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# Changing treatment and drug resistance

- **What to do if your viral load rebounds**
- **Resistance testing and other tests**
- **Switching for side-effects**
- **Experimental & new drugs**

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## Contents

Summary	3
Introduction	4
Changes to the September 2008 edition	4
Resistance, cross-resistance and adherence	5
What, why, how...	7
What to do about a rising viral load?	9
Why a combination can fail?	13
Important monitoring tests	15
Choices for your next combination	19
Other treatment strategies:	20
Intensify treatment	20
Using T-20	20
Using 5 or more drugs	21
Treatment interruptions	22
Drug boosting and recycling	22
Using drugs in development	23
Using viral fitness	23
Benefits of staying on treatment	24
Changing treatment to avoid side effects	25
Expanded access and experimental drugs	26
Pages to record your treatment history:	
Adherence diary	27
CD4 and viral load results	28
Antiretroviral treatment history	29
Resistance test results	30
Further information	30
Glossary	31

If you have questions after reading this guide, i-Base runs a free treatment information phoneline on all aspects of HIV treatment.

**0808 800 6013**

**Monday, Tuesday and**

**Wednesday**

**12-4.00 pm**



The phoneline service is currently available in English, Luganga, Bulgarian and Russian.

Calls are free from UK landlines and Orange network. If calling from outside the UK, please call +44 20 7407 8488

The website also has a question and answer service where questions can be answered online and by email:

[www.i-base.info/questions](http://www.i-base.info/questions)

and

[questions@i-Base.org.uk](mailto:questions@i-Base.org.uk)

Disclaimer: Decisions relating to your treatment should always be taken in consultation with your doctor. Information in this booklet is intended to support those discussions.

## Summary

Deciding on which HIV drugs will work best after developing drug resistance is complicated. It 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.

1. If your viral load starts to rise after being undetectable, don't panic, but do take it seriously.
2. Have a new test on the same day you get the first test results 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 is continuing to rise, then changing more quickly, if you have other drugs available, will give your next combination the best chance of reducing viral load levels to undetectable again.
4. Think about why your current combination failed. Find out whether this related to prior resistance, adherence, drug absorption, or a combination of these reasons. This also applies to people whose first treatment never reached undetectable levels (for example after 3-6 months). Getting a resistance test is very important and is included in UK guidelines.
5. Get your doctor to consult with other colleagues that are experienced in treating people in a similar situation. If you are being treated at a clinic with relatively few patients, your doctor can e-mail or call experts at larger centres.
6. 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.
7. Monitor your new treatment carefully. Get a viral load test 2–4 weeks after the treatment change. Then have regular viral load tests every 1–2 months. If you have problems with adherence or side effects, make sure you discuss these with your doctor.
8. Keep up-to-date on latest research. Find out which new treatments are likely to become available in the next year, especially through expanded access programmes. Don't rush to use one if it is the only drug you aren't resistant to and if you are otherwise in good health. Always use at least two new drugs in your combination.
9. If your CD4 count is low (less than 100 cells/mm<sup>3</sup>) ask about IL-2 which can boost your immune system.
10. Remember that 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 100 cells/mm<sup>3</sup>.

*“his is a very exciting and hopeful time.  
for people with HIV drug resistance*

## Introduction

This is a very exciting and hopeful time for people with HIV drug resistance.

This is because it is the first time in many years that several new drugs became available at the same time. This includes protease inhibitors (darunavir), integrase inhibitors (raltegravir), CCR5 inhibitors (maraviroc) and NNRTIs (etravirine).

The approach to treatment has therefore changed dramatically.

**The goal of treatment for treatment-experienced patients is now to get viral load reduced to less than 50 copies/mL.**

These new drugs must all be used with other active drugs, probably in new combinations with each other. Using them individually carries a high risk that they will quickly fail, and the next new drugs are probably several years away.

This booklet starts with information about drug resistance, because it is resistance that stops drugs from working. Understanding this will reduce the risk of further resistance in the future.

One of the difficult things about writing a guide to changing treatment is that the information will be read by people who are in very different treatment situations.

Within the group of people who are the most treatment-experienced, the options will also be different depending on their current health and risk of becoming ill.

Although most people now have a good chance of getting their viral load undetectable, some people are still likely to develop resistance to these newest drugs.

We look at different experimental strategies that are likely to vary depending on how strong your immune system is.

Someone in this situation whose CD4 count is stable at any level above 50 cells/mm<sup>3</sup>, should probably delay changing treatment until there are another two new drugs to use at the same time.

If your CD4 count falls below 50 cells/mm<sup>3</sup>, then single new drugs can be used as life saving drugs, even though the benefit is likely to be short-term.

***Drugs from a new class will not be cross-resistant to drugs from other classes. These drugs need to be used with other active drugs or they will be wasted.***

***Do not start a new regimen with only one or two new active drugs.***

## Changes to this edition

We have updated this guide to include the latest available drugs.

- Darunavir, raltegravir and maraviroc have been approved in Europe.
- Etravirine (a new NNRTI) is close to being approved and is available in an expanded access programme.

The booklet is now A5 size and text has been modified throughout to improve clarity.

We have also added several new pages where you can record your own treatment history.

## Resistance, cross-resistance and adherence

### How does resistance occur?

Resistance can often develop against treatment for viruses like HIV or hepatitis B, to bacterial infections like TB or to fungal infections like candida. Resistance to drugs only develops when you are taking treatment that does not fully suppress the infection.

It occurs because treatments are not strong enough. This is why you normally need at least three drugs in a combination to treat HIV.

Resistance occurs more quickly if the infection has a high replication rate. HIV has one of the highest, with HIV several billion new copies of the virus are produced in an HIV-positive person every day.

In making this vast number of copies of itself, the virus also makes very small mistakes called mutations.

This means that an HIV-positive person is really infected with thousands of slightly different viruses, which continue to evolve and change over time.

When you are not taking treatment, these changes do not generally affect how you will respond to treatment. There is no reason for any particular mutation to be produced, because they are usually not as strong as the original HIV non-resistant HIV which is called 'wild-type' virus.

However, if you are on treatment, the mutations that are resistant to treatment will continue to reproduce.

The higher your viral load rises when you are on treatment, the more likely that you are developing resistance.

You then become more resistant to those drugs, as well as cross-resistant to other similar drugs.

This is why it is so important to get your viral load as low as possible. Even between 50 and 500 copies/mL you have enough HIV produced each day for resistance to be able to develop.

However, if your viral load remains below 50 copies/mL there is so little new HIV produced each day that mutations are very unlikely to develop. This means you could use the drugs for many years.

### Do some drugs develop resistance more easily?

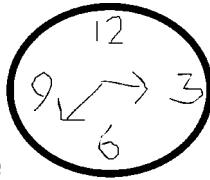
Some drugs only need one mutation for the virus to become completely resistant to them. This is the case with 3TC, FTC, nevirapine and efavirenz (see Figure 1).

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.

For other drugs, including protease inhibitors, resistance occurs more gradually. It usually takes several mutations to stop the drug from working (see Figure 2).

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



## Resistance and adherence

**Resistance and adherence are also closely related. If you miss, or are late, taking one or all of your drugs, you increase the chance of developing resistance.**

**This is because drug levels fall below a minimum safe level to control the virus.**

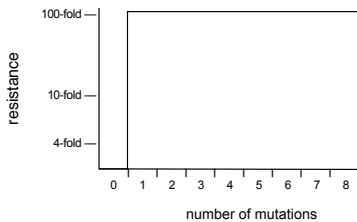
The mutations that occur when you only have low concentrations of your drugs can

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.

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

**Fig 1. How one mutation can stop some drugs working**

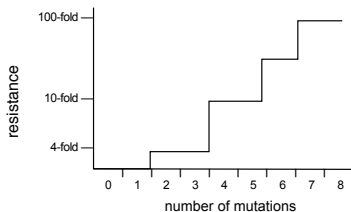


*One mutation is enough to stop NNRTIs working completely*

Some drugs stop working after only one mutation. These include nevirapine and efavirenz (NNRTIs) and 3TC and FTC (nukes). Other drugs need to develop a series of mutations before they stop working.

Having less than 4-fold resistance is usually sensitive and over 10-fold resistance is usually resistant (see page 12)

**Fig 2. Resistance increases slowly with some drugs**



*With PIs, as mutations accumulate, each one can add to greater resistance*

With protease inhibitors, you first develop one or two mutations (which may stop the drugs working a little). If you then continue taking the same drugs without changing your treatment, more mutations will develop that will stop the drugs working completely.

Sometimes you can overcome protease inhibitor resistance by increasing the doses of these drugs, usually by boosting with ritonavir.

## What, why, how...

### What is 'MDR' treatment?

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 three or more types of HIV drug.

It is also called third-line, rescue or salvage therapy. Although we no longer use the term salvage therapy in this booklet, it is still likely to be used in some clinics.

### Why change treatment?

There are several times when you need to consider changing treatment, even if you are well:

- If your current combination hasn't reduced your viral load to less than 50 copies/mL
- If your viral load has started to rise again while you are on treatment ('viral rebound')
- If your combination is working but the side-effects are too difficult

This booklet mainly deals with the first two situations. However, we include a section on changing treatment due to side effects on page 25. It is now very common, and usually very easy, to change treatment because of side effects.

If you have developed resistance to any drugs, then your options will now depend on your own individual treatment history. What is likely to work for one person would not always be recommended for another.

- 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 approach.

### How can drugs 'fail' and I feel fine?

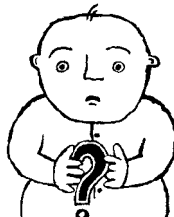
When the term 'fail' is used to describe an increase in your viral load, this should really be referred to as **virological failure**.

It relates to results from blood tests but has no immediate relationship to 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).



### Why viral load tests are important

Regular viral load tests show whether your viral load is undetectable or whether it has rebounded and is rising again.

If, for example, your viral load increases from undetectable to 1000 copies/mL and continues to rise, then you are not going to become ill immediately. In fact, if there were a way of staying at this relatively low level then it would be safe to continue with your current treatment.

However, even at 1000 copies/mL, the virus will be able to develop stronger resistance to your current drugs. At some point, your viral load will rise much higher

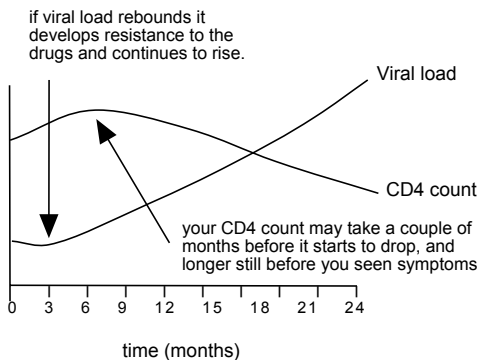
and the drugs will stop working completely. Trying to bring your viral load back down again then may be more difficult.

There are also a few people whose viral load remains low but detectable for many months without continuing to climb. One explanation may be that the new resistant mutations have also made the virus 'less fit'. Over time, the virus usually develops further 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 23.

**Fig 3. If viral load increases, there is usually a delay of several months before the CD4 count drops**



## What to do about a rising viral load

- *If your viral load starts to rise after being undetectable, don't panic, but do take it seriously.*
- *Do a new test on the same day you get the first test results 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).*

### Spikes and blips

It is common to have a 'spike' or 'blip' result. This is where your viral load jumps from undetectable to between 50–2000 copies/mL and then drops back down below detection by itself, within a few weeks. (See Figure 4).

Blips 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 stop you changing from a treatment which is still working, and which you could continue to use for many years.

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 5).

Fig 4. Single spikes or blips are not uncommon

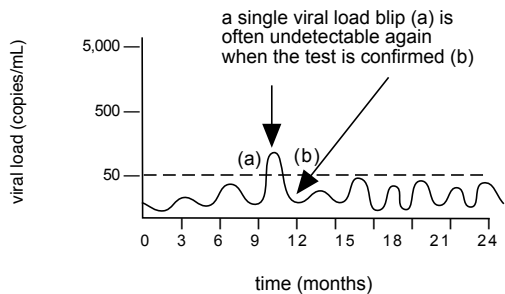
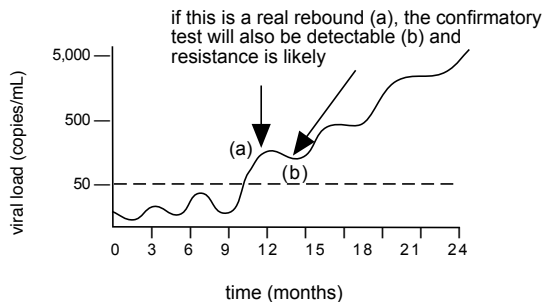


Fig 5. A real viral rebound is picked up by the confirmatory test



## Test sensitivity

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

Research looking at whether reducing viral load down to less than 5 copies/mL, has not found any clinical benefit from getting much lower than 50.

Intuitively you may want to go as low as possible, but 50 copies/mL seems to be the key cut-off.

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

This is why it is important to confirm any unexpected viral load result and to never rely on just one test to make a treatment decision.

## When should I change?

- ***If your viral load is continuing to rise, then changing more quickly, if you have other drugs available, will give your next combination the best chance of reducing viral load levels to undetectable again.***

The earlier that you detect a rise in your viral load, the earlier you will have the chance to 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 current and lowest ever 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 copies/mL - you can sometimes intensify treatment, though this is generally not recommended. (See page 20).

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.

This is more likely if you have not been getting tests very frequently or if you have not been getting 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 you can continue on the same treatment, even with a high viral load, and remain healthy, sometimes for several years. Nukes and PIs will continue to contribute to the combination, NNRTIs and integrase inhibitors easily develop complete resistance, and will not be having any effect on your viral load.

Waiting until new drugs are available, so that when you do change, it is to a stronger combination, is an important strategy.

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

## 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 trials have been where people have used at least two and preferable three new sensitive drugs (see Figures 6 and 7).

For example, using raltegravir plus darunavir/r plus T-20 as a new drug usually with recycled nukes. Or using etravirine instead of T-20.

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).

A drop from 20,000 down to 20 is a drop of three logs. The greater the log drop in a trial, the more potent the combination is.

Another way of looking at results is to ask about the percentage of people taking the drug whose viral load goes below 50 copies/mL. The closer this is to 100% the

**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 = 3000	3.7 log = 5000
4 log = 10,000	4.5 log = 30,000	4.7 log = 50,000

more potent the drug and the more likely it will work.

It isn't straight forward to just compare published results from different studies. You need to consider the health of the people in the trial and whether they started from a similar situation.

If they all started with a very low viral load or a high CD4 count then it would be easier to achieve impressive results.

Look at how long the trial lasted and how long people were followed. Knowing the results lasted over a year or two will give you more long-term confidence.

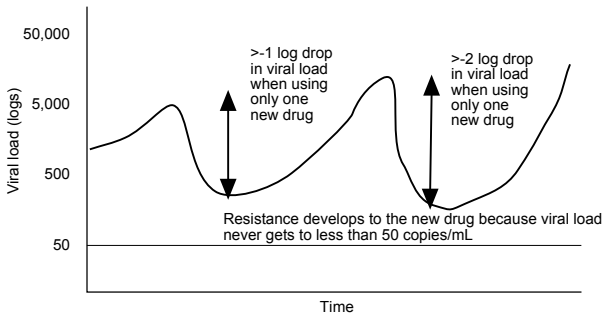
Impressive short-term results may just mean it is a combination that is easy to tolerate or adhere to.

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

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

## Importance of using new drug in combination with other sensitive drugs

**Fig 6. Using only one or two sensitive drugs will only work for a short time**

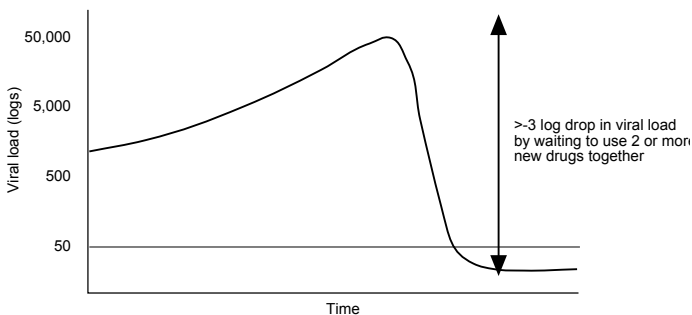


Using a new drug in a combination without other active drugs will not be strong enough to get viral load to <50 copies/mL. It may reduce viral load by 1-2 logs each time, but the benefit will only be short term and viral load will rebound with resistant virus.

This strategy is only worth considering if your CD4 count is very low (under 50 cells/mm<sup>3</sup>) or if you have other serious symptoms.

Using each new drug without other sensitive drugs, reduces the chance of getting viral load reduced to <50 copies/mL and increases the chance of early resistance and viral rebound.

**Fig 7. Waiting to use three new drugs is much more likely to get viral load under 50 copies/mL**



Waiting until you can use at least 2-3 new drugs means the new combination can reduce viral load by 3 logs to below 50 copies/mL.

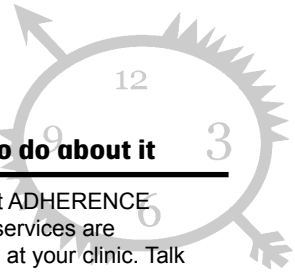
Even though your viral load may continue rising before you switch, if you wait until you can use at least two or more sensitive drugs, that combination is more likely to get your viral load below 50 copies/mL. This makes the likelihood of developing resistance much lower. Treatment can then work for much longer – hopefully for years.

By waiting until there are at least two new sensitive drugs to use together, increases the chance of getting viral load reduced to <50 copies/mL. This will provide a longer benefit.

## Why a combination can fail

- **Think about why your current combination failed. Find out whether this was related to prior resistance, adherence, drug absorption, or a combination of these reasons? This also applies to people whose first treatment never reached undetectable levels (for example after 3-6 months).**
- **Getting a resistance test is very important and is included in UK guidelines.**

Reasons a combination can fail		What to do about it
i) The previous combination was not potent enough.	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.
ii) 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 is provided for all UK clinics at Liverpool University.  Individual differences can be significant. These tests are for PIs, dual-PIs and NNRTIs and possibly T-20.
iii) 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 AZT. If you then used AZT, this drug 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.



**Reasons a combination can fail**

**What to do about it**

iv) 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 regularly missed doses of some or all of the drugs in your previous combination, or weren't able to follow the diet guidelines and food restrictions, you have to find a way of not repeating the same patterns in your next combination.

You need to ask for support to help you tackle adherence differently this time.

Ask what ADHERENCE support services are 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.

Get a genotypic and/or a phenotypic RESISTANCE TEST to find out which drugs you can still use.

v) 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.

Check that your HIV doctor and pharmacist know about any other medications or supplements that you take and that there are no potential interactions. See:

[www.hivdruginteractions.org](http://www.hivdruginteractions.org)

## Important monitoring tests

### VIRAL LOAD TESTS

Viral load tests are the most sensitive test to check whether a combination is still working well. Your clinic should use tests sensitive to 40 or 50 copies/mL.

Viral load should be checked 2-4 weeks after any treatment change.

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

### RESISTANCE TESTS

Resistance tests can show which drugs you have developed resistance to and which drugs are unlikely to work.

UK treatment guidelines recommend that everyone changing treatment should have a resistance test.

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.

By checking the changes in your virus to these known mutations you get a good idea of which drugs are unlikely to work.

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.

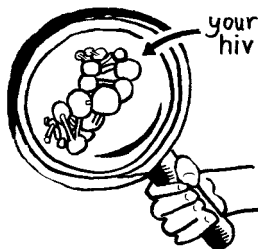
Results should take about a week.

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

Fig 8. Types of resistance tests

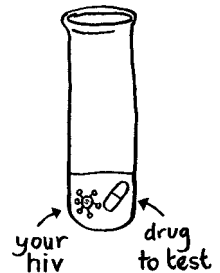
#### 1. genotype

*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.*



Note: 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.

### Phenotype tests ('fold' changes)

A phenotypic resistance test adds each drug to your HIV in a test tube. It shows how sensitive or resistant you are and how well each drug is working. Results are given in terms of how much more resistant your virus is compared to a sensitive virus.

For example, 10-fold resistance to a drug means you would need 10 times as much drug to get the same anti-HIV 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 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, available in some clinics, uses results from a genotype test and compares this to a large database of matched phenotype results.

### 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 = letters and numbers

Genotypic resistance tests give results as a list of mutations.

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

The first letter stands for the chemical that is normally expected at that position in the virus. ie 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 reverse transcriptase section of the HIV genome.

The final letter stands for the new chemical that the mutation makes, ie 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 interpretation charts for every genotypic mutation.

<http://hivdb.stanford.edu>

### Phenotype = 'fold-change'?

Phenotype results have different cut-off values for each drug (which sometimes change with new research) and for each manufacturers test.

Figure 1 below shows the range of cut-offs for different drugs for the loss of 80% response compared to wild-type non-resistant HIV (for the test made by Virco).

**Figure 1: Examples of phenotypic cut-offs for one make of test**

AZT	9.6	indinavir/r	40.1
3TC	3.4	saquinavir/r	26.5
ddl	2.6	nelfinavir	7.3
d4T	2.0	lopinavir/r	56.1
abacavir	1.9	amprenavir/r	9.6
tenofovir	2.1	tipranavir	5.4
efavirenz	6.0	darunavir	96.9
nevirapine	8.0		

## TDM TESTS (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.

In the UK, TDM is available free for people using nelfinavir, saquinavir, indinavir and lopinavir/r through programmes sponsored by the manufacturers.

Even if your clinic has to pay for a test, they only cost around £60 per drug. TDM in the UK is available from Delphic:

<http://www.delphicdiagnostics.com>

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

TDM can check doses in many situations. These include:

- When using combinations that haven't been studied where one drug may affect the level of another. This is particularly important with new drugs.
- To individualise dosing when there are no dosing recommendations, for example, with some dual-PIs.
- 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. Reducing the dose in these cases is recommended and safe.

This may be true for some other drugs if they take longer to leave your body because your liver is not working to

clear them as well. Dosing is easier to individualise for people 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.
- TDM should also be considered in other cases where you may not be absorbing drugs properly. For example, if you have severe diarrhoea.

***TDM is recommended in UK BHIVA 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.***

## INHIBITORY QUOTIENT and VIQ TESTS

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 TESTS**

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 test for tropism, or just switch to use a CCR5 inhibitor, if your viral load is undetectable.

The only CCR5 inhibitor currently approved is maraviroc; vicriviroc is a CCR5 inhibitor that is still in clinical trials.

## **Getting the tests in the UK**

Many hospitals routinely use all these tests which are recommended in UK treatment guidelines (<http://www.bhiva.org>) - 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 does have some effect.

Write to your consultant, clinic and laboratory heads, and Primary Care Trust (PCT) executives and your MP if your PCT isn't providing 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 phonenumber may be able to help advocate in these situations.

## Choices for your next combination

### Which combination to change to

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

It will depend on the reason that previous combinations failed (see pages 12-13) and the results of the tests listed on pages 15-18.

### After first treatment failure

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

In practice, if your first combination included an NNRTI then your second combination will include protease inhibitors and vice versa, even if a resistance test doesn't show NNRTI or PI resistance.

The current recommendation is also to change to two new 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 drugs in families that you have some resistance to, are likely to work.

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 and 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 (ie 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 holding back some drugs. 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 is usually only after very early failure.

You can sometimes intensify by *adding* a drug to a combination that has worked well but not quite got your viral load below detection.

- Add a drug you have never used (ie add a new nuke to a first-line triple combination to make a more potent 4-drug combination).
- Add a drug you have already used but which may still work. This includes continuing to take 3TC or FTC to maintain a weaker HIV, or a new PI in case there isn't complete cross-resistance to previous PIs.

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 concentration of some of 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 12-13) 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.

Guidelines recommend using T-20 earlier in treatment failure and before resistance to all other drugs has occurred, especially to support the newest drugs including darunavir/r, etravirine and raltegravir.

As other new drugs become available, they will also be expected to produce better results when used with, rather than without T-20.

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<sup>3</sup>, 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 than 50 cells/mm<sup>3</sup> then T-20 is recommended to 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 increasing your chance of reducing viral load to less than 50 copies/mL it can protect the other drugs in your combination from developing resistance.

T-20 may be a drug that you only need to use for a limited period until a new sensitive drug becomes available to switch to. For example, recent studies have shown that people who used T-20 several years ago to get their viral load to undetectable can now safely switch T-20 to raltegravir.

However inconvenient or difficult a 'salvage' regimen is, it is not likely to be forever. It is a means to get through a very risky period, in order to access better treatments that undoubtedly will come later.

## 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 which 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.

Because these combinations can be difficult to use, you may need additional support. Some clinics are better than others are at providing adherence support but you should always tell your doctor or a nurse, at any time, if you have difficulties with any treatment.

***The weaker a combination is, the less likely it will work in the long term. Multi-drug resistant therapy, at its most basic, 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 positive reasons to stop treatment, when treating multidrug resistant HIV, the risks of treatment interruptions are now thought to outweigh any benefits.

Disadvantages include the risk that:

- Your 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. Sometimes the CD4 drop can also be difficult to regain, even if the next treatment works well at reducing your viral load.

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.

You should monitor your CD4 count very carefully. This should be 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.

Doctors occasionally 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 increase the risk of resistance.

## 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 PIs combinations is underway.

ddI may be a useful drug to recycle as the Jaguar study showed that it still reduced viral load even with nucleoside resistance (up to 4 mutations).

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.

## Using 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 inhibitor's 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 latest research on new drugs and treatment strategies.***

## Using viral fitness

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

The genetic changes and mutations that make HIV resistant to different drugs also make HIV less fit at reproducing. So, resistant virus is often a weaker strain of the virus.

For example, continuing to use 3TC or FTC even with the 184V mutation keeps viral load lower because the virus with this mutation is less fit.

This shows a benefit of maintaining either 3TC or FTC in any treatment experienced combination.

Another strategy for using the effect of reduced HIV fitness could include cycling different combinations every 1-3 months. This is only a proposed strategy for someone who has already developed resistance to all available treatments.

The effect of each drug or combination, would be to force back the resistance linked to those drugs. Early resistance is usually related to reduced viral fitness for at least the first 4-8 weeks.

Reduced fitness is eventually overcome by additional mutations, and cycling to the next set of resistant drugs brings back a new range of resistant viruses, that are also less fit at replicating.

Although UK studies of this strategy have not yet started this could be a new and important approach for people with no other options.

It could also use fewer drugs in each combination, and reduce the risk of side effects from five-drug combinations.

However, an Italian study reported how this may be used in practice in a group of 34 highly treatment-experienced patients.

Combination therapy was changed based on results from genotype resistance results 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 with each combination lasting an average of approximately 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 (but only using drugs that are still active)**

- *Remember that 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 under 100 cells/mm<sup>3</sup>.*

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 under 200 cells/mm<sup>3</sup>.

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

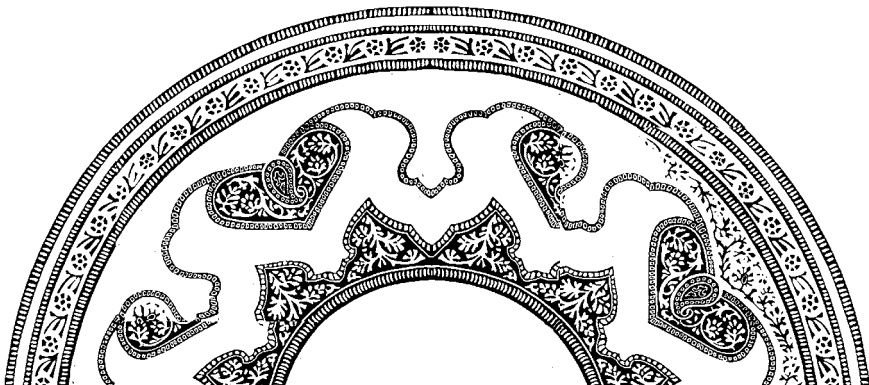
a resistance test shows that you have the key mutations associated with resistance to these drugs, then they are unlikely to be contributing any activity against HIV.

However, if you do not have other treatments to choose, and 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.

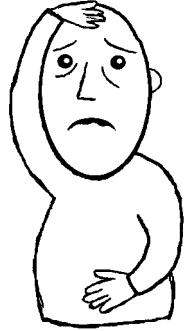
This strategy prioritises keeping your CD4 count at a safe level over the risk of developing resistance. If the next new drug you are waiting to use is a PI, then some researchers suggest cutting back to a nuke-only 'holding' regimen. This will reduce the risks of developing further cross-resistance 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 the information in this booklet is to help people who want to change treatment because their current combination has stopped working.

However, many people also change treatment either to avoid side effects or to have a regime that is easier to follow.

Adapting combinations to improve tolerability may even be more common than changing because of drug failure. In the end, any combination has to be one you can tolerate.

With over 20 drugs available, there is a great deal of individual choice. Newer drugs may also have become available since you last changed treatment.

As long as you maintain drugs with a similar potency, switching individual drugs can be very safe. If in doubt, use four or more drugs, rather than just three drugs, in your new combination.

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

Again, your own treatment history is important. You will need close viral load monitoring at least 2-4 weeks after any change.

### Common 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, and results in 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 so switching to abacavir or tenofovir is now common.
- If you continue to get nausea or fatigue using AZT (or Combivir or Trizivir, which both contain AZT) then you could switch to another combination.
- Nevirapine and efavirenz have similar potency against HIV but different side effects. Nevirapine has been more associated with skin rash and liver toxicity. Efavirenz is linked to mood disturbance, disturbed sleep patterns and vivid dreams. If you have difficult side-effects from one of these drugs, you can usually just switch from one to the other - or to a boosted PI - without stopping treatment or changing the other drugs in your combination. When switching to nevirapine, remember to start at the lower dose of 200mg once a day for the first two weeks.
- If you have injections site reactions with T-20 and an undetectable viral load, switching to raltegravir may be an option for many people.

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

***Call 020 7407 8488 for a free copy.***

## Expanded access and experimental drugs

Expanded access programmes (EAPs) and Named Patient Programmes (NPPs) let some people use drugs before they are licensed.

This is after research has shown they are effective but while approval is being processed (which can take over 6 months). EAP and NPP access is provided for most new drugs, but it is sometimes very difficult to predict when each programme will start.

These drugs can be the key to a successful regimen. 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.

As we went to press some of the new drugs in ongoing studies include:

*NRTIs:* apricitabine, amdoxovir, CHX157

*NNRTIs:* rilpivirine, IDX899, RDEA806

*Integrase inhibitors:* elvitegravir

*CCR5 inhibitors:* vicriviroc

*Maturation inhibitors:* beviramat

Additional new trial drugs may become available before this booklet is updated.

### Experimental treatments

Several other 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, shown to reduce risk of new illnesses in a study with CD4 counts below 50 cells/mm<sup>3</sup>.

**IL-2:** An experimental drug, given by injection for 5 days every 8 weeks. IL-2 can boost your CD4 count, especially if it remains under 200 cells/mm<sup>3</sup> when on HIV treatment. Heavy flu-like side effects.

**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.

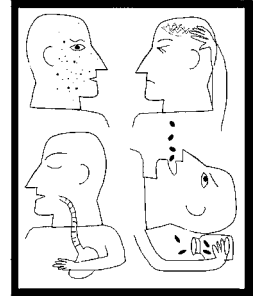
**hydroxyurea (HU):** A 30-year-old anti-cancer drug that can resensitise HIV to ddI. Now rarely used. Used at reduced dose of 300mg, once daily.

**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 date: \_\_\_\_\_

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





## Resistance tests

Date	Results (continue on separate pages if necessary)

## 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**

Positive Nation, a UK magazine is a good source of general information and support:

[www.positivenation.co.uk](http://www.positivenation.co.uk)

For further information on individual HIV drugs try the following community sites.

Non-technical basic factsheets

[www.aidsinonet.org](http://www.aidsinonet.org)

A general overview on each drug and online discussion groups

[www.aidsmeds.com](http://www.aidsmeds.com)

An online 'drug guide'

[www.tpan.com](http://www.tpan.com)

Detailed research and references

[www.aidsmap.com](http://www.aidsmap.com)

Full prescribing information in most European languages and other scientific documents are available from the EMEA - use link for 'product information/human medicine':

[www.emea.europa.eu](http://www.emea.europa.eu)

## Glossary

>: mathematical symbol meaning 'greater than'

<: mathematical symbol meaning 'less than'

**ARV:** Anti-retroviral - any drug that works against HIV.

**CCR5 inhibitor:** a type of HIV drug that blocks HIV from attaching to a CD4 cell. Maraviroc and vicriviroc are CCR5 inhibitors.

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

**Cross-resistance:** where resistance that has developed to one drug is also resistant to other 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').

**Fusion inhibitor:** a type of HIV drug that works by stopping the virus attaching to a CD4 cell. T-20 (enfuvirtide) is the only licensed fusion inhibitor.

**Genome:** term for the genetic material (DNA) of any organism

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

**Integrase inhibitor:** a family of HIV drugs that includes raltegravir and elvitegravir.

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

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

**NNRTI:** Non-Nucleoside Reverse Transcriptase Inhibitors, a family of drugs that includes nevirapine and efavirenz and drugs in development including etravirine and rilpivirine (TMC-278).

**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 nucleotide RTI and works in a similar way.

**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 anti-HIV drugs used after your first treatment has failed.

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

**Treatment-naïve:** someone who has never taken any anti-HIV treatments before. *[note: people who are treatment naïve 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 a virus 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. Tests can only measure down to certain levels (ie 50 copies/mL).

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

**Wild-type virus:** HIV that has not developed any mutations. This is usually the virus that you are first infected with.

abc...

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**i-Base treatment  
information  
phonenumber**

**mon > tues > wed >  
12.00–4pm**

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

**[questions@i-Base.org.uk](mailto:questions@i-Base.org.uk)**  
**[www.i-base.info/questions](http://www.i-base.info/questions)**

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## **i-Base publications**

All i-Base publications are available free. Treatment guides are written in everyday language. HTB is written in more technical medical language. Please send me:

- Introduction to Combination Therapy
- Changing Treatment: Guide to Second-line Therapy (*this guide*)
- Pregnancy and Women's Health
- Guide to HIV and Hepatitis C
- HIV Treatment Bulletin (HTB)
- Guide to Avoiding and Managing Side Effects
- Treatment Passport - booklet to record your treatment



Publications in other languages are available in pdf format at [www.i-Base.info](http://www.i-Base.info)

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\_\_\_\_\_ Postcode: \_\_\_\_\_

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**Please post to: i-Base, HIV i-Base, 3rd Floor East, Thrale House,  
44-46 Southwark Street, London SE1 1UN or fax to: 020 7407 8489**