

aids treatment update

antiretroviral side-effects dominate Seattle Retroviruses conference

Hard to believe, but it's now almost five years since the first case reports of body fat changes were described at a major HIV conference. In a field where we've become used to such a roaring pace of development, progress in understanding lipodystrophy has seemed frustratingly pedestrian. At this year's Annual Retroviruses meeting, however, it became clear that efforts to unravel this particular puzzle of HIV medicine is now a major focus for those involved in AIDS research worldwide. Of nine papers selected for presentation at the conference's closing 'late breakers' session, seven featured various side-effects – some old, some new – which are dogging the advancement of antiretroviral therapy.

How to contextualise the risk of side-effects is perhaps one of the biggest challenges for people considering, or taking, HAART. An analysis of a large US cohort treated with HAART between 1996 and 2001 found that severe side-effects occurred in 27%. This was double the rate at which new AIDS-defining illnesses occurred within a similar, thirty-month follow-up period.

In this month's lead article, we report on a new international effort to contextualise lipodystrophy – an initiative to develop a case definition which will ultimately lead us to a better understanding of this problem – who is most at risk, what may be the causes, and how it should be managed.

managing body fat
changes 2

switching drugs to
avoid fat loss 6

news in brief 10

managing body fat changes

2 mixed news from Seattle Retroviruses conference: progression on the development of a lipodystrophy case definition plus preliminary findings on new treatments by [anna poppa](#)

One of the challenges in responding to the lipodystrophy syndrome has been the lack of a clear definition of precisely what the syndrome is. Individuals who are affected present with a wide range of symptoms, some of which can be difficult to distinguish from the wasting and metabolic dysregulation which occur as a direct result of HIV infection. Clearly also, losing and gaining fat is a fairly normal process, particularly as humans age. Whilst many people's experience of lipodystrophic changes is clearly not normal, for others the issue may be more marginal. By defining what is lipodystrophy and what is not, it may become clearer in time what may be causing the syndrome, who is most likely to be affected, and what measures might ameliorate it.

So far, the most convincing efforts to define the syndrome have been led by the HIV Lipodystrophy Case Definition Study Group, a joint academic / pharmaceutical industry initiative developed in response to questions raised by the European drug approval body, the European Medicines Evaluation Agency. The Group presented its first report at the Seattle Retroviruses Conference in late February¹.

The study involves 32 HIV treatment centres in North and South America, Europe, Asia and Australia. Of 1,371 adults with HIV, but no active AIDS-defining illnesses, who were approached to take part, 1,081 agreed. Four hundred and seventeen of these were designated as lipodystrophy cases on the basis of their having at least one lipodystrophic feature (either fat loss, localised fat gain, or diffuse fat gain) which both patient and doctor defined as moderate to severe. Three hundred

and seventy-one people were designated as controls because they had no lipodystrophic features, and the remaining 288 participants were termed 'non-assigned'. In most cases, the inability to assign individuals as either cases or controls arose after patients and their doctors were unable to agree over whether lipodystrophy was or was not present.

Matthew Law, of the National Centre in HIV Epidemiology and Clinical Research in Darlinghurst, Australia, and a statistician working on the Lipodystrophy Case Definition project, spoke to *ATU* about how information about participants was used to generate the case definition: "For the cases and controls, a whole series of objective data were recorded, including HIV clinical data, metabolic parameters, body composition data, and DEXA and CT scans. We then used statistical models to choose the combination of objective variables which best discriminated between cases and controls. This statistical model essentially boils down to a scoring system – patients with a high score are more likely to be cases, patients with a low score more likely to be controls."

Overall, the lipodystrophy case definition which was developed by this method was found to have a sensitivity of 78% and a specificity of 80%. In other words, the model could be used to detect around 80% of cases of lipodystrophy, but may miss the other 20%; and secondly, of those cases detected by the model, 20% would be false positives.

The model will require further validation, and may be difficult to use in routine care at

present because it relies on techniques which may not be available, such as DEXA scans. Those with milder cases of lipodystrophy are those most likely not to be recognised by the model in its present form. Women made up only 15-18% of those participating, and so the applicability of the case definition to women is limited. In order to reduce possible bias, people with active AIDS (who may be experiencing wasting), and those presenting with localised fat accumulation on the belly only (which may be age-related), were excluded. Again, this may make the model less appropriate for people who share these features. Finally, as this is an adult model, it cannot be applied to children.

Putting lipodystrophy into context

The introduction of HAART in 1996 led to a dramatic fall in rates of illness and death (sometimes called morbidity and mortality) in people with HIV in those countries and communities where the drugs were used. To get a more up-to-date assessment of the effects of HAART however, it's necessary to look at more recent epidemiology.

Data from the Royal Free Hospital in London were presented at the Seattle conference². The analysis concerned trends in clinical, virological and immunological response to HAART in Royal Free patients between January 1999 and June 2001. Close to 1,500 people were seen at the clinic during this period. The proportion receiving antiretroviral therapy rose from 61% to 70%. The rate of response to therapy was impressive, and improved over time, suggesting that effective responses were durable. Amongst patients taking three or more antiretrovirals for at least 30 weeks, the proportion with viral load below 400 copies rose from 78.9% at the beginning of the study period, to 88.1% at the end. The median CD4 count rose, and the proportion of patients with a CD4 count which presented a real risk of opportunistic infections fell – from 21.6% to 12.2% for CD4 below 200 cells, and from 3.6% to 2.1% for CD4 below 50. Importantly, the rate of new AIDS events, and of deaths both remained low throughout the period, and there were no significant trends, meaning there is no evidence – in this clinic cohort at least – that these rates have risen, or fallen, in recent years.

Clearly these data reflect HAART in its most positive light because they don't capture information about toxicity, tolerability and quality of life. Nevertheless these are important and encouraging findings.

Discussing the analysis for aidsmap.com, Dr Caroline Sabin, a statistician with the Royal Free, said: "If a patient's viral load is controlled then as long as he or she maintains adherence, then there's very low rate of rebound with the treatments which are currently available. There will be problems with toxicity, but if you can get through these, then really the drugs are very good. One thought was that it would take a long time for the [virological] failure to be seen. Well, actually the failure rate wasn't particularly high and didn't seem to get higher with increased time on therapy."

How far are these data from London supported by observational cohorts elsewhere? The ATHENA study follows HAART-treated patients in the Netherlands. In Seattle, an analysis of trends in illness and survival amongst 3,580 people who began HAART prior to June 2000 was presented³. Between 1996, when HAART was introduced, and 2000, there was a continuous decline in the death rate (4.8 deaths per 100 person/years in 1996; 2.0 in 2000). The proportion of deaths which were not directly related to HIV rose, and according to the study authors, approximately one third of this increase was due to side-effects of HAART.

Mortalite 2000 is a survey of deaths in people with HIV in France in 2000, the findings of which were also presented in Seattle⁴. Of 65,000 people being followed by the French National AIDS Research Agency (ANRS), 978 were reported to have died in 2000, giving a crude mortality rate of 1-2%. The analysis presented in Seattle concerned the cause of death in the first 422 cases. Whilst half of these deaths were AIDS-related, a third occurred in people with CD4 counts over 200 cells and viral load suppressed below 500 copies. Ten percent of deaths were caused by hepatitis C, 8.5% by cancer and 6.9% by cardiovascular disease.

editor's note

This article focuses on body fat changes rather than metabolic changes. The latter have been covered in recent issues of *ATU*, however. See numbers 111, 108 and 104 plus more detailed coverage on aidsmap.com.

Ninth Retroviruses Meeting

Much of the new data we report in this issue were presented at the recent Ninth Annual Retroviruses Conference, a key forum for discussion of research relating to HIV medicine which was held in February in Seattle, USA.

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- Unless stated otherwise, all data referenced here was presented at the Ninth Retroviruses Conference, Seattle, 2002. All conference abstracts are online at <http://www.retroconference.org>.
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managing body fat changes continued

Management strategies

Since the emergence of the lipodystrophy syndrome in 1997, HIV researchers have pursued a range of options in an effort to manage this side-effect of anti-HIV therapy. The different approaches being taken can be summarised as follows:

Switches in antiretroviral therapy. This approach, the subject of Keith Alcorn's report in this issue, is based on both observed statistical associations and hypotheses about the causative role of specific anti-HIV drugs in the development of lipodystrophy. By stopping or avoiding these drugs, it is theorised that body fat changes will resolve or improve.

Non-antiretroviral drug options. So far there is little evidence that switching anti-HIV therapy produces significant and lasting improvements in body fat changes, though this approach may improve some of the metabolic problems. In this context, changing drugs which are otherwise controlling HIV infection effectively may not be attractive to some. In addition, individuals' treatment history can mean that switching regimens is simply not an option. Other pharmaceutical means of managing body fat changes are therefore under investigation, and several of these are reviewed here.

Cosmetic options. This category includes a variety of surgical, and other less invasive methods of cosmetically altering the body, such as fat transfer and the use of injectable substances. There is evidence that some of these procedures can restore a more normal facial appearance in people who have lost fat around their cheeks. However, the long-term safety of these approaches is not established, and they may not be readily available through the NHS. These processes were reviewed in *ATU* issue 108.

Continued monitoring. Individuals' response to changes in their body shape and appearance varies. Some people choose to make no immediate changes to their medications, and instead take a 'watch and wait' approach, with support from their doctor and health care team.

Dietary changes and exercise. These may be adopted alone or alongside other options.

News on non-antiretroviral drug options

This article reviews recently reported data on experimental treatment approaches in recognition that a significant number of our readers are concerned about lipodystrophy. However, this information needs to be prefaced by a reminder that these data are preliminary. At present, the available studies tend to include small numbers of patients, who have been treated and followed for short time periods. This is normal wherever medicines are first used experimentally, before their safety and usefulness have been proven. But it can be difficult to draw meaningful conclusions from early-stage research, particularly about its applicability to routine patient care. This caveat is particularly relevant to lipodystrophy because it may take long periods of time before improvements become visible.

Rosiglitazone

In Seattle, researchers from Helsinki presented data from the first controlled study to evaluate the use of rosiglitazone as a treatment for body fat changes⁵. Rosiglitazone is used in the treatment of diabetes. It's one of a relatively new class of drugs, termed PPAR-gamma agonists. A similar drug, troglitazone, has been shown to improve lipodystrophic signs in HIV-negative patients⁶. A small study at last year's Lipodystrophy Workshop reported apparently beneficial results following the drug's administration to HIV-positive people with facial fat loss⁷. Other trials involving rosiglitazone are ongoing, including the HALT trial in London, details of which can be found on aidsmap.com.

This blinded Finnish study involved twenty-five men and five women on stable HAART, with self-reported, investigator-confirmed lipodystrophy. Participants were randomised to

receive either 8mg rosiglitazone or matching placebo for the 24 week study period.

Lipodystrophic factors were measured at entry and at 24 weeks by a range of methods, (including a series of sixteen MRI scans around the body, spectroscopy of liver fat, skinfold thickness, serum leptin (a correlate of body fat mass), bioimpedance analysis, and self-assessment; DEXA scanning, the method most often used to assess peripheral fat, was not used).

At the end of the 24 week treatment period, there was no evidence that rosiglitazone improved body fat changes. The drug appeared to improve insulin resistance. However, unexpectedly, the drug was also associated with a significant increase in both cholesterol and triglyceride levels, causing one individual to discontinue treatment early. No other adverse events were reported.

In seeking to explain the study's negative findings, presenting author Dr Sutinen offered several possible explanations – inadequate dosing, inadequate treatment duration, or perhaps the small sample size. Professor David Cooper, a leading Australian physician, questioned the power of such a small study to detect a difference between treatment arms. According to Sutinen, the power was based on the 34% increase in subcutaneous fat observed when troglitazone was administered to HIV-negative patients.

Niacin

The vitamin niacin (B3, or nicotinic acid) may have a beneficial effect on central or abdominal fat accumulation, according to information from a small, sixteen person

observational cohort reported in Seattle⁸. Note this was not a randomised, controlled trial.

Participants in the cohort at Kaiser Permanente in San Francisco received an average of 3000mg of niacin a day. After an average duration of one year, 81% of patients had experienced reductions in intra-abdominal fat as measured by a single slice abdominal CT scan. The average reduction in those who experienced improvement was 27%.

However, not all patients were able to tolerate niacin, due to side-effects at high doses which include flushing, tingling and burning sensations, especially in the upper body, as well as nausea, diarrhoea and headaches. Doses of 2000mg or higher should not be attempted without medical advice, and people with irregular heart beats should consult their doctor before taking large doses of niacin, due to the potential for altered heart rate.

Metformin and gemfibrozil

In a Spanish study, 66 people on protease inhibitor-based HAART, with abdominal fat accumulation and raised triglycerides, were randomised to receive treatment with placebo, or with one of two drugs used to treat diabetes: metformin or gemfibrozil⁹. Participants were followed for a year, their body fat and composition being assessed every three months (by bioimpedance analysis and sonography), along with various metabolic measurements. There was no evidence of a significant difference between arms at any point during follow-up, suggesting that neither treatment had a beneficial effect on body fat changes. The study was designed to detect a 25% improvement in lipodystrophy in the best arm, assuming there was no improvement due to the placebo.

key conclusions

- HIV researchers have begun developing a case definition for lipodystrophy. At present, the definition may misdiagnose less severe cases, and may be harder to apply to women.
- Studies continue to show the effectiveness of anti-HIV therapy in controlling HIV and reducing the occurrence of AIDS. This positive news is balanced by the risks of treatment, one of which is lipodystrophy.
- Treatments for body fat changes continue to be investigated but the evidence in favour of any specific drug is weak at present. This suggests that lipodystrophy should be managed on an individual basis.

glossary

- adherence** The act of taking a treatment exactly as prescribed.
- antiretroviral A** substance which acts against retroviruses such as HIV.
- cardiovascular** Pertaining to the heart and blood vessels.
- CD4** A molecule on the surface of some cells onto which HIV can bind. The CD4 cell count roughly reflects the state of the immune system.
- cholesterol** A waxy substance, mostly made by the body and used to produce steroid hormones.
- clinical event** The occurrence of a physical sign or symptom, rather than an abnormality that can only be detected by laboratory tests.
- clinical trial** A research study with people, usually to find out how well a new drug or treatment works and how safe it is.
- CT scan** Computerised tomography scan. A type of specialised X-ray that gives a view of a 'slice' through the body.
- DEXA** Dual-energy X-ray absorptiometry. A type of scan that gives a view of a 'slice' through the body.
- diabetes** A condition characterised by raised concentration of sugar in the blood, due to problems with the production or action of insulin.
- DNA** Deoxyribonucleic acid, the material in the nucleus of a cell where genetic information is stored.
- continued page 7**

switching drugs to avoid fat loss

6 as more data from antiretroviral switch studies are reported, are we any clearer about the possible role of specific drugs in body fat changes? by keith alcorn

A number of recent studies have raised questions about whether body fat can be recovered by replacing d4T (stavudine, *Zerit*TM) with another drug in your anti-HIV regimen. d4T is sometimes blamed for the problem of fat loss, although the evidence for its role is far from conclusive.

Three studies presented at the Ninth Retroviruses Conference in Seattle last month all suggested that when patients switched from d4T to either AZT or abacavir, fat loss was arrested or actually improved. However, the changes were small and were not noticed by patients or their doctors after six months. The results raise many questions about the strategy of trying to limit fat loss by altering your combination. Will they have any effect on clinical practice?

"I think clinical practice has already altered because of people's perceptions about d4T",

said Dr Mike Youle of the Royal Free Hospital in London.

Dr Graeme Moyle of Chelsea and Westminster Hospital in London believes that the only sound evidence on the subject of which drugs cause fat loss shows that there is no difference between AZT and d4T. He points to a German study in which people took either AZT or d4T as part of their first triple drug combination. After two years, people who received d4T were no more likely to have lost fat than people who took AZT.

d4T is implicated in some studies, he says, because it may be a marker for other things which have also been independently linked to fat loss in studies, such as:

- duration of treatment (many people took d4T after AZT, when it became available in 1996, so would have been exposed to

nucleoside analogues (NRTIs) for longer than people new to treatment who were taking AZT/3TC in the 1997/2000 period which is generally studied)

- CD4 count below 100 at the time treatment began or prior to treatment (people with low CD4 counts are likely to have included many of the same patients who took d4T after AZT)
- CD4 count increase of less than 100 after nearly two years of observation on treatment, regardless of drugs taken or total duration of treatment (as above)
- low to average body mass (another marker of advanced HIV disease)
- White race (which may indicate better access to HIV treatment, a finding reported by some US researchers, but probably relates to higher frequencies of certain genes in this population which may promote lipodystrophy; see below).

These findings tend to suggest that it is the degree of immune suppression you suffer, and the extent you recover from it, which determine your risk of fat loss, not the drugs you take. However, they also contradict the most convincing alternative to the drug-driven theory of fat wasting: namely, that it's a paradoxical long-term consequence of a successful response to HAART.

This theory suggests that protease inhibitor (PI) treatment suppresses a process called apoptosis (cell suicide) among T-cells, preserving a group of T-cells that produce large amounts of a chemical called TNF-alpha. This chemical induces apoptosis in fat cells (leading to their loss), inhibits the uptake of free fatty acids (starving remaining fat cells), and encourages lipid production (leaving large amounts washing around the body looking for a new home, which in turn leads to high lipid levels in the blood).

People with lipodystrophy have been shown to have higher levels of T-cells primed to produce TNF-alpha. A study at Liverpool University has

shown that people with lipodystrophy are more likely to have a mutation in the gene which governs TNF-alpha production and are likely to have a larger number of receptors which can soak up TNF-alpha¹, suggesting that there is an interaction between genetics and response to HIV treatment.

Mitochondrial toxicity

So, why would changing from d4T to abacavir have any effect?

Some researchers think that d4T (and to a lesser extent AZT) damage structures in cells called mitochondria and that this drives fat loss in some way. A fat loss distribution abnormality syndrome in HIV-negative people caused by mitochondrial mutation has been reported, (though most inherited or acquired lipodystrophies are not related to mitochondrial disorders). Experience in the field of inherited mitochondrial disorders has shown that the brain is commonly affected but the only nervous system disorder seen with NRTI-associated mitochondrial toxicity is peripheral neuropathy. Indeed, nucleoside analogues have a protective effect against the development of HIV-associated dementia.

However, supporters of the drug-damage theory of fat loss point to lower levels of mitochondrial DNA in the subcutaneous fat of people with lipoatrophy as evidence to support this view²⁻⁴. In one study², people with lipoatrophy had 39% lower levels of mitochondrial DNA than HIV-positive people without fat loss, even though both groups had been taking nucleoside analogues for the same length of time. The only significant difference between the groups lay in exposure to d4T; the lipoatrophy group were more likely to have taken d4T, and to have taken it for longer than the group without fat loss. The length of time on a protease inhibitor was also greater in the lipoatrophy group, but there was no difference in mitochondrial DNA levels between people who had taken PIs and people who hadn't.

In another study⁴, mitochondrial DNA in adipose tissue of people taking d4T was just 12% of the level seen in people with HIV not on treatment (compared with 51% in a

glossary

HAART Highly Active Antiretroviral Therapy, term used to describe anti-HIV combination therapy with three or more drugs.

HDL High density lipoprotein, a form of cholesterol which protects against heart disease.

hypersensitivity An allergic reaction.

insulin A hormone produced by the pancreas that tends to lower blood sugar levels.

lipid A general term for fats in the blood.

lipoatrophy Loss of body fat.

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

metabolism The mechanisms which sustain life, turning sugar and fat into energy.

mitochondria Cellular compartment involved in energy production.

neuropathy Damage to the nerves.

NNRTI Non nucleoside reverse transcriptase inhibitors, a family of antiretrovirals that includes efavirenz and nevirapine.

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

opportunistic infections Specific infections which cause disease in someone with a damaged immune system.

protease inhibitors Family of antiretrovirals which includes lopinavir, indinavir, nelfinavir, ritonavir, saquinavir.

continued page 9

switching drugs to avoid fat loss continued

matched AZT-treated group). When the group looked at how long people had been on d4T, it was apparent that an eightfold reduction in mitochondrial DNA occurred within months of starting d4T. Mitochondrial DNA content recovered swiftly when people switched from d4T to AZT. Professor Simon Mallal, who conducted the study in Perth, Australia, says larger, randomised studies are needed to explore his theory that fat wasting is caused by mitochondrial DNA depletion due to d4T.

Another possibility, not excluded by the findings above, is that an interaction between protease inhibitors and nucleoside analogues is responsible for fat loss – and abdominal fat gain. Five year follow-up from a study of ritonavir/saquinavir in which some people added a nucleoside analogue (usually d4T) shows that people who took PIs and an NRTI together were eight times more likely to have experienced facial fat loss after five years of treatment than people who took PIs alone. Although the numbers are relatively small in this study (66 patients, 32 taking NRTIs), they echo the findings of a larger Dutch study in which patients added d4T to ritonavir/saquinavir, which also found that the combination of an NRTI and protease inhibitors upped the risk of all body fat changes compared to PI treatment alone.

Nucleoside analogues may contribute to fat loss because subcutaneous fat contains more mitochondria that can be damaged, whilst protease inhibitors may be responsible for fat gain because they induce insulin resistance, a phenomenon associated with visceral fat accumulation. When HDL cholesterol levels are low, less HDL cholesterol is transported to the liver and more is stored in central fat stores. These fat cells are less likely to be damaged by mitochondrial toxicity because they have fewer mitochondria⁵. A recent observational pilot

study presented at the Ninth Retroviruses Conference suggested that niacin therapy, which raises HDL levels, was associated with reductions in central fat mass, indicating that at least part of this theory is plausible, (see *Managing body fat changes* in this issue).

The switch studies

Three antiretroviral switch studies were reported at the Ninth Retroviruses Conference, each testing a slightly different strategy.

In the MITOX study, 111 patients were randomised to switch from d4T or AZT to abacavir or stay on these drugs, and no one changed any of their other drugs⁶. After 24 weeks, DEXA scanning demonstrated that people who switched had gained fat relative to the d4T group, but patients themselves did not report noticeable improvements.

“The change in fat is so small it’s not surprising it’s not detectable by patients or doctors in this study,” said Dr Graeme Moyle. “These patients went on average from having 50% of normal limb fat mass to 55% or normal, or 390g of fat distributed over both arms and both legs. People with lipodystrophy don’t especially care what the scanner says; they want to know if friends and colleagues are less likely to notice facial changes. In this regard, there were no benefits but there were risks. There was a 10% rate of [abacavir] hypersensitivity in this study – this may vary across populations – and a 20% rate of grade 4 (severe) adverse events among people who switched; versus 6% in those who stayed with their existing therapy. And, they only reported grade 4 adverse events in this study.”

“There are advantages of switching from a protease inhibitor to abacavir or an NNRTI in terms of reduced pill burden, better adherence and metabolic improvements, but what are the

advantages of switching from d4T to abacavir – there's no reduction in number of doses or tablets. At least if you switch to AZT whilst on 3TC you can take *Combivir*TM."

"We need to investigate other alternatives, such as switching to tenofovir, or switching to ddI, and comparing these with abacavir, and it may be better if people wait to join a trial of this sort rather than just switching."

In a second Australian study, 40 patients taking d4T/3TC plus nelfinavir or indinavir or AZT/3TC/indinavir were randomised to switch d4T *and* their protease inhibitor for AZT and abacavir, or to stay on existing therapy, so that everyone who switched ended up taking AZT/3TC/abacavir⁷. After 48 weeks, those in the switch group experienced a 0.018kg/month increase in arm fat (compared to a 0.005kg/month increase in the control group), and a 0.013kg/month increase in leg fat (compared to a 0.011kg/month decrease in the control group). This difference translates into a weight difference very similar to that seen in the MITOX study – approximately 300 grams – suggesting no additional improvement a further six months after switching.

The improvement was most pronounced in those who switched from both d4T and their protease inhibitor. Three abacavir hypersensitivity reactions were reported in this study.

In an American study with no control group, 118 people replaced d4T with either abacavir (86 people) or AZT (32 people)⁸. After 24 weeks, those who switched showed much greater improvements than those seen in the two studies described previously – from 6% in the legs to 26% in the arms. Why this difference should exist is unclear. Five out of 86 patients who received abacavir experienced hypersensitivity reactions.

Possible consequences of avoiding d4T

"Increasingly I think some people will avoid using d4T with protease inhibitors because of the evidence [that the risk of lipoatrophy is higher when it is combined with a PI]. I don't necessarily think this is the *right* thing to do – I

actually think attempting to find ways of preventing the loss is better" Dr Mike Youle told *ATU*.

Dr Graeme Moyle points out that avoiding d4T may have its own drawbacks. "If you defer, or switch to a d4T or AZT-sparing regimen and it fails, you will have to switch back to a d4T or AZT-based regimen, and since you are likely to have been taking an NNRTI as well, you will also have to switch to a protease inhibitor, and studies show that combining a protease inhibitor with a thymidine nucleoside analogue carries the highest risk of lipoatrophy – and other changes. The risk is also higher in patients who had a low CD4 nadir. The thymidine-sparing, PI-sparing approach up front may place the riskiest combination together in the most at-risk patients."

In other words, avoiding d4T today, and taking a combination like abacavir/3TC/NNRTI – theoretically less hard on the fat – could result in having to take d4T plus a protease inhibitor in the future if that combination fails.

Key conclusions

In people already on treatment who have not yet experienced fat loss, these studies don't currently provide any convincing evidence for people to switch from d4T.

"We would not recommend that anyone start treatment with d4T/ddI now, but if you're doing well on d4T/ddI and don't have high lactate levels or peripheral neuropathy, it's not clear if there would be any advantage to changing. If you do have these problems, clearly it appears to be the riskiest combination" said Dr Moyle.

In people experiencing fat loss, the findings provide limited support to the idea that switching from d4T to abacavir may reduce fat loss, but at the risk of hypersensitivity reaction – potentially a more serious medical problem if not spotted promptly. Because abacavir hypersensitivity resembles the symptoms of colds or flu, it may be ignored until the problem becomes more serious, at which point prompt medical attention is required.

glossary

randomisation The process of selecting by chance the treatment that a clinical trial participant will receive.

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

T-cell A type of immune system cell which is damaged in the course of HIV infection. CD4 and CD8 cells are both sub-types of T-cell.

thymidine analogue

Term which describes both AZT and d4T.

triglycerides The basic 'building blocks' from which fats are formed.

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

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Cannabis expected to be reclassified under UK law

An expert review of the social and health consequences of cannabis use has recommended the drug be down-graded under UK law. The report, from the Advisory Council on the Misuse of Drugs (ACMD), a quango, was delivered to the UK Home Secretary David Blunkett in mid-March.

The ACMD advise that cannabis, currently a Class B drug under the 1971 Misuse of Drugs Act, be dropped to Class C. Under the Act, illicit drugs are categorised according to the harm they may cause; Class A is reserved for heroin and other opiates, and Class C for benzodiazepines (drugs like *Valium* and temazepam), and anabolic steroids. A key effect of the change in cannabis classification would be that police officers would no longer be able to arrest individuals caught with small amounts of the drug, though supplying the drug (dealing) would remain a criminal offence which could incur a jail sentence.

The ACMD report, (which can be read on the internet at <http://www.drugs.gov.uk/reportsandresearch/communities/cannabis/cannabis.pdf>), finds that cannabis use "is not associated with major health problems for the individual or society". For most people, occasional use is not associated with significant health problems, though these

appear to occur more frequently in people with heart or circulatory problems, and in people with mental health problems such as schizophrenia.

Many cannabis users smoke the drug with tobacco in cigarette-style joints, presenting similar risks to health as smoking cigarettes. The ACMD report states that cannabis "is not a harmless substance and its use unquestionably poses risks both to individual health and to society". Whether these risks should invoke a similar judicial and social response as other Class B drugs – amongst them amphetamines and barbiturates – is the key issue behind this likely change in policy.

US consumer warning issued on kava kava

As NAM launched our new *Directory of Complementary Therapies in HIV & AIDS*, news reached us that the US drug watchdog, the Federal Drug Administration (FDA) has issued a warning to consumers over potential liver damage caused by the herbal supplement kava kava. Kava (*Piper methysticum*), which is used to relieve anxiety, has been linked to serious liver conditions including hepatitis, cirrhosis and liver failure.

Though this risk appears small, the FDA is warning people with liver disease, liver problems, or who are taking medications that can affect the liver, to consult their doctor before taking kava. This is good advice for

anyone taking both prescribed and over-the-counter medicines.

The FDA consumer advisory can be read online at <http://www.cfsan.fda.gov/%7Edms/addskava.html>. Here in the UK, sales of kava-containing products were voluntarily suspended by manufacturers in December, a move supported by the UK Medicines Control Agency.

Seattle Retroviruses Conference briefs

This month's lead articles feature new information from the recent Ninth Annual Retroviruses Conference held in Seattle in late February. We plan further coverage of this key HIV scientific meeting in forthcoming issues of *ATU*. News stories from Seattle, plus a roundtable discussion of the conference highlights involving leading UK HIV experts, are available at aidsmap.com. The official conference website is at <http://www.retroconference.org> and features live broadcasts plus a searchable online abstract book. Further coverage is now on the web at medscape.com, thebody.com and hivandhepatitis.com.

New drugs

Early data on a new NNRTI, TMC125, indicated that the drug produced significant reductions in viral load when given to people with resistance to efavirenz, another drug from this class – at least over an initial one week observation period. Though these preliminary findings provide no information about the drug's safety, observers noted that TMC125 may be a hope for the future for people with NNRTI resistance, "A patient population where we need more options," according to Dr Ian Williams of London's Mortimer Market Centre. (9th Retroviruses Conference, abs 4, 2002)

HIV drugs and heart disease risk

As we've previously reported (see *ATU* issues 111, 108 and 104), raised levels of fats in the blood which can occur as a side-effect of HIV treatment, have caused concern over whether these increases may cause an upswing in heart

and circulatory problems in people with HIV in future. New data from large HIV cohort studies presented contradictory messages in Seattle.

Data on over 36,000 people with HIV in the Veterans Administration cohort noted a slight decline in cardiovascular illness and deaths in the years following the introduction of protease inhibitor-based HAART. Another large US database, the Kaiser Permanente, found higher rates of heart attack in HIV-positive people compared to HIV-negative control patients. (9th Retroviruses Conference, abs LB9 and 696, 2002)

How experienced is your doctor?

People with HIV whose doctor sees few other HIV-positive patients may survive for a shorter period than people with more experienced doctors, despite the availability of HAART. This was the finding of an analysis of participants in the British Columbia HIV cohort. A link between physician experience and survival in people with HIV was reported by Kitahata and colleagues in the pre-HAART era, but whether this observation held true in the context of more effective therapies has been unclear.

Researchers analysed 1,416 people who began three-drug antiretroviral therapy in the period between August 1996 and July 1999. In a multivariate analysis, after adjusting for the effect of AIDS diagnosis at baseline, age, baseline viral load and CD4 count, people with an experienced physician (defined as having enrolled more than five people into an HIV treatment programme), were almost seven times less likely to die than those with an inexperienced physician, within the 12 month follow-up period. (9th Retroviruses Conference, abs 749-W, 2002)

aids reference manual

NAM's comprehensive guide to the psychosocial aspects of the AIDS epidemic, the *AIDS Reference Manual*, is now available to individuals who are personally affected by HIV at the special price of £12.95. This 400 page volume, edited by *ATU* contributor, Robert Fieldhouse, can be purchased by telephoning NAM on 020 7627 3200.

nam booklets

2002 revisions to our popular *Information series for HIV-positive people* are now tumbling off the presses.

Following the new title *Lipodystrophy*, which many of you will have received with *ATU* last month, look out for *Anti-HIV drugs*, *Glossary*, *Clinical trials* and *Nutrition* coming soon. These plain-language guides are free to people personally affected by HIV. We plan to launch three further new titles during 2002, covering HIV / hepatitis C co-infection, adherence, and a summary of the UK's HIV treatment guidelines. If you have suggestions about how we can improve this series, please contact Series Editor, Michael Carter at NAM.

nam forum

April's Information Forum takes place on Monday 29th April from 7-9pm. The venue is University of London Union, Malet Street, London WC1. The event is free and a sign language interpreter is available.



credits

editor

Anna Poppa

AIDS Treatment Update
founded by Peter Scott

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design

Alexander Boxill

printing

Cambrian Printers

ISSN

0969-4706

charity number

1011220

medical advisory panel

Dr Fiona Boag

Dr Ray Brettle

Professor Janet Darbyshire

Dr Martin Fisher

Professor Brian Gazzard

Dr Diana Gibb

Professor Frances Gotch

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thanks to our funders

NAM's treatments information for people living with HIV is provided free thanks to the generosity of:

Department of Health, London HIV Commissioners Consortium, International HIV/AIDS Alliance, Crusaïd, British HIV Association, Elton John AIDS Foundation, GlaxoSmithKline, Bristol-Myers Squibb, Roche Products, Bristol-Myers Squibb Pharma, Abbott Laboratories, Positive Action, Boehringer Ingelheim, Merck Sharp & Dohme, Gilead, Roche Products Hep C Division, Roche Molecular Systems, Serono, Visible Genetics, Virco, and these health authorities: Barking & Havering, Birmingham, East Surrey, East Sussex, Brighton & Hove, Manchester, Newcastle and North Tyneside, Norfolk, North Nottinghamshire, Salford & Trafford, Stockport, West Pennines, West Surrey, West Sussex, Wigan and Bolton, and Manchester City Council



any questions

For an introduction to HIV treatment issues

The booklets in NAM's Information Series for Positive People are free to people with HIV. This easy-to-read series includes: Anti-HIV Drugs, Clinical Trials, Glossary, Lipodystrophy, Nutrition, Resistance, and Viral Load & CD4.

The HIV & AIDS Treatments Directory

This 600 page book, published twice a year, is a comprehensive guide to the medical aspects of HIV. Available at only £12.95 to people with HIV, £64.95 to professionals.

<http://www.aidsmap.com>

NAM's resources are also available online at [aidsmap.com](http://www.aidsmap.com). These include our extensive and searchable treatments database, the latest news on treatment developments, our online directory of AIDS service organisations, hundreds of links to recommended HIV-related sites, and free downloadable resources.

Monthly NAM information forums in London

Each month an expert speaker discusses a treatment-related topic. Entry is free. Future forums are advertised inside this newsletter.

THT Living Well Phonenumber 0845 9470047 Mon-Thu 6-9pm
i-Base Treatment Phonenumber 0808 8006013 Mon-Wed 12-4pm

NAM recommends that you discuss all your treatment decisions with your doctor.



subscriptions

AIDS Treatment Update is available free to individuals in the UK affected by HIV or AIDS.

Professional/organisational rate: £75/year.

Voluntary organisation rate: £55/year.

Overseas rate: within EU add £10/year; outside EU add £15/year.

AIDS Treatment Update is available on audio tape, and can be emailed to you as a pdf file for viewing with Acrobat Reader. Telephone NAM on 020 7627 3200 for details.

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