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Changing treatment: second-line therapy and drug resistance

If viral load rebounds

Resistance testing

**Intensifying, interruptions
& other strategies**

Switching for side-effects

Experimental & new drugs

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Glossary

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

CCR5 inhibitor: a type of HIV drug that blocks HIV from attaching to the CD4 cell. CCR5 is a coreceptor and drugs in development include maraviroc and vicriviroc.

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.

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

Integrase inhibitor: a new family of HIV drugs that includes raltegravir (MK-0518) and elvitegravir (GS-9137).

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'.

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 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 a virus in order to attach (and then infect) a cell

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.

Disclaimer: Information in this booklet is not intended to replace information from your doctor or other healthcare workers.

Decisions relating to your treatment should always be taken in consultation with your doctor.

Introduction to the April 2007 edition

In 2007, for the first time in many years, the approach to treating treatment experienced patients has changed dramatically. This is a very exciting and hopeful time because it is the first time that several new drugs have become available at the same time.

This includes protease inhibitors that are active against most PI-resistant virus (tipranavir and darunavir) and drugs from two new families (integrase inhibitors and CCR5 inhibitors). These drugs must all be used with other active drugs.

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

In 2007, results from combinations that included three new sensitive drugs – for example with raltegravir, darunavir and T-20 - enabled up to 70% of treatment experienced patients to get their viral load to less than 50 copies/mL after 16 weeks. The availability in expanded access programmes of the raltegravir (MK-0518), the NNRTI etravirine, and the CCR5 inhibitor maraviroc makes this an option for patients in the UK.

This booklet starts with a note about resistance, because this determines which drugs are likely to work. Getting viral load to undetectable determines whether a combination will work for only a few months or for many years.

For most people whose viral load gets to below 50 copies/mL, there is only a very low risk to develop resistance. So long as the treatment is tolerable, you should be able to use that combination indefinitely.

This is just as true for your second, third or any other subsequent combination.

Previous resistance usually limits the effectiveness of new drugs. However, drugs from a new class will not be cross-resistant to drugs from other classes. For these drugs to work they always need to be used in combinations that include other active drugs.

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

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 highly treatment-experienced, the options will also be different depending on their current health and risk of becoming ill.

Although most people with treatment failure to existing drugs can expect a good chance of getting their viral load undetectable in 2007, some people are still likely to develop resistance to these newest drugs.

For someone in this situation whose CD4 count is stable at any level above 50 cells/mm³, the general recommendation is to delay changing treatment until there are another two new drugs to use at the same time. If you can delay your switch until there are three new drugs, this is even better.

If CD4 count falls below 50 cells/mm³, then single new drugs are recommended, but this is done with the understanding that they are being used as lifesaving drugs, and the benefit is likely to be limited.

Changes to this edition

Since the previous edition of this guide, several new treatments have become available as approved drugs or in expanded access programmes:

- Tipranavir has been approved in Europe.
- Darunavir is close to being approved and is available in an expanded access programme.
- Promising results from the first integrase inhibitor called raltegravir (MK-0518), which is active against currently resistant HIV have been presented. An early access programme for this drug is now available in the UK.
- A new NNRTI in development called etravirine (TMC-125) is available in expanded access.
- The CCR5 inhibitor maraviroc is available on expanded access in the UK.

We have also added several new graphs and illustrations throughout the guide and expanded the section on expanded access drugs. Information is also included about a new tropism test that needs to be used before taking CCR5 inhibitors.

A note on resistance and adherence

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

It occurs when treatments are not strong enough to stop the cause of infection reproducing. 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 - and 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.

These changes or mistakes are 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 is called 'wild-type'.

However, when you are on treatment, some mutations that develop will stop the drugs from working. These resistant mutations will continue to reproduce and because they have a competitive advantage over wild-type virus, will eventually become the major type of your HIV.

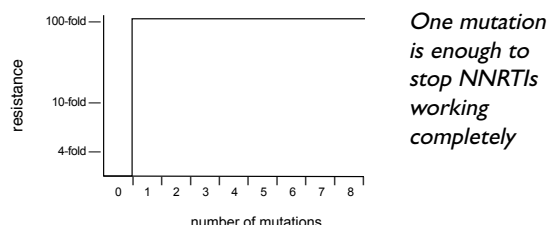
You then become more resistant to those drugs, as well as to other similar drugs.

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

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 new HIV produced each day to be at risk of developing resistance.

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 and still not develop resistance.

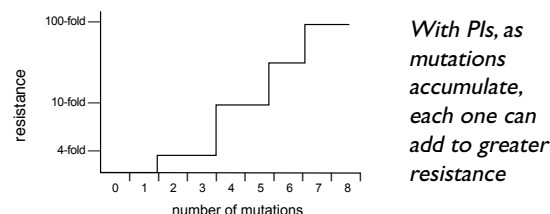
Fig 1. How one mutation can stop some drugs working



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 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.

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*.

Summary

Deciding on which HIV drugs will work best after developing drug resistance is complicated, and is a specialised area of HIV care. This booklet should help in discussions with your doctor. Although everyone's treatment situation is different, the following summary covers the most important key points.

- 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 produced an accurate result. 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. 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.**
- 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 under 100 cells/mm³ 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/mm³.**

What, why, how...

What is 'MDR treatment'?

Multiple Drug Resistant (MDR) treatment is the name given to any combination after you have developed resistance to your first or second regimen. Sometimes it refers to treatment for someone with resistance to three or more families of HIV drugs.

It is also called third-line or rescue therapy.

Although we don't use the term 'salvage therapy' in this booklet anymore, it is still likely to be used in some clinics.

There are over 20 anti-HIV drugs to choose from – more if you include those available in trials or open access programmes. However, many of these will not work if you are already resistant to other drugs in the same class.

Any drug you use now should be in a combination that is most likely to minimise the chance of further resistance. However, before choosing new drugs, you need to know why the previous treatment failed. (See 'Why a combination can fail' on page 11).

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 21.

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.

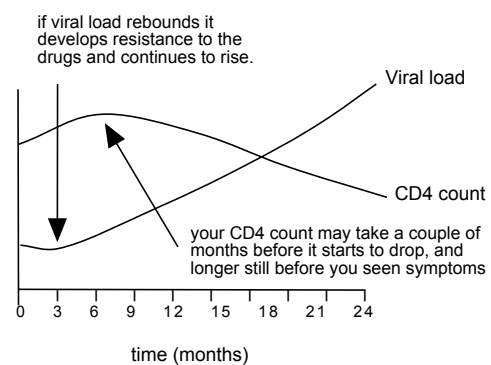
However, even at 1000 copies/mL, the virus will be able to develop stronger resistance to your current drugs. At some point, your viral load will rise much higher and the drugs will stop working completely. Trying to bring your viral load back down again then may be more difficult.

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 19.

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



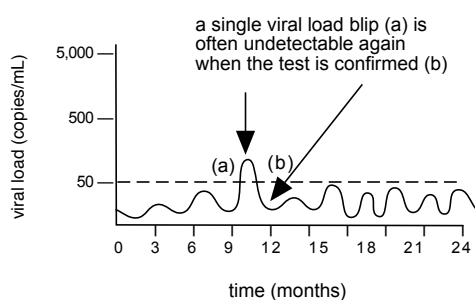
What to do about a rising viral load

- 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 2 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.

Fig 4. Single spikes or blips are not uncommon

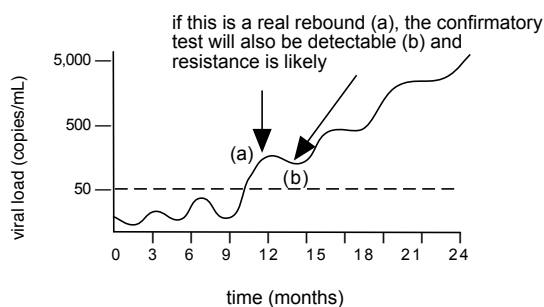


Other infections, such as flu or herpes, can cause a temporary rise, as can some vaccinations. Some tests are contaminated at the lab, giving a false result.

One study showed that over 50% of blips to between 50 and 500 copies/mL were only test errors. 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.

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



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.

Tests sensitive to 50 copies/mL

All hospitals should now routinely use viral load tests that measure down to 50 copies/mL. These have been recommended in UK treatment guidelines for several years.

Research is looking at whether reducing viral load down to less than 5 copies/mL, has a longer term benefit, but the results so far are unclear.

Also, 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.

Whenever you reduce viral load to less than 50 copies/mL, you are likely to get a long-term benefit.

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 (see page 16).

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, but you may need to do more than simply add one new drug. The earlier you change a failing treatment, the greater the chance that the following combination will work.

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.

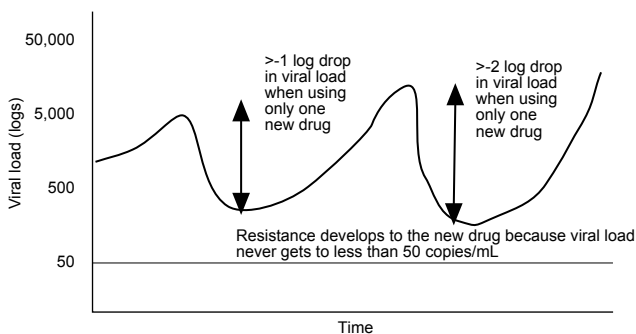
This is more likely if you have not been getting tests very frequently or if you have not been getting the results in 'real time' two weeks after giving blood.

If you do not have enough new drugs for a new combination, then you can continue on the same treatment, even with a higher viral load, and remain healthy, sometimes for several years. Nukes and PIs will continue to contribute to the combination, NNRTIs 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.

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

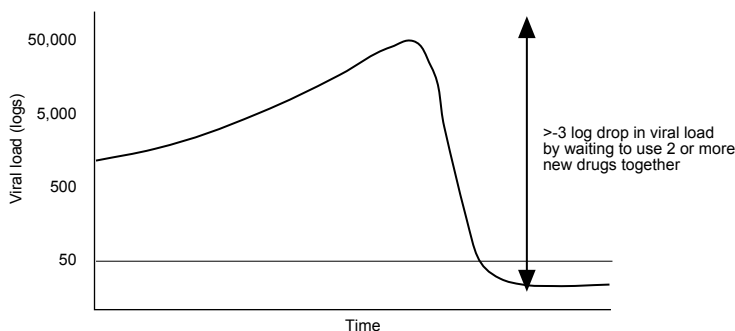


Using each new drug without other sensitive drugs, reduces the chance of getting viral load reduced to <50 copies/mL and increases the chance of early resistance and viral rebound.

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/mm³) or if you have other serious symptoms.

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



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.

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

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.**

Ask for results from trials of people in your situation. People who are starting second or third combinations usually do less well than those who have not used drugs before.

Although all drugs have been tested both on their own and in different combinations, there will not always be studies that match your exact situation.

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 is a multiple of $\times 10$. 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 measure is to look at the percentage of people taking the drug whose viral load goes below 50 copies/mL. The closer this is to 100% the more potent the drug and the more likely it will work.

It isn't straight forward to just compare these 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.

Log scale: A log scale is a multiple of a factor of 10.

1 $\log_{10} = 10$	1.5 log = 30	1.7 log = 50
2 $\log_{10} = 100$	2.5 log = 300	2.7 log = 500
3 $\log_{10} = 1,000$	3.5 log = 3000	3.7 log = 5000
4 $\log_{10} = 10,000$	4.5 log = 30,000	4.7 log = 50,000

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.

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.

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.

Some drugs, including ddI and d4T, develop resistance in a way that is not well understood. It is not always possible to link a set of mutations with drug resistance.

However, drugs from the nucleoside class can be cross-resistant to each other. NNRTIs are usually cross-resistant to other NNRTIs.

Although protease inhibitors as a class can be cross-resistant, some PIs are more likely than others against different PI resistant patterns.

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.**

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

Make sure you and your doctor understand the importance of all of these causes in choosing your next combo. You don't want to repeat the same mistakes.

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 to, for example, 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.
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.

Important monitoring tests

VIRAL LOAD TESTS

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

When on treatment your viral load should be monitored at least every three months.

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

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.

Although more sensitive resistance tests are being developed, you generally need to have a viral load over 500-1000 copies/mL for them 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:

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.

This test costs much less than the ineffective drugs that you might otherwise use. Results should take a week to come back.

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.

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 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 results have different clinical cut-offs for each laboratory. The figures below (from Virco) are a guide for loss of 80% response compared to wild-type (non-resistant) HIV, for the following individual drugs. These cut-off values will be different with different makes of test:

AZT	9.6	indinavir/r	40.1
3TC	3.4	saquinavir/r	26.5
ddI	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		

Phenotype tests are recommended in the UK guidelines when genotype results alone do not provide a clear result. Phenotype resistance tests are more expensive than genotype tests. They take longer to get results, maybe 2-4 weeks, because the tests cannot be run in your own clinic and it takes time for the virus to grow.

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.

TDM – THERAPEUTIC DRUG MONITORING

These tests check whether you are getting adequate blood levels of a protease inhibitor or NNRTI. Recent studies have indicated that drugs levels of T-20 are related to treatment response, and that TDM may have a role for people using T-20.

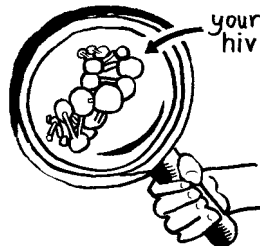
TDM is available free for many people using nelfinavir, saquinavir, indinavir, fosamprenavir, atazanavir, lopinavir/r, tipranavir or darunavir through programmes sponsored by the manufacturers.

Even if your clinic has to pay for a test, they only cost

Types of resistance tests

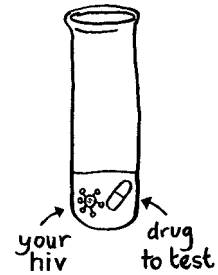
1. genotype

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.

around £45 per drug. TDM in the UK is available from Liverpool University:

<http://www.hiv-druginteractions.org>

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

TDM has an immediate practical use in checking doses in many situations. These include:

- When using combinations that haven't been studied such as new dual PI combinations, or using PIs and NNRTIs where one drug can affect the level of another. This is particularly important with new drugs.
- To individualise dosing in dual-PI combinations. When there are no dosing recommendations for dual-PIs, TDM can help you safely adjust doses to obtain one that is best for you.
- If you have pre-existing liver or kidney damage, or have haemophilia or other medical conditions that require careful monitoring.

For example, long after they were being used by patients, studies of drug levels of both amprenavir and abacavir were found to be too high in people with liver damage. Reducing the dose in these cases is recommended and safe.

This will also be true for other protease inhibitors. They will take longer to leave your body because your liver is not working to clear them as well. Dosing is much easier to work out individually for patients in this situation.

- For all children on treatment. 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

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 itself. Different resistant and non-resistant viruses are stronger 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 TEST

This is a new test that is only used if you are going to use a drug from the family of CCR5 inhibitors.

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 the virus sometimes switches to a different receptor called CXCR4. After this switch, and also possibly in people with a mixture of both receptors, a CCR5 inhibitor will not work.

For current tests to work you need a similar level of detectable viral load as for resistance tests ie 500-1000 copies/mL. This means that you cannot just switch to use a CCR5 inhibitor if your viral load is undetectable.

CCR5 inhibitors currently in development are maraviroc and vicriviroc.

Getting the tests in the UK

Many hospitals routinely use all these tests but you may have to be persistent to get them.

Viral load and resistance tests, and TDM in some circumstances, are recommended in UK treatment guidelines. (<http://www.bhiva.org>).

All these tests are important though 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.

Some people pay for tests privately and some hospitals may split the cost with you.

TDM is already available through Liverpool University with costs paid for by the manufacturers of many drugs.

<http://www.hiv-druginteractions.org>

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 offer suggestions on access and advocacy help in this situation.

Choices for your next combination

Which combination to change to

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

It will depend on the reason that previous combinations failed and the results of the tests listed on pages 12 and 13.

Second-line therapy

(If your last combination was the first time you used treatment).

The recommendation for someone whose first combination has failed is to switch to at least three completely new drugs.

All PIs have some cross-resistance to all other PIs, and all current NNRTIs have cross-resistance to other NNRTIs. It is therefore probably safer to switch this part of your combination, even if a resistance test did not show resistance to these drugs.

- If you previously used an NNRTI-based triple combination, then you can now use three or four new drugs including one or two PIs.
- If you previously used a protease-based combination, then you can use three new drugs which now include an NNRTI.

Protease after protease

If you change a single protease-based combination early enough, you can change to a new protease inhibitor, boosted by ritonavir, in a four-drug combination. You could also change to newer PIs that may be less cross-resistant.

- The earlier you change from the first combination, the more likely that your next combination will be successful.
- Using ritonavir-boosted protease inhibitors result in a more potent therapy.
- The chance of success is related to being able to change other drugs at the same time.
- Using two new nukes (d4T, AZT, 3TC, FTC, ddl, abacavir, tenofovir) will give the strongest

response. Some nukes cannot be used together (ie d4T and AZT; or tenofovir and ddl' or 3TC and FTC)

Cross-resistance between nukes is complicated, and is the subject of ongoing research. If you have developed resistance to AZT and 3TC then abacavir or tenofovir may or may not work well – depending on the exact pattern of mutations. If you have developed resistance to abacavir then 3TC or FTC will not work. The significance of cross-resistance between AZT and d4T is not clearly understood.

How to choose new drugs

Trial results, even for new drugs, are the best place to find information to predict how well a new drug will work. This should also include information about different patterns of resistance. 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.

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

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:

- Adding a second PI (i.e. add ritonavir to an atazanavir, indinavir or saquinavir combination to boost the performance of the main PI).
- 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 was the first entry inhibitor drug to be approved and it will work against HIV that is resistant to nukes, NNRTIs and PIs.

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

Guidelines therefore recommend using T-20 earlier in treatment failure and before resistance to all other drugs has occurred, especially to support the newest PIs, tipranavir/r or darunavir/r, or with raltegravir (MK-0518).

When either of these PIs were used in a combination where someone also used T-20 for the first time, response rates were almost double compared to those using just the new PI.

As other new drugs become available, they will be expected to produce better results when used with T-20, than if T-20 is the only new drug that is used.

T-20 is given by subcutaneous injection twice a day, and training is provided so you can do this yourself at home. Recent studies in the US include a 'needle free' injection device called Biojector, which may make this process easier in the future.

If you have resistance to all available drugs, and your CD4 count is stable, almost at any level above 50 cells/mm³, it is 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/mm³ 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 may be a drug that you only need to use for a limited period - until a new sensitive drug becomes available to switch to.

Some people using T-20 successfully now, but who have difficulty with side effects, may be able to switch to raltegravir (MK-0518).

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.

What you are trying to do is:

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

For example:

- If you have used AZT, 3TC and ddI previously, there is a good chance that abacavir will not help very much. If you use this drug with only two others, it will not be powerful enough. If you use it with five or 6 others though, even if it only works a little, this could provide the extra booster you need to get your viral load below detection.
- If your current failing combination includes a protease inhibitor you may have developed resistance to PIs.

If you just switch to one new protease inhibitor as part of a triple combination, this may not be enough. By including one or two protease inhibitors on top of a triple combination, you are more likely to get an undetectable viral load.

You could consider using 3TC or FTC in any combination, even if you have developed resistance to this drug. This is because HIV that is resistant to these drugs is a weaker strain of HIV.

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, the risks of treatment interruptions are now thought to outweigh the benefits, when treating multidrug resistant HIV.

Disadvantages include:

- Your viral load will rebound, sometimes to high levels over 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.
- A higher risk of HIV-related illness because of CD4 drop was shown in one study but not in another. This may relate to current and previous lowest CD4 counts.

If you want to take a treatment break, consider whether a simple maintenance regimen may be better. 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.

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.

Future research on dual-boosted PIs combinations is underway.

ddI may be a useful drug to recycle as one small 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 protease inhibitors such as darunavir (TMC-114) which was approved in Europe in March 2007 may work for people who have resistance to existing PIs.

The NNRTI that is furthest in development and may work against NNRTI resistant virus is etravirine (TMC-125), which is also now available on expanded access. These and other drugs may be available in studies at your clinic.

CCR5 inhibitors - a type of entry inhibitor - are also in development. The compound in furthest development is maraviroc, which is now available in the UK on expanded access.

It is not clear whether CCR5 inhibitors will be effective when HIV is very advanced and CD4 counts are very low. This is because in advanced disease the virus can stop using CCR5 and switch to a different receptor called CXCR4.

Integrase inhibitors work at another stage of the virus lifecycle - by stopping the integration of the virus DNA into the DNA in the nucleus of the CD4 cell. Raltegravir (MK-0518) is an integrase inhibitor that is now available in expanded access. In early trials it produced earlier and more substantial reductions in viral load compared to efavirenz (both with tenofovir and FTC).

Maturation inhibitors are another potential new class and interfere with one of the last processes in the HIV lifecycle and result in non-infectious virus being produced. None of these compounds are available yet.

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

Using viral fitness

Most of the approaches to salvage therapy in this booklet have been used for several years. Recently some researchers have looked at whether viral fitness can be used in a new way.

Viral fitness refers to how well HIV is able to reproduce. 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.

Many people, for example, continue to use 3TC or FTC even though they have developed the 184V mutation. This is because this mutation makes the virus less fit and therefore keeps viral load lower.

This means that there could be 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 strategy also produced a significant CD4 increase over every four-month period, and suggests an alternative to the use of either combinations with five or more drugs or treatment interruptions.

It stresses the importance of aiming for undetectable viral load, but for when this is not possible, it offers a new 'holding' strategy until new drugs are available.

Benefit of staying on treatment

- **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/mm³.

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/mm³.

If you have a high viral load, then there may not be any benefit from continuing to use efavirenz or nevirapine. For example, 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.

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, it is likely to still provide some benefit.

This strategy prioritises keeping your CD4 count in 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 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 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 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. Although many doctors were originally reluctant to change any regimen that was working well against HIV, this has changed.

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.

Switching a PI to an NNRTI

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 a combination with fewer pills and diet restrictions.

This is also more likely to help if you have fat accumulation (stomach, breasts, shoulders).

Switching between nukes

Most combinations involve at least two nukes (AZT, d4T, ddI, 3TC, FTC, abacavir, tenofovir) and many nukes have similar anti-HIV activity. As long as you haven't developed resistance, you can often switch to an alternative drug from this class.

- If you get symptoms of peripheral neuropathy (pain or numbness in your hands or feet) this may be related to ddI, d4T or, more rarely, 3TC. You should switch these drugs before the nerve damage becomes serious and permanent

- Both 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. Triple nucleoside combinations are only recommended in a few specific circumstances.

Switching between NNRTIs

Both 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 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.

Switching between PIs

When switching from one PI to another you have to be just as careful to not switch to a less potent combination.

Switching from any PI to a boosted-PI is easy, as this is considered more potent. Switching between PIs used in boosted-PI combinations, although not well studied, but is also likely to be okay.

Using new classes: integrase and CCR5 inhibitors

As long as potency of drug from new classes matches the drug you are switching from, you are unlikely to see viral load rebound. Newer drugs will hopefully not have all the same side effects associated with current meds. The tropism test that you need to take before using a CCR5 inhibitor only works if your viral load is over 500 copies/mL.

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. Versions in other languages are available online .

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 salvage 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.

The four most important pipeline drugs available on expanded access in 2007 (darunavir, MK-0528, etravirine and maraviroc) are briefly summarised below.

Additional new trial drugs may become available before this booklet is updated, including new protease inhibitors from Pfizer (AG-001859) and NCI (UIC-020301); CCR5 inhibitors from Takeda (TAK-652) and Merck (CMPD 167); and a maturation inhibitor from Panacos (PA-457).

It is unlikely that all these compounds will become licensed drugs, but this gives you an idea of the breadth of ongoing research.

New drugs available in early access programmes 2007

Darunavir

Darunavir is a protease inhibitor being developed by Tibotec. It was previously called TMC-114, and the tradename is Prezista.

As this booklet went to press, darunavir is likely to be the next approved drug in Europe. It was approved in the US in June 2006 and has been available in the UK on a named patient programme since December 2005.

Darunavir needs to be boosted by ritonavir and is dosed at 600mg plus 100mg ritonavir, both twice daily. **When used with other active drugs it can be active against a broad range of protease-resistant HIV.**

People who used started T-20 for the first time when they also started darunavir had a 63% chance of getting their viral load undetectable to less than 50 copies/mL.

Raltegravir (MK-0518)

Raltegravir is being developed by Merck and is expected to be the first integrase inhibitor approved.

As it works in a different way to existing drugs, it will also work against virus that is resistant to existing drugs. **It needs to be used with other active drugs in order to prevent resistance from developing.**

Raltegravir needs to be taken twice daily with, or without food and does not require ritonavir boosting.

When compared to efavirenz, it produced very rapid declines in viral load. Although there is currently

only safety information on around 300 patients, no important side effects have been seen and there is less impact on lipids compared to efavirenz.

Etravirine

Etravirine is a second generation NNRTI being developed by Tibotec, that was previously called TMC-125.

Although etravirine is expected to work against HIV that is resistant to efavirenz and nevirapine, **it is essential that other sensitive drugs are used in the new regimen.**

Drug interactions between etravirine and protease inhibitors, including boosting ritonavir doses mean that it is unclear how best to use this drug, even when it is available in an expanded access programme.

Maraviroc

Maraviroc is an entry inhibitor which is available in expanded access, and will be active against other HIV that is resistant to other drug classes.

It may only have a limited role in treating very advanced HIV, because it attaches to a receptor on the CD4 cell that is predominantly used in early and chronic infection.

It needs to be used with other active drugs.

New, expanded access and experimental drugs – April 2007

darunavir (TMC-114)	The next PI expected to be licensed. It is boosted with ritonavir and has activity against PI resistant virus.	Approved in Europe in March 2007.
raltegravir (MK-0528)	The first integrase inhibitor. Active against virus resistant to other classes of drugs. Greater than -2 log reductions in viral load.	Named-patient programme since Jan 2007.
etravirine (TMC-125)	NNRTI with activity against NNRTI-resistance, if switched early, and if other sensitive drugs are used in the combination.	EAP started in early 2007.
maraviroc	Entry inhibitor that showed activity in early studies against resistant HIV. Available in UK trials.	UK trial sites. EAP started in Feb 2007.
vicriviroc	Entry inhibitor in early studies.	Look for new studies
PEG Interferon (Interferon A)	Once weekly injectable hepatitis C drug. Anti-HIV activity (and side-effects) increase with dose used (as with regular interferon A).	Named-patient access may be available.
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.	Approved drug already available.
IL-2	An experimental drug, given by injection for 5 days every 8 weeks. IL-2 can boost your CD4 count, especially if on HIV treatment it remains under 200 cells/mm ³ . Heavy flu-like side effects.	Some named-patient availability – can be prescribed.
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.	Approved drug already available.
hydroxyurea (HU)	A 30-year-old anti-cancer drug that can resensitise HIV to ddl. Now rarely used. Used at reduced dose of 300mg, once daily.	Licensed drug. Don't use with both ddl & d4T.
mycophenolic acid	May boost abacavir levels in a similar way to hydroxyurea and ddl. Limited studies showed benefit using 500mg twice daily.	Licensed drug.
L-acetyl carnitine	An amino acid that has no anti-HIV effect but may minimise or reverse peripheral neuropathy associated with (nuke) drugs.	Unlicensed drug. Can be prescribed on named patient.

Further information**i-Base Information Phoneline**

i-Base runs a specialised information support service by phone, post and email where you can discuss any aspect of HIV treatment in confidence. This is a freephone number from land lines in the UK.

0808 800 6013

Mon, Tues, Wed 12pm–4pm

e-mail: info@i-Base.org.uk

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

i-Base produce other HIV treatment guides:

- *Introduction to Combination Therapy*
- *Avoiding and Managing Side Effects and*
- *Pregnancy, HIV and Women's Health.*

Please ask at your clinic or call *HIV i-Base* directly.

Information support organisations include:

aidsmap.com: UK website with treatment news and referenced articles

Body & Soul: Popular with women, families and African people. Includes teenage support group.

020 7383 7678: Monday–Friday, 11am–6pm

George House Trust: based in Manchester.

0161 274 4499, treatment information available

Mainliners: HIV and drug support agency.

020 7378 5496, Tuesday–Friday, 10.00am–4pm

(especially HIV & Hepatitis C treatment info)

Positively Women: Long-running support group.

020 7713 0222 (helpline), Monday–Friday 10–4pm

Waverley Care: HIV+ support group in Scotland.

0131 661 0982, with treatment information

THT Direct: 0845 122 1200

10am–10pm weekdays; 12–6pm weekends

Ugandan AIDS Action Fund (UAAF):

020 7394 8866, African support group



How to access our services



Call Free on 0808 800 6013
Treatment Information Phonenumber
Open Mon–Wed: 12.00–16.00

You can now ask a question online or by email:
www.i-Base.info

adherence - could you use some support?

side effects - or about anything in this booklet

trials - discuss the benefits and risks of joining a trial or study

information service - we can send you the latest research

HIV i-Base, 3rd Floor East, Thrale Hse, 44-46 Southwark St, London SE11UN. Tel: 020 7407 8488 admin@i-Base.org.uk www.i-Base.info.

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- Changing Treatment: second-line therapy and drug resistance)
- Pregnancy HIV and Women's Health
- Avoiding and Managing Side Effects
- HIV and hepatitis C coinfection (May 2007)
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