

ASHM 2006: Spotlight on Sculptra

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The annual conference of the Australasian Society for HIV Medicine ([ASHM](#) [1]Australasian Society for HIV Medicine. The peak Australasian organisation representing the medical and health sector in HIV/AIDS and related areas.) was held in Melbourne in November. PAUL KIDD summarises some key developments.

Facial fat wasting (lipoatrophy) continues to be a significant concern for many people with HIV/AIDS, so one of the most eagerly-awaited presentations at ASHM concerned the FLASH trial, an Australian study investigating the [effectiveness](#) [2](Of a drug or treatment). The maximum ability of a drug or treatment to produce a result regardless of dosage. A drug passes efficacy trials if it is effective at the dose tested and against the illness for which it is prescribed. In the standard procedure, Phase II clinical trials gauge efficacy, and Phase III trials confirm it. of injected poly lactic acid (Sculptra, once known as New-Fill)[1]. While anecdotal evidence from people who have undergone this treatment has mostly been positive, there is limited [clinical trial](#) [3]A clinical trial is a research study to answer specific questions about vaccines or new therapies or new ways of using known treatments. Clinical trials are used to determine whether new drugs or treatments are both safe and effective. Carefully conducted clinical trials are the fastest and safest way to find treatments that work in people. Trials are in four phases: Phase I tests a new drug or treatment in a small group; Phase II expands the study to a larger group of people; Phase III expands the study to an even larger group of people; and Phase IV takes place after the drug or treatment has been licensed and marketed. data showing its effectiveness, and the Australian trial was designed to address this.

Surprisingly, the trial failed to find a significant clinically-measurable benefit for the treatment, despite positive subjective assessments by both participants and the treating doctors.

A total of 100 people were [enrolled](#) [4]The act of signing up participants into a study. Generally this process involves evaluating a participant with respect to the eligibility criteria of the study and going through the informed consent process. into the trial, all of whom had moderate to severe facial fat loss associated with HIV antiretroviral toxicity. Participants had to have been HIV-positive over a long period and be stable on their current treatment, or off treatment with no plans to restart within 24 weeks, and had to have clinical signs of lipodystrophy at at least one other site apart from the face.

Participants were [randomised](#) [5]A method based on chance by which study participants are assigned to a treatment group. Randomization minimizes the differences among groups by equally distributing people with particular characteristics among all the trial arms. The researchers do not know which treatment is better. From what is known at the time, any one of the treatments chosen could be of benefit to the participant into two arms – an immediate treatment arm and a deferred treatment arm, which acted as the [control group](#) [6]A group of patients in a clinical trial who do not receive the drug or treatment being investigated, for the purpose of comparison with those who do. Participants in the control group of a clinical trial are either given standard treatment (excluding the drug being studied) or a placebo.. Participants in the immediate treatment arm received a course of four Sculptra injections at the start of the trial, while those in the deferred arm were treated after 24 weeks. The analysis presented at ASHM compared participants in the immediate treatment arm with those in the deferred treatment arm at 24 weeks (i.e. after the first group had finished their treatment but before the second group had started theirs). A further analysis is planned at week 96, when both groups have been treated.

Researchers used spiral CT scans to measure the change in subcutaneous tissue volume before and after the treatment, as well as asking patients and their doctors to give a subjective assessment of the effectiveness of the procedure in improving their appearance. The study design set a target of increasing facial tissue volume by at least 10 percent (as measured by spiral CT) as the criteria for successful treatment.

The results after 24 weeks showed that just 8 percent of those who had undergone the treatment had an increase in total facial tissue volume of 10 percent or more, compared with 5 percent of the untreated group. The difference between the groups was not statistically significant, leading researchers to conclude that the treatment did not increase the facial tissue volume, although it did prevent deterioration in the affected areas. There was a detectable improvement in tissue volume around the injection sites; however this did not translate into a substantial gain in the total facial tissue volume.

The CT scan results contrast starkly, however, with the subjective assessments of participants and their doctors, with more than 80 percent of patients saying their appearance had improved after the injections. A similar proportion of doctors said they believed the patients' appearance had improved. By contrast, fewer than 20 percent of patients in the untreated group thought their appearance had improved.

Making sense of these apparently contradictory findings is difficult, not least because this is the first trial to use the spiral CT technology to measure facial tissue volume in this way. The strong endorsement of the treatment's efficacy by participants and their doctors cannot be ignored – after all this is essentially a cosmetic procedure and subjective assessments are important. But equally important is the need to objectively demonstrate the effectiveness of the treatment (particularly given its high cost), not least if public funding for the procedure is to be gained.

Treatment interruptions

Wafaa El-Sadr, of Columbia University in the US, presented a review of the implications of the SMART study². This is the large international study comparing continuous treatment with treatment breaks guided by CD4 count. The study was halted early in 2006 after it became apparent that there was a significantly greater risk of developing AIDS or dying in the group taking treatment breaks.

El-Sadr presented data from subgroup analyses which confirmed the study's earlier finding: regardless of nadir CD4 count, [baseline](#) [7]1. Information gathered at the beginning of a study from which variations found in the study are measured. 2. A known value or quantity with which an unknown is compared when measured or assessed. 3. The initial time point in a clinical trial, just before a participant starts to receive the experimental treatment which is being tested. At this reference point, measurable values such as CD4 count are recorded. Safety and efficacy of a drug are often determined by monitoring changes from the baseline values. CD4 count, baseline [viral load](#) [8]A measurement of the quantity of HIV RNA in the blood. Viral load blood test results are expressed as the number of copies (of HIV) per milliliter of blood plasma., prior AIDS, hepatitis coinfection or previous antiretroviral use, the risk of disease progression and death was higher among those taking treatment breaks compared with those who stayed on treatment continuously. Surveys of quality of life also favoured the continuous treatment group, she said.

"There was no evidence for superiority of drug conservation [treatment breaks] in any of the subgroups evaluated," she said.

While none of these subgroup analyses identified a group for whom treatment breaks were safe, some groups did even more poorly than others, El-Sadr explained. People with higher CD4 counts at the start of the trial, those with higher CD4 percentages, those with viral load below 400 copies and black participants were more likely to experience disease progression if they took treatment breaks.

El-Sadr also discussed the results of Staccato, a recent, smaller study which did find a benefit in treatment breaks. While the Staccato findings do not contradict the SMART study, El-Sadr acknowledged that the different findings opened up new questions. In particular, what might the result have been had SMART set a higher CD4 threshold for stopping and starting treatment breaks, as Staccato had done? While there is "no evidence" the results would have been different, this does pose a possible question for a future study, she said.

Despite the disappointing results of the SMART trial, El-Sadr hasn't given up on treatment breaks. "There needs to be further studies to try and find an effective interruption strategy – if we can find one," she said.

Apricitabine

Susan Cox gave a presentation on apricitabine (ATC), a new nucleoside drug being developed by Avexa, an Australian company³. ATC is structurally similar to the existing drugs 3TC and FTC, with a similarly low toxicity profile, but is designed to remain active against several common [resistant](#) [9]HIV which has mutated and is less susceptible to the effects of one or more anti-HIV drugs is said to be resistant. viral strains and to have a high barrier to resistance.

A small 10-day study of apricitabine monotherapy found that the drug produced significant decreases in viral load

at all the doses studied, including among those with pre-existing resistance mutations. A Phase-2 study (AVX-201) is currently underway in Australia and Argentina, with twice-daily doses of 600mg and 800mg. To date the drug appears to be well-tolerated, Cox said, with the most common side effects being headache, nasal congestion, and gastrointestinal upset. Apricitabine use doesn't lead to significant mitochondrial toxicity or [liver](#) [10] A large organ, located in the upper right abdomen, which assists in digestion by metabolising carbohydrates, fats and proteins, stores vitamins and minerals, produces amino acids, bile and cholesterol, and removes toxins from the blood. toxicity, the conference was told, and appears to have few interactions with other antiretrovirals.

Cox's conclusion was that apricitabine appears to be effective for moderately or heavily pre-treated patients, especially those who are resistant to 3TC or FTC, perhaps in combination with CCR5 antagonists or other future entry inhibitors. A Phase-3 trial is expected to begin in 2007.

Metabolic complications

Kathy Petoumenos presented an update from D:A:D, a large observational [cohort](#) [11] 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. study focusing on the risk of myocardial infarction ([heart attack](#) [12] A life-threatening emergency in which the blood supply to the heart is suddenly cut off, causing the heart muscle (myocardium) to die from lack of oxygen.) in people with HIV⁴. Previous reports from this study have shown a strong link between antiretroviral use and increased risk of heart attack.

Up to 2005, a total of 345 heart attacks were recorded (40 of which were second or subsequent events) among the 23,400-plus participants in the study. The researchers have calculated that the risk of experiencing a heart attack increases by about 16 percent for each year on [HAART](#) [13] Highly Active AntiRetroviral Therapy ??? aggressive treatment of HIV infection using several different drugs together., although Petoumenos noted that the number of heart attacks over the five years of the study was "fairly stable" despite increasing exposure to treatment.

Much of the increased risk can be explained by the increased blood lipids ([cholesterol](#) [14] 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 triglycerides) seen in people on HAART – high blood lipids have long been known to be a risk factor for heart disease. But this doesn't completely explain the number of heart attacks observed in people on HAART. The precise mechanism by which this occurs is not known, however it appears to be particular to protease inhibitors.

In particular, non-nucleosides do not appear to significantly increase the risk of heart attack. "We found no evidence that increased NNRTI exposure is associated with risk of [heart attack]," she concluded.

Another presentation, by Handan Wand, looked at the incidence of metabolic syndrome (MS) among people with HIV⁵. MS refers to a 'cluster' of related conditions, including [high blood pressure](#) [15] Persistently high blood pressure, an outwardly symptomless condition which carries an increased risk of serious illnesses such as stroke, heart disease and heart attack., increased blood lipids, high blood sugar and low levels of HDL 'good' cholesterol, usually in combination with fat accumulation around the belly. All of these are potential risk factors for heart disease. Between 23 and 25 percent of the Australian population has MS.

Wand's report was based on data from INITIO, a cohort study involving 881 HIV-positive participants starting treatment for the first time. At the beginning of the study (i.e. before starting treatment) the prevalence of MS in the cohort was about 9– percent, however after three years on treatment this figure more than doubled. Again, the risk was highest among people taking protease inhibitors – the risk of developing MS within three years was between 64 and 69 percent higher for those taking PI-based combinations compared with those on NNRTIs.

Positive people can take some comfort in the fact that, for most people, the risk of suffering a heart attack is still fairly low, even after many years on treatment. However those with other risk factors for HIV – such as smoking, high blood pressure, being overweight, having a family history of heart disease or being over 50 – these results will be of concern; you may wish to discuss with your doctor strategies to reduce the risk.

Adherence

Dr David Baker presented an outline of the OneDA study, which is looking at ways to improve treatment adherence among Australian patients⁶. This 48-week study is looking at whether treatments simplification (switching to less complex regimes, typically with fewer pills or dose times) improves adherence. Baker presented preliminary (week 4) data with adherence measured using four different methods (electronic MEMS caps, patient questionnaires, physician assessment and therapeutic drug monitoring).

Participants had 89.6 percent adherence, measured by MEMS caps, over the 4-week period, slightly down on the 95 percent recommended adherence rate but higher than the rate in some overseas studies. The study is ongoing.

¹ Carey D et al, 2006: "Poly-L-Lactic Acid Injections for Facial Lipoatrophy: A Randomised, Multicentre Trial". ASHM 2006.

² El-Sadr, W, 2006: "SMART Study and Implications". ASHM 2006.

³ Cox, S, 2006: "Properties of Apricitabine, A New NRTI for HIV Infection". ASHM 2006.

⁴ Petoumenos, K et al, 2006: "Exposure to PIs and NNRTIs and Risk of Myocardial Infarction (MI): Results from the D:A:D Study". ASHM 2006.

⁵ Wand, H et al, 2006: "Incidence of Metabolic Syndrome, Cardiovascular Disease and Type 2 [Diabetes Mellitus](#) [16][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. After Initiation of Antiretroviral Therapy in HIV-Infected Adults". ASHM 2006.

⁶ Baker, D et al, 2006: "Multiple Measurements of Adherence to [ARV](#) [17]A medication or other substance which is active against retroviruses such as HIV. Therapy in Primary Care". ASHM 2006.

- [adherence](#)
- [diabetes](#)
- [heart disease](#)
- [Lipodystrophy and lipoatrophy](#)
- [polylactic acid](#)
- [treatment interruption](#)
- [treatment side effects](#)

Links:

[1] <http://www.napwa.org.au/glossary/term/382>

[2] <http://www.napwa.org.au/glossary/term/486>

[3] <http://www.napwa.org.au/glossary/term/89>

[4] <http://www.napwa.org.au/glossary/term/489>

[5] <http://www.napwa.org.au/glossary/term/513>

[6] <http://www.napwa.org.au/glossary/term/93>

[7] <http://www.napwa.org.au/glossary/term/472>

[8] <http://www.napwa.org.au/glossary/term/416>

[9] <http://www.napwa.org.au/glossary/term/109>

[10] <http://www.napwa.org.au/glossary/term/102>

[11] <http://www.napwa.org.au/glossary/term/477>

[12] <http://www.napwa.org.au/glossary/term/103>

[13] <http://www.napwa.org.au/glossary/term/96>

[14] <http://www.napwa.org.au/glossary/term/88>

[15] <http://www.napwa.org.au/glossary/term/98>

[16] <http://www.napwa.org.au/glossary/term/95>

[17] <http://www.napwa.org.au/glossary/term/122>