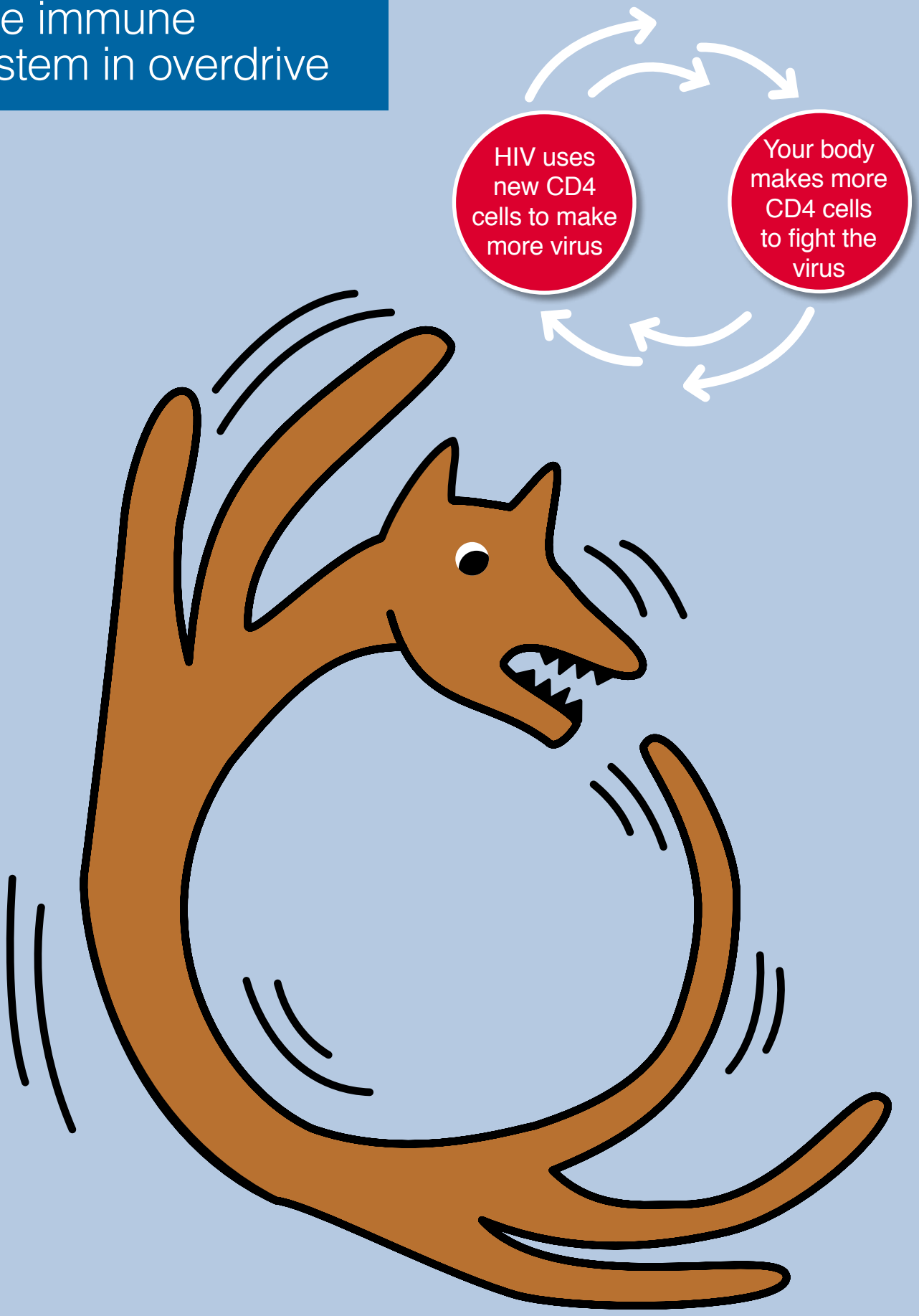
- **Treatment is now more effective and easier to take than ever before**.
- **Life expectancy is similar to being HIV negative – especially if you are diagnosed early and begin treatment.** Being HIV positive might actually help you live longer because you will access medical care throughout your life.
- **ART prevents HIV transmission**. This means that our sexual partners, if they are HIV negative, are protected too. This should also help reduce the fear about HIV. It should help reduce stigma.

This resource looks at medical aspects of HIV including the HIV lifecycle and natural history, the impact of ART and even research into a cure.

KEY POINTS

- Finding out that you are HIV positive can be tough.
- For all the difficulties, HIV can also bring positive experiences.
- The chance to learn about HIV and treatment can help you feel more in control of your health. It can help you have better health by being more confident with your doctor.
- Helping others through this process can also be good.

The immune system in overdrive



The first drawing is about an idea.

A dog chasing its own tail represents your immune system if you are HIV positive and not taking ART.

Continuous HIV replication burns up energy. Your immune system eventually becomes worn down and exhausted.

When not on ART, your body produces CD4 cells to fight the infection. But HIV uses these cells to make more virus. In response, the immune system makes more CD4 cells – continuing the overactived cycle.

Over time, for most people, the immune system loses – even though this might take many years. When viral load is detectable, your immune system is in overdrive. It is burns up energy and becomes exhausted.

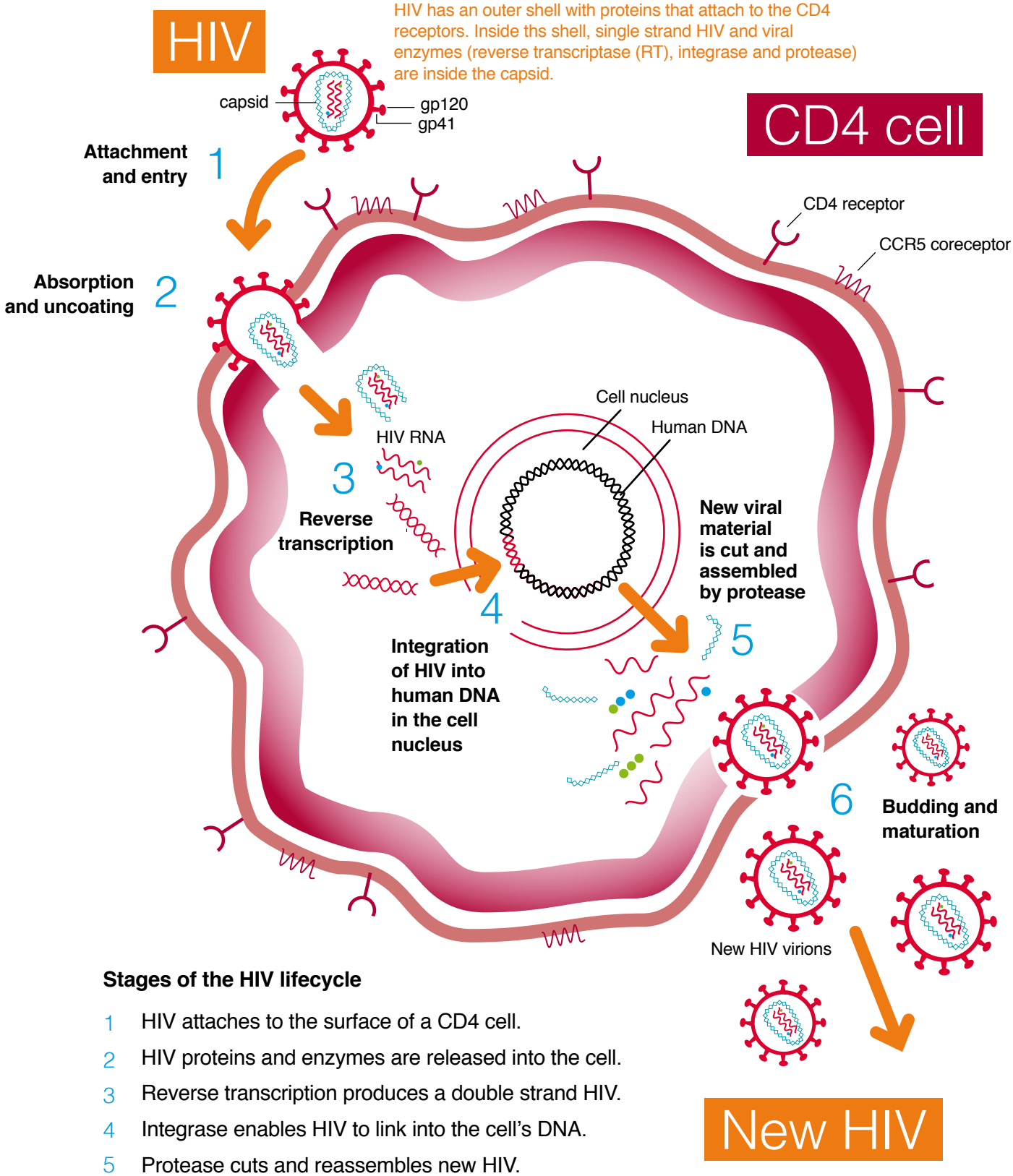
The increased activity is called immune activation or immune inflammation.

It increases the risk of serious illnesses that were not previously linked to HIV. This includes a higher risk of heart disease, stroke, liver and kidney disease and some cancers.

For the last ten years doctors have become more worried about immune activation when not on ART.

After ART reduces viral load to undetectable levels, nearly all of this overactivation stops. Your immune system gets a chance to rest and repair itself, and your CD4 count can recover.

The HIV lifecycle



Stages of the HIV lifecycle

1. HIV attaches to the surface of a CD4 cell.
2. HIV proteins and enzymes are released into the cell.
3. Reverse transcription produces a double strand HIV.
4. Integrase enables HIV to link into the cell's DNA.
5. Protease cuts and reassembles new HIV.
6. Each cell produces hundreds of new virions.

HIV is a tricky virus. Instead of being destroyed by the immune system it uses immune cells to reproduce.

CD4 cells are part of your immune system. They are white blood cells.

For the first 10 days or so, HIV stays hidden. It is impossible to detect or test for. But millions of copies of the virus are already being made in lymph nodes near the body site of infection.

When these swollen lymph nodes burst, HIV is carried throughout the body. In response, your immune system makes even more immune cells, especially CD4 cells. This process lasts a several weeks until your immune sytsem starts to reduce levels of HIV. The period is called seroconversion.

Instead of clearing the virus, CD4 cells are used by HIV to replicate. This continues until ART is started.

The replication cycle

Each replication cycle lasts for about two days and has several stages. Each stage can be a target for HIV drugs.

1. First, HIV attaches to the surface of the cell. Then it is absorbed through the cell wall, losing its outer coating or shell.
2. The inner capsule – called the capsid – then releases proteins and enzymes that HIV uses to replicate (called RT, integrase and protease) into the cell.
3. The next stage is to convert the single strand of HIV molecules to match double-strand human DNA.
4. This double strand of HIV then crosses into the central nucleus of the CD4 cell, where it joins (or integrates) into human DNA.
5. The nucleus now produces the raw material to make new HIV. But these particles need to be cut up and reassembled by protease before new virus can fully function. This process starts inside the CD4 cell and continues after new virus leaves the cell.
6. Each CD4 cell produces hundreds of new copies of HIV particles – called virions. These virions bud from the cell while HIV continues to develop. The CD4 cell then dies.

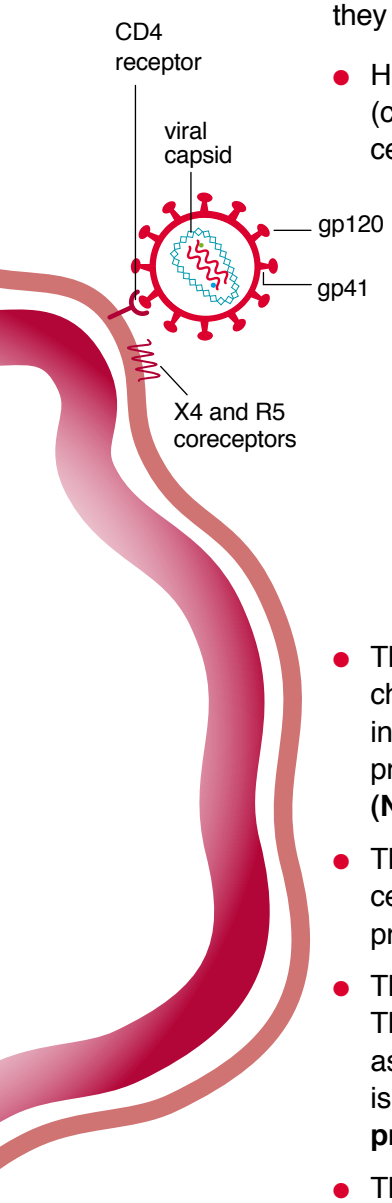
- New HIV then infects other CD4 cells and this process is repeated millions of times each day.
- Although HIV only infects one in a thousand CD4 cells, these cells signal to uninfected CD4 cells to also die early.
- Without ART, the immune system becomes worn down. The immune system puts up a good fight – often for many years – but steadily and eventually loses.
- But with ART, the HIV lifecyle is stopped and the immune system can repair itself.

The HIV lifecycle in detail

Like other living things, viruses need to be able to reproduce. When viruses reproduce it is called replication. HIV uses CD4 immune cells to replicate. And each infected CD4 cell produces hundreds of new copies of new HIV particles.

The process is called the HIV lifecycle.

Each replication cycle only lasts 1 to 2 days. It has several stages and different HIV drugs are active at different stages. HIV drugs are called inhibitors because they inhibit or stop parts of the cycle.



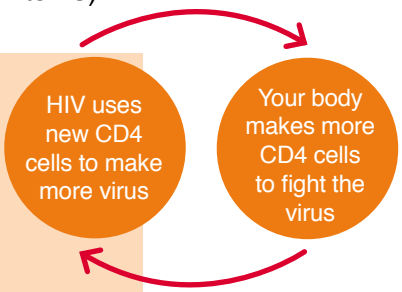
- HIV first has to attach to a CD4 cell. The proteins on the outer surface of HIV (called gp41 and gp120) connect with receptors on the surface of the CD4 cell (usually the CD4 receptor and the CCR5 coreceptor).
    - HIV drugs that block this process are called **entry inhibitors**. This family of drugs block attachment to gp41 or gp120 on the CD4 receptor or block the coreceptor CCR5. **Monoclonal antibodies** (mAbs) can also block this stage.
    - After HIV attaches to the CD4 cell, it is absorbed into the main body of the cell. As this happens, HIV first loses its outer shell. This leaves viral capsid with HIV and three key enzymes (a type of protein) that HIV uses to replicate. Some scientists say capsid releases its contents after infecting the cell. Others think the capsid only releases its contents into the cell nucleus just before the integration stage.
- The first enzyme is called RT. This stands for reverse transcriptase. RT changes the single strand of HIV (called RNA) into a double strand to fit in with human DNA. Two different types of RT inhibitors (RTIs) block this process: (i) **nucleoside/tide (NRTIs/NtRTIs)**, and (ii) **non-nucleoside (NNRTIs)**.
- The new double-stranded HIV crosses into the central nucleus of the CD4 cell. This is where HIV is integrated into human DNA. Drugs that block this process are called **integrase inhibitors**, abbreviated to INIs or INSTIs.
- The CD4 nucleus then starts producing raw material to make new HIV. These long strands of new HIV particles need to be cut up and assembled as new virus. The enzyme involved in the cutting and assembling process is called protease. The HIV meds that block this process are called **protease inhibitors**.
- The newly formed virus then has to leave the cell. Although there are currently no HIV drugs that block this stage, several drugs are in development. **Budding inhibitors** stop new HIV from leaving of the CD4 cell. **Maturation inhibitors** block the final assembly process.

- The newly released viruses (called virions) go on to infect new CD4 cells – to repeat the process over again. The old CD4 cell then dies. This continuous process happens millions of times every day when not on ART. Without ART, HIV is one of the most active and rapidly reproducing virus.

An important concept about ART, is that HIV drugs only work on CD4 cells in your body that are awake and actively producing HIV.

However, most CD4 cells in your immune system are sleeping or resting. The resting cells, even if they contain HIV, are not affected by ART.

Reaching HIV in resting cells is a main aim in HIV cure research (see p 22 to 23).



KEY POINTS

- HIV uses CD4 cells to replicate.
- Different HIV medications block different stages of the HIV lifecycle.
- Each infected CD4 cell produces about 300 new infectious viruses – called virions.
- ART stops the HIV lifecycle. On ART, the only virus in your body is in sleeping or resting CD4 cells.
- You need to continue taking ART every day because some of these sleeping cells wake up every day.

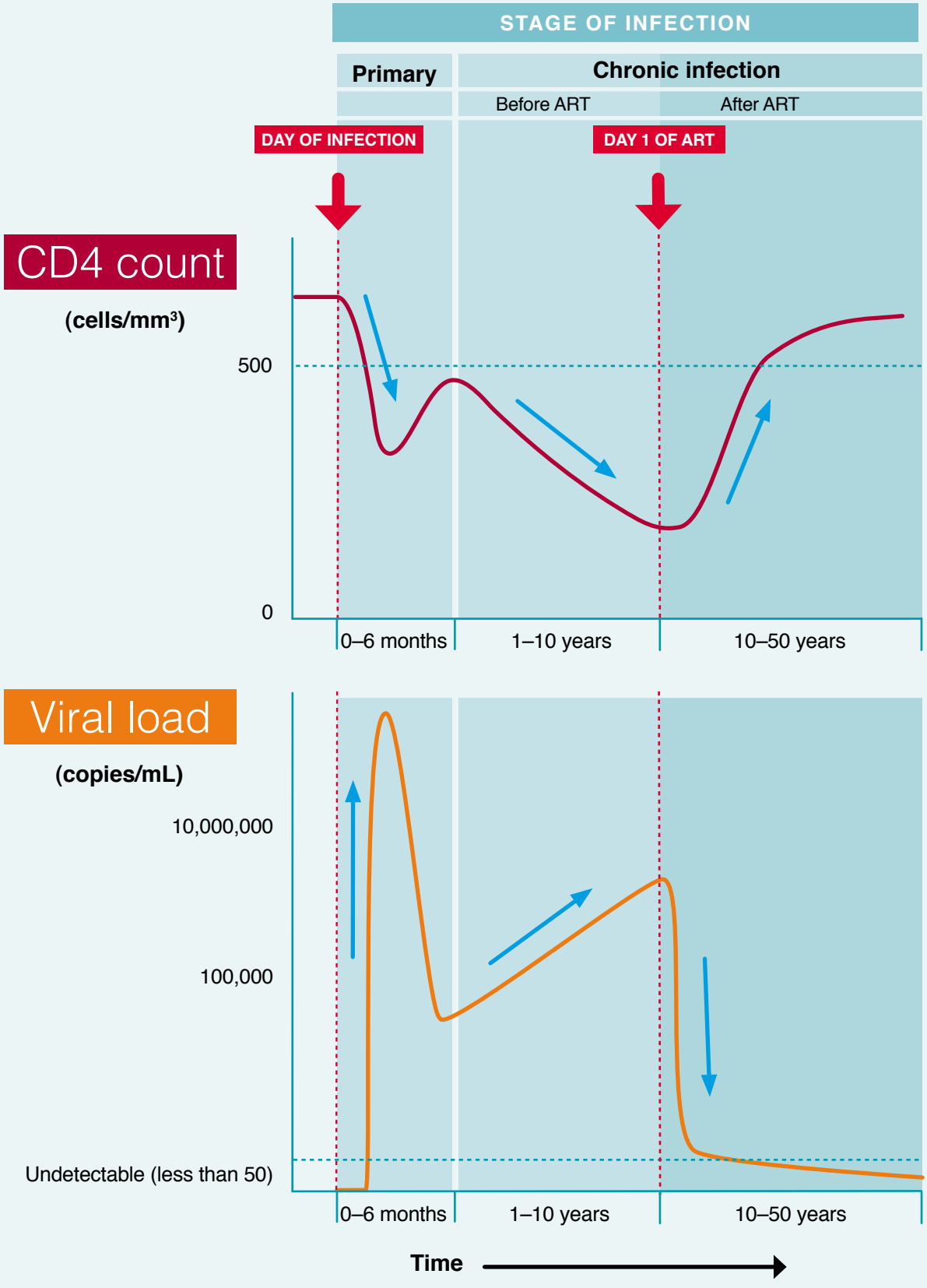
Main types of HIV drugs

There are six main types (or classes) of drugs that work against different parts of the HIV lifecycle.

There are more than 30 HIV drugs and formulations. Only a few combinations are now commonly used.

Abbreviation	Full names
NRTIs/NtRTIs (“nukes”)	Nucleoside/tide reverse transcriptase inhibitors or nucleoside/tide analogues
NNRTIs (“non-nukes”)	Non-nucleoside reverse transcriptase inhibitors
PIs	Protease inhibitors
INIs (or INSTIs)	Integrase (strand transfer) inhibitors
CCR5 inhibitors	CCR5 inhibitors are a type of entry inhibitor
Fusion inhibitors	Fusion inhibitors are a type of entry inhibitor
mAbs	Monoclonal antibodies

The natural history of HIV without ART



The natural history of HIV refers to what happens after infection before ART is used. It is explained by results from two blood tests: the CD4 count and viral load.

The **CD4 count** is a marker of how much HIV damages your immune system. Without ART, CD4 counts steadily go down over time in most people.

Viral load shows how much virus is circulating in the body, measured in blood. Without ART viral load steadily goes up over time.

There are two main phases of HIV infection.

1. **Primary infection** covers the first six months after infection. It is also called "acute" or "early" infection.
2. **Chronic infection** covers everything after the first six months. If you are not treated in early infection, chronic infection has two phases: before ART and after ART.

Viral load and CD4 changes

- The two graphs on page 10 show how the first six months is a time of dramatic activity. Viral load rises into the millions and then, even without ART, it comes back down again.
- The left of both graphs shows what happens to the CD4 count and viral load if HIV is not treated in early infection.
- After an initial drop, the CD4 count quickly recovers, but not completely. Without ART, the CD4 count then declines over many years. How quickly it drops varies between different people. As the CD4 count goes down, the risk of HIV-related illnesses increases.
- In contrast, within weeks of infection, viral load increases to very high levels. This is often many millions of copies/mL.
- Over the next few months the immune system can reduce viral load without ART – but rarely to undetectable levels. Then, over several years viral load steadily increases again.
- The right side of both graphs show how ART changes everything.
- CD4 and viral load results mirror each other. When one is high or increasing the other is usually low or decreasing – and vice versa.
- On ART, so long as you are good at taking your meds, viral load can stay undetectable for years. Your CD4 count can then steadily increase every year.
- The graphs show average responses. As with all averages, some people will have higher and lower levels. Or the time scale for these changes will be faster or slower for some people.

The natural history of HIV in detail

Primary HIV infection

Primary infection usually refers to the first six months after infection. During this period, HIV and the immune system are engaged in a very active battle.

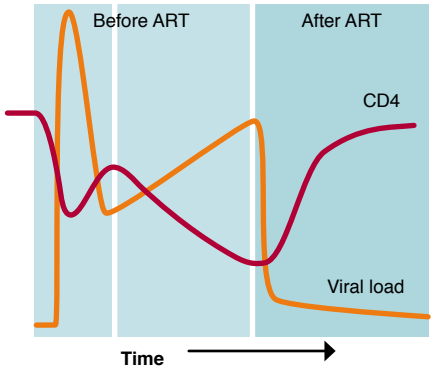
- For the first 10 days or so, everything appears quiet. Even though HIV infection has occurred, there are rarely symptoms. The first virus – and usually it is just one virus – is picked up by an immune cell and taken to the closest lymph nodes. For most infections, the story would end here because the immune cells in the lymph nodes destroy most infections.
- With HIV something very different happens. HIV uses CD4 cells inside the lymph nodes to reproduce many times. This activity causes these lymph nodes to swell and enlarge. After two weeks the infected lymph nodes are so full that they burst. HIV then travels throughout the body.
- During the next few weeks, viral load increases to very high levels. This is often higher than 10 million copies/mL. HIV reaches every part of the body – brain, lungs, kidneys, liver etc. A large proportion of CD4 cells are permanently lost from the stomach and gut. HIV wipes out 80–90% of the total CD4 cells in your body in just a few weeks. This is long before most people are even diagnosed.
- The immune system then fights back. This process of making antibodies to HIV is called **seroconversion**. During these weeks, about 70% of people have symptoms. These are usually flu-like symptoms, including fevers and fatigue. Some people are hospitalised with very serious infections. The high viral load means that someone is very infectious. Seroconversion symptoms usually resolve after a week or two, but some people have no symptoms.
- Over the next few months, even without ART, viral load drops to lower levels. Your CD4 count recovers, though not as high as before infection. The first six months are therefore a very active, dynamic and busy time.

Most people in the UK are only diagnosed in chronic infection. Even with free testing and treatment, many people are not diagnosed until many years after they were infected. However, 20% of people are diagnosed within a year of being infected and this figure is increasing.

Although most people are only diagnosed during chronic infection, an increasing percentage of people in the UK are diagnosed during acute infection.

A modified CD4 test called RITA (or STARHS) can show whether infection is likely to have been within the previous 4 to 6 months.

There are many potential advantages of starting ART during this early period. During this window period, each month or week or day earlier might be associated with benefits. Very early treatment overlaps with cure research. The chance to use ART in early infection is therefore an important individual choice (see p 22 to 23).



When CD4 and viral load curves are put together they mirror each other. When one is going up the other is going down and vice versa.

Chronic HIV infection

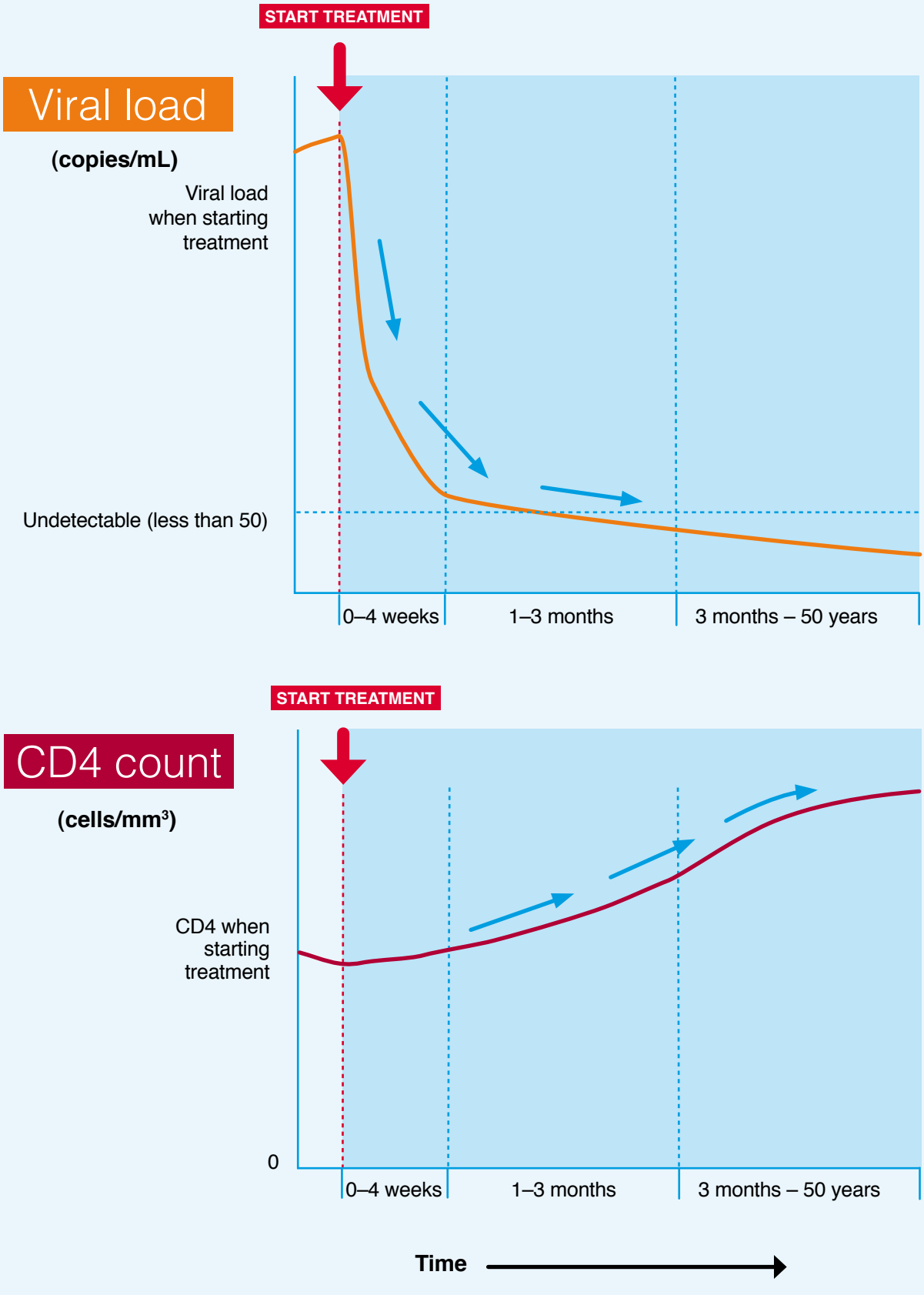
- After six months, HIV enters the chronic phase. Compared to the activity during primary infection, this phase usually progresses slowly. Even without ART, many people can go for years without complications from HIV. However, over time, the CD4 count will steadily drop and viral load will steadily increase. As the CD4 count drops the risk of a serious infection increases.
- During chronic infection, especially if the CD4 count is still high, the risk from HIV complications is low. However, ART is still protective at high CD4 counts. In general, starting ART sooner is better than later.
- The lower the CD4 count in chronic infection, the higher the risk from HIV-related infections. But even when the CD4 count is very high, HIV can still cause serious problems without ART. The START study showed that ART has benefits even at CD4 counts above 500.
- ART quickly reduces viral load – by 90% in a few days. Viral load should then become undetectable within 1 to 3 months. How quickly this happens depends on the choice of ART and how high viral load is.
- The CD4 count increases more slowly. But the higher the CD4 count when starting the quicker the response and the higher it will become. People starting with low CD4 counts are more likely to have a slower CD4 recovery.
- Once stable on ART, so long as adherence is good, the same combination can last for years and even decades.

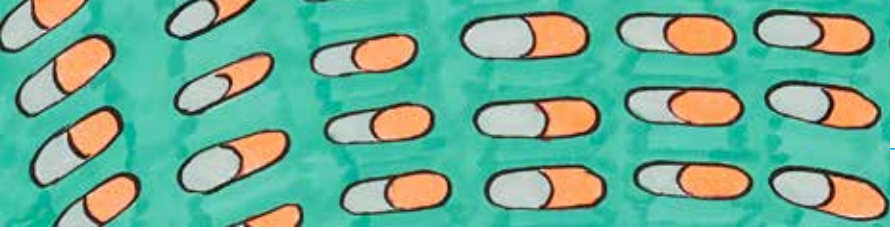
In the UK, about 40% of people each year are only diagnosed after their CD4 count has dropped to below 350. Most people in this situation are likely to have been HIV positive for several years.

ANALYSING TEST RESULTS

- It is easy to worry about CD4 and viral load results, especially when you find out you are HIV positive.
- These tests are good markers for damage caused by HIV, but there is a lot of variability in the results. The trend of several results over time is more important than a single result.
- The first CD4 count will not tell you whether you are in early or late infection. Interpreting the CD4 count with your sexual history and potential symptoms can estimate when infection occurred. For most people though this will only be a guess.
- A second set of results can show whether the trend is increasing, decreasing, or roughly stable. However, as ART is increasingly started at high CD4 counts, fewer people wait to monitor this trend.
- CD4 counts also fluctuate by the time of day, whether you have recently exercised, and eaten.
- The normal CD4 range for HIV negative people is between 400 and 1,600 cells/mm^3 but people with higher or lower results can be perfectly healthy. For HIV negative people, there is no relationship between health and CD4 count.

HIV after starting ART





ART starts to work with the very first pill.

Viral load on treatment

- ART first stops active CD4 cells with HIV from making any more virus. viral load can drop by 90% within the first few days, and by 99% within the first few weeks.
- Viral load then continues to drop over the next few months.
- Many people become undetectable within a month and most within three months. The time taken partly depends on the choice of ART. Integrase inhibitors reduce viral load faster than other HIV drugs. Guidelines increasingly recommend integrase inhibitors when starting ART.
- How quickly viral load becomes undetectable will also depend on how high viral load was when you started treatment.
- Starting with a viral load count above 100,000 copies/mL might take three months to become undetectable.
- More rarely, if viral load starts in the millions, it might stay stable at low levels (between 50 to 200 copies/mL) for over a year. So long as this doesn't get higher, there is no need to change ART. [1]

CD4 on treatment

- As ART wipes out most actively infected CD4 cells, the immune system then has chance to recover naturally.
- Because there is much less virus, the immune system slows down production of excess CD4 cells.
- Stopping this overproduction is a good thing.
- HIV drugs do not directly increase the CD4 count, but they help make an environment where this can happen. ART enables the CD4 count to increase to higher and safer levels.
- In contrast to viral load, CD4 usually increases more slowly and steadily. The biggest rise occurs during the first 6–12 months and this continues over the second year. Reaching a CD4 count above 500 is referred to as normal, but even if it doesn't reach this high, the risk of HIV-related complications is dramatically reduced.
- Once on stable ART, so long as adherence is good, the same combination can last for years. CD4 counts can also continue to increase each year, even after ten years.

Reference

1. Halvas EK et al. Nonsuppressible viremia on ART from large cell clones carrying intact proviruses. CROI 4 – 7 March 2019, Seattle. Oral abstract 23.

See: http://i-base.info/htb/35801

HIV after ART in detail

ART begins to work within hours. This is much faster than most people realise. Viral load drops dramatically and quickly in three phases.

First phase – 1 to 2 days: During the first phase, ART blocks replication in short-lived CD4 cells that are actively infected. Because these cells only live for 1 to 2 days, viral load drops by 90% within a few days.

Second phase – 2 to 3 weeks: Over the next couple of weeks, viral load continues to drop, though slightly less steeply. After a few weeks viral load has usually dropped by 99% or more.

Third phase – up to 12 weeks: If viral load is not undetectable after a month, it will continue to fall over the following few months, in the third phase. Most people reach undetectable within three months.

- How quickly viral load drops will depend on the choice of drugs.
- How quickly viral load becomes undetectable will depend on how high it was before starting ART.
- Good adherence is essential. Meds can only work if they are taken as prescribed.
- The main aim of ART is to get viral load to below 50 copies/mL. This is called undetectable.
- Once viral load gets this low, it can stay undetectable for years. As long as someone is taking their meds, the chance for the virus to develop drug resistance is very low.
- Although viral load tests do not measure below the 50 copy cut-off, viral load can go much lower. Many people get viral load to less than 5 copies/mL and for some this is not detectable on tests measuring down to 1 copy/mL.
- Compared to the 10 million copies/mL in early infection, it is easy to see why ART stops HIV transmission.
- Becoming non-infectious on ART is another reason that many people start ART. The PARTNER study showed the dramatic impact of having an undetectable viral load. There were no linked HIV transmissions after serodifferent couples had sex without condoms more than 58,000 times.

When to start ART

- ART is now routine recommended for everyone who is HIV positive.
- For most of the last 30 years, the decision to start ART depended on the CD4 count. ART was generally delayed until the CD4 count reached a certain level. This is because HIV-related complications were rare at high CD4 counts.
- The decision to treat even at high CD4 counts was due to the START study.

Early treatment in the UK

- UK treatment guidelines recommend treatment at any CD4 count.
- These UK guidelines are now similar to guidelines in other countries including the US, France and South Africa.
- World Health Organization (WHO) guidelines for low- and middle-income countries also recommend treatment for everyone.
- If your doctor says that your CD4 count is too high to need treatment, and you want to start ART, say that you want to reduce the risk to your partners.
- Many clinics now offer ART as soon as the HIV test is confirmed. Starting ART on the same day or week you are diagnosed is a choice that can make it easier to come to terms with being HIV positive.

Same-day ART

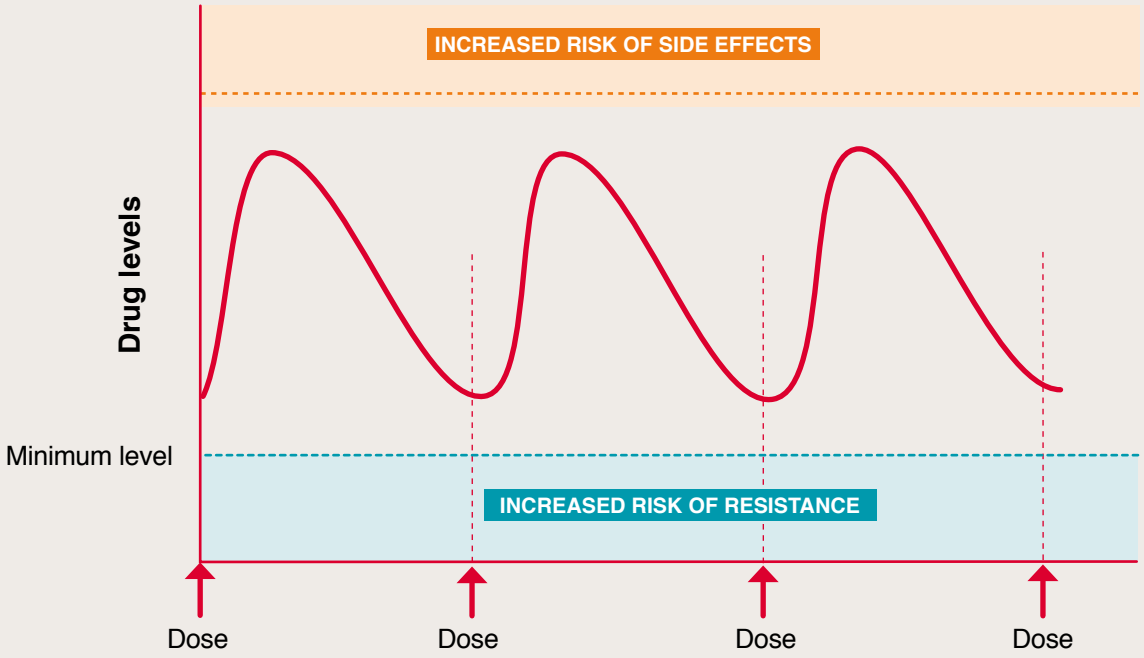
- Several studies have reported very positive results from offering ART when someone is diagnosed. This can be on the same day or in the same week.
- HIV is already being treated while coming to terms with being HIV positive.
- These studies had very high of uptake when people are given this choice. Rather than taking weeks or months of referrals and seeing specialists, ART is working immediately.
- Viral load became undetectable more quickly in these studies.

LONG-TERM ART – SUMMARY

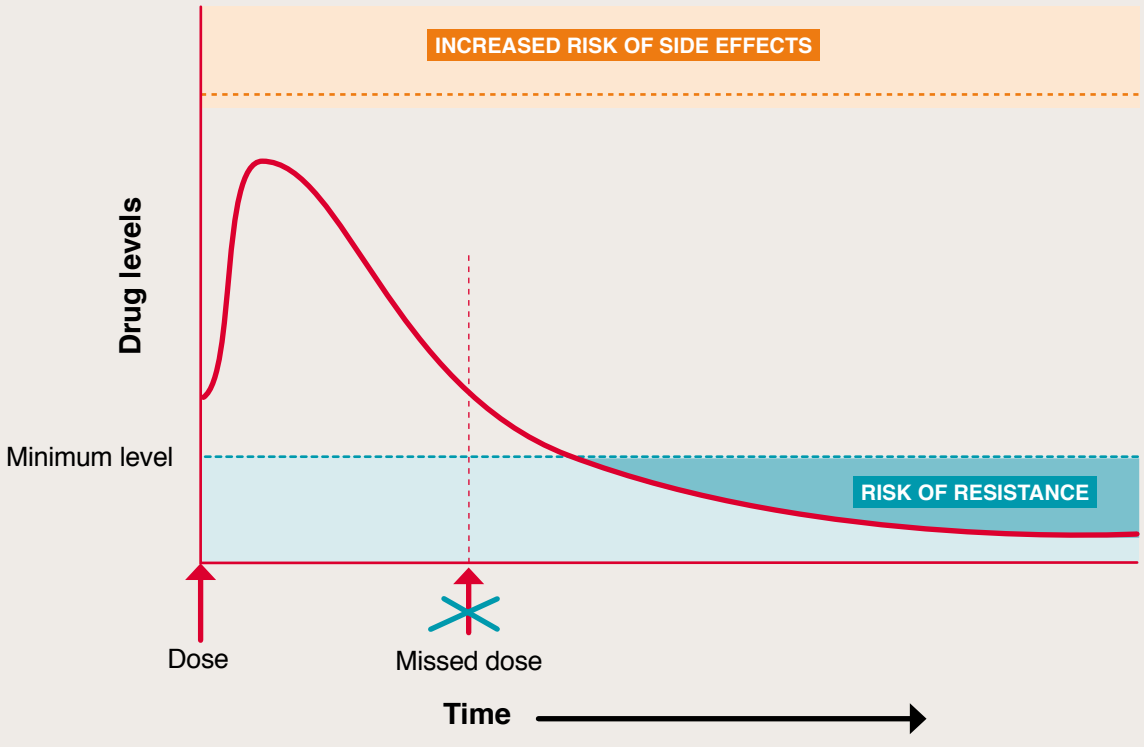
- ART has dramatically changed the outcome for people living with HIV.
- More than 20 years of experience shows ART is effective and with low risk.
- Over this period, drugs have become better and research continues to make better ART. Even if no new drugs are developed, most of us will lead long and active lives.
- But scientists are pushing further – not just for better ART but for a cure. We discuss this research on pages 22 to 23.
- Longer life expectancy means that complications relating to HIV and ageing are now an important focus for research.

Drug levels and adherence

Taking meds on time



Missing a dose or taking it late



HIV meds are usually taken as pills or tablets. How well we take meds is referred to as adherence.

Good adherence includes both getting the time right and following advice about food.

Rather than feeling life has to be lived on a schedule, understanding how timing affects drug levels can make adherence a more empowering part of life.

- Most oral drugs start to be absorbed into the bloodstream through the stomach wall. It is why food restrictions and recommendations are important. Some drugs – especially rilpivirine, protease inhibitors and Stribild and Genvoya – need to be taken with food to achieve the right levels.
- Once in the bloodstream these drugs are filtered though the liver and kidneys. So a lot of the active ingredients are cleared before they come into contact with HIV. But being transported in the blood also reaches CD4 cells, where the meds are directly active.
- Most drugs take 1 to 2 hours to reach a peak level in blood. This level needs to be high enough for the drugs to work, but not so high as to cause side effects.
- Drug levels then steadily fall as your liver and/or kidneys continue to filter them out.
- The dose for each HIV drug is based on making sure that drug levels will be above a certain minimum level throughout the whole dosing period. By the time of the next dose, drugs levels still need to be high enough to stop drug resistance.
- So long as you don't miss your meds, ART will control HIV for 24 hours a day, 7 days a week, 365 days a year.
- The top graph on page 18 shows that taking meds on time keeps average drug levels above the minimum needed to avoid drug resistance.
- The lower graph shows that if you are late or miss a dose, drug levels will continue to fall. If levels become too low to control HIV, drug resistance can develop.
- Sometimes, especially for children, meds can be in a syrup or other formulation. Ongoing research is also looking at long-acting injections every two months. The same principles of adherence work for all formulations.

Drug adherence in detail

Adherence to HIV meds: how much is enough?

- Adherence refers to taking medicines as prescribed.
- This includes getting the right dose, at the right time, plus following any other advice, such as taking with or without food.
- When ART was first available, adherence needed to be very high – routinely taking 95% or more doses.
- Now that ART involves fewer pills and fewer doses, adherence is also easier. Although perfect adherence is ideal, occasional missed doses are okay.
- Most people living with HIV are pretty good at taking meds. Adherence to ART is higher than for many other medicines. But doctors can only help if they know that someone is having problems.

Window periods for different drugs

The graphs on page 18 show an average way to describe drug absorption and adherence.

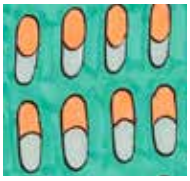
- Drugs are usually absorbed quickly to reach the maximum concentration (Cmax). Levels then fall until the time for the next dose (Cmin or Ctrough)
- It is good to aim for the same time each day, but an hour or two either side is also okay for all ARVs. A routine helps with remembering to take them though.
- Actual drug levels will be higher for some people and lower for others, but these just need to be within a target range. Drugs that leave the body more slowly allow more flexibility with late or missed doses.

  For example, efavirenz, emtricitabine and tenofovir (TDF) all have long half-lives. This combination (these meds are combined in Atripla) is easier if you sometimes miss doses.

  By comparison, the NNRTI rilpivirine has a shorter half-life and leaves the body more quickly. Even when rilpivirine is used with TDF and emtricitabine (in Eviplera/Complera), adherence needs to be more exact.

Differences between people

- Although some drugs have different doses based on body weight, most HIV drugs use a standard dose for adults.
- Dosing for children is more difficult and is often worked out by age or in relation to height and weight.
- Some HIV meds – but not all – need the dose to be adjusted if someone has reduced liver or kidney function.
- Doses are sometimes changed if you have drug resistance.



How important is food advice?

- Some meds need to be taken with food (mainly boosted protease inhibitors or boosted integrase inhibitors). The food is needed for the drugs to get to effective drug levels. Sometimes forgetting the food is like only taking half a dose.
- The type of food can also sometimes be important.

  Some drugs needs a certain number of calories. For example, rilpivirine needs at least 400 to 500 calories. For others, any amount of food is okay to help absorption. Sometimes this is because food changes stomach acidity levels.
- Sometimes avoiding food is to stop high drug levels. For example, efavirenz should not be taken close to a high fat meal as fat increases drug absorption and this increases side effects.

What about drug interactions?

Information about drug interactions is important to mention in this section because it is related to the way your body processes drugs.

For example, drugs that are mainly processed by the liver do this using liver enzymes. Other drugs can affect the levels of these enzymes, which in turn will affect the level of HIV meds.

For example, if another drug increases the level of these enzymes, the HIV drugs will be cleared more quickly and drug levels will be too low.

If another drug reduces the levels of these enzymes, the HIV drugs will stay around for longer and drug levels will be too high.

A similar process happens for drugs that are processed by the kidneys.

DRUG INTERACTIONS

Drug interactions can occur with:

- Other HIV drugs.
- Other medicines (including ones sold without a prescription).
- Over-the-counter meds like antacids.
- Herbs and supplements.
- Multivitamins (i.e. with integrase inhibitors).

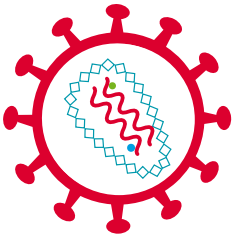
The best online HIV resource for checking drug-to-drug interactions is: www.hiv-druginteractions.org

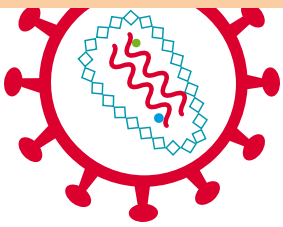
The HIV reservoir

The difference between active CD4 compared to sleeping (or resting) CD4 cells has already been mentioned several times.

- HIV that is inside sleeping CD4 cells cannot be reached by ART. These cells are often referred to as the latent reservoir – or more fully, as “the latently infected CD4 viral reservoir”.
- Actually, most of our CD4 cells are usually resting and this is healthy. This part of our immune system is like a huge reference library with thousands of books on the shelves, not being read, but waiting for when they are needed.
- Each book is like an immune response that the body developed earlier that is stored away to be quickly activated if it is needed in the future.
- Throughout life, the library continues to grow. The body produces new CD4 cells which in turn are primed to respond to an infection – and then they sleep.
- Some of these cells will be infected with HIV, especially during early HIV infection. These cells then sleep with HIV trapped inside. In this resting state, HIV meds have no way of working – because the viral lifecycle is not active.
- Some of these cells can also sleep for decades. But they can also wake up at any time and the timing is not predictable. This is one reason why ART needs to be taken every day.
- This is also why viral load generally rebounds if ART is stopped – even after many years on treatment.
- Two contrasting research cases below show the complexity of HIV, especially when looking for a cure. References for these studies are on page 25.

Case 1: Some people who started ART very early in infection have stopped treatment after a few years and their viral load did not rebound. The most widely reported examples are a group of French patients called the VISCONTI cohort. This is rare but a similar case has been reported in the UK.





Case 2: A man in the US started ART within weeks of infection. He stayed on ART for 10 years with an undetectable viral load. Special tests were needed to search two billion cells before finding one that contained HIV. As part of a study, this person stopped ART, but viral load still rebounded.

The HIV cure puzzle

Over the last five years, there has been a dramatic increase in research into finding a cure for HIV.

- Not only has funding for cure research increased but researchers in many different countries are working together on this shared goal.
- Although ART is good, a cure would be better!
- One type of cure is called **eradication**. This approach aims to clear HIV completely from your body. The reservoir makes this very difficult. A single long-lived resting cell could activate decades after someone might think they are cured.
- Another type of cure is called a **functional cure**. This approach attempts to get your immune system to control HIV, without needing ART.
- In practice, most people living with HIV would welcome either type of cure. But in both cases an HIV cure would be similar to remission after cancer.
- Any cure for HIV is likely to need a combination approach. Different research will provide different pieces of the puzzle.

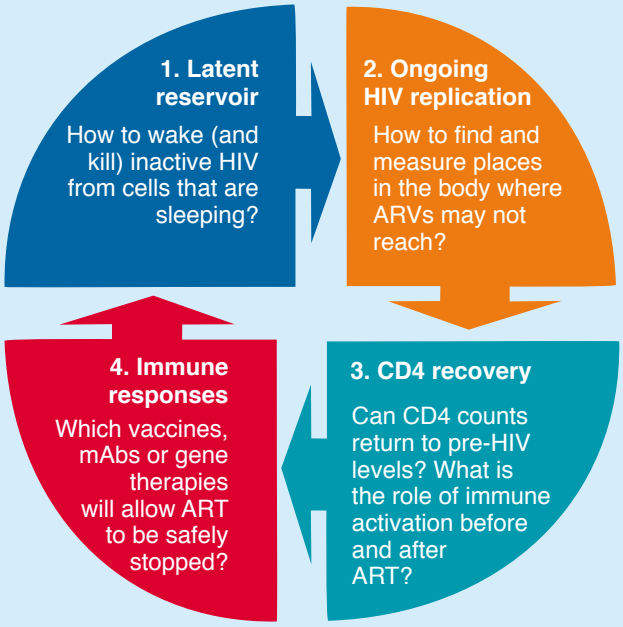
Cure research brings new ethical issues.
- Cure treatment might be riskier than lifelong ART.
- Stopping ART will by definition be needed to test whether a cure is effective.
- The risk from HIV relapsing – maybe after years of remission – will have implications for partner safety unless condoms are still used.

Similar to the way ART uses drugs that target different parts of the HIV lifecycle, cure research is likely to use multiple treatments to cover four areas:

1. To activate sleeping cells in the viral reservoir.
2. To answer questions about ongoing HIV replication on ART. For example, are there places in the body that ART doesn't reach?
3. To see whether immune damage from HIV can be reversed.
4. To use a vaccines or immune-based treatment to keep viral load under control, but without needing ART.

As an advocate, it is always good to be optimistic – and hope is a powerful thing.

Just as science developed ART, one day there will be a cure.



For more information on Towards an HIV Cure: www.iasociety.org/hivcure

Understanding test results

Your HIV health is monitored by results from blood tests.

These are mainly the CD4 count and viral load, but also CD4% (if there is an unexpected result) and CD4:CD8 ratio (when the CD4 count is above 500).

ART is also routinely monitored by other blood tests. These include ALT/AST (for liver function), eGFR (for kidney function), cholesterol and triglycerides (for heart disease) and glucose levels (for diabetes).

Other monitoring includes your height and weight (combined for BMI), heart rate, blood pressure, and asking about your mood, memory, sex life and general happiness.

Understanding results - especially from blood tests - will help people understand their health.

Several principles are useful for understanding all test results.

Your doctor should be able to give you a print out of your results.

- Lab results should come with a “normal” range. Anywhere within this range is good. Anything outside should mean the result needs to be checked.
- Most tests have a range of accuracy and variability. Interpreting results should allow for this fluctation. For example, both CD4 count and viral load can be 30% higher or lower and still be within the range for the test.
- Find out how often each test should be run and the time for checking an unexpected result.
- Keeping a record of results can make it easier to see if there is a pattern over time. For example, if kidney function or cholesterol are steadily improving or getting worse.
- Never make a change in treatment based on one result. Always have this confirmed with a second test. As well as fluctuation with results, sometimes other lab errors can occur, including mixing up samples.

i-Base treatment passport

i-Base produce a booklet – also online – for recording a summary record of your medical notes, including test results.

http://i-base.info/guides/passport

References and further information

The following links are included as references for further information.

HIV training manual for advocates

A free online training course in nine chapters.

http://i-base.info/ttfa

Treatment guidelines

UK guidelines

The British HIV Association (BHIVA) has produced an extensive range of HIV guidelines.

www.bhiva.org

Other guidelines

Other guidelines including for Europe (EACS), the US (DHHS) and the World Health Organization (WHO).

www.eacsociety.org

aidsinfo.nih.gov/guidelines

www.who.int/hiv/pub/guidelines/en

Drug interactions

A comprehensive web site for interactions with HIV drugs is run by Liverpool University.

The same group run a similar site for interactions with hepatitis C drugs.

www.hiv-druginteractions.org

www.hcv-druginteractions.org

Selected research links

START study

This large study showed the benefits of ART even at very high CD4 counts.

http://i-base.info/start-study

PARTNER and PARTNER 2 studies

These studies showed how ART stops HIV transmission. No partners became HIV positive after gay and straight couples had sex more than 100,000 times without condoms, when VL was undetectable.

http://i-base.info/partner-study

Cure research

The International AIDS Society (IAS) publishes the *Towards a Cure* report.

www.iasociety.org/hivcure

Viral rebound after long-term ART

Single case of very early ART. After ten years HIV was only in 1 out of 1.7 billion CD4 cells. After stopping ART, viral load still rebounded.

Chun T-W et al. AIDS 2010. doi: 10.1097/QAD.0b013e328340a239.

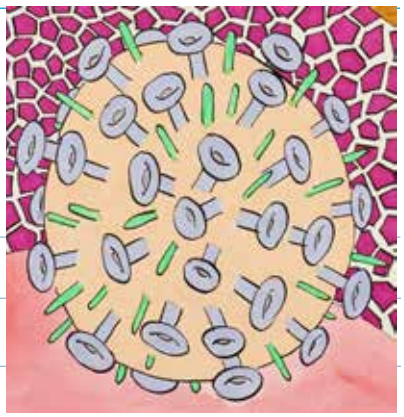
journals.lww.com/aidsonline/Abstract/2010/11270/Rebound_of_plasma_viremia_following_cessation_of.6.aspx?

No rebound after long-term ART

The people in the VISCONTI cohort started ART in early infection. When they stopped ART after several years, viral load did not rebound. This is not common. Sáez-Cirión A et al. PLOS Pathogens, 2013. doi: 10.1371/journal.ppat.1003211.s

www.plospathogens.org/article/info%3Adoi%2F10.1371%2Fjournal.ppat.1003211

Notes



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How easy was the information in this guide to understand?

Too easy ☐ Easy ☐ Difficult ☐ Too difficult ☐

How much of the information did you already know?

None ☐ A little ☐ Most ☐ All ☐

Will the guide help you be more confident when speaking to your doctor?

Yes, a lot ☐ Yes, a little ☐ Maybe ☐ No ☐

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