

# Restorative Treatment for HIV-Associated Lipoatrophy

## A Report from the 6th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV

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IF HIV INFECTION IS TO BE RECOGNIZED AS A CHRONIC, MANAGEABLE condition, researchers and clinicians still have an enormous undertaking ahead of them: coming up with tangible strategies to prevent and treat the adverse events associated with antiretroviral therapy. Numerous treatment-related adverse events have been documented and have been shown to have serious clinical consequences that can ultimately have a profound effect on the durability of treatment.

The adverse effect most unique to HIV and antiretroviral therapy is lipodystrophy—generally defined as peripheral lipoatrophy with or without central fat accumulation—which remains one of the most complex, multidisciplinary, and challenging fields of HIV research and clinical management. Other adverse effects, including dyslipidemia, abnormalities in glucose homeostasis, mitochondrial toxicity, and accelerated cardiovascular disease have also become matters of prime clinical importance.

In order to better understand the mechanisms behind, and potential treatment of, these adverse events, there is a dire need for continued dialogue among researchers, clinicians, and community advocates. The annual International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV was established to foster these much-needed discussions and to translate research efforts into more effective clinical management and care for HIV-infected people.

The 6th International Workshop was held in late October in Washington, DC. While there were no eureka moments, bits and pieces of new data fell into place, answering some lingering questions and generating new questions that have yet to be explored. Of particular interest at this year's Workshop were several presentations focusing on restorative modalities for lipoatrophy, one of the most stigmatizing and difficult-to-manage adverse events associated with antiretroviral therapy use.

Other data presented at the 6th International Workshop, including those from ongoing research focusing on the pathogenesis and treatment of metabolic abnormalities, will likely be included in future *Notebook* articles, including a summary of Dr. Donald Kotler's November 2004 lecture scheduled for publication in the March 2005 issue. Because so little has been published in the pages of the *Notebook* regarding restorative therapies for lipoatrophy—and because it is a topic on the minds of many HIV-infected patients with this condition—it is with hope that an introduction to the topic, focusing on the presentations at the 6th International Workshop, will set the stage for future reviews of this important treatment modality.

## Poly-L-Lactic Acid (Sculptra)

ON AUGUST 3, 2004, THE U.S. FOOD AND DRUG ADMINISTRATION permitted Dermik Laboratories to begin marketing Sculptra, the first product specifically approved for the correction of facial fat loss in HIV-positive patients with lipoatrophy. Sculptra is an injectable poly-L-lactic acid (PLA) implant in the form of a sterile lyophilized cake. It contains microparticles of poly-L-lactic acid, a biodegradable synthetic polymer from the alpha-hydroxy-acid family. Sculptra, branded as New-Fill in more than 30 countries outside of the United States, requires reconstitution prior to injection to form a sterile non-pyrogenic suspension.

The clinical basis for the approval of Sculptra was the outcome of four clinical studies. Based on skin thickness measurements, along with serial photographs assessed as a component of these studies, the FDA granted approval on the grounds of demonstrated safety and efficacy for restoration of facial lipoatrophy in HIV-positive patients.

One of the four studies reviewed by the FDA was conducted by the Blue Pacific Aesthetic Medical Group, under the direction of Dr. Douglas Mest. A review of the data from this open-label safety and efficacy study was presented at the 6th International Workshop (Mest, 2004).

HIV-infected patients, all of whom were receiving antiretroviral therapy and had lipoatrophy, were eligible for inclusion. Exclusion criteria included facial injections within the last three months, active infections of the face, antiretroviral therapy non-compliance, signs and symptoms of lactic acidosis, known pre-existing renal disease, and poorly controlled diabetes mellitus.

Buccal skin thickness was measured using calipers at bilaterally fixed points located at the intersection of the vertical axis through the lateral canthus of the eye and the horizontal axis of the nares. These measurements were conducted at baseline, prior to each treatment visit, and six and 12 months following the final treatment sessions. Patients were graded according to the lipoatrophy scale created by Dr. Julia James and her colleagues with the Division of Dermatology and Department of Ophthalmology of the University of British Columbia in Vancouver (1 = mild and localized lipoatrophy; 4 = severe lipoatrophy over a wide facial region including the orbits) (James, 2002).

Laboratory testing—including serum chemistry, liver function tests, serum bicarbonate and lactate levels, prothrombin time, and complete blood counts—was conducted every three months and six and 12 months following the final treatment session. Patient and physician satisfaction was also examined, using a five-point rating

system, along with a psychological well-being questionnaire, completed at the end of treatment and at the six- and 12-month follow-up visits.

Two vials of PLA were prepared per treatment session. A criss-cross technique was used to ensure even product distribution in the treated area. A 25 G 1½ needle was used to inject the PLA deep into the dermis or dermal/subcutaneous junction. The two basic techniques for injection PLA are: tunneling (also called threading) and depot. Tunneling, used to deposit PLA deep in the dermis, is used for injections of the lower face (e.g., cheeks and nasolabial folds). Depot, used to deposit PLA between the periosteum and muscle, is used for injection of the upper zygoma and temples. Injection was followed by a thorough five minute massage, with ice applied to the treated area for 24 hours post-injection.

A total of 99 patients aged 32 to 65 years were injected with PLA. Lipoatrophy grading ranged from 1 to 4 with an average severity of 2.8. Of these 99 patients, 70 and 54 patients were assessed at six and 12 months respectively. The majority of patients required at least three treatment sessions.

At baseline, the average skin-caliper thickness was 7.1 mm. After the final injection, the average skin thickness increased to 11.2 mm, an increase of 57.8% from baseline. Similar measurements were found at six (53.5%) and 12 months (54.9%) post-final injection. Restored volume contours were seen in all patients post-treatment, with progressive improvement over time.

The participating patients reported high satisfaction scores at the end of treatment and six and 12 months post-injection. These results were consistent with those reported by the treating physicians, who also indicated a similar degree of success. Patients also indicated a progressive increase in confidence and improved self-image with treatment, as per the questionnaires.

Adverse events were minimal and did not require treatment interruption or adjunctive therapies. Light bruising was a typical side effect that occurred in 31% of patients and resolved over time. Small (<3 mm), non-bothersome, and non-visible subcutaneous papules were found in 13% of patients injected. The papules spontaneously resolved within three to 12 months post-treatment in 46% of patients.

These data are consistent with others reported in similar studies. Because PLA is a biodegradable product, injections will likely need to be repeated—usually within one to two years—in order to maintain the restorative benefits. However, as these and other data illustrate, it is an effective volume enhancement technique that helps to resolve the disfiguring characteristics of HIV-associated facial lipoatrophy.

## Polyalkylimide (Bio-Alcamid)

BIO-ALCAMID, MANUFACTURED BY POLYMEKON RESEARCH IN Milan, is an injectable hydrophilic biopolymeric fluid that contains 96% sterile water and 4% biopolymer known as polyalkylimide. Unlike PLA, polyalkylimide is nonbiodegradable. It is frequently characterized as a “semi-permanent” filler: the implants will

not be reabsorbed, but can be removed in cases of overfilling or adverse reactions. Repeated injections may only be necessary if the lipoatrophy continues to worsen with advancing HIV disease or ongoing antiretroviral therapy.

Bio-Alcamid is not approved for any cosmetic/restorative purpose in the United States. It has been used throughout Europe for soft-tissue augmentation and for the correction of different tissue deficiencies. It is also available in Mexico, where numerous HIV-positive patients with lipoatrophy in the United States have headed—most notably to the Clinic'estetica in Tijuana—to receive treatment.

Dr. Luis Casavantes of Clinic'estetica, in collaboration with Dr. Michael Gottlieb of Polymekon USA, presented data involving 100 patients receiving Bio-Alcamid through the Tijuana clinic (Casavantes, 2004). Basal facial lipoatrophy was graded according to a Clinic'estetica classification system. For safety evaluations, biopsies were taken at different times after the procedures.

The volume of polyalkylimide needed to replace the lost subcutaneous fat in the 100 patients evaluated was relative to the initial severity and the patient's facial structure. Treatment was reported to be well tolerated and the facial deficits were “fully and permanently restored” after two to four sessions in 100% of the patients. In all cases, the recuperation time was minimal, ranging from no down time to three days. Biopsies showed minor acute inflammation with no signs of chronic inflammation or granulomas.

Additional clinical trials, including one being conducted in Los Angeles, are expected to yield more extensive data soon.

## Polymethylmethacrylate (PMMA)

ANOTHER INJECTABLE, NONBIODEGRADABLE FILLER THAT IS UNDER investigation for the treatment of HIV-associated lipoatrophy is polymethylmethacrylate (PMMA), best known for its use in manufacturing hard contact lenses and Plexiglass. For soft tissue augmentation, microspheres of PMMA are suspended in 0.3% denatured bovine collagen and mixed with 0.3% Lidocaine and sold under the brand name Artecoll. Like Bio-Alcamid, the implants should be long-lasting, yet can be removed if need be. While the FDA has indicated that it is safe and effective for the correction of facial wrinkles, lines, and furrows, it has not been evaluated by the agency for the treatment of HIV-associated lipoatrophy.

In a study reported by investigators in Rio de Janeiro and Sao Paulo, Brazil, HIV-positive patients with lipoatrophy of the buttocks, legs, and arms were treated with PMMA (Serra, 2004). Three different concentrations were used: a 30% solution for subcutaneous injections involving the buttocks, upper legs, and around the knees; a 20% to 30% solution for injections involving the lower legs; and a 10% solution for injections involving the arms and hands. Patients were photographed and were asked to present for follow-up evaluations every 45 days. Sessions were performed with a minimum interval of 10 to 12 weeks for each treated area.

The experiences of 22 HIV-positive patients—10 men and 12 women—were reported. Twenty-seven areas were treated: 14 but-

tock areas, nine legs, three arms, and one pubis and perineum area. The patients needed, on average, two to three sessions to achieve the desired cosmetic results.

Dermal thickness data, measured using calipers or ultrasound, were not collected. What were reported by the Brazilian investigators were generalizations, based largely on the observations of the clinicians and the self-reporting of the patients, along with before-and-after photographs. “Some” patients reported excellent results in hiding the appearance of arm and leg veins. The investigators also noted “good improvement” of the overall appearance of arms and legs. As for patient self-reports, all claimed to be satisfied with the results of treatment and reported improvements in self-confidence.

Side effects included edema of the treated area, with light to moderate pain lasting for two to three days. No infections or inflammatory granuloma were observed.

Additional data from studies evaluating PMMA, as well as its use in the treatment of facial lipoatrophy, are very much needed.

## Autologous Fat Transfer

SEVERAL POSTER PRESENTATIONS AT THE 6TH INTERNATIONAL WORKSHOP—all by the same group at the University of Modena and Reggio Emilia and the San Raffaele Hospital in Italy—looked at various safety and efficacy parameters of autologous fat transfer (AFT) surgery for HIV-related lipoatrophy. In short, this surgical procedure involves removing subcutaneous fat from one part of the body—for example, the abdominal area—which is then transferred to hollows in the face. Given that this procedure is performed using standard equipment by qualified surgeons, AFT is not regulated by the FDA and is available to HIV-positive patients seeking treatment for lipoatrophy in the United States.

One poster presentation detailed the results of a prospective study evaluating the subjective and objective efficacy and durability of AFT surgery in HIV-positive patients with facial lipoatrophy (Guaraldi, 2004). Among 109 patients undergoing AFT, 57 had been followed for at least six months. The population was divided into three groups according to post-surgery follow-up: patients followed for six to 12 months (group 1), patients followed for 13 to 24 months (group 2), and patients followed for 25 to 36 months (group 3). Subjective improvements were assessed using a visual analogue scale (VAS) and objective improvements were documented using ultrasound.

In 72% of the patients, fat grafts were harvested from subcutaneous abdominal fat stores; 15% of patients had fat harvested from enlarged dorsocervical fat pads.

VAS improved in all groups, with no statistically significant differences between the three groups. Ultrasound evaluations also demonstrated improvements in subcutaneous thickness (ST). In group 1, right-cheek ST increased by 3.3 mm and left-cheek ST increased by 3.8 mm. In group 2, right-cheek ST was increased by 5.5 mm over baseline and left-cheek ST was increased by 5.6 mm. In group 3, right-cheek ST increased by 5.89 mm over baseline and left cheek ST increased by 5.7 mm. All improvements in skin

thickness were statistically significant when compared to baseline measurements.

These data, the investigators concluded, help to demonstrate that AFT is effective and durable over time for the correction of HIV-associated facial lipoatrophy. However, they also noted in another poster presented at the Workshop that graft hypertrophy—“hamster cheeks”—seen in some patients after AFT was more likely to occur in patients with fat harvested from enlarged dorsocervical fat pads, compared to fat harvested from the abdominal area (Guaraldi, 2004a). In turn, the investigators specified that when AFT is chosen for the treatment of facial lipoatrophy, the subcutaneous adipose graft site should not be the fat from enlarged dorsocervical pads.

## A Comparative Study

AN ADDITIONAL REPORT FROM THE ITALIAN TEAM PROVIDED A GLIMPSE at what is probably the first head-to-head comparison of restorative modalities for lipoatrophy (Guaraldi, 2004b). The prospective, partially randomized study compared the safety and efficacy of AFT surgery, injections of PLA, and injections of non-biodegradable polyacrylamide (PCA), branded throughout the world as Aquamid and Argiform. The objective outcome of the study involved ultrasound measurements of subcutaneous thickness; subjective outcomes included patient satisfaction using VAS, an assessment of body change and distress (ABCD) questionnaire, and before and after photographs.

Fifty-nine patients were evaluated. Twenty-four patients underwent AFT surgery; the remainder of the patients were randomized to receive either PLA (n = 20) or PCA (n = 15) injections. On average, patients undergoing AFT required two transfers of fat—taken from enlarged dorsocervical fat pads or from the abdominal area—and patients receiving PLA and PCA required five and six injections respectively.

Twenty-four weeks of follow-up data were reported by the investigators. Subcutaneous thickness increased by 3.3 mm in the AFT group, 3.5 mm in the PLA group, and 3.0 mm in the PCA group, with no statistically significant differences between the three groups. Significant increases in VAS measurements were also reported, again with no statistically significant differences between the three groups.

As for adverse events, four of the 24 patients who underwent AFT developed fat graft hypertrophy, nine required aesthetic retouching, and 12 developed post-operative edema. In the PLA group, eight patients had incomplete PLA absorption. PCA tolerability was considered to be excellent.

The study authors concluded that all three reconstructive techniques were highly effective in improving the aesthetic satisfaction of the patients. There were no significant differences in the objective or subjective variables among the three study arms. However, they were careful to note that longer follow-up is necessary to determine the most suitable treatment in terms of durability.

## Conclusion


IN SUMMARY, IT IS HEARTENING TO SEE MUCH ANTICIPATED DATA from studies evaluating the safety and efficacy of restorative treatments for HIV-associated facial and peripheral lipoatrophy. In the absence of data illustrating a clear-cut benefit associated with more simple approaches (e.g., switching antiretrovirals) or data clearly indicating a lipoatrophy-reversing benefit associated with the use of adjunctive therapies (e.g., glitazones), these reports—and others like it that have emerged in recent months—indicate that progress is at hand.

But there are shortcomings to consider as well. For starters, most studies completed to date have been open-label evaluations employing a relatively small number of patients followed for a relatively brief period of time. What's more, the parameters used to evaluate the effectiveness of these therapies have varied con-

siderably from study to study and, in many cases, lack scientific integrity. For these therapies to be approved by regulatory agencies, embraced by standard-of-care committees, and reimbursed by public and private insurance, standardization of safety and efficacy parameters must be established.

Fortunately, the Forum for Collaborative HIV Research—the sponsor of a half-day roundtable discussion, preceding the 6th International Workshop, focusing on appropriate endpoints for lipodystrophy studies—has already put the wheels of standardization into motion (a summary of this roundtable can be found on the Forum's website: [www.hivforum.org](http://www.hivforum.org)). As was summarized by Dr. William Powderly during a mid-Workshop summary of the Forum roundtable discussion, there is agreement among experts regarding the parameters that need to be incorporated into clinical trials evaluating therapies for lipodystrophy, including facial lipoatrophy.

Dr. Powderly explained that there is a need for greater inclusion of objective parameters, such as ultrasound and photography at baseline, along with a standardized measure/grading scale used as a central component of the response criteria. Subjective parameters have their place as well, first in establishing the entry criteria for studies. Subjective changes in response to therapy, determined by using standardized quality-of-life and visual scoring, are also necessary. However, Dr. Powderly remarked that randomized, blinded studies would be ideal in terms of giving weight to reports of subjective improvements. He also remarked that durability is a key when evaluating the efficacy of therapies for lipoatrophy. Clinical trials, he stressed, should be expected to yield at least two years of follow-up data to allow for pertinent evaluations regarding the durability of treatment.

It is with hope that such studies will evolve and produce clinically significant results in the months to come. 

### At a Glance: Potential Restorative Fillers for Facial Lipoatrophy

Active Ingredient	Brand Name(s)
<b>Biodegradable Fillers</b>	
Autologous fat transfer	N/A
Autologous fibroblasts, grown in culture, and then injected as filler	Isolagen
Bovine collagen	Zyplast
Human cadaveric dermis	Alloderm Cymetra
Human fascia	Fascian
Human collagen	Cosmoderm
Hyaluronic acid	Dermalive Restylane Perlane Hylaform
Poly-L-lactic acid	Sculptra* New-Fill
<b>Nonbiodegradable Fillers</b>	
Calcium hydroxylapatite	Radiance
Extended polytetrafluoroethylene (ePTFE)	Advanta Gore-Tex Gore S.A.M. SoftForm UltraSoft
Polyacrylamide	Aquamid Argiform
Polyalkylimide	Bio-Alcamid
Polymethylmethacrylate (PMMA)	Artecoll
Silicone	N/A
*FDA approved for the managements of HIV-associated facial lipoatrophy	

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