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information series for HIV-positive people

resistance

acknowledgments

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If you're HIV-positive and you're taking, or thinking about starting treatment for HIV, you'll need to know about drug resistance. Resistance is an important reason why anti-HIV drugs can stop working. By learning about resistance and what can reduce the risk of it developing, you will increase your chances of getting the most out of your HIV treatment. A short summary of the key points raised in this booklet can be found on page 15.

A glossary of technical terms used is on page 16. This booklet has been written to help you decide what questions to ask your doctor about any course of treatment you might be considering. We don't intend for it to replace discussion with your doctor about your treatment.

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1 What is resistance?

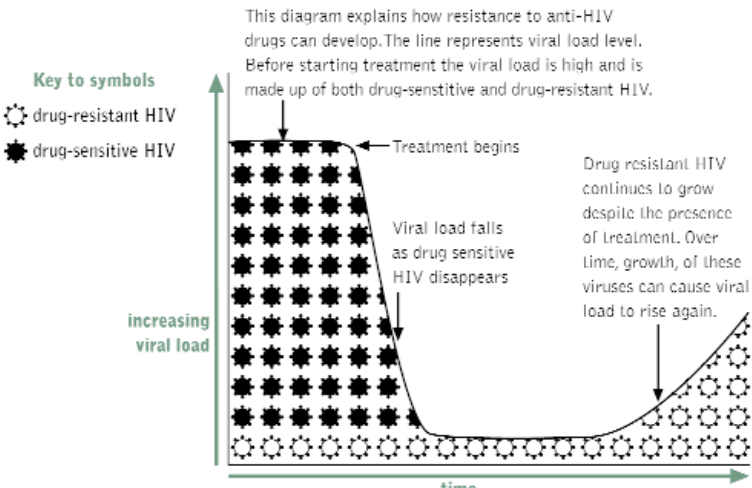
HIV reproduces itself very quickly, making billions of new viruses every day. Because the virus often makes mistakes when copying itself, each new generation differs slightly to the one before. These tiny structural differences are called *mutations.*

Some mutations occur in the parts of HIV which are targeted by anti-HIV drugs. This can result in strains of HIV that have reduced sensitivity to the drugs. These HIV strains are called *drug* resistant.

Drug resistant HIV strains vary – some may be highly resistant to anti-HIV drugs while others may be less so. When an anti-HIV drug is started, HIV that is fully susceptible to that drug disappears rapidly, leaving behind drug resistant viruses. These viruses continue to reproduce themselves despite the drug's presence. Diagram 1 on page 2 shows how this works.

Resistance is an important reason why anti-HIV treatment can fail. Viral load, which should drop when you start a new drug combination, may *rebound* if a population of drug resistant HIV is able to emerge.

Diagram 1


This diagram explains how resistance to anti-HIV drugs can develop. The line represents viral load level. Before starting treatment the viral load is high and is made up of both drug-senstitive and drug-resistant HIV.
Key to symbols
drug-resistant HIV
drug-sensitive HIV
Treatment begins
Viral load falls as drug sensitive HIV disappears
Drug resistant HIV continues to grow despite the presence of treatment. Over time, growth, of these viruses can cause viral load to rise again.
increasing viral load
time

3 Reducing the risk of resistance

Suppress viral load

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

People whose viral load falls and remains below 50 copies when they start treatment, are at a lower risk of developing resistance than people whose viral load does not fall that low. The current standard is for anti-HIV treatment to involve three drugs. Some people may receive four or more, for instance if you have very high viral load, or if you have taken several anti-HIV drugs already.

The lowest point to which viral load falls after starting treatment, often called the *nadir*, predicts the likelihood that viral load will rebound in the future whilst you continue with your treatment. The lower the nadir, the lower the risk of rebound, and therefore the lower the risk of developing resistance.

Take care when changing to new drugs

Adding a single new drug to a combination which is not keeping viral load fully suppressed can allow resistance to that drug to emerge rapidly, because the impact of that one drug is unlikely to be enough to stop HIV reproducing. This means that if you are switching from treatment which is not suppressing your viral load, you should replace as many drugs as possible in your combination – ideally all of them – to give the best chance that your new combination will work.

The replacement drugs should be chosen with help from a test to detect whether your HIV is resistant to particular drugs. There is more about this issue in the later section called *Resistance* tests.

If you are switching drugs because of side-effects, and your viral load is suppressed, this does not present the same risk of resistance emerging. In this situation, your doctor may change just a single drug.

Switch early

The speed at which resistance to different anti-HIV drugs develops varies. HIV needs only one mutation to become fully resistant to 3TC, to efavirenz and to nevirapine. This simple change – just a single mutation – can happen easily even at quite low levels of viral load rebound.

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

For this reason, a rising viral load should signal the need to consider changing to a new combination, (so long as you have options to switch to).

Take your HIV treatment as prescribed

It's very important to take anti-HIV drugs exactly as your doctor prescribed them. This means taking every dose on time, and following any guidance about the kind of foods you can or should eat with your dose. Sticking to these instructions is often called adherence.

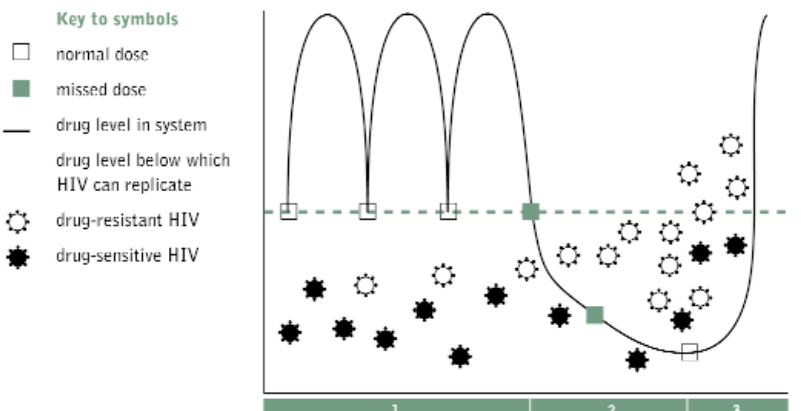
Missing or delaying doses, or taking a dose without recommended foods, will lower the amount of the drug which is active in your body. This reduces your drug combination's attack on HIV. Virus which was suppressed will then begin to reproduce, increasing the risk of resistant viruses emerging. Diagram 2 on page 7 shows how this works.

Missing even a few doses a month may be enough to cause your treatment to fail, which is why it's vital that you're well prepared to start a new combination, and that you continue to be supported whilst you take it. There are many sources of support available – your treatment centre, a local AIDS organisation, friends and family, other people with HIV.

Choosing a combination which suits the way you live, developing a pill-taking routine, and finding ways to avoid missing doses will all be important. But over time, there may be many other issues which might help or hinder your adherence. If you have any concerns, or if you feel your treatment isn't right for you, speak to someone at your treatment centre. Don't stop your treatment abruptly without seeking advice first – for some combinations this can allow resistant HIV to emerge.

7 Diagram 2

The effect of missed doses



Before treatment begins, the HIV viral population is a mix of mostly drug-sensitive viruses plus a range of drug-resistant viruses.

1

These peaks and troughs show how drug levels in the body rise and fall as doses are taken, the drug's anti-HIV effect is maximised and HIV reproduction is minimised.

2

Missed doses allow drug levels to fall. HIV reproduction speeds up again and viral load rises as both drug-sensitive and drug resistant HIV grows.

3

With the next dose taken, the drug's anti-HIV effect is restored. Drug-resistant HIV may have gained a foothold, however, and may continue to cause a rise in viral load. One missed dose is unlikely to cause your treatment to fail, but the more doses missed, the greater the risk.

9 Cross-resistance

Single mutations or patterns of mutations in HIV can produce resistance to several different anti-HIV drugs. This means that once resistance to one drug has emerged, this HIV may also be resistant to drugs you haven't taken yet. This is called *cross-resistance*.

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

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

Infection with drug resistant HIV

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

Becoming infected with a drug resistant strain may seriously limit your treatment options in the same way as developing resistance while taking treatments, narrowing down the range of drugs which you might benefit from.

Whether someone who is already HIV-positive can become infected a second time with a drug resistant strain is much less clear. Though there is some evidence that it may occur, it's difficult to know how great the risk is. If you would like to discuss any concerns about this, such as how it may affect your sexual behaviour, a health advisor or psychologist in your treatment centre can help.

In the UK, the transmission of drug resistant HIV is on the increase. This is also the case in other parts of Europe and in North America. With time, and the greater use of multiple classes of HIV drugs, the transmission of HIV which is *multi-drug resistant* (resistant to a number of drugs and therefore more difficult to treat), is becoming more common.

11 Resistance tests

Blood tests are available which detect whether the HIV in your body is resistant to anti-HIV drugs. These tests are a relatively recent addition to HIV care. In the coming years, we can expect to learn more about the best way to use them, and for technology to improve to make them a more accurate measurement tool.

At the moment, it's recommended that drug resistance tests are used whenever HIV treatment which is failing to suppress viral load is going to be changed. Resistance testing may be considered in people who take treatment for the first time, but these are less likely to be reliable because where treatment has never been taken, drug resistant strains may not be present in large enough quantities to be detected by the test.

An exception to this is where HIV infection is very recent. Resistance tests are recommended for people who start treatment within six months of contracting HIV. Within this period, any transmitted drug resistant strains may be detected by the test.

Resistance tests are also recommended to help guide the choice of treatment in women who are pregnant, and in children.

Using and interpreting resistance tests

Resistance tests are a complex new development in HIV care and so results should be interpreted by someone who is experienced in using them. Test results should be considered alongside a full treatment history, rather than in isolation. This is because drug resistance is not the only reason why HIV treatment can fail – missed doses, poor absorption and drug interactions are other possible causes to consider.

Resistance tests may be unreliable if your viral load is below 1,000 copies. You may need special advice about the results of a drug resistance test if you are infected with a type of HIV called *non-B subtype*. These subtypes are found more commonly in most parts of the world, particularly outside Europe and North America. Most HIV-positive people in the UK who contracted HIV in Africa will be carrying a non-B subtype of HIV, as well as an increasing proportion of those who have contracted HIV through heterosexual sex.

Resistance tests will also be more accurate if done while you are still taking a failing combination rather than after you've stopped it. This is because when you stop your current drugs, drug resistant HIV

will be no more likely to reproduce than drug sensitive HIV – and usually less likely. Resistant viruses that once were the most common will be out-grown by sensitive viruses until they form one of many *sub-groups* of HIV within the body. Resistance tests are unable to detect sub-groups which make up less than 10-20% of the total HIV in your body. Starting a drug which a sub-group of your HIV is resistant to will allow that group to grow back again, causing your treatment to fail.

Which tests to use

There are two main methods of testing for HIV drug resistance:

- *Genotypic tests* which look for specific mutations in HIV's genes that are known to be linked with resistance to anti-HIV drugs.
- *Phenotypic tests* which measure the concentration of a drug required to reduce viral replication by a set amount. When resistance to a drug begins to develop, higher levels of that drug will be required to stop HIV growing.

There is no clear indication that one type of test is more useful than another at the moment – each has its pros and cons. Genotypic tests are cheaper and deliver results sooner; within around fourteen days of the blood being taken. Changes in phenotype result from changes in genotype, so genotypic testing may produce the earliest clues about emerging resistance.

Phenotypic testing provides a quantitative guide to a drug's effects on the HIV in your body. However, these tests are more expensive and take longer to produce results, requiring around four weeks.

The Virtual Phenotype™ is an interpretation system which may be used more often to analyse genotypic resistance test results in future.

It provides a 'phenotypic' result based on the matching of resistant HIV strains within a large database of genotypic and phenotypic information.

15 Summary

- Resistance is an important reason why anti-HIV drugs stop working.
- HIV which is resistant to one drug may also be resistant to other drugs which you haven't taken yet.
- The chance of developing resistance will be reduced if your viral load while on treatment is undetectable, and you take every dose of the drugs prescribed to you.
- The more you miss doses, the more likely it will be that your drug combination will fail.
- Some people contract HIV which is drug resistant when they become infected.
- Resistance tests can be used to help choose replacement drugs if your anti-HIV drug combination is not controlling your viral load.

Glossary

adherence The act of taking a treatment exactly as prescribed.

antiretroviral A substance that acts against retroviruses such as HIV.

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.

genotype The genetic make-up of an organism.

mutation A single change in gene sequence.

NNRTI Non nucleoside reverse transcriptase inhibitor; the family of antiretrovirals which includes efavirenz and nevirapine.

nucleoside analogue Family of antiretrovirals which includes AZT, ddI, 3TC, d4T, ddC and abacavir.

phenotype Trait or behaviour which results from a particular genotype.

protease inhibitor Family of antiretrovirals which includes indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir.

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.

resistance test Blood test which detects resistance to anti-HIV drugs.

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.

Notes

Notes

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