

aids treatment update

understanding body fat changes

This month we review a number of important developments in the study of lipodystrophy, the body fat changes which can appear as a side-effect of HIV treatments. Two large cross-sectional studies have provided a snapshot of body composition in men and women with HIV relative to that of similarly-aged HIV-negative people. These have been in clear agreement on two key points. First, the dominant symptom of body fat changes in people with HIV is fat loss, particularly in the peripheral areas of the body, namely the face, arms and legs. Second, fat loss in these areas is not usually seen alongside fat gain in the trunk area - in fact it seems that 'Crix belly,' the early name given to fat accumulation in the abdomen, is less common in people with HIV than without. Moreover, the apparent lack of connection between the two - lost fat in one area and gained fat in another - leads us to conclude that this is not a redistribution of fat, but rather these are two distinct problems with distinct causes.

Though there continues to be few remedies available for the treatment of fat loss, 96 week follow-up from the French Vega study suggests the cosmetic use of poly-lactic acid, a thickening agent injected into the hollows of the cheek, is restoring more than facial features. When we last reported on this procedure there were few UK doctors practiced in the technique. Over the page, we talk to three who have now treated over 130 people between them. And with the usual caveats about these still relatively early results, all agree the effects on esteem and quality of life have been substantial.

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saving face

2 cosmetic options to manage body fat changes by edwin j bernard

Since we last reported on the treatment of facial lipoatrophy (fat loss) in *ATU 108*, there have been significant developments in our understanding of the lipodystrophy syndrome, not least a growing awareness of the psychological distress that it can cause. Aside from the news that some people place more importance on being lipodystrophy-free than on the length of their life, as Anna Poppa notes in the following article, a recent French study¹ reported that people with lipodystrophy tended to have more unprotected sex with casual partners than those without. And a Spanish study² described how the psychological impact of lipodystrophy may be experienced as an additional burden by those already marginalised by society — gay men, the unemployed, and people receiving current psychiatric therapy with HAART-related body fat changes were more likely to report reduced quality of life than other patient populations.

Treating lipodystrophy consists of two major strategies: switching antiretroviral drugs and having reconstructive surgery. It is beyond the scope of this article to review drug switching strategies, but so far results have been variable. Reconstructive surgery has now been better studied, and until we better understand the cause of lipoatrophy and lipohypertrophy, this treatment appears to provide the most effective and rapid outcome based on current knowledge. The areas that have been most studied are the restoration of facial fat and the removal of buffalo hump. In the UK, anecdotally at least, facial fat loss is seen far more frequently than buffalo hump. Buffalo hump has been reported mostly in the US, and this may be due to

differences between the UK and US diet or other factors. Although one cannot underestimate the physical and psychological effects of other lipodystrophy symptoms like increased breast and belly size, diet and exercise appear to be the initial treatment options in use for body fat gain at this point.

Buffalo hump

Three posters^{3,4,5} at the recent Retroviruses Conference in Boston reported on the success of buffalo hump surgery; two from the US, and one from Italy. Dr Graeme Moyle, Assistant HIV Research Director, Chelsea and Westminster Hospital, London has referred three patients for buffalo hump surgery. "There appeared to be a low recurrence rate," says Dr Moyle of the studies, which concurs with his own experience. "However, the problem with a buffalo hump — which is a mass of fat and connective tissue — is that you cannot easily define its limits. At least one of the patients that I saw had markedly diminished sensation on the back of his neck after the operation."

Weighing up the pros and cons of surgery on quality of life are obviously important, and more studies are needed.

Fat transfer

Three poster reports in Boston assessed surgical treatment of facial lipoatrophy. Two focused on *New-Fill* (polylactic acid), whilst the third⁶ examined autologous fat transfer; taking fat from either the abdomen or buffalo hump and placing it into the cheeks. Although the results of autologous fat transfer were promising, showing a significant improvement in patients'

quality of life and high satisfaction scores, and that the effects at 52 weeks appear durable, the authors conclude that “a limitation of this procedure is that 40% of the patients with facial wasting do not have sufficient fat to be transferred.” Additional limitations would be the cost of this surgery, which requires ultrasound and local or general anaesthetic. It is unlikely to be approved in the UK as an NHS treatment for these reasons.

New-Fill

New-Fill is an 'immunologically inert' substance with an established safety record in cosmetic procedures. It is injected into the hollows of the cheek and works by first increasing fibroblast production and then production of natural collagen. This results in the thickening of the skin, literally filling the void where fat has been lost.

Treatment with *New-Fill* for facial lipoatrophy was first reported in September 2000 at the 2nd International Workshop on Lipodystrophy and Adverse Events in Toronto⁷. In 2001, early data from the VEGA study, a French trial of *New-Fill* in HIV patients with facial lipoatrophy, were presented in a European AIDS conference in Athens.

At Boston, 96 week follow-up of the fifty VEGA participants was reported.⁸ At entry, the median facial fat thickness, measured by ultrasound, was zero. Patients received four sets of *New-Fill* injections on their first day in the study, and then every two weeks for six weeks. Most patients received four sessions (26 people), with many others requiring five (20 people). At six weeks, median cutaneous thickness had increased by 5.1mm, and this was sustained to 96 weeks when the increase from baseline was 6.8mm. Though improvements in quality of life were observed at weeks 24 and 48, these were reduced (though still above baseline) by weeks 72 and 96. Side-effects were minimal and limited to the appearance of small nodules in the injected area in 44% of participants.

The second report from France evaluated *New-Fill* in forty people with HIV.⁹ After six months, cheek thickness was increased and there were no serious side-effects. Mild pain was reported by 76% of participants, despite *New-Fill* being administered with xylocaine, an anaesthetic.

***New-Fill* in the UK**

Over the past year, several HIV clinics in London, Manchester, Liverpool and Brighton have been offering *New-Fill* to a limited number of patients. Funding has been the major stumbling block for these clinics, most of whom would like to scale-up treatment. Additionally, there are many more HIV centres who would like to offer this treatment, but are unable to do so due to budget constraints. This may change if *New-Fill* is recommended as a treatment for lipoatrophy in the British HIV Association (BHIVA) Antiretroviral Treatment Guidelines currently under review.

ATU spoke with three doctors who now have collective experience of more than 130 *New-Fill* patients. Dr Moyle has treated thirty patients at the Chelsea & Westminster Hospital as part of a clinical trial; Dr Stephen Ash has treated around forty patients at Ealing Hospital and Dr Gillian Dean has treated more than sixty patients in Brighton. All agree that no matter what the cause of facial fat loss — whether it is solely antiretroviral-related or also due to host-factors like duration of HIV infection and CD4 nadir — it is a life-changing event that stigmatises and depresses people, and that treatment is necessary.

“I think we all accept that lipodystrophy is a direct, or partially direct consequence of therapy, and of doing well on therapy,” argues Dr. Moyle. “Therefore, it's wholly appropriate that the NHS should cover it. There are measurable mental health consequences to the physical changes that accompany lipodystrophy,¹⁰ and managing the cosmetic problem is not simply managing the cosmetic problem, but managing a global health problem that has an impact on mental health.”

“I would encourage anyone else struggling to set up a similar service to persevere,” adds Dr Dean, who has been treating patients since March 2002. “I think this addition to our service has been a great success and altered many people's lives for the better.”

“The North West Sector of London had planned to offer the treatment to all its patients from January 2003, but I think there have been some 'hiccoughs',” adds Dr. Ash. “There will be three

glossary

adherence The act of taking a treatment exactly as prescribed.

antiretroviral A substance that acts against retroviruses such as HIV.

cardiovascular Relating 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.

cerebrovascular Involving the brain and the blood vessels supplying it.

cholesterol A waxy substance, mostly made by the body and used to produce steroid hormones. High levels can be associated with atherosclerosis.

cohort A group of people who share at least one common factor (e.g. being HIV-positive) and who are studied over a period of time.

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

lipid A general term for fats.

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

median The central value of the distribution, so that half the values are less than or equal to it and half are greater than or equal to it.

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

naive Never having taken anti-HIV treatments before.

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saving face continued

centres taking referrals: Ealing, St Mary's and Chelsea & Westminster. I think we are probably the only centre up and running. I hope this system will set a precedent for patients in centres outside the North West Sector of London."

New-Fill is not the only soft-tissue filler available, but because it has been studied in VEGA, is available in the UK, and appears cost-effective and relatively simple to administer, it has become the treatment of choice so far. It's relatively long and problem-free track record in cosmetic surgery makes it very attractive, says Gillian Dean. "It rapidly reverses the stigmatising appearances of facial lipoatrophy, lasts longer than many of the more expensive alternatives (e.g. collagen) and it is almost impossible to overcorrect." However, *New-Fill* has previously been used in very small amounts for smoothing out fine lines and in lip enhancement. "We don't yet know if there are unforeseen complications of injecting much larger amounts — five to ten times as much per session, and twenty to fifty times as much in total," she adds.

The process begins with a referral from the patient's primary HIV physician, who assesses the impact that the facial lipoatrophy is having on the patient's life. "A small minority of patients confuse lipoatrophy with changes in facial shape normally expected with ageing, and therefore request treatment when I, or their regular physician, don't particularly think it's indicated," comments Dr. Dean, "but most referrals are entirely appropriate."

"We don't have a very objective measure to say when someone has severe enough lipoatrophy to warrant treatment," admits Stephen Ash, who has been offering *New-Fill* to patients for nearly two years. "If someone is worried enough about

it, that's enough for me. It's a little painful, so people don't volunteer for it too lightly."

Indeed, a treatment with *New-Fill* is more akin to a visit to the dentist than the acupuncturist. "The treatment sessions require a series of injections which are generally well tolerated, but not surprisingly, some patients struggle with needles in the facial area," admits Dr. Dean, who has had two patients with moderate-to-severe bruising. However, the patients "had prior warning so weren't particularly distressed, and this minor complication resolved over 48-96 hours." Dr. Ash has also had two patients with short-lived bruising. "I've only had one person who developed a reaction to some constituent of the fluid," he says, "with itching, swelling, and pain over the cheeks." In Dr. Moyle's study there was one case of mild bruising and one of cellulitis, neither of which required treatment.

One of the early findings of VEGA was that *New-Fill* can cause subcutaneous nodules that feel lumpy, although it does not affect physical appearance. Consequently, all three recommend massaging the injected areas several times a day for at least the first 48 hours. "The idea is to spread the substance evenly within the skin area so that it doesn't encapsulate and cause lumpiness," says Dr. Moyle who had one patient with subcutaneous nodules. "The experience of the operator is important," adds Dr. Ash. "There are tricks to avoid getting a lumpy response." One of Dr. Dean's early patients also experienced the subcutaneous nodules. "She noticed, but did not complain about these very small palpable lumps which are barely visible to the naked eye. The overall effect of treatment is still good for her one year later. She has also put on a substantial amount of weight since treatment, which may be relevant."

One of the concerns about BHIVA recommending, and the NHS funding, *New-Fill* is that, as Graeme Moyle, puts it "there are very few objective evaluations of cosmetic surgery: it is about how happy you are with the results of the surgery within the boundaries of realistic expectations." It was an issue he attempted to overcome in his study by using objective evaluations from three doctors, students and lay-people using a specially-designed visual analogue scale. He discovered, however, that there is no such thing as an objective visual evaluation of facial lipoatrophy. "How you wake up and feel that morning affects how you rate someone's lipodystrophy over the course of that day," he says, after discovering that the same photo two weeks apart often got wildly different scores. "In a way, I think that's quite comforting to the patients. In other words, if you're thinking when you get on the bus that people are thinking, 'What's wrong with that guy's face?' the reality is that the general population can't really tell whether somebody has lipoatrophy or not."

Gillian Dean observed a link between improvements in depression and social function in her patients, although "the clinic was specifically not set up as a research project — it was meeting a clinical need. So, it's qualitative, rather than quantitative evidence, and probably should be interpreted as such."

However, her anecdotal evidence is remarkable for its strikingly positive findings. "Patients, almost without exception, are delighted with their post-treatment appearance," she reports. "Several patients were having fun made of them in the street, others felt their appearances were

giving away their HIV diagnosis. Many described having HIV 'written all over their faces'. There were others who hadn't realised how much they'd altered until they had 'got their faces back'."

The affects went much deeper than vanity, she adds. "Patients who were 'housebound' because of their appearance have reported huge improvements in their social lives. Others have had the confidence to apply for, and get, new jobs, others have started new relationships. Most have reported the absence of being told how ill they look, which they reported as wearing and depressing."

Most significant, perhaps, was the effect on HAART adherence. "Some patients have been re-established on antiretroviral medication, which they had previously stopped because of their appearance," reports Dr Dean.

As evidence mounts that *New-Fill* is a safe, effective and, in many cases, necessary, treatment for facial lipoatrophy, it can surely only be a matter of time before it becomes more generally available. However, as Graeme Moyle notes, it is a treatment for just one aspect of lipoatrophy, and not the holy grail.

"One of the women we treated immediately shifted the focus of her appearance to her legs. 'I'm very pleased with my face, but now everyone will comment on my thin, veiny legs'. There's a hierarchy of anxiety about different body parts: you sort out one, and the anxiety just shifts to another part."

"What can you do about that?"

key conclusions

- Cosmetic surgery continues to be the most commonly used treatment for facial fat loss, a side-effect of HIV drugs.
- A substance called *New-Fill* has become the most popular product for use in this way. Evidence suggests that *New-Fill* injections into the cheek area generally result in a visible improvement which lasts for up to two years, and perhaps longer.
- Cosmetic procedures for facial fat loss are provided in a number of HIV treatment centres in the UK on the basis of need, though this form of treatment is not formally recommended at present.

New-Fill

For the latest information on where *New-Fill* is available, visit aidsmap.com.

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defining lipodystrophy

6 new case definition published, but disagreement continues over how the syndrome presents by anna poppa

As Edwin J Bernard describes in this month's accompanying article, the emergence of body fat changes (lipodystrophy) in people taking antiretroviral therapy has significantly altered our perceptions of HAART. Despite the substantial health benefits which have been derived through antiretroviral therapy, the visible symptoms of fat loss (lipoatrophy) and fat accumulation (lipohypertrophy) can be a stigmatising experience for those affected, disclosing HIV status and associating HIV infection once more with a wasted appearance.

All medicines have side-effects, and in the case of HAART drugs these can be severe or even life-threatening, something which the body fat changes seen in the lipodystrophy syndrome certainly are not. Nevertheless there is little doubt that lipodystrophy holds a special place in the minds of many people living with HIV, highlighting so clearly the tension between HAART's pros and cons. When a group of 75 HIV-positive Americans were asked about the effects of their diagnosis, they judged HIV infection to have reduced their quality of life by 26%. Lipodystrophy however, was considered to have added a further 20% loss. Asked if they would trade their life expectancy to be free of body fat changes, two thirds said they would give up at least a year of life to avoid developing lipodystrophy.¹

Moreover, fat accumulation can be painful, particularly around the back of the neck and shoulders, and lost fat around the buttocks can make sitting uncomfortable. Treatment adherence, and therefore response to HAART, has also been noted to suffer as a consequence of developing lipodystrophy in both the French APROCO cohort and the Italian ICONA cohort.^{2,3}

In the absence of alternative management strategies, switching antiretroviral drugs to avoid exposure to those which have been most clearly associated with lipodystrophy has become a common approach to the problem (see *ATU* issue 119). Improvements in abnormal lipid values have been observed more frequently than improvement of body fat changes, however, and where the latter has occurred, progress appears slow.

The relationship between physical body fat changes and the metabolic abnormalities which also characterise the lipodystrophy syndrome is not well understood. There's evidence that people with body fat changes who switch antiretrovirals to manage raised lipids may do less well, in terms of the effect on lipids, than people without body fat changes. In the Spanish NEFA trial, where people changed the PI component of their HAART regimen for either abacavir, efavirenz or nevirapine, after 24

weeks, the effect on lipids of switching from PIs was less in patients with lipodystrophy compared to those without.⁴

Establishing a case definition

Though the first case reports of lipodystrophy in people taking anti-HIV therapy appeared over five years ago, this still unexplained collection of signs and symptoms has remained poorly defined. Without a clear agreement between doctors over what does and does not constitute lipodystrophy, our ability to understand the problem better, develop management strategies, and assess those at risk, is reduced.

Last month in *the Lancet*, a working group convened by the European Medicines Evaluation Agency published the first validated lipodystrophy case definition to be based on objective measurements.⁵ This initiative involved 1,081 HIV-positive adults who were recruited at 32 sites in Argentina, Australia, Europe, Japan, North America and Singapore. Participants underwent a physical examination to look for signs of body fat changes, and completed a questionnaire. Those who had one or more lipodystrophic feature, by agreement of both doctor and patient, were classified as cases (417 people), and 371 people without were classified as controls. The remaining 288 participants could not be assigned to either group because of a lack of agreement between doctor and patient. People with an active AIDS-defining illness were excluded from the study, and women made up just 15% of the cohort.

In a random sample of cases and controls, clinical and metabolic parameters and body composition were measured objectively and used to develop a case definition for the syndrome. This case definition was then validated in the remaining participants, where it was found to have 79% specificity and 80% sensitivity. This means that it could accurately detect four out of every five cases of lipodystrophy.

The case definition can be used to diagnose lipodystrophy in any adult (male or female) using ten variables: sex, age, duration of HIV infection, HIV disease clinical stage, waist/hip circumference ratio, anion gap (a measure of lactate levels), HDL cholesterol, leg fat,

trunk/limb fat ratio, and intra-abdominal/subcutaneous abdominal fat ratio. The latter three variables however, must be measured using scanning equipment (DEXA and CT) which is not routinely available in clinical care, and without these values the model is less accurate. This leaves a question mark over the clinical application of this definition.

At February's Retroviruses Conference in Boston, Dr Andrew Carr of St Vincent's Hospital, Sydney, described how further work on the case definition is attempting to address the question of severity.⁶ The case definition diagnoses lipodystrophy by scoring the ten measurements described above. Now a grading system has been developed which ranks cases between 0 and 4 according to this score, and this will be evaluated further in future.

FRAM: Another view

One of the more controversial reports at last year's International AIDS Conference in Barcelona concerned the FRAM (Fat Redistribution and Metabolic Change in HIV Infection) study, a US initiative designed to assess the prevalence and presentation of lipodystrophy in people with HIV. Though not yet published, the FRAM findings have been reviewed at subsequent conferences, including the Boston meeting in February.⁷

FRAM is a case-control study involving HIV-positive men aged 33 to 45, and 153 similar HIV-negative men participating in a non-HIV metabolic study called the CARDIA study. The 412 HIV-positive men were recruited from eighteen sites in the US. All participants were asked, on one occasion, to self-report changes in body fat distribution at peripheral (cheeks, arms, legs, face, buttocks) and central (waist, abdominal fat, neck, chest, upper back) body sites. These patient reports were then verified by a physical examination performed by a doctor.

The most common feature of body fat changes in HIV-positive men was loss of fat in peripheral sites, reported in 38.9% compared to 4.6% of HIV-negative men, where self-report and physical examination were in agreement. Loss of fat in the central areas was also more common in positive than negative men (7.8% versus 2.6%).

glossary continued

NNRTI Non nucleoside reverse transcriptase inhibitor, the family of antiretrovirals which includes efavirenz, nevirapine and delavirdine.

NRTI Nucleoside analogue reverse transcriptase inhibitor, the family of antiretrovirals which includes AZT, ddI, 3TC, d4T, ddC and abacavir.

PI Family of antiretrovirals which target the protease enzyme. Includes amprenavir, indinavir, lopinavir, ritonavir, saquinavir, nelfinavir, and atazanavir.

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

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.

lipodystrophy case definition website

The lipodystrophy case definition which appeared in *The Lancet* on March 1st 2003 is available online at <http://www.med.unsw.edu.au/nchecr>

Boston lipodystrophy webcast

Lipodystrophy was the subject of a symposium at the 10th Conference on Retroviruses and Opportunistic Infections held in Boston in February. A webcast of this session, held Thursday February 13th, is available online at <http://www.retroconference.org> providing an audio soundtrack alongside speakers' presentations.



defining lipodystrophy continued

In relation to fat gain however, the results were more surprising. HIV-positive men were found to have central fat accumulation less frequently than HIV-negative men (40.3% versus 56.2%). Moreover, whilst in the HIV-positive men, having lost fat in the peripheral sites was associated with *loss* of central fat, it was not related to having *gained* fat centrally. This is an important finding because it suggests that fat accumulation in central sites is not a redistribution of fat which has been lost from peripheral sites, and that different mechanisms are behind these two distinct features.

The FRAM group also evaluated buffalo hump, the name given to fat accumulation around the back of the neck and shoulders.⁸ Four hundred and twenty-one HIV-positive men were compared with age-matched controls from the CARDIA study. Each underwent physical examination to determine the presence of buffalo hump, and where appropriate, this was measured vertically and horizontally by tape measure.

Whilst there was no significant difference in the frequency at which buffalo hump was observed between the positive and negative men (8.0% versus 11.3%), men with HIV tended to have a larger hump, on average two and a half times larger.

Body fat changes in women

Whilst female participants were in a clear minority in the Lipodystrophy Case Definition Study, they were of course completely absent from the all-male FRAM study. Where then should our understanding of body fat changes in women with HIV be coming from?

The US Women's Interagency HIV Study (WIHS) began collecting data on body shape in 1999. In a new report in Boston, researchers

described lipodystrophic changes in 1,057 HIV-positive women (who were predominantly Black or Latina) and compared these with age-matched HIV-negative controls.⁹ Women self-reported changes in body fat in peripheral (arms, legs, buttocks) and central (waist, chest and upper back) sites, and these were confirmed by anthropometric measurements, weight and bioelectrical impedance analysis.

During an eighteen month follow-up period, weight and total body fat remained stable in the HIV-positive group but increased in the HIV-negative women. The incidence of fat loss in both peripheral and central sites in women with HIV was double that observed in women without. In comparison, peripheral fat gain was less common in HIV-positive women, and there was no difference in the frequency of central fat gain.

Interestingly, because this mirrors the findings of the FRAM study, the predominant body fat change seen in HIV-positive women was a loss of fat in peripheral and central sites. And where women experienced a combination of changes, these were most commonly a mixture of peripheral and central fat loss, or of peripheral and central fat gain. The simultaneous occurrence of peripheral fat loss and central fat gain was seen very rarely.

Lipodystrophy in children

Lipodystrophy has also been reported in HIV-positive children, but has been less-well characterised than in adults, mainly because studies have often involved small numbers of patients. It's also more difficult to assess body fat redistribution in children, given that normal physical development in this group involves growth and change.

Dr Claire Thorne and colleagues from the

Italian Register on HIV Infection in Children, and the European Collaborative Study, reported on lipodystrophic changes in their cohorts of HIV-positive children at the Boston conference.¹⁰ All HIV-infected children aged between 3 and 18 attending twenty-four treatment centres in Italy, Spain, Germany, Poland, Sweden and Switzerland, were observed over a two to three month period. Body fat redistribution was defined as one or more clinically determined sign of central fat gain (trunk, buffalo hump, breast enlargement) or peripheral fat loss (face, arms, legs, buttocks).

The 403 children studied included 209 girls and 194 boys. The median age was 9.5 years. Eighty-eight per cent were White, 8% were Black, and 4% were from other ethnic groups. Most had acquired their HIV infection vertically, and 80% were taking a HAART combination of three or more drugs. Sixteen per cent were taking dual therapy, and the remaining three per cent were naïve to HIV treatment.

Fat redistribution was noted in 117 children (29%). Of these, the most common presentation was a mixed pattern of central fat gain and peripheral fat loss, which occurred in 38% of cases. Central fat gain alone was seen in 35%, and peripheral fat loss alone in 27%. It's important to note, however, that unlike the FRAM and WIHS studies, these are uncontrolled data.

This study also evaluated the frequency of metabolic abnormalities within the cohort and found dyslipidemia (elevated trygliceride or

cholesterol levels in the blood) in 52%. Overall, lipid problems were substantially more common in children with lipodystrophy than without (around 70% versus 40%), as were abnormalities in two specific measures, triglycerides and HDL cholesterol.

Fat redistribution and metabolic abnormalities were two and a half times more common in girls than in boys, and eleven times more common in children currently taking three or more HIV drugs compared with those taking two or less.

Managing lipodystrophy

UK guidance on the management of lipodystrophy is currently under review as part of a revision of the British HIV Association Treatment Guidelines. However, new recommendations from the International AIDS Society — USA Panel were published in *the Journal of AIDS* in November last year.¹¹

Whilst the group discuss the range of interventions under investigation for body fat changes — diet, exercise, insulin sensitisers, human growth hormone, testosterone, cosmetic surgery and switches in antiretroviral therapy — they conclude that there are no specific techniques or therapies which can be routinely recommended for assessment or monitoring of body fat changes, or for their treatment where they occur in the absence of metabolic abnormalities.

While we await advances in our understanding of this problem, the best management for many people will remain the support of their clinical team, and an individualised approach to care.

key conclusions

- Body fat changes (lipodystrophy) which may occur as a side-effect of HIV treatments can be stigmatising and may have a significant impact on quality of life.
- A case definition of the lipodystrophy syndrome was developed recently which could accurately detect four out of every five cases of lipodystrophy in HIV-positive adults.
- Recent findings in both men and women on HIV treatment suggest that fat loss, particularly in the limbs and face, is the most common symptom of lipodystrophic body fat changes. Fat gain in the central area of the body seems to appear less frequently, and may not be directly related to lost body fat in other areas.
- Body fat changes have also been reported in HIV-positive children.
- There are no routinely recommended treatments for body fat changes at present.

further reading

An introductory booklet on lipodystrophy is available free from NAM to people affected by HIV. More detailed information can be found at <http://www.aidsmap.com>

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US trial stopped early

Investigators running a large American HIV treatment trial have announced the closure of an arm in which participants received the three NRTI combination *Trizivir*, after a review of response to treatment found the regimen inferior to two efavirenz-containing combinations.

ACTG A5095 was designed to compare three protease inhibitor (PI)-sparing combinations in people starting anti-HIV treatment for the first time. This three arm, double-blinded trial allocated participants at random to receive either:

- Three NRTIs (AZT/3TC/abacavir in the form of *Trizivir*)
- Two NRTIs (AZT/3TC in the form of Combivir) and one NNRTI (efavirenz)
- Three NRTIs (AZT/3TC/abacavir) plus one NNRTI (efavirenz).

The trial was open to anyone with viral load over 400 copies regardless of their CD4 count, so long as they had not taken anti-HIV treatment before. Amongst 1,147 recruited individuals, median viral load at entry was 78,825 copies and median CD4 count was 238 cells. Forty-three per cent had viral load above 100,000 copies (considered high) at this point.

An interim analysis performed after all participants had completed at least sixteen weeks on therapy (the median treatment duration being 32 weeks), found a higher rate of virological failure (defined as a confirmed viral load over 200 copies after 16 weeks) in those receiving *Trizivir* rather than an efavirenz-containing regimen. Of 167 people who experienced viral load failure,

21% had received *Trizivir*, compared to 10% in the other two arms. (Data from the two ongoing efavirenz-containing arms remains pooled in order to maintain blinding).

A post-hoc analysis found that virological failure had occurred earlier in *Trizivir* recipients than those taking efavirenz and two or three other drugs. During the first three months of treatment, the risk of viral load failure on *Trizivir* was estimated to be double that of the other two arms (7% versus 3.5%).

The effect of blinding treatment allocation meant that all trial participants received a total of seven pills per day. Advocates of *Trizivir* will argue this removes one of the regimen's strengths, as in 'real life' taking *Trizivir* involves taking two pills a day.

T-20: First HIV fusion inhibitor on the way

Drug licensing authorities in both the European Union and the United States last month gave the go ahead to the first of an entirely new class of anti-HIV therapies. As a result, T-20 (enfurvitide, *Fuzeon*) from Roche Products is expected to be available in European pharmacies within three months. The US supply should begin a little earlier.

The European Medicines Evaluation Agency will licence T-20 for use in people who have previously taken drugs from each of the three currently available classes, protease inhibitors, nucleoside analogues and NNRTIs. The drug will also be available to those for whom intolerance to drugs from a particular class makes constructing a viable regimen difficult.

T-20 has been shown to improve virological response when added to a background regimen in multiply drug-experienced individuals, (reported previously in *ATU* issue 116). Without the support of additional active agents however, resistance to T-20 should be expected to develop, and so the drug should not be used in this way.

Roche have been scaling-up T-20 production throughout its development. However, the drug poses significant manufacturing challenges and supplies will be limited for the next two or three years. The proposed price, around £12,000 per year, is likely to limit access to the drug further.

T-20 is administered by injection and reactions at the injection site has been the main side-effect reported so far. New information presented to drug licensing bodies suggests the drug may be associated with the occurrence of bacterial pneumonia, and an allergic reaction called hypersensitivity.

Nevirapine PREP

US researchers are developing plans to test the anti-HIV drug nevirapine as a 'pre-exposure prophylaxis' (PREP), a means of preventing HIV transmission prior to sexual exposure to the virus.

Initial investigations, reported in a recent issue of *AIDS*, found the drug was well-tolerated by 33 HIV-negative people at high risk of HIV infection. Participants in a Phase I/II dose-ranging study were randomised to receive 200mg of nevirapine either weekly, twice weekly, or every other day. After twelve weeks of treatment, drug levels fell within the target range and laboratory abnormalities (including effects on liver function) were minimal. Nine people left the trial early however, seven of whom were lost to follow-up.

The trial was not designed to test the effect of nevirapine on HIV transmission. A much larger trial will be required to answer this question. A second antiretroviral, tenofovir, is to be investigated as a potential PREP agent, after the Bill and Melinda Gates Foundation agreed to sponsor a large international trial.

Reference: Jackson JB et al. A phase I/II study of nevirapine for pre-exposure prophylaxis of HIV-1 in uninfected subjects at high risk. *AIDS* 2003;17:547-53.

Sexual attitudes of UK Africans

Research conducted by the former Camden and Islington Health Authority, London Borough of Islington, and the African HIV Policy Network (AHPN) has reported new information on attitudes to sex and sexual practices amongst African people with HIV living in the UK. The report, titled *Padare*, was commissioned in order to highlight areas of HIV service provision which may require development.

Two hundred and fourteen respondents completed confidential questionnaires covering their beliefs, knowledge and behaviour, their use of services, and experience of discrimination. For more information on *Padare*, contact AHPN on 020 7814 6722.

Health Protection Agency launched

April 1st was the chosen date for the establishment of the Health Protection Agency, a new organisation for England and Wales which will monitor threats to public health in the form of infectious diseases, poisons, chemicals, and biological and radiation hazards.

The Agency will take over from the Public Health Laboratory Service and Communicable Disease Surveillance Centre in gathering and reporting epidemiological information on HIV and other infectious diseases in England and Wales. The Agency's website is at <http://www.hpa.org.uk>

World TB Day

March 24th marked World TB Day. Following our earlier report on TB in the UK in *ATU* 122, the latest reports on epidemiology are available at the former Public Health Laboratory Service website, at this address: http://www.phls.co.uk/topics_az/tb/tbfrontpage.htm

nam forum

'Understanding HIV Therapy' is the subject of the NAM forum on Monday, 28th April, 7-9 pm at ULU, Malet Street, London WC1.



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For more information, and details of our other publications and services, please contact us, or visit our website, www.aidsmap.com.

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