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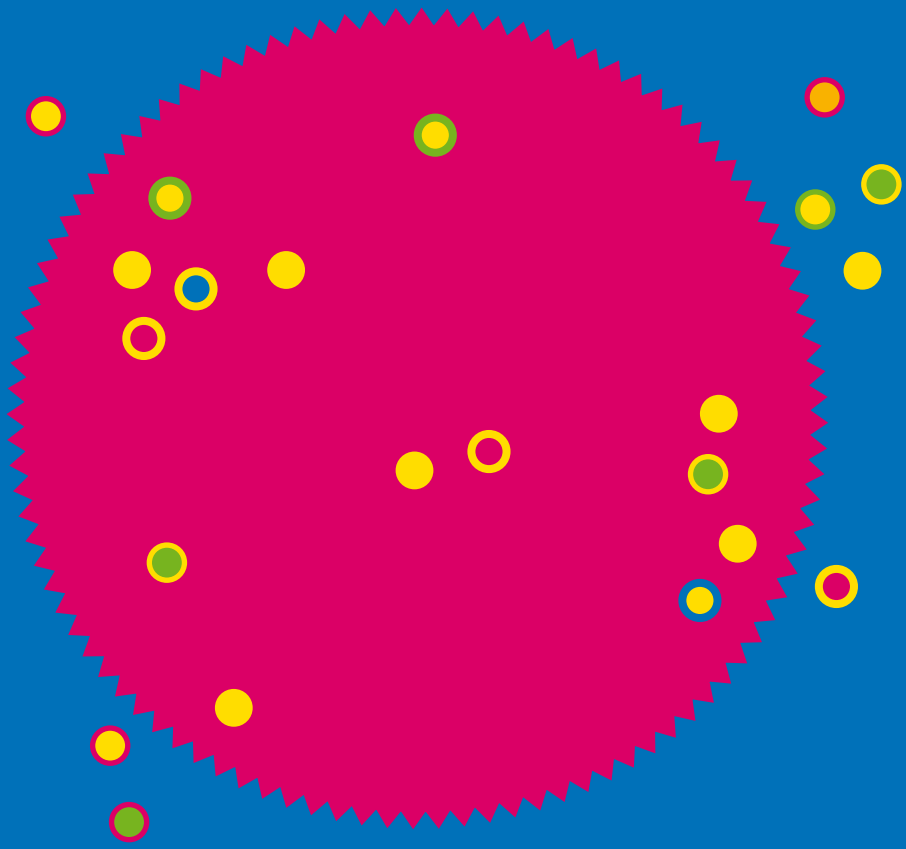
Changing treatment & drug resistance

February 2013

updated!



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Watch for out-of-date information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

Written and edited 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.

This booklet about changing HIV treatment and drug resistance explains:

- When and why treatment needs to be changed.
- Which tests are used and what the results mean.
- How to choose drugs for the next combination.
- How to help make sure the next treatment will work well.

It also includes information about new drugs in development and other research.

Summary

Although everyone's treatment situation is different, these are the most important key points. Each point is discussed in more detail later in the booklet.

Drug resistance is a specialised area of HIV care.

1. If your viral load is detectable on treatment, don't panic, but take this seriously.
2. If your viral load was previously undetectable, repeat the test on the same day you get the results. Sometimes tests are wrong. Collect the new test results as soon as they are available (within 2 weeks).
3. If your viral load is confirmed and it continues to rise, the earlier you change treatment (if you have this option), the less resistance will develop.
4. Talk to your doctor about why your current combination failed. Was this related to resistance, adherence, drug absorption, or a combination of reasons.

   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. When choosing the next combination, use drugs that are most likely to work. This should involve an expert reviewing results from a drug resistance test.
7. Monitor your new treatment with a viral load test after 2–4 weeks, and then every month until it is undetectable. Tell your doctor if you have problems with adherence or side effects.
8. Keep up-to-date on research. Find out which new meds are likely to become available, including early 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 - especially if your CD4 count is under 200.

Introduction

Most people starting treatment in the UK in 2013 will get an undetectable viral load on their first treatment.

But there are several reasons to change treatment.

- About 10% of people change because their viral load does not become undetectable. This is usually because of problems with adherence, poor drug absorption or prior drug resistance.
- In addition, some people who have been using treatment for many years, may already have drug resistance to more than one earlier combination.

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

  Most people with multidrug resistance are also doing very well. This is because of newer drugs developed in the last few years.
- A few people have resistance to all drugs, including these latest meds. People in this situation 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.

Finally, we include information about changing treatment because of side effects. For most people this can be an easy option - and can lead to an improved quality of life.

Changes to this edition

The main changes to the 13th edition of this guide are:

- Editing changes that simplify the text and pictures to improve readability.
- Printing the text in a larger font size
- Updated information on new drugs and drugs in development.

Changing treatment and drug resistance

Reasons to change treatment

The main reasons to change treatment 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 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.

Treatment when there is extensive drug resistance is sometimes called salvage therapy, 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.

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

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

How quickly a combination is changed depends on your individual response.If viral load is still detectable after six months, most people would change treatment.

How can drugs "fail" when I feel fine?

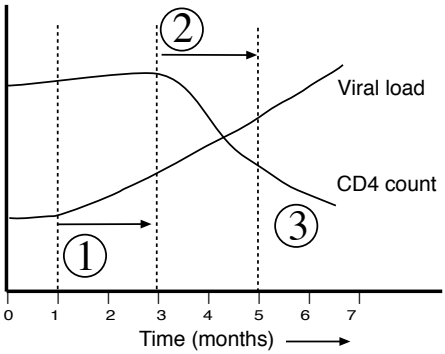
When the word "fail" is used to describe an increase in your viral load, this is called "**virological failure".**

It relates to results from a blood tests but not how well you feel.

The term "**clinical failure"** is used to describe any new or progressing illnesses. This is when you feel unwell.

Viral load rises first (virological failure). If you stay on a failing treatment, your CD4 count will start to drop, which then puts you at greater risk of becoming ill (clinical failure) - see Figure 1.

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



1. If your viral load rebounds and you continue on treatment, more resistance develops and viral load continues to rise.
2. It may take several months before your CD4 count starts to fall.
3. If your CD4 count is high It will take even longer before clinical symptoms develop. By this time the resistance will be more difficult to treat.

Resistance and adherence

What is HIV drug resistance?

Drug resistance can explain why a drug 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 drug resistance increases when drug levels are low. This happens if you do not take all your treatment at the correct time. See Figure 2.

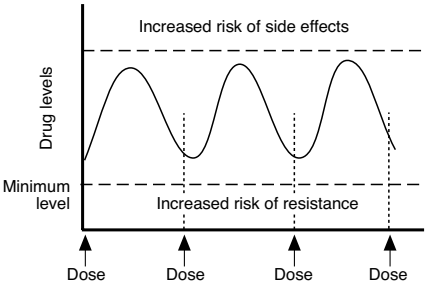
How do missed doses lead to resistance?

If you miss doses or are late taking your meds, this increases the chance of resistance. See Figure 3.

This is because when you are late, drug levels can fall below the minimum level needed to control the virus. The mutations that develop when you have only low levels of meds can stop the drugs working. Then, when you restart treatment, they may not work as well.

Adherence is even more critical when you are on your second, third or later combination as you have fewer drugs left to use.

Figure 2: Drug levels with good adherence

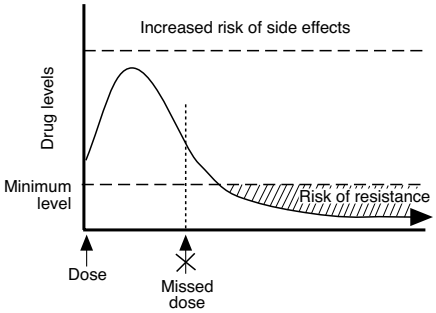


Drug doses are calculated on average levels over the whole dose period.

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 your meds lets the drug levels fall below the minimum level needed. Drug resistance can then develop.

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

Do some drugs develop resistance more easily?

Some drugs only need one mutation for the virus to be completely resistant. This is the case with NNRTIs and some nukes like 3TC and FTC. See Figure 4.

These drugs are more vulnerable if used in a combination that doesn't keep your viral load below 50 c/mL.

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

Other drugs, including protease inhibitors, develop resistance more gradually. The first mutations do not make much impact but as more complex resistance develops the drugs eventually stop working. See Figure 5. These drugs take longer to develop cross-resistance to other drugs in the same family.

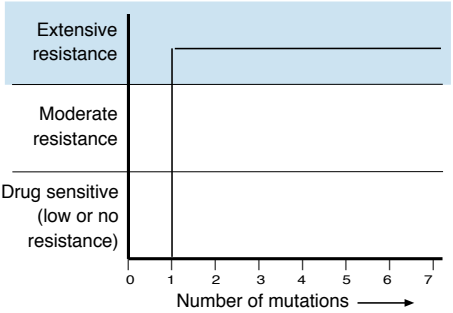
Some nukes need only one mutation and some develop more complicated patterns of resistance.

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

The online i-Base *HIV and Drug Resistance Course* explains drug resistance in greater detail.

www.i-Base.info/ hiv-and-drug-resistance/

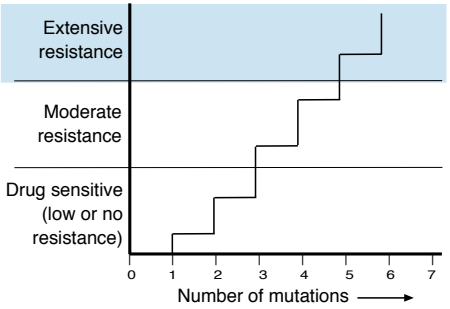
Figure 4. How one mutation can stop some drugs working



Some drugs stop working after only one mutation.

These include NNRTIs (nevirapine, efavirenz, rilpivirine and etravirine), integrase inhibitors (raltegravir) and 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 is detectable on treatment, don't panic, but take this seriously.

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

Find out the new test results 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.

But half the time a low rebound may be a fault of the test. In many other cases it may be a random 'blip' and treatment is still active.

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, this is more likely to be a real viral load rebound. In this case, guidelines recommend changing treatment.

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

Viral load blips

Viral load 'blips' are common. A blip is when viral load becomes detectable but then drops back down with the next test result. See Figure 6.

Most blips are never detected because viral load is only tested a few times each year.

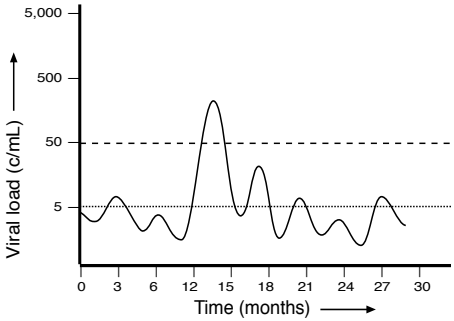
Blips are usually defined as an increase from less than 50 to up to 1000, but they are usually under 500. Blips can be caused by other infections, such as flu or herpes, or a recent vaccination.

Also, viral load tests are not very accurate at low levels.

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

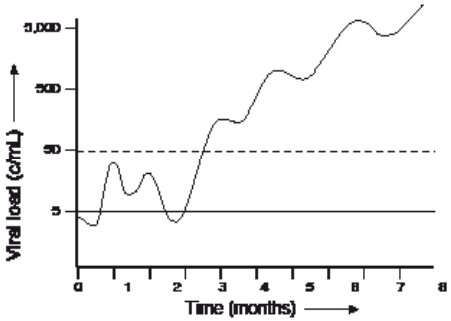


An undetectable viral load (less than 50) is often less than 5 copies/mL.

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 much difference between these tests.

Several studies have reported that for many people with an undetectable viral load (more than half) are less than 5 copies/mL

Viral load tests have "a three-fold margin of error". So a result of 900 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 essential to confirm an unexpected result.

When should I change?

If your viral load is confirmed and continues to rise, the earlier you change treatment (if you have this option), the less resistance will develop.

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

The longer you wait to confirm the results, the greater the chance that resistance will develop.

If viral load rebound is confirmed then your choice of new drugs depends on:

- The drugs that you have already used and whether you developed resistance to them.
- Your current CD4 count and lowest ever CD4 count (called CD4 nadir).
- Your general health.

Some people change treatment if their viral load stays consistently detectable above 50 c/mL.

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

Then, changing treatment should ideally be to use three new drugs that will be active.

At low levels–between 50 and 500–you can sometimes intensify treatment, though this is generally not recommended. See page 22. In people using boosted PI monotherapy (ie whose combination only includes boosted darunavir) the first recommendation is to intensify by adding two nukes.

In practice, many people have to start their next combination with much higher levels of viral load.

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 more 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 include more new drugs and will be 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 when changing treatment.

- Viral load
- Drug resistance, IQ and VIQ
- Therapeutic Drug Monitoring (TDM)
- Viral tropism

Viral load tests

Viral load is the most sensitive test to check whether a combination is still working. See pages 10-12.

Testing 2-4 weeks after any change in treatment will show whether the new drugs are working, repeating monthly until undetectable.

Once undetectable, monitor every 3-6 months, based on the CD4 count.

Resistance tests

UK guidelines recommend a resistance test before changing treatment. This is because you need to have blood taken while you are still on the failing combination.

There are two main types of drug resistance 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.

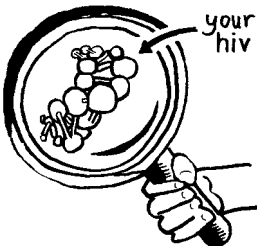
Although this test does not register very low levels of resistance, it can still be vital as a guide to choosing drugs for your next combination.

Results should take about a week.

Figure 8. Types of resistance tests

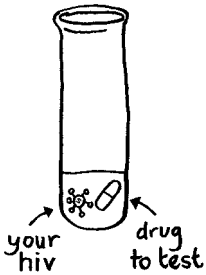
1. Genotype

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 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 increasing concentrations of a drug to a test tube that contains your HIV. It shows how sensitive or resistant 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' 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 test results

Resistance tests can be complex to interpret, but also include a summary report on whether each drug is sensitive, intermediate or resistant.

Genotype test 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.

These usually follow the format of a letter followed by a number followed by a letter - i.e. K103N.

The first letter stands for the amino acid that is normally at that junction in the virus - i.e. 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 - i.e. N stands for asparagine.

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

The Stanford Resistance Database includes a chart for every mutation.

http://hivdb.stanford.edu

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

Phenotype results are based on fold-changes in sensitivity. The cut-off values are different for each drug and for each make of 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 also include an interpretation report that summarises which drugs are still sensitive, which are partly resistant and which are completely resistant.

TDM (Therapeutic Drug Monitoring)

TDM measures the levels of a drug in your blood. TDM can be used for protease inhibitors, NNRTIs, T-20, maraviroc and raltegravir.

TDM is only used in certain situations to individualise dosing, including:

- When using combinations where they may be a drug interaction. This is important with new drugs.
- With pre-existing liver or kidney damage, or haemophilia, and some other medical conditions. For example, drug levels of both amprenavir and abacavir can be too high if your liver is damaged. TDM can find the safest dose.
- If you may not be absorbing drugs properly. For example, if you have severe diarrhoea.
- 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.

TDM is recommended in UK guidelines in these and other situations. Poor drug absorption or faster clearance can cause a combination to fail.

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

TDM costs around £70 per drug from Lab21:

http://www.lab21.com/ClinicalLab

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 report on how well your virus reproduces (called “viral fitness”).

IQ and VIQ tests are being integrated with TDM and resistance tests to further individual results.

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 maraviroc, which is an HIV drug called a CCR5 inhibitor.

In the UK and Europe, tropism is tested using a genotype resistance test. A special type of resistance test (testing proviral DNA) can be used if your viral load is low or undetectable.

There are UK guidelines for the use of these tests.

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.

Each test is important in different situations.

If your doctor says they are not available, 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 be effective.

You can write to your consultant, clinic and laboratory heads, Trust or hospital executives and even your MP if you are not getting the care recommended in the UK (BHIVA) guidelines.

If you can’t get a test, ask the hospital to store 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

Talk to your doctor about why your current combination failed. Was this related to resistance, adherence, drug absorption, or a combination of reasons.

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

Changing treatment should be informed by 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 if good adherence or the risk of resistance was not explained properly. If adherence was not perfect this could explain why the meds failed.	ASK questions about treatment until you are happy with the answers. TALK to your doctor, health advisors and 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.	You may have been using less than three active drugs.	Use the most potent combination. Find out your choices and which might be most likely to work.
3) You were taking your meds on time but they were not being absorbed properly.	Different people can take the same dose of a drug but absorb different levels. Dosing may be weight related – if you are above or below average you may need to adjust the dose.	Ask for TDM (Therapeutic Drug Monitoring) to measure your drug levels. Individual differences can be significant. These tests are for PIs, NNRTIs, maraviroc, raltegravir and T-20.

Reasons a combination can fail		What to do about it
4) You were already resistant to one or more of the drugs before you started.	Adding new drugs to a failing combination increases the risk of resistance. If you were infected with drug resistant HIV and this was not detected with a resistance test, you would have only been 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. No matter how good your combination is on paper, if doesn't fit your life or you have difficult side effects, ask if there are other options.
6) A drug interaction may have reduced the drug levels your HIV drugs.	Interactions with other HIV drugs, other medications, some foods and some herbs or supplements can reduce levels of your HIV drugs.	Your HIV doctor and pharmacist need to know about all drugs and supplements to check for potential interactions. See: www.hivdruginteractions.org Get a genotypic and/or a phenotypic RESISTANCE TEST to find out which drugs you can still use.

Deciding on your next combination

Anyone with drug resistance needs to consider their treatment history before choosing the next meds.

- 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.

How do I find out about the strongest combination?

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

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

The most impressive results come from using at least two and ideally three new sensitive drugs. See Figures 9 and 10.

Ask for results from studies of people in a similar situation as you, even though matching your exact treatment history may be difficult.

Check whether drug interactions are likely in more unusual combinations.

One measure of 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 to 50 is a reduction of three logs. The greater the drop, the more potent the drug.

Another measure is the percentage of people taking the drug whose viral load went below 50 copies/mL. But look out for how high it was when people started the study. If viral load started low or the CD4 count was high, it is easier to get good results.

Comparing results from different studies is difficult because the health of people in each study may be different. Look at how long the trial lasted and how long people were followed. If it continued for over a year you can have more confidence in the results.

Short-term results may just show a drug is easy to tolerate or adhere to. Results will also reflect how many active drugs were also being used.

Monitor your new treatment with a viral load test after 2–4 weeks, and then every month until it is undetectable.

Tell your doctor if you have problems with adherence or side effects.

How to choose new drugs?

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).

Three factors increase the chance of your next treatment working.

1) Using drugs from a new class.
2) Using drugs from classes you have used but did not develop resistance to (i.e. switch when your viral load is still low.
3) Using more, rather than fewer drugs, may have an added benefit.

When looking at trial results for new drugs check the information about drug resistance.

After first treatment failure

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

For example, if your first combo used an NNRTI, change to 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.

It is also recommended 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 or later combo, the choice is more complex.

Resistance tests will help pick meds that may work, even in classes to which you have some resistance.

Cross-resistance is common for every type of HIV drug. All PIs NNRTIs, nukes and integrase inhibitor have some cross-resistance to other meds in the same class.

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

Using up options

'Using up options' is often given as a reason for not using the strongest combination. However, there are few reasons to save just one drug on its own, if you need treatment now. This may give the extra power you need.

An exception is if you know another new drug will soon be available. 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. (See Figures 9 and 10).

When to use new drugs and when to wait?

Using new drugs without other meds that are active is unlikely to get viral load to less than 50 copies/mL. Viral load may drop by 1-2 logs each time, but the benefit will only be short term and viral load will rebound with resistant virus.

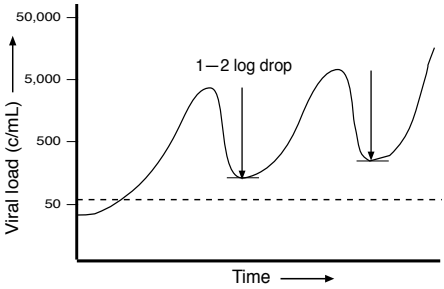
This is only worth considering if your CD4 count is very low (less than 50 cells/mm3) or if you have other serious symptoms.

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, waiting to use at least two or more sensitive drugs, is more likely to get your viral load undetectable.

This is the best chance to get long term benefit from new drugs. See Figure 9 and 10.

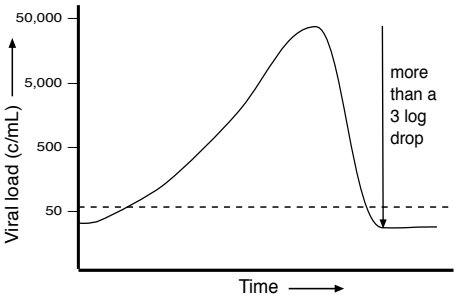
Figure 9. Using only one active drug will only work for a short time



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.

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

Under some circumstances, you may be able to 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, perhaps becasue you did not develop resistance.

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, for example by:

- Adding a drug that boosts one of your current drugs
- Increasing 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.

If it is done early, intensification may reduce viral load below detection again.

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 until a new drug becomes available.

However inconvenient or difficult it is, it could be a lifesaver while waiting for new drugs.

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, a treatment interruption are not recommended.

- Viral load will rebound, sometimes to high levels after only a few weeks.
- Your 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 even after restarting treatment.

If you want to take a treatment break, a simpler combination may be better than stopping all drugs. If you already have resistance to 3TC or FTC, then 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.

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, check your CD4 count at least monthly. Use the change in your CD4 count to decide when to restart therapy.

Drug recycling using viral fitness

Even if you have used every drug, you may not have developed complete resistance to all of them.

More importantly, complete resistance is unlikely to be on every virus. Some of your HIV may be resistant to nukes but different virus may be resistant to PIs. Each resistant virus is also likely to be less fit or active (compared to non-resistant HIV).

Some researchers think that viral fitness can be used to control HIV by cycling different combinations. This is a theoretical strategy for someone with resistance to all classes.

The effect of each drug or combination change 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 working by changing combination whenever viral load reached 10,000 c/mL.

Drugs in development

Keep up-to-date on research.

Find out which new meds are likely to become available, including early access programmes.

Don't rush to use one new drug if it is the only drug that will be active, especially if your health is good.

New drugs are being developed in existing and new drug classes.

Following this reseach can keep you optimistic for new options and can help you plan when to change and when to wait.

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

Every summer, i-Base jointly publishes a pipeline report on the HIV, hepatitis and TB drugs that are most advanced in development.

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.

Even with drug resistance, it is better to continue to use some meds compared to stopping treatment altogether.

This is especially important if your CD4 count is less than 200.

As long as you are able to tolerate treatment, nukes and PIs are likely to still help.

If you have the key mutations associated with resistance to NNRTIs, T-20 or integrase inhibitors, then there may be no benefit from still taking them as they are unlikely to still be active.

If the next new drug you are waiting to use is a PI, cutting back to a nuke-only 'holding' regimen will reduce the risk 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 short-term approach needs more frequent monitoring.

Changing treatment to avoid side effects

This booklet is focussed on changing treatment when your current combination has stopped working.

However, most treatment changes are to reduce side effects or to find a combination that is easier to take.

With over 25 drugs available, there is a lot of choice. Newer drugs or formulations may also have become available that you didn't know about.

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. 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 cause facial fat loss and switching to abacavir or tenofovir is strongly recommended.
- 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 newer drugs like darunavir/r or raltegravir is an option for many people.

See: HIV and your quality of life: a guide to side effects and other complications

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

Expanded access drugs and pipeline drugs

Sometimes new drugs are available before they are licensed. This is in an Expanded Access Programme (EAP) or Named Patient Programme (NPP).

These 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 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, many of which may be active against drug resistance, are included the current online i-Base/TAG pipeline report.

http://www.PipelineReport.org/

NRTIs: GS-7340 (improved version of tenofovir), BMS-986001 (similar to d4T). CMX157 (also similar to tenofovir), EFdA, apricitabine (similar to 3TC).

NNRTIs: MK-1439.

Integrase inhibitors: dolutegravir, S/GSK1265744 (similar to dolutegravir).

CCR5 inhibitors: cenicriviroc

Attachment inhibitors: BMS-663038

Fusion inhibitors: albuvirtide.

Maturation inhibitors: beviramat.

As we went to press, only dolutegravir was currently available in the UK in an EAP.

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

Non ARV drugs

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) increase with the 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: A CMV drug with anti-HIV activity that may resensitise AZT-resistant virus. This has been used annecdotally for short periods (2-4 weeks) to reduce viral load before starting a new regimen. Foscarnet is 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. This is included mainly for historical reasons.

mycophenolic acid: May boost abacavir levels in a similar way to hydroxyurea and ddI. Limited studies showed a benefit using 500 mg 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 2001 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 helps us improve this guide and develop new resources. All comments are appreciated. Comments can be posted free to:

FREEPOST RSJY-BALK-HGYT, i-Base, 57 Great Suffolk St, 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. Will the guide help you be 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 _____

Email _____ @ _____

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Guide to Side Effects and Other Complications ..... ☐

Guide to HIV testing and risk of sexual transmission ..... ☐

Treatment passport (to record your treatment history) ..... ☐

HIV Treatment Bulletin (HTB) ..... ☐

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.....

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Glossary

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

ART: Antiretroviral treatment

ARV: Antiretroviral - an 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 sensitivity) means you need 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.

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 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'.

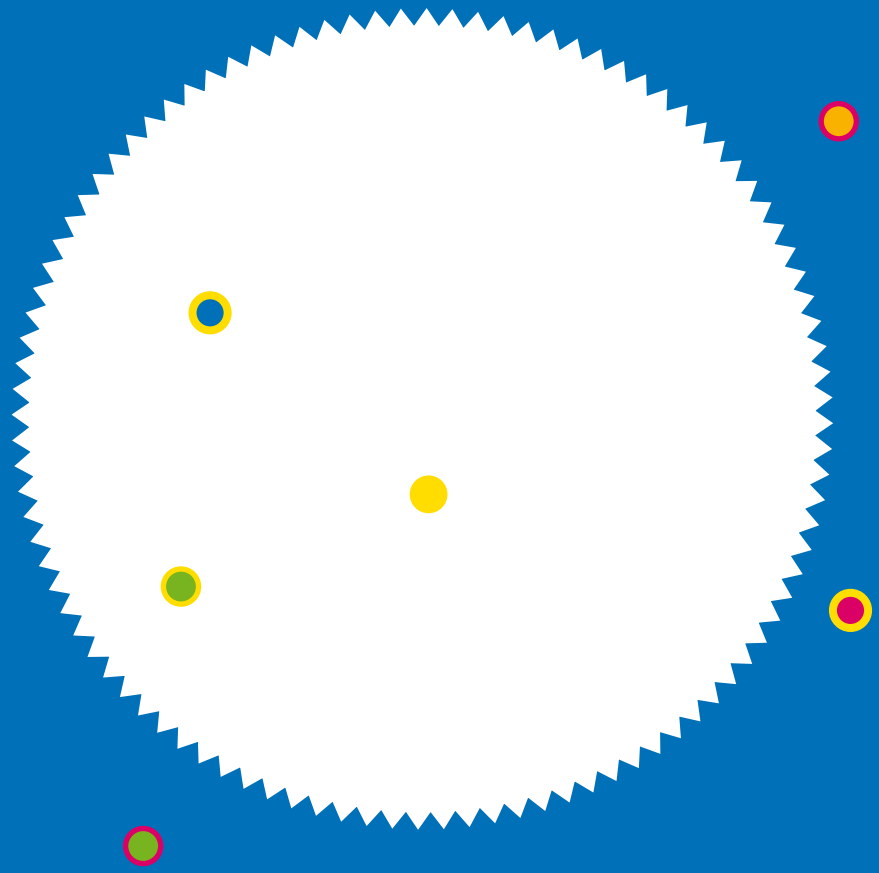
viral rebound: when current treatment fails and viral load starts to rise again.

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