February 2005
Always watch for out-of-date info
ISSN 1475-0740

avoiding & managing side effects

- when, what, why...
- changing drugs
- alternative and regular treatments
- you and your doctor
- internet links

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Contents

Disclaimer:

Information in this booklet is not intended to replace information from your doctor. Decisions relating to your treatment should always be taken in consultation with your doctor. Starting or stopping treatment without expert medical advice is potentially dangerous.

Introduction

This is the third edition of a booklet that was first produced in 2001. Since then over 50,000 copies have been distributed in the UK and it has been translated into French, Spanish, Italian, Chinese, Bulgarian, Slovak and Greek.

This edition has been updated to include T-20, atazanavir, tenofovir, fosamprenavir and FTC in addition to the previous information on older treatments. The section on lipodystrophy and metabolic changes has been revised and expanded and a new section added on the risk of heart disease and stroke.

This booklet will help you get the most out of your relationship with your doctor and other health professionals. It should also help you get better medical care, improved health and, most importantly, a better quality of life.

It has been written by people who are HIV-positive, who have been on many of the treatments, had many of the side effects and have learnt to negotiate their own health care in the NHS with hospitals and clinics.

The information will help you with your treatment, so that you don't have to experience the daunting list of side effects on the contents page.

Every drug will cause some side effects in some people. But not everyone will get the same side effects with the same drugs. Although you may have difficulty with one treatment, there is nearly always something you can do about it: by altering the dose, changing to another drug, or using a separate treatment to reduce the side effect.

However, many people do not receive adequate help to manage side effects.

Very often, this is a result of poor communication when you see your doctor. This may be because there is not enough time, or perhaps your doctor doesn't understand exactly how you are being affected. Sometimes you may just forget to mention a problem. Ways of improving this communication are included throughout this booklet.

Sometimes, if side effects continue for several months, people think it is easier not to mention them at all and just put up with them. This is not a good approach as they may be symptoms of a more serious illness. Newer treatments may also have become available since you first reported them, which you may not know about.

The first section of this booklet includes general information, including recording side effects, communication with your doctor and your rights as a patient.

The second section includes specific information on each side effect or set of symptoms. We have included the range of approaches for managing each side effect, including regular medications and alternative treatments where appropriate.

Finally, there is a short list of recommendations for further reading on the internet. These links will help you find addional information and will help you keep up-to-date with future research.

General questions

What are side effects?

Every drug is generally tested on, and licensed, to treat a specific illness. Any other effect is called a side effect. Side effects are also called adverse events (ae's) or drug toxicities.

In this booklet we will focus on unwanted side effects of HIV antiretroviral drugs (ARVs).

Many of the symptoms of side effects are similar to symptoms of illnesses. Different treatments are needed when these symptoms relate to illnesses.

Why do side effects occur?

Although drugs are designed to work against specific illnesses, they sometimes interfere with other ways that your body works.

It is difficult enough to develop a drug that works against HIV, and any drug that reaches the market has undergone a lot of research trying to minimise toxicity. Often, very promising drugs have their development stopped because of toxicity. The aim is always to develop safer and more tolerable, as well as better drugs.

Most people – people living with HIV, doctors and researchers – recognise that the current drugs available to treat HIV are far from perfect. New drugs in the future should be easier to tolerate.

Do all drugs have side effects?

Most drugs have side effects of some sort. In the majority of cases these wil be mild and easily manageable.

Sometimes side effects are so mild that they are rarely noticed, and they may only affect a small proportion of the people who use the drug.

Sometimes side effects only become apparent after the drugs have been licensed and approved, when many more people use them over a much longer period than the original studies.

All drugs have side effects, but not all people taking drugs will experience the same effects and to the same extent.

The leaflet included in the packaging with your drugs (called the Summary of Product Characteristics, SPC) lists all the reported range of possible side effects associated with each drug. The SPC also includes other useful information including how the drug needs to be taken, possible interactions with other medications, etc.

How are side effects for drugs reported?

When drugs are first studied, every side effect that occurs is recorded, even if it only affects a few people, and even if it cannot be directly linked to the drug being studied. This means that if you look at the leaflet that comes with your treatment you usually find a long list of potential side effects.

Side effects that are serious or occur most frequently are also usually discussed in more detail.

If side effects only become apparent after the drug has been approved, as with lipodystrophy, the drug leaflet may not have this latest information.

Starting treatment for the first time?

Everyone worries about the risk of side effects before they start HIV treatment for the first time. It will help if you know what to expect from different drugs before choosing your combination.

Ask for information about each of the drugs you might take, including the likelihood of side effects occurring. For example, what percentage of people had side effects related to each drug and how serious they were?

You may be asked to consider entering a study looking at side effects in different combinations and these studies are important to define the extent of side effects when different drugs are used together.

Can I change drugs easily?

If this is your first combination, you will usually have a lot of flexibility in choosing and changing drugs until you find a combination that works and is tolerable.

There are already 20 HIV drugs approved in the UK, including several formulations that include more than one drug in each pill. While you can't quite mix and match them all, you have a lot of choice. If one or more of the drugs in your combination are difficult to tolerate, you can change it for another.

Often people are not given a choice when starting treatment. However, the fewer drugs you have used previously, the more choice you have to change.

If you change a drug because of tolerability, you can usually go back and use it later if you need to *[note - except for abacavir - see page 28]*. Just because you used a drug once, doesn't mean you have 'used up your option' of using it again in the future.

Usually side effects improve after the first few weeks or months, but sometimes they don't. Read the sections on individual side effects for more recommendations for how long you should put up with them before changing.

You do not have to continue with a drug to prove anything to yourself or to please your doctor. If something is wrong, ask your doctor to change to something else. Some drugs are just not for everyone.

Can I predict if I will get side effects?

Generally you cannot predict how difficult or easy you will find it to take any particular drug beforehand. Sometimes, if you already have similar symptoms related to the side effects, these may make the risk of side effects greater.

For example, if routine liver tests show that you have raised liver enzymes, they may increase even higher if you use nevirapine. If you have high cholesterol or triglycerides before treatment, these are more likely to increase if you use some protease inhibitors.

Are side effects different in men and women?

Many trials in the past enrolled far too few women to be able to study differences adequately. Sometimes differences in side effects between men and women are reported later.

Women have shown higher rates of side effects in some nevirapine studies (both liver toxicity and rash), which highlights the importance of careful monitoring.

In this example it took many years before we found out that women were at a higher risk if their CD4 count was over 250 cells/mm^3 when they started treatment with nevirapine, and this is now not recommended.

With lipodystrophy *(changes related to fat distribution - see pages 34-39)*, there may be difference relating to gender.

What about side effects and adherence?

Whether you are starting your first treatment or have been using HIV drugs for a long time, your doctor should have talked to you about the importance of adherence.

This is the term that describes taking the meds in your combination exactly as they are prescribed - ie on time and following any diet advice. There is special section about adherence and side effects on page 12.

Getting your doctor to help…

Unfortunately,

- some doctors generally think that their patients ***over***estimate side effects. They think that their patients exaggerate side effects, and that they are not really as bad as their patients say.

It is also true that:

- most patients actually ***under***estimate side effects. Patients generally say that side effects are less inconvenient or less difficult than they really are, or often forget to mention them at all.

This means there can be a big difference between what is actually going on and what your doctor thinks is going on. This is why side effects are often under-treated.

What happens if side effects persist?

If the first treatment you are given to help with a side effect does not work, there are usually other drugs that you can use and these may be more tolerable.

This is why we have listed a range of options, including alternative treatments, for each of the main symptoms. If one doesn't work – try the other options.

Changing or stopping treatment are important options that you can discuss with your doctor.

If your quality of life is very bad because of the side effects, you may chose to look at experimental strategies like treatment interruption or immune-boosting treatment such as IL-2. Contact details for UK studies are included on page 35.

How to report side effects

If you want your doctor to understand your side effects and how they affect you, you need to be able to describe them very clearly.

Your doctor can then check for other important possible causes (ie that diarrhoea is not related to food poisoning; or low sex drive to low testosterone levels).

The best way to do this is to keep a side effects diary from when you start a new treatment until you next see your doctor.

Information about how to describe symptoms is given in detail in each section. It generally includes information about the following areas:

Frequency:

- How often do you get symptoms?
- Once or twice a week? Once every day, or 5 – 10 times a day etc?
- Do they occur at night as well as during the day?

Duration:

- How long do the symptoms last?
- If you feel sick or get headaches, does this last for 20 minutes or for 3 – 4 hours, or for different times?
- Is there a pattern to when they occur – ie when you take your medications or at a regular time afterwards?

Severity:

- How bad are the symptoms?
- Often it helps to rate them on a scale (from 1 for very minor to 10 for very severe).
- A scale is a useful tool for describing anything that involves pain.
- Recording how severe side effects are when they occur is better than recording them later.
- Have you noticed anything that helps to reduce or stop them.

If you are feeling more anxious or nervous, are not sleeping properly, have a lower sex drive... or are too nauseous to eat proper meals, it is important that your doctor understands this.

Quality of life:

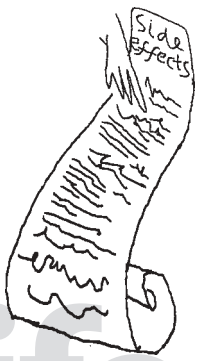
This can really help your doctor understand how difficult the side effects are for you. Many people put up with chronic diarrhoea without explaining to their doctor that it stops them ever going to the pub or the cinema.

If you are feeling more anxious or nervous, are not sleeping properly, have a lower sex drive, have experienced taste changes, or are too nauseous to eat proper meals, it is important that your doctor understands this.

Symptoms of lipodystrophy are difficult to evaluate. Although minor changes may not be a problem, some people find that more severe symptoms can change their whole outlook on life, and become a cause for underlying depression.

If side effects are affecting adherence (ie you are not taking all your meds at the correct time) and how you take your treatment, you must tell your doctor about this.

A side effects diary is included on page 7. Take this diary with you when you see your doctor at your next appointment.



Frequency
Duration
Severity
Quality of life

Side effects diary

Use this page to record any changes in your health that could be related to side effects. You may not get any side effects but if you do, then this diary will be useful. The most common side effects are listed below but include others even if they are not listed here.

1	Tingling or pain in hands/feet	7	Rash	13	Weight loss	19	Changes to your eyesight
2	Pain in hands/feet	8	Diarrhoea	14	Changes in taste or appetite	20	Mood swings
3	Nausea/vomiting	9	Stomach pains	15	Sexual problems	21	Feeling depressed
4	Headache	10	Hair loss	16	Sleep disturbance	22	Injection site reactions
5	Feeling tired	11	Body shape changes	17	Vivid dreaming	23	Yellow eyes or skin
6	Dry skin	12	Weight gain	18	Feeling anxious/nervous	24	Other(s) specify

Side effect symptom	Day	Time(s)	Scale: 1= very mild 10 = very bad
			1 2 3 4 5 6 7 8 9 10
			1 2 3 4 5 6 7 8 9 10
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Other comments and questions to ask your doctor:

How side effects are graded

Most information about the risk of side effects comes from the original studies when the drugs were first developed. This is why it is important to report all side effects to your doctor if you take part in a trial.

Trials collect information about how often all side effects occur and how serious they are. Studies for new HIV drugs use relatively small groups of people for relatively short periods of time.

Some side effects only become apparent after the drugs have been approved and they have been used by thousands more people over a longer period of time.

Knowing what the risk of side effects are for a particular drug – ie what percentage of people get these side effects – can help you to make an informed decision about which drugs to choose. Where a side effect is very common, knowing what percentage of people who needed to change therapy because of it, is useful too.

More accurate information may be provided by your doctor, or from a community treatment organisation. It is usually also included in the information that you should get with all HIV drugs.

Although there are slightly different details for reporting the severity of each side effect, they are graded from 1 to 4. Grade 1 is very mild and grade 4 is very serious – life threatening or requiring hospitalisation.

GRADE 1 (Mild)

Transient (goes away after a short time) or mild discomfort; no limitation in your daily activity; no medical intervention/therapy required.

GRADE 2 (Moderate)

Your daily activity is affected mild to moderately – some assistance may be needed; no or minimal medical intervention/therapy required.

GRADE 3 (Severe)

Your daily activity is markedly reduced – some assistance usually required; medical intervention/therapy required, hospitalisation or hospice care possible.

GRADE 4 (Potentially life threatening)

Extreme limitation to daily activity, significant assistance required; significant medical intervention/therapy, hospitalisation or hospice care very likely.

A indication of grading (from the United States Division of AIDS) is shown below together with specific details for some of the most common side effects.

Side effect	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhoea	3–4 loose stools a day OR mild diarrhoea lasting less than one week	5–7 loose stool a day OR diarrhoea lasting more than one week	Bloody diarrhoea OR over 7 loose stools a day OR needing IV treatment OR feeling dizzy when standing	Hospitalisation required (possible also for Grade 3)
Fatigue	Normal activity reduced by less than 25%	Normal activity reduced by 25–50 %	Normal activity reduced by over 50 %; cannot work	Unable to care for yourself
Liver toxicity: *AST or ALT levels*	1.25–2.5 Upper Limit Normal	>2.5–5.0 ULN	5.0–7.5 ULN	> 7.5 ULN
Mood disturbance	Mild anxiety, able to continue daily tasks	Moderate anxiety/dist-urbance, interfering with ability to work, etc	Severe mood changes requiring medical treatment Unable to work	Acute psychosis, suicidal thoughts
Nausea	Mild OR transient reasonable food intake	Moderate discomfort OR intake decreased for less than 3 days	Severe discomfort OR minimal food intake for more than 3 days	Hospitalisation required
Rash	Redness or itchy skin on part or whole body	Rash that breaks skin, hard or soft pimples OR light peeling/scaling	Blistering, open ulcers, wet peeling, serious rash over large areas	Severe rash, Stevens Johnson syndrome. Severe broken skin, etc
Vomiting	2–3 episodes a day OR mild vomiting for less than one week	4–5 episodes a day OR mild vomiting for more than one week	Severe vomiting of all food and fluids over 24 hours OR needing IV treatment OR feeling dizzy when standing	Hospitalisation for IV treatment (possibly also for Grade 3)

Side effects and drug levels

Side effects are sometimes related to the level of a drug in your blood.

There can be large differences in levels of drugs absorbed between different people and by the same people at different times. Many different drug and food interactions can affect drug levels.

You need a certain minimum level in the body for the drugs to work properly, but some people absorb levels that are much higher.

A high concentration often provides a stronger anti-HIV effect, so it is important to get the balance right.

For some HIV drugs, these levels can be tested, and the dose modified if appropraite.

- Protease inhibitors and NNRTIs ***are*** suitable drugs to measure
- Blood levels of nucleoside analogues (d4T, AZT, 3TC, FTC, ddI, abacavir and tenofovir) are ***not*** suitable for drug level monitoring because the important levels of these drugs are inside cells and tests to measure this are not currently available

Some clinics do this routinely but you may need to ask for it.

When is Therapeutic Drug Monitoring (TDM) appropriate?

TDM usually involves taking a blood sample after you have been on a treatment for at least two weeks. *The hospital will need to know the exact time that you took your previous dose in order for the test to be effective.*

Sometimes a sample is taken just before you are due to take your next dose, and sometimes it is also taken 2–3 hours afterwards as well.

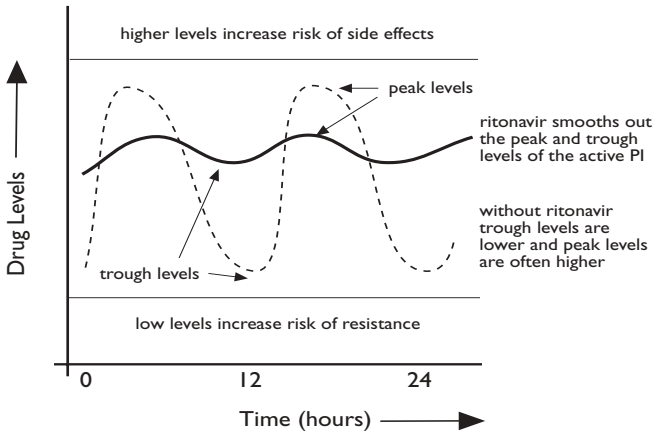
TDM is most likely to help in the following cases:

- If you are using a single protease inhibitor-based combination
- If you are using a dual protease inhibitor combination (such as indinavir/ritonavir or saquinavir/ritonavir or atazanavir/ritonavir)
- If you are using both PIs and NNRTIs in the same combination

TDM is also particularly important for children and people with pre-existing liver damage when routine recommended dosing is not always appropriate.

It is also appropriate whenever drug levels or drug interactions may be linked to side effects.

Benefits from using ritonavir to boost other PIs



For example, atazanavir is the most recently licensed protease inhibitor (in 2004). The adult dose of atazanavir is 300mg with 100mg ritonavir, both once daily. This is because it is more active and more effective when used with boosting ritonavir.

If you get side effects with ritonavir boosting though, it may be possible to drop the ritonavir and use a higher dose of atazanavir (400mg daily), but this should always be checked with TDM.

Checking your own level makes a lot of sense. TDM is available in the UK through programmes subsidised by the manufacturers of most PIs and NNRTIs.

Another example is using the older protease inhibitor indinavir with ritonavir. These two drugs have been studied in twice daily regimens in the following doses:

indinavir	+	ritonavir
400mg	+	400mg
800mg	+	200mg
800mg	+	100mg
600mg	+	100mg

Other doses (such as 400mg/100mg) may be possible on an individual basis. ***Reducing doses is only recommended if you have been given drug level monitoring with expert interpretation.***

Ritonavir is generally more difficult to tolerate, so this is the benefit for keeping the ritonavir dose low.

However, higher peak levels of indinavir are linked to higher rates of side effects (such as kidney stones).

It is strongly recommended to ask your doctor to access subsidised TDM if you are using a dual PI combination. TDM can detect low levels that need increasing and high levels that cause side effects.

Changing treatment

Responses to drugs vary a lot between different people. If you can't tolerate one treatment, then you can switch to an alternative without it affecting your future options.

Many side effects become easier over the first few weeks of treatment. If your initial symptoms are only mild or moderate, seeing whether they settle down before changing treatment, can be good advice.

If you are considering stopping or interrupting any treatment it is vitally important that you discuss this with your doctor.

The decision to change treatment in order to manage side effects will depend on whether:

i) there are other HIV drugs you can use
ii) the side effects are likely to get worse if you remain on the same drugs
iii) you think that the side effects are related to drugs – even though there may not have been a proven link. Close monitoring after a change of drugs will help you know whether the treatment that you switched from was causing that side effect.

With over 20 drugs available, and dozens of similar combinations, a high level of individual tailoring is possible.

In the end, any combination has to be one you can tolerate and many people change their combination to improve tolerability. Switching individual drugs can be safe and may improve your quality of life, and still keep your viral load undetectable.

When switching drugs it may be safer to add in the new drug to check that it is tolerable before discontinuing the drug that is causing the side effect. If you have a detectable viral load before switching you should also have a resistance test.

Switching between PIs and NNRTIs

Several studies have looked at this to avoid or reverse fat accumulation or metabolic changes associated with lipodystrophy - see page 34. This can sometimes help reduce cholesterol and triglyceride levels although the results haven't always been clear.

If your current combination is not your first treatment, there is a greater risk that your viral load will rebound. This has happened to approximately 10% of treatment-experienced people.

If you cannot tolerate nevirapine or efavirenz, switching from these drugs to a protease inhibitor is possible. If you previously have used protease inhibitors, the choice of PI would depend on your previous treatment history.

Changing only one or two drugs in a combination is only recommended when viral load is undetectable prior to the switch. Some people may switch to four or more drugs if they have resistance from earlier combinations.

Switching between nukes

Most combinations involve at least two 'nukes' (AZT, d4T, ddI, 3TC, abacavir, tenofovir) which all have similar anti-HIV activity. ddC is now very rarely used.

So long as you haven't developed resistance to the other nucleosides (and you don't use AZT and d4T in the same combination), you have the freedom to use these drugs in many different combinations.

- If you get peripheral neuropathy (pain or numbness in your hands or feet) this may be due to d4T, ddI or 3TC and you should switch or reduce the doses of those drugs, or join a study for neuropathy treatment before the neuropathy becomes more serious.
- d4T and AZT are associated with fat loss from the face, arm and legs. Switching to abacavir or tenofovir will reduce this risk and may reverse previous fat loss.
- If you continue to get nausea or fatigue using AZT (or Combivir or Trizivir, which both contain AZT) then you could switch to another nucleoside.

Switching between NNRTIs

Nevirapine and efavirenz have similar potency but they have different side effect profiles. Nevirapine has been more associated with skin rash and liver toxicity – usually in the first 1-2 months of treatment. Efavirenz is linked to mood disturbance, disturbed sleep patterns and vivid dreams when starting and more rarely in the long term.

If you have difficult side effects from one of these drugs, you should be able to switch from one to the other without stopping treatment or changing the other drugs.

Switching between PIs

Switching from one PI to another is also straight-forward, especially if both PIs are being boosted by ritonavir.

- Switching form one boosted PI to another (such as from Kaletra to atazanavir/r) is likely to be okay
- Switching from nelfinavir to indinavir is okay
- Switching from a single-PI to a dual/boosted-PI is okay
- Switching between PIs used in dual-PI combinations, although less well studied, is also likely to be okay
- Switching from a boosted PI to an unboosted PI is not recommended unless drug levels are checked with TDM *(see page 9)*.

Options to consider when switching drugs to avoid toxicity

Drug causing side effect	Alternative to switch to	Cautions
Nucleoside/nucleotide		
AZT, 3TC, d4T, ddI, abacavir FTC, (and ddC - rarely used) tenofovir (nucleotide)	another nucleoside/tide	Cross-resistance between nucleosides. AZT/d4T shouldn't be used in the same combination. Neither should 3TC/FTC. During 2004 several studies reported a possible concern from using tenofovir/ddI. Until the action of these two nukes is understood, it is better to avoid this combination.
	PI or dual PI or NNRTI	Will depend on previous treatment history and current combination. Nucleoside-sparing combinations (mainly using two PIs boosted by ritonavir, with no nukes) may be important if you have nucleoside-related toxicity.
NNRTI		
efavirenz or nevirapine	another NNRTI	
	PI, boosted PI, boosted dual PI, dual PI **	Previous PI use will determine choice of next PI.
	abacavir	Similar caution to switching to NNRTI. There is limited long-term data on efficacy or side effects on triple nucleoside combinations.
PIs		
Any single or dual PI	another dual PI or boosted PI **	Switching from a single to dual PI combination generally increases potency against HIV. TDM should be used to check drug levels and reduce side effects.
	NNRTI	Generally NNRTIs are easier for tolerance and adherence. If you have used several nukes before, risk of viral load rebound is higher.
	abacavir	Similar caution to switching to NNRTI. Triple nucleoside combinations are not generally recommended but may be an option for a limited number of patients.
Dual/boosted PI	Change dosing	Confirm dosing with TDM.
	NNRTI	Generally NNRTIs are easier to take and tolerate. If you have used several nucleosides previously, the risk of your viral load rebounding is slightly higher.
	T-20, other entry inhibitors	T-20 may be an option for people who have difficult progessive side effects such as lipodystrophy because it works in a different way to other drugs. Other entry inhibitors may be used as they become available.

** ***'Boosted PI' is when smaller doses of ritonavir are used to boost the drug levels of one or sometimes two main PIs. 'Dual PI' is when two different PIs used against HIV are both used at therapeutic doses.***

Side effects and adherence

...94% of people reported at least one symptom after 4 weeks... If you are getting side effects, they need to be taken seriously, as early as possible by both you and your clinic..

Whether you are starting your first treatment or have been using HIV drugs for a long time, your doctor should have talked to you about the importance of adherence.

This is the term that describes taking the medications exactly as they are prescribed. This includes taking them on time and following any dietary advice.

It also means taking them on regular week days, at weekends and when you are away on holiday.

Along with numerous studies showing that not getting adherence right will lead to early treatment failure, there have been studies that look at the relationship between adherence and side effects.

One of these studies looked at side effects over the first month on a new treatment.

People who reported higher numbers of side effects after the first month of treatment were less adherent and had lower viral load reductions three months later. A lot of this seems like common sense – but this French study was most successful because it gave people a chance to provide a detailed record of all the side effects that they experienced.

This study provided a more realistic picture than is generally recognised of the real effect of side effects on everyday life. Ninety-four percent of people reported at least one symptom after 4 weeks, which dropped slightly to 88% after 3 months. Feeling more tired and having diarrhoea were the most frequently reported side effects, 40% of which were mild and 7% were severe.

People reported an average of four side effects after four weeks, which dropped to an average of three at 16 weeks. And importantly, the severity of these side effects reduced over this time.

The conclusion was very straightforward. If you are getting side effects, they need to be taken seriously, and as early as possible by both you and your clinic.

There are many treatments that help with nausea and diarrhoea. You can be given a small supply of these to take to prevent side effects when you first start treatment. You should also be able to collect these easily from your clinic as soon as you get symptoms.

Adherence and lipodystrophy

Adherence can be more difficult when the medications that you take make you feel less well. It is now recognised that some of the longer-term side effects like lipodystrophy, can also reduce adherence.

Lipodystrophy includes changes in body shape, particularly fat accumulation or fat loss, and is discussed in more detail on pages 30–33.

If you are experiencing these side effects then the underlying effect on your self confidence, your social life and how you feel about yourself is very important.

You and your doctor

Developing a good working relationship with your doctor and other healthcare workers is essential. Doctors are not the only people at your clinic who are able to help. Nurses are an excellent source of support and advice on all aspects of your treatment including on side effects and adherence (taking your medication on time). They are able to make referrals to other professionals including dieticians, pharmacists, psychologists and social workers.

Changing your doctor or treatment centre should really be seen as a last resort when other negotiation has failed.

Both you and those involved in your care have certain rights and responsibilities. Below is a list of things you can do, followed by the rights you have as a patient.

Things you can do to help...

- Find a clinic that is convenient and that you feel comfortable with
- Find a doctor who you feel comfortable with: if you're a woman and want to see a female doctor, or a gay man and want to see a gay doctor, then this should be possible
- Make a list of things you want to discuss with your doctor and take this to your appointment
- Keep a list of your drugs, dosages, when you need to take them, and whether you get these from your clinic or GP
- See the same doctor at each visit – this is important. It is very difficult to develop a relationship if you always see a different doctor. However, it is often useful to see a different doctor for a second opinion
- Plan to have your routine bloods taken 2–3 weeks before your regular appointment. The results will then be available to discuss at 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, so they can give the appointment to another patient
- Treat all people involved with your care with the same respect you would wish to receive yourself
- Listen carefully to health advice that you are given and act upon it
- If you don't understand anything, 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 – legal, street, recreational, prescription or complimentary

  Alternative treatments and recreational/illegal drugs can cause side effects themselves and can interact with HIV treatments
- Be honest about your adherence (taking your meds according to schedule). If people managing your care don't know you are having problems, they can't help
- Be interested in potential research. Studies generate data that can help yours and others future care

Some of your rights as a patient...

- To be seen within 30 minutes of your appointment or expect an explanation
- Have all options for treatment explained to you. This includes the risks and benefits of each option
- To be fully involved in all decisions regarding your treatment and care
- To be treated with respect and confidentiality
- For your records to be kept securely and to be available for you to see if you ask
- To refuse to participate in research trials without this affecting your current and future care
- To make a complaint about your treatment without it affecting your future care. To have any complaint fully investigated
- To receive a second opinion from a suitably qualified doctor
- To receive a written response within 14 days from any letter that you write to your hospital or clinic
- 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 although sometimes this can help resolve a problem if there has been a misunderstanding
- To have all test results and a summary of your treatment history forwarded to your new doctor or treatment centre

Diarrhoea

Associated drugs: Most HIV medications list diarrhoea as a side effect. Drugs particularly associated with diarrhoea include: nelfinavir (Viracept), saquinavir (Invirase and Fortovase), lopinavir/r (Kaletra), fosamprenavir (Lexiva), ritonavir (Norvir), abacavir (Ziagen and Trizivir) and ddI (Videx).

Diarrhoea remains one of the least talked about and yet most common side effects of HIV therapy.

HIV itself can also cause diarrhoea as can many HIV-related infections.

Up to 50% of people with HIV will develop diarrhoea at some point and those with lower CD4 counts are at a greater risk. Diarrhoea can last for a few days, weeks, months or, in some cases, years.

Diarrhoea relates to increased frequency as well as looser and more watery consistency of stool.

It can be embarrassing to talk about diarrhoea or bowel habits. This may be one of the reasons that it is so badly managed. However, it is important that diarrhoea is treated, as otherwise it can lead to dehydration, lack of absorption of essential nutrients and drugs, weight loss and fatigue.

Finding out the cause

Often diarrhoea is temporary and may be due to starting or changing treatment. In these cases short courses of anti-diarrhoea medications such as Imodium or Lomotil can be effective. Symptoms often reduce within a few days or weeks, when you get used to the medications.

If diarrhoea persists for more than a few days and is not directly linked to starting a new combination it is important to run tests to check that it is not being caused by bugs or parasite infections.

Non drug-related causes

If you have persistent diarrhoea for more than a few days ask your doctor to arrange for a stool sample to be analysed to see what is causing the diarrhoea. Some of the tests can take a couple of weeks to come back.

Depending on the severity and history of the symptoms and following examination, your doctor may prescribe a course of antibiotics along with medication such as Imodium, lomotil or codeine phosphate to decrease the amount of times you need to go to the toilet.

When stool samples fail to show any causative bugs and symptoms are persisting, then your doctor may want to perform an endoscopy. For this, a biopsy (a tiny piece of tissue) is obtained for analysis in the laboratory. This can rule out other bowel problems such as colitis. As diarrhoea can be a symptom of other HIV related illnesses it is very important to run these tests.

Treatment

When the possible causes have been investigated and nothing shows up, then the treatment of the symptom itself becomes important. You may be given a course of antibiotics to try and treat any underlying infection that may be hidden.

Many HIV medications can cause diarrhoea and some are more problematic than others. If you are tolerating your combination generally, you may be able to manage diarrhoea with anti-diarrhoeal drugs or dietary changes, both of which are listed below.

Depending on your treatment options you can also look at changing the drug that is likely to be causing this.

Diet

- Many people with HIV have difficulty in digesting lactose, which is found in milk and dairy products. Reducing milk and dairy products in your diet can really help. Alternatives such as rice and soya milk do not contain lactose.
- 'Rice water' can also help. Variations on a similar theme include boiling a small amount of rice in water for 30–45 minutes (or microwave for a shorter time), flavouring with ginger, honey, cinnamon or vanilla when cooled, and then drinking throughout the day.
- Eating less insoluble fibre can also help. Foods that contain insoluble fibre include vegetables, whole wheat breads and cereals, skins, fruit, seeds and nuts.
- Eat more soluble fibre. This is particularly helpful when watery stools are a problem as they help to absorb the excess water and bulk the stool. Soluble fibre can be found in white rice, pasta. Ispaghula (psyllium) husk (i.e Fybogel or Isogel) and oat bran tablets increase soluble fibre in your diet.
- Caffeine (and recreational drugs) can cause the gut to speed up and result in more bowel movements. Caffeine is found in coffee, tea and cola.
- Avoid high fat, greasy and high sugar foods.
- Don't drink with your meals but make sure you take plenty of fluids between meals to replace the fluid being lost due to diarrhoea.
- Eat foods rich in potassium such as bananas, peaches, potatoes, fish and chicken. Potassium is lost when you have diarrhoea.

Fig 1: how opiod anti-diarrhoeals work

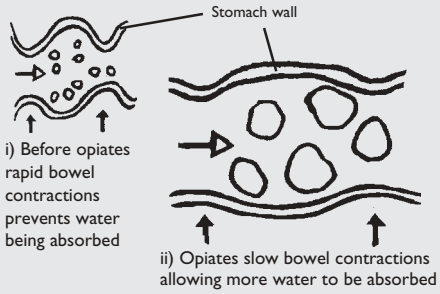
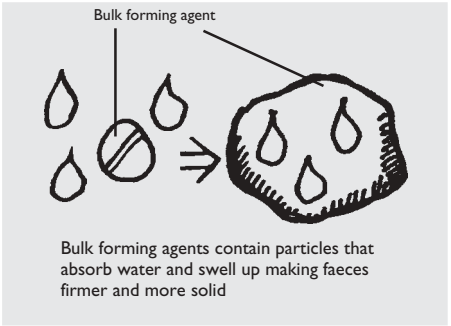


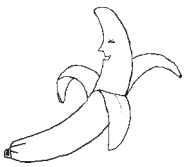
Fig 2: How bulk-forming agents work



Treatments:

- diet changes
- dioralyte (electrolyte replacement)
- Imodium (loperamide) or Lomotil
- calcium supplements
- Ispaghula (psyllium husk or seeds)
- Glutamine
- MST (slow-release morphine sulphate)
- octreotide injections

It is vitally important that diarrhoea is treated as it can lead to dehydration, lack of absorption of essential nutrients and drugs, weight loss and fatigue.



- Try eating live yoghurt to enhance the helpful bacteria in your gut. If you have a problem with dairy products then acidophilus can be taken in pill form. If your CD4 count is under 50 this may not be advisable.
- Whatever changes you make to your diet, make sure it remains balanced; don't live on just a few food products, as you will be missing out on essential vitamins and minerals. Excellent advice and support about diet can be obtained from the dietician at your treatment centre.

Medications and supplements

- Fluid and electrolyte replacement (such as dioralyte and sports rehydration solutions like Gatorade etc)
- Imodium (loperamide), Lomotil and codeine phosphate are the drugs most commonly prescribed for diarrhoea. They work by slowing gut motions and the speed that you process food, hopefully reducing the number of stools each day.
- Your doctor will normally prescribe these first and, for many people, these medications work well. It is important that the medications are taken regularly until the diarrhoea is well controlled. Start with low doses. If you are taking the maximum daily dose (for example 8 pills a day for Imodium) and you are still not getting the problem under control, go back to your doctor to get the medications changed.
- Calcium supplements can help reduce diarrhoea associated with nelfinavir and possibly other protease inhibitors. The normal dose is 500mg twice a day and will help those who are avoiding dairy products as they are a major source of calcium in the diet.
- Glutamine has been used experimentally to try and improve bowel function. There is still some debate about the dosage – opinion ranges from 5g to 40g a day. It is available either as a powder that must be dissolved in water or a regular pill.
- Bulk forming laxatives, although contradictions in terms, are useful when watery stools are a problem. They absorb fluid and bulk out the stool – and lengthen the time the stool stays in the bowel. These drugs are generally taken following a meal and you should not drink for 30 minutes after taking them. Don't take at the same time as meds. Brands include Fybogel, Isogel, Regulan, Celevac and Normacol.
- Studies on oatbran tablets taken by people with diarrhoea using protease inhibitors were successful and work on the same principle. The dose was 2–3 oatbran tablets before meals or after each protease inhibitor dose.

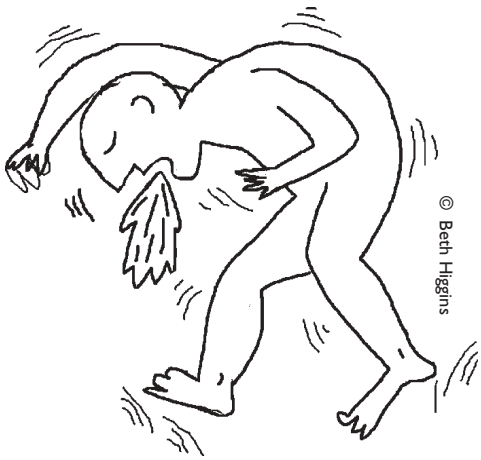
as a last resort...

Slow release morphine sulphate (MST) or octreotide injections can be used if all the usual medications have failed to make a difference – although it is used less to control side effects and more to treat other causes of diarrhoea. The slow-release formulation of MST means that low doses of the drug are provided throughout the day. It comes in a wide range of strengths, each coloured differently, so you can be very careful about only taking the dose that you need. The liquid formulation of morphine sulphate can be used for diarrhoea that occurs at specific times – ie in the hours after dosing.

MST works because one of the side effects of opiates is constipation, and it works by slowing down the gut.

Because it is an opiate, many doctors do not readily offer MST, so you may have to be persistent to get to use it. For some people it is the only thing that works – and even very low doses mean you can get back to a normal life.

Nausea and vomiting



Associated drugs:

most HIV medications include nausea as a potential side effect

Many of the HIV medications currently available can cause nausea.

Nausea, and occasionally vomiting, is quite common when starting a new combination. However, for most people, this improves after a few weeks when the body has adjusted to the drugs.

Using an anti-emetic (anti-sickness) pill regularly in the first few weeks is often all that is needed. If one anti-emetic does not work, it is worth trying others that are available. Some anti-emetics work by emptying your stomach more quickly and others by stopping the signals that tell your brain that you feel sick.

For some people the nausea never improves and you may need to change to other anti-HIV medication. There may also be an underlying cause not related to HIV medication which should be investigated.

If you are taking abacavir and you are feeling nauseous or vomiting, then contact your clinic straight away to rule out a hypersensitivity reaction. *(See page 28)*

How to describe nausea to your doctor:

- How often each day do you feel sick, or are you sick?
- How many days a week does this happen?
- How long does the feeling of nausea last?
- Has this affected how much you can eat or drink?
- Do you feel more tired or weak as a result?

Medications used for nausea

Domperidone (Motilium): 10-20mg every 4-8 hours. Suppositories 30-60mg every 4-8 hours are also available and are a good alternative to swallowing pills when you are feeling sick.

Metoclopramide (Maxolon): usually 10mg, 3-times a day. There are slow-release versions, which can be used twice a day, including Maxolon SR and Gastrobin Continuous; however, they should not be used in anyone under 20 years old. Be aware of dystonic reactions (twitching movements) at higher doses.

Prochlorperazine (Stemetil): usually 5-10mg, 2-3 times daily. A special preparation is available called Buccastem, 1 or 2 tablets are placed between the upper lip and gum and left to dissolve; not having to swallow more pills is useful when you are feeling sick.

Haloperidol: 1.5mg daily or twice daily where nausea is severe. Particularly useful as can be taken at night to avoid early morning nausea.

Sometimes these medications have side effects themselves that you should ask your doctor about.

Where other medications and lifestyle changes have failed and nausea continues, then medications that are normally reserved for patients receiving very strong chemotherapy may be prescribed.

These medications include granisetron, ondansetron and tropisetron and they are highly effective.

Other suggestions

If changing your medication is not an option and the nausea is continuous, then any of the following suggestions can help.

- Eat smaller meals and snack more frequently rather than eating just a few larger meals
- Try to eat more bland foods and avoid foods that are spicy, greasy or strong smelling
- Leave some dry crackers by your bed and eat one or two of them before getting up in the morning
- Ginger is very helpful and can be used as capsules, ginger root powder or fresh root ginger peeled and steeped in hot water
- If cooking smells bother you then open the windows while cooking and keep the room well ventilated
- Microwave meals prepare food quickly and with minimum smells, so you can eat a meal as soon as you feel hungry. Getting someone else to prepare your meals can help, if this is possible
- Don't eat in a room that is stuffy or that has lingering cooking smells
- Eat meals at a table rather than lying down and don't lie down immediately after eating
- Try not to drink with your meal or straight after: it is better to wait an hour and then sip the drink slowly
- Try eating cold rather than hot food or let hot food cool well before you eat it
- Peppermint is also useful and can be taken in tea, sweets or chewing gum
- Acupressure and acupuncture can also be very helpful, anti-nausea acupressure bands are available from most chemists
- Try to avoid things that irritate the stomach such as alcohol, aspirin and smoking

Fatigue - *feeling tired*

Associated drugs:

most HIV medications include fatigue as a potential side effect

Fatigue is a general feeling of tiredness that does not really go away, even after you have been able to rest.

With physical fatigue you are not able to be as active as you used to, even with simple tasks like going up stairs or carrying shopping.

With psychological fatigue, you are not able to concentrate as well as normal or you lose the motivation to do things.

Fatigue can be caused by:

- HIV and related illnesses
- HIV drugs
- lack of sleep
- poor diet
- stress
- depression
- antihistamines (used to treat hay fever) and flu and cold remedies
- alcohol and recreational drug use
- underlying HIV-related illnesses.

Fatigue can also be caused from being more active than you are able to manage.

It can also be caused by a hormone imbalance such as low testosterone or DHEA (dehydroepiandrosterone) levels in both men and women.

If you are feeling very tired and have any of the other symptoms associated with lactic acidosis (vomiting, nausea, sometimes pain in the stomach and/or liver, unexplained weight loss, difficulty breathing etc - see page 27) it is very important that you report this to your doctor.

How to describe fatigue to your doctor

Fatigue can build up slowly, and build up without you realising it. To be able to describe this to your doctor it helps to be able to give specific examples of which activities make you feel more tired.

If you can compare how you feel now with how you felt six months or a year ago, this will also help.

Describe how often you are tired or out of breath for example. As fatigue can be related to poor sleep, include information about your sleep patterns.

Treatments

Blood tests can check whether your fatigue is caused by anaemia (low red blood cells). This can be a side effect of AZT and can be treated easily with medication or with a blood transfusion in more serious cases.

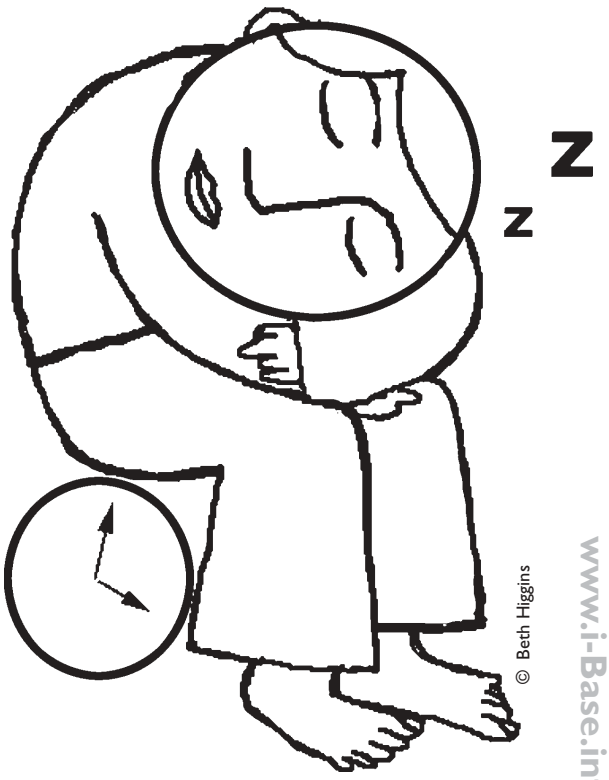
You may be feeling more tired because you are not sleeping properly, and one study found this explained fatigue in over 60% of cases. There is more information about difficulties with sleep on page 21.

If you are not eating a balanced diet – ie not getting sufficient calories and nutrients for your body to function normally – this can leave you feeling more tired.

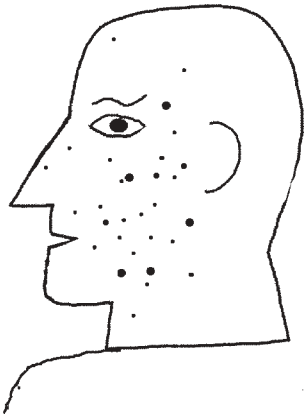
Multivitamins can be prescribed by your doctor, and supplements of vitamin B12 can sometimes help you feel more energetic.

You can also ask to be referred to a dietician who can help you assess and plan changes to your diet.

Psychostimulants like methylphenidate (Ritalin) and pernoline (Cylert) used in low doses, have sometimes been used to treat HIV-related fatigue but side effects include hyperactivity, addiction, loss of appetite and liver toxicity.



Skin rash



Associated drugs: abacavir (Ziagen and Trizivir), FTC (Emtriva), nevirapine (Viramune) and efavirenz (Sustiva), delavirdine (Rescriptor), amprenavir (Agenerase), fosamprenavir (Lexiva), atazanavir (Reyataz), T-20 (enfuvirtide, Fuzeon).

Several of the HIV drugs are linked to rashes, but the severity of rash and how long it lasts varies considerably.

If you develop a rash during the first few weeks of therapy with some drugs you must report this immediately to your doctor. This is because it can sometimes lead to very serious reactions. These drugs are **abacavir** (Ziagen, and in Trizivir and Kivexa), **nevirapine** (Viramune), **efavirenz** (Sustiva), **fosamprenavir** (Lexiva) and **T-20** (enfuvirtide, Fuzeon).

Other rashes are more likely to be short lived and disappear without treatment, or can be easily treated with antihistamine drugs such as cetirizine (Zirtek) or loratadine (Clarityn).

Atazanavir can cause a mild rash during the first two months in 10% of people but this disappears without additional treatment within a few weeks.

FTC studies reported rash on the palms of the hands in up to 10% of African Americans, but these have been reported less frequently since the drug has been licensed.

Although antihistamines are available over the counter, it is important that you check with your doctor or pharmacist before taking them, as there can be interactions with HIV drugs.

Rashes can also occur as a reaction from exposure to the sun, and will normally resolve. Any rash that makes you feel sick may not be a side effect but a symptom of an underlying disease (such as scabies).

Other things that can help:

- Bath or shower in cool or warm water rather than hot water as this can irritate your rash.
- Avoid heavily scented or coloured soaps and shower gels. Try to use those products that are marked hypoallergenic or wash with aqueous cream.
- Use liquids and not powder to wash your clothes as tiny amounts of powder can build up on your clothes. Try using non-biological makes that are designed for sensitive skin.
- Wear cool fibres such as cotton and not synthetic ones. When possible at home wear as few clothes as possible.
- Try not to use too many bedclothes. Keep as cool as possible in bed as being too warm can irritate your rash. Again, use natural, cool fibres such as cotton.
- Calamine lotion can be soothing when a rash is very irritating.

Nevirapine and efavirenz rashes

Up to 17% of people using nevirapine, and 3-5% of people using efavirenz, will experience a mild to moderate rash in the first weeks of treatment. For most people this disappears over the next few weeks and they experience no further side effects. Women are at a slightly higher risk of rash with nevirapine than men. Women should not start treatment with nevirapine if their CD4 count is over 250 cells/mm^3.

Nevirapine needs to be dosed in two stages. For the first two weeks, you should only take one 200mg tablet, once a day. After the first two weeks the dose increases to two 200mg tablets daily, split into one tablet every 12 hours. The dose should NOT be increased though if there are any symptoms of rash.

If you get a rash with nevirapine, you should make sure your doctor checks this carefully. Everyone starting nevirapine should visit their clinic every two weeks for the first two months to check for liver toxicity (see page 26), so getting a rash examined should be very easy.

Approximately 5% of people discontinue nevirapine due to a rash.

Anything more than a mild rash may require stopping nevirapine – but only on the advice of your doctor.

More serious rash (reported in 0.5% of cases) can be life-threatening (Stevens-Johnson Syndrome) and can be dependent on how early nevirapine is discontinued. This is why getting an expert medical assessment when a rash appears is essential.

Abacavir and rash

A rash can sometimes be one of the symptoms of the hypersensitivity reaction associated with abacavir (Ziagen, Kivexa and Trizivir) that occurs in 4-5% of people using abacavir.

It is very important that you see your doctor if a rash appears when using abacavir in a combination. If abacavir is not stopped - or if it is used again in the future, this can lead to a life-threatening reaction.

Page 28 has more details on the abacavir reaction.

Dry skin, hair loss, nail problems, frozen shoulder

Dry skin & chapped lips

Associated drugs:

indinavir (Crixivan), 3TC (Epivir) and hydroxyurea (Hydrea)

Dry skin and chapped lips are a problem for many people taking HIV drugs, particularly indinavir.

Where dry skin is a problem with indinavir (particularly if you are using it in combination with ritonavir), then ask your doctor for a blood test to measure the levels of indinavir. See page 9 on therapeutic drug monitoring (TDM).

TDM for indinavir is available free of charge through a programme provided by the manufacturer.

All the measures listed on page 19 on rashes are helpful where dry skin is a problem, along with the use of emollients (moisturisers) such as aqueous cream, diprobase, oilatum, and balneum. Try to drink plenty of fluids as well.

Vitamins and a healthy diet are also important for better skin health.

Where rashes and dry skin are unmanageable with medications or simple interventions then ask your doctor to change the medication that is responsible if you are able to do so.

You can also ask to be referred to a specialist dermatologist.

Chapped lips have been linked to indinavir in a similar way to dry skin. Regularly using a lip balm and checking indinavir blood levels are both recommended.

Frozen shoulder (capsulitis)

Associated drugs: indinavir (Crixivan)

Frozen shoulder (also called adhesive capsulitis) is a painful disorder that reduces movement of this joint. It has been associated with indinavir.

Conservative therapies include rest, painkillers and range-of-motion exercises and the shoulder can return to normal over 1-2 years although persistant pain can remain in 5-10% cases. More active treatments include more active exercise, oral corticosteroids, corticosteroid injection and manipulation under anesthesia.

Hair loss

© Beth Higgins

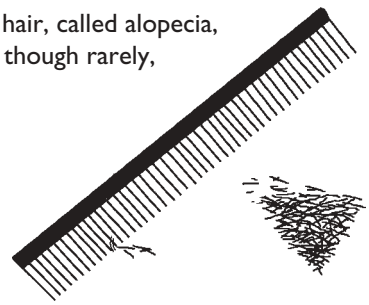
Associated drugs:

indinavir (Crixivan), 3TC (Epivir) and hydroxyurea (Hydrea)

Many people have reported that the thickness and quality of their hair changed while using indinavir – usually becoming thinner – and that this has been reported for both head and body hair.

Usually this is reported as being mild and reversing when indinavir is switched to another drug.

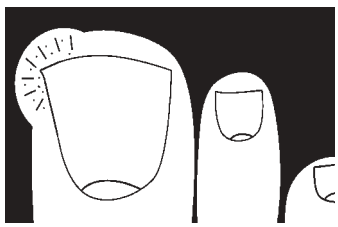
Balding patches of head hair, called alopecia, has also been reported, though rarely, with 3TC.



Nail problems

Associated drugs:

indinavir (Crixivan), 3TC (Epivir) and hydroxyurea (Hydrea)



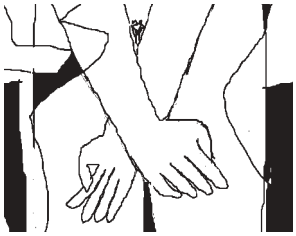
Paronychia (inflammation around the finger nails) and ingrown toe nails have both been reported as rare side effects with these two drugs.

Many of the people using indinavir are likely to have also used 3TC - so the cause and contribution of each drug is uncertain.

It took a long time and a lot of painful feet before the link between these drugs and nail problems was established. If you are using indinavir and have these problems ask for a referral to a chiropodist – if they continue, consider switching to another drug.

Hydroxyurea and AZT have been associated with nail changes and skin pigment changes in African people.

Sexual problems



Sexual dysfunction, whether due to HIV, side effects of HIV treatments, or other factors, can have a big impact on the quality of your life.

Sexual dysfunction includes reduced sex drive (a loss of interest in sex) and physical difficulties (such as loss of erection or difficulty reaching orgasm).

Although sexual dysfunction is not generally noted as a side effect of HIV drugs, several reports have linked this to treatments containing protease inhibitors.

Under-reporting in studies and at clinics is likely because many people find it difficult to talk to their doctor about this aspect of their lives. It is something that doctors rarely ask patients about directly.

Although most research into sexual dysfunction associated with HIV has been carried out in men, when women have been included in these studies, a similar level of concern has been reported.

For example, a study by anonymous questionnaire in over 900 HIV-positive people using combination therapy (80% men, 20% women) found that 38% of men and 29% of women reported a decrease in sexual interest. A decrease in sexual potency was reported by 29% of men.

Causes

Sexual dysfunction in HIV-positive people can be caused by a wide range of medical and psychological issues.

- HIV-positive men and women have reduced testosterone levels compared to HIV-negative people.
- Depression can affect sexual health.
- Many treatments for depression (including fluoxetine (Prozac), citalopram (Cipramil), paroxetine (Seroxat) and sertraline (Lustral) can decrease libido and lead to erection difficulties in men. Mirtazapine (Zispin) may be considered as it has little or no effect on sex drive and fewer interactions with HIV drugs.
- Sedatives, tranquillisers and other medications can cause sexual dysfunction, as can smoking, alcohol and recreational/illegal drug use.
- Long-term use of steroids or male hormones.
- Relationship or work-related stress can be a factor.
- Protease inhibitors have been linked to sexual problems.
- Lipodystrophy and neuropathy are also associated with higher rates of sexual dysfunction.
- Sexual dysfunction is more common in HIV-positive people who are not using anti-HIV drugs compared to HIV-negative people.
- Age (>40 years), diabetes, pelvic surgery, fear of failure, hypertension can also cause changes is sexual function.

Treatments

With so many possible causes it is important that you establish the cause before deciding a treatment. Approaches to treat erectile dysfunction include counselling, vacuum devices, cockrings and treatments like Muse (an implant) and caverject (an injection). Oral medications include sildenafil (Viagra), vardenafil (Levitra), tadalafil (Cialis), apomorphine (Uprima) and yohimbine (Yohimbine, Yocon).

Testosterone levels

If you have a reduced sex drive then ask your doctor to check testosterone levels with a simple blood test.

For men, the range for normal levels is 10-30nmol/l but this does not allow for changes in age. If your levels are lower than this, testosterone replacement treatment can be given by patch, gel, implant or injection.

If you have other symptoms (low sex drive, fatigue, etc) then testosterone treatment is one option you can try, even if you are within 'normal' levels.

If effective, increased testosterone levels should reduce depression and fatigue and increase sex drive.

Testosterone (at much lower doses) is being studied as a treatment for sexual dysfunction in women. Hair growth, deeper voice and clitoral enlargement are side effects that require caution in women.

Sildenafil (Viagra)

HIV medications interact with Viagra. Lower doses – usually one 25mg in any 48-hour period – are used for people using a PI or NNRTI based combination. Viagra should never be used with poppers (amyl nitrate). Viagra and apomorphine (Uprima) are not currently licensed for women although some studies are underway.

Psychological issues

How you feel about yourself and your body and how you feel about HIV can affect your sexual health. HIV-negative people and society in general can react in irrational ways to HIV, which can contribute to how you feel as an HIV-positive person.

Dealing with an HIV diagnosis, whether or not you are on treatment, takes a lot of courage and perseverance. If treatments work well, you can be faced with new choices in life and if they are not working well and you are dealing with illness or side effects, you would expect this to impact on other areas of your life.

Talk to your doctor. Referral to erectile dysfunction clinics or counselling support is often appropriate. Many clinics have psychologists who are trained and experienced in sexual dysfunction.

Insomnia - *disturbed sleep*

NOTE: - See pages 22–23 for sleep disturbance associated with efavirenz (Sustiva)

Sleep is an essential part of a healthy life as it is a time when your body is able to rest and repair.

If you are not able to get regular, good quality sleep, either in the long or short term, your ability to think, speak and concentrate will be reduced. You can become more irritable and have slower reactions, and your memory and judgement will be affected.

Sleep problems are generally under-reported, under-diagnosed and under-treated and keeping a sleep diary for the week before you see your doctor can help diagnose some of the problems.

Factors affecting sleep include:

- Do you have problems falling asleep at night?
- Do you wake up too early in the morning?
- Do you wake throughout the night and only get intermittent sleep?

The diary should include when you fall asleep and when you wake up on week days and weekends. Include any naps you have during the day.

- Record how you feel about the general quality of your sleep, including vivid dreaming or nightmares
- Record drug and alcohol use – or changes in use such as withdrawal or cutting back on either
- Caffeine, present in tea, coffee and cola, can affect your ability to sleep, even many hours before you go to bed. Keep a record of how much caffeine you drink during the day and see if changing to a non-caffeine alternative helps
- Include details about your sleep environment– How comfortable is your bed? Is the room warm and quiet?
- Include when you normally eat. Leaving a couple of hours between your last meal and going to sleep will improve the chance of a better sleep

Stress and worry can easily disrupt your sleep pattern, as can ongoing health concerns, especially if they are painful or uncomfortable.

Your doctor should also give you a physical check up and blood tests to check for cardiovascular, respiratory or hormonal reasons, especially thyroid function, that may be causing sleep disturbance.

Suggestions to help

It is important that the causes of insomnia are diagnosed before any treatment is given. The wide range of possible causes mean that non-pharmaceutical approaches, such as having a warm bath or hot milky drink before bedtime, can often make a big difference and are sufficient.

Do:

- sleep only enough to be refreshed
- get into a routine where you can go to sleep and wake up at the same time each day
- try to take some form of exercise every day
- avoid extremes of noise or temperature
- drink chamomile and other herbal teas
- make your bedroom as comfortable and relaxing as possible.
- eat an evening meal so that you are not hungry when you go to bed

Don't:

- if you use sleeping pills, don't use them every night
- drinking caffeine drinks or alcohol before bedtime will reduce the chance of sleeping well
- smoke close to bedtime – it makes sleeping difficult
- try to not to nap during the day, so that you are more tired at night when you need to sleep

Medication

Sleeping pills are only usually prescribed when other self-help remedies have been tried. They are used to help re-establish a pattern or habit of sleeping – and are not recommended or generally prescribed for long-term use.

Sleeping tablets should only be used for the shortest period and at the lowest dose.

All sleeping pills work in a similar way by reducing brain activity, but the type of sleep they produce varies between different types of drug. They can help you sleep, but the depressed brain activity means that the quality of sleep is often not as good as natural sleep, and you may still not feel rested the next day.

Sleeping pills reduce the amount of 'dream sleep' that you get and this is an important component of good sleep. Sometimes this can leave you feeling drowsy the next day. They can become less effective after even a few days' use, and you can develop a physical or psychological dependency if they are used for more than 1–2 weeks.

Although benzodiazepines (ie temazepam) have relatively few side effects they can interact with protease inhibitors. Non-benzodiazepines such as zopiclone and zolpidem work in a similar way, are shorter acting, and are preferred when anxiety is not a contributing factor.

Melatonin is a hormone produced at night linked to your 'biological clock'. As a supplement it is used to help deal with jet lag and may help to help return sleep patterns to normal, although side effects also include vivid dreams.

Efavirenz side effects: Mood alteration, anxiety, dizzyness, sleep di

Associated drugs: efavirenz (Sustiva)

The side effects associated with efavirenz affect the central nervous system (CNS) and have not been reported with other anti-HIV drugs.

There are several difficult things about these side effects.

Nearly everyone will get some of these side effects but for most people they will be mild and easy to manage. This means that you may have some strange dreams, or find yourself daydreaming or getting more worried, or you may get more upset than usual.

If you have been told about this before you start treatment, they will be easier to manage and should be less alarming. Information about what to expect before you start taking efavirenz is therefore essential.

Efavirenz CNS side effects can occur after a few hours or after several days and are more common over the first few weeks and months of treatment. They also generally become easier to tolerate as you get used to them.

About a quarter of people in the first efavirenz studies recorded serious CNS side effects. This definition includes 'difficulty carrying out daily work'. So although very few people stopped efavirenz in these studies because of the side effects, you have about a 25% chance that it could make it difficult to work as normal until you get used to them.

You should therefore start efavirenz at the weekend or when you have some time off work, when you are more relaxed and less worried or stressed.

Many of the symptoms described here can also be symptoms of HIV-related diseases that are now seen less frequently such as dementia, TB or cryptococcal meningitis. These can develop slowly over time, so describing symptoms to your doctor, in order that they can rule out these factors is therefore very important.

Severe side effects

Some people will experience these side effects much more intensely and it is essential that you get more support as soon as you need it. If you are in this situation it is probably better and easier to just switch to a different treatment.

About 2–3% people stopped efavirenz in the first studies because they couldn't tolerate the side effects. Reports from the general population suggest the discontinuation rate may be 10–20% or even higher over time. Many people only chose to switch after trying efavirenz for several months, but if you know that the drug is not for you, then switch much sooner.

Although most people get used to side effects, they may continue at a low level for longer than the first few months.

Severe side effects can lead to or exaggerate clinical depression, including suicidal feelings and clinical paranoia. It is very important therefore that you are aware that such moods swings can be related to efavirenz and that you are not 'going mad'.

If you are feeling paranoid and worried about going outside, or have stopped seeing your friends as much, this can also be related to efavirenz side effects.

Why these symptoms are associated with efavirenz is not understood. It is also not possible to predict who will experience more severe symptoms.

Some studies have cautioned against using efavirenz if you are already depressed or have a history of psychiatric illness, but people without such a history have also found symptoms intolerable.

Several reports have been published of severe reactions in people with no previous psychiatric symptoms or illness. Often side effects are related to high blood levels of efavirenz.

Some studies have linked higher efavirenz levels to low body weight. Importantly, research in 2004 showed that race may be an important factor. Several studies showed that some poeple, particularly African women, clear efavirenz more slowly from their bodies.

This results in higher doses than they need. Measuring these levels with TDM can allow dose reductions without reducing the HIV effect of the combination or risking resistance.

Reducing CNS side effects

Although you can take efavirenz with or without food, a high fat meal can increase levels by 60%. If you have been taking it with high fat meals this could have increased the side effects.

Taking efavirenz a couple of hours before you go to sleep, rather than at bedtime, makes it more likely that you will be asleep when the drug levels are at their highest – about four hours after taking efavirenz.

Haloperidol to reduce anxiety and sleeping pills to help with sleep disturbance may also help, although these have not been formally studied.

If you experience difficult side effects with efavirenz and you are not happy with how you feel, then the best advice is to change it for another NNRTI (nevirapine) or to a protease inhibitor.

You do not have to continue with efavirenz to prove anything to yourself or to please your doctor. If you know something is wrong, don't worry about asking your doctor to change to something else.

isturbance

Symptoms include:

- impaired concentration, confusion and abnormal thinking.
- mood swings including anxiety, agitation, depression, paranoia (feeling very anxious or nervous) and euphoria (feeling very happy).
- sleep disturbance including insomnia, drowsiness, vivid dreaming and nightmares.

Even if you have only used efavirenz for a few days, if you know it is not for you, you should change to a different drug. Some drugs are not for everyone.

How to report symptoms

Some of the symptoms associated with efavirenz are easier to decribe than others. The advantage of writing down the effects you experience will let you see whether they are getting less over the first few weeks or months.

Sleep disturbance:

- Keep a diary of how often your sleep is disrupted.
- Try to describe this in a clear way.
- Is this every night or several nights a week?
- Can you estimate how much time you sleep each night, and how much you would sleep in a normal night before starting your current treatment?

Other HIV drugs have also been linked to insomnia.

Concentration and memory:

- Are you finding it more difficult to concentrate?
- Have you been aware of memory loss recently?

Dreams and nightmares:

- How often do you have dreams or nightmares?
- Do these disturb you sufficiently to leave you unsettled the next day?

Mood changes:

- If you are aware of mood changes during the day then try to describe these clearly in a diary to take to your doctor.
- Your family or friends may have noticed a change in your behaviour, even if this is not clear to you.
- Examples of how your mood has changed can give the doctor a clearer idea of how you are affected.

Depression and feelings of suicide:

- A small percentage of people who experience severe side effects have reported feelings of unexplained depression that are out of character, including suicidal thoughts.
- Symptoms at this level mean that it is critical to discuss this with your doctor in order to change to another treatment.
- If you are currently taking efavirenz, you may find it easier to talk to a close friend about how you feel and take them with you for support when you visit your doctor. There is never a problem with taking a friend or family member with you whenever you see your doctor.

Information about what to expect before you start taking efavirenz is essential.

... some African women clear efavirenz from their bodies more slowly. This results in higher doses than they need.

About a quarter of people in the first efavirenz studies recorded grade 3 or 4 level CNS side effects. This definition includes 'difficulty carrying out daily work'.

Although many people use efavirenz without problems, some drugs are not for everyone.

Peripheral neuropathy (peripheral = furthest away; neuro = nerve; pathy = damage)

Associated drugs: ddC (Hivid), d4T (Zerit), ddI (Videx), 3TC (Epivir),

Peripheral neuropathy (PN) is a relatively common side effect from some anti-HIV drugs. It can also be caused by HIV itself. It is difficult, if not impossible, to know for certain which the cause is but if the numbness or pain is symmetrical in both hands or both feet it is more likely to be a side effect of treatment.

The symptoms include increased sensitivity or numbness, or tingling in your hands and/or feet. Often it is something you hardly notice, or that comes and goes.

If neuropathy gets worse it can become very painful. It is a side effect that you should take very seriously.

PN is mainly associated with nucleosides, especially the 'd' drugs. PN has been reported in studies of ddC (now rarely used), ddI, d4T and less frequently with 3TC.

Using more than one of these drugs together can increase the risk as can use of other drugs such as hydroxyurea, dapsone, thalidomide, isoniazid and vincristine.

Alcohol use, smoking, amphetamines, deficiency of vitamins B12 and E and other illnesses like diabetes and syphilis can also cause and aggravate neuropathy; B12 and folate levels can be tested.

Can PN be measured?

Recent neuropathy studies have measured nerve damage in skin in a small biopsy sample.

Simple tests for neuropathy include comparing ankle to knee reflexes, or using a pin to test sensations from the toes up the leg. A tuning fork will show a reduced vibration in a foot with neuropathy.

It is likely that your doctor will just rely on what you report is happening. If your symptoms are causing you any discomfort or pain, you must make sure your doctor understands this and takes it seriously.

It is common for doctors to underestimate how much pain people are experiencing because they think that their patients always exaggerate pain. In fact, most people underestimate pain when talking to their doctor.

Sensitivity tests that measure your reactions to different pressure, are not used so frequently, and it can sometimes take 4-6 weeks to get the results. Getting these results recorded regularly though can help you measure any worsening of the symptoms.

Is neuropathy reversible?

The earlier you switch treatment, and the less severe the side effects, the more likely that the symptoms will reverse, but this does not happen for everyone.

Moderate and severe neuropathy very rarely resolves fully but switching drugs can stop the symptoms getting worse. If you have other drugs to use, switching at the first sign of symptoms may be the best thing you can do. Neuropathy can be irreversible and debilitating.

If d4T is the cause of your neuropathy it may be possible to reduce the twice daily 40mg dose to 30mg or even 20mg twice daily. For this approach it may be better to stop all drugs for a couple of weeks before restarting with the lower dose.

Your choices depend on your previous drug history and you should talk through all the possibilities with your doctor – you still have to consider your HIV treatment but avoidance of neuropathy altogether is the best way of treating it.

If you do stop using the drug you think is responsible (by switching to another or stopping all treatment altogether) then you may have to wait up to two months to know how much the discontinuation has helped. Often during this time symptoms can continue to get worse before you notice an improvement.

Treatments for neuropathy

There are currently no treatments that are approved to repair or regrow damaged nerves. One study has shown that L-acetyl carnitine (Alcar) at a dose of 1500mg, twice daily, can lead to nerve improvement. L-acetyl carnitine can be prescribed on a named-patient basis. Some clinics in the UK already use this treatment routinely.

Research into a synthetic human Nerve Growth Factor (hNGF) in the US which looked promising has since been put on hold and the development has been stopped.

Painkillers

Treatments which are prescribed to manage neuropathy are basically used to mask the pain. Sometimes these painkillers can have side effects themselves which make them difficult to use.

Amitriptyline, nortriptyline and gabapentin don't reduce the pain, but change how your brain perceives it. Gabapentin (licensed at 600mg, three times a day, though some reports of 1200mg have been used in the US) may help. These drugs work for some people but others find their sedative properties too difficult – even when they ease the pain from neuropathy.

Opiate-based painkillers such as methadone, morphine and codeine, although not always appropriate for neurological damage, sometimes benefit people with severe symptoms. It sometimes takes several days to find the appropriate dose, and these drugs can interact with some HIV drugs. A side effect of opiates is constipation.

If neuropathy gets worse it can be very painful... It is a side effect that you should take very seriously.

Treatments that may help:

- Change HIV drug(s) that are responsible
- L-acetyl carnitine (Alcar)
- Cod liver oil
- Painkillers such as gabapentin, amitriptyline or nortriptyline (or marujuana) may mask symptoms
- Acupuncture
- Magnetic insoles

You should also have appropriate care from a pain control nurse specialist, rather than your HIV doctor. They will be able to make a full assessment of your level of pain, and adequately prescribe medication to reduce it.

More rarely, when pain is so great that it is not treatable, alcohol can be injected into a nerve junction. Nerve blocks can be very effective when they work, and are a specialist procedure, but can also cause loss of sensation and sometimes produce unpredictable results.

Alternative treatments?

Alternative treatments often produce a more acceptable, and more effective, way of managing neuropathy.

Although not proven in studies, there has been substantial anecdotal reports on all of the approaches listed below. With a condition that is so painful, it is worth trying all of these in case they help.

L-acetyl carnitine (Alcar) is a supplement that has been effective in small studies and anecdotally. It is being studied again in the UK, US, France and Italy for PN.

Acupuncture is a lifeline for many people who report improved quality of life. A study comparing acupuncture to placebo showed no benefit, but the acupuncture was a standardised rather than individualised treatment. It is definitely worth trying to decide for yourself.

Magnets – Using magnetic insoles have reported benefits in diabetic-related neuropathy.

Local anaesthetic creams such as Lidocaine (5%), and Lidocaine patches reported benefit in a recent study.

Capsaicin – Topical cream made from chilli peppers that causes increased local blood flow when applied to the skin. Mixed reports, many of them not encouraging.

Voltarol (NSAID) – a nonsteroidal anti-inflammatory.

Alpha-Lipoic Acid – 600 to 900mg daily may help protect nerves from inflammation.

Cod liver oil – One or two tablespoons a day has anecdotally produced beneficial reports, especially if the symptoms have not become very severe. This is not as bad as it sounds as modern oils are palatable and also come in flavours.

Topical Aspirin – suggested in one recent study that aspirin, crushed and dissolved in water or gel and applied to the painful area can relieve symptoms.

Vitamin B6 (pyridoxine) – requires caution with dosing as B6 can also worsen neuropathy (100mg daily is sometimes recommended).

Vitamin B12 – available as injections, lozenges, or nose-gel. B12 levels should be checked by your doctor. Dosage varies but if levels are too high this can worsen neuropathy.

Magnesium – 250mg – 2 capsules each morning

Calcium – 300mg – 2 capsules each evening

Other suggestions:

- Avoid tight fitting shoes and socks which restrict blood circulation.
- Keep your feet uncovered at night - keeping them cooler and out of contact with sheets or bedding.
- Try deep tissue massage.
- Don't walk or stand for long periods.
- Soak your feet in cool water.

Clinical Trials:

So little is known about treatments for neuropathy that enrolling in a study may be very important. Current trials using L-Acetyl Carnitine for neuropathy are running at:

Royal Free Hospital, London
T: 020 7472 6232
North Manchester General Hospital
T: 0161 720 2615
St Mary's Hospital, London
T: 020 7886 6790

Further reading:

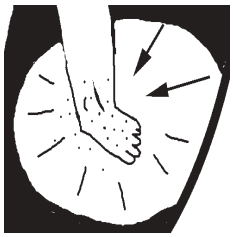
Useful recommended reference books written in non-technical language are *Numb Toes and Aching Soles* (July 1999) and *Numb Toes and Other Woes* (July 2001) both by John A. Senneff. ISBN: 0967110718 and 0967110734.

Lark Lands has pioneered research in the use of diet and supplements for PN:
http://www.larrylands.com/lark/

Neuropathy Trust (UK) offer information and support:

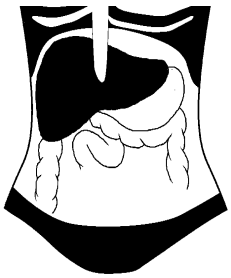
http://www.neurocentre.com

Neuropathy Association (US):
http://www.neuropathy.org



Liver toxicity, rash and nevirapine

Associated drugs: nevirapine (Viramune). [Most anti-HIV drugs have potential for liver toxicity].



Most HIV drugs can affect your liver as this is the way that they are filtered by your body. This is why your routine blood tests will include tests to check your liver function.

Ritonavir and nevirapine are particularly associated with liver toxicity. Several studies have shown that liver toxicity may be similar between nevirapine and efavirenz.

The following factors can increase the risk of liver complications from HIV treatment:

- Gender: women are more prone to liver problems with HIV drugs
- Viral hepatitis: hepatitis A, B or C (or other liver disease)
- Increased alcohol consumption
- Use of other drugs, including recreational drugs, that are toxic to the liver alongside HIV therapy.

Your doctor will normally test your liver function at the same time as testing CD4 count and viral load. If you have hepatitis or previous liver damage, use therapeutic drug monitoring (TDM) when using protease inhibitors or NNRTIs, as a dose reduction may be necessary.

When taking anti-HIV drugs you should report any side effects to your doctor. Especially if you have abdominal pain, nausea and vomiting, yellowing of the skin or the whites of the eyes.

Where liver toxicity is suspected, the drugs will normally be stopped to allow the liver to rest and return to normal. When the liver tests have returned to normal HIV drugs may be restarted; often a different combination of drugs or reduced doses may be necessary to prevent further liver problems.

Nevirapine

In 2004 new research showed that the risk of liver toxicity was different between men and women, and that the risk was related to CD4 count when starting this treatment.

Women starting treatment for the first time should not use nevirapine if their CD4 count is over 250 cells/mm^3 and men should not use nevirapine if their CD4 count is over 400 cells/mm^3.

These CD4 levels do not relate to people switching one of their current drugs to nevirapine. They do not relate to pregnant women who are using a single dose of nevirapine as part of a one-week course of treatment to reduce the risk of transmitting HIV to their baby.

Close monitoring (every two weeks) in the first two months of therapy is important for anyone who starts a nevirapine-based combination. This is when liver problems first start to occur. Liver toxicity may also build up slowly and so routine monitoring after the first two months is also important.

Nevirapine must be taken as one tablet (200mg) ***once*** daily for the first two weeks.

Only if you have none of the symptoms listed below and your liver function tests are within the acceptable levels can you increase your nevirapine dose to one tablet (200mg) ***twice*** a day.

Blood samples should be taken every two weeks in the first two months to check liver function, then at the end of the third month, and then every three to four months if they are within normal limits.

During this first eight weeks you should contact your doctor straight away if you have any of the following symptoms:

- Rash
- Blistering of the skin – seek immediate medical attention
- Mouth sores
- Facial or general swelling
- Fever
- Flu-like symptoms, aching muscles or joint pains

Your doctor will do another liver function blood test if you have one of these symptoms.

If the results are not higher than twice the normal limit, and depending on the severity of your symptoms, a decision will be made whether or not to continue with nevirapine. If a decision is made to continue, you will be very closely monitored to ensure that the symptoms do not progress or your liver function tests get worse.

If at any point your liver function tests get to five times the normal limit or mild symptoms get worse, then your nevirapine must be stopped. Your doctor will recommend whether you need to stop all your treatments or just switch the nevirapine to another drug.

If you stop nevirapine for these reasons, you must not take it again in the future.

Lactic acidosis, pancreatitis and fatty liver

Associated drugs:
All nucleoside analogues. d4T, ddI, tenofovir, 3TC, AZT and hydroxyurea have been linked in reports of lactic acidosis and pancreatitis. PIs and efavirenz have also been associated with pancreatitis.

Lactic acidosis

Lactic acid is a by-product formed when the body breaks down starches and sugars. Levels of lactic acid are normally carefully regulated by the liver. Small increases in lactic acid (called hyperlactataemia) are relatively frequent, and are temporary, especially after exercise.

If they reach a higher level, there is a risk of lactic acidosis. This is a more rare and potentially fatal side effect related to nucleoside/tide analogues (AZT, 3TC, d4T, ddI, abacavir and tenofovir).

Not only are these drugs included in nearly all HIV combinations, but the symptoms of lactic acidosis are common side effects of other drugs and indeed symptoms common anyway.

Symptoms include:

- unexplained tiredness, often severe
- sickness (vomiting) and nausea
- pain in the stomach, abdomen and/or liver
- unexplained weight loss
- difficulty breathing
- poor blood circulation – cold hands or feet or bluish skin colour
- sudden peripheral neuropathy

Before combination therapy was available, this was only very rarely seen in HIV, and may well have been under diagnosed. Recently the number of reports of lactic acidosis have increased and drug packaging now includes a clearer caution about this risk.

Pregnancy may be an additional risk factor for lactic acidosis when using nucleosides.

Lactic acidosis is diagnosed through examination, lab tests, an abdominal CT scan or liver biopsy. Although this toxicity is believed to be a result of damage to part of the cell called mitochondria, there is no simple test for determining people at highest risk.

Although lactic acid in blood can be measured, it is not clear whether high levels increase the risk of lactic acidosis. Over 50% of people showing a high reading on one result, return to normal with the confirmatory test. There appears to be no pattern between high levels and risk of severe toxicity.

Because lactic acid increases with any physical activity, confirmatory tests should be taken after complete rest for at least 20 minutes. Even going to the gym the day before may affect the results.

Treatment and monitoring

Early diagnosis is essential – and contacting your doctor if you have any of the symptoms is important. HIV treatments may need to be stopped immediately depending on blood levels (see inset box).

Diagnosis and treatment:

- Measure levels of lactic acid and blood pH.
- If lactic levels are >5mmol and if you have symptoms or levels are over 10 mmol discontinue HIV medication immediately.
- Use of intravenous anti-oxidants: L-carnitine and vitamin B complex including thiamine, riboflavine, nicotinamide, pyridoxine, dichloracetic acid and dexpanthenol is recommended.

High doses of vitamin B complex with L-carnitine (both IV) until lactate levels normalise were reported in a Dutch study to improve the chances of survival.

Antioxidants may help to overcome mitochondrial toxicity and use of oral antioxidant supplements such as vitamin C, vitamin B complex, L-carnitine or co-enzyme-Q may help and are prescribed by some doctors.

There are no clear guidelines for restarting nucleoside therapy after a serious case of mitochondrial toxicity. Although caution is warranted, lack of other antiretroviral options has lead to people restarting without further toxicity.

Mitochondrial toxicity is thought to be responsible for other side effects including nerve and muscle damage.

Pancreatitis

Pancreatitis is an inflammation of the pancreas characterised by abdominal or back pain and vomiting. It can also be alcohol induced and there is little specific treatment. Blood tests measuring amylase lipase are usually checked to confirm a diagnosis of pancreatitis. Pancreatitis can be fatal if not treated early, and can be prevented by stopping or changing HIV drugs.

Fatty liver

Hepatic steatosis is a medical term for 'fatty liver' which can develop from alcohol use, hepatitis, obesity and drug toxicity with nucleosides.

This build-up of fat in the liver can affect the way it processes fats. Hepatic steatosis often also leads to lactic acidosis, described above. People who weigh over 70kgs, especially women, may be more at risk of developing hepatic steatosis and lactic acidosis. Ultrasonography is a sensitive, accurate, non-invasive screening tool to detect steatosis as this is not always shown in liver function tests.

Steatosis is also common in HIV-infected children. It has no impact on disease, testing or management.

Abacavir hypersensitivity reaction (HSR)

Associated drugs: abacavir (Ziagen), Trizivir (abacavir+AZT+3TC), Kivexa (abacavir+3TC)

Abacavir is a nucleoside analogue that is very potent against HIV. The main side effect associated with this drug is a hypersensitivity reaction (HSR) which occurs in around 5% of people.

It means that the body is oversensitive to the drug. In some cases the reaction can be fatal. The risk increases if it is not diagnosed quickly and abacavir treatment stopped. Hypersensitivity reactions can also occur with nevirapine, T-20, fosamprenavir and cotrimoxazole (Septrin).

Hypersensitivity reaction to abacavir occurs during the first six weeks of therapy in over 90% of cases, but can occur at any time during abacavir use even after over a year without previous symptoms.

The drug licensing authority in Europe (EMEA) issued new guidelines for the use of abacavir. These state that close medical supervision is needed during the first two months of therapy and recommends that doctors see people every two weeks during these first two months.

It is very important that people are aware of the symptoms of abacavir HSR before starting therapy. These include:

- Temperature
- Rash – normally raised and differing in colour from surrounding skin
- Diarrhoea and abdominal pain
- Tiredness and feeling generally unwell
- Nausea and vomiting
- Headache
- Flu-like aches and pains including muscle pain
- Cough and shortness of breath
- Sore throat

These symptoms are very general and can be mistaken for many other illnesses including cold, flu and chest infections, especially during the winter period.

It is very important that if you get any of these symptoms after starting abacavir, you see your doctor straight away so that hypersensitivity can be ruled out.

If these symptoms get progressively worse each day it is an indication that they may be symptoms of a hypersensitivity reaction.

A rash is not present in all cases of HSR.

Do not stop taking your medication until you have seen a doctor and a diagnosis of hypersensitivity has been made.

It is very important that people are aware of the symptoms of abacavir HSR before starting therapy.

... if you get any of these symptoms... see your doctor straight away. Do not stop taking your medication until you have seen a doctor...

If you stop using abacavir before you have seen a doctor with these symptoms then you will not be able to restart, as hypersensitivity can't be ruled out. This means you will be reducing your future treatment options.

If HSR is diagnosed by a doctor then abacavir will be stopped straight away. These symptoms should then disappear very quickly after abacavir is stopped.

Abacavir must never be restarted at any time if you have had the hypersensitivity reaction, as this can prove fatal.

The overall mortality rate from hypersensitivity reaction in patients using abacavir is 0.03% – which is very small, but highlights the importance of awareness of these symptoms.

It is also reassuring that the incidence of hypersensitivity reactions has remained constant and has not increased since the drug was approved following wider use.

The mortality rate from people who have used abacavir, and then taken it again after stopping due to hypersensitivity symptoms, is 4%. This is very high – and highlights the importance of not returning to use abacavir if you have had suspected HSR symptoms.

If you are restarting abacavir following an interruption in treatment then you and your doctor should observe the same cautions as if you were starting treatment for the first time.

Abacavir (Ziagen) is one of the drugs in Trizivir (abacavir/AZT/3TC in the same pill) and Kivexa (abacavir/3TC in the same pill).

Kidney toxicity including kidney stones

(Crystalluria = crystals in urine; Nephrolithiasis: nephro = kidney; lithiasis = stone formation)

Associated drugs: indinavir (Crixivan) for kidney stones; tenofovir for other renal toxicity

Tenofovir-related toxicity

Tenofovir is cleared mainly through the kidneys. Routine blood tests for people using tenofovir should detect any changes in kidney function.

Your risk of kidney toxicity is higher if you are using other drugs cleared by the kidney, or if you have used these drugs in the past. There is a caution against using other such drugs with tenofovir.

Recommendations for reducing the dose of tenofovir in people with existing kidney damage are included with the prescibing information for this drug.

Recently there has been concern that tenofovir-related toxicity may be greater when tenofovir is used with ddI. Until this interaction is understood, these two drugs are generally not recommended to be used in the same combination.

Indinavir-related kidney stones

Indinavir originally was taken three times a day on an empty stomach, but now it is mainly prescribed with ritonavir. Ritonavir boosts the levels of indinavir so that it can be taken twice daily, with or without food.

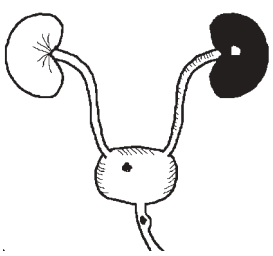
Indinavir is mainly processed through the kidneys (most drugs are cleared through the liver) and one of the side effects is a build up of indinavir crystals in the kidneys. About 20% of people will have indinavir crystals, and 4–10% of people will show symptoms of kidney blockage.

This is why you need to drink at least 1.5 litres of water a day (about three pints or six large glasses), especially just after taking your medications. This helps the tiny crystals of indinavir flush cleanly through your kidneys.

The risk of a blockage is related to the peak levels of indinavir. If the drug levels are too high, or if you don't drink sufficient water, then a blockage can be caused because the crystals can accumulate as a sludge.

This is not the same as a real kidney stone, but the symptoms are still very similar: stomach cramps, bladder pain and, most predictably, a dull pain or ache which can quickly develop into an extremely sharp pain in your lower back. Dark urine, or urine containing blood can indicate kidney stones.

A kidney blockage is very painful and very serious and requires immediate attention. If untreated a blocked kidney can lead to irreversible damage.



A family history of kidney stones may increase the risk of this side effect – and require additional fluid intake.

If you use higher indinavir doses (usually 800mg or 600mg) with smaller doses of ritonavir (100mg or 200mg) then you will have a higher peak level of indinavir ***and greater hydration may be important.***

In hot weather, and after exercise, increase your water intake even more. Tea, coffee and alcohol will cause you to dehydrate, so do not include these when adding up your fluid intake.

Avoiding stones:

- Maintain fluid intake to 1.5 litres a day – higher if you have a family history of kidney stones.
- Increase fluid acidity – drink more cranberry or orange juice.
- Check indinavir levels with TDM.
- Have routine urine checks with your regular blood tests to see if you are at higher risk.

Treatment

If you have these symptoms, try to drink as much water as you can (and sit upright or stand up to try to help any blockage to clear).

Acidic drinks like orange juice and cranberry juice can help as indinavir is more soluble in acidic conditions. If the pain gets worse seek medical advice at your hospital or Accident and Emergency Unit. When you get to hospital, tell the doctor that you are on a medication that can cause this. A regular x-ray, which is routine for kidney stones, won't show indinavir blockage.

The blockage can be diagnosed by an 'IVU' x-ray – where you are given a small amount of iodine solution injected into your blood, which is then followed by an x-ray every hour to check how well your body processes this fluid.

With an indinavir-related blockage, treatment is through increasing fluid intake (by intravenous drip and drinking) together with pain killers to control the pain.

Using indinavir again

Once you have cleared the problem it is safe to continue to take indinavir again – especially if it was working well for you – but make sure you keep drinking sufficient fluid.

Having the levels of indinavir checked with a blood test, especially if you are using indinavir with ritonavir (see TDM on page 9) is strongly recommended.

Increased bilirubin, jaundice (yellow skin or eyes):

(Bilirubin is a yellow-orange waste product from liver; Hyper = increased; aemia = 'in blood')

Associated drugs: atazanavir (Reyataz); indinavir (Crixivan)

An increase in bilirubin is a common side effect in 25-50% of people who use the protease inhibitors atazanavir or indinavir. Only a small percentage of people with increases in bilirubin develop jaundice.

The main symptoms of jaundice are a yellowing skin, or the white of the eyes being more yellow. This side effect in itself does not damage your body.

What is bilirubin?

Bilirubin is an orange-yellow part of bile. Bile is the bright green fluid secreted by the liver to help digestion.

Bilirubin is mainly formed by the normal breakdown of haemoglobin. Haemoglobin carries oxygen in red blood cells.

Bilirubin passes through the liver. It is then excreted as bile through the intestines.

When this process is interrupted, excess bilirubin stains other body tissues yellow. Fatty tissues like skin, eye tissue and blood vessels are the most easily affected.

Increased levels of bilirubin are linked with a range of illnesses and conditions. This includes jaundice associated with hepatitis and cirrhosis, anaemia, Gilbert's disease and sickle cell disease. Jaundice is common in babies. Very high levels in babies can cause permanent damage.

Two types of bilirubin

There are two types of bilirubin in the blood.

• **Unconjugated** (indirect) bilirubin is insoluble in water. This is the bilirubin before it reaches the liver

• **Conjugated** (direct) bilirubin has been converted to soluble bilirubin in the liver. It then goes into the bile to be stored in the gall bladder or sent to the intestines.

Routine blood tests for total bilirubin measure both unconjugated and conjugated bilirubin.

*Increases in bilirubin with atazanavir are of **unconjugated** bilirubin. This occurs in around 30% of people using atazanavir. People who have lower levels of the enzymes responsible for converting bilirubin in the liver will be at a higher risk of increases in bilirubin from atazanavir.*

Normal lab values and when to change

Total bilirubin (normal range) 3 – 17 mmol/l.

Direct bilirubin (normal range) 0 – 3 mmol/l.

Normal values may vary between different labs.

Jaundice becomes clinically detectable at levels above 40 mmol/l. You need good natural light to see this.

Treatment should be changed or the dose of atazanavir (or ritonavir) should be modified if bilirubin levels become five times the upper limit of normal (5xULN). This is at around 60-70 mmol/l.

This yellowish skin can be unusual. When related to atazanavir though it is harmless and it is not causing damage to your body.

Only a few percent of people using atazanavir discontinue because of jaundice. Jaundice reverses within a couple of days of stopping atazanavir.

Key points:

• When related to atazanavir, high billirubin is not causing your body any damage

• If this is too disturbing or unpleasant then it often disappears when using higher dose atazanavir without ritonavir

• Check atazanavir levels with TDM

Using ritonavir

Just like many other protease inhibitors, atazanavir produces better results when used with ritonavir.

- Atazanavir levels are higher after you have taken a dose, and lowest when you are due to take the next dose. Ritonavir produces higher and more consistent levels of atazanavir thoughout.
- The higher levels of atazanavir at the end of the dose will reduce the risk of resistance in people with low levels. Higher drug levels may make atazanavir stronger at reducing viral load.
- Atazanavir needs the lowest daily dose of ritonavir compared to other ritonavir-boosted regimens.

Because some people absorb higher levels of drugs anyway, some people may not need the additional boost from ritonavir. High levels of bilirubin may be a marker of high levels of atazanavir. You can't guess this though. It is best confirmed using TDM (see page 9).

In practice, people who get yellow skin or eyes when they use 300mg/day atazanavir boosted with 100mg ritonavir are often able to change to unboosted atazanavir (at 400mg/day). Note that the daily unboosted dose of atazanavir (2 x 200mg) is a higher dose than the boosted dose (2 x 150mg capsules).

It is very important that your doctor changes the formulation when not using ritonavir.

Other drugs that affect bilirubin

Many other drugs can also increase bilirubin levels. This includes anabolic steroids, some antibiotics, anti-malaria drugs, codeine, diuretics, morphine, oral contraceptives, rifampin and sulfonamides.

Drugs that can decrease bilirubin measurements include barbiturates, caffeine and penicillin.

T-20: injection site reactions (ISRs) and other side effects

Associated drugs: T-20 (enfuvirtide, Fuzeon)

T-20 is the first drug in a new class of HIV drugs called entry inhibitors.

The main advantages of T-20 are:

- that it is active against HIV that is resistant to any of the other classes of drugs
- that it is an 'entry inhibitor'. This means that it works on HIV before CD4 cells are infected. Nukes, PIs and NNRTIs work on cells that are infected by HIV. Side effects associated with some nukes, PIs and NNRTIs, such as mitochondrial toxicity and lipodystrophy, are unlikely to be caused by entry inhibitors.

The main disadvantages are that:

- T-20 has to be used in combination with other active drugs. Otherwise the benefit is only temporary and resistance develops
- It is not an oral drug. T-20 is given by sub-cutaneous injection (under the skin, not into a vein or muscle).

Because the benefits are significant and life saving for people with both resistance to existing drugs, and who have a low CD4 count, and because of the more complicated way that the drug is given, we have taken several pages to cover T-20 in detail.

Comments and suggestions for this section were provided by people who already use T-20 successfully in their combination.

ISRs - Injection site reactions

Nearly everyone who uses T-20 gets some level of skin reaction where the T-20 is injected but some people report no problems at all. Less than 5% of people discontinue treatment for this reason.

These reactions can include soreness and redness; nodules, bumps or cysts; and itching or other irritation. ISRs commonly last for a week or less in 75% people.

Often these symptoms are mild and manageable, and they may be minimised by good injection practice described below

The severity of the reactions is difficult to predict, and can vary in the same person. Some people follow all the best advice and are still unlucky and get erratic reactions. Sometimes this may be due to factors that you can't control.

The information in this guide only provides a limited overview on how to reduce the risk of these reactions.

The manufacturer (Roche) has developed extensive support material that everyone receiving T-20 is given. You will be given this detailed information, together with training before you use T-20.

This pack includes:

- detailed printed information
- 1-2-1 training from nurses (or from your hospital)
- a training video (if appropriate)
- phone numbers of patients already on treatment

Preparation and reconstitution

T-20 needs to be given twice a day.

Although one study looked at giving both doses at the same time once a day, this was not as effective as twice daily. In some people, drug levels at the end of the 24 hour period were too low, and this increased the risk of the treatment failing, and getting resistance to T-20.

However, each day both doses T-20 can be mixed up at the same time. It is very safe to mix both doses in the morning,for example, and leave the evening dose in the fridge until you come to use it later.

- Set aside an hour for preparation, especially when starting out, so that you are not rushed or hurried.
- Wash you hands before starting the preparation and don't touch anything other than the preparation materials during this process.
- Don't touch the needles or the tops of the vials after they have been cleaned with alcohol swabs.
- Prepare a clear space that is not cluttered with anything else. Use the preparation mat to lay out all the equipment.
- Lay out all the materials before you start and make sure that nothing is already opened or used.
- Only use the sterile water to reconstitute T-20. Never use tap water or other water.
- Always use the exact quantities recommended. Take your time when drawing up water into the syringe. Inject the water slowly into the T-20 vial at an angle. It should drip down the side of the vial into the powder.
- Gently tap the vial to start the T-20 dissolving. Then set it to one side to let it slowly finish dissolving completely. This may take up to 45 minutes.
- Don't shake the vial as this will cause the mixture to foam and it will take longer to settle down before you can inject it.

T-20 side effects (continued)

When the T-20 is fully dissolved, the liquid should be clear. There should not be any powder left on the sides of the vial. If there is, you should not use this vial.

There should also not be any air bubbles or foam. If there is, then the vial needs more time to settle.

Once mixed, the reconstituted T-20 should be used straight away, or put into the fridge for use in the evening. Reconstituted T-20 that is kept in the fridge needs to be used within 24 hours.

Detailed information on how to use the syringes is provided in the training pack given to every patient. Different syringes have been used, including fine diabetic needles, and these may change again in the future. This is why we have not included information on specific syringes in this guide.

Choice of injection sites

T-20 is injected under the skin so you need to pick an area that has most tissue or fat. Do not inject into muscle, and never inject into a vein.

The sites recommended for injections are:

i) thighs - the top of legs
ii) abdomen - your stomach, but not near your belly button
iii) upper arms and back
iv) buttocks are not generally recommended unless you have no other options and your doctor or nurse agrees to try this.

Changing where you inject T-20 each day is important.

- Do not inject into an area that is still swollen or inflamed from an earlier injection. Feel for any earlier bumps under the skin so that you can avoid these.
- Do not inject into moles, scars, bruises, not the area around your belly button or any area of skin that will be rubbed - ie by a belt.
- If you are prone to ISRs, wearing lose clothing can limit any inflammation.
- You may want to ask a friend to help you with injections, especially in some of the more difficult to inject sites like the upper arms.

This person should also receive training, including precautions if they accidentally prick themselves with a needle after giving you an injection.

Because T-20 is injected under the skin, and not into a vein, it is very unlikely to present a risk factor for HIV transmission.

- Some people report that having a warm bath first helps to soften the skin and make the injection process easier.

Clean the area to inject with an alcohol swab and allow to air-dry.

Pinch the area of skin that will be injected. Make sure the skin is dry and the cleaning alcohol has evaporated.

- Make sure that no T-20 touches the surface of the skin and that it is only injected once the needle is under the skin. Both these things will limit any burning sensation.

Then insert the needle at a 45-degree angle with the flat angled edge facing up, and inject the T-20 very slowly.

Several posts to the FuzeonSupport email discussion group have included varying the angle up to 90 degrees. It may be that you have to experiment to see if one method is better for you.

A half-inch needle should go all the way in to the hub.

The injection needs to be under the skin and not so deep that it reaches muscle. If you have very little body fat then choosing the area with the most fat is recommended.

After injecting, put all the used syringes and needles into the sharps container.

This should be kept away from children and collected by your clinic when it is full.

Never throw needles into general rubbish bins.

Massage and ice packs

Gently massaging the injection site after giving the injection may help reduce the risk of injection site reactions. This can be using your hands, with or without non-irritating oils, or using an electrical massager.

It will also help distribute the drug more quickly and more evenly. The nodules that sometimes occur have T-20 in those tissues, although the inflammatory reaction is unlikely to be related to the local concentration of T-20.

Some people find that an ice pack afterwards can help reduce the swelling. Some people use a warm hot-water bottle. You will have to experiment to see whether or not these options help you.

Creams such as a mild hydrocortisone or benedryl cream may help with more severe reactions.

Getting used to needles

Most people report that they get used to using needles very quickly. But it may seem strange at first. Try to focus on the benefit you are getting against HIV.

For example, contact lenses are very strange when you use them for the first time and T-20 can be a bit like that.

Carrying needles, travelling and leading a normal life

Many people are able to fit using T-20 into a normal and active life. If you travel you can always find a quite space to inject if you need too. One person took their first dose of T-20 in an aeroplane on their way to Moscow.

Take a letter with you from your doctor, that says you need the syringes for medical treatment, and that you are fit and healthy to travel.

The injection process may sound strange when you first have to think about it. Talking to someone already using T-20 may help and your hospital can arrange this.

Needle free injections in the future?

As this booklet was going to press, patients in the US were waiting to use a new system to inject T-20.

Instead of needles, the 'Bioject' system is a pre-filled disposable device that uses pressurised gas to inject a drug though the surface of the skin.

This may not reduce Injection Site Reactions though, because ISRs are related to the active drug. This system may make it much easier to inject hard-to-reach areas and make the whole injection process easier.

It is not clear whether this system will become available soon in the UK and the rest of Europe.

Quality of life

T-20 studies have reported overall increases in quality of life. This was despite having to inject T-20 twice a day, on top of taking other pills,

This may be related to knowing that HIV treatment is working. Often, people who have used many treatments in the past, are eventually able to get an undetectable viral load using T-20. This is especially true when T-20 is used with tipranavir/r or other new active drugs.

Because T-20 works outside the cell, there are other benefits.T-20 is not linked to lipodystrophy.

Some people are lucky and do not get any injection site reactions, though they are definitely a minority. Some people will use all the tips to minimise ISRs and inject perfectly, but still be unlucky and always get ISRs. The range of reactions is wide and variable.

Other T-20 side effects

Hypersensitivity reaction

A very small percentage of people get a 'hypersensitivity reaction' to T-20, but this is rare.

Symptoms include difficulty breathing, fever, nausea and vomiting, rash, chills, stiffening of muscles, low blood pressure and increased liver enzymes. This can be serious and life-threatening. If you have any such reaction, you should stop taking T-20 and call your doctor immediately.

Bacterial pneumonia

People in the main T-20 studies were at higher risk of bacterial pneumonia if they used T-20 in their combination. The reason for this is not clear.

People with HIV are more susceptible to getting bacterial pneumonia than HIV-negative people.

This risk is higher if your viral load remains high, and your CD4 count is low. If you have trouble breathing, or develop a cough with a fever, then you should once again contact your doctor immediately.

Mood changes - including euphoria

Some people have reported a feeling of euphoria when using T-20. This has often been after using T-20 for many months. This 'euphoria' can last for up to a couple of hours after injecting. It can include a general sense of well-being, contentment, excitement, or feeling 'buzzy'.

This was not seen in the large T-20 studies but has been reported anecdotally since T-20 was approved. If you already receive T-20, then keep an eye out for this.

Other information:

Please refer to the patient information leaflet and support material in your pack for full details.

You can join a community-run email support group by sending a blank email to:

FuzeonSupport-subscribe@yahoogroups.com

Patent support material provided by the drugs manufacturer is available at:

http://www.fuzeon.com/

The i-Base phoneline is a source of information about all aspects of treatment, including whether T-20 is an appropriate choice. The phoneline can also put you in touch with HIV-positive people who are using T-20.

Lipodystrophy

(lipid = fat; dystrophy = disorder)

Lipodystrophy is one of the most difficult side effects to write about for this booklet. This is because there is still no agreement for the underlying causes of these symptoms.

This is important to understand, because you may want your doctor to make changes in your treatment, even though studies haven't shown that one particular approach will work, or that one approach is best.

Although awareness of lipodystrophy has improved, you may still have to take an active role in getting the best monitoring and treatment.

This booklet was revised in January 2005. Our understanding of these symptoms will undoubtedly advance over the next few years and it is important to follow results from new research from scientific meetings.

What are the symptoms?

There are three broad sets of lipodystrophy symptoms:

- Fat loss (from legs and arms leaving veins more prominent, also from buttocks and the face)
- Fat gain (in the stomach, breasts in both women and men, shoulders, neck and sometimes lipoma - small lumps of fat under the skin)
- Metabolic changes that increase the levels of fats and sugar in blood and intefere wth the way your body produces and processes fat and sugar

Any discussion about lipodystrophy therefore needs to refer to specific symptoms.

Fat loss has been linked to nucleoside analogues and fat gain has been linked to protease inhibitors. Both fat loss and fat accumulation have been reported by people using NNRTI-based combinations. At least one study showed that lipodystrophy occured more often when using a three-class combination with PIs, NNRTIs and nucleosides compared to two-class regimens.

However, not all drugs in the same class have the same risk of lipodystrophy symptoms.

Lipodystrophy is likely to be the result of several different factors rather than any single cause. These include HIV infection, individual drugs, when treatment was started and family health history.

Lipodystrophy has been reported in men, women and children from a wide range of racial backgrounds.

How many people are affected?

Depending on what is being defined and how sensitively it is being measured lipodystrophy can affect between 5-80% of people on treatment. Only a smaller percentage of people will show clinical symptoms. In order to treat HIV, many of the current drugs are likely to affect the way our bodies process fats and sugar.

Over the short-term, most people do not have serious problems. The benefits from treatment still clearly outweigh the risks. However, for a significant minority of people the problems can occur more quickly, or can become more serious, especially after several years.

Preventing lipodystophy is more important and more successful than trying to treat lipodystophy after it has developed. As no one can predict who will be affected before starting treatment, monitoring in order to change treatment if you get early symptoms is very important.

Monitoring changes in fat distribution

There are several ways that changes in body fat distribution can be measured and monitored.

Most people are more sensitive to physical changes related to fat distribution in their body, than their doctors are. This means that 'self-reporting', perhaps with careful measuring by a dietician, or photography is more likely to provide a record of any change.

Some HIV clinics may have access to scanning equipment, but in practice lipodystrophy is rarely monitored in this way. MRI and DEXA scans look at the breakdown within your body of fat and muscle. A test called BIA (Bio Impedance Analysis) is also reliable. See side bar, right for more details.

Measurements and DEXA scans can have a wide amount of variation, but they are still sufficiently sensitive to detect larger changes over a 6-12 month period. MRI scans are very accurate and can show exact distribution of fat, but are more expensive and difficult to get.

Getting a DEXA scan, or well-lit photo, even if you only have slight changes, will give you a reference to know how quickly symptoms are progressing or improving. Some specialist clinics, including the lipodystrophy clinic at St Thomas' Hospital in London (to which you can self-refer), provide baseline DEXA scans to all patients.

Like your CD4 and viral load results, single test results may not provide much useful information, and you may need several tests over time to monitor changes.

If you are worried that you have lipodystrophy, make sure this is taken seriously. You should be offered monitoring and have any treatment choices explained.

If you are worried about lipodystrophy, make sure your doctor takes it seriously and offers you monitoring and explains treatment choices.

Changing treatment

Switching from d4T or AZT can reverse fat lost from limbs. This is supported by several studies. It is discussed in more detail in the section on lipoatrophy on page 36.

With fat accumulation, most of the studies looking at switching individual drugs have been less helpful. These are discussed in the section on fat accumulation on page 37. But, just because studies haven't shown a benefit, doesn't mean that other treatments may not be better for you. Whether you decide to change your treatment will depend on several things, including:

- How bad your lipodystrophy is
- How effective your current treatment is
- Which other treatments you can use
- Your previous HIV treatment history
- How serious your HIV illness was before you started treatment.

Many doctors are reluctant to change a combination which has worked well in terms of viral load and CD4 results, especially if you were previously very ill. However, this may not be appropriate if lipodystrophy has significantly reduced your quality of life.

If you change your combination, you have to change it to one that is effective against HIV.

One caution would be if you have developed resistance to earlier combinations, which may limit your choices.

For example, if you developed resistance to AZT then you may want to switch to tenofovir instead of abacavir. If you have already developed resistance to protease inhibitors then switching from Kaletra to atazanavir/r may be more difficult.

Using combinations without nucleosides is one new strategy that is being studied. Another might be to use entry inhibitors like T-20 as this drug has not shown an increased risk of lipodystrophy.

If you make a treatment change, test your viral load at least monthly afterwards until you can confirm that the new combination is working. If your viral load rebounds, you can always return to your previous combination immediately, so there is little to lose in at least seeing whether the lipodystrophy will improve.

It will be much easier to know if the switch has worked if you have been monitored before you make any change.

Even if this does not reverse the symptoms, using different drugs may stop them getting worse.

Monitoring tests

These tests can monitor changes – and baseline measures by a dietician for everyone before starting treatment would make interpreting later changes easier.

Measurement: careful measurement by a dietician using calipers can be useful if nothing else is available. This may be useful for fat increases but will be less sensitive for fat loss – and will not help for facial fat loss. Unless the changes are very marked then this may not be sufficiently accurate and may vary depending on the dietician.

DEXA scan (Dual X-ray Absorptiometry)**:** these scans are available at most main hospitals as they are routinely used for checking bone changes as people get older. You lay on flatbed scanner for about 20 minutes for a full body scan (head is not included though). They are not expensive (only about £70) and the results provide a breakdown of your body composition into fat, bone and muscle. Some doctors would like to see DEXA scans provided before any HIV treatment is started, and repeated annually to monitor for changes.

MRI scan (Magnetic Resonance Imaging)**:** these scans are much less readily available and the equipment required is more sophisticated and expensive. An MRI scan provides a computer image of the tissues, muscle and bone in a cross-section of any part of your body. An MRI scan can show how fat is distributed – whether it is subcutaneous (under the skin) or visceral (around your central organs) – and is very accurate at measuring any changes.

Bio-electrical Impedance Analysis (BIA): BIA is a simple painless procedure that calculates the percentages of fat, muscle and water in the body according to height, weight, sex and age.

It has mainly been used for HIV-related wasting but may also be useful in monitoring lipodystrophy.

Weight in people with lipodystrophy is generally stable. Fat redistribution rather than weight gain or loss that is usually the issue. However, weighing yourself is important in case you have lost or gained weight without realising it.

Fat loss (lipoatrophy)

Associated drugs: d4T (Stavudine), AZT (zidovudine, Retrovir)

Lipoatrophy symptoms

Lipoatrophy is the medical term for fat loss, and it is currently seen as the main symptom behind the lipodystrophy syndrome.

Symptoms include loss of fat from under the skin on your arms and legs, which can make your veins look more prominent. It also includes loss from the face - generally resulting in sunken cheeks and temples.

Role of d4Tand AZT

Lipoatrophy is common after long-term treatment that includes either d4T or AZT. Both these drugs affect the way that fat cells are produced, sometimes after only a few weeks or months of treatment.

Some studies report a higher risk when these drugs are used with protease inhibitors. There is an even higher rate seen with combinations that include drugs from the three main classes: i.e. nukes, a PI and an NNRTI.

Nucleosides have been shown to damage the energy producing part of healthy cells called mitochondria.

In most studies, d4T damages fat cells at around twice the rate of AZT. d4T may also lead to lipoatrophy that is more difficult to reverse than that caused by AZT. This is because it may damage cells at an earlier stage.

Other nukes?

Not all nukes cause lipoatrophy. 3TC, FTC, tenofovir and abacavir do not seem involved. The role of ddI is unclear.

The risk of lipoatrophy for people who are starting their first treatment should now be low. Newer drugs do not cause this side effect, and increased monitoring should pick this up if you are using older drugs like AZT.

The importance of corrective treatment for facial lipoatrophy is recognised in the UK treatment guidelines.

Switching treatment

Switching d4T or AZT to either abacavir or tenofovir, or using other combinations of drugs, can reverse the fat lost in limbs. Reversing facial fat loss appears to be more difficult, but this may be possible if you switch treatment at the first symptoms.

There may be a risk of viral load rebounding if you have resistance to other HIV drugs. Otherwise, switching is very safe. Increasing the number of new drugs may reduce this risk of viral load rebounding.

Any reversal of the fat loss is likely to take at least six months to become noticeable. These symptoms developed slowly and if they are going to reverse this will also take time.

In studies where people switched to abacavir, the return of small amounts of leg fat (+ 0.3kg) was detected by scans at 6 months. It took about two years (+1.3kg) before these patients noticed a difference themselves.

New-Fill

New-Fill (polylactic acid, PLA), given by injections every 2-3 weeks, has shown promising results in correcting the effect of facial fat loss. Most people require 4-5 sets of injections but severe cases may require more sessions.

New-Fill does not replace fat but generates new collagen growth. The effect is that essentially your skin grows thicker, sometimes by up to 1cm. This process continues for months after the injections have finished.

There is already some access to New-Fill on the NHS in some of the larger HIV clinics. These include Brighton, Manchester, and Ealing and St Mary's in London. The London HIV Consortium agreed to fund New-Fill in 2005 for patients registered at London clinics.

Access to treatment is clearly not equally available throughout the UK. Although access should continue to improve, you may have to lobby hard, or even change clinic in order to access this treatment.

Private treatment costs approximately £400 per set of injections. Private treatment should ONLY be from a practitioner with experience of HIV-related lipoatrophy.

UK HIV treatment guidelines recommend that corrective treatment such as New-Fill or surgery should be provided on the NHS.

Bio-Alcamid

Bio-Alcamid is a 'gore-tex' filler. This can be injected in greater volumes than New-Fill, so that with severe facial lipoatrophy, only one or two treatments may be needed.

The effect is likely to be permanent, whereas New-fill may require top-up treatment every few years. However, Bio-Alcamid is not currently available on the NHS, and this is unlikely to change for many health authorities unless the product is studied in trials.

Autologous fat transfer (Coleman technique)

This process was an early intervention before New-Fill became available. Fat is collected from one part of your body - usually subcutaneous fat from the stomach - and is then transplanted to the face.

Fat that has accumulated as a result of lipodystophy, for example shoulder pad fat is not suitable for transplanting as it may continue to expand in a process that is not reversible with liposuction.

This is a more traumatic surgical procedure and the process is now less frequently used.

Other injectable substances

Most other approaches try to inject or implant material (fat or silicon) and hope it will stay in position. Very often, it disperses, moves or appears lumpy. Silicon injections are both dangerous and ineffective and were banned in the US many years ago, although a study of a new finer grade of silicon is ongoing in the US.

Fat accumulation

Associated drugs: nukes, NNRTIs and protease inhibitors

Abdominal fat accumulation associated with lipodystrophy is generally *visceral* rather than *subcutaneous*. Visceral fat is around the organs inside the abdomen rather than being just under your skin.

With visceral fat your stomach walls are pushed out from the inside, so your stomach muscles can sometimes be quite defined, but your stomach will still be very extended.

In severe cases, your internal organs can become compressed so that normal functions like breathing and eating can be affected.

In these cases there is a greater medical urgency to reverse the fat accumulation. This may help your doctor access treatments like growth hormone (rHGH) or T-20.

Fat can also accumulate across the back of your neck and shoulders. This is sometimes called **Buffalo hump**. It was one of the earliest symptoms of lipodystrophy to be reported and can be very distressing.

Treatments for fat accumulation

Many of the approaches used to lower cholesterol and triglycerides are being studied to treat fat accumulation. These include diet, exercise, and investigational drugs (see 'switching studies' below).

Steroid treatment for lipodystrophy, particularly for fat accumulation, is also being studied. Although steroids have the potential to reduce fat accumulation, they should be used with cautions as they may also worsen symptoms of fat loss.

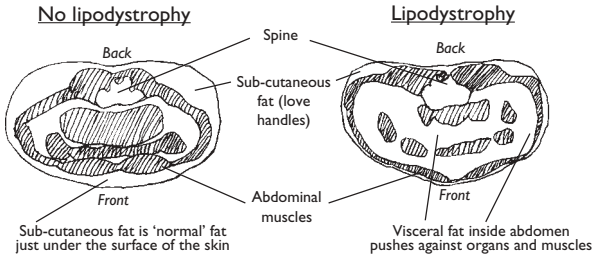
Recombinant Human Growth Hormone (rHGH) showed the potential to reduce visceral abdominal fat and fat pads from the back of the neck and shoulders in several small studies. Dosing at 2, 3 or 4 mg daily rather than the 6mg in early studies will minimise side effects.

Often the benefits are short-term and fat reappears after the rHGH is stopped. Current studies are looking at whether a smaller maintenance dose can retain this benefit. Growth Hormone will not reverse fat-loss.

Growth hormone can increase insulin resistance, and screening and monitoring is very important. It may be available in the UK in studies or on a named-patient basis. Access is generally very limited because this is an unlicensed use and is relatively expensive.

Removing fat pads using liposuction or surgically have worked well for some people. The fat returned after several months in 25-50% of people. There may be a higher likelihood of a permanent result if HIV treatment is modified at the same time.

Unless the underlying metabolic mechanism is altered, as with rHGH, fat accumulation is likely to return after several months.



An MRI scan through your stomach shows that fat is inside the abdomen and around the organs rather than being directly under your skin.

Liposuction cannot be used for visceral fat accumulation in the abdomen.

Anecdotally, testosterone cream massaged onto the fat pads has reduced fat pads on the shoulders. A much lower dose would be used for women than for men.

Dihydrotestosterone gel (Andractim) has been used to treat breast enlargement (gynaecomastia) in men.

Women with lipodystrophy may have higher levels of testosterone than either HIV-positive women without lipodystrophy or HIV-negative women. It is not clear whether this is due to high insulin levels associated with lipodystrophy, although a link between the length of time on PI-therapy (but not other drugs) and a greater chance of higher testosterone was found in one study.

Switching studies

Studies switching individual drugs have been less helpful with fat accumulation than with fat loss.

If you change your combination, you have to change it to one that is just as effective against HIV.

Studies switching a PI to an NNRTI have been too poorly designed to show any change clearly. Often background nucleoside were not changed, when we now think that this would have helpded too. There are often reports of better adherence, easier regimens, fewer pills, and most importantly no viral load rebound, but not always.

There have been anecdotal reports and case studies of people whose shoulder and/or abdominal fat decreased after switching to atazanavir.

Atazanavir does not cause the elevated blood lipid levels associated with other protease inhibitors, but long-term impact on risk of other symptoms of lipodystrophy is still being studied.

If one particular drug is linked to these body changes then it is very reasonable to at least try another one, in case this works for you.

Cholesterol and triglycerides

Cholesterol and triglycerides are two types of lipids (fats) that can be measured in blood and plasma.

They should be measured before starting or changing treatment, and repeated a month afterwards. Routine monitoring for someone on stable treatment should involve checking levels of cholesterol and triglycerides every 3-6 months.

Most clinics will do this at the same time as your CD4 and viral load, but you may need to check that this is being done. These tests are best done fasted so don't eat or drink anything for breakfast on blood test days.

Management of lipid levels should be part of an assessment of absolute risk for heart disease.

This is generally related as much to numbers of other risk factors that you have, than to any single elevated blood test.

Fasted triglyceride levels

High triglycerides are closely linked to increasing the risk of heart disease. For each increase of 1.1 mmols/L the risk of a heart attack increases by about 25% in men and 60% in women.

Although there is a lot of individual variability target fasted levels of under 2.2 mmol/l are considered normal and of 2.2-4.4 mmol/l are borerline. Above this the risk of heart disease increases. Levels above 11 mmol/L are considered very high.

Cholesterol

Total cholesterol is the usual monitoring test. If these results are high then a further test will break this down into two different types of cholesterol:

i) High Density Lipoprotein (HDL) is a 'good' cholesterol because it removes fats from your arteries; and

ii) Low Density Lipoprotein (LDL) is a small molecule that carries fats from the liver to other parts of your body and can lead to heart disease.

	Target level	Increased risk of Cardiovascular disease
Total cholesterol	under 5.2 mmol/l	over 6.9 mmol/L
LDL cholesterol	under 3.4 mmol/l	over 3.4 mmol/L
HDL cholesterol	over 0.9 mmol/l	over 3.4 mmol/L

Changing HIV drugs in your combination

Lipids generally improve after switching away from HIV drugs that have caused this change.

This usually involves switching from a protease inhibitor - particularly if they include ritonavir – indinavir/ritonavir, saquinavir/ritonavir, or lopinavir/r (Kaletra) - to nevirapine, abacavir or atazanavir/r.

Abacavir may have a greater impact on reducing cholesterol, and nevirapine may help with increasing HDL (good cholesterol). The debate on the impact of different strategies on reducing risk for heart disease is likely to develop and change over the next few years.

Atazanavir is a once-daily protease inhibitor that is being widely used because it does not cause lipid increases, even when used with a boosting dose of 100mg ritonavir.

The choice of individual drugs will depend on your previous treatment history and and previous history of resistance.

Diet, exercise and lipid lowering drugs

Cholesterol and triglyceride levels can sometimes be improved or controlled by reducing fat and cholesterol in your diet and by starting or increasing exercise.

Omega-3 supplements can also have a significant impact on cholesterol levels. This may be much more efficient than trying to obtain sufficient quantities of omega-3 from diet alone.

For example, a 4 g daily dose Omacor, (90% omega-3 acid ethyl esters) is equivalent to 150g mackerel, 700g tuna, 210g herring, 1.1 kg cod, 280g salmon, 1.7kg eel or 850g shrimps!

If diet, supplements, and exercise are not enough then adding lipid-lowering drugs like fibrates to reduce triglycerides and statins to reduce cholesterol is recommended. Statins can interact with HIV drugs and need to be prescribed by an HIV specialist.

Other lipid-lowering drugs including gemfibrozil, niacin (nicotinic acid/vitamin B3) need to be used with caution as they may affect the levels of HIV drugs. Studies are also looking at metformin (an insulin sensitising drug), rosiglitazone and growth hormone.

A study of HIV-positive men in a study looking at the effects of exercise and testosterone found that testosterone significantly reduced levels of 'good' cholesterol (HDL). This is a concern for people with lipodystrophy who already have elevated triglycerides and 'bad' cholesterol (LDL).

Although muscle gain and fat loss were greater in the testosterone group, levels of good cholesterol increased in people who used exercise without testosterone, and this may be more appropriate for people with lipodystrophy.

Although anabolic steroids can increase muscle mass they can also reduce fat, and have the potential to worsen lipoatrophy and lipid levels.

Improved blood lipids have not so far shown an improvement in either fat loss or fat accumulation.

Increased blood-sugar levels and risk of Type-2 diabetes

Glucose and insulin
Glucose is type of sugar and your body relies on glucose to provide energy. A hormone called insulin processes the sugar and allows it to enter cells. Insulin also regulates production of new glucose by the liver, levels of glucose in the blood, and metabolic aspects of fat cells.

Insulin resistance is the term for when this system fails to work properly. Although your body produces more insulin to compensate, if insulin resistance continues, and sugar levels remain high, you can develop diabetes.

Insulin levels are difficult to measure but glucose levels, usually checked by fasting or non-fasting blood tests, are routinely used for monitoring risk.

Types of diabetes
Type-2 diabetes is a adult illness that develops slowly. It can take years or decades for mild insulin resistance to progress to diabetes, but the impact on the risk of heart disease is serious. Some protease inhibitors can increase glucose levels and the risk of Type-2 diabetes.

Type-2 is different from Type-1 diabetes, a childhood illness caused by low insulin production, which is managed by insulin injections.

Risk of long-term health problems
High untreated blood-sugar is related to many long-term health problems including the kidneys, nerves, eyes and vision, risk of heart disease and stroke, and erectile dysfunction in men and pregnancy complications in women. Diabetes increases the risk of having a heart attack as much as smoking.

Fat and sugar metabolism are also closely linked and insulin resistance is a complication of HIV therapy that is gets little recognition. It is directly related to some protease inhibitors and possibly indirectly related to nukes through their effect on fat distribution. Changes in blood glucose levels and insulin sensitivity are closely related to other symptoms of lipodystrophy.

What can help
As with HIV-negative people mild insulin resistance can be managed by diet, exercise and stopping smoking. Switching HIV drugs associated with increases in blood-glucose is recommended when appropriate.

Dietary advice involves reducing processed sugars, refined and fast foods, white flour and potatoes as they cause quick sugar 'highs'. More complex carbohydrates like wholemeal bread and wholemeal and al-dente pasta, porridge and most vegetables provide energy more slowly with less impact on sugar levels.

Metformin may help people with insulin resistance and fat accumulation. Rosiglitazone or pioglitazone may help people with insulin resistance and fat loss. The possibility of interactions with other HIV drugs (PIs and NNRTIs) means that they should also be used with caution, and perhaps with drug-level monitoring (TDM).

Symptoms of high blood-sugar, and diabetes

- Feeling thirsty or excessively hungry
- Feeling tired
- Low concentration
- Blurred vision
- Unexplained weight loss
- Frequent need to urinate
- Slow healing of cuts
- Tingling in hands or feet (neuropathy)
- Nausea and vomiting

Risk factors for abnormal glucose

- Liver damage or coinfection with HepC
- Family history of diabetes
- Overweight (BMI>30)
- Lipodystrophy or lipoatrophy
- Low exercise
- Age over 40
- High blood pressure
- High cholesterol and triglycerides and low HDL (good) cholesterol
- History of insulin resistance or high glucose
- Other meds, including niacin, glucocorticoids, megestrol and Growth Hormone and some PIs

Tests to diagnose and monitor

Fasting glucose test - measures blood sugar after an 8-hour fast. This should be measured before starting ARV treatment and checked every 3-6 months after switching treatment. Fasting levels over 6.1 mmol/L in plasma (5.0 in blood) indicate insulin resistance, and over 7.0 usually indicates diabetes.

Random glucose test - Unfasted glucose levels are less accurate but are taken shortly after someone has had something to eat or drink. If it is greater than 5.17 mmol/L other tests are run. Diabetes is over 11.1 mmol/L.

Oral glucose tolerance test - Monitors levels of glucose every 30-60 minutes for two hours after fasting for 8-hours and then drinking a measured glucose drink. Healthy glucose on this test should be less than 3.62 mmol/L. If it is greater than 5.17 mmol/L other tests are run. Diabetes is over 11.1 mmol/L.

Haemoglobin A1c - tests how much glucose adheres to red blood cells. It is used to determine average glucose levels over several months. Normal range for someone without diabetes is 4-6% and managed treatment for someone with diabetes should aim to keep this under 7%.

Fasting insulin test - and results used to calculate HOMA-IR score. Measuring glucose is generally preferred to measuring insulin directly.

Insulin tolerance test (also called glycemic clamp) - where insulin in infused by intravenous line, and glucose given until normal blood sugar levels are reached. This is expensive and again is rarely used.

Heart disease

When lipodystrophy and metabolic changes associated with combination therapy became more widely recognised, there was an initial concern that these symptoms - particularly increased cholesterol and triglycerides - could lead to an increased risk for heart attack or stoke.

This is because increased levels of blood lipids can lead to blocking blood vessels (atherosclerosis) and are a well-established risk factor for heart disease.

Although heart disease can be a disease in itself, it is important to include information about this in a book about side effects of HIV drugs.

This concern was prompted by a series of case reports of heart attacks in HIV-positive men who were too young to be considered as traditionally at high risk.

Several large studies have reported results that calm some of these initial fears.

- Benefits of combination therapy still far outweigh the possible slightly increased risk of heart disease for most HIV-positive patients
- The largest study so far (D:A:D) has shown that there may be a small additional increase in risk of heart disease from each year on treatment
- People at high risk for heart disease may need to take this additional risk more seriously
- In people who are HIV-positive, risk factors for heart disease are the same as for people who are HIV-negative
- Making lifestyle changes that minimise risk factors are now strongly recommended as part of a long term health plan for HIV-positive patients.

There is a lot of information and research about risk factors for heart disease in HIV-negative people. This has often come from very large studies (Framingham, Caerphilly etc) that followed a large group of people for many decades. These studies led to the development of risk calculators that are easy to access online.

If you put in your age, gender, cholesterol and triglyceride levels and other risk factors such as smoking, you get your 5-year or 10-year risk of heart disease.

People with high risk factors for heart disease who need HIV treatment, should use newer HIV drugs that have the least risk of increasing the risk of cardiovascular disease any further, and receive support for lifestyle changes. It is hoped that the most 'lipid-friendly' HIV drugs will not have the same impact on cardiovascular risk as combination therapy in the D:A:D study.

Risk factors for heart disease

The following factors increase the risk of heart disease; some of which are fixed and some are modifiable by lifestyle.

Fixed risk factors:

- older age (men over 45, women over 55)
- gender (men are at higher risk at the same age)
- family history of heart disease

Modifiable risk factors:

- smoking
- high levels of fat in blood - ie high cholesterol and/or triglyceride levels
- lack of exercise
- high blood pressure, especially diastolic BP
- high levels of sugar in blood, insulin resistance and diabetes

Symptoms of heart attack or stroke

Symptoms of cardiovascular disease include:

- shortness of breath
- fatigue
- feeling dizzy or light-headed
- fainting
- chest pains (that can extend to the shoulders, back, arms, head and jaw)
- Chest pains after exercise or exertion.

Additional symptoms for a stroke include:

- sudden numbness
- paralysis of the face or limbs, especially affecting just one side of the body
- difficulty speaking
- loss of balance or coordination
- severe headache
- brief loss of consciousness.

If you experience these symptoms, you should seek urgent medical attention.

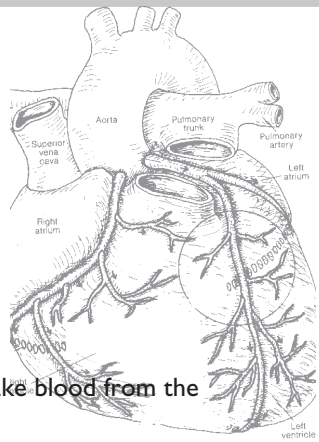
Rapid treatment after a stroke (within 2-3 hours) can limit permanent brain damage.

D:A:D Study

The D:A:D study is the largest study to look at the risk of heart disease in relation to HIV treatment.

The study collected information from over 20,000 patients from Europe, the US and Israel.

This diversity of patients is one of the study's strengths. D:A:D found that duration of HIV treatment was related to a small but significant increased risk of heart disease. This was found in different countries and in both men and women.



Relative rate and actual risk

The D:A:D study showed that the relative rate for heart disease increased by around 16% for each year of HIV treatment.

Whether this makes a real difference to your individual risk though depends on whether you are at a high or low risk to start with. Individualising HIV care will be linked to your other risk factors.

If you have high blood cholesterol for example but no other risk factors, then it is less urgent to reduce these levels. However, for a 50-year old male smoker who has high cholesterol and is on HIV medication, it is more important to change one or more of these factors.

How to make lifestyle changes

Changing the risk factors for heart disease can have a direct impact on future risk. By implication, this will also make HIV drugs safer to use.

The advice given to the general population is even more important if you are using HIV treatment.

• Stopping smoking is probably the most important lifestyle change in term of general health and risk of heart disease. Support groups and other interventions including replacement therapy like nicotine patches are now available on the NHS.

The most recent research suggests trying a range of products over the first week or two to cope with nicotine withdrawal such as patches, gum, inhalers and sprays so that you find the ones that work best for you.

Your HIV doctor should be able to refer you to specialist services to help you quit.

• Diet changes are other significant changes that can reduce your risk for heart disease. For information on reducing cholesterol and triglycerides see the section in this guide on lipodystrophy.

• Reducing fatty foods can reduce lipids to some extent. Cutting down on salt reduces blood pressure. Eating less processed sugars reduces your risk of developing insulin resistance and diabetes.

• Exercise is the other main modifiable factor. This may include direct exercise or sport, or just being more active in your day-to-day life, by walking more and using the lift less etc.

Any change in level of activity will probably have to start gradually. People who start an exercise programme report benefits in quality of life. This can include increased well-being and energy levels.

Glossary

Arteries are the blood vessels that take blood from the heart to the lungs.

Veins are blood vessels that delivery blood back to the heart again.

Arrhythmia is the medical terms for a disturbance of the heart's natural rhythm. **Tachycardia** refers to when the heart beats too fast. **Bradycardia** is when the heart beats too slowly.

Atherosclerosis refers to a narrowing or hardening of large and medium sized arteries. The narrowing is caused by a build-up of plaque, and usually takes many years. As the walls of the artery thicken, the heart has to work harder to pump the same amount of blood through a narrower gap.

Cardiovascular refers to the heart and blood vessels.

Cardiovascular disease (CVD) is the general term for disease to the heart and related blood vessels.

Cerebrovascular refers to the blood vessels taking blood to the brain. A blockage that restricts blood to the brain is called a stroke. Strokes can occur when blood vessels in the brain block, or when a clot formed in another part of the body is carried to the brain.

Coronary Heart Disease (CHD) refers to the three main arteries that supply blood from the heart. A coronary by-pass is a surgical operation to provide a new route for blood to reach the heart when coronary arteries become blocked.

Hypertension is the medical name for high blood pressure (BP). Blood pressure is measured as two numbers ie 120/80. The first number is systolic BP - the pressure when your heart beats. The second number is diastolic BP, which is the pressure when you heart rests between beats. Hypertension increases the risk of a heart attack, particularly when diastolic BP is high.

Hypotension is the medical name for low blood pressure.

Pulmonary hypertension refers to high blood pressure in the arteries taking blood from the heart to the lungs. HIV-positive people are more likely to develop pulmonary hypertension than HIV-negative people.

Myocardial Infarction (MI) is the medical term for 'heart attack'

Peripheral arterial disease refers to atherosclerosis in the arteries in the arms or legs.

Bone mineral changes

(osteo = bone; necrosis = death; porosis= thin)

Several conditions have been reported linked to bone changes.

Even though these symptoms may not be linked to HIV drugs – ie not a side effect – we have included a section here as this is a new area of research that is important to know about.

The two main changes linked to bone are:

i) changes in content and structure of bone where your bone becomes thinner. This is called osteopenia at mild levels and osteoporosis is at more severe levels, and requires treatment; and

ii) interruption of proper blood supply to the bone, which causes death of bone tissue - osteonecrosis and avascular necrosis (AVN).

Protease-based combinations have been linked in several studies to reduced bone mass – and this was found comparing HIV-positive people on treatment to HIV-positive people not using treatment.

However, other studies have not found this link, and one study found people using nelfinavir maintained stable levels and that people using indinavir may have had improved bone mass changes when using an indinavir-based combination.

Osteopenia and osteoporosis

Changes in bone mineral density have been reported recently in people using combination therapy. However, it is unclear whether these symptoms are the result of HIV or side effects of the drugs used to treat it.

These changes in bone structure often overlap with issues of lipodystrophy and may be related to those metabolic changes and the way your body processes sugar and fat. In HIV-negative people corticosteroids (like prednisone) and heavy alcohol use are associated with higher risk of bone problems.

Other risk factors for osteoporosis include Caucasian/ Asian race, low body weight, cigarette smoking, lack of physical activity, family history of osteoporosis, and early menopause.

Your bones are a living structure, 10% of which naturally die each year to be replaced by new cells. If the bone isn't replaced quickly enough or in sufficient quantities, your bones can becomes thinner and more brittle.

Osteopenia and is very common in older people and several studies showed high levels (between 20–40%) in people with lipodystrophy.

Osteoporosis is a more serious progression of osteopenia and can be diagnosed with a DEXA scan. Unlike osteopenia this can lead to fractures and pain (commonly to the spine in men and the hip in women, although this is as yet unknown in HIV).

Osteonecrosis and avascular necrosis

With osteonecrosis and AVN, inadequate blood supply reaches the bone, and these tissues then die as a result. It is much less common, and usually affects hip, shoulder or knee joints, and requires replacement surgery.

It is very common for corticosteroid use to be a contributing factor in cases of AVN.

Early diagnosis of AVN makes a big difference to the success of treatment as well as your quality of life. If you experience pain in these joints, ask your doctor to refer you to a specialist, and to provide an MRI scan that can make an appropriate diagnosis.

Protecting bones

Treatment and prevention measures are similar, regardless of whether you are HIV-positive or not - although closer monitoring of HIV-positive people is clearly important.

Reducing smoking and alcohol, taking exercise and eating a diet adequate in calcium, protein and vitamin D (and spending some time in the sunshine) should protect you against bone mineral loss.

Bone building nutrients include calcium and vitamin D_3 (colecalciferol) and any deficiency should be corrected by increasing dietary intake or use of supplements. The recommended calcium dose for protecting bones is 500-1000mg daily for adults. The dose of vitamin D_3 for osteoporosis is probably 400-800 IU/day. These nutrients should be prescribed by your doctor and sometimes require special monitoring and dosing.

A link has also been suggested between bone damage and mitochondria damage, and a link to high levels of lactic acid has also been reported. The HIV medications related to these changes may therefore be nucleosides. This may be a reason to use mitochondria protecting nutrients such as vitamins C and E, L-carnitine and co-enzyme Q.

Other potential treatments to improve bone mineral density for people with diagnosed bone problems include bisphosphonates such as alendronate (Fosamax) and lipid-lowering statins (though both studies showing these benefits were not in HIV-positive people).

Further information

A good general home reference book (not just HIV-related side effects) including illustrated information on how drugs work and on many individual drugs is the:

'BMA New Guide to Medicines and Drugs'. Produced by the British Medical Association, 2004 6th edition. Published by Dorling Kindersley for £16.99.

Much of the most easily readable and up-to-date information on side effects and HIV is available on the internet.

The following links were correct when we went to press. If you have trouble finding an article or link call the i-Base phoneline on 0800 800 6013 and we'll try to help.

If you are not reading this in electronic format the i-Base website contains all these references as active links - to save you retyping addresses:
http://www.i-base.info/pub/guides/side0205

Internet references

One of the most useful HIV sites with search facilities for many community, activist and medical professsional publications is at:
http://www.aegis.com
http://www.aegis.com/ni/pubs/treatmnt.asp

Try publcations CATIE, IAPAC journal and Women Alive if you have not seen these before:
AEGiS.com also includes an excellent and comprehensive database of conference abstracts, that are posted to the internet shortly after international meetings.
http://www.aegis.com/conferences/

Many conferences publish studies on the internet and some also let you hear lectures and see slides from some sessions. Important sites for 2005 meetings include:

Conference on Retroviruses and Opportunistic Infections:
http://retroconference.org/

International AIDS Society Conferences:
http://www.ias.se

Reports from these and other meetings are usually available shortly after the meetings on the following sites:
http://www.i-Base.info
http://www.hivandhepatitis.org
http://www.natap.org
http://www.medscape.com/

Alternative treatments

A useful site for supplements, nutrients and alternative treatments (including New-Fill injections for facial fat loss and Lark Lands on neuropathy) is the DAAIR site:
http://www.daair.org

Also for neuropathy:
http://www.pn.uku.co.uk/links/Treatments.html

General information

Excellent regularly updated fact sheets, written in a clear non-technical language on many side effects are available in English and Spanish on the New Mexico AIDS Infonet:
http://www.aidsinfonet.org/topics.php

The UK aidsmap site has a range of basic factsheets that are available in English, French, Spanish and Portuguese:
http://www.aidsmap.com/en/docs/ux/treatment.asp

This site also has very useful overviews of individual drugs and their side-effects in the 'Drugs used by people with HIV' link from the above page.

A list of UK clinical trials is also available on aidsmap, but not all studies are included, so you may want to also check with your own hospital and the larger London hopsitals.

A site with useful links to longer articles from community publications is the Opportunistic Infection (OI) page of The Bodys treatment publication section:
http://www.thebody.com/treat/oipage.html

Beta, the quarterly newsletter from San Francisco AIDS Foundation includes very good articles on individual side effects and older articles tend to remain useful and relevant. An index of issues is at:
http://www.sfaf.org/treatment/beta/chronological.html

HIV and hormones - Issue 55
Overcoming Depression - Issue 54
Oral Health and HIV - Issue 54
Insulin Resistance and Diabetes - Issue 54
Cardiovascular disease - Issue 51
New-Fill to treat facial wasting - Issue 50
Nausea and diarrhoea - Issue 50
Bone disease - Issue 49 and 48
Fatigue - Issue 47
Mitochondrial toxicity - Issue 44

Other useful single issue articles include:
Insomnia: (Insomnia in HIV and its management)
http://www.centerforaids.org/rita/1200/insomnia.htm

Fatigue: Interviews with Lisa Capaldi in ATN (1998)
http://www.thebody.com/atn/291.html#tired
http://www.thebody.com/atn/292.html#tired

Depression and HIV: Older article (2001) but still useful
http://www.projectinform.org/fs/depression.html

Physician Research Notebook - for excellent detailed articles on Treatment for Lipoatrophy; Insulin resistance in HIV disease; Risk of heart disease and HIV therapy etc
http://www.prn.org/prn_nb_cntnt/past2004.htm

i-Base treatment information phoneline

0808 800 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 seropositive - gratuis et en confidence
Service d'information speciallise 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 2004)* ☐
- Changing Treatment: Guide to Second-line & Salvage Therapy *(Feb 2005)* ☐
- Pregnancy HIV and Women's Health *(Feb 2005)* ☐
- HIV Treatment Bulletin (HTB) – conference and medical reports (monthly) ☐
- Avoiding and Managing Side Effects – *(this publication)* ☐

In English ☐ In French ☐ In Chinese ☐

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

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S FOUNDATION
This publication was produced with a generous donation from the Peter Moores Foundation

Written by Simon Collins, Andrew Moss and Lawrence Gibson. Drawings by Beth Higgins Produced by HIV i-Base.