



information series for HIV-positive people

HIV therapy



acknowledgments

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HIV therapy

The British HIV Association (BHIVA) is the UK's professional body for doctors who care for people with HIV and AIDS. BHIVA produce guidelines on how the medical care of people with HIV should be managed. Recently, BHIVA have agreed revised practice guidelines for 2001/2 on the use of drugs given to treat HIV infection. A short summary of the key points is provided on page 19. A glossary of technical terms used is on page 20. This booklet has been written to help you decide what questions to ask your doctor about any course of treatment you might be considering. We don't intend for it to replace discussion with your doctor about treatment.

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BHIVA HIV treatment guidelines

1

This booklet is a summary of the BHIVA HIV treatment guidelines: a set of recommendations about how anti-HIV therapy should be used to treat people with HIV infection in the UK. Several of the subjects covered within the guidelines are not included in this booklet, one example being the side-effects of treatment including lipodystrophy, the syndrome of blood and body fat changes which can affect people taking HIV therapy. If you would like to read the 2001/2 BHIVA treatment guidelines in full, they are available on aidsmap.com.

BHIVA formulate their recommendations through a consensus-building exercise where advice is based partly on evidence from

clinical trials, and partly on the opinion of HIV experts. This is because scientific research is not able to answer all the questions about the best use of HIV treatments. Research in the HIV field moves unusually quickly, which means that the guidelines summarised in this booklet should be seen as a 'best guess' based on what we know about HIV infection and its treatment at the moment.

These guidelines are not a recipe book for treating HIV. People with HIV always require individualised care, which is based both on their past and present state of health, and on the wider factors which influence daily life.

2 What is anti-HIV therapy?

Drugs given to treat HIV are also called antiretrovirals. Another name commonly used is HAART, which stands for Highly Active Antiretroviral Therapy. This means taking three or more anti-HIV drugs in combination, and is the standard way of treating HIV in most people.

Currently available anti-HIV therapy does not eliminate the virus from the body. Instead, it is given to prolong life and good health by reducing the harmful effects of HIV on the immune system.

When should anti-HIV therapy be started?

3

There is no clear evidence on when is the best time to start taking anti-HIV drugs. This means that doctors and patients must weigh up, on an individual basis, the likely benefits and risks of taking treatment now, as opposed to waiting until later. According to what is known about HIV treatment at the moment, the benefits of treatment are most clear for:

- people who have symptoms of HIV or AIDS
- people with low CD4 counts, another sign that the immune system is damaged.

BHIVA's recommendations about the timing of treatment differ according to the disease stage of the individual, meaning the length

of time of infection, the CD4 count and viral load, and whether or not symptoms of HIV are present. These are summarised in Table 1 on page 4.

4 Table 1: When should anti-HIV treatment be started

HIV disease stage	CD4 Count	Recommendation
Early (primary) infection	Any CD4 level	If treatment is being considered, start as soon as possible, and certainly within six months of infection
Established (chronic) infection without symptoms	CD4 above 350	Take treatment later
	CD4 between 200 and 350	Start treatment, taking into account the rate of CD4 decline, symptoms, patient's wishes and viral load
	CD4 below 200	Start treatment
Established (chronic) infection with symptoms	Any CD4 level	Start treatment

People who have contracted HIV very recently

The six month period which follows immediately after contracting HIV is called primary infection. There is no proof that starting treatment at this time will definitely lead people with HIV to live longer, healthier lives. However, doctors believe that this time may offer a unique opportunity to intervene which may be lost later in infection as the immune system sustains ongoing damage, and so may be less able to respond to HIV itself. This potential benefit has to be weighed against the risk of getting side-effects, finding that treatment reduces your quality of life, and the possibility that if the treatment you take

stops working effectively against HIV, you may be left with drug resistant virus.

A few people who took anti-HIV treatment very soon after infection seem to have maintained extremely low levels of HIV, even after stopping treatment. Others who have tried the same strategy have not had this response. Because there is a lack of clarity, it's recommended that people who do choose to take treatment in primary infection join a clinical trial, wherever possible.

People with established infection who have not had HIV symptoms

The research evidence which informs decisions about when people with established, or 'chronic' HIV infection should start treatment suggests that, ideally, people should begin before their CD4 count falls below 200. This is because people who start treatment when their CD4 count is *below* 200, face a greater risk of death, in the short-term, than those who start *before* their CD4 drops below this level.

At higher CD4 counts, the picture is less clear. Most studies suggest there seems to

be no difference in the short-term risk of ill health in people who begin treatment at CD4 counts above the 200 level. Therefore, the timing in these circumstances will depend on the level of viral load, the speed at which the CD4 count is falling, the likelihood of achieving good adherence, the presence of symptoms, and the patient's wishes.

Some people may choose an earlier start, particularly those whose CD4 count is falling by more than 80 cells per year, because this is likely to mean that the count will fall below 200 within the near future. Similarly, because people with a high viral load, who are not taking treatment, lose CD4 cells more quickly than others, and are

at greater risk of illness or death in the short-term, they too may choose to start treatment sooner.

Delaying therapy reduces the impact of long-term side-effects and the development of drug resistance. Therapies of the future may be easier to take, less toxic and perhaps more effective against HIV. The best responses to anti-HIV treatment are generally seen when people take it for the first time, and so these are important considerations.

People who are advised to start treatment but choose not to, should review their decision regularly and have their CD4 count and viral load monitored more frequently than usually recommended, for example every two months.

People with symptoms of HIV disease or AIDS

Everyone who has symptoms of HIV infection and has a CD4 count consistently below 200, or who has previously been diagnosed with AIDS, or a severe or recurring HIV-related illness, should start treatment. This is because each of these circumstances present a high risk of further opportunistic infections which although treatable, may cause irreversible damage to health, or be life-threatening.

8 What to start therapy with

Standard anti-HIV treatment for people who begin for the first time will involve a combination, or 'regimen', of three antiretrovirals. There are exceptions to this, such as women who take treatment when they are pregnant; and people with very high viral load who may need to take more than three drugs to get a powerful anti-HIV effect.

There is no research evidence to indicate which of the available combinations is best in terms of reducing ill health and extending survival. This means that choice of treatment is made after considering the risks and benefits of the available combinations on an individual basis. This should involve thinking about potency against HIV, adherence, tolerability, side-effects and problems with interactions between different medications being taken.

The anti-HIV drugs which are currently available on prescription in the UK, and the drug class to which they belong, are shown opposite in Table 2:

Notes for Table 2:

AZT and 3TC available in combined pill called *Combivir™*

§ AZT, 3TC and abacavir available in combined pill called *Trizivir™*

¥ lopinavir/ritonavir is a 'boosted' PI where the effects of lopinavir are enhanced through the use of a small dose of ritonavir

*saquinavir hard gel capsule should not be used in combinations where it is the only PI

Also available for treatment experienced people are the protease inhibitor amprenavir (*Agenerase™*) and the nucleotide analogue tenofovir (*Viread™*).

Table 2: Anti-HIV drug names

Anti-HIV drug class	Common names	Brand name
Nucleoside analogues	AZT, zidovudine# §	<i>Retrovir™</i>
	ddI, didanosine	<i>Videx™</i>
	3TC, lamivudine# §	<i>Epivir™</i>
	d4T, stavudine	<i>Zerit™</i>
	abacavir§	<i>Ziagen™</i>
NNRTI (Non nucleoside reverse transcriptase inhibitors)	efavirenz	<i>Sustiva™</i>
	nevirapine	<i>Viramune™</i>
PI (Protease inhibitors)	lopinavir/ritonavir‡	<i>Kaletra™</i>
	indinavir	<i>Crixivan™</i>
	nelfinavir	<i>Viracept™</i>
	saquinavir (hard gel capsule)*	<i>Invirase™</i>
	saquinavir (soft gel capsule)	<i>Fortovase™</i>
	ritonavir	<i>Norvir™</i>

Two nucleoside analogues plus one NNRTI

- It is recommended that people starting anti-HIV treatment for the first time take a combination of two nucleoside analogues and one NNRTI.

NNRTIs appear to present fewer problems with side-effects than protease inhibitors. This, together with the potential for easier adherence, are the main reasons why most doctors choose NNRTI-based combinations for use in people starting anti-HIV treatment. Their major disadvantage is that it is very easy to develop drug resistance to an NNRTI drug, and if this happens, it is unlikely that you will benefit from any other NNRTI. A further issue is that there is a

lack of information on how NNRTI-based combinations perform over the longer-term.

Two nucleoside analogues plus one, or two protease inhibitors

- People starting anti-HIV treatment may consider taking a combination of two nucleoside analogues and one, or two protease inhibitors.

Combinations including indinavir, ritonavir and saquinavir have each been shown to reduce the risk of ill health in trials. Saquinavir is available in two formulations, and the hard gel capsule is not recommended for use in combinations where it is the only protease inhibitor. The main disadvantages of PI-based

combinations are that they present a higher risk of longer-term side-effects and are less easy to adhere to.

Many doctors use one protease inhibitor with a small dose of ritonavir. This boosts the blood levels of the other drug and may allow both fewer pills and fewer doses, which may improve adherence. Boosted protease inhibitors may also have a stronger anti-HIV effect, and may be less vulnerable to the risk of drug resistance. On the other hand, there is some evidence that boosted PIs may cause more side-effects than single PIs and so one strategy cannot be recommended above the other at the moment.

Three nucleoside analogues

- People starting anti-HIV treatment may consider taking a combination of three nucleoside analogues if they have low viral load or concerns about adherence.

The major advantage of triple nucleoside regimens are that they are simpler, more tolerable, involve fewer pills, and cause less problems with drug interactions and side-effects. An exception is a side-effect of abacavir called 'hypersensitivity', which although uncommon has caused severe illness and death, on occasion, in people who have restarted the drug after experiencing this problem.

People who develop resistance to a triple nucleoside combination should still be able to take drugs from the other two classes, as they will not have developed resistance to those drugs. The major disadvantage of this treatment strategy is that there is no information on their ability to reduce illness and death. Instead, trials have reported on their effect on viral load and CD4 count over the short-term only. Evidence which is available suggests these combinations may be less effective in people who start treatment with high viral load.

When to change therapy

The goal of anti-HIV treatment in people taking it for the first time is to reduce viral load to below 50 copies, a level which is sometimes called 'undetectable'. When viral load does not fall to this level, it is more likely that treatment will not suppress HIV for sustained periods of time. A continued rebound in viral load from very low levels means that treatment is failing. What may follow is a fall in the CD4 count, a possible risk of HIV-related illness, and an ongoing risk of developing drug resistance. This means that treatment which is not suppressing viral load to the undetectable level should be changed if there are other drugs available which do seem likely to achieve this.

Sometimes viral load rises to just above the detectable level and then falls back below on the next test. This is called a 'blip', and means that viral load should be re-tested as soon as possible, ideally within two weeks. Though one-off blips may be caused by a problem with viral load testing itself, they should also be a trigger to consider other possible causes, such as drug interactions, adherence problems, illnesses or vaccinations.

Treatment would be considered to have failed to control HIV only if there have been two viral load tests at least two weeks apart which both show that viral load is above 50 copies. It is recommended that a test for drug resistance is done to help

choose the replacement treatment, or, if this is not possible (i.e. if your viral load is too low to have a resistance test), that the replacement treatment involves a completely new set of drugs.

If treatment is being changed because of side-effects, but viral load is undetectable, it is okay to switch only the drug(s) causing problems. If there have been problems with adherence, the failing treatment should be replaced with drugs which are easy to take, and support with adherence should be provided.

Some doctors may consider delaying a switch in treatment if viral load rebounds to a low level, such as between 500 and 1,000

copies. This is because tests for drug resistance (which may help pinpoint which drugs are unlikely to be effective in the replacement treatment) are more reliable at viral loads above 1,000 copies. Choosing to delay may increase the risk of further drug resistance developing. Because of this risk, people whose viral load has rebounded above 1,000 copies may be better off stopping their treatment while waiting for the results of their drug resistance test. The timing of a switch in therapy will be influenced by the drug options you have available. If a second combination seems very likely to reduce your viral load to undetectable levels, then an earlier switch will offer the least

possible risk of resistance developing. If you have fewer drug options available, you may be more inclined to switch later.

The causes of treatment failure may be complex, and there is no clear evidence to guide the choice of replacement drugs, though drug resistance testing may be helpful. Options for people whose first anti-HIV drug combination is failing are shown in Table 3:

16 Table 3: What to change after first viral load failure

Initial combination	Replace with
2 NAs + 1 PI	2 NAs + 1 NNRTI
	2 NAs + 2 PIs
	2 NAs + 1 NNRTI + 1 or 2 PIs
2 NAs + 1 NNRTI	2 NAs + 1 or 2 PIs
3 NAs	2 NAs + 1 NNRTI
	2 NAs + 1 or 2 PIs
	2 NAs + 1 NNRTI + 1 or 2 PIs

Notes:
NA = Nucleoside analogue
PI = Protease inhibitor
NNRTI = Non nucleoside reverse transcriptase inhibitor
Nucleoside analogues in the replacement regimen should be new, rather than recycled from the old combination.

Changing therapy after more than one regimen failure: 'Salvage therapy'

Doctors often make a distinction when talking about people who need to change their HIV drugs for the first time and those who've already made changes before. The term 'salvage therapy' is used to describe treatment for people who have already taken drugs from the major anti-HIV drug classes.

People whose HIV is resistant to a number of anti-HIV drugs may find it difficult to assemble a replacement regimen which can lower their viral load to undetectable levels. Nevertheless, much smaller reductions in

viral load lead to health improvements. In people with advanced HIV disease, the CD4 count is a better predictor of future risk of ill health than viral load, and so it may be more important to look for potential for CD4 increase in a replacement regimen.

Salvage therapy is more likely to be successful where a new class of drugs can be added, or drugs to which the individual is sensitive rather than resistant; where therapy is changed at lower viral load levels; and where a resistance test is used to choose the new drugs. Drug level tests may also be useful.

Treatment interruptions usually lead to a rapid fall in the CD4 count and rise in viral

load, and therefore they may present a risk to people who require salvage therapy. However, it is always important to consider whether the risks of continuing treatment might outweigh the risks of stopping.

Anti-HIV drugs require an unusually high level of dedication from patients. Adherence is the term used to describe taking your HIV drugs exactly as prescribed, with no missed or late doses, and eating the correct type of food with your drugs if that's required. Missing even a few doses can cause drugs to fail – adherence levels of over 90-95% are what's needed to get the best response.

Adherence is more likely where people with HIV take part in decisions about treatment and are committed to taking it. The following issues are important elements within effective adherence and should be considered periodically as part of your HIV care, and whenever you start a new HIV drug combination:

- Your motivation to start and continue with your treatment
- Your understanding of adherence and drug resistance
- The impact of treatment on your lifestyle and well-being
- The support of memory aids
- Your mental health
- Risk of side-effects, and their management
- The risk and benefits of treatment
- That you have the information you need to be able to take your treatments, including information in written form.

20 Summary

- People with HIV always require individualised care.
- Currently available HIV therapy does not eliminate HIV from the body.
- There is no clear evidence for the best time to start taking anti-HIV therapy. Decisions need to be taken by doctors and people with HIV on an individual basis.
- Everybody who is ill because of HIV, or has a low CD4 count, is advised to take treatments.
- It is unclear which is the best combination to start with, but it is recommended that people starting HIV therapy for the first time take a combination of two NRTIs and an NNRTI.
- HIV therapy which is not suppressing viral load to undetectable levels should be changed if there are other drugs available which seem likely to achieve this.
- Special treatment strategies are needed for people who have taken lots of different HIV drugs.
- To work, HIV drugs have to be taken properly. This is more likely to happen in people who take part in decisions about their treatment and are committed to taking it.

adherence The act of taking treatment exactly as prescribed.

antiretroviral A substance that acts against retroviruses such as HIV.

CD4 A molecule on the surface of some cells onto which HIV can bind. The CD4 cell count roughly reflects the state of the immune system.

genotype The genetic make-up of an organism.

hypersensitivity An allergic reaction.

lipodystrophy A disruption in the way the body produces, uses and distributes fat.

NNRTI Non nucleoside reverse transcriptase inhibitor. The family of antiretrovirals which includes efavirenz and nevirapine.

nucleoside analogue Family of antiretrovirals which includes AZT, ddI, 3TC, d4T, ddC and abacavir.

nucleotide analogue Family of antiretrovirals which includes tenofovir.

protease inhibitor Family of antiretrovirals which includes amprenavir, indinavir, lopinavir, nelfinavir, ritonavir and saquinavir.

regimen A drug or treatment combination and the way it is taken.

resistance A drug resistant HIV strain is one which is less susceptible to the effects of one or more anti-HIV drugs because of its genotype.

resistance test Blood test which detects resistance to anti-HIV drugs.

salvage therapy Any treatment regimen used after a number of earlier regimens have failed.

undetectable viral load A level of viral load which is too low to be picked up by the viral load test being used.

viral load Measurement of the amount of virus in a sample. HIV viral load indicates the extent to which HIV is reproducing in the body.

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