

Lipo: any progress?

Created 1 Dec 2007 - 6:07pm

For part of the past ten years I have felt I looked like a scarecrow. With my skinny arms and legs, bulging midriff, and sunken cheeks, at times I have looked a little scary or at best, a bit unusual. So too have a lot of other HIV-positive people who have spent a decade or more on nucleoside analogue drugs (mainly d4T, AZT, ddl or ddC), which by the mid nineties, researchers were realising were major contributors (along with the virus itself) to the wasting of fat and muscle from the bodies of those who took them.

The new generation of protease inhibitors which were first introduced here in 1996 were life-saving additions to the antiviral arsenal but were soon to be seen to bring their own added complications with raised [cholesterol](#) [1]An essential component of cell membranes and nerve fibre insulation, cholesterol is important for the metabolism and transport of fatty acids and the production of hormones and Vitamin D. Cholesterol is manufactured by the liver, and is also present in certain foods. High blood cholesterol levels have been linked to heart disease and may be a side effect of some anti-HIV medications. and [triglyceride](#) [2]A type of fat in the blood. Elevated triglyceride levels may be a side effect of some anti-HIV drugs. levels, [insulin resistance](#) [3]A diabetes-like condition in which, while adequate amounts of insulin are produced by the pancreas, the body does not respond normally to the action of insulin. In the wider community, insulin is related to obesity, while in HIV it may be related to lipodystrophy. and the development of unusual fat accumulation, in the abdomen (nicknamed "protease paunch"), breasts and buffalo hump at the back of the neck.

Fortunately it seems likely that new generation [antivirals](#) [4]A medication or substance which is active against one or more viruses. May include anti-HIV drugs, but these are more accurately termed antiretrovirals. will limit the chances of new HIV patients having to experience either the fat accumulation or fat loss, or at least to the same extent. For treatment-experienced people though, the loss of fat (or lipoatrophy) has been a very stigmatising condition, particularly when it affects the face, producing sunken cheeks or heavily ageing folds, often 'outing' people's HIV status to those around them whether they wish it or not. In recent times studies have shown small successes in reversing lipoatrophy by switching classes of drugs and there has been some progress in using other treatments to try to help fat gain. None have been earth shattering in their impact and for some, plastic surgery interventions may still offer the best hope of restoring facial appearance and starting to look normal again.

Switching off NRTIs

At the Conference in Retroviruses and Opportunistic Infections (CROI) Conference in 2006, Dr Graeme Moyle from the Chelsea and Westminster Hospital in London presented data from the 48- week RAVE study which showed that patients switching from thymidine analogues (d4T or AZT) to thymidine-sparing backbones – Abacavir-3TC or Tenofovir-3TC – reported few instances of lipoatrophy over prolonged follow-up.[1](#)

The trial also compared patients remaining on d4T or AZT with Tenofovir and Abacavir containing regimens to see if people who had treatment experience with the two nucleosides could gain fat. At week 48 of the trial, limb fat increased by 393 grams in those switching to a regimen including Tenofovir versus limb fat increases of 316g in the Abacavir arm (not a statistically significant difference). This represented a 12 percent gain back in lost peripheral fat. The AZT arm did better than those on d4T and those on Tenofovir did better than those on AZT. It was however a relatively small study (105 patients) and we will need to wait to get results of further studies to get firmer conclusions in this area.

The above trial and other 'switch trials' since have shown that when fat cells return they do so extremely slowly, over a period of years, and then only a partial return is achieved. Further to this, at the 2007 CROI, data was presented on the metabolic outcomes of ACTG 5142 a trial that compared NRTI, NNRTI, and PI-sparing regimens over a two-year period. The trial confirmed the superiority of Tenofovir and Abacavir as backbone drugs but surprisingly, when matched with two nucleosides (NRTIs), the Efavirenz arm showed a higher level of lipoatrophy (32 percent fat loss) than the Kaletra (Lopinavir and Ritonavir) arm with 2 nucleosides (17 percent fat loss).

The arm of the above trial that used Kaletra with Efavirenz only experienced 9 percent fat loss. Why should this be so? For starters there were no fat-stripping NRTIs involved and recent research is suggesting that Ritonavir may be

able to stimulate the growth of fat cells. It is unclear at this stage whether Efavirenz has a role in lipoatrophy or not. The other approved non-nucleoside, Nevirapine, has not been linked with lipoatrophy. It will also be interesting to see if drugs like the new non-nucleoside, TMC 125, just made available in Australia on compassionate access have any effect on fat wasting. [2](#)

Uridine trial

Other treatments are being tried to see if they can aid fat gain. Uridine, (NucleomaxX), a naturally occurring nucleoside molecule, is being used by some HIV-positive people to try to reverse lipoatrophy. One study presented by Sutinen at the Lipodystrophy Workshop in 2005 showed patients on Uridine gained significant increases in limb fat (between 400g and 1500g) after three months. [3](#) The supplement is only known to reverse fat in people who are using lipoatrophy-causing treatment though (such as AZT or d4T). However, a small trial of uridine is being conducted in 40 patients by St Vincent's Hospital in Sydney. The study, over 24 weeks, is in people who have ceased NRTI therapy and are receiving Kaletra. Uridine retails overseas for about \$400A per month's supply but it is not currently available for import into Australia under the [Special Access scheme](#) [5] Before a drug has been approved, manufacturers often provide the drug free of charge to people who cannot participate in a clinical trial and who meet certain criteria under a Special Access Scheme (SAS).

The "glitazone" family of drugs (drugs such as rosiglitazone and pioglitazone, used also to treat Type 2 [diabetes](#) [6][Diabetes mellitus] A disorder in which sugars in the diet cannot be metabolised into energy due to a lack of the enzyme insulin. Late-onset diabetes mellitus may be a long-term side effect of some anti-HIV drugs.) has been only mildly successful in reversing fat loss — with fat gains up to half a kilogram over twelve months. Some glitazones have been found to increase lipids and the people most likely to benefit from using these drugs are those who have not used d4T before (the people who need it the most), one study found.

Some positive people are using dietary supplements, including L-carnitine and coenzyme Q-10 as well as C and B-complex vitamins to try to improve mitochondrial health and prevent greater fat loss. None of these have been proven to help with fat gain. There is no magic pharmaceutical bullet at the moment, which leaves treatment-experienced people considering the appeal of the facial fillers to try to bring back some of their old face.

Facial fillers

In 2000 a number of plastic surgeons in Australia started to use Sculptra (New-Fill or PLA) for the treatment of HIV-related lipoatrophy with high levels of patient satisfaction reported. A recent trial conducted by the National Centre for HIV [Epidemiology](#) [7]The branch of medical science that deals with the study of incidence and distribution and control of a disease in a population. and Clinical Trials in Sydney was unable to find a significant increase in soft tissue thickness in HIV-positive patients given four treatments of Sculptra after a 48-week follow-up but both patients and doctors did report that there were visual improvements and there were favourable quality of life measures shown. Overseas trials have also shown that patients felt significantly better about their appearance after several injections, including lower anxiety levels and rates of depression. The Victorian, New South Wales and Queensland state governments have provided funds to help positive people to access Sculptra treatments, given their expense.

Sculptra has been approved by the Food and Drugs Administration in the USA as safe to use. A small percentage of people have papules (small bumps or nodules at the injection sites) after the injections that are usually only visible on blowing out the cheeks, although for some, these can become prominent. The cost can be \$800 or above per treatment (some people will need multiple injections) if government funded assistance is not available.

I have had six Sculptra injections myself since 2000 from Melbourne plastic surgeon Dr Brett Archer and found the procedure of several injections into both facial cheeks bearable for the small amount of pain involved. (Some friends with a low threshold for pain took painkillers before the procedure but I found it much less uncomfortable than say, visiting a dentist). There were no complications for me and over the four year period that I had further injections, I found my face filled out, the sunken cheeks went and people no longer ask me if I'm "tired" all the time: the lipoatrophy look does give that impression to others, even if you're feeling perfectly well inside. It is now three years since my last injections and, though I could probably benefit from a "top-up", my face has not returned to the fat-stripped state that it was in 2000. The collagen that is produced in the face by Sculptra can last up to five years after the injections— but it is not clear how many times people will need re-treatments into the future.

Permanent filler

In recent months, a series of advertisements have appeared in some gay press around the country from cosmetic surgeons offering a treatment called Polyacrylamide hydrogel (PAAG or Aquamid) for facial lipoatrophy. A number of my friends with HIV lipoatrophy have tried the new treatment in recent months with a favourable response. I decided to investigate this so-called “permanent facial filler” to find out what kind of alternative treatment it may offer to HIV-positive people – albeit probably those with sufficient finances as it would seem unlikely to be provided free by the government at any near stage in the future.

Aquamid is a non-reabsorbable watery gel that employs an injection technique into the subcutaneous skin. It mixes with the water in the skin and creates a vacuum like a permanent sponge inside your cheek. It is a permanent filler, which doesn't require re-treatment after the initial series of injections (well, at least for ten years, the manufacturers say, when ageing may have some effect). It has been widely used for other plastic surgery purposes including for treatment of facial lines, lip augmentation and depressed scars, for instance. It has been used in Europe for HIV-related lipoatrophy for the past four years.

One trial, conducted by Guaraldi and others at the University of Modena in Italy, showed similar improvements in the thickness of fat in what is known as the Bichat's pad region of the face in three different treatments: Aquamid, Sculptra and autologous fat transfer (AFT). AFT does not seem to have been widely used in Australia for this purpose but it involves the harvesting of fat tissue from subcutaneous fat in the groin, abdomen and dorso-cervical region of the body. There was a high level of satisfaction reported by patients on all three arms but four patients on the AFT arm experienced a serious [adverse event](#) [8] An unwanted effect caused by the administration of drugs. Onset may be sudden or develop over time. called “hamster syndrome” caused, it seems, by using “sick” fat in the face taken from areas of the body where buffalo humps related to HIV fat accumulation had developed. More trials are needed to prove conclusively that Aquamid has longer term benefits for use against HIV lipoatrophy and findings from a longer study of a Spanish [cohort](#) [9] In epidemiology, a group of individuals with some characteristics in common. A cohort study is a special kind of clinical trial which looks at a treatment or treatment strategy in a cohort of people. of HIV-positive people on the treatment are due to be released shortly. [4](#)

I spoke to Dr Peter Bartnicki from the Melbourne Collagen Foundation, a cosmetic surgery in Melbourne. He has had some experience using both Sculptra and Aquamid and finds that a number of HIV-positive people have come to him because the Sculptra has not worked or they are after something more permanent that doesn't require extra top-up treatments.

“I prefer to use Aquamid because, in my experience, it works for more people. The effects can be quite dramatic in a relatively short time frame compared with Sculptra. With Aquamid you could have up to 6 mls, say over a 3-week period, allowing for a week between injections. Sculptra takes longer to work (if it does) and periods between injections are longer (generally 4 weeks). There can be some bruising with Aquamid because it is a harder substance than Sculptra, but this goes away fairly quickly. There is a 1 percent chance of infection that has to be treated with antibiotics. Some practitioners treat their patients with antibiotics just in case this happens but I tell my patients to get straight back to me at the first sign of swelling, redness or soreness. Generally there are no problems at all and the procedure is quite painless.”

The cost however is not so painless. It is around \$1000 per ml syringe and Dr Bartnicki predicts that someone with moderate HIV lipoatrophy may need six injections, and the more severe cases will need more than that. (Discounts generally apply if larger quantities are used). Some people may balk at the idea of a “permanent” filler because faces change with age and HIV-related wasting may continue as an underlying cause after the injections. The manufacturers' claim that Aquamid integrates with the skin and mirrors any facial changes, such as ageing. They also say there have been no problems with this over the 13 years it has been sold. The manufacturer suggests that people who have had a semi-permanent filler (such as Sculptra) should wait for twelve months before trying Aquamid although one plastic surgeon I spoke to recommends a two-year wait.

Belly-busters?

Initial optimism about the use of growth hormone to help reduce the protruding bellies that some of us have developed after years on protease inhibitors (with maybe some other classes of antivirals involved as well – the

causes are still not fully understood) was tempered by significant toxicities including headaches, fluid retention, arthralgia and elevations in blood glucose levels for those taking the treatment. At the 2007 CROI however, results of a [phase 3](#) [10] A large clinical trial designed to establish whether a drug is effective and safe enough for widespread use. Phase III studies include expanded controlled and uncontrolled trials after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather additional information to evaluate the overall benefit-risk relationship of the drug and provide an adequate basis for physician labeling. study of TH29507, a growth hormone releasing factor analogue, look more promising. There was a reduction of 20 percent shown in visceral adiposity in the treating arm of the trial over a six-month period. There were no significant toxicities or metabolic complications observed. Patients did have to inject daily and it is unknown whether the reduction of fat will continue if the treatment is stopped. Further trials are continuing.

For further research on changing drugs and new therapies to reverse fat go to: www.thebody.com/lipo/drug.html [11]

David Menadue was funded through an unrestricted educational grant to attend the IAS 2007 Conference in Sydney by Contura Pty Ltd, manufacturers of Aquamid. Thanks to Dr Andrew Carr for help with this article.

1. [1](#). Moyle G J et al 'A randomised comparative trial of tenofovir DF or abacavir as replacement for a thymidine analog in persons with lipoatrophy', AIDS 2006;20:2043-2050
2. [2](#). Haubrich, R et al, 'Metabolic Outcomes of ACTG 5142: A Prospective Randomised Phase 111 Trial of NRTI-, and NNRTI-sparing regimens for Initial treatment of HIV-Infection', Abstract 38, 14th CROI Conference. For further details on ACTG 5142, see www.catie.org [12]
3. [3](#). Ibid.
4. [4](#). G.Guaraldi et al, 'Comparison on three different interventions for the correction of HIV-associated facial lipoatrophy: a prospective study', HIV Metabolic Clinic, University of Modena, Italy as reported in Antiviral Therapy, 10:753-759

- [Lipodystrophy and lipoatrophy](#)
- [polylactic acid](#)
- [rosiglitazone](#)
- [treatment side effects](#)
- [uridine](#)

Links:

- [1] <http://www.napwa.org.au/glossary/term/88>
[2] <http://www.napwa.org.au/glossary/term/114>
[3] <http://www.napwa.org.au/glossary/term/99>
[4] <http://www.napwa.org.au/glossary/term/123>
[5] <http://www.napwa.org.au/glossary/term/112>
[6] <http://www.napwa.org.au/glossary/term/95>
[7] <http://www.napwa.org.au/glossary/term/490>
[8] <http://www.napwa.org.au/glossary/term/469>
[9] <http://www.napwa.org.au/glossary/term/477>
[10] <http://www.napwa.org.au/glossary/term/92>
[11] <http://www.thebody.com/lipo/drug.html>
[12] <http://www.catie.org>