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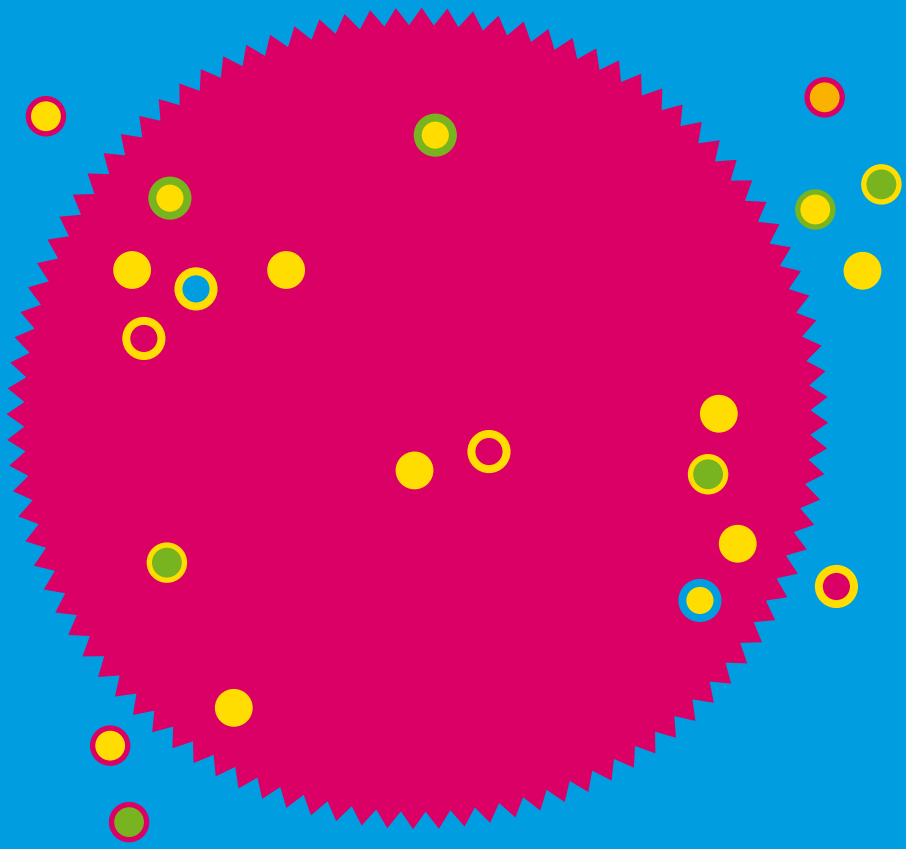
Changing treatment & drug resistance

February 2011



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Watch for out-of-date information

What to do if your viral load rebounds
Resistance testing
Switching for side effects
New and experimental treatments

Contents

This booklet includes information about changing treatment.

The main focus is on treatment failure because of drug resistance.

This booklet will help explain:

- Why your treatment failed.
- Which tests you need and what the results mean.
- Choices for your next combination.
- How to help make sure your next treatment works.

It includes information about drugs in development and other research.

This guide was written and compiled by Simon Collins for HIV i-Base. Thanks to the advisory group of HIV-positive people and healthcare professionals for comments and to Monument Trust for funding this publication.

Summary

Drug resistance is a specialised area of HIV care. Although everyone's treatment situation is different, the following summary covers the most important key points from this booklet.

Each summary point is highlighted on the pages where it is discussed later.

1. If your viral load starts to rise after being undetectable, don't panic, but do take it seriously.
2. Repeat the test on the same day you get the first test results. This is to find out whether the first test was accurate. Collect the new test results as soon as they are available (within 2 weeks).
3. If your viral load continues to rise, the earlier you change treatment (if you have this option), the less resistance will develop. This will make it easier to reduce viral load to undetectable again.
4. Think about why your current combination failed. Find out whether this related to resistance, problems with adherence, drug absorption, or a combination of these reasons. This also applies if your first combination never reduced your viral load to undetectable levels.

   If adherence was the cause, you will need support to make sure this doesn't happen on the new combination.
5. Ask whether your doctor is experienced in treating people in your situation. If you are being treated at a clinic with relatively few patients, your doctor can talk to experts at larger centres.
6. Choose the strongest combination you can for the next treatment. Use as many new drugs that are not cross-resistant to previous drugs.
7. Monitor your new treatment carefully. Get a viral load test 2–4 weeks after the treatment change. Then test viral load every month until you know if you are undetectable. If you have problems with adherence or side effects, discuss these with your doctor.
8. Keep up-to-date on the latest research. Find out which new treatments are likely to become available in the next year, especially through expanded access programmes.
9. Don't rush to use one new drug if it is the only drug that will be active, especially if your health is good. Always try to use at least two new drugs in your combination.
10. Even if you have a detectable viral load and are waiting for new treatments, staying on treatment that includes nukes and a protease inhibitor is much safer than stopping all your drugs. This is especially true if your CD4 count is under 200.

Introduction

Most people starting treatment in 2011 get their viral load to undetectable levels on their first treatment. If a treatment change is needed it is usually to reduce side effects.

However, about 10% of people change because their viral load does not become undetectable. This is usually because of prior drug resistance or problems with adherence.

In addition, some people have already developed resistance to more than one earlier combination.

This is still usually easy to treat because of the number of available drugs.

Less than 5% of HIV-positive people in the UK have developed resistance to all drugs. These people are waiting for new drugs to be developed.

Within this group of most treatment-experienced people, the options will also depend on current health and risk of becoming ill.

This booklet includes information on all these different situations.

Although most people have good options, each chance at a new treatment is too important to waste.

Even with over 25 meds from five families of drugs, cross-resistance can mean that you only get three or four good chances at treatment.

Each chance needs to be seen as life saving. This booklet should help you understand the best way to help your next treatment work.

Changes to this edition

This edition has been reorganised and rewritten throughout.

There are more graphics and many have been redrawn.

More emphasis is given to the need for support, including for adherence.

It includes the most recently approved drugs.

- Etravirine (a new NNRTI) has been approved in Europe.

It also includes information about potential new drugs that are in development.

- Rilpivirine (a new NNRTI) is close to being approved.
- New compounds are in development from all major drug classes.

Changing treatment and drug resistance

Reasons to change treatment

Sometimes you need to change treatment, even if you are feeling well.

The main times are:

1) If your current combination did not reduce your viral load to less than 50 copies/mL
2) If your viral load was undetectable but has started to rise again while you are on treatment ('viral rebound').

In both these cases your treatment would be said to have failed.

A third reason to change treatment is:

3) If your combination is working but the side effects are too difficult.

This booklet mainly deals with the first two situations. However, we include some information on changing treatment due to side effects on page 27. It is now very common, and usually very easy, to change treatment because of side effects.

What is second-line treatment?

Second-line is the name for your second treatment, if you have to change your first treatment because of treatment failure.

If this second treatment fails, your next treatment is called third-line.

Multiple Drug Resistant (MDR) treatment is the name given to any combination that you use after you have developed resistance to your first or second regimen.

Sometimes it refers to treatment for someone with resistance to all HIV drugs.

This is also called salvage therapy in some clinics, although most community publications no longer use this term.

How long should I use my first combination?

An active combination, if you are taking the meds on time, should reduce viral load to undetectable levels within three months. Sometimes this might take longer, perhaps up to six months if you start with a very high viral load.

Treatment usually reduces viral load by 90% (by 1 log) in the first week, though it is rarely monitored this early. It should reduce by 99% (by 2 logs) during the first four weeks.

If your viral load hasn't reduced by at least 90% within 4 weeks your doctor will need to find out why. This will include having another resistance test.

These times are all based on somebody taking all their treatment on time.

If you have been missing some of your doses, your doctor needs to know to take this into account.

If your viral load hasn't dropped by 90% in the first month or had not become undetectable by six months, you would usually expect to change treatment

How can drugs ‘fail’ and I feel fine?

When the term ‘fail’ is used to describe an increase in your viral load, this should really be referred to as **virological failure.**

It relates to results from blood tests but not how well you feel. It does relate to your risk of becoming ill in the future.

The term **clinical failure** is used to describe any new or progressing illnesses. This is when you feel unwell. It is often related to virological failure, but may follow several months later.

Your viral load rises first (virological failure), followed by a drop in your CD4 count, which then puts you at greater risk of becoming ill (clinical failure) - see Figure 1.

What is HIV drug resistance?

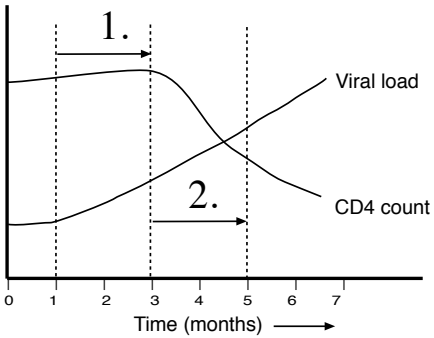
Drug resistance is when a drug that would normally be active no longer works.

Resistance can develop to drugs used to treat viral, bacterial and fungal infections.

The drugs stop working because the virus (or other organism) has evolved or changed while on treatment.

The risk of resistance increases when drug levels are low. This happens if you do not take all your treatment at the correct time. See Figure 2.

Figure 1. Time from viral load rebound to CD4 changes and clinical symptoms



If your viral load rebounds and you continue on treatment, resistance develops and viral load continues rising higher:

1. It may take several months before you see a drop in your CD4 count.
2. If you have a strong CD4 count It will take even longer before you have clinical symptoms. If your CD4 count is below 200, then you could experience symptoms more quickly.

Resistance and adherence

How do missed doses lead to resistance?

Resistance and adherence are closely related. If you miss doses or are late taking your meds, this increases the chance of resistance. See Figures 2 and 3.

This is because drug levels fall below the minimum needed to control the virus.

The mutations that occur when you have only low concentrations of your drugs can stop the drugs working. Then, when you restart or continue treatment, they may not work at all.

Adherence is just as critical when you are on your second, third or later combination.

Do some drugs develop resistance more easily?

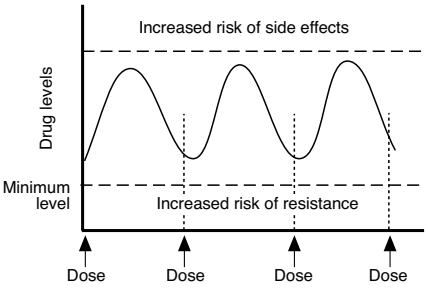
Some drugs only need one mutation for the virus to become completely resistant to them. This is the case with NNRTIs (nevirapine and efavirenz) and some nukes (3TC and FTC) - see Figure 4.

These are potent drugs but they are more vulnerable to early failure if used in a combination that does not reduce your viral load to below 50 copies/mL.

They are also usually easily cross-resistant to similar drugs in the same class.

Other drugs, including protease inhibitors, develop resistance more gradually.

Figure 2: Drug levels with good adherence

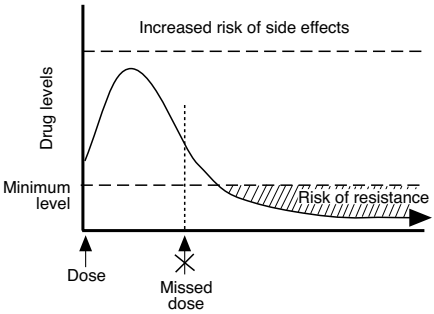


Drug doses are calculated on average levels over the whole dose period.

They need to be high enough to be active against HIV without risking resistance.

They need to be low enough to minimise the risk of side effects.

Figure 3: A missed or late dose increases the risk of resistance



Missing or being late with a drug lets the drug levels fall below a minimum safe level. Drug resistance can then develop.

The more often you are late or miss a dose, the greater the chance this will occur.

The first few mutations do not have much impact but they are the pathway to more complicated resistance. It then usually takes several mutations to stop the drug from working - see Figure 5.

Drugs that require accumulated resistance take longer to develop cross-resistance to other drugs in the same family.

Nukes can vary - some need only one mutation and some develop more complicated patterns of resistance.

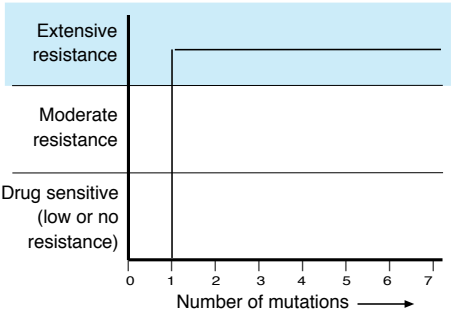
Integrase inhibitors are more similar to NNRTIs in being vulnerable to resistance.

The i-Base *Guide to HIV Drug Resistance* is a booklet that explains drug resistance, resistance tests and understanding the results in detail.

Resistance and adherence are discussed in detail in the i-Base booklet *Introduction to Combination Therapy.*

www.i-Base.info

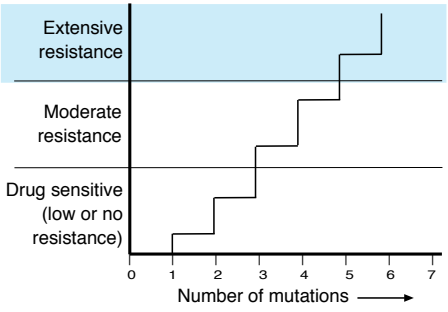
Figure 4. How one mutation can stop some drugs working



Some drugs stop working after only one mutation.

These include NNRTIs (nevirapine and efavirenz) (NNRTIs), some nukes (3TC and FTC).

Figure 5. Resistance increases slowly with some drugs



With some other drugs, the first one or two mutations make little difference.

If you continue taking the same drug, more mutations will develop that eventually stop the drugs working.

These include most PIs and some nukes.

What to do if viral load rebounds

If your viral load starts to rise after being undetectable, don't panic, but do take it seriously.

Repeat the test on the same day you get the first test results. This is to find out whether the first test produced an accurate result.

Collect the new test results as soon as they are available (within two weeks).

Why viral load tests are important

Most people only find out that they need to change treatment when their viral load increases.

In at least 50% of cases a low level viral rebound may be a lab error.

In many cases it may be a random 'blip'.

You need a second test, taken the same day as you get the original result, to investigate further.

If your viral load has continued to rise with the second test, guidelines recommend changing treatment.

This is because, even when viral load is relatively low (between 50—500 copies/mL), HIV can develop resistance. At some point, your viral load will rise much higher and the drugs will stop working completely.

Sometimes viral load remains low but detectable for many months without continuing to climb. This is because the virus is now 'less fit'. Over time, the virus usually develops new "compensatory" mutations) that make it fit again.

The tests being developed to measure the fitness of a virus are not yet routinely available in the clinic.

Fitness of HIV is discussed in more detail on page 25.

Spikes and blips

It is common to have a 'spike' or 'blip' result. Most blips are never detected (because viral load is only tested every few months. A blip is when your viral load jumps from undetectable and then drops back down below detection by itself within a few weeks. See Figure 6.

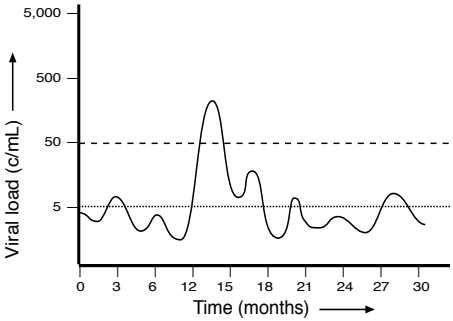
Blips can be anything from over 50 up to 2000, but are usually to less than 500. They can be caused by other infections, such as flu or herpes, or a recent vaccination.

Also, tests can be contaminated at the lab giving a false result. One study showed that over 50% of blips to between 50 and 500 copies/mL were test errors. These lab errors can occur with all viral load tests.

The confirmatory test will show whether the treatment is really failing.

If the second test also shows your viral load at a similar or higher level, *and you have been taking all the prescribed drugs*, it is likely you have started to develop resistance to some or all of the drugs in your combination. See Figure 7.

Figure 6. A single spike or blip is common

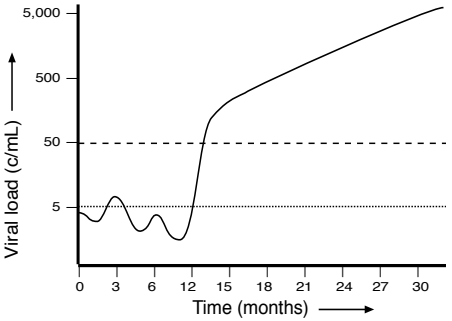


When viral load is undetectable (less than 50), it is often less than 5 copies/mL.

A single blip above 50 is common and doesn't mean you need to change treatment.

If it is really a blip, it will be undetectable again with the confirmatory test.

Figure 7. A real viral rebound will be confirmed by the confirmatory test



If viral load becomes detectable, have a second viral load test to confirm this.

If the confirmatory test shows that viral load is still detectable, this is likely to be a real rebound.

You need a confirmatory test result before you change treatment.

Test sensitivity

All hospitals in the UK now routinely use viral load tests that measure down to 20, 40 or 50 copies/mL.

Current research does not show a difference from using each of these tests.

Several research studies show that more than 50% of people actually have a viral load that is less than 5 copies/mL Although you may want to go as low as possible, 50 copies/mL seems to be the key cut-off.

Viral load tests have a three-fold margin of error. This means a result of 900 copies/mL could really be anywhere between 300 (3-fold lower) and 2700 (3-fold higher). A result of 90,000 could be anywhere between 30,000 and 270,000.

This is why it is important to confirm any unexpected viral load result.

Never rely on just one test result to make a treatment decision.

When should I change?

If your viral load continues to rise, the earlier you change treatment (if you have this option), the less resistance will develop. This will make it easier to reduce viral load to undetectable again.

The earlier that you detect a rise in your viral load, the earlier you can do something about it.

The trend of your viral load results over time is still important. However, the longer you wait to check that a trend is emerging, the greater the chance that resistance will develop.

If viral load rebound is confirmed then your choices depend on several things:

- The drugs that you have already used.
- Your lowest ever CD4 count (called CD4 nadir) and current CD4 count.
- Your general health,

Some people change treatment if their viral load remains consistently detectable above 50 copies/mL.

At low levels–between 50 and 500–you can sometimes intensify treatment, though this is generally not recommended. See page 22.

Another option is to wait until your viral load is confirmed at 500 copies/mL or higher. This will enable you have a resistance test.

In practice, many people have to start their next combination with far higher levels of viral load. This is often due to delays involved in checking whether viral load is really rising.

A higher viral load is more likely if you wait a long time between tests or do not get the results in 'real time' - i.e. two weeks after giving blood.

If you do not have enough new drugs for a new combination, then some drugs, even with a high viral load, are better to keep taking. They can help you remain healthy, sometimes for several years.

Nukes and PIs will continue to be active and are worth continuing. NNRTIs, T-20 and integrase inhibitors develop complete resistance, and are better to switch.

Waiting until new drugs are available is an important strategy. This is so that when you do change, it will be to a combination that is more likely to last.

This will stop you from using up each new drug as it becomes available in a weak combination that only lasts a few months.

Important monitoring tests

The following tests are used in different circumstances when changing treatment.

- Viral load tests
- Resistance tests
- Therapeutic Drug Monitoring (TDM)
- IQ and VIQ
- Viral tropism tests

Viral load tests

A viral load test is the most sensitive test to check whether a combination is still working. See pages 10—12 for more information on viral load.

After any treatment change, viral load should be checked every 2-4 weeks until it becomes undetectable.

Once viral load is undetectable you should be monitored with a viral load test every 3—4 months.

Resistance tests

Resistance tests can show which drugs are unlikely to work.

UK treatment guidelines recommend a resistance test before changing treatment.

You generally need to have a viral load over 500–1000 copies/mL to produce a reliable result. You also need to have blood taken while you are still using your failing combination.

There are two main types of these blood tests. See Figure 8.

Genotype tests (mutation changes)

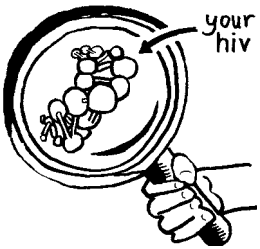
A genotypic resistance test looks at the structure of your virus and how it has changed from normal 'wild-type' virus. Different changes are associated with resistance to different drugs.

Checking the changes in your virus gives a good idea of which drugs are unlikely to work.

Figure 8. Types of resistance tests

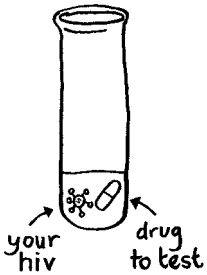
1. Genotype

Genotype tests look to see how the structure of a sample of your HIV may have changed.



2. Phenotype

Phenotype tests see whether HIV drugs still work to control your type of HIV.



Resistance tests can only detect resistance to drugs that you are currently taking or have recently been taking. A 'virtual phenotype' test compares results from your genotype test to a large database of phenotype results to predict your phenotype.

Although this test does not register very low levels of resistance, it can still be vital as a guide to choosing drugs for your next combination.

Results should take about a week.

Although genotype tests cannot predict which drugs WILL work, they can predict which drugs WILL NOT. With drug resistance, this information is just as important.

Phenotype tests ('fold' changes)

A phenotypic resistance test adds each increasing concentrations of a drug in a test tube that contains your HIV. It shows how sensitive or resistant you are and how active each drug is.

Results are given in terms of how much drug is needed to have the same effect as a regular dose on non-resistant HIV.

For example, 10-fold resistance to a drug means 10 times as much drug is needed to get the same antiviral effect.

Interpreting phenotype tests is complicated. Sometimes it is not clear at what level individual drugs remain active, and each drug can be different.

Phenotype tests are only recommended in the UK guidelines when genotype results alone do not provide a clear result.

Phenotype resistance tests are 3-4 times more expensive than genotype tests. They take longer to get results (usually 2–4 weeks) because the tests cannot be run in your own clinic and it takes time for the virus to grow.

Virtual phenotype tests

The 'Virtual Phenotype' test compares results from a genotype test to those in a large database of matched phenotype results.

This test is therefore not really a phenotype test but can still be useful.

How to interpret resistance tests

Resistance tests are complicated to interpret, but luckily test results also come with a summary that lists each drug as sensitive, intermediate or resistant.

Genotype results are given as letters and numbers.

Results from genotypic resistance tests are given as a list of mutations. These mutations are changes in the structure of the virus, usually where one amino acid has changed to another. The order of amino acids determines how the gene is able to function.

These usually follow the format of a letter followed by a number followed by a letter - i.e. K103N which results in complete resistance to efavirenz and nevirapine.

The first letter stands for the amino acid that is normally at that junction in the virus. The K stands for lysine.

The number says where on the HIV DNA that the change has taken place - like junction numbers on a motorway. In this example 103 refers to the 103rd amino acid in the RT section of the HIV genome.

The final letter stands for the new chemical that the mutation makes. The N stands for asparagine.

Some mutations like K103N are easy to interpret but most others are more

complicated. This is because they may only have a small effect, or because they are more rare, or because they commonly occur whether or not you are on treatment.

The Stanford Resistance Database includes charts for every mutation.

http://hivdb.stanford.edu

Phenotype results are reported as a number (a fold-change in sensitivity)

Phenotype results have different cut-off values for each drug and for each manufacturers test.

A 4-fold change in sensitivity (also called 4-fold resistance) could mean complete resistance for one drug and complete sensitivity for another.

Luckily, phenotypic tests include an interpretation report. This report summarises which drugs are still sensitive, which are partly resistant and which are completely resistant.

TDM (Therapeutic Drug Monitoring)

These tests check whether you are getting adequate blood levels of a protease inhibitor, NNRTI or T-20. Tests for maraviroc and raltegravir are also available.

Doses for HIV drugs are worked out for an average person. However, individual differences in absorption can vary.

TDM can check doses in many situations. These include:

- When using unstudied combinations where they may be a drug interaction. This is important with new drugs.
- To individualise dosing when there are no dosing recommendations.
- If you have pre-existing liver or kidney damage, or have haemophilia or other medical conditions that require careful monitoring. For example, drug levels of both amprenavir and abacavir can be too high if your liver is damaged. Using TDM you can safely reduce the dose when recommended.

  This may be true for some other drugs. If your liver is not working to clear then they can take longer to leave your body. Dosing is easier to individualise in this situation.
- For children. Differences in growth rates and the way children process drugs at different ages are not always accounted for. Even when doses are calculated by body weight or body surface area they often need altering.
- If you may not be absorbing drugs properly. For example, if you have severe diarrhoea.

TDM is recommended in UK guidelines and your doctor should be able to order this for you. If you have been taking all your drugs at the right time, this may be why your combination did not work so well.

Using TDM and resistance tests together produces better results than either test alone.

TDM costs around £70 per drug from Delphic:

http://www.delphicdiagnostics.com

IQ and VIQ

Research is looking to individualise treatment further by using tests that measure the Inhibitory Quotient (IQ) or Virtual Inhibitory Quotient (VIQ). These blood tests look at the effect of viral fitness – how well your virus reproduces. Different resistant and non-resistant viruses are more 'fit' than others.

IQ and VIQ tests are being integrated with TDM and resistance tests to provide information on drug sensitivity (which is related to drug concentration) for an individual patient. This has the potential to result in more targeted and effective care.

These tests are not yet available but they are an exciting area of research.

Viral tropism

This is a test that is only used if you are going to use a CCR5 inhibitor.

Most people have HIV that uses a receptor on the surface of the CD4 cell called CCR5 to enable the virus to attach to the cell. In advanced HIV infection, the virus sometimes switches to a different receptor called CXCR4. After this switch, and also in people with a mixture of both receptors, a CCR5 inhibitor will not work.

For current tropism tests to work you need a detectable viral load of at least 500-1000 copies/mL. This means that you cannot use the tropism test if your viral load is undetectable.

However, genotype resistance tests can also predict tropism. If your viral load is less than 500, you can use a special type of resistance test (proviral DNA) to find out whether you can use a CCR5 inhibitor.

The only CCR5 inhibitor currently approved is maraviroc.

Getting the tests in the UK

Many hospitals routinely use all these tests when they are recommended in UK treatment guidelines, but you may have to be persistent to get them.

All these tests are important in different situations. Ask your doctor, write to your clinic and don't accept no for an answer.

Sometimes, if you don't ask, you won't get. Patient demand can have an effect.

Write to your consultant, clinic and laboratory heads, Primary Care Trust (PCT) executives and your MP if you are not receiving the care recommended in the BHIVA guidelines.

If it really is not going to happen, then make sure the hospital at least stores a sample of blood for analysis later. This is particularly important for resistance tests.

Have blood taken while you are still taking your failing combination and keep a note of the date.

The i-Base phoneline may be able to help advocate in these situations.

Why a combination can fail

Think about why your current combination failed. Find out whether this related to resistance, problems with adherence, drug absorption, or a combination of these reasons. This also applies if your first combination never reduced your viral load to undetectable.

If adherence was the cause, you will need support to make sure this doesn't happen on the new combination.

Any choice to change treatment should be informed by the reason your current treatment failed. This is usually due to one or more of the six reasons below.

You need to find a way of not repeating the same patterns in your next combination.

Reasons a combination can fail		What to do about it
1) You did not have enough information or support to understand how to use treatment.	Treatments can fail because the DRUGS are not good enough, but they are the best we have. Treatment can fail because good adherence or resistance was not explained properly. Or because you were not able to understand the importance of each dose.	ASK questions about your treatment until you are happy with the answers. TALK to your doctor, health advisors and your friends. READ community leaflets and websites. Take control of your own health. ASK FOR HELP if you need it.
2) The previous combination was not potent enough.	HIV treatment is complicated. You may have been using less than three active drugs, or three weaker drugs.	Use the most potent combination possible. Find out all the choices you have and which might be the most likely to work.
3) You were taking your drugs on time but they were not absorbed by your body properly.	Different people can take the same dose of a drug and get different amounts of the drug absorbed by their body. Dosing can be weight related – if you are above or below average you may need to adjust the dose.	Ask for TDM (Therapeutic Drug Monitoring) – an inexpensive test that measures how much drug is absorbed in your blood. TDM can be provided for all UK clinics. Individual differences can be significant. These tests are for PIs, NNRTIs and T-20.

Reasons a combination can fail		What to do about it
4) You were already resistant to some of the drugs before you started.	If you added new drugs to others you were already using, this would increase the risk of resistance. Also, if you were infected with a strain of the virus that was already resistant, for example, to efavirenz. If you then used efavirenz, it wouldn't have been working for you and you would be using only 1 or 2 active drugs.	Get a RESISTANCE TEST to find out which drugs you can still use now. Change as many drugs in your next combination as possible. Avoid drugs that have cross-resistance to drugs in your last combination.
5) You were not taking every dose at the right time.	Adherence is critical and perfect adherence is as good as a new drug. If you missed or were late with your meds, this could explain why your treatment failed. You also need to follow the diet and food requirements. Ask for support to help you tackle adherence differently this time.	Ask what ADHERENCE SUPPORT is available at your clinic. Talk to your doctor, nurse or other healthcare worker trained to help adherence. Contact i-Base for more information about other support material. No matter how good your combination is on paper, if you can't follow it, or have intolerable side effects, you have to find something you can follow.
6) A drug interaction may have reduced the levels of some or your HIV drugs.	Interactions with other HIV drugs, other medications, some foods and some herbs or supplements can reduce levels of your HIV drugs.	Get a genotypic and/or a phenotypic RESISTANCE TEST to find out which drugs you can still use. Your HIV doctor and pharmacist need to know about any other drugs or supplements you take to check for potential interactions. See: www.hivdruginteractions.org

Choosing your next combination

If you have developed resistance to any drugs, then your options depend on your treatment history.

- Usually you will have to change all your drugs.
- Sometimes you can just change one or two drugs.
- Sometimes you can just add in drugs to intensify a treatment.

There are very specific circumstances for when to use each of these approaches.

How do I choose the strongest combination?

If your current treatment is already your second, third or later combination, and you decide to change treatment, then choose the strongest combination you can for the next treatment.

Use as many new drugs as possible that are not cross-resistant to previous drugs.

The most impressive results from recent trails have been where people have used at least two and ideally three new sensitive drugs. See Figures 9 and 10.

Ask for results from trials of people in your situation. Although all drugs have been tested both on their own and in different combinations, there will not always be studies that match your exact treatment history.

Check whether drug interactions are likely in more unusual combinations.

One measure of the potency is how far a drug causes viral load to fall. This is usually measured in 'logs'. A log 10 is a multiple of x10. See Table 1.

Table 1: Log scales (a log 10 scale is a multiple of a factor of 10).

1 log = 10	1.5 log = 30	1.7 log = 50
2 log = 100	2.5 log = 300	2.7 log = 500
3 log = 1,000	3.5 log = 3,000	3.7 log = 5,000
4 log = 10,000	4.5 log = 30,000	4.7 log = 50,000

A drop from 50,000 down to 50 is a drop of three logs. The greater the log drop, the more potent the combination.

Another way of looking at results is to ask about the percentage of people taking the drug whose viral load went below 50 copies/mL. The closer this is to 100% the more potent the drug and the more likely it will work.

You cannot compare results from different studies without considering the health of people in the study. If everyone started with a very low viral load or a high CD4 count then it would be easier to show good results.

Look at how long the trial lasted and how long people were followed. If the results continued for over a year it will give you more confidence.

Impressive short-term results may just mean it is a combination that is easy to tolerate or adhere to. But is could also mean that good drugs were not supported by other active drugs.

Monitor your new treatment carefully. Aim for a viral load test 2–4 weeks after a treatment change. Then have regular viral load tests every 1–2 months.

If you have problems with adherence or side effects, discuss these with your doctor.

Using a new drug in a combination without other active drugs will not be strong enough to get viral load to less than 50 copies/mL. It may reduce viral load by 1-2 logs each time, but the benefit will only be short term and viral load will rebound with resistant virus.

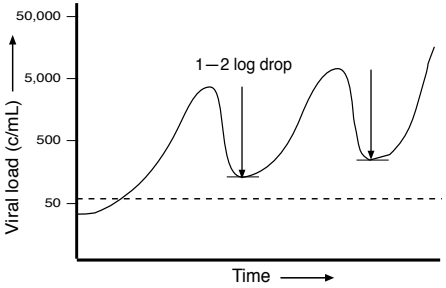
This strategy is only worth considering if your CD4 count is very low (less than 50 cells/mm3) or if you have other serious symptoms.

Waiting until you can use at least 2–3 new drugs together at the same time will make the new combination stronger. It will then perhaps be able to reduce viral load by 3 logs to less than 50 copies/mL.

Even though your viral load may continue rising before you switch, if you wait until you can use at least two or more sensitive drugs, that combination is more likely to get your viral load below 50 copies/mL.

This makes the likelihood of developing resistance much lower. Treatment can then work for much longer – hopefully for years.

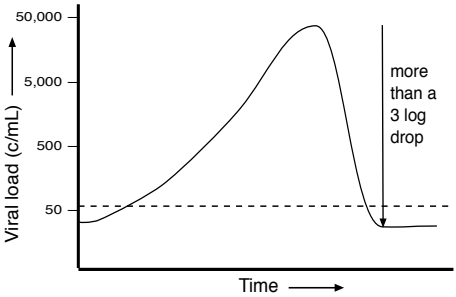
Figure 9. Using only one active drug will only work for a short time



Using only one active drug will only reduce each viral load drops by 1—2 logs, and not to less than 50 copies/mL.

If a new drug is not supprted by other active drugs, resistance will develop.

Figure 10. Waiting to use three new drugs is more likely to get viral load undetectable



Waiting until you can use two or three new drugs together will make the new combination stronger.

Viral load can now drop by over 3 logs.

If viral load gets to below 50 it is likely to stay there without rebounding or developing further resistance.

Which combination to change to

The combination you choose will depend on your drug history and test results.

It will depend on the results of the tests listed on pages 13—16 and the reason that previous combinations failed (see pages 17—18).

After first treatment failure

The recommendation for someone whose first 3-drug combination has failed is to switch to three or more new drugs.

If your first combination included an NNRTI then your second combination will include a boosted protease inhibitor and vice versa. This is even if a resistance test doesn't show NNRTI or PI resistance to the first combinations.

The current recommendation is also to change to two new nukes.

If your first combination was boosted PI monotherapy, then the recommendation is to add two nukes.

After multiple treatment failure

If you are changing to a third, fourth or later combination then the choices become more complicated.

Resistance tests will help identify whether meds are likely to work even in classes to which you have some resistance.

Cross-resistance is common for every type of HIV drug. All PIs have some cross-resistance to other PIs. The same is true for NNRTIs, nukes and integrase inhibitors.

Cross-resistance is complicated. Your care needs to be managed by an expert in drug resistance.

How to choose new drugs

Several general points increase the chance of your next treatment working.

- If you can use drugs from a new class.
- If you can use drugs from classes you have used before but not developed resistance to (i.e. switch while your viral load is still low).
- If you use more, rather than fewer drugs, you may get added benefit from all of them together.

Trial results, even for new drugs, are the best place to find information to predict how well a new drug will work for you. These results should also include information about drug resistance mutations.

Using up options

'Using up options' is often given as a reason for not using the strongest combination when you change. However, this means that the regimen used is not as potent as it could be. There are few reasons to save just one drug on its own if you really need a treatment now. Although you may be using your last unused drug, it may provide the extra power you need.

An exception to this would be if you know another new drug will definitely be available in the near future. In this situation, it may be better to wait for the new drug before changing treatment.

This is especially true if your viral load is stable (at any level). Starting all new drugs together will be stronger than starting them in a staggered way.

Other treatment strategies

The best results will always come by using a new combination that includes three new sensitive drugs.

When this is **not** possible, there are several other approaches. You may need to use more than one of these approaches in multi-drug resistant therapy.

Intensify treatment

There is an exception to the general rule of always changing as many drugs as possible. This is when, under some circumstances, you can add in a single new drug to your existing combination.

This can include:

- Adding a drug you have never used.
- Adding a drug you have already used but which may still work.
- Adding a drug you used before but did not get resistance too (for example, AZT during pregnancy).

You should only aim to intensify by adding a completely new drug **while your viral load is still falling or if it has stabilised**.

If you intensify after your viral load has started to rebound or when it is higher than 500 copies/mL, you may be adding monotherapy to a failing combination. You then run the risk of developing resistance to the new drug.

You can also intensify by **boosting** current drugs. Here you increase the potency of the combination by increasing the levels of some drugs.

- Add a drug that boosts the levels of one of your current drugs
- Increase the dose of a drug if drug level monitoring tests (see pages 15—16) have shown that you are not absorbing adequate concentrations at the regular dose.

Intensification by **boosting** drugs can be done even if your viral load has started to go up. If it is done early, this may get you below detection again without developing new resistance to your current drugs.

Using T-20

T-20 is also called enfuvirtide or Fuzeon. It is an entry inhibitor that will work against HIV that is resistant to other drug classes.

T-20 has to be used in combination with other active drugs if it is to provide long-term benefit. Do not use T-20 if it is the only active drug in your combination.

T-20 is given by subcutaneous injection twice a day, and training is provided so you can do this yourself at home.

If you have resistance to all available drugs, and your CD4 count is stable, almost at any level above 50 cells/mm^3, it is be better to save T-20 until you can use it with these or other new drugs.

If your CD4 count is less that 50 cells/mm^3 then T-20 can boost your CD4 count in the short term, even though resistance can easily develop if viral load stays detectable.

T-20 is an important option. As well as reducing viral load it can protect you from developing resistance to the other drugs in your combination.

T-20 may be a drug that you only need to use for a limited period until a new drug becomes available.

However inconvenient or difficult a 'salvage' regimen is, it is not forever. It is a means to get through a very risky period, in order to access better treatments when they become available.

Using five or more drugs

If you do not have enough new drugs left to make a new combination, and have resistance to drugs from all the current drug classes including integrase inhibitors and other new drugs, you could use more than four drugs in your next combination.

Using as many drugs as possible that may still contribute to reducing your viral load has produced very good results. These combinations often include 2–3 protease inhibitors.

Unfortunately though, the Optima trial that looked at this approach, did not find a benefit from increasing the number of drugs.

What you are trying to do is:

- Use ANY drug that may work.
- Not RELY on a drug that may not work.

The weaker a combination is, the less likely it will work long term. Multi-drug resistant therapy is really a way to buy time until new drugs are developed.

The studies using five or more drugs that reported the best results also used TDM to ensure the most effective individual doses of protease inhibitors and NNRTIs.

Treatment interruptions

Unless there are medical reasons to stop treatment, the risks from a treatment interruption outweigh the benefits.

Disadvantages include:

- Viral load will rebound, sometimes to high levels after only a few weeks.
- CD4 count will drop. This may be more serious if your CD4 count is already low. It may also be a more serious risk if it has ever been very low in the past.
- The CD4 drop can also be difficult to regain and this can affect your long-term health.

If you want to take a treatment break, a simple maintenance regimen may be better than stopping all drugs. If you already have resistance to 3TC or FTC, than continuing to take either drug on its own, or perhaps with a boosted PI, will keep your viral load reduced while waiting for the next regimen.

Doctors can recommend a treatment interruption to manage serious side effects. Specialist advice on how to stop treatment is important as different HIV drugs leave the body at different rates. Stopping all drugs in some combinations at the same time can cause resistance.

If you stop, then check your CD4 count at least monthly. Use the change in your CD4 count to decide when you have to restart therapy. This may mean restarting treatment after only a few weeks – or you may be able to stay off for many months.

Drug boosting and recycling

Even if you have used all of the available drugs, you could still put together a combination using drugs you have used previously. Sometimes you may not have developed complete resistance to all the drugs used in a previously failing combination.

Resistance to some drugs can sometimes be overcome by increasing drug levels.

This has been done for many years by using ritonavir to boost the levels of other protease inhibitors in the blood. Response to treatment is often higher with these boosted doses.

Some protease inhibitors may also boost the levels of other PIs inside cells, which is the most important concentration. For example, when atazanavir and saquinavir are both boosted by a small dose of ritonavir in the same combinations, the levels of saquinavir inside cells stays higher for longer.

Research on dual-boosted PI combinations has not shown benefits over single boosted PI combinations.

Some nukes may be able to be recycled.

Even when only a couple of drugs are new in a six- or seven-drug combination, they may work. If you have used up other options then it is worth trying regimens that include drug recycling.

Drugs in development

Find out which new treatments are likely to become available over the next year, especially through expanded access programmes.

Don't rush to take one if it is the only drug you aren't resistant to, and if you are otherwise in good health.

New drugs are being developed in existing and new drug classes, but most are only in early stages of development.

This includes new nukes, NNRTIs, PIs, CCR5 inhibitors and integrase inhibitors.

Maturation inhibitors are another potential new class. They should interfere with one of the last processes in the HIV life cycle and result in non-infectious virus being produced. These compounds are not available yet.

Keep up-to-date on research on new drugs and treatment strategies.

The i-Base website includes update on new drugs and new research.

i-Base jointly publishes a pipeline report on new research into HIV, hepatitis and TB drugs.

Using viral fitness

Some researchers think that viral fitness can be used to control HIV.

The mutations that make HIV resistant drugs also make HIV less able to reproduce. Resistant HIV is often a weaker strain.

For example, continuing to use 3TC or FTC with the M184V mutation may keep viral load lower because this mutation makes HIV less fit. 3TC or FTC could therefore be used in any treatment-experienced combination. Additional mutations do not appear to develop in this case.

Another strategy for using reduced fitness could be to cycle different combinations. This is a theoretical strategy for someone who has already developed resistance to all available treatments.

The effect of each drug or combination would be to keep changing the type of resistance. Early resistance is usually related to reduced viral fitness for at least the first 4—8 weeks.

Reduced fitness is usually overcome by new mutations, so you want to change before this occurs. Cycles could be weekly or monthly.

This could be a new and important approach for people with no other options. It could also use fewer drugs in each combination.

An Italian study reported this strategy in a group of 34 highly treatment-experienced patients.

Combination therapy was changed based on results from genotype resistance whenever viral load rebounded above 10,000 copies (indicating that a more fit virus had developed). Only 3–4 drugs were included in each combination and this strategy was maintained for over 2 years. In this study each combination lasted an average of 6 months.

This study stressed the importance of aiming for undetectable viral load, but when this is not possible, it showed a new 'holding' strategy until new drugs are available.

Benefit of staying on treatment using drugs that are still active

Even if you have a detectable viral load and are waiting for new treatments, staying on treatment with nukes and a protease inhibitor is safer than stopping all your drugs.

This is especially true if your CD4 count is less than 200 cells/mm^3.

It is definitely better to continue to use treatment compared to just stopping treatment altogether.

These combinations should include nukes plus one or two protease inhibitors even if you have resistance to current drugs.

Continuing treatment is especially important if you have a CD4 count less than 200 cells/mm^3.

If you have a high viral load, then there may not be any benefit from continuing to use NNRTIs, T-20 or integrase inhibitors. If a resistance test shows that you have the key mutations associated with resistance to these drugs, then they are unlikely to be contributing any activity against HIV.

However, if you do not have other treatments to choose, especially if you have a low CD4 count, then as long as you are able to tolerate treatment, nukes and PIs are likely to still provide some benefit.

This strategy prioritises keeping your CD4 count at a safe level over the risk of developing resistance. If the next new drug you are waiting to use is a PI, then some researchers suggest cutting back to a nuke-only 'holding' regimen. This will reduce the risks of developing further cross-resistance to the new PI.

If the next drug you are waiting for is a nuke, it may be better to use boosted-PIs in the holding regimen.

This benefit may continue for several years while new drugs are developed but it will not continue forever. Closer monitoring should be carried out if you are in this situation.

Changing treatment to avoid side effects

Most of this booklet is to help you if you want to change treatment because your current combination has stopped working.

However, you may want to change treatment to avoid side effects or to have a regime that is easier to follow.

Changing a combination to one that is more tolerable is more common than changing because of drug failure. Your combination has to be one you can tolerate.

With over 25 drugs available, there is a great deal of choice. Newer drugs may also have become available since you last changed treatment.

As long as you use drugs with a similar potency, switching individual drugs can be very safe. If in doubt, use more potent drugs in your new combination.

Changing meds can improve your quality of life, and still keep your viral load undetectable.

Your choices depend on your treatment history. You will need viral load monitoring at least 2-4 weeks after any change.

Examples of reasons to switch

- Switching from a PI to NNRTI may help avoid or reverse fat accumulation or metabolic changes associated with lipodystrophy. Some switches can improve cholesterol and triglycerides, using a combination with fewer pills and diet restrictions.
- Peripheral neuropathy (pain or numbness in your hands or feet) may be related to ddI, d4T or, more rarely, 3TC. Switch these drugs before the nerve damage becomes serious and permanent.
- d4T and AZT can cause facial fat loss and switching them to abacavir or tenofovir is common.
- Efavirenz is linked to mood changes, disturbed sleep patterns and vivid dreams. If you have difficult side effects you can usually switch to another NNRTI or to a boosted PI.
- If you have an undetectable viral load, and are using T-20, switching to darunavir/r or raltegravir is an option for many people.

The i-Base Guide to Side Effects has detailed information on changing treatments to avoid side effects.

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

Expanded access and experimental drugs

You can sometimes use new drugs before they are licensed by using an Expanded Access Programme (EAP) or Named Patient Programme (NPP).

These programmes allow limited access to a promising drug while approval is being processed.

EAP and NPP access is provided for most new drugs, but it is sometimes very difficult to predict when each programme will start. They are provided for people in the greatest need.

These drugs can be the key to your next combination. You will also be monitored very carefully for side-effects and to check they are working.

These programmes are not always available at all hospitals. You may need to register at another clinic to access them. Your doctor should be able to help you do this. Get to know which drugs are in the pipeline and ask your doctor to give you the choice to use them.

The following compounds are being studied as new treatments:

NRTIs: CMX157 (similar to tenofovir).

NNRTIs: rilpivirine, lersivirine, GSK761, RDEA806.

Integrase inhibitors: elvitegravir, GSK572.

CCR5 inhibitors: TBR-652.

Maturation inhibitors: beviramat.

As we went to press, these drugs were not yet available in the UK in EAPs.

Additional new drugs are likely to become available before this booklet is updated.

Other treatments

Several non-HIV drugs may have a role because they have some activity against HIV or for other reasons.

Many of these drugs are approved for other uses and can be prescribed on a named patient basis.

PEG Interferon (Interferon alpha): A once-weekly injectable hepatitis C drug. Anti-HIV activity (and side effects) increases with dose used (as with regular interferon alpha).

Gm-CSF: A drug used to boost your immune system, reduced the risk of new illnesses in people with a CD4 count less than 50 cells/mm3.

foscarnet: CMV drug with anti-HIV activity that may resensitise AZT-resistant virus. Best used for only 2-4 weeks to reduce viral load before starting a new regimen, as probably too toxic for long-term use.

hydroxyurea (HU): A 30-year-old anti-cancer drug that can resensitise HIV to ddI. Now rarely used or only at a reduced dose of 300 mg once-daily.

mycophenolic acid: May boost abacavir levels in a similar way to hydroxyurea and ddI. Limited studies showed a benefit using 500mg twice-daily.

L-acetyl carnitine: An amino acid that has no anti-HIV effect but may minimise or reverse peripheral neuropathy associated with (nuke) drugs.

Adherence diary

Use the table below to mark when you take each drug in the first few weeks of your combination. This will help you know if you have just taken a dose - or if you are late or miss a dose.

Getting everything right will help protect your new combination.

Week begining: _____

	Drug names + times (morning)	Drug names + times (evening)
Monday		
Tuesday		
Wednesday		
Thursday		
Friday		
Saturday		
Sunday		

CD4 and viral load results

These blood tests monitor your health and your response to treatment.

CD4 count - This test checks your immune system.

CD4% - This is similar to the CD4 count but is often more stable.

Viral load - This test measures the amount of HIV in a sample of blood. It is used to decide when you need to start treatment, and whether the treatment is working effectively.

Even rough figures are useful from your previous history and your doctor can provide you with these.

The lowest CD4 count and highest viral load results when you were first diagnosed and before you started treatment are the most important.

Date (month/year)	CD4 (cells/mm3)	CD4%	viral load
e.g july 08	*234*	*14*	*180,000*

Date (month/year)	CD4 (cells/mm3)	CD4%	viral load

ARV treatment history

Your choice of new and future drugs will depend on:

- the drugs you used in the past, and
- the reason you stopped using them.

It is important to know whether this was because of resistance or side effects.

If you can't remember exact details, even rough dates are useful (ie taking ddI for 6 months in 1998 etc).

e.g AZT 300 mg	*Feb 04*	*Jan 06*	*Fat loss from the face*

Resistance test results

Date	Results (continue on separate pages if needed)

Further information

If you have questions after reading this guide or would like to talk to someone about treatment contact the i-Base information service by phone or email.

0808 800 6013

questions@i-Base.org.uk

Full prescribing information on individual HIV drugs and other scientific documents are available in most European languages from the EMA:

www.ema.europa.eu

The following community sites include information on new drugs, and include updated reports from HIV conferences.

www.i-Base.info

www.aidsinfonet.org

www.aidsmeds.com

www.natap.org

www.aidsmap.com

www.tpan.com

Feedback

Your feedback on this guide helps us develop new resources and improve this resource. All comments are really appreciated. Comments can be posted free to:

FREEPOST RSJY-BALK-HGYT, i-Base, 57 Great Suffolk Street, London SE1 0BB.

Or made directly online at: www.surveymonkey.com/s/MK9R928

1. How easy was the information in this guide to understand?

☐ Too easy ☐ Easy ☐ Difficult ☐ Too difficult

2. How much of the information did you already know?

☐ None ☐ A little ☐ Most ☐ All

3. Did the information help you feel more confident when speaking to your doctor?

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

4. Which information did you find most useful?

5. Do you still have questions after reading this guide? Please give examples.

Please include a contact email address if you would like us to reply.

6. Any other comments?

Contact details (if you would like a reply): Name _____

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Glossary

amino acids - chemical building blocks that make up the genetic structure of living organisms.

ARV: Anti-retroviral - any HIV drug.

CCR5 inhibitor: an HIV drug that blocks HIV from attaching to a CD4 cell (eg 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: programmes that allow early access to drugs before they are approved for people who need them urgently (also called 'early access' or 'named-patient').

fold-change: a term relating to drug or resistance after a phenoype test. 4-fold resistance (also called a 4-fold loss in sentivity) means you need to use four times the dose to get the same reduction in viral load.

fusion inhibitor: an HIV drug that stops the virus attaching to a CD4 cell (eg T-20).

genome: term for the genetic material (RNA or DNA) of any organism.

genotype: relating to the genetic structure of an organism.

HAART: a term for combination therapy (Highly-Active Anti-Retroviral Therapy), usually 3 or 4 ARVs.

integrase inhibitor: an HIV drug that stops HIV from integrating with the DNA in a cell (eg raltegravir, elvitegravir).

log: one log usually relates to a factor of 10. An increase by one log is x10 and by two logs is x100 etc. A reduction by 90% is one log and two logs = 99% etc.

mega-HAART: a term for drug combinations that use five or more HIV drugs, usually including 2–3 protease inhibitors. Rarely used.

mutation: a change in the structure of the virus that can stop a drug from working.

NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor, a type of HIV drug (eg nevirapine, efavirenz and etravirine).

NRTI or '**nuke**': Nucleoside Reverse Transcriptase Inhibitors (also called nucleoside analogues) are a family of drugs that includes AZT, d4T, 3TC, FTC, ddI and abacavir. Tenofovir is a nucleo*tide* RTI and works in a similar way.

phenotype: relating to how an organism behaves, based on how its genotype relates to its environment.

PI: Protease Inhibitors are a family of drugs that includes indinavir, nelfinavir, ritonavir, saquinavir, fosamprenavir, atazanavir, lopinavir, tipranavir and darunavir.

salvage therapy: a term for combination therapy once someone has resistance to three or more classes of HIV drugs. Also called 'third-line' or 'rescue therapy' or 'treatment of patients with multidrug resistance'.

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

treatment-experienced: someone who has previously used anti-HIV treatments.

treatment-naive: someone who has never taken any anti-HIV treatments before. *[note: people who are treatment naive can still be resistant to anti-HIV drugs if they were infected with a drug resistant strain of HIV]*

viral tropism: the type of receptors 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 (ie 50 copies/mL). Results below this cut-off are called 'undetectable'.

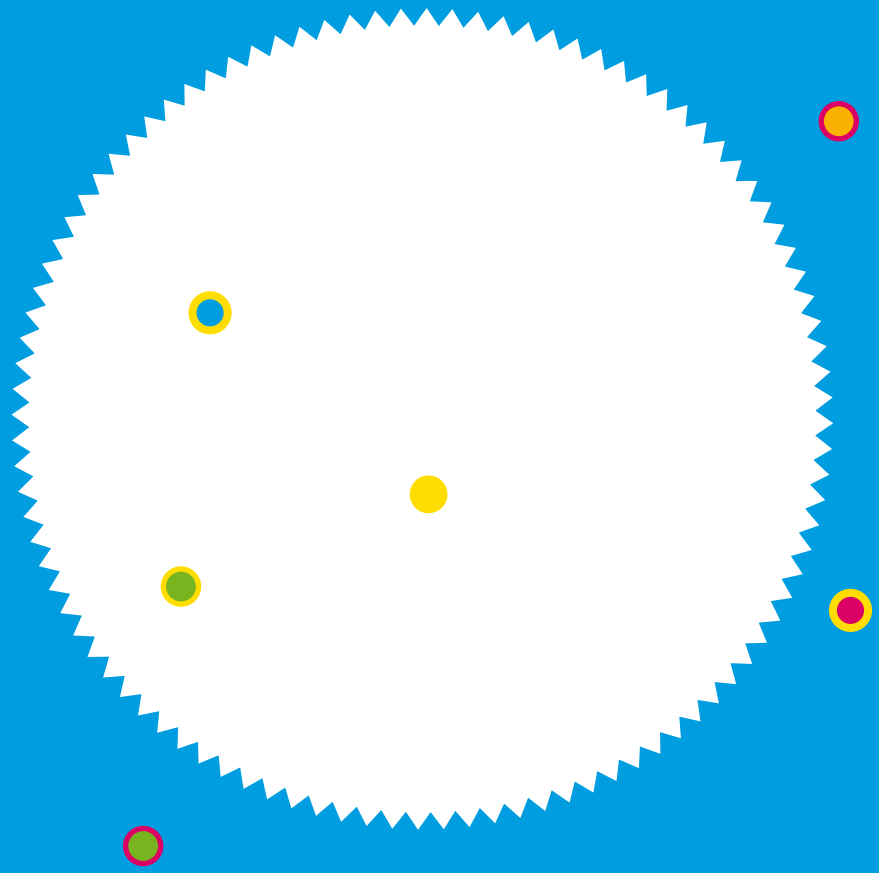
viral rebound: when current treatment fails and viral load starts to rise again.

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

Call us on
0808 800 6013

i-Base Treatment Information Phoneline

Monday to Wednesday
12 noon to 4pm



i-Base can also answer your questions by email or online

questions@i-Base.org.uk
www.i-Base.info/questions