

aids treatment update

lipodystrophy: inside and out

Heart disease and cosmetic surgery are two subjects I didn't expect to be quite so familiar with at this stage of my life, and I'm sure the same is true of many people with HIV and others who work in this area. But the emergence of lipodystrophy, a side-effect of anti-HIV drug therapy, has introduced us to several whole new areas of medicine. As HIV treatments have altered expectations of life with HIV, more generic (at least to Westerners) health issues have reared their heads.

In this month's lead article, Keith Alcorn discusses the management of raised cholesterol in people on HAART, and the concern that this may forecast a growth in cardiovascular problems – such as heart attacks – in HIV-positive people on treatment in future. Further in, Robert Fieldhouse tackles facial wasting and the battery of stop-gap measures being turned to in the absence of a better understanding of how to prevent the problem in the first place.

It may be a sign of a maturing epidemic that HIV is being seen less narrowly in so many contexts today. The change to the World Health Organisation's agreement over observation of drug patents which occurred mid-November, was understood by many to be coupled to the US government's declared intent to ignore patent law in order to employ medicine to protect Americans against bioterrorism. You can read more about unfolding developments relating to treatment access and HIV on our website aidsmap.com.

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managing raised lipids

key conference on lipodystrophy presents differing views on the long-term significance of raised cholesterol and heart disease risk in people taking anti-HIV drugs by keith alcorn

There continues to be considerable controversy over the significance of raised levels of cholesterol in people on HAART, with some researchers arguing that we should expect to see growing numbers of heart attacks and other cardiovascular problems in patients taking protease inhibitors (PIs), while others think it will take years before we know for sure if relatively short-term increases in lipids will translate into an epidemic of heart disease among people with HIV.

Some drug companies are aggressively highlighting the issue of cholesterol increases on HAART in order to persuade doctors to switch patients to drugs that have shown a tendency not to increase cholesterol levels, such as abacavir and nevirapine. But should people with HIV be worried about heart disease, and do new British guidelines on the use of HIV treatments take into account that not everyone will have the same degree of risk from lipid increases?

What is atherosclerosis?

Atherosclerosis – or ‘furring’ of the arteries – is a serious form of cardiovascular disease which occurs as a consequence of cholesterol particles called LDL (see sidebar page 3) being deposited on the walls of arteries (the intima media). Here they are absorbed into the artery walls in an accumulation of fat and cells called a plaque. Eventually the plaque may become unstable, and may rupture, leading to what is called thrombosis – blockage of an artery by a blood clot.

This process is accelerated by smoking, by diabetes, and by having low levels of another

type of cholesterol called HDL (see sidebar page 3). High blood pressure also affects the rate at which plaques develop.

High LDL cholesterol levels are a surrogate marker for subclinical atherosclerosis (artery damage that hasn’t begun to cause physical symptoms such as chest pain). Direct damage can be measured by ultrasound imaging of the intima media of the carotid artery in the neck. Thickening of the intima media is associated with a higher risk of cardiovascular events such as heart attack.

Atherosclerosis in people with HIV

An analysis by Vincent Mooser and colleagues at the University of Lausanne recently published in *AIDS* showed that HIV-positive individuals, (when compared to an HIV-negative control group), were significantly more likely to have plaques and carotid artery intima media thickening, but this was not directly associated with protease inhibitor therapy¹. Instead, the classic cardiovascular risk factors – high LDL cholesterol (above 4.0mmol/L), smoking and age – were associated with an increased risk of plaques, as was HIV infection.

People with HIV may be more predisposed to thickening of the intima media because of lifestyle factors such as smoking which have nothing to do with being on HIV treatment, although the inflammatory effect of HIV infection itself is unclear.

However, Mooser argues that just because HIV treatment doesn’t show up in analyses like the one described above, this doesn’t mean that we

Flow diagram of the process of atherogenesis

Cholesterol and triglycerides leave the liver in VLDLs and circulate in the blood.

VLDLs drop off triglycerides, which are used by tissues as energy. Empty VLDLs become LDLs.

Some LDLs are whisked back to the liver by Apo E.

Some may be picked up by HDLs and carried back to the liver.

Some LDLs are grabbed by protein receptors and pulled into cells where they can do productive work.

The more saturated fat and cholesterol you eat, the more VLDLs are made by the liver. Triglyceride and VLDL production also increases in people on HAART.

LDLs that can't be used by the body or disposed of stick to blood vessel walls to form plaques.

Plaque build-up narrows the blood vessel and can lead to heart attack.

can ignore the effects of cholesterol increases, even in individuals with no other risk factors.

Speaking at the recent Third Lipodystrophy Workshop in Athens, Mooser discussed an analysis of 120 cases of premature coronary artery disease (CAD) in Switzerland. Thirty-five per cent of individuals who developed CAD before the age of 50 had only one risk factor, whilst a further 35% had just two risk factors. The most common risk factors were: smoking, which was practiced by 85% of the premature CAD cases compared to 30% of an age matched reference group from the general Swiss population; and hyperlipidemia (40% in the CAD group versus 35% in the general Swiss population).

In a major analysis of studies carried out in the United States involving a general population group of 366,559 individuals, smoking, high blood pressure and cholesterol levels above 5.17mmol/L together increased an individual's risk of coronary heart disease or death due to cardiovascular disease seven-fold².

Should raised cholesterol be treated?

However, clinicians disagree about the implications of relatively short-term lipid elevations in people on HAART.

Dr Stefan Mauss, one of Germany's leading HIV clinicians, recently looked at the make up of the cholesterol in the bloodstreams of 172 of his patients, and found that it may not be as atherogenic as first thought³.

A total cholesterol test measures the sum of the HDL portion, the LDL portion and the VLDL portion, while an LDL cholesterol test looks only at the total amount of LDL and VLDL cholesterol. VLDL cholesterol normally represents around 10-15% of circulating cholesterol in a healthy adult. Dr Mauss found that the ratio of VLDL cholesterol to total cholesterol was much higher in his HIV patients than in people with elevated cholesterol in the general population. When VLDL cholesterol is elevated in this way, the risk of heart disease is less, because many of the VLDL particles are simply too big to pass through the wall of the artery to deposit their

what the LDL?

The total amount of cholesterol in the blood is divided into three portions:

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

LDL cholesterol Low density lipoprotein, which increases the risk of heart disease.

VLDL cholesterol Very low density lipoprotein. Raised levels of VLDL reduce the risk of heart disease.

glossary

antiretroviral A substance which acts against retroviruses such as HIV.

artery Blood vessel which carries blood to the heart.

cardiovascular Relating to the heart and blood vessels.

cholesterol A waxy substance, mostly made by the body and used to produce steroid hormones.

diabetes A condition characterised by raised concentration of sugar in the blood, due to problems with the production or action of insulin.

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managing raised lipids continued

cholesterol. Less than one third of patients with a high total cholesterol had elevated LDL cholesterol in the Mauss study.

The VLDL portion of total cholesterol is approximately equal to the total triglyceride level divided by five, provided that the triglyceride level is below 10.5mmol/L. High VLDL levels are associated with elevated triglyceride levels (because VLDL particles carry triglycerides to the tissues). Elevated triglyceride levels occur because of increased production and turnover of fatty acids in the liver on protease inhibitor therapy. VLDL particles will tend to carry more cholesterol if the dietary intake of cholesterol is high.

"I used to treat very aggressively but now I would treat [cholesterol elevations] only in patients with multiple risk factors and elevated LDL cholesterol", Dr Mauss told *AIDS Treatment Update*.

Dr Jonathan Cartledge of London's University College Medical School is also skeptical. "I'm not convinced that just because we are seeing intima media thickening in people on HAART, that this translates into a long-term increase in risk [attributable to protease inhibitors]. If people stop or switch therapy, we know that the cholesterol goes down. Also, people may typically only be on protease inhibitors for a few years and other therapies in the future may not have the same effect [on lipids]. I'm not sure that short-term elevations will have the same effect on long-term risk as lifestyle factors which may go on for years and years, such as smoking."

Dr Graeme Moyle of the Chelsea and Westminster Hospital pointed out that it may be far too early to tell whether treatment of

lipid elevations will have an effect on clinical outcomes, and in the meantime, it may be expensive and may carry more risks than benefits. "Are we really treating a blood test result, or are we doing something that's going to be beneficial in our patients, given the numbers needed to treat in order to show benefit?" he asked during a discussion on the effects of statin therapy on cardiovascular risk at the Athens Lipodystrophy Workshop.

A study of the use of a lipid-lowering drug called pravastatin in the general population in Scotland, found that 45 men with high cholesterol must be treated for five years to prevent one non-fatal heart attack or death from cardiovascular causes, and 143 men must be treated to prevent one death from a cardiac cause⁴.

This means that long-term data from studies of switching anti-HIV therapy will be needed in order to show that any trends are sustained. At the Lipodystrophy Workshop, Allain Lafaillade presented 48 week results of the Trizal study, which looked at the effects of switching from stable PI-containing therapy to *Trizivir*, the combination of three nucleoside analogues; AZT, 3TC and abacavir⁵.

This study showed that after 48 weeks, there was no difference in the percentage with viral load below 50 copies, but cholesterol and triglyceride levels fell significantly in the *Trizivir* group (median cholesterol reduction 0.80 mmol/L). However, cholesterol also fell by 0.44mmol/L in those who continued their PI-containing HAART group (individuals with 24 months prior HAART and a median baseline cholesterol of 5.6mmol/L). This reduction was also statistically significant, despite the fact that cholesterol elevations worsened in 29% of the PI recipients.

A study from Houston, Texas, showed that in patients with high lipid levels, lipid-lowering therapy was only partially successful⁶. Sixty-three consecutive patients were analysed. An average cholesterol reduction of 19% was reported on the first lipid-lowering regimen (predominantly fibrates), and LDL cholesterol levels fell by just 5%. Only 16% of patients who continued protease inhibitor therapy

achieved target levels of LDL and total cholesterol after more than one year of lipid-lowering treatment. Presenting the study, Dr Fahmida Visnegarwala said that management of lipid dysregulation alone without correcting the underlying metabolic disturbances may not be effective. Dr Michael Dube of the University of Indiana pointed out that a disappointingly small proportion of non-HIV patients (typically less than 40%) ever reach the lipid goals set out at the beginning of lipid-lowering therapy.

The new British HIV Association treatment guidelines, (available online at the NAM BHIVA website aidsmap.com), recommend action to lower lipid levels in people with cholesterol above 6.5mmol/L or triglycerides above 8mmol/L, but in the absence of evidence about the risk of heart disease in HIV-positive individuals, it is unclear whether this advice should apply to *everyone* with lipid elevations, or just those with other risk factors for heart disease. According to BHIVA, the options include switching off protease inhibitors (if you are taking your first anti-HIV drug combination); reducing fat intake, stopping smoking, taking regular exercise, blood pressure reduction; and/or the use of medications – pravastatin or atorvastatin in the case of raised cholesterol; fenofibrate or gemfibrozil in the case of raised triglycerides.

Yet models developed by Dr Matthias Egger of the University of Bristol show that there are big differences in estimated risk. Using data from a lipodystrophy study described in *AIDS*

Treatment Update issue 95 (November 2000), Dr Egger notes that a 50 year old male smoker with diabetes and severe lipodystrophy has a 14% risk of some sort of coronary event within five years, but the risk is considerably smaller for a younger non-smoker with increased lipid levels but no diabetes.

At a recent Glaxo SmithKline-sponsored symposium on managing lipid elevations in HIV patients, over 70% of participating British doctors said they wouldn't switch patients from their existing therapy if they developed lipid elevations in the absence of other risk factors for heart disease. Of those who would intervene, the overwhelming majority preferred the idea of using lipid-lowering drugs rather than switching therapy. Apart from being an answer that is likely to disappoint Glaxo SmithKline, it is also an answer that may trouble some people with HIV, who may be expected to add another layer of medication in the absence of evidence that it will provide long-term benefit. Patients in the general population with elevated cholesterol and other risk factors would not be encouraged to start treatment to lower their cholesterol until they had attempted to reduce the levels by dietary changes and exercise.

In HIV patients, a study comparing dietary advice to pravastatin treatment has shown that dietary advice alone is ineffective at reducing cholesterol⁷. Pravastatin resulted in a 22% reduction in cholesterol levels after six months of treatment.

key conclusions

- Atherosclerosis, a narrowing of the arteries, is a condition which can lead to a heart attack.
- The risk of heart disease is higher in people who smoke, who are physically inactive, have high cholesterol levels, or have high blood pressure.
- HIV treatment can raise levels of blood cholesterol which cause atherosclerosis. This

may lead to an increased risk of heart problems in people taking HIV treatment, but the level of this risk is not known at present.

- It's unclear if standard treatment for high cholesterol is warranted in people whose cholesterol is raised whilst taking HIV treatment. The use of these treatments is likely to be influenced by the presence or absence of other risk factors of heart disease.

glossary

continued from page 3
HAART Highly Active Antiretroviral Therapy, term used to describe anti-HIV combination therapy with three or more drugs.

lipid A general term for fats.

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

nucleoside analogues Family of antiretrovirals which includes efavirenz and nevirapine.

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

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

references

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- 2 Stamler J et al. *Journal of the American Medical Association* 282 (21): 2012-2018, 1999.
- 3 Mauss S et al. *Antiviral Therapy* 6 (supp 4): 58, 2001.
- 4 Shepherd J et al. *New England Journal of Medicine* 333: 1301-1308, 1996.
- 5 Lafeuillade A et al. *Antiviral Therapy* 6 (supp 4): 20, 2001.
- 6 Visnegarwala F et al. *Antiviral Therapy* 6 (supp 4): 21, 2001.
- 7 Moyle GJ et al. *AIDS* 15: 1503-1508, 2001.

facial wasting

6 new reports on cosmetic procedures to restore facial appearance by robert fieldhouse

Current estimates suggest that between 30-40% of people using HAART will develop some form of facial wasting, a component of the lipodystrophy syndrome and side-effect of treatment with anti-HIV drugs. For some groups the risk may be higher. Early reports suggest that people co-infected with hepatitis C virus may be more likely to experience some form of wasting, or 'lipoatrophy'¹.

How to prevent or reverse facial wasting is not known at present. Instead, there has been a move towards the use of cosmetic procedures intended to restore a more normal facial appearance. In the main, access to these procedures has been restricted to those who can afford their considerable expense. In the UK, it appears that provision via the NHS may be widening, if slowly.

Evidence of the effects and safety of these procedures, for this application, has been

limited to the short-term, another factor affecting access. However, at two recent conferences held in Athens, new data, much of which was observational in nature, were presented on a range of strategies for facial wasting. None of these reports compare different strategies 'head-to-head', though this may in any case be inappropriate here as it's possible that different products may be more or less suited to different individual's circumstances. A further consideration is that the effects gained are likely to be dependent on the skill and experience of the person conducting the procedure. The reports mentioned in this article all involve the work of highly experienced cosmetic surgeons.

Polylactic acid: *New Fill*

New Fill is the trade name for a substance used in cosmetic surgery called polylactic acid. *New Fill* works by stimulating the growth of collagen, a structural component of the skin and other body tissues. As such, its effect is expected to remain after the polylactic acid itself has dispersed – absorption is a common problem with several of these products. *New Fill* is injected under the skin (subcutaneously), and the effect is local to the injection site.

Dr Aubron-Olivier of the Pitie-Salpetriere Hospital, Paris, presented preliminary data from the Vega study on 50 patients with severe facial wasting, enrolled between June 2000 and February 2001². To be included in the trial, patients had to have been on HAART for a minimum of three years, have a viral load of less than 5,000 copies and subcutaneous adipose (fat) facial tissue thickness of less than 2mm as measured by ultrasound.

Treatment with *New Fill* in this trial consisted of injections of one vial of *New Fill* (0.15g) in each cheek at day 0, 15, 30 and 45. Prior to the first injection, the median thickness of facial adipose tissue was 0mm (range 0-2.1mm). An improvement in facial thickness could be detected in most patients as soon as the second injection, and improved further with subsequent injections. At two months the median increase in dermal thickness in all patients was 8.1mm, by six months this had increased to 9.5mm. A further fifth injection

was offered at day 60, if dermal thickness was still less than 8mm. All patients are being followed up by clinical examination, further ultrasound and by photograph at month 3, 6, 12, 18 and 24. All of these procedures are performed by the same person in each case to ensure consistency of approach.

So far, four patients had received three injections, 29 patients the course of four injections, and 17 the additional fifth injection. Nobody had discontinued the course of injections early and no serious side-effects were reported, though some mild swelling at the injection site did occur which generally took between 24-48 hours to resolve. In 10% of patients, non-visible subcutaneous nodules around 3-5mm in size occurred after three to six months but these soon resolved.

Participants completed a validated quality of life questionnaire at the beginning of the study, and part way through. Overall, perceived well-being improved significantly over the course of the study.

PMMA

Polymethyl methacrylate (PMMA) is an adhesive traditionally used in hip replacement surgery which has been used in cosmetic surgery for some years in an attempt to defy the ageing process.

Brazilian cosmetic surgeon Dr Marcio Serra presented a poster discussing 120 HIV-positive patients with facial wasting who were followed for thirty months after their initial treatment³. As with *New Fill*, the treatment is injected into the hollow of the cheeks. Typically, some patients required additional injections after 12 to 18 months, either in different areas or to 'touch up' previous implants following lipodystrophy progression. Again, this is a common feature of several of these products. Results here were based on questioning of patients subsequent to treatment rather than other methods. Patient satisfaction with the results was reported to be high, with all patients reporting an improvement in their self-esteem and quality of life. No infection, inflammation, granulomas or allergic reactions were reported.

Speaking to *ATU*, Dr Serra, who has been carrying out these procedures in HIV-positive people for over three years, said "After the procedure the patient goes home, but will need to do a cold compress on day one every two hours, because of the swelling. It usually goes away after two to three days. After that, the patient comes back in seven to thirty days for a touch up. The cost of the treatment (implant plus touch up) is \$400."

Evolution

Dr Vincenzo Del Pino presented data on the use of injected microspheres of polyvinyl/ polyacramide gel (trade name *Evolution*)⁴. Between October 1999 and December 2000, 35 patients were evaluated. In total, 23 of the patients were male and 12 were female. The median age was 41 years. All patients had been receiving a protease inhibitor-containing regimen for an average time of 2.5 years. On average, facial wasting had developed nine months prior to surgical intervention. Around two thirds of the patients required two sessions. In total, 33 of the 35 patients described the results as very good or excellent after one year of follow-up. The treatment was also well tolerated, with only two patients experiencing mild, transient local swelling.

Fat transfer

Another procedure to tackle facial wasting is to have one's own fat removed from one body area, and injected into the hollows of the face.

Dr Jeffery Brande is a New York-based plastic surgeon who has been performing these 'autologous' fat injections for ageing for many years. Dr Brande's work was reported in abstract form at the ECCATH meeting in Athens⁵, though Dr Brande was unable to attend and present his data more fully due to events in New York. He had planned to discuss outcomes in 300 people.

The re-absorption of injected fat has been proposed as a possible problem with this procedure. Discussing his patients with *ATU*, Dr Brande said "I think that almost everyone that compares their preoperative pictures with themselves, or with postoperative pictures agrees that the fat that remains after the

glossary

See also pages 3 and 5.
glucose A form of sugar found in the bloodstream.
granuloma A type of tumour or growth.
insulin A hormone produced by the pancreas that tends to lower blood sugar levels.
lipodystrophy A disruption to the way the body produces, uses and distributes fat.

further reading

This subject was covered previously in *ATU* 95.

references

Data presented at 3rd Lipodystrophy Workshop (LW), Athens, 23-26 October, 2001, or at the 8th European Conference on Clinical Aspects and Treatment of HIV Infection (ECCATH), Athens, 28-31 October, 2001.
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4 Del Pino V et al. 3rd LW, abstract 50, 2001.
5 Brande J. 3rd LW, abstract P101, 2001.
6 Visnegarwala F et al. 3rd LW, abstract 124, 2001.

facial wasting continued

swelling has resolved does not waste away.” This result may be subject to change over longer time periods, however.

Dr Brande acknowledges that fat transfer may be challenging in severely wasted individuals. “I think the major factor in the success rate in HIV patients is the amount of fat there is to be harvested. I usually can, however, harvest some fat from almost everyone.”

Dr Brande charges between \$1,500 and \$6,000 for treatment, depending on the amount of surgery involved and whether an anaesthesiologist is required. This procedure is also available privately in the UK.

Rosiglitazone

Rosiglitazone is a diabetes drug. In HIV-negative people with a lipodystrophic syndrome it has been shown to reduce glucose levels, improving insulin resistance and promoting weight gain. Improvements in facial fat wasting were observed in four of nine HIV-positive patients after 24 weeks of treatment with rosiglitazone⁶. Though this study is too small to be of great significance, it raises interest given that a study to explore this area further is underway at the Chelsea and Westminster and St George’s Hospitals, London.

Access to *New Fill*

At present, it appears that there are only two HIV treatment centres in the UK that have successfully negotiated for the NHS to meet the costs of *New Fill* treatment in people with HIV. These are North Manchester and Ealing. Dr Stephen Ash of Ealing Hospital told *ATU* that the hospital began offering the treatment earlier this year after he had been trained in the technique by the UK distributors Medi-Phill Ltd. So far, eight patients have been treated and three more are about to start.

A trial of *New Fill* underway at the Chelsea and Westminster Hospital, London is recruited.

Other clinics across the UK are in the process of negotiating contracts to be able to provide the treatment free of charge. Even if successful, access may be limited to those most severely affected. Paying privately for *New Fill* costs around £1,200 to £1,500.

New Fill is classified by regulatory authorities as a medical device rather than a drug, and in the USA, this distinction has been employed by the Federal Drug Administration to prevent the New York based buyers club DAAIR from supplying *New Fill* to their HIV-positive clients.

Speaking to our website aidsmap.com following the recent conferences in Athens, Dr Martin Fisher of the Royal Sussex County Hospital in Brighton expressed concern over inequity of access to *New Fill*, “There’s a danger that if certain units are set up and others aren’t, we’ll be back where we were two or three years ago with people having to move treatment centre to get the latest service”.

key conclusions

- A significant proportion of people on anti-HIV therapy will experience facial wasting.
- New information on the safety and effects of a range of cosmetic procedures designed to fill out sunken cheeks in people with facial wasting is now available. Over the short-term, these appear to show some improvement in facial appearance and there is some evidence that the process has improved quality of life. The long-term effects and safety are not established.
- A number of UK treatment centres are negotiating with health purchasers to provide some access to cosmetic procedures through the NHS. Access should be expected to be limited, however.

who funds NAM?

aids treatment update is provided free to people with HIV – how is this, and the rest of NAM’s treatments information paid for? by caspar thomson

NAM’s aim is to support the fight against AIDS and HIV with comprehensive, accurate, independent and relevant information. We are a registered charity, all our funds being used to support this aim. In the UK, we’re probably best known for our information on HIV treatment issues and contact listings for organisations, including treatment and testing centres. Increasingly however we are recognised internationally, and disseminate resources on all aspects of HIV to individuals affected by the virus, professionals and community organisations around the world.

NAM’s treatments information

NAM tries to reach as wide an audience as possible by creating a range of differently pitched materials, in a variety of media. With just one exception*, all are free to people in the UK who are directly affected by HIV:

- *AIDS Treatment Update* and *NAM Factsheets*.
- *ATU* and *Factsheets* on audiotape.
- Our web site, aidsmap.com.
- Our annually updated booklet series.
- Monthly information forums and fortnightly treatment support sessions in London
- The *HIV & AIDS Treatments Directory**.
- The *Directory to Complementary Therapies in HIV and AIDS*, to be published in 2002.

This year we have also published our first *HIV Treatments Training Manual*, for use by trainers working with people with HIV, healthcare and other professionals in the field.

If you know people affected by HIV who don’t already receive our information, please let them know about our resources. To get the free subscription to *ATU*, all they need do is telephone us on 020 7627 3200 and we’ll put them on our strictly confidential mailing list.

Who funds NAM?

This year we need to raise just over £1 million to fund what we believe are vital information services. Roughly 23% of NAM’s income comes from the fees that professionals and agencies pay to subscribe to our publications. There are five other major sources of funding: the Department of Health and health authorities around the UK (25%); pharmaceutical companies (20%); the International HIV/AIDS Alliance (9%); charitable trusts such as Crusaid and the Elton John AIDS Foundation (9%) and finally the European Commission (3%).

Valuing independence

The funds we receive from drug companies are an important contribution to our work to help people to improve their knowledge of HIV treatments and we are very grateful for this support. There is no question, however, of companies being able to interfere with our editorial stance or to influence us in any other way that undermines our independence. Our coverage of treatment issues will remain impartial and fair regardless of whether a particular company does or doesn’t fund us. Our medical advisory panel, which brings together a cross section of medical opinion, underpins this approach. All our funders are listed on the back of every issue of *ATU*, so that who *is* funding NAM is out in the open.

How to make a donation

Anyone who would like to discuss how to support our work with a one-off or regular donation, or by remembering NAM in their will, can telephone me on 020 7627 3200. I would be delighted to hear from you. Individual giving can make a huge difference in helping NAM provide better services to more people who need them.

more from NAM

There’s more information about NAM’s range of resources on the back page of this newsletter.

editor’s note

Caspar Thomson is Director of NAM.



Salvage therapy may work better after a drug holiday

A randomised trial investigating the effects of a treatment interruption in people starting a multi-drug regimen following advanced treatment failure, suggests the break results in an improved initial viral load response to the new combination. These new data, from the French GIGHAART study (ANRS 097), are preliminary and it's unclear how long this benefit will persist.

GIGHAART randomised 70 people with heavy treatment experience to switch their failing HIV treatment to a salvage regimen of at least eight drugs either immediately, or after an eight week treatment interruption. The rationale for this comparison is that in the absence of treatment, drug resistant HIV – which would be expected to be present in this context – would disappear from the circulation as it is outgrown by wild-type HIV, the name given to HIV which has not been exposed to antiretroviral treatment.

Treatment interruptions are commonly associated with a loss of CD4 cells, and so their use has raised particular concern in people whose CD4 count is low, or has previously been so. In GIGHAART, the average CD4 count was already very low – around 27 cells. Use of HIV treatments was also very advanced – over 80% of participants had high level resistance to AZT, at least three AZT/d4T resistance

mutations, at least one NNRTI mutation, and at least two protease mutations.

After twelve weeks on the new 'mega-HAART' regimen, significantly more of those in the treatment interruption arm had at least a one log drop in viral load, and had viral load below 400 copies, than the immediate treatment group, (67% versus 28%, and 40% versus 16% respectively, by on treatment analysis).

Despite the high number of drugs involved, tolerance of treatment appeared surprisingly good over this short initial period. Five people reduced the number of drugs in their regimen to less than six, and sixteen stopped hydroxyurea, one of the mandated treatments used in the study.

Because drug resistant HIV is 'archived' and can re-grow if drugs to which these viruses are less susceptible are re-introduced, it's possible that the virological benefit observed in the treatment break group will be short-lived. Nevertheless, any enhancement in viral load response may be viewed positively in this setting. What GIGHAART is unable to establish is whether effective salvage therapy requires the use of so many drugs. A trial currently recruiting in the UK and abroad, OPTIMA, is looking at both this question, and the strategic use of a treatment interruption in people with a similar shortage of viable treatment options. Details of this study are on aidsmap.com and in last month's *ATU*.

Reference: Katlama C et al. 8th European Conference on Clinical Aspects and Treatment of HIV, Athens 28-31 Oct, abstract 016, 2001.

T-20 open-label study announced

Roche Products have announced plans for widening access to their experimental fusion inhibitor, T-20 (pentafuside), a new type of anti-HIV treatment. A worldwide open-label safety study, codenamed T-20 305, is due to begin sometime between January and April of next year.

T-20 has been trailed as an important new treatment option for people whose prior experience of available drugs leaves them with few other choices. Studies so far have indicated that the inclusion of T-20 in 'salvage' regimens for people with multiple class experience, improves the virological response to the new combination compared to switching to a regimen that does not include T-20.

The drug is difficult to manufacture, however, and supplies have therefore been very limited. Roche now say that, in addition to ongoing clinical trials, 450 people will gain access to T-20 via an open-label study next year. The study will recruit in the UK, Belgium, France, Germany, Italy, the Netherlands, Portugal, Spain, Switzerland, North America, and Brazil. Participating centres are expected to be those which took part in an earlier T-20 study, codenamed T-20 302.

Entry to the study is targeted at people on HAART who have had a CD4 count below 50 within the last 90 days. In addition, people who have had an AIDS-defining event during this period will be given first preference over those who have not. A quota of places on the study is allocated to each participating country based on the World Health Organisation's HIV prevalence figures. We understand that UK treatment centres are to be allocated fifteen places on the study.

T-20 is given by injection rather than as a tablet, and in common with all anti-HIV drugs, resistance to T-20 will emerge if the drug is taken without the support of other agents which are active against HIV.

BMS PI: New trials recruiting in the UK

Atazanavir is an experimental protease inhibitor in development from Bristol-Myers Squibb. Formerly known as BMS 232632, atazanavir is a once daily drug, taken as one or two pills, without regard to food.

A pivotal study comparing two doses of an atazanavir-based HAART regimen to one containing another PI, nelfinavir, in people new to treatment has now reported results to 48 weeks. This randomised study found no difference in viral load response between arms, and a comparable increase in CD4 cells. (A fuller report of this trial is available on aidsmap.com, and will be included in a review of new anti-HIV drugs in next month's *ATU*.)

Increased levels of bilirubin appear to be a significant side-effect of atazanavir, and though this is not in itself harmful, it can cause jaundice (yellowing of the skin). More positively, data so far suggest that this drug may have a less pronounced effect on levels of cholesterol and triglycerides in the blood, a significant problem associated with other HIV drugs in this class. It is this feature which is arousing most interest in atazanavir at present.

Now two new trials are recruiting protease inhibitor experienced individuals in the UK. The first compares atazanavir with two NRTIs, to lopinavir/ritonavir plus two NRTIs in people who have experienced virological failure on one protease inhibitor-containing regimen. The second is a randomised, open-label trial for people who have experienced failure of at least two anti-HIV treatment regimens which have contained drugs from all three classes, but have been unable to maintain an undetectable viral load. This study will test the safety and efficacy of atazanavir when taken in combination with other anti-HIV drugs, including tenofovir. A third trial, for people whose first-line NNRTI-containing regimen has failed, is due to open in December. Details of these trials, including participating centres, are available on aidsmap.com.

coming soon in *ATU*
In next month's *ATU*, we start 2002 with a review of the latest crop of anti-HIV drugs, including the soon-to-be licensed tenofovir, along with T-20 and atazanavir (see left).

***ATU* reader survey**
Last month's *ATU* included a copy of our yearly reader survey for people who receive a free subscription. If you've yet to complete it, it's not too late – we'd like to hear your views.



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Anna Poppa

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medical advisory panel

Dr Fiona Boag
Dr Ray Brettle
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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 covers six key topics: Viral Load, Clinical Trials, Nutrition, Anti-HIV Drugs, Resistance, and a Glossary.

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.

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



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