

JUNE 2005

Always watch for out-of-date info

ISSN 1475-2077

HIV i-Base

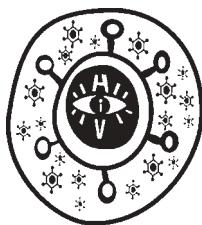


introduction to **combination therapy**

introduction
you & your doctor
adherence
resistance
combinations
drugs

www.i-Base.info

HIV i-Base publications: *Guide to Changing Treatment, Guide To Avoiding and Managing Side Effects, Guide to HIV and Pregnancy* and *HIV Treatment Bulletin (DrFax)*. All publications are free. Please call 020 7407 8488 www.i-Base.info



Contents

Introduction to the June 2005 edition	2
Introduction: what, why, when & other questions...	3
You and your doctor	11
Adherence: why it is so important	12
Adherence diary	14
Resistance	15
Which drugs, which combination?	16
Drugs and doses	19

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 June 2005 edition

Information about HIV treatment can change quickly. So only read information that is up to date. Be careful of information, whether printed or from the internet, that is not clearly dated.

We have updated this guide every 6-12 months for the last six years. If you are reading this after June 2006, please call i-Base to check for a new edition.

Changes made from the June 2004 edition of this i-Base booklet include:

- The drugs and dosing table on page 16 now includes two new dual nucleoside formulations (abacavir+3TC; and tenofovir+FTC).
- Choice of nucleosides on pages 14-15 has been rewritten to include recent changes to the UK treatment guidelines.
- References to the UK and US treatment guidelines are to the July 2005 and April 2005 versions respectively. These documents are each around 60 pages including tables. They are both available on the internet (www.bhiva.org and www.aidsinfo.nih.gov/) and are very useful reference documents.

Changes to the 2005 UK BHIVA treatment guidelines include:

- A new section has been added on gender and ethnicity.

- NNRTIs are recommended over protease inhibitors for first line therapy. Efavirenz is preferred over nevirapine.
- The link between AZT and fat loss is included as a factor to consider when choosing treatment.
- New-fill is recommended as a corrective treatment for people with facial fat loss (lipatrophy).
- Resistance testing is recommended for anyone with a new HIV diagnosis, whether or not you intend to start treatment straight away. It is also recommended before you start treatment.
- Resources such as the i-Base treatment passport are recommended for HIV-positive people to keep a record of their test results and treatment history.
- The section on monitoring tests has been expanded.
- The relative cost of different HIV drugs is included as a factor in considering long-term treatment.

If you have questions after reading this guide, then i-Base runs a free treatment information phonenumber for advice, support and information on all aspects of HIV therapy.

Please call: 0808 800 6013
Monday, Tuesday and Wednesday 12-4 pm

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

Introduction:

what, why, when & other questions...

This guide is mainly written for people starting their HIV combination, and for anyone currently

using HIV treatment who was never given support information before they started treatment.

What is combination therapy?

Combination therapy is the term for using three or more drugs to treat HIV. It is also called triple or quadruple therapy or HAART (Highly Active Anti-Retroviral Therapy).

These drugs work in different ways and at different stages of the HIV life cycle. (See Figure 1).

Do the drugs really work?

In every country that uses HAART, AIDS-related deaths and illnesses have dropped dramatically.

Treatment works for women, men and children. It works no matter how you were infected with HIV. Whether this was sexually, through IV drug use, or by blood transfusion.

Taking HIV drugs, exactly as prescribed, will reduce the virus in your body to tiny amounts. This then lets your immune system recover and get stronger by itself.

Regular monitoring, using blood tests, will check that the drugs continue to work.

- Viral load tests measure the amount of HIV in your blood. Results are given as copies/mL.
- CD4 tests measure how strong your immune system is. Results are given as cells/mm³.

Even if you start with a very low CD4 count, you could regain enough of your own immune system for your body to recover from many HIV-related illnesses.

If you use HIV treatment at the right time, and in the right way, you should stay well much longer.

HIV uses CD4 cells as factories to make hundreds of copies of itself. Different drugs work at different stages of the HIV life cycle.

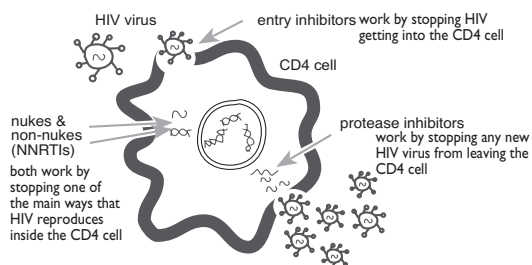


Fig 1: HIV drugs work in different ways

How long will the drugs work?

Combination therapy using at least three drugs has now been used for over six years. Many of the individual drugs have been studied for even longer.

The length of time that any combination will work depends mainly on you not developing resistance. This depends on getting, and keeping, your viral load to undetectable levels, below 50 copies/ml.

If your viral load stays undetectable, you can use the same combination for many years.

UK guidelines state that getting your viral load below 50 is a main goal when starting treatment.

Does everyone need treatment?

At some point, most HIV-positive people will need treatment. When people will need it though, can vary a lot. HIV infection progresses in different people at very different rates.

- About one third of HIV-positive people will stay well for up to 10 years after infection, even without treatment.
- About 60% will start treatment after 4-5 years.

Even if you are well, it's a good idea to get to know something about treatment now...

This is particularly important if your CD4 count is falling or if you have a high viral load.

- 2-3% of people can become ill more quickly and need treatment much earlier.
- 2-3% can go for 15-20 years without treatment.

Whether you need treatment is something you have to discuss with your doctor. This will usually take place over several visits.

When discussing treatment:

- Ask as many questions as possible until you are happy with the answers.
- Get useful information from other sources. This includes the internet, friends, newsletters and phelines.

Even if you are well, it is a good idea to get to know something about treatment now, before you need it.

This is particularly important if your CD4 count is falling, or if you have a high viral load.

When should I start treatment?

When to start treatment is something you and your doctor must discuss together. You are the person who has to take the pills. So, you have the choice over whether you start, as well as which drugs you use.

It is recommended to start treatment before your CD4 count falls below 200. Even at this level, there is unlikely to be an urgent need for you to start treatment straight away, if you are not ready.

- Ask your doctor to tell you about the different drugs that you can use. You need to know the

good and bad things about each of them.

- Take time to think about what you want to do. Do not feel rushed or pressurised into doing something you don't understand. If you have only recently been diagnosed HIV-positive, you will need to deal with that first.

While your CD4 count is above 300, you still have a good immune system. Below 300, you are at a higher risk of infections that cause diarrhoea and weight loss.

If your CD4 count falls below 200, your risk of developing a pneumonia called PCP increases. If it falls below 100, then your risk of serious illnesses increases even further.

A low CD4 count does not mean that you will definitely become ill. It is, however, much more likely. Most of the drugs used to treat these HIV-related illnesses can be more toxic and difficult to take than regular anti-HIV drugs.

Although you may be worried about using treatments, HIV and AIDS is still a very real and life-threatening illness. It is possible to delay treatment until it is too late. Illnesses that can occur at any time when your CD4 count is below 200 can be fatal.

Are recommendations the same for men and women?

There are some differences between HIV in women and men. One of these is that at the same CD4 count, women can have a slightly lower viral load than men. Some studies also show that women have a higher risk of becoming ill than men at the same CD4 count. This may be a reason for women to start treatment earlier than men. The evidence to support this was not strong enough for this to be included in treatment guidelines.

An American study found that viral load levels vary during the different stages of the menstrual cycle. It may be a good idea, for you and your doctor, to make a note of where you are in your cycle when you have these tests. You can then make an allowance for this when you get the results.

What about treatment in pregnancy?

Many studies have shown that women's HIV can be treated very effectively during pregnancy.

In addition, treatment with combination therapy that reduces your viral load to below detection will reduce the risk of transmitting HIV to your baby to almost zero.

Recent studies showed that women who start treatment with a CD4 count that is above 250 cells/mm³ should not use the drug nevirapine because they are at a higher risk of liver toxicity. This caution also applies to pregnant women who are starting treatment with a CD4 count above 250 cells/mm³.

This is a specialised area and for more information on HIV and pregnancy see the i-Base guide *HIV, Pregnancy and Women's Health*.

How do children use HIV treatment?

The principles for treating children with HIV are very similar to those for treating adults. But, there are some important differences.

The immune system and drug absorption can be different in babies, toddlers, infants, children, adolescents and adults. This is why specialist paediatric HIV care is recommended at all ages.

One of the main differences between children and adults is that CD4 counts are much higher for children. A new-born baby for example can have a CD4 count that is 2-3000 cells/mm³. This means that CD4 levels that are used to decide when adults should start treatment are not appropriate for children.

Children are monitored using CD4 percentage (CD4%). This is the percentage of lymphocytes that are CD4 cells. The CD4% of an HIV-negative person is around 40%.

A guide to children's CD4 count and CD4% by age is in Table 1.

Table 1: CD4 range and equivalent CD4% for babies and children by HIV disease category:

	<12 mo	1-5 yrs	6-12 yrs
Cat 1 no supp	>1500 >25%	>1000 >25%	>500 >25%
Cat 2 mod	750-1500 15-24%	500-1000 15-24%	200-500 15-24%
Cat 3 severe	<750 <15%	<500 <15%	<200 <15%

For this reason, there are separate treatment guidelines for treating children. However, they tend to be updated less frequently than adult guidelines. It is therefore important to be aware of changes in adult care that may be just as relevant for children.

Adherence is the term for taking all your medications exactly as prescribed. This is also essential at any age. Resistance can develop regardless of age if you use a treatment that does not get your viral load to undetectable levels.

For more information about children and HIV, visit the Children with HIV Association (CHIVA) and PENTA websites:

www.bhiva.org/chiva

www.penta.org

Is age an important factor in adults?

Combination therapy may reactivate an important part of your immune system called the thymus. Previously, most doctors thought it stopped working in adolescence.

One study showed that the thymus may become active again in people in their 30s who are HIV-positive and using combination therapy. This finding isn't yet fully understood. It may mean that there are advantages to starting treatment when in your 20s or 30s in order to make use of this.

Ageing suppresses our immune systems and reduces our CD4 count. People over 50 have an increased risk of

damage caused by HIV. The argument for starting treatment probably gets stronger as you get older.

Treatment guidelines do not yet comment on this apart from in reference to heart disease (see below).

Age, HIV drugs and heart disease

Risk factors for heart disease include age (over 45 for men and over 55 for women), sex (male), lack of exercise, family history of heart disease, high blood pressure, smoking and diabetes.

Other risk factors associated with heart disease include raised levels of cholesterol and triglycerides, which can be a side effect of HIV treatment.

The benefits of HIV treatment far outweigh the additional risks of heart disease. However, people with higher risk of heart disease have to carefully choose their HIV drugs to minimise any additional risk.

The additional risks that HIV treatment may cause, means that an assessment of cardiovascular and HIV risk factors should be made before starting HIV treatment.

Free risk assessment programmes are available on the internet for your doctor to use.

UK site with cholesterol measurement in mmol/l:
www.riskscore.org.uk/

US site with cholesterol measurements in mg/dl:
hin.nhlbi.nih.gov/atp/iii/calculator.asp

Site with pdf download files with total cholesterol and HD cholesterol look-up tables and manual risk calculators:

nhlbi.nih.gov/about/framingham/riskabs.htm

It may be better for a 55-year-old male smoker who is well, but takes little exercise and has a family history of heart disease to delay HIV treatment until he makes lifestyle changes that reduce some of these risks. If his HIV risk factors are also high (if he has a low CD4 count or a high viral load), then lifestyle changes and choice of HIV treatment become even more important.

Early diagnosis and primary infection

Some people who discover that they are HIV-positive within six months of being infected decide to start treatment straight away. This is regardless of their CD4 and viral load counts.

People treated in this six-month period hold on to a part of their immune system that is ordinarily lost in almost everyone without early treatment. It is retained, however, by people in whom HIV progresses only very slowly. This is the HIV-specific immune response.

Unfortunately, researchers have not yet been able to turn this finding into an improved health benefit. Using early treatment may enable you to benefit from immune treatments or vaccine-related research in the future.

But, you need to balance these potential benefits, against side effects and the risk of resistance. Also, that you may not medically need treatment for many years. Treatment in primary infection is therefore largely only provided in clinical trials.

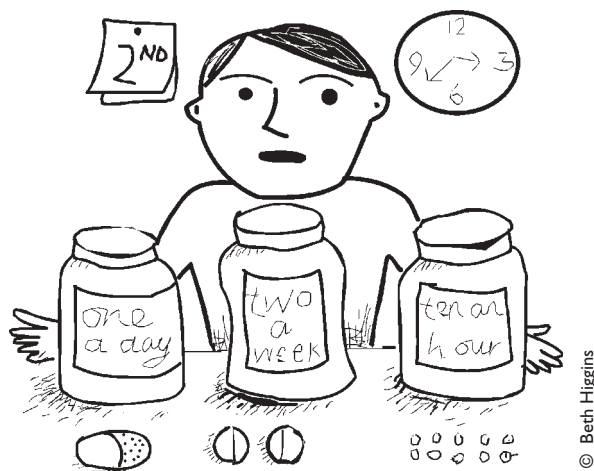
If you think that you were infected within the last six months, you can ask for a de-tuned (STARHS) HIV test. This can confirm a recent infection. Your doctor can access this test free from the Health Protection Agency (HPA) HIV laboratory in Colindale (020 8200 4400).

If you are interested in a trial, and one is not available at your clinic, you can contact the research centres at either St Mary's Hospital (020 7886 6047) or the Royal Free Hospital (020 7472 6232) in London.

Late HIV diagnosis and low CD4s

Some people, across all age ranges, only find out they are HIV-positive when they become ill and admitted to hospital. This often means starting treatment straight away, especially when the CD4 count is below 100 cells/mm³.

Even with a very low CD4 count, even below 10 cells/mm³, if you follow your treatment very carefully, you can expect treatment to work. Your viral load will drop and your CD4 count will rise again to safer levels.



What about side effects?

Everyone considering HIV treatment worries about side effects. But within a few weeks, most people find that taking treatment becomes an ordinary and manageable part of their daily life.

- Most side effects are usually mild;
- They can often be reduced with other medication that is easy to use;
- There is only a small risk of serious side effects, and these should be picked up by careful routine monitoring.

Ask your doctor, nurse or HIV pharmacist about the most common side effects of the drugs that you want to use. Ask how likely they are to occur. Ask how many people stop treatment because of them (usually very few). Even rough estimates will give you a good idea of what is involved.

Nausea, diarrhoea and tiredness are the most common general side effects. These often become easier after the first few weeks. Very rarely, nausea and tiredness can be very serious. This is why you should tell your doctor of any problems.

Ask your doctor or pharmacist for anti-nausea and diarrhoea medications when you first start therapy so you can use these as you need them.

If these medications aren't effective, ask your clinic for stronger or more effective drugs.

Lipodystrophy

Lipodystrophy refers to changes in blood fat and blood sugar levels. It also includes changes in fat cells and the distribution of body fat.

It is a set of side effects that is a worry for many people who are about to start treatment.

However, most severe cases of lipodystrophy are in people who have used many different drugs, or have used treatment for many years. Newer drugs used in

first-line therapy are less likely to cause these problems. The greater awareness of lipodystrophy, means that you will be monitored carefully. You can change treatment if you get early symptoms.

Different drugs may be responsible for fat gain and fat loss. Fat accumulation, to the stomach or breasts and/or across the shoulders, has been more linked to protease inhibitors and NNRTIs. Fat loss (from arms, legs, face and buttocks) has been linked to nucleosides. This is mainly to d4T, and to a lesser extent to AZT.

We do not know what causes lipodystrophy.

Symptoms can occur rarely in HIV-positive people who are not on treatment. Lipodystrophy usually, but not always, develops slowly over many months.

Early symptoms may reverse if you switch to different HIV drugs. Exercise and dietary changes can also help.

Careful body measurements by a dietician, by DEXA scan, or photographs can monitor changes.

Regular blood tests will check for other side effects. If you have any difficulties make sure your doctor takes them seriously and does something about it.

Other side effects

Side effects that are more serious occur rarely with most combinations. They also relate to specific drugs. It is important to be aware of those associated with the drugs that you will use before you start treatment.

Because some of these symptoms include rash, nausea and tiredness that are common side effects, it is important that your doctor knows about any difficulty you are having.

The i-Base Guide to Avoiding and Managing Side Effects includes detailed information about both common and rare side effects.

It also contains useful information about how to report side effects to your doctor. For a free copy please call 020 7407 8488.

Regular blood tests will check for some side effects. If you have any difficulties make sure your doctor takes these seriously... Nausea and fatigue can be very serious...

What is the best combination?

There isn't one answer to this question. This is because drugs that agree with one person can be much more difficult to tolerate for another.

Any combination should be selected with two points:

- That you are using a combination that is potent enough to reduce your viral load to below detection. This may sometimes mean using more than three drugs.
- That you can tolerate the drugs *and* follow the daily schedule *and* any dietary restrictions.

The most commonly used combinations, which balance these two aspects of treatment, are discussed in more detail on page 14.

Your doctor will discuss with you which combinations are more likely to get your viral load undetectable. If you have taken HIV drugs before, this will affect how well your next treatment works.

Ask for information about dosing schedules, pill size and side effects. This will help you pick a regimen that will be easier to follow.

Can I change treatments?

If your first combination is too difficult to follow, or if any initial side effects have not improved after the first few weeks, you can always change the drug or drugs that you find most difficult.

If this is your first combination, you have many choices. You should not put up with difficult side effects for months on end.

Many people use one combination to get their viral load undetectable, and then change to an easier combination afterwards.

Can I take a break in my treatment?

Originally, and not very helpfully, 'treatment breaks' were called 'drug holidays'. Other names include STIs, which stands for Structured (or Strategic) Treatment Interruptions.

Several trials, including the SMART study in the UK, are looking at stopping and restarting treatment based on CD4 count. The higher that your CD4 count was above 200 cells/mm³ when you first started treatment and the higher it is now, the less risk there should be from taking a treatment break in the future. This could be an advantage to starting treatment with a higher CD4 count.

Stopping treatment for a short period - perhaps only 1-2 months - may help people who are resistant to available drugs. This has to be balanced against a real risk of a drop in CD4 count. One recent study showed that a break of four months was worse than not taking a break.

Other trials looking at how the immune system responds to HIV did not find a benefit from treatment interruptions.

- Stopping treatment for any short period is not generally recommended. Your viral load can increase again very quickly (from undetectable to several thousand in a few weeks). Each interruption of treatment also carries a risk of developing drug resistance.
- An interruption may be reasonable if you have a very strong CD4 count or have very difficult side effects.
- If you want to take a treatment break, it is essential you talk to your doctor first. Some drugs have to be stopped together and others at different times, in order to reduce the risk of resistance.
- In someone with resistance to 3TC or FTC (the M184V mutation), taking either 3TC or FTC as a single drug may be better than stopping everything.

What does 'treatment naive' mean?

The term for someone who has never used any anti-HIV drugs before is 'treatment-naive' or 'drug-naive'. This is a very special position to be in. It means that any of the available drugs should work.

The first time you use anti-HIV drugs is the time they are most potent. This is why it is best to get it right first time.

Should I enter a trial?

Many hospitals are also research centres and you may be asked to join a trial.

Remember, many combinations are already available to use that have proven their effectiveness. There is no need to join a trial if you do not want to.

Treatment is now recommended when your CD4 count is about 200 cells/mm³. This should also be the case for new HIV treatment in trials. If your CD4 count is much higher than 200 cells/mm³, then it should be clearly explained to you that treatment would not be routinely recommended.

Well-planned studies can offer better monitoring and care than you would normally receive at your regular clinic. This may mean attending your clinic more frequently.

If asked to join a trial, or if you are interested in a trial, take plenty of time to find out about it. Ask for independent advice. Women should ask the percentage of women that are included in the study.

Trials are very important for developing new treatments. They can improve our knowledge of how to use both new and existing drugs. However, if you are recently diagnosed, or are only just finding out about treatment, you should not feel pressurised into taking part.

Ask about the alternatives to the treatment proposed in the study. Ask what advantages the study offers over existing treatment.

Your future care will not be affected if you choose not to take part in a trial.

What else do I need to know?

Ongoing research means that ideas about how to use anti-HIV drugs are changing. The treatment your doctor will advise today is likely to be different from 12 months ago.

This isn't just because there are newer drugs available. It is to do with understanding how the drugs work, why they sometimes stop working, and especially increasing knowledge about resistance.

Ask questions about anything you don't understand. You can then take responsibility for whatever you decide.

Why do treatments not always work?

For some people the treatments will not work as well. There are several reasons why:

- The combination may not be potent enough.
- You may already be resistant to one or more of the drugs in your combination.
- The regimen may be difficult to follow (even if you are only missing one dose a week).
- One or more of the drugs may not be absorbed properly. There can be big variations between people and tests can check for this.
- Side effects may be too difficult to tolerate.

Trial results never show a 100% success rate. BUT if you have a good doctor, and you follow your regimen carefully, anyone starting treatment for the first time should be able to get an undetectable viral load.

Success rates for people on their second or third therapy are usually lower than for those starting treatments for the first time.

This is often because people continue to make the same mistakes and move to a new combination without understanding why the original one failed.

This booklet concentrates mainly on the effect of treatment on viral load and CD4 results. This is because these are the main markers that doctors use to decide if a treatment is working. Some people may never reach undetectable levels but still stay well and healthy for many years. There are always more responses to treatment than can be summarised here.

You may not get an undetectable viral load, perhaps because of resistance. However, you can still benefit from continuing treatment.

The first time you use anti-HIV drugs is the time they are most potent. This is why you should try to get it right first time.

Don't look at the drugs you start with now as a treatment that you will be taking forever...

Look at them as something you have to be really committed to for the next couple of years.

You could also benefit from new drugs developed in the future. New drugs become available before full approval through early-access programmes.

If you need new drugs in order to put together a new combination then make sure you and your doctor keep up-to-date on the latest research.

For more information on second-line and salvage treatment, see the i-Base *Guide to Changing Treatment*.

Are the drugs a cure?

The current drugs are a treatment but they are not a cure. They stop the progression of HIV. They let your immune system start to repair itself. But, you will still be HIV-positive.

Even people taking combination therapy for many years, with a viral load below 50 copies/ml, still have very small amounts of HIV. This HIV is in cells that are 'resting' or 'sleeping' and it becomes detectable again when they 'wake-up'.

These sleeping cells are one of the reasons that it is very difficult to find a cure for HIV. Some of these cells can sleep for 70 years.

The drugs are getting us closer to finding a cure. You may need medication for a long time, but newer drugs may be easier to take and more effective.

This means you may still get to die of old age rather than from HIV.

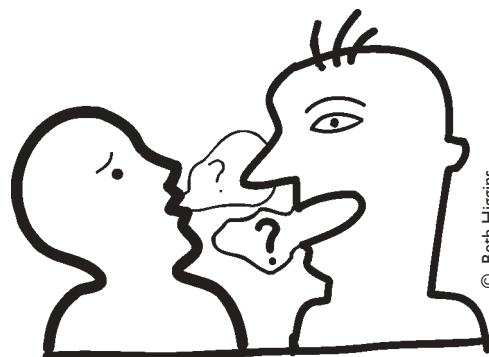
It may also mean that you are still alive when we find a cure - and this is something good to aim for.

Don't look at the drugs you start with now as a treatment that you will be taking forever.

Look at them as something you have to be really committed to for the next couple of years.

Take this new aspect of your life more seriously than anything else until you get it right.

You and your doctor



© Beth Higgins

Develop a good working relationship with your doctor and other healthcare workers.

Nurses and pharmacists are also an excellent source of support and advice on all aspects of your treatment (including adherence and side effects).

They are able to make referrals to other professionals, including dieticians, psychologists and social workers.

In the UK, you always have the option to change your doctor. You can also change your treatment centre.

But, if you have generally been happy with your treatment, then changing your doctor or clinic should be a last resort. Careful negotiation can usually help in most cases.

Both you and those involved in your care have certain rights and responsibilities. A list of your rights as a patient and things you can do to help are below.

Your rights as a patient...

- To be seen within 30 minutes of your appointment. If this is late, you should expect an explanation.
- To have different options for treatment explained to you. This should include the risks and benefits of each option.
- To be fully involved in all decisions about your treatment and care.
- To be treated with respect and confidentiality.
- For your records to be kept securely. They should be available for you to see if you ask.
- To choose whether to take part in research trials. This will not affect your current and future care.
- To make a complaint about your treatment. Any complaint must be fully investigated. Again, this must not affect your future care.
- To have a second opinion from a suitably qualified doctor.
- If you write to your hospital or clinic, you should have a written response within 14 days.
- To change your doctor or treatment centre without it affecting your future care. You do not have to give a reason for changing doctors or clinics. However, if there has been a misunderstanding, then giving a reason can sometimes help resolve the problem.

- To have test results and a summary of your history forwarded to your new doctor or treatment centre.

Things you can do to help...

- Find a clinic that is convenient to you and that you feel comfortable with.
- Find a doctor who you feel comfortable with. If you are a woman and want to see a female doctor then ask for this.
- Make a list of things you want to discuss with your doctor. Remember to take it to your appointment!
- Try to see the same doctor at each visit. This is important. It's difficult to develop a good relationship if you always see a different doctor.
- Plan to have your routine bloods taken 2-3 weeks before your regular clinic visits. The results will then be available for your appointment.
- Book routine appointments in plenty of time.
- Turn up for your appointments on time. Tell the clinic if you can't make it. Then they can give your slot to another patient.
- Treat all people involved in your care with the same respect you would wish to receive yourself.
- Listen carefully to the health advice that you are given, and act upon it.
- If you don't understand something, ask your doctor to explain it again or in a different way.
- Be honest with those caring for you. Tell them about any other drugs that you are taking. This includes legal and illegal drugs or complementary treatment.
- Be honest about your level of adherence. If those managing your care don't know you are having problems, they can't help.

Further advice on your NHS rights are detailed in the department of health booklet *Your Guide to the NHS* available by phoning 0800 555777 or on the internet:

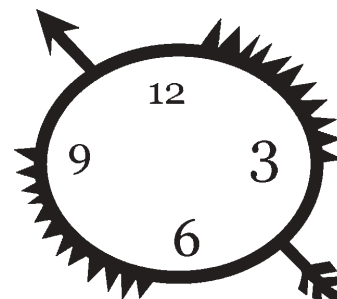
www.nhs.uk/nhsguide/home.htm

Information about healthcare services including core principles and information on how patients can make a complaint are online:

www.nhs.uk/patientsvoice/default.asp

Adherence

why it is so important



What is adherence?

Adherence is a word to describe taking your drugs exactly as prescribed. This includes taking them at the right time. It also includes following any special diet restrictions.

It is important that you develop a routine. Treatment for HIV involves a complicated daily schedule. You may need some support to get used to the changes it makes in your life. Adherence can be very difficult.

This is the most important thing you have to think about when you start taking a new combination.

Start treatment when you can give yourself the extra time and space you may need to adjust.

During the first few weeks, nothing else should take priority over getting your treatment right.

Many treatment centres now have an adherence clinic or an adherence nurse.

How much is enough?

Taking medication exactly on time is very important. However, there is usually a window period of about an hour that is still okay. Some drugs, and some people, have a wider window period than others.

Because of this variation, it is still better to aim for the same time each day.

Diet restrictions are very important. Ignoring these can be like only taking half a dose. You will not absorb enough of the drug for it to work properly. Resistance is then more likely to occur.

This may mean you lose the chance to use these drugs in the future.

The next question is: 'exactly how close to perfect adherence do you have to get?'

Unfortunately, the answer is 'almost 100%'...

Many studies have shown that even missing one or two doses a week can have a big impact on the chances of a successful treatment.

The study results opposite show this. Even with 95% adherence, only 81% people achieved undetectable viral load levels. That is only one in every 20 doses that was missed or late.

Adherence rates	% of people undetectable
over 95%	81%
90-95%	64%
80-90%	50%
70-80%	25%
under 70%	6%

On the other hand, a US study of people in prison who took every dose showed much better results.

Because these patients were in prison, every dose was supervised. All had viral loads below 400 copies/ml after a year and 85% were below 50 copies/ml.

This result was more impressive than nearly every clinical trial. Most of these people had already failed previous treatments and so were even less likely to get a good result.

The point is not that you need to be in prison! It is that if you find a way to take all your drugs as prescribed, you will get good results.

- Be strict with yourself in assessing how adherent you are through a regular week.
- If it's not looking so good, you need more support. It is available but you will need to ask.
- Talk to your doctor!

Tips to help...

- Choice of treatment.
Get all the information on what you will need to do before you start treatment:
How many tablets? How big are they?
How often do you need to take them?
How exact do you have to be with timing?
Are there food or storage restrictions?
Are there easier choices?
- Use the daily chart on page 12 to plan your timetable and use it to get used to the routine. For the first few weeks mark off each dose and the time that you took it.
- Make sure that you contact your hospital or clinic if you have difficulties with side effects. They can prescribe additional medication to help. They can also change the treatment if necessary.

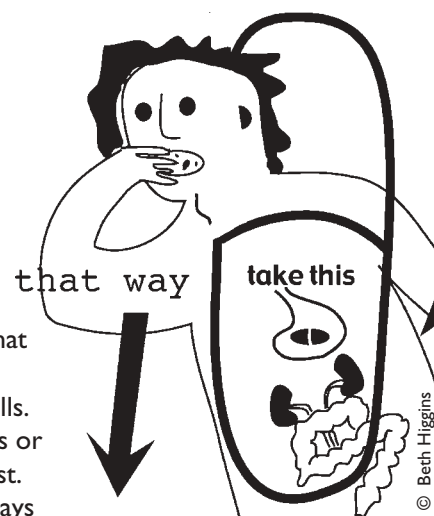
- Divide your day's drugs each morning and use a pillbox. Then you can always check if you think you have missed a dose.
- Use a pill beeper or alarm watch. Use it for both morning and evening doses.
- Take extra drugs if you go away for a few days.
- Keep a small supply where you may need them in an emergency. This can be in a cool place in your car, at work or at a friend's house.
- Get friends to help you remember difficult dose times. Ask them to remind you when you are out at night.
- Ask friends who are already on treatment what they do. Ask them how well they are managing. Most treatment centres can arrange for you to talk to someone who is already taking the same treatment if you think this will help.
- Ask your doctor for a supply of medications to control nausea and diarrhoea. These side effects are the most common when starting therapy.
- Most combinations are twice-daily regimens. This usually means taking them every 12 hours. However, several drugs only need to be taken once a day. This usually means taking them every 24 hours.
There are trials looking at other once-daily drugs. So a once-daily regimen may be available.
- Completely missing a once-daily dose may be more serious than forgetting a dose from a twice-daily regimen. Adherence is especially important with once daily regimens.

What if I forget to take my pills?

Almost everyone will forget or be late with their drugs at some time. There is a difference though between occasionally missing a dose, and regularly forgetting on a daily or weekly basis. You need to aim to take all your doses at approximately the right time.

You may be regularly taking them late or missing doses completely. If this is the case it may be better to talk to your doctor about stopping treatment altogether.

This would at least limit your risk of resistance. You can restart treatment later when you are more able to cope with the regimen.



There may be an easier combination that you can use. Some people hate lots of pills. Some hate fatty foods or having to eat breakfast. Some people will always have trouble with taking medicine at work during the day.

All these things are important in deciding which combination will suit you best.

You have to follow your regimen everyday. This includes both during the weekend, and in the different situations involved in life.

Taking days off your regimen is a very dangerous way of using treatment.

There are always things that can help you to avoid missing doses, whatever your lifestyle.

If you realise you have missed a dose; take it as soon as you remember. BUT, if you only realise when you're going to take your next dose, do not take a double dose.

Recreational drugs and complementary therapy

Some HIV drugs interact with recreational drugs, street drugs, methadone and complementary therapies.

The interactions can be complicated and involve both higher and lower levels of HIV or other drugs.

It is therefore very important that your HIV doctor and pharmacist know about any other drugs or supplements that you use. Even if you use them rarely. Your doctor will treat this information in confidence.

Alcohol does not interact with HIV medications. However, heavy alcohol use, as with recreational drug use, may reduce adherence. It would help if your healthcare workers know about this.

Adherence diary: Use the diary on the next page to work out your regimen timetable with your doctor, nurse or pharmacist.

Resistance

What is resistance?

Resistance to anti-HIV drugs occurs when the structure of the virus makes tiny changes. These changes are called mutations. This can mean that the drugs no longer work as well or even at all.

You can also be infected with a strain of HIV that is already resistant to some or all HIV drugs.

This is why UK guidelines now recommend that everyone should have a resistance test before starting treatment. You should have a resistance test if you have just been diagnosed with HIV, whether or not you plan to start treatment.

How does resistance occur?

Mutations that lead to drug resistance are generally only produced when you continue taking a treatment with a detectable viral load.

If your viral load is still above 500 copies/ml after 2-3 months, or above 50 copies/ml after 6 months, you may need to change your treatment.

Your doctor should look closely at why the results are not as good as they could be. They will want to discuss how you are managing adherence and side effects. They should also test for resistance and possibly drug levels.

Resistance can develop even at low viral load levels between 50 and 500 copies/ml.

You should have a viral load test four weeks after starting or changing treatment. This should then be checked at least every 3 months when on treatment.

Get the results when they are ready (usually after two weeks). Don't just wait until your next visit.

It is better to get your blood tested 2-3 weeks before you see your doctor. Then you will have the results back for the appointment.

If your viral load has increased you should then get a second test on the same day, to confirm the results.

Often slight increases are due to errors in the test. You can also have small increases that go back down again that are called 'blips' or 'spikes'.

A re-test will check what is happening. If the combination is failing, you minimise the risk of further resistance by checking this straight away.

You will get a better response to a second treatment if you change when viral load levels are still low.

What is cross-resistance?

Some drugs are cross-resistant to others. This means that if you become resistant to one drug you will also be resistant to other similar drugs, even if you have never taken them before. This is particularly true of drugs in the same class.

There are also varying degrees of cross-resistance.

Sometimes you may still get some benefit from the second drug but the response is less likely to be as strong or as durable.

How do I avoid resistance?

Avoiding resistance is one of the most important conditions for using combination therapy. You need to use a combination that is potent enough to minimise the risk of getting resistance to any of the drugs you take.

The best chance you have of stopping resistance involves reaching and maintaining undetectable on viral load tests that measure down to 50 copies/ml.

If you are starting treatment, this is a realistic goal.

Letters and numbers: what they mean

Resistance mutations are usually given a number to say where on the virus that the change has taken place - like a junction on a motorway. If there is a letter afterwards, this stands for the new chemical that the mutation makes. If there is a letter before this stands for the chemical that should be there first.

Fig 2 -The importance of different viral load levels when on treatment:

less than 50 (<50 copies/ml)	So little HIV is produced at this level that resistance is unlikely to develop to your combination. So long as you continue taking the drugs carefully, you could use them for many years.
between 50–500 (>50 and < 500 copies/ml)	This is not low enough to stop resistance developing. At some point, as resistance becomes more extensive, the drugs will stop working and your viral load will rebound much higher.
over 500 (>500 copies/ml)	If you continue to take treatment while your viral load is detectable (and not still falling) you run a high risk of resistance and will only be able to use your combination for a limited time.

Which drugs, which combination?

Glossary of four main kinds of HIV drugs:

RTI = nucleoside or nucleotide analogue, also called 'reverse transcriptase inhibitor' or 'nukes'

NNRTI = 'non-nucleoside reverse transcriptase inhibitor' or 'non-nukes'

PI = 'protease inhibitor'

EI = 'entry inhibitor' [T-20 (enfuvirtide) is the only EI approved and is not used in first-line therapy]

The strategy for using HIV drugs has been consistent for the last seven years. The main principle is that any combination needs to include at least three drugs.

Although this is still generally true, at the end of this section we also discuss a few different approaches.

Combinations usually include drugs from two different families. This involves choosing two 'nukes', plus *either* an NNRTI or a protease inhibitor (PI) boosted by ritonavir.

The best results have been using combinations like these. This is reflected in both UK and US treatment guidelines.

The UK treatment guidelines recommend the third drug to be an NNRTI, with a preference for efavirenz over nevirapine. This is mainly because NNRTIs require fewer pills or diet requirements than most PIs.

If you are not using an NNRTI as the third drug, UK guidelines now recommend that you should use a protease inhibitor boosted by ritonavir.

This includes lopinavir/r (Kaletra), which has ritonavir inside the capsule. It also includes saquinavir, fosamprenavir or indinavir, which all require a small dose of ritonavir to also be taken at the same time.

Atazanavir can also be used - although this is usually only after side effects with an earlier combination. Atazanavir is a once-daily PI. The daily dose is 2x150mg pills when it is boosted by 100mg of ritonavir. If this dose causes side-effects, the ritonavir can sometimes be stopped and a slightly higher atazanavir dose (2x200mg) used instead. Ongoing studies may lead to atazanavir being more routinely used as a first-line choice in the future.

Other protease inhibitors in development (tipranavir, TMCI 14) also need to be boosted by ritonavir, but both these drugs are designed for people with PI-resistance.

Using a small dose of ritonavir in these combinations provides better and more sustained drug levels. This reduces the risk of resistance. It also reduces the numbers of pills and dietary requirements compared to unboosted PIs. Some people though find even small doses of ritonavir increase nausea.

Whether you use NNRTI or PI-based regimens will depend on discussions with your doctor, your previous health and whether you have any prior drug resistance.

Which nukes?

There are currently six nucleosides or nucleotides ('nukes') available. These are 3TC, FTC, abacavir, AZT, ddI and tenofovir.

UK guidelines focus on three main pairs of nukes, and the differences between these three choices are discussed below.

ddI is rarely used as a first-line choice because it needs to be taken on an empty stomach.

Although d4T was previously widely used, this is not currently recommended for first-line therapy because of the link to lipoatrophy (fat loss).

UK choices - which dual nukes?

3TC and FTC are very similar drugs and are seen as interchangeable. All combinations should include one of these two drugs, but they should not be used together in the same combination.

The main choice then comes down to whether the second nuke is tenofovir or abacavir or AZT.

This is slightly simplified - or complicated depending on your point of view - as there are three 'dual-nuke' combinations where two nukes are in the same tablet:

- tenofovir + FTC (Truvada) - once-daily
- abacavir + 3TC (Kivexa) - once-daily
- AZT + 3TC (Combivir) - twice-daily

All drugs can be used in their separate components and may be prescribed separately depending on cost.

The most commonly used and studied combinations recommended in UK guidelines are made up using two drugs from Column A ('nukes') plus one of the choices from Column B.

Column A 2 Nukes	Column B		
	<i>EITHER</i> 1 x NNRTI	<i>OR</i>	1 x PI boosted with ritonavir
AZT + 3TC * tenofovir + FTC * abacavir + 3TC * ddl **	efavirenz or nevirapine	<i>OR</i>	Kaletra (lopinavir/r) or indinavir + ritonavir or saquinavir + ritonavir or amprenavir + ritonavir [or atazanavir + ritonavir <i>depending on ongoing studies</i>]

* Currently recommended 'dual-nukes' that are available in combined pills.

Tenofovir and ddl should not be used in the same combination. Tenofovir and abacavir should not be used together in a triple combination until a potential interaction found in two recent studies has been further explained.

** ddl is not usually used in first-line combinations because it has to be taken on an empty stomach, without eating for an hour afterwards. First-line combinations using ddl have been studied less and have no obvious advantages over the three pairs discussed above.

AZT, used with 3TC in a twice-daily combination, has been widely used and studied. Until recently it was recommended as part of first-line therapy in both the UK and US. The disadvantages of AZT are related to side effects of anemia and fatigue. More recently there has been stronger evidence linking AZT to lipoatrophy (fat loss).

With short-term use, (up to a year) the fat loss may not be noticeable in most people, and may reverse when the AZT is then switched to tenofovir or abacavir.

However, UK guidelines now recommend that people who are currently stable on AZT-based combinations should discuss whether they want to switch to an alternative nucleoside before fat loss occurs.

Tenofovir is a once-daily nuke. It is cleared by the kidneys and so monitoring for kidney toxicity, and not using tenofovir with other drugs that are cleared the same way, are important safety cautions.

Tenofovir is not linked to lipoatrophy.

Abacavir was originally approved as a twice-daily nuke, but more recently has been approved to be used once-daily. The main side-effect of abacavir is a hypersensitivity reaction that occurs in up to 7% of people who use this drug.

Symptoms include fever, rash, headache, sore throat, diarrhoea, abdominal pain, tiredness, nausea, vomiting, flu-like aches etc that get progressively worse each day.

Anyone who gets these symptoms must seek urgent medical advice with a view to stopping the abacavir.

Once stopped, abacavir must never be used by that person again, as the reaction can return with much greater severity and is potentially fatal.

A genetic test may become available to limit use by people who are at higher risk of this reaction, but it isn't commonly being used in the UK yet.

The concern of key resistance mutations with both tenofovir (K65N) and abacavir (L74V) is that these changes have cross-resistance to other nukes. For the small percentage of people who do not get a successful result, the resistance will be important.

However, there is not clear recommendation to guide the choice between abacavir and tenofovir.

In relation to side effects, unless there is an interaction (see below), most nukes are interchangeable. This means that if you get side effects with one drug you can switch to another.

Nukes that shouldn't be used together

Some combinations of nukes should NOT be used together are:

- AZT and d4T
- 3TC and FTC
- ddl and tenofovir
- abacavir and tenofovir (in a 3-drug combo until an interaction is explained by further research).
- d4T and ddl should not be used together during pregnancy.

Which NNRTI – efavirenz or nevirapine?

The difference between efavirenz and nevirapine has been the subject of a lot of debate.

In practice, both drugs have been widely used with perhaps 60% people using NNRTIs using efavirenz and 40% nevirapine.

However, the 2005 UK guidelines recommended efavirenz as first choice and nevirapine as an alternative. This was largely because of the small risk of serious reactions against nevirapine.

Both drugs have some similar side effects. This includes risk of rash and liver toxicity, which can be serious and occasionally fatal. Careful monitoring should check for this.

A serious allergic reaction called Stevens-Johnson Syndrome (SJS) is reported in 0.3% of people using nevirapine and 0.1% people using efavirenz. Nevirapine is not recommended in people with hepatitis and HIV.

The reactions with nevirapine usually only occur in the first two months. Over this time, you should be monitored more carefully. Otherwise, nevirapine is an easy drug to tolerate.

The main side effects of efavirenz relate to the Central Nervous System (CNS). They include mood changes such as anxiety, euphoria, depression and sleep disturbance that includes vivid dreams and nightmares.

They occur in nearly everyone when they first use efavirenz but usually reduce after a few days or weeks. About 10-15% of people in the clinic stop because of the general effect on their quality of life. However, about 3% of people stop efavirenz because of more severe psychiatric symptoms, and these can occur very early after starting treatment.

Before starting efavirenz, your doctor should give you specific information about these side effects.

Choice of protease inhibitors

The new UK recommendation is to use ritonavir-boosted protease inhibitors. Lopinavir/r (Kaletra) is the only combined pill, but other options are included in the table on page 16.

A new formulation of saquinavir (500mg) will reduce the number of pills required. UK guidelines do not recommend nelfinavir for first line therapy but it is often chosen as the third drug for use during pregnancy. Some people who are very sensitive to

ritonavir side effects can use un-boosted PIs. You can confirm drug levels for both single and boosted PIs using therapeutic drug monitoring (TDM).

Triple nucleoside combinations

Triple 'nuke' combinations are not recommended in the UK and US treatment guidelines, as they are less effective as first-line treatment.

Although a combination with only 'nukes' is not recommended for starting treatment, you may be able to cut down to a 'nuke'-only combination of abacavir, AZT and 3TC. This is usually only after a successful response to PI or NNRTI-containing treatment and only if you have no resistance to these nukes. Other triple-nuke combinations are not recommended.

The main reason to try this would be to reduce side effects related to PIs or NNRTIs. This includes increased blood lipids or fat accumulation (lipodystrophy).

New non-standard approaches

Using two 'nukes' plus either an NNRTI or a boosted PI has produced the most effective, durable and tolerable results for combination therapy.

Recent trials are looking at other approaches. So far, we only have limited data on these approaches.

For example, some studies do not use 'nukes' at all. By using either dual-boosted PIs (and in one case single-boosted PI), or PI+NNRTI combinations, they hope to avoid some of the side effects associated with 'nukes'.

However, not all 'nukes' have similar side effects. This is especially true for the link to lipodystrophy and fat loss. It may therefore be better to choose from abacavir, tenofovir, 3TC and FTC, rather than cut out 'nukes' altogether.

Also, many people do not get side effects on these drugs. It may again be better to see whether this is an issue before breaking from the recommended combinations.

Combinations with more drugs

Some people use combinations of five or more drugs. This is usually for people who have resistance to current drugs. It can also include people who have a very high viral load when they start treatment.

Once your viral load consistently stays below the level of detection, it is sometimes possible to cut back on the number of drugs used.

Drugs and doses

The following table is a reference for different names of drugs, dosing, total pill count and brief details of food restrictions. Alternative doses are required for some combinations. Some drugs (ritonavir, nevirapine) start at lower doses for the first 1 or 2 weeks. An asterisk * is for a drug which may be available on an expanded access programme and/or which is expected to be licensed shortly. All combinations and doses should be discussed with your doctor.

Name	Brand & other names	Dosing	Total daily pills	Food restrictions
REVERSE TRANSCRIPTASE INHIBITORS (RTIs)				
d4T	Zerit, stavudine	1 capsule, twice daily	2	none
AZT	Retrovir, zidovudine	1 capsule, twice daily	2	none
ddl/EC	'Enteric coated' formula	1 capsule, once daily	1	do not eat for 2 hours before and 1 hour after
3TC (150mg)	Epivir, lamivudine	1 tablet, twice daily	2	none
3TC (300mg)	Epivir, lamivudine	1 tablet, once daily	1	none
abacavir	Ziagen	1 tablet, twice daily	2	none
abacavir+3TC	Kivexa, Epzicom	1 tablet, once daily	2	none
AZT+3TC	Combivir	1 tablet, twice daily	2	none
AZT+3TC+abacavir	Trizivir	1 tablet, twice daily	2	none
tenofovir	Viread	1 tablet, once daily	1	take with food
FTC	Emtriva, emtricitabine	1 capsule, once daily	1	none
tenofovir+FTC	Truvada	1 tablet, once daily	1	none
NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIs)				
efavirenz	Sustiva	1 tablet (600mg), once daily	1	not with high-fat meal
nevirapine	Viramune	1 tablet, twice daily	2	none
DUAL & BOOSTED PROTEASE COMBINATIONS <i>[the most used doses - individual monitoring (TDM) of drug levels is recommended]</i>				
lopinavir/r	Kaletra, ABT-378/r	3 capsules, twice daily	6	take with food
indinavir/ritonavir	400mg/400mg	1xIDV / 4xRTV twice daily	10	none
	800mg/100mg	2xIDV / 1xRTV, twice daily	6	none
saquinavir/ritonavir	400mg/400mg	2xSQV / 4xRTV, twice daily	12	food reduces side effects
saquinavir/ritonavir	1000mg/100mg	5xSQV / 1xRTV, twice daily	12	food reduces side effects
<i>[When boosted by ritonavir, Invirase, hard gel saquinavir is used instead of Fortovase soft gel. Invirase is a smaller pill with less side effects]</i>				
fosamprenavir/ritonavir	700mg/100mg	1xFosAPV / 1xRTV, twice daily (once-daily possible)		none
atazanavir/ritonavir	300mg/100mg	2xATV/ 1 x RTV, once daily	3	none
tipranavir*/ritonavir	500mg/200mg	2xTPV/ 2 x RTV, twice daily	8	food reduces side effects
SINGLE PROTEASE INHIBITORS (PIs) <i>[Some PIs are used without ritonavir boosting. This is not generally recommended.]</i>				
nelfinavir	Viracept (film coated)	5 tablets, twice daily	10	take with meal
atazanavir	Reyataz (400mg/day)	2 capsules, once daily	2	take with food
ENTRY INHIBITORS (Fusion inhibitors)				
enfuvirtide	T-20, Fuzeon	subcutaneous injection, twice daily		none
OTHER DRUGS USED IN HIV TREATMENT				
Interleukin-2 (IL-2)	<i>Experimental immune treatment used with combination therapy to boost CD4 counts. IL-2 is given by injection for five days every 2 months and heavy flu-like side effects are expected during each five-day course.</i>			

i-Base treatment information phonenumber

0808
8000
6013

mon > tues > wed > 12-4pm



- adherence - could you do with some support?
- side effects - 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

vous parlez français? notre service est en français et anglais

lundi, mardi, mercredi 12-4pm

pour parlez avec une advocate séropositive - gratuit et en confiance

Service d'information specialise sur les dernieres recherches peuvent etre vue et envoyer par poste ou e-mail.

publications

All i-Base publications are available free. Treatment guides are written in everyday language.

HTB and reports from meetings are written in more technical medical language.

Please send me: *(please write clearly)*

- Introduction to Combination Therapy *June 2005 (this publication)*
- Changing Treatment: ...if treatment fails: (second-line therapy and drug resistance) *April 2005*
- Pregnancy HIV and Women's Health *Spring 2005*
- Avoiding and Managing Side Effects *February 2005*
- HIV Treatment Bulletin (HTB) – conference and medical reports (monthly)



Publications in other languages are available in pdf format at www.i-Base.info

Name: _____

Address: _____

Postcode: _____

Tel: _____ Email: _____

**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**

Not-for-profit copying is encouraged or call for extra free copies. This booklet aims to help you find out about your own treatment, but all treatment decisions should be taken in consultation with your doctor. HIV information dates quickly. If you're reading this after Summer 2006 call for a newer version. Written by Simon Collins and Andrew Moss & produced by HIV i-Base. Drawings: Beth Higgins.