

August 12, 2009

The Honorable Kerry Weems  
Acting Administrator  
Centers for Medicare & Medicaid Services  
Department of Health and Human Services  
Attention: CMS-1403-FC  
P.O. Box 8013  
Baltimore, MD 21244-8013

Re: NCA Tracking Sheet for Dermal injections for the treatment of facial lipodystrophy syndrome (FLS) (CAG-00412N)

Dear Acting Administrator Weems:

As President of the American Society for Dermatologic Surgery Association (ASDSA), a medical specialty organization representing over 5,000 physician members across the nation, I would like to thank you for the opportunity to comment on the use of injectable dermal fillers to treat lipodystrophy syndrome (FLS) associated with treatment of persons infected with the human immunodeficiency virus (HIV) or persons who have Acquired Immune Deficiency Syndrome (AIDS) whose treatment includes highly active antiretroviral therapy (HAART).

I am pleased that the Centers for Medicare and Medicaid Services (CMS) has determined that dermal injections for the treatment of HIV-associated FLS falls under a Medicare benefit category, being non-cosmetic and therefore not automatically excluded from coverage. I understand that CMS has now opened a National Coverage Analysis (NCA) process to determine if such treatments are reasonable and necessary.

**The use of injectable dermal fillers to treat HIV-associated FLS is necessary.**

FLS, which occurs in HIV-positive patients taking highly active antiretroviral therapy (HAART), refers to abnormal fat distribution including both lipohypertrophy (fat accumulation) and lipoatrophy (fat wasting or loss). "...HAART is associated with a number of side effects, including lipodystrophy syndrome, which is characterized by facial [lipoatrophy] hyperlipidemia, insulin resistance, and visceral fat redistribution. Of these symptoms, facial [lipoatrophy], which typically occurs in the buccal, temporal, and subzygomatic areas, but can also occur in the periorbital, frontal, and perioral regions, is the most overtly stigmatizing and distressing sign of HIV-positive status...Moreover, patients with HIV-associated lipodystrophy syndrome can isolate themselves from medical care and are more likely to discontinue HAART because of their appearance. (Asher, B; Katz, P; "Facial Lipoatrophy and the Place of Ultrasound," *Dermatol Surg* 2006;32:698-708)

**The use injectable dermal fillers to treat HIV-associated FLS is reasonable.**

As a result of the increasing recognition of the need to treat HIV-associated facial lipoatrophy, the FDA approved both poly lactic acid (PLLA) and calcium hydroxylapatite (CaHA) specifically for the restoration and/or correction of the signs of facial lipoatrophy in patients with HIV. "The approval of injectable CaHA for correction of HIV-associated lipoatrophy was based on the results of a registrational trial, in which 100 patients were treated with CaHA and followed up at 3, 6, 12, and 18 months. Patient satisfaction was rated 97% to 100% at every evaluation point over an 18-month period. Thicker cheek measurements accompanied subjective improvements

in appearance.” (Carruthers, A; Carruthers, J; “Evaluation of Injectable Calcium Hydroxylapatite for the Treatment of Facial Lipoatrophy Associated with Human Immunodeficiency Virus,” *Dermatol Surg* 2008;34:1486–1499)

Enclosed please find studies which demonstrate high levels of efficacy, safety, and patient satisfaction rates for the treatment of HIV-associated FLS using injectable dermal fillers. As stated in one article, “Although the exact mode of operation is not fully understood, research has demonstrated that PLLA injections lead to the production of a fibrous-tissue response that persists over time. Tissue augmentation with injectable PLLA affords results that are clinically comparable with those obtained through fat grafting, although the results with injectable PLLA are more consistent and longer lasting, and the treatment itself is far less involved.” (Mest, D; Humble, G; “Retreatment with Injectable Poly-L-Lactic Acid for HIV-Associated Facial Lipoatrophy: 24-Month Extension of the Blue Pacific Study,” *Dermatol Surg* 2009;35:350–359)

As dermatologic surgeons, members of the ASDS are on the front lines of treating facial lipoatrophy. In addition to the enclosed studies, ASDS has published several other scientific articles on the use of dermal fillers to treat HIV-associated facial lipoatrophy, and we would be pleased to offer further information or access to experts in this area should this assist CMS with its determination that these are reasonable and necessary.

Thank you for your consideration. Should you have any questions, or need more information, please do not hesitate to contact Director of Advocacy and Public Policy Lisle Poulsen at (847) 956-9126 or [lpoulsen@asds.net](mailto:lpoulsen@asds.net).

Sincerely,



Robert A. Weiss, MD  
President

cc: Jeffrey Dover, MD, FRCPC, President-Elect  
Richard G. Bennett, MD, Vice President  
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## Facial Lipoatrophy and the Place of Ultrasound

BENJAMIN ASCHER, MD, AND PHILIPPE KATZ, MD<sup>†←</sup>

**BACKGROUND** Interest in facial lipoatrophy (LA) has recently intensified; this phenomenon is linked to the rise in the number of people adversely affected by the condition as a side effect of antiretroviral treatment for HIV, combined with the growing number of cosmetic products that claim to be able to correct the appearance of LA. Despite growing awareness of the problem, there is at present no standard and accepted technique with which to assess the severity of LA.

**OBJECTIVE** This review explores facial LA, the use of ultrasound in the evaluation of facial LA, its advantages and disadvantages, and will place the technique in the context of other means of assessing regional skin and fat thickness.

**METHOD** Review of literature published on PubMed.

**RESULTS** Ultrasound, as with any technique used to assess facial LA, is associated with distinct advantages and disadvantages.

**CONCLUSIONS** Studies that use a number of different techniques to evaluate changes in dermal thickness provide the greatest insight into both perceived and actual changes in facial LA. Further investigation into the use of these techniques is warranted, along with a formal consensus of facial LA grades.

*Benjamin Ascher, MD, and Philippe Katz, MD, have indicated no significant interest with commercial supporters.*

Facial lipoatrophy (LA), the loss of subcutaneous adipose tissue, can be a sign of aging, trauma, or a manifestation of serious disease (most commonly HIV); since, clearly, neither age nor illness is considered attractive, attempts to disguise the appearance of LA are in great demand. Therefore, driven by consumer desire, a number of cosmetic products or techniques are currently being marketed, either directly or indirectly, to correct the appearance of facial LA.

At present, there is no consensus as to how facial LA should be

defined and assessed. The absence of validated diagnostic criteria and tools with which to assess the severity of the condition is associated with a number of difficulties. First, it is difficult to make meaningful comparisons of the severity of LA across study populations and, thus, problematic to synthesize data generated by multiple investigators. Second, if treatment is available, clinical judgment as to who should receive (and most benefit from) it becomes subjective and open to criticism. Third, there is no standardized objective means by which to evaluate treatments that

improve the appearance of LA. Methods of comparing the thickness of facial tissue layers, before and after treatment, are required to inform patients as to which procedure would be most appropriate. It should also be noted that the extent of LA is only one of a number of issues that can impact the requirement for cosmetic correction: intervention must be carefully tailored to the individual. Factors such as facial morphology and the quality and age of skin, muscle, and bone also influence how a patient looks and the amount of subcutaneous fat possessed.<sup>1</sup>

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The assessment of bodily fat has become an increasingly important area of research in light of the growing levels of obesity and obesity-related diseases, such as Type 2 diabetes and cardiovascular disease.<sup>2,3</sup> Therefore, the evaluation and correction of facial LA (which is not only associated with HIV and age but also other inherited and acquired lipodystrophies) has benefited from other areas of medical research. A number of techniques have been used to assess dermal and subcutaneous thickness, including magnetic resonance imaging (MRI), computed tomography (CT), dual-energy X-ray absorptiometry, and anthropometric measures. The varying physical properties of the layers of the skin mean that ultrasound represents a further means of quantifying skin thickness and LA. This paper will explore facial LA, the use of ultrasound in the evaluation of facial LA, its advantages and disadvantages, and will place the technique in the context of other means of assessing regional skin and fat thickness.

### Facial Lipoatrophy

Facial LA is both a natural expression of the aging process and is associated with trauma and certain disease states, most notably HIV. Its occurrence with other diseases, such as end-stage cancer, is not usually considered important because survival is the issue rather than appearance; in contrast, patients with HIV can ex-

pect to enjoy a healthy life for many years, thanks to highly active antiretroviral therapy (HAART). However, HAART is associated with a number of side effects, including lipodystrophy syndrome, which is characterized by facial LA, hyperlipidemia, insulin resistance, and visceral fat redistribution.<sup>4</sup> Of these symptoms, facial LA, which typically occurs in the buccal, temporal, and subzygomatic areas (Figure 1), but can also occur in the periorbital, frontal, and perioral regions, is the most overtly stigmatizing and distressing sign of HIV-positive status.<sup>5</sup> As a result of the increasing recognition of the need to treat HIV-associated LA, the Food and Drug Administration has recently approved poly-L-lactic acid (PLLA, Sculptra, Dermik Laboratories, Berwyn, PA, USA) specifically for the restoration and/or correction of the signs of facial LA in patients with HIV.

Aging is also associated with facial LA, although the pattern of contour change does not mirror those changes most typically associated with HIV-associated lipodystrophy syndrome. For example, the aging process causes particular facial zones to undergo fat atrophy, while others experience fat hypertrophy. Lipoatrophy occurs in the periorbital, forehead, buccal, temporal, and perioral areas; whereas fat hypertrophy occurs in areas such as the jowls, lower face, and neck.<sup>6</sup> As a result, cheeks look

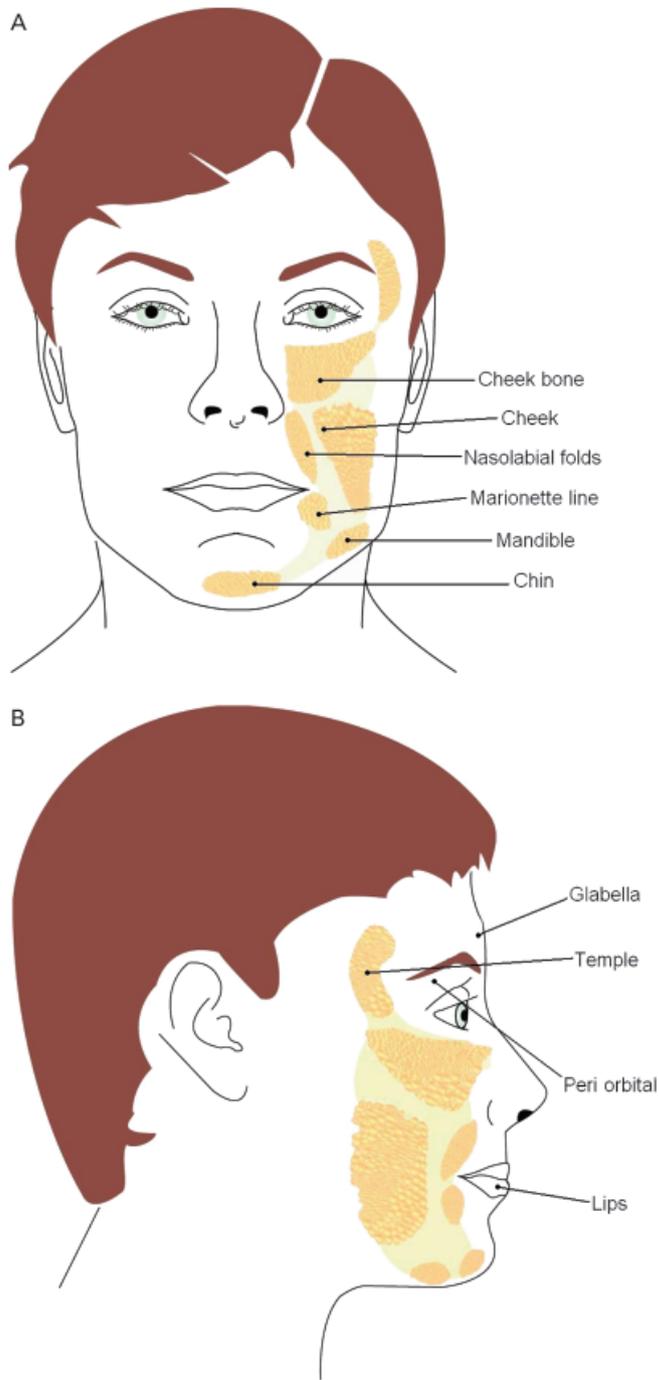
sunken, nasolabial and maxillary folds become more noticeable, marionette lines appear, and the facial muscles protrude; the aged lipoatrophic face has a flat labial profile and vermilion border.<sup>7</sup>

Irrespective of the cause of LA, severely affected individuals look prematurely old and can experience an erosion of self-esteem and quality of life.<sup>8</sup> Moreover, patients with HIV-associated lipodystrophy syndrome can isolate themselves from medical care and are more likely to discontinue HAART because of their appearance.<sup>9,10</sup>

### Treatment Approaches to Facial Lipoatrophy

Treatment approaches to LA have included surgical face lifts, fat grafts, surgical volumetric cosmetic procedures, and the injection of cosmetic products. None of these approaches address the underlying cause of LA, and only one, fat transplantation, directly corrects the loss of fat. Therefore, although an appreciation of the thickness of subcutaneous fat is required to evaluate the extent of facial LA, changes in dermal thickness serve as a benchmark for the success of many treatments.

The ideal treatment for facial LA is yet to be developed, although there have been a number of promising advances. Most patients desire natural-looking correction of areas of depression with



**Figure 1.** Typical areas of lipoatrophy. (A) Darker shading: main areas of lipoatrophy (cheekbone, cheek, nasolabial folds, marionette lines, mandible, chin). Lighter shading: main global area of fat tissue. (B) Secondary areas of lipoatrophy (glabella, temple, periorbital, lips).

safe, immunologically inert products of non-animal origin. Arguably, these attributes have been

achieved by many products, but patients also desire “long-lasting” correction. However, there is a

fundamental contradiction between the desire for very long-lasting products, which are cost-effective and only inconvenience the patient once, and requirement for flexibility. Those that are so “long-lasting” that they can be considered permanent are yet to be developed with the flexibility to accommodate the changes that occur with continued senescence or with alterations in subcutaneous facial fat volume.

**Surgical Procedures**

Rhytidectomies have been used since the turn of the century to rejuvenate the aging face. A major development occurred in 1976 when Mitz and Peyronie pioneered the SMAS (superficial musculoaponeurotic system) technique, whereby sagging tissue is connected to the underlying facial bones to give a firmer, more youthful appearance.<sup>11</sup> While achieving good results in rejuvenating the lower face and neck, such techniques are less able to address the changes related to LA in the mid-face and nasolabial folds. The composite rhytidectomy, developed by Hamra in 1990 and modified in 1992, was designed to reposition the malar fat pad, thereby addressing the depressed mid-face and prominent nasolabial folds.<sup>12</sup> Similarly, Le Louarn<sup>13</sup> developed a surgical technique whereby the depth of nasolabial folds is decreased while simultaneously increasing the volume of the malar eminence and enhancing the cheek region. A

more direct surgical approach to volumetric restoration is achieved by using a malleable subperiosteal onlay, such as coral microgranules, to create desired volume.<sup>14</sup> In addition, bone grafts, taken from the parietal area while performing a subperiosteal face-lift, can be used to remodel the glabella, cheek bones, and nasogenial folds.<sup>15</sup> Nevertheless, although recontouring is achievable with these techniques, volume is not restored to the soft tissues, and aesthetic benefits diminish as the aging process continues.

### **Fat Grafting**

Facial LA has also been addressed by using autologous adipose tissue from other parts of the body. The principle of removing subcutaneous fat and reintroducing it to areas of depression was initially developed by the French physicians Illouz and Fournier,<sup>16-19</sup> and a relatively recent technique was pioneered by Coleman.<sup>20</sup> Fat is harvested using a very fine cannula, with care exercised to ensure minimal trauma. The tissue is then centrifuged to allow whole fat cells to be selected from the mixture of blood, anesthetic, and oil obtained. Small amounts of fatty tissue are then inserted into multiple tunnels using a blunt 17-gauge cannula, potentially achieving long-lasting volumetric correction. Unfortunately, for many patients with HIV-associated LA, there is a paucity of fat to be harvested, and controversy remains over optimal technique and

the durability of results. A systematic review of the literature revealed that autologous fat can be absorbed in as little as 4 weeks, although correction has been shown to persist for up to 8 years.<sup>21</sup>

### **Injectable Products**

There is a diverse range of products that promise to recontour and add volume to the face, but it is beyond the scope of this paper to review their efficacy in detail here. Moreover, many products are unsuitable for the correction of anything other than mild facial LA. For example, collagen products (bovine, autogenic, or isogenic) do not provide long-lasting correction and are designed to fill lines and wrinkles, rather than larger areas of atrophy. Similarly, hyaluronic acid-based products cannot correct large areas, although some of the more viscous gels achieve results in some patients for up to 12 months.<sup>22,23</sup> Permanent injectables, such as polymethylmethacrylate microspheres and liquid silicone, and synthetic implants, such as Gore-Tex and silicone, can provide volumetric correction. However, their permanence can be problematic: long-term complications can manifest and the face may alter with age in such a way that the implants can appear unnatural. A semi-permanent option for the correction of facial LA is PLLA, the aesthetic results of which have been shown to last for up to 96 weeks in patients with

HIV-associated LA,<sup>5</sup> and for up to 40 months in cosmetic patients treated in Europe.<sup>24</sup>

## **Measurement of Facial Lipoatrophy**

### **Ultrasound**

As mentioned previously, in order to establish treatment efficacy, it is important for the extent of volume loss to be evaluated before and after therapy. Ultrasound has emerged as a promising method of assessing lipoatrophy and volume gain post-treatment. The skin comprises the epidermis, dermis, and subcutis; an understanding of the physical properties and dimensions of each layer is vital for the selection of the appropriate ultrasonic equipment to evaluate LA.

The epidermis consists of differentiated layers of keratinocytes. It can be further subdivided into the stratum corneum, stratum granulosum, stratum spinosum, and the stratum basale. The cells of the stratum corneum are fully differentiated and have lost their organelles. Epidermal lipids occupy the interstitial spaces between the superficial epidermis and the stratum corneum; therefore, the corneum forms the major cutaneous barrier. The epidermis generally lies to a depth of 50 to 100  $\mu\text{m}$  beneath the surface of the skin, depending on anatomic location (being thinnest on the face).<sup>25</sup>

The dermis forms the connective tissue stratum of the skin and is largely composed of type 1 collagen synthesized by dermal fibroblasts. This layer lies to a depth of 1,200 to 1,800 μm beneath the surface of the skin and also contains water, glycosaminoglycans, elastin fibers, blood vessels, nerves, and a variety of adnexal structures. The thickness of the dermis varies greatly with anatomic area, the presence of disease, and age: skin thickness decreases significantly linearly from 20 years of age.<sup>26</sup> It is thought that reduced collagen in the dermis is responsible for this gradual loss in skin thickness, as this constitutes, by far, the major part of skin thickness<sup>26</sup>; whereas fat loss is most responsible for the loss of volume associated with age and HIV-related LA.<sup>27</sup> As discussed previously, products that improve the appearance of LA, such as PLLA injections, do so by enhancing the dermis, rather than directly compensating for fat loss; therefore, the accurate measurement of the dermis is crucial for determining treatment efficacy.

The subcutis lies beneath the dermis, to a depth that varies greatly according to anatomic location, sex, body habitus, and degree of LA.<sup>25</sup> The physical characteristics of the subcutis and its components—adipose tissue separated by connective tissue trabeculae, which contain blood vessels, nerves, and lymphatics—differ markedly from the overlying dermis; thus, the boundary between layers appears distinct when examined with ultrasound.

**Selection of Ultrasound Equipment**

Different ultrasound transducers penetrate to different depths and are associated with varying levels of resolution, both laterally and axially. In general, axial resolution is determined by bandwidth, and lateral resolution is directly correlated with the center frequency and indirectly with the focal length. There is a “trade-off” between resolution and depth of penetration: by raising the center frequency and bandwidth, resolution increases but signal penetration decreases.<sup>25</sup>

Given that layers of the skin exist at various depths, depending on location, age, disease, and the severity of LA, the choice of ultrasound equipment will be influenced by the exact layer(s) to be assessed. Most relevant to dermatologists and plastic cosmetic surgeons interested in correcting LA is the thickness of the subcutis and dermis, pre- and post-treatment. The frequency and resolution of transducers used in dermatology and available to plastic/cosmetic surgeons are shown in Table 1, along with their associated depths of penetration.

Transducers operating above a frequency of 20 MHz will not offer the depth of penetration required to discern the thickness of the dermis and/or subcutis. When transducers of 20 MHz are used, epidermal structures become visible only if they are greatly thickened. Sound waves bounce off the fibrous collagen and elastic network, rendering the dermis echogenic. As the dermis is sharply demarcated against hypoechoic subcutaneous fat, its thickness can be estimated. The

**TABLE 1. Depth of Penetration of High-Frequency Transducers**

Frequency (MHz)	Depth of Penetration (cm)	Axial Resolution (μm)	Lateral Resolution (μm)	Target Layer(s)
7.5	> 4	200	400	Epidermis, dermis, subcutaneous fat. Underlying muscle and bone can be visualized and measured
10	> 1.5	150	300	Dermis, subcutaneous fat. Underlying muscle and bone can be visualized but too deep to measure thickness
20	0.6–0.7	50–100	200–350	Epidermis, dermis

dermis also provides a contrast against which dermal appendages, growth, or edema appear as echo-poor areas.

At 7.5 to 10 MHz, the dermis again appears as a thin regular stratum that is more echogenic than subcutaneous fat. The epidermis, even at its thickest, cannot be resolved, and skin appendages, such as hair follicles, cannot be visualized. The interface between the echogenic skin and the hypoechoic hypodermis is clearly visible, allowing measurement of dermis thickness.<sup>28</sup> The thickness of the skin measured at 10 MHz has been reported to range between 1.4 mm at the dorsal aspect of the hand and 4.8 mm at the heel of the foot.<sup>28</sup>

Lower frequency transducers (5–7.5 MHz) have been used to visualize subcutaneous structures deeper than 1.5 cm;<sup>25</sup> at 7.5 MHz, ultrasound has been successfully used to measure the thickness of subcutaneous fat at various sites in normal subjects,<sup>29</sup> although this frequency is yet to be applied to cosmetic surgery.

### **Reproducibility and Validity of Ultrasound in Measuring Lipotrophy**

As discussed above, transducers of 7.5 to 20 MHz are theoretically most suitable for measuring dermal thickness; to measure the thickness of subcutaneous fat, frequencies of 7.5 MHz or below

appear to be most appropriate. The accuracy and precision (reproducibility) of measurements must be demonstrated if ultrasound results are to be meaningful.

Tan and colleagues<sup>26</sup> evaluated the reproducibility, validity, and variability of pulsed ultrasound in measuring skin thickness. Reproducibility and variability were determined by two observers taking five readings each of the flexor aspects of the mid-forearms of 20 subjects. Measures of dermal thickness were validated by comparing the results with those obtained histologically after excision of the same site, and with xeroradiographic assessment.<sup>26</sup> The results obtained by the two observers revealed no systematic differences and a high degree of correlation. The inter-observer variations were small (1.0–1.7%) and insignificant. Intra-observer variations, as measured by coefficients of variation, ranged from 0.0 to 13.3%, reflecting the variation involved in taking repeated readings and the variation in skin thickness because of the undulating interface between the dermis and subcutis. It was concluded that ultrasound was a highly reproducible technique with little variability between observers, although the authors recommended that measurements should ideally be made by the same observer, and that the means of several measurements should be taken.<sup>26</sup> Interestingly, skin thickness determined *in vitro* was found to be

greater when either ultrasound or xeroradiology was used. This was attributed to the release of *in vivo* tension within the dermis after excision. A comparison of the ultrasound and xeroradiologic results revealed similar mean values at each reference point.<sup>26</sup>

Ultrasound assessment of subcutaneous malar and brachial fat in patients with HIV-associated lipodystrophy has been found to be both sensitive and specific to the diagnosis of abnormal fat distribution.<sup>30</sup> For example, in a study by Martinez and colleagues<sup>30</sup> of patients with and without HIV-related lipodystrophy, values of malar fat <4 mm were 74% sensitive and 87% specific to the clinical diagnosis of HIV-associated LA.

### **Application of Ultrasound in Measuring Treatment Effects**

The potential of ultrasound to measure changes in dermal thickness as a response to cosmetic therapy is beginning to emerge, as clear aesthetic improvements are mirrored by ultrasound-measured increases in cutaneous thickness. Two major studies have used the technique in combination with other methods to evaluate improvements in dermal thickness as a response to PLLA implants.<sup>5,31</sup> Following the same principles, sonography has also been used to evaluate reductions in masseter muscle thickness following treatment with botulinum toxin type A.<sup>32,33</sup>

The open-label study of PLLA implants to correct HIV-related LA is the largest trial to date to use sonography to evaluate treatment success. A total of 50 patients with severe facial LA were enrolled. Patients received four sets of injections of PLLA on Day 1 and then every 2 weeks for 6 weeks thereafter. Dermatologic response was evaluated by ultrasound at screening and at weeks 2, 24, 48, 72, and 96. A trained radiologist (Katz, 2003) used a digital multifrequency 7.5 to 13 MHz transducer and a 7 MHz color Doppler transducer (Figure 2) to quantify dermal, epidermal, and subcutaneous fat thickness. All measurements were performed in the nasogenian area below the malar bone and ahead of the masseter (Figure 3). The primary end point was defined as the proportion of patients with a total cutaneous thickness (TCT) > 10 mm at the nasogenian fold at week 24. For each patient, the TCT measurements were summarized by the mean of the minimal and maximal value for each cheek.

A significant increase in TCT was observed as a response to treatment at all time points ( $p < .001$ ); by week 24, 41% of patients attained TCT > 10 mm. Increases in skin thickness were maintained to 96 weeks post-treatment, at which point the median increase in thickness was 6.8 mm.<sup>5</sup>

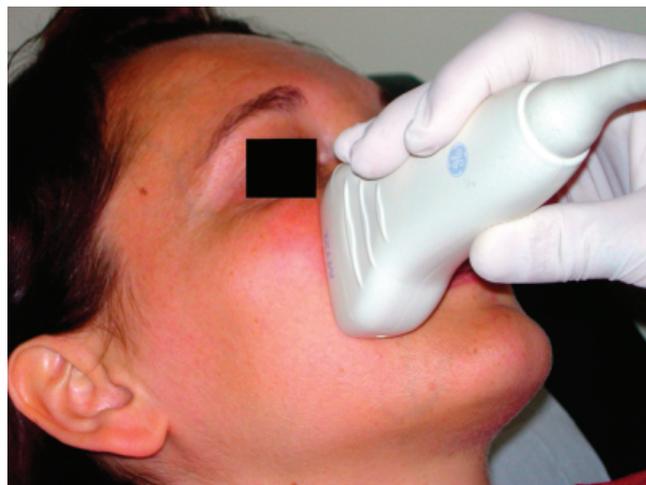
A more recent study also used ultrasound to confirm the ability of



**Figure 2.** LOGIQ 9 ultrasound system (GE Healthcare Technologies, Waukesha, WI, USA).

PLLA injections to increase dermal thickness in patients with HIV-associated facial LA. A total of 30 patients were administered PLLA as three injections 2 weeks apart into the deep dermis overlying the diminished buccal fat pad. Ultrasound was performed by a single radiologist using a

linear array transducer 13.5 MHz variable frequency probe. Generous gel contact was made with the probe to avoid skin compression, and measurements of dermal thickness were made perpendicular to the skin at the nasolabial fold, corner of the mouth, zygomatic arch, and between



**Figure 3.** Patient undergoing ultrasound measurement of the nasogenian area.

these points in the buccal fat pad. The ultrasound data revealed increases in dermal thickness at injection-site areas, but not in untreated areas, suggesting that changes were due to treatment rather than external factors. A mean increase in dermal thickness of 4 to 5 mm was noted in the cheek and nasolabial areas at 12 weeks ( $p < .001$  vs. untreated patients at 12 weeks) and these benefits persisted up to at least 18 weeks post-treatment.<sup>31</sup>

### **Alternative Means of Assessing Lipoatrophy**

In addition to ultrasound, the direct quantification of dermal and hypodermal fat thickness has been accomplished through the use of MRI, CT, and anthropometric approaches.<sup>26,34,35</sup> Subjective assessments have been based on patient and physician appraisal, using either questionnaires, analog scales, or the evaluation of photographic images against standardized photographs.

### **Computed Tomography and Magnetic Resonance Imaging**

Computed tomography is a radiographic technique that assimilates multiple X-ray images into a two-dimensional cross-sectional image that is able to reveal many soft tissue structures not shown by conventional radiography. Of relevance to the dermatologist/cosmetic surgeon, the technique can provide information about the spatial arrangement of tissues

within specific regions of the body, based on how these tissues attenuate X-ray energy. For example, as subcutaneous adipose tissue is less dense than water, it can be discerned from underlying muscle and overlying dermis,<sup>36</sup> and thus the thickness of the dermis and hypodermis can be evaluated. This technique has been successfully used to measure the effects of botulinum toxin type A (BTX-A) on bilateral masseteric hypertrophy.<sup>37</sup> For example, in the study by Kim and colleagues,<sup>37</sup> changes in masseteric volume were assessed before and 12 weeks after injection of 30 U BTX-A per side. As assessed by CT, using the method described by Xu and colleagues<sup>38</sup> 9 of the 11 subjects treated showed a mean reduction of approximately 22% in masseteric muscle volume.<sup>37</sup>

MRI uses similar computational analytical techniques, but adipose tissue is distinguished from other tissues on the basis of differential proton movement within tissues rather than on the basis of defined attenuation values.<sup>36</sup> Research has found that there is generally good agreement between CT- and MRI-derived evaluations of regional body fat<sup>39</sup> and both methods generate highly reproducible and reliable results.<sup>34,35</sup> Furthermore, subcutaneous and ectopic fat can be delineated with both techniques.<sup>2</sup>

Unfortunately, both MRI and CT are very costly and are not routinely available for dermatologists

and cosmetic or plastic surgeons. Computed tomography also has the disadvantage of exposing the patient to ionizing radiation, and MRI is associated with lengthy scanning times.<sup>30</sup> Moreover, CT and MRI essentially measure the properties (X-ray attenuation value or proton movement) of units of tissue volume, rather than depth, so although ideally suited to measure volume changes, changes in tissue thickness are less readily calculated. Dual-energy X-ray absorptiometry (DEXA) involves less radiation exposure than CT and at a much lower cost. As the technique measures fat mass (triglycerides) and assessment of regional fat mass is subject to large error,<sup>40</sup> it is not ideally suited for the purposes of measuring facial LA.

### **Anthropometric Approaches**

In contrast to MRI, CT, and DEXA, skinfold thickness, as measured by handheld callipers, is inexpensive, widely available, and easy to use. These advantages mean that the technique is attractive for population-based studies and large-scale clinical trials. A disadvantage is that the technique cannot always distinguish between dermal and epidermal thickness and the thickness of the subcutis. Furthermore, results obtained by different observers may be difficult to compare because subtle differences in technique may translate into significant variations in measurements.<sup>41</sup> Recent research has also found significant

differences between skinfold thickness measurements according to the type of calipers used (variation of 1.8–31.0%, depending on the site of measurement;  $p < .01$ ).<sup>42</sup>

To maximize the validity of using skinfold calipers, studies should use a single, well-trained researcher to measure changes in skinfold thickness, rather than absolute values. If changes in skinfold thickness are noted, then results need to be interpreted in light of other evidence to determine whether such changes stem from alterations in subcutaneous or dermis thickness. Clearly, care should be exercised to measure the same site on each individual at each time point and with the same instrument.

### **Subjective Approaches**

As cosmetic surgery is concerned with aesthetics, and notions of beauty are largely subjective, subjective comparisons are commonly used to assess treatment success. Patient satisfaction is a large factor in determining treatment efficacy, be it for procedures such as rhinoplasty or the correction of facial LA.<sup>43</sup> Unfortunately, although various instruments have been used to assess outcomes, none has thus far achieved universal acceptance. Body-image and quality-of-life questionnaires have recently been determined to be of the greatest value in assessing aesthetic surgery outcomes, based on the feasibility, validity,

reliability, and sensitivity to change of these measures.<sup>43</sup> Indeed, quality-of-life questionnaires have been used specifically in studies that have assessed the impact of treatment to improve facial LA.<sup>5</sup> Linear analog scales are also commonly used to rate subjective experiences, such as satisfaction with appearance, and have been applied in studies that have assessed lipodystrophy.<sup>5,40</sup> Such instruments provide continuous data in contrast to discrete categories and can, therefore, measure more subtle changes in perceived severity.

The extent and/or changes in facial LA have also been assessed subjectively by comparing photographs against standardized images, which are assigned a grade of severity.<sup>31</sup> Although these subjective approaches can form quantitative evaluations of facial LA, they do not relate directly to the physical dimensions of the dermis or adipose tissue, and are therefore subject to bias. For example, self-reported HIV-related lipodystrophy has been found to be associated with a higher education level, Caucasian origin, and the use of alternative therapies.<sup>44</sup> Physicians are also subject to bias of the assessment of LA because of their existing knowledge and experience of the condition, awareness of more subtle signs of lipodystrophy, and time constraints of consultation.<sup>35</sup> Nevertheless, subjective ratings of aesthetic improvements form the core of many outcome measures

in trials of cosmetic products, as patients seek cosmetic augmentation in pursuit of psychosocial benefit,<sup>45</sup> and such benefits cannot usually be objectively quantified.

### **Summary of Different Techniques**

Objective measures of LA correction offer a different set of advantages and disadvantages. CT and MRI are the most accurate and reproducible techniques of assessing regional dermal thickness but are also the most impractical and expensive. Conversely, ultrasound is relatively inexpensive, but there is some evidence that it is not as accurate as CT scans.<sup>46</sup> At the opposite end of the spectrum, anthropometric approaches are extremely cost-effective and easy to use but are associated with significant variability related to the technique and type of caliper used.<sup>42</sup> Subjective approaches, such as the use of questionnaires, linear analog scales, and the visual assessment of photographs, do not attempt to quantify actual changes in the skin, but rather perceived changes in appearance or feelings of well-being. Although subject to bias, such methods are very cheap, do not require specialist equipment, and are of direct relevance to the patient. In routine clinical practice, such patient-focused techniques should be given utmost consideration, as it is the patient who seeks and pays for treatment.

Clearly, it would be beneficial to further refine and adapt techniques used in other areas of medicine and apply them to the measurement of dermal thickness following cosmetic procedures. Furthermore, it would be desirable to calibrate skin thickness derived from quantitative techniques to "actual" thickness, based on biopsies (and take into account the increase in thickness due to the release of pressure once the skin is removed). As a means of corroborating results, a further useful step would be to link subjective ratings of LA to actual measures of dermal thickness.

## Discussion

The need for accurate, objective assessment of the severity of facial LA is required for a number of distinct reasons. In the case of patients with HIV-associated LA, facial LA is more than a cosmetic concern, as it can have a profound impact on quality of life; patients may even stop or delay HAART as a result of the way they look.<sup>10</sup> Therefore, at-risk patients should be identified and offered strategies with which to cope with the condition, which may extend to cosmetic augmentation.

Facial rejuvenation by volumetric augmentation is not a recent development; however, in the last 10 years, refinement of medical and surgical techniques, combined with the improved quality of available products, has extended the scope of what is possible to

achieve. Nevertheless, any recommendation for cosmetic augmentation must be reinforced with sound empirical data that testify to the efficacy of treatment. This applies equally to cases of patients with HIV-related LA and to individuals seeking facial rejuvenation because of LA as a result of aging.

Without means of comparing dermal thickness before and after treatment, evaluation of the relative merits of treatment options is problematic. Objective and subjective methods of evaluating changes in LA should be viewed as complementary. While empirical data are more scientifically convincing than subjectively derived data, this does not necessarily translate into greater relevance to the patient. An improvement in dermal thickness, as measured by ultrasound, calipers, or CT scan, should ideally converge with patient-assessed satisfaction with treatment and improvements in subjective dimensions, such as self-esteem. Indeed, it has been demonstrated that objectively determined changes in dermal thickness correspond to improvements assessed by the subjective evaluation of photographs. For example, in the study by Moyle (2004), results from ultrasound evaluation indicated that injection with PLLA significantly improved dermal thickness in patients with LA. These benefits translated into more subjective improvements in facial appearance (assessed by in-

dependent investigators examining photographic images and by using a visual analog scale), and a corresponding decline in anxiety and depression scores.<sup>31</sup>

At present, studies such as these, which use a number of different techniques to evaluate changes in dermal thickness, provide the greatest insight into both perceived and actual changes in facial LA. Further investigation into the use of these techniques is warranted, along with a formal consensus of facial LA grades.

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# Evaluation of Injectable Calcium Hydroxylapatite for the Treatment of Facial Lipoatrophy Associated with Human Immunodeficiency Virus

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**OBJECTIVE** To evaluate the safety and effectiveness of soft tissue augmentation with calcium hydroxylapatite (CaHA) microspheres in an aqueous gel in patients with facial lipoatrophy (FLA) secondary to human immunodeficiency virus (HIV) disease.

**METHODS** This 12-month open-label, prospective study enrolled 30 subjects (29 men and 1 woman) with HIV-associated FLA. After the initial treatment phase (up to 2 injections, 30 days apart), patients were followed up at 3, 6, and 12 months. Patients were offered touch-up injections at 6 and 12 months. Measurements included confirmed changes in the Global Aesthetic Improvement Scale and in cheek thickness.

**RESULTS** Average initial treatment volume was 9.5 mL per patient (both sides); total volumes per patient after 12 months averaged 16.1 mL. At all time points, all patients were rated as improved or better and responded affirmatively to satisfaction questions. Cheek thickness measurements increased substantially over baseline ( $p < .001$ ). Most commonly reported adverse events were edema (93%), ecchymosis (83%), and erythema (77%).

**CONCLUSIONS** CaHA is an appropriate and well-tolerated treatment for patients with HIV-associated FLA. With an excellent safety profile, CaHA provides immediate correction of FLA and appears to provide lasting improvement in appearance.

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First described in the literature in 1998, human immunodeficiency virus (HIV)-associated lipoatrophy (LDS) occurs in HIV-positive individuals who are being treated with highly active antiretroviral therapy (HAART).<sup>1,2</sup> Peripheral lipoatrophy, central lipohypertrophy, hyperlipidemia, and insulin resistance characterize the syndrome.<sup>1-3</sup> Individuals with HIV-associated LDS typically experience loss of subcutaneous fat (lipoatrophy) in the face, arms, legs, and buttocks and fat accumulation (lipohypertrophy) in the dorsocervical neck, breasts, and trunk areas. Lipoatrophy may occur in the absence of lipohypertrophy.<sup>4</sup> These changes in body composition are thought to result from alterations in glucose and lipid metabolism brought about by the combination of protease inhibitors and nucleoside analogues.<sup>3,5</sup>

In North America, the prevalence of LDS is estimated to be 25% to 50% of HIV-infected patients receiving combined antiretroviral therapy.<sup>3</sup> Because HAART remains the regimen of choice for suppressing HIV, HIV-associated LDS is likely to continue to be a clinical challenge for those managing HIV-infected patients—and for those living with HIV. A variety of pharmacologic and nonpharmacologic approaches have been identified for managing the medical aspects of HIV LDS; these are outside the scope of this article. Our focus is the management of HIV-associated facial lipoatrophy (FLA).

The facial areas most often affected by HIV-associated lipoatrophy are the temporal and infraorbital regions and particularly the submalar

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and malar regions and nasolabial fold (NLFs).<sup>6,7</sup> The resulting facial atrophy can be severe and affect large areas, in contrast to the less-dramatic lipoatrophy associated with normal aging or ill health. Patients with HIV-associated LDS may find FLA to be particularly distressing, because it cannot be disguised with clothing or cosmetics and is, in essence, a readily identifiable “mark” of their HIV-positive status. Patients may feel marginalized or stigmatized, which in turn can lead to psychological distress, social and professional barriers, and even impaired compliance with HAART regimens.<sup>3,6</sup>

Physicians with cosmetic expertise play a role in managing some of the outward manifestations of HIV-associated LDS. Available procedures include the use of liposuction for lipohypertrophy and the use of soft tissue fillers and implants for FLA. The use of injectable silicones, autologous fat injections, collagen, hyaluronic acid products, and microsphere-based products (e.g., poly-L-lactic acid [PLLA] and calcium hydroxylapatite [CaHA]) for correction of FLA have been described in the literature.<sup>6,8–13</sup>

### Calcium Hydroxylapatite

CaHA gel (Radiesse, BioForm Medical, San Mateo, CA) is an injectable filler material composed of synthetic CaHA microspheres (30%) suspended in an aqueous carrier gel (70%). The components of CaHA, although completely synthetic, are identical to the mineral portion of bone and teeth and are therefore inherently biocompatible.<sup>14</sup> Injectable CaHA has been extensively studied *in vitro* and *in vivo* through toxicology assessments, standardized biocompatibility testing, and a 3-year animal study and has been demonstrated to be biocompatible, nontoxic, nonirritating, and nonantigenic.<sup>14</sup> Because CaHA contains no animal or human tissue derivatives, there is no need for patient sensitivity testing before use.<sup>14</sup>

When placed into soft tissue, CaHA provides immediate correction. The gel carrier is absorbed over a

few weeks, leaving behind a scaffolding of CaHA microspheres that serves as a matrix for new tissue formation and collagenesis.<sup>15</sup> The resulting implant is long lasting, and the new collagenous matrix that forms at the implant site is similar to the surrounding tissue in texture and feel.<sup>15,16</sup> The safety and mechanism of action of CaHA have been studied *in vivo* using standard light and electron microscopy techniques to evaluate punch biopsies from patients who received CaHA.<sup>16</sup> At 1 month postinjection, examination of biopsies showed scattering of CaHA microspheres at the dermal–subcutaneous junction with minimal inflammation. At 6 months, the microspheres were still present in the tissue, with evidence of new fibroelastic fibers surrounding the microspheres and no apparent migration. At neither time was there evidence of granuloma formation, ossification, or foreign body reactions. The investigators also reported that aesthetic clinical benefits remained apparent at 6 months.<sup>16</sup>

*In vivo*, the durability of correction provided by CaHA depends on multiple factors, including injection technique, site of material placement, and patient age and metabolism. In the literature, reported longevity of the aesthetic improvement with this product in the face ranges from 10 to 14 months, with an average correction of 1 year.<sup>17,18</sup> It is reasonable to assume that the motility of a particular site might affect the durability of CaHA and other fillers.

### Applications of CaHA

CaHA has been used for more than 20 years in various forms in plastic and reconstructive surgery, otology, otolaryngology, neurosurgery, orthopedic surgery, maxillofacial surgery, and dentistry.<sup>19</sup> Radiesse was previously known as Radiance FN (fine needle). In late 2006, Radiesse was approved in the United States for correction of moderate to severe facial wrinkles and folds, such as the nasolabial folds, and restoration and correction of the signs of facial fat loss (FLA) in people with HIV.<sup>6,20</sup> Radiesse HIV FL is expressly dosed and packaged for use in HIV-associated FLA.

The approval of injectable CaHA for correction of HIV-associated lipoatrophy was based on the results of a registrational trial, in which 100 patients were treated with CaHA and followed up at 3, 6, 12, and 18 months.<sup>6</sup> Patient satisfaction was rated 97% to 100% at every evaluation point over an 18-month period. Thicker cheek measurements accompanied subjective improvements in appearance.<sup>6</sup> The use of CaHA for HIV-associated FLA has also been reported elsewhere in the literature.<sup>7,13,18,21-23</sup>

By virtue of its volumizing properties and its favorable safety profile, we sought to study the safety, efficacy, and patient satisfaction levels of injectable CaHA in our population of HIV-positive patients with FLA. This article summarizes the results of our efforts with 30 patients over 12 months.

### **Design and Methods**

The present study was designed to evaluate changes in Global Aesthetic Improvement Scale (GAIS) scores and cheek thickness, as well as safety and satisfaction, in patients with HIV-associated FLA receiving CaHA treatment.

#### **Design**

From December 2004 to February 2005, a total of 30 patients (29 men and 1 woman) with HIV-associated FLA were enrolled in the prospective, open-label study. The same treating investigator administered all injections. After the initial treatment phase, patients were followed up at 3, 6, and 12 months. Patients received take-home diaries in which to record adverse events during the 2-week period after each injection.

At baseline and each follow-up visit, photographs of each patient's upper face were taken using the same standardized photographic procedures. Adverse events were also recorded. The initial treatment phase included up to 2 injections spaced 1 month apart. At the 6- and 12-month visits, touch-up treatments were administered at the physician's

discretion. No injection enhancements were performed at the 3-month visit. Effectiveness evaluations were performed at 3, 6, and 12 months. Additional follow-up is planned at 18 and 30 months.

#### **Patient Population**

Subjects were eligible for inclusion if they were HIV positive and had a CD4 count 250/mm<sup>3</sup> or greater and a viral load less than 5,000 copies/mL. Patients had to have been receiving HAART for a minimum of 3 years and have HIV-associated FLA that was at least grade 2, 3, or 4 on the Carruthers Facial Lipoatrophy Severity Scale<sup>24</sup> (Figure 1). At the enrollment visit, patients were assessed to determine whether they met the selection criteria. All patients had baseline facial cheek thickness measurements taken using a Lange Skinfold Caliper (Beta Technologies, Santa Cruz, CA) at bilateral fixed points located at the intersection of the vertical axis through the lateral canthus of the eye and the horizontal axis of the nares. Photographs were taken of their FLA.

Patients had to be aged 18 or older and sign a written informed consent. Subjects also had to understand and accept the obligation not to receive any other treatment affecting FLA throughout the 12-month follow-up and agree and be able to be present for all scheduled follow-up visits. The female patient had to have a negative urine pregnancy test and be using reliable methods of birth control. Exclusion criteria are listed in Table 1.

#### **End points**

The primary effectiveness end point was change from baseline on the GAIS with confirmation using a standard photograph at 3 months postinjection (Table 2). Secondary effectiveness end points included change from baseline GAIS for photographic confirmation at 6 months and change in cheek thickness from baseline at 3, 6, and 12 months. A blinded nonparticipating observer performed photographic assessments. The safety end point



GRADE	DESCRIPTION
1	Mild and localized facial lipoatrophy
2	Deeper and longer atrophy, with the facial muscles beginning to show through
3	Atrophic area is even deeper and wider, with the muscles clearly showing through
4	Lipoatrophy covers a wide area, extending up toward the eye sockets, and the facial skin lies directly on the muscles.

**Figure 1.** Carruthers Facial Lipoatrophy Severity Scale<sup>24</sup> Stage 1, upper left; Stage 2, upper right; Stage 3, lower left; Stage 4, lower right.

was the incidence, severity, and duration of all local and systemic adverse events recorded through 12 months.

### **Statistical Techniques**

Descriptive statistics, including measures of central tendency, were used. Appropriate statistical evaluations were performed on the primary and secondary efficacy outcomes. Data were summarized using descriptive statistics (n, mean, standard deviation, minimum, median, and maximum) for continuous variables (e.g., age) and counts and percentages for discrete variables (e.g., success vs failure for efficacy). Detailed patient line listings

were generated from case report form (CRF) data obtained during the study. SAS statistical software, version 8.02 was used for all data analyses (SAS Institute, Inc., Cary, NC). The primary dataset contained primary (derived directly from CRFs) and secondary (calculated based on the primary) end points.

### **Injection Procedure and Techniques**

Anesthesia of the treated area was achieved using a topical ointment containing 15% lidocaine and 5% prilocaine, along with infraorbital nerve block anesthesia using lidocaine with epinephrine (1:100,000) (Xylocaine, Astra-Zeneca, Wilmington, DE) in patients in whom the lipoatrophy approached the nose

**TABLE 1. Exclusion Criteria**

*Reasons For Exclusion*

- Known bleeding disorder
  - Patient had received or was anticipated to receive antiplatelets, anticoagulants, thrombolytics, vitamin E, or anti-inflammatories from 1 week pre- to 1 month postinjection
- Patient was receiving systemic or topical corticosteroids or anabolic steroids
- Other medical condition that precluded study participation or suggested an AIDS diagnosis (e.g., Kaposi sarcoma, recurrent infection, recurrent pneumonia)
- Patient had received collagen within the previous 6 months, or silicone injections, facial tissue augmentation other than collagen, grafting, or any other surgery in the cheek area at any time
- Patient had used over-the-counter wrinkle products (e.g., alpha-hydroxy acids) or prescription treatments (e.g., retinoids) within 4 weeks before the study or intended to do so during the study period
- Patient had facial hair that would preclude ability to assess facial lipoatrophy
- Patient had a history of keloid formation
- Patient was pregnant or lactating or not using a reliable form of birth control if female of child-bearing potential (a negative pregnancy test within 24 hours of injection was required)
- Patient was enrolled in an interfering study

**TABLE 2. Global Aesthetic Improvement Scale (GAIS)**

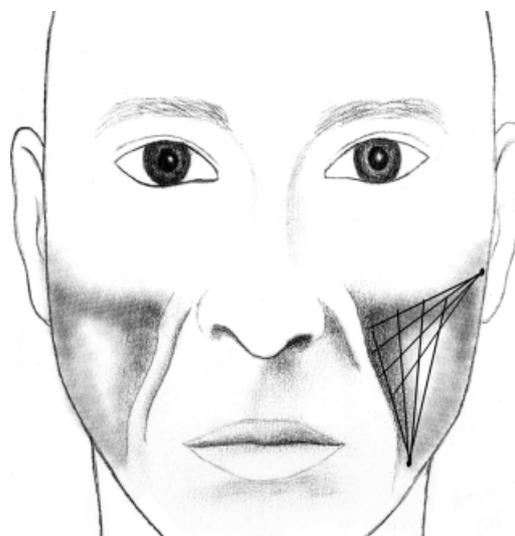
<i>Rating</i>	<i>Description</i>
Very much improved	Optimal cosmetic result for the implant in this patient
Much improved	Marked improvement in appearance from initial condition but not completely optimal for this patient; a touch-up would slightly improve the result
Improved	Obvious improvement in appearance from the initial condition, but touch-up or retreatment indicated
No change	Appearance essentially the same as the original condition
Worse	Appearance worse than the original condition

Narins R, Brandt F, Leyden J, et al. A randomized, double-blind, multicenter comparison of the efficacy and tolerability of Restylane versus Zyplast for the correction of nasolabial folds. *Dermatol Surg.* 2003;29(6).

more complete correction. The temples were not treated in this study. Average injection volumes are reported in the Results section. The injection site was massaged immediately postinjection to smooth the result and reduce lumpiness.

and lower eyelid area. A 25-gauge, 1.5 needle was used for all patients to inject the filler material.

The CaHA gel was injected into the subdermal and supramuscular planes using a linear threading technique, using as many strands as needed to provide for optimal correction (Figure 2). The majority of these individuals had little or no subcutaneous fat in the treated areas, so the subdermal and supramuscular planes coincided. If the subjacent muscle was seen to twitch during injection, indicating that the muscle was being injected, the needle was repositioned more superficially. The injecting physician did not think that any of the material was injected intradermally. Although the chief area of concern for HIV lipoatrophy patients is typically the submalar region, we find that extending correction to the malar eminence and over the zygoma may provide



**Figure 2.** Deposition of calcium hydroxylapatite for lipoatrophy associated with human immunodeficiency virus—areas of treatment in submalar region (illustration courtesy of BioForm Medical Inc).

**Post-Treatment Care**

Ice compresses and medications were used postinjection at the discretion of the treating physician to reduce bruising and swelling. For a 24-hour period after injection, patients were instructed to avoid significant movement or massage, application of makeup, and extensive sun or heat exposure.

**Results**

A total of 30 patients, 29 male and 1 female, with a mean age of 51 were enrolled and treated. Baseline patient demographic characteristics are listed in Table 3.

The initial treatment phase occurred in up to two treatment sessions. Volumes for the first session ranged from 5.2 to 17.0 mL per patient, with an average volume of 9.5 mL of CaHA per patient. For the 26 patients (87%) who received an additional injection at 1 month, the average volume was 1.5 mL CaHA per patient. A smaller number of patients (approximately 30%) received touch-ups 6 months after the initial treatment phase, with an average

volume of 2.3 mL CaHA. At 12 months, 27 patients (90%) received an average of 5.1 mL CaHA. Treatment volumes are listed in Table 4.

**Efficacy Results**

*GAIS Ratings* All patients were rated as improved or better on the GAIS at 3, 6, and 12 months. Specifically, at 3 months, 80% of patients had GAIS ratings of very much improved, and 20% were rated as much improved. At 6 months, before reinjection, 59% were rated as very much improved, 31% as much improved, and 10% as improved. At 12 months, before reinjection, 6.9% were rated very much improved, 45% much improved, and 48% improved. There were no ratings of no change or

Characteristic	Value
Age, mean	51
Male, %	97
Race, %	
American Indian	0
Asian	3
Black	0
Caucasian	97
Hispanic	0
Other	0
Fitzpatrick Score, %	
I	10
II	73
III	17
IV	0
V	0
Baseline Facial Lipoatrophy Severity Scale grade, %	
2	47
3	53

Patient	Initial	1 month	6 months	12 months	Total
LA-4-001	8.9	1.6	4	–	14.1
LA-4-002	9.1	1.5	–	–	10.6
LA-4-003	6.9	1.6	1	1.3	10.8
LA-4-004	08.0	1/0	–	5.2	14.2
LA-4-005	5.2	–	–	2.6	7.8
LA-4-006	7.4	1.0	–	10.5	18.9
LA-4-007	7.7	2.0	–	6.5	16.2
LA-4-008	7.0	1.0	–	5.2	13.2
LA-4-009	7.0	–	–	2.6	9.6
LA-4-010	7.2	1.0	–	3.9	12.1
LA-4-011	6.8	1.9	–	1.3	10.0
LA-4-012	14.0	–	–	2.6	16.6
LA-4-013	11.0	1.0	4	7.8	23.8
LA-4-014	6.0	0.7	–	6.5	13.2
LA-4-015	14.0	2.0	2	4.7	22.7
LA-4-016	11.0	2.0	–	4.7	17.7
LA-4-017	17.0	3.0	5	9.1	34.1
LA-4-018	13.0	2.4	–	7.8	23.2
LA-4-019	11.5	0.7	–	–	12.2
LA-4-020	14.0	1.7	–	6.5	22.2
LA-4-021	5.7	–	–	2.6	8.3
LA-4-022	14.0	1.0	–	7.5	22.5
LA-4-023	10.0	2.6	–	5.2	17.8
LA-4-024	11.3	1.0	2	5.2	19.5
LA-4-025	9.0	2.0	1	2.6	14.6
LA-4-026	10.9	3.0	–	7.8	21.7
LA-4-027	10.0	1.5	–	6.9	18.4
LA-4-028	9.0	0.4	–	2.6	12.0
LA-4-029	5.7	1.7	2	2.6	12.0
LA-4-030	7.7	0.5	1	5.2	14.4
Average	9.5	1.5	2.3	5.1	16.1

**TABLE 5. Global Aesthetic Improvement Scale Score**

	3 Months	6 Months	12 Months
	n (%)		
Very much improved	24 (80.0)	17 (58.7)	2 (6.9)
Much improved	6 (20.0)	9 (31.0)	13 (44.8)
Improved	0 (0)	3 (10.3)	14 (48.3)
No change	0 (0)	0 (0)	0 (0)
Worse	0 (0)	0 (0)	0 (0)

worse at any point during the 12-month study period.

GAIS ratings are shown in Table 5.

**Mean Cheek Thickness** Mean cheek thickness measurements followed a similar pattern and are shown in Table 6. At baseline, average cheek thickness was 5.3 mm on the right and left sides. At 3 months, cheek thickness increased to an average of 10.6 mm (right) and 10.3 mm (left). At 6 months, average cheek thickness remained at 10.3 mm (right) and 10.0 mm (left). At 12 months, average cheek thickness remained greater than at baseline, at 8.8 mm (right) and 8.7 mm (left). At all 3 time points,

changes from baseline were highly statistically significant ( $p < .001$ ).

**Patient Satisfaction**

Patients involved in the study completed a survey to determine their level of satisfaction with their treatment results. Questions asked are shown in Figure 3. At the 3 time points measured (3, 6, and 12 months), 100% of patients reported satisfaction on all patient satisfaction measures.

Representative results are shown in the before and after photographs in Figures 4 through 7.

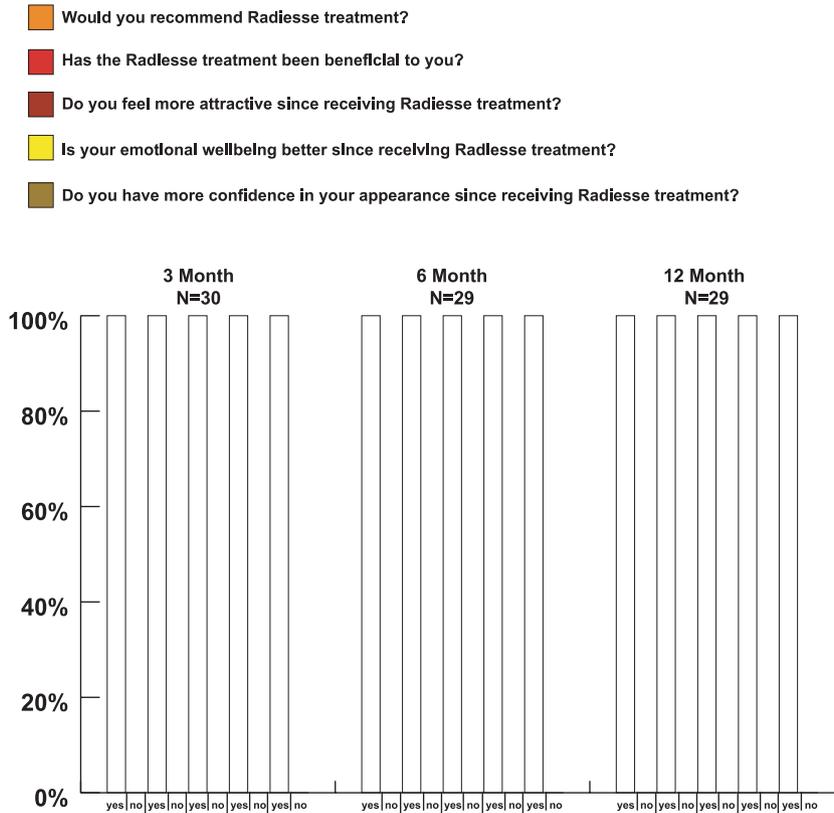
**Adverse Events**

All adverse events reported through 12-month follow-up were recorded. Surveillance for adverse events included, but was not limited to, the use of 2-week diaries given to patients after any injection, 72-hour phone calls to patients, and 1-month safety visits after any injection and adverse events observed by patients or research staff at any other time during the investigation. Generally, adverse events were mild or moderate in severity and resolved without

**TABLE 6. Cheek Thickness Evaluation at Baseline and 3, 6, and 12 Months**

	Baseline N = 30	3 Months N = 30		6 Months N = 29		12 Months N = 29	
	mm	mm	Change from Baseline	mm	Change from Baseline	mm	Change from Baseline
<b>Left side</b>							
Mean ± SD	5.3 ± 0.9	10.3 ± 1.7	5.0 ± 2.0	10.0 ± 1.7	4.7 ± 1.7	8.7 ± 1.5	3.6 ± 1.6
Minimum	4.0	7.3	1.3	7.0	1.0	6.3	0.0
Maximum	7.3	15.0	9.7	14.7	9.3	12.0	6.0
P-value		<.001		<.001		<.001	
<b>Right side</b>							
Mean ± SD	5.3 ± 0.9	10.6 ± 2.1	5.3 ± 2.5	10.3 ± 1.9	5.0 ± 2.0	8.8 ± 1.6	3.4 ± 1.4
Minimum	4.0	6.3	0.7	7.3	1.3	6.0	1.3
Maximum	7.0	16.3	12.0	15.3	9.3	12.0	6.7
P-value		<.001		<.001		<.001	
<b>Both sides (combined)</b>							
Mean ± SD	5.3 ± 0.8	10.5 ± 1.8	5.2 ± 2.1	10.1 ± 1.6	4.8 ± 1.7	8.8 ± 1.5	3.5 ± 1.3
Minimum	4.0	7.5	1.0	7.8	1.3	6.5	1.0
Maximum	7.2	14.8	9.8	13.8	8.7	12.0	6.0
P-value		<.001		<.001		<.001	

SD = standard deviation.



**Figure 3.** Patient satisfaction questionnaire and results.

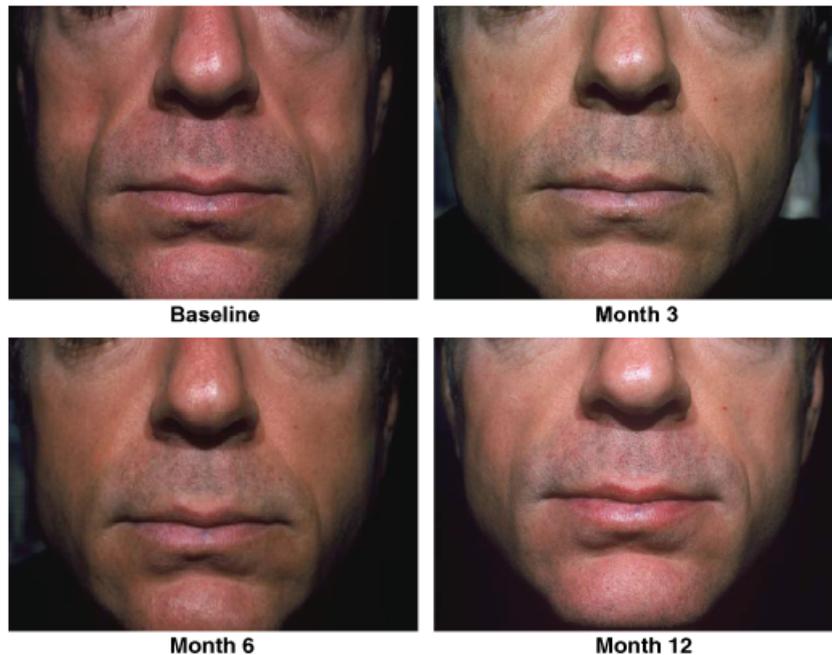
treatment (Table 7). The most commonly reported adverse events were edema (93%), ecchymosis (83%), and erythema (77%). In nearly all cases, edema, ecchymosis, and erythema were rated as mild or moderate, and no treatment was necessary. For most patients, pain occurring during the procedure resolved within 3 minutes. Some patients reported mild postprocedure discomfort at the injection site, but this discomfort resolved in a few days and did not require treatment. There was one incident of lumpiness (i.e., minor irregularities in contour) requiring treatment with triamcinolone 10 mg/mL (Kenalog, Bristol-Myers Squibb, New York, NY). There were no reports of nodules and no granulomas.

**Discussion**

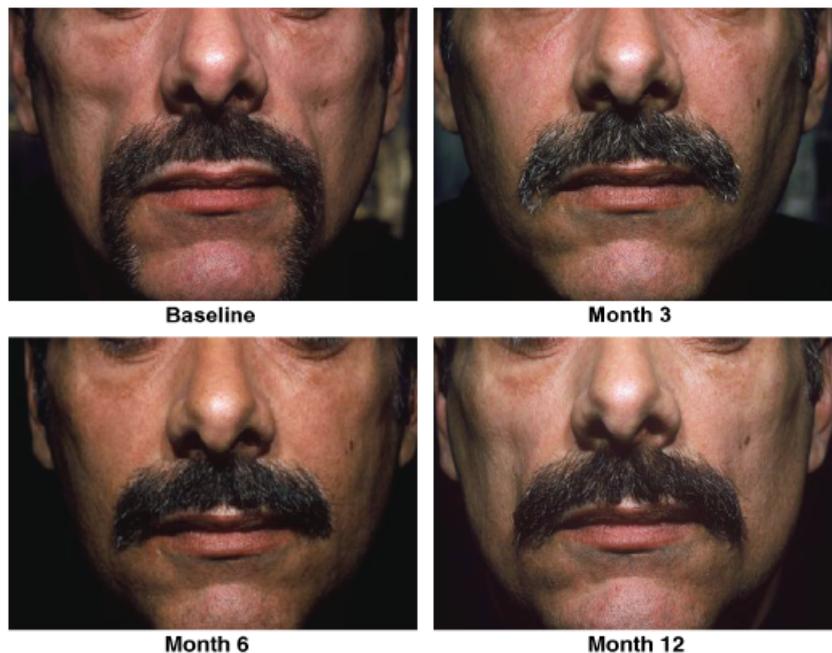
Patients with HIV-associated FLA tend to have different needs from those seeking facial augmentation to correct volume loss associated with normal

aging. Specifically, HIV-associated FLA tends to occur in a specific and recognizable pattern, may affect large areas, and may be particularly severe. For this reason, an injectable filler with volumizing properties may be necessary to achieve the desired degree of correction. Furthermore, because of the medical needs and immune status of the HIV-positive population, good biocompatibility and low immunogenicity are also desirable attributes.

Injectable CaHA was shown to provide robust correction of HIV-associated lipoatrophy in all of the patients enrolled in our study. These patients were overwhelmingly male, and nearly all had Grade 2 or 3 FLA, as judged using the Carruthers Facial Lipoatrophy Severity Scale. Improvements were demonstrated in objective and subjective parameters. Our study showed excellent patient satisfaction results and highly statistically significant changes in cheek thickness from baseline. Other studies with Radiesse



**Figure 4.** A 47-year-old man before and 3, 6, and 12 months after the injection of calcium hydroxylapatite (CaHA) for correction of lipoatrophy associated with human immunodeficiency virus. Initial injection volume at baseline and 1-month touch-up was 8.4 mL of CaHA. No injections were given at 3 and 6 months. An additional 10.5 mL of CaHA was injected at 12 months after the photographs were taken. (Total injection volume over 12 months was 18.9 mL of CaHA.) The patient's Carruthers severity grade was 2 at baseline; Carruthers severity grades were not calculated post-treatment.



**Figure 5.** A 51-year-old man before and at 3, 6, and 12 months after the injection of calcium hydroxylapatite (CaHA) for correction of lipoatrophy associated with human immunodeficiency virus. Initial injection volume at baseline and 1-month touch up was 8.0 mL CaHA. No injections were given at 3 months or 6 months. An additional 5.2 mL was injected at 12 months after the photographs were taken. (Total injection volume over 12 months was 13.2 mL CaHA.) The patient's Carruthers severity grade was 2 at baseline; Carruthers severity grades were not calculated post-treatment.



**Figure 6.** A 70-year-old man before and at 3, 6, and 12 months after the injection of calcium hydroxylapatite (CaHA) for correction of lipatrophy associated with human immunodeficiency virus. Initial injection volume at baseline and 1-month touch up was 16.0 mL of CaHA. No injections were given at 3 months. An additional 2.0 mL and 4.7 mL of CaHA was injected at 6 and 12 months, respectively after the photographs were taken. (Total injection volume over 12 months was 22.7 mL of CaHA.) The patient's Carruthers severity grade was 3 at baseline; Carruthers severity grades were not calculated posttreatment.



**Figure 7.** A 51-year-old man before and at 3, 6, and 12 months after the injection of calcium hydroxylapatite (CaHA) for correction of lipatrophy associated with human immunodeficiency virus. Initial injection volume at baseline and 1-month touch up was 15.0 mL. No injections were made at 3 or 6 months. An additional 7.5 mL of CaHA was given at 12 months after the photographs were taken. (Total injection volume over 12 months was 22.5 mL of CaHA.) The patient's Carruthers severity grade was 2 at baseline; Carruthers severity grades were not calculated post-treatment.

**TABLE 7. Adverse Events through 6 Months**

Event	Patients with event n (%)	Maximum Severity			Duration, days, mean (Range)
		Mild	Moderate	Severe	
Allergic reaction	0 (0)	0 (0)	0 (0)	0 (0)	NA
Ecchymosis	25 (83)	11 (44)	13 (52)	1 (4)	7.9 (1–26)
Edema	28 (93)	10 (36)	16 (57)	2 (7)	6.4 (1–18)
Embolization	0 (0)	0 (0)	0 (0)	0 (0)	NA
Erosion	0 (0)	0 (0)	0 (0)	0 (0)	NA
Erythema	23 (77)	15 (65)	8 (35)	0 (0)	2.8 (1–13)
Extrusion	0 (0)	0 (0)	0 (0)	0 (0)	NA
Granuloma	0 (0)	0 (0)	0 (0)	0 (0)	NA
Hematoma	0 (0)	0 (0)	0 (0)	0 (0)	NA
Infection	0 (0)	0 (0)	0 (0)	0 (0)	NA
Necrosis	0 (0)	0 (0)	0 (0)	0 (0)	NA
Needle jam	1(3)	1 (100)	0 (0)	0 (0)	NA
Nodule	0 (0)	0 (0)	0 (0)	0 (0)	NA
Pain	10 (33)	6 (60)	3 (30)	1 (10)	3.1 (1–18)
Pruritus	6 (20)	5 (83)	1 (17)	0 (0)	6.4 (3–9)
Other	13 (43)	8 (62)	5 (38)	0 (0)	15.8 (4–28)

in patients with HIV-associated lipoatrophy have also reported high degrees of patient satisfaction and improvements in cheek thickness.<sup>6,13</sup>

Patients received up to 2 injections in the initial treatment phase spaced 1 month apart and touch-up treatments at the 6- and 12-month visits as indicated. Re-injection was performed if, in the opinion of the patient and the injecting physician, further injection would produce improvement in the appearance of the treated areas. Re-injection criteria were biased in favor of the subject (i.e., more correction) especially at the 12-month visit, when it was not anticipated that many of the subjects would receive any further injections under the study protocol.

Injection volumes in our study were higher than those reported by Silvers and colleagues. For example, in our study, the average volume injected through 6 months was 13.3 mL, compared with 8.4 mL,<sup>6</sup> although patients in our study generally had higher GAIS ratings in the same period. At 3 months, 80% of patients in our study were rated as very much improved, compared with 26% in Silvers; at 6 months, nearly 59% of patients in our study

were rated as very much improved, compared with 7%. Changes from baseline cheek thickness were also greater in our study at 3 and 6 months. Although limited by being 6-month data only, these results suggest a possible relationship between higher injection volumes and better outcomes that warrants further study. We plan to see and follow up these patients at 18 and 30 months.

We also found injectable CaHA to be safe for this patient population. The most common adverse events (ecchymosis, erythema, and edema, as well as pain at the injection site) are consistent with those reported when CaHA is administered in the general population and are similar to those reported with other soft tissue fillers.<sup>25</sup> In general, the adverse events were mild in nature and short in duration and did not require treatment. One case of “lumpiness” was successfully treated with triamcinolone acetate injection. Lumpiness should be distinguished from granulomas and nodules. There were no cases of nodule or granuloma formation in our study. There was also a single incident of needle jam, which occurred when the operator bent the needle intentionally during administration. After the operator’s

injection technique was adjusted, there were no further reports of needle jamming.

Another question that has emerged is whether CaHA, which is radiopaque, might confound or impede interpretation of X-rays. Previously, this question was examined in a radiographic study of patients who were treated with CaHA for HIV-associated FLA or correction of nasolabial folds. This study found that there are no overt radiographic safety concerns with CaHA and that its appearance on computed tomographic scans is distinct from surrounding bony tissues and does not interfere with normal analysis.<sup>26</sup> This study also provided evidence that CaHA particles do not migrate and remain localized at the injection site.

A number of fillers have been studied for HIV-associated FLA. These include autologous fat, poly-L-lactic acid (PLLA; Sculptra, Dermik, Berwyn, PA), and liquid injectable silicone. The fact that subcutaneous lipoatrophy may also occur in the abdominal and buttock area, which are typically used as donor sites, may limit the use of autologous fat for HIV-associated FLA. The durability of transferred fat may also be variable. When used for HIV-associated FLA, PLLA may require several treatments, spaced at 2-week intervals. In a 12-month study of PLLA in 99 patients with HIV-associated FLA, the mean increase in skin thickness was 4.0 mm at 6 months and 4.2 mm at 12 months.<sup>27</sup> Forty-three percent of patients in this study received a total of 6 injections during the 12-month study period. The most frequent adverse events observed in this study were bruising (30.3%), swelling (17.2%), and papule formation (13.1%). Bruising and swelling resolved within days, although for some patients, papules persisted throughout the study period.<sup>27</sup> Papule formation may depend on technique, occurring when PLLA is injected above the subdermal space.<sup>28</sup> Injectable liquid silicone (Silikon 1000; Alcon, Fort Worth, TX) has also been studied as a more-durable option for HIV-associated FLA. When used for this purpose, injectable silicone should be administered via a serial puncture microdroplet

technique, with injections only into the subdermal plane or deeper, to minimize the risk of nodule formation and inflammatory reactions. Injection of large volumes at once increases the risk for migration along tissue planes; therefore, injection of limited volumes at monthly intervals is recommended. The number of sessions required depends on the patient's stage on the Carruthers scale.<sup>29</sup> The use of hyaluronic acid-based fillers for HIV-associated FLA has also been reported, although the large volumes required for these agents and their limited duration may be constraining factors.<sup>30,31</sup> Of nonpermanent fillers, we find that Radiesse's ability to provide immediate, full correction in a single session, its safety record, and its durability relative to shorter-lived fillers such as hyaluronic acid distinguish it.

Because of the large volumes of CaHA needed for correction of FLA, cost may be a concern for some patients. In recognition of this concern, BioForm Medical, the manufacturer of Radiesse, has developed a Patient Access Program designed to increase access to Radiesse for eligible patients, although the need for large volumes of filler is not unique to CaHA and is reflective of the severe, extensive FLA associated with HIV and its treatment.

## Conclusion

Based on our experience, Radiesse safely and effectively ameliorates the appearance of FLA in patients with HIV-associated FLA. We believe that CaHA offers a viable alternative to other volume fillers for this treatment population.

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## COMMENTARY

The three most common injectable fillers employed for HIV associated facial lipoatrophy are polylactic acid (PLA), calcium hydroxylapatite (CaHA), and liquid injectable silicone (LIS). Currently, only PLA (Sculptra<sup>™</sup>) and CaHA (Radiesse<sup>™</sup>) are specifically FDA-approved for HIV facial lipoatrophy, while LIS, which is permanent filler, is available off-label. Unfortunately, none of these products have been compared

to one another in head to head clinical trials, which confounds attempts to understand which product may be superior in terms of efficacy, safety and durability. In addition, the majority of efficacy trials on PLA and CaHA, including FDA “pivotal” trials, have utilized differing efficacy endpoints such as change in mean skin thickness using ultrasound or skin calipers, photographic documentation of global improvement, or psychological questionnaires.<sup>1-3</sup> While these studies on PLA and CaHA have shown post-treatment improvement on all of these end-points, treatment often falls short of optimal correction, which in this study by the Carruthers is defined as “very much improved” on GAIS scale (where a touch up is not required). Patients often seek and demand optimal correction, which may be difficult to achieve to in patients with HIV facial lipoatrophy, as volume “requirements” may be immense. This study on HIV facial lipoatrophy by the Carruthers was identical in design to the study with CaHA by Silvers et al.<sup>3</sup> However, the efficacy endpoints were substantially different in the Carruthers’ study with 80% of patients achieving the top GAIS score of “very much improved” at 3 months and 59% at 6 months, compared with only 26% at 3 months and 7% at 6 months in the Silvers’ study. The only variable that differed between the two studies was that a mean cumulative volume was 13.4 mL of CaHa had been injected in the Carruther’s study compared to only 8.4 mL in the Silver’s study. It is interesting that the only other study which has outlined volume requirements of injectable filler to achieve optimal correction of HIV facial lipoatrophy is a 2004 study with LIS, which suggests that on average 3 treatments (2 mL of LIS per treatment) are required for each stage of facial lipoatrophy on the Carruther’s Facial Lipoatrophy Severity Scale.<sup>4</sup> For grades 2 or 3 lipoatrophy, one would therefore expect volume requirements of 12 to 18 mL, which is in line with the volume requirements of CaHA required in the Carruthers study to reach optimal correction. For PLA, only a 2007 study outlines the average product amount needed to achieve optimal correction, which was on average 8.44 vials of PLA over 4.6 injections.<sup>5</sup> Large amounts of PLA to achieve improvement of HIV facial lipoatrophy have also been documented by Mest and Humble.<sup>1</sup>

The most important point of these studies is that the amount of product to achieve optimal correction of HIV facial lipoatrophy is quite high, as can be the associated cost. It is imperative that the physician be able to correctly estimate the treatment volume of a particular filler for a specific patient with HIV facial lipoatrophy prior to treatment, and communicate this in the consultation visit. If the volume is underestimated, the patient will often be dissatisfied with a less than optimal correction. In the author’s experience, the most cost effective, durable and cosmetically elegant corrections are obtained with LIS, which has shown a favorable safety profile and superior patient satisfaction over 5 years in this population. However, for patients who are uncomfortable receiving permanent filler or who want instant correction, Radiesse is a logical option as long as appropriate volumes are employed.

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# Retreatment with Injectable Poly-L-Lactic Acid for HIV-Associated Facial Lipoatrophy: 24-Month Extension of the Blue Pacific Study

DOUGLAS R. MEST, MD, AND GAIL M. HUMBLE, MD

**BACKGROUND** Facial lipoatrophy occurs in HIV-positive patients taking highly active antiretroviral therapy and during natural aging. Injectable poly-L-lactic acid (PLLA) is a device approved internationally for restoration and correction of the signs of HIV-associated facial lipoatrophy.

**OBJECTIVE** To evaluate the long-term safety, duration of effect, and satisfaction with serial injections of PLLA for HIV-associated facial lipoatrophy.

**METHODS AND MATERIALS** In this single-site, open-label, retreatment study, 65 HIV-positive patients were treated with injectable PLLA every 5 weeks (until optimal recorection). Presenting degree of lipoatrophy based on the James scale (1=mild, 4=severe) was reviewed. Skin thickness was measured at fixed points with calipers. Patients completed a post-retreatment satisfaction questionnaire.

**RESULTS** Nearly 10% of patients had persistent correction >36 months, based on patient report. Approximately 50% required three or fewer retreatments to maintain satisfactory correction (determined by patient and physician). Milder lipoatrophy on initial presentation required fewer retreatments and had more sustained correction. Time to first retreatment varied according to James scale score: 1 (21.4 months) and 4 (13.0 months). The mean patient satisfaction score was 4.9 (1 = dissatisfied, 5 = very satisfied) at study end. No serious adverse events were reported.

**CONCLUSION** Injectable PLLA is a safe and effective long-term treatment option for HIV-associated lipoatrophy.

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Facial contouring has become an important means of combating the potentially devastating effects of HIV-associated lipodystrophy syndrome associated with highly active antiretroviral therapy (HAART). Facial lipoatrophy can be a physically and emotionally disturbing consequence of HIV-associated lipodystrophy syndrome.<sup>1</sup> Patients experiencing facial lipoatrophy report low self-esteem, depression, and stopping their HAART to avoid fat wasting and its psychosocial consequences.<sup>1-7</sup> There are numerous approaches to facial contouring, including surgery and autologous fat transfer, as well as minimally invasive procedures, such as the use of the injectable devices calcium hydroxylapatite and poly-L-lactic acid (PLLA).

Injectable PLLA is a device approved in Europe and the United States for the treatment of HIV-related facial lipoatrophy. PLLA is a biodegradable, biocompatible, immunologically inert polymer of non-animal origin, eliminating the need for pretreatment allergy testing.<sup>8</sup> Although the exact mode of operation is not fully understood, research has demonstrated that PLLA injections lead to the production of a fibrous-tissue response that persists over time.<sup>8</sup> Tissue augmentation with injectable PLLA affords results that are clinically comparable with those obtained through fat grafting, although the results with injectable PLLA are more consistent and longer lasting, and the treatment itself is far less involved.<sup>9</sup>

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The facial contour improvements resulting from treatment with injectable PLLA have been shown to alleviate the emotional ramifications of facial wasting associated with HAART and to improve the quality of life for people who are HIV positive.<sup>9,10</sup> Clinical trials in patients with HIV-associated facial lipoatrophy have demonstrated that initial treatment with injectable PLLA results in significant and prolonged increases in skin thickness and is associated with high patient satisfaction. The open-label VEGA study demonstrated significant correction of facial lipoatrophy as early as week 6 after treatment initiation with PLLA injections. This correction increased progressively through week 48 and was sustained at week 96.<sup>11</sup> Burgess and Quiroga demonstrated that multiple treatments with injectable PLLA over a 5-month period led to substantial and sustained improvements in dermal thickening in 61 HIV-infected male patients.<sup>1</sup> A similar study by Cattelan and colleagues also demonstrated high efficacy, safety, and patient satisfaction rates in 50 HIV-infected patients receiving between four and six PLLA injections or sessions over a 3-month period.<sup>12</sup> The patients in this study reported statistically significant improvements from baseline in their self-perception of well-being as a result of the treatments.<sup>12</sup>

The long-term psychological effects of injectable PLLA in the management of HIV-associated facial lipoatrophy were recently demonstrated in a follow-up study that used visual analog scales to record patient satisfaction approximately 2 years after initial participation in an open-label, single-center study.<sup>2</sup> Results from the original study demonstrated improvements in patient self-perception, anxiety, and depression after treatment with injectable PLLA that persisted and increased through the recall visit.<sup>2,10</sup>

We previously reported the results of the single-center, open-label Blue Pacific study in which 97 patients (95 men, 2 women) with HIV-associated facial lipoatrophy received up to six treatment sessions of injectable PLLA.<sup>13</sup> Most patients (65 of 97)

**TABLE 1. James Facial Lipoatrophy Severity Scale<sup>1,18</sup>**

<i>Description</i>	
Grade 1	Mild and localized facial lipoatrophy.
Grade 2	Deeper and longer atrophy, with the facial muscles beginning to show through.
Grade 3	Atrophic area is even deeper and wider, with the muscles clearly showing.
Grade 4	Lipoatrophy covers a wide area, extending up toward the eye sockets, and the facial skin lies directly on the muscles.

Table 1 reproduced with permission from Burgess CM et al. *J Am Acad Dermatol*, 2005.

had James scale scores of moderate (3) to severe (4) (Table 1). Of the 97 patients, 75 returned for measurement at month 12 and therefore were eligible for inclusion in the data analysis regarding the efficacy on skin thickness. All patients experienced an increase in skin thickness (a mean increase of 65.1% from baseline through the end of treatment); the skin thickness continued to increase post-treatment and was maintained at 73% at the month-12, treatment-free, follow-up visit. At all time points, the increases in skin thickness were statistically significant ( $p < .001$ ). At the conclusion of the 12-month, treatment-free follow-up, patients who completed the study were eligible for retreatment as participants in a 24-month injectable PLLA retreatment (extension) study. This report describes the results of this retreatment study.

## Methods and Materials

### Study Objectives

The primary objective of the study was to continue the evaluation of the safety and quantifiable improvement in facial wasting (lipoatrophy) and duration of effect (after serial deep dermal or subcutaneous injections) of PLLA. Secondary objectives focused on the evaluation of the long-term acceptance of injectable PLLA as a treatment option for HIV-associated facial lipoatrophy.

### ***Informed Consent***

The study was conducted in compliance with the Western Institutional Review Board and informed consent regulations set forth in the U.S. Code of Federal Regulations (CFR) 21, Part 56, and CFR 21, Part 50. This study was conducted according to International Conference on Harmonization standards of Good Clinical Practice guidelines and in agreement with the latest revision of the Declaration of Helsinki, as well as applicable local regulations.

### ***Patient Selection***

Patients were eligible for inclusion in the retreatment study if they had completed the Blue Pacific study (completed on-site measurement at the month-12, end-of-study, follow-up visit), had HIV-associated facial lipoatrophy with clinically significant facial wasting after previous treatment with injectable PLLA in the Blue Pacific study, and desired maintenance of facial correction. All patients were willing to participate in the study, as supported by signed, written informed consent. Inclusion and exclusion criteria for patients in the original Blue Pacific study have been described in detail previously.<sup>13</sup>

### ***Study Design***

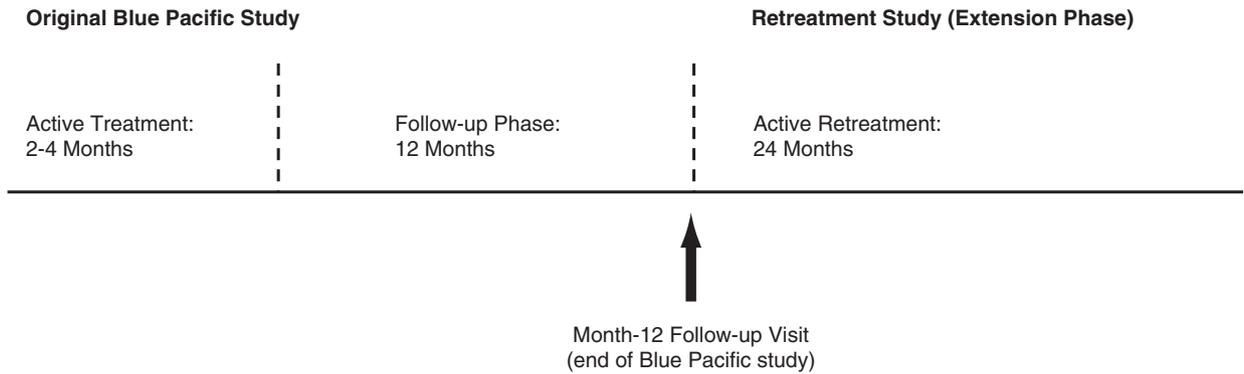
This was a single-site, open-label, 24-month retreatment study initiated after the 12-month, treatment-free, follow-up phase of the Blue Pacific study. The design for the initial Blue Pacific study has been described elsewhere.<sup>13</sup> Based on the design of this study, all eligible patients had a screening evaluation on day 1 of their retreatment phase that included a clinical evaluation, with history and limited physical examination, facial digital photography, and an initial caliper skin-thickness measurement. The original, presenting degree of facial lipoatrophy according to the James scale (1 = mild, 4 = severe) was recorded. A study intake questionnaire was completed before retreatment and included the following clinical data: time from last treatment completion, patient weight, recent weight change, viral load and T-cell counts (within the prior 2 months),

concurrent anabolic steroid use, concurrent recreational drug use, and current medications.

One of the two study investigators administered each treatment. Injectable PLLA was reconstituted with 5 mL of sterile water for injection 2 hours before injection, as described in the package insert, and was injected into target treatment areas in the deep dermal or subcutaneous layer. A total of 1 to 10 mL of the product was given using a cross-fanning injection technique; using a 25-gauge 1.5-inch needle, 0.1- to 0.2-mL threads of PLLA were placed per injection in a retrograde manner. Similar injections were then placed at approximately 90° to the original injections in the treatment areas. This technique differs from that described in the prescribing information.<sup>14</sup> No more than 10 mL of reconstituted product was injected at any single treatment session. Patients were treated at 5-week intervals (maximum deviation of 10 days) until full correction was obtained. Patients could receive a maximum of 12 treatment sessions over the 24-month study period if the treating physician and the patient mutually agreed on the need (Figure 1).

Caliper skin thickness was measured, and serial digital photographs were taken before each subsequent treatment session to assess the continued efficacy of injectable PLLA. Baseline caliper skin thickness for each patient was determined at bilateral fixed points located at the intersection of the vertical axis through the lateral canthus of the eye and the horizontal axis of the nares. While seated, patients were photographed using an anterior-posterior and lateral-oblique technique at a distance of 3 feet. Digital photographs were also taken in case of an adverse event.

Before their first retreatment session, patients were asked to complete a questionnaire in which they ranked the relative importance of the following factors with respect to desire for retreatment: social, sexual, employment, self-worth, and cost of treatment. At each retreatment session, patients were asked to rate their satisfaction with the overall



**Figure 1.** Study design.

treatment on a scale of 1 to 5 (5 = very satisfied). Patients were contacted by telephone within 48 to 72 hours after each treatment session to monitor for any adverse events. The investigator recorded all events on the case report form. Treatment was stopped in the case of local skin reaction, infection, patient intolerance, or patient request.

**Results**

**Study Population**

Seventy-five patients completed the month-12 follow-up visit in the original Blue Pacific study and were eligible for inclusion in the retreatment study. Of those 75 patients, 65 (63 male and 2 female) required retreatment and consented to participate in the retreatment study (Table 2). Of the 10 eligible patients who did not enter the retreatment study, nine continued to have persistent correction after 36 months and did not require retreatment during the extension phase, and one was treated at 30 months by his local physician. The mean age of the patients was 45.9 (range 34–66), 85% of the patients were white, and 97% were male. The patients had been HIV positive for a mean of 14.7 years (range 3–23 years) and had been taking antiretroviral therapy for a mean of 10.4 years (range 3–23 years).

**Retreatment Outcomes**

Table 3 demonstrates the study results according to severity of original (presenting) facial lipoatrophy by

the James scale: 1 ( $n = 8$ ), 2 ( $n = 11$ ), 3 ( $n = 32$ ), and 4 ( $n = 14$ ). The time to first retreatment varied according to the original James scale score: 1 (21.4 months), 2 (15.7 months), 3 (14.0 months), and 4 (13.0 months). Patients with mild (James scale score 1) facial lipoatrophy had a mean of 1.9 retreatments, whereas those with moderate to severe facial lipoatrophy required more retreatments; for James scale score 2, 3, and 4, the mean number of retreatments were 3.4, 4.4, and 4.8, respectively. Approximately 50% of patients ( $n = 34$ ) required three or fewer retreatment sessions to maintain satisfactory correction as determined by patient and physician.

**TABLE 2. Distribution of Age, Sex, and Race (N 65)**

Demographic measures	Value
Age, mean (range)	45.9 (34–66)
Sex, $n$ (%)	
Male	63 (97)
Female	2 (3)
Race, $n$ (%)	
White	55 (84.6)
Black	3 (4.6)
Hispanic	6 (9.2)
Other	1 (1.5)
Number of years with HIV, mean (range)	14.7 (3.0–23.0)
Number of years taking antiretrovirals, mean (range)	10.4 (3.0–23.0)

**TABLE 3. Distribution of Treatments and Retreatments**

<i>Original James scale classification</i>	1 (n = 8)	2 (n = 11)	3 (n = 32)	4 (n = 14)
Mean number of treatments in original Blue Pacific study	3.3	4.3	5.2	5.5
Mean skin thickness change before first retreatment (mm)	+ 0.2	0	0.3	+ 0.3 <sup>†</sup>
Mean time to first retreatment (months)	21.4	15.7	14.0	13.0
Mean number of retreatments over the 24-month study	1.9	3.4	4.4	4.8

Change from end of treatment in the Blue Pacific study to time of first retreatment. <sup>†</sup>Includes one patient who presented for initial retreatment with areas of overcorrection and irregular growth. Exclusion of this patient yielded 0.2 mm.

Figure 2 depicts a patient with mild lipoatrophy who underwent his first retreatment at month 36 after his initial treatment series. Figure 3 depicts a patient with more severe lipoatrophy (James scale score 3) who had a total of four retreatments over the course of the follow-up study. In both patients, end-of-treatment photos in the original study were taken 3 weeks after the final treatment (per protocol), although a longer time interval may allow better assessment of the continued augmentation that has been observed after treatment with injectable PLLA.

The mean skin thickness change before first retreatment generally varied according to presenting James scale score: 1 (+ 0.2 mm), 2 (0), and 3 (- 0.3). The mean increase (+ 0.3) in skin thickness observed in patients with severe facial lipoatrophy (James scale score 4) was solely attributed to areas of overgrowth in one patient, which skewed the results. Mean change for all other patients with James scale scores of 4, excluding this patient, was 0.2 mm.

### **Patient Satisfaction**

Patient satisfaction with retreatment was extremely high. The mean satisfaction score after the first retreatment, recorded at the 5-week follow-up visit, was 5.0 (1 = dissatisfied, 5 = very satisfied). At the conclusion of the retreatment study, the mean satisfaction score was maintained at 4.9.

### **Adverse Events**

There were no serious adverse events, and none of the patients discontinued the study because of an adverse event. Most patients experienced localized injection-site swelling for a few days that was related

to underlying treatment technique. All but one of the small (<3 mm) papules that formed during the original study had resolved by the end of the retreatment study. In addition, in five (7.7%) of the 65 patients, a total of five new, small (<3 mm), non-visible papules were reported, all occurring within 2 to 7 months after retreatment. Four resolved spontaneously; one patient elected surgical excision of an infraorbital papule that was resistant to conservative treatment measures (including needle desiccation and dilution and treatment with intralesional 5-fluorouracil/steroid injection). Another patient presented at retreatment with areas of relative overcorrection. This patient had severe lipoatrophy (James scale score of 4) in the original study; the overgrowth was believed to be secondary to an overaggressive original treatment dosage per area. The patient responded to treatment that was administered in adjacent areas of the face to minimize the contour irregularities.

### **Discussion**

The results of this 24-month retreatment study demonstrate that retreatment with injectable PLLA was effective and well tolerated, with most patients requiring 1 to 4 retreatments to maintain correction of HIV-associated facial lipoatrophy. Patients with milder facial lipoatrophy (James scale score 1–2) on initial presentation (before any treatment) required fewer retreatment sessions and had more sustained correction.

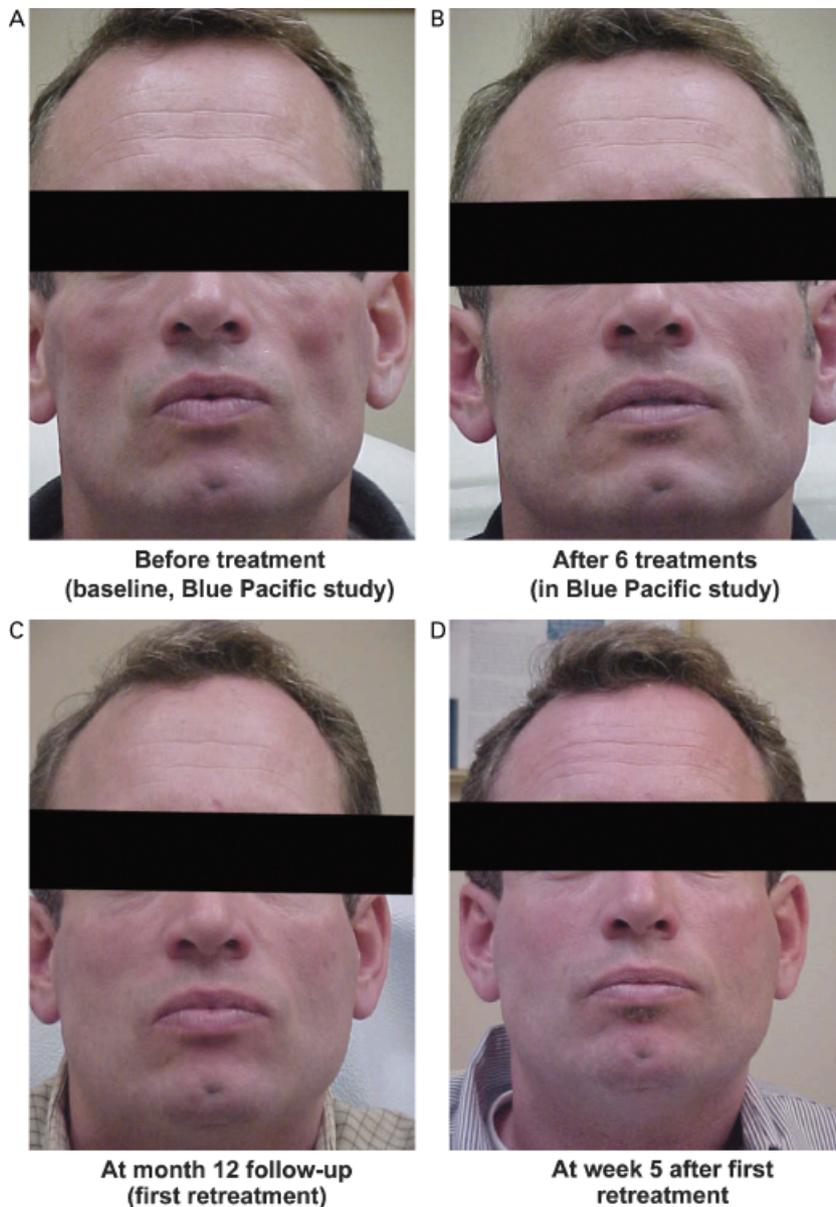
There was a low incidence (7.7%) of small (<3 mm) non-visible papules in this retreatment period, which was less than that observed in the original study



**Figure 2.** Representative patient with mild lipoatrophy (James scale score 1). First retreatment (to temples and buccal fat pad areas) was administered at the completion of the retreatment study (month 36). Labels (A) to (D) indicate progression of photographs.

period (13.1%). The incidence reported in other studies varies from less than 5% to greater than 40%.<sup>1,2,11,14</sup> Higher incidence rates may reflect study design differences; the authors of the Chelsea and Westminster and VEGA studies specifically searched and palpated for papules, which may have contributed to the relatively higher incidence than in other studies, such as ours, that relied on patient reports. Although the mechanism underlying papule

formation is not completely understood, product preparation and injection techniques may be contributing factors. Increasing the dilution time to a minimum of 2 hours and preferably to longer than 24 hours, increasing the dilution volume to 5 mL, and using postprocedure massage have been recommended to minimize adverse events.<sup>9,15</sup> In the retreatment study, we increased the dilution volume from 3 mL, used in the original study, to 5 mL.



**Figure 3.** Representative patient with more severe lipoatrophy (James scale score 3). Four retreatments (to the temples, buccal fat pad, and perizygomatic areas) were administered during the retreatment study. Labels (A) to (D) indicate progression of photographs.

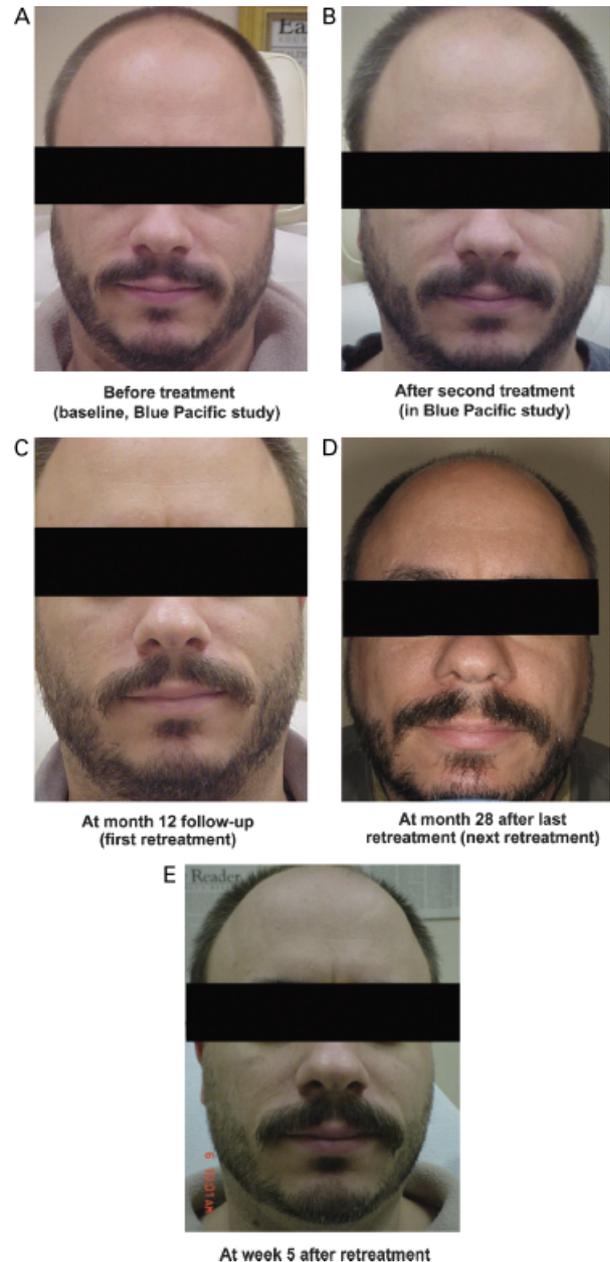
At our clinic, we increased the time interval between reconstitution to administration from 30 minutes in the original study to the manufacturer-recommended 2 hours in the retreatment study.<sup>14</sup> In addition, patients received postinjection massage in the retreatment study but not during the original study. Finally, the clinicians who performed the injections were far more experienced with the injection technique by the time of the retreatment phase. The treatment interval

in the retreatment study was comparatively longer than in the original trial (5 weeks vs 3 weeks) and also may have been an important factor in reducing adverse reactions that may result from overtreatment.<sup>15</sup> Lengthening the interval between injections from 3 to 5 weeks may have allowed the investigators and patients to more accurately determine the need for additional treatments. Our collective experience supports that it is essential to wait and assess a

patient after treatment with injectable PLLA, because the effect is gradual, and the patient may respond well to smaller amounts of product. Use of excess product may lead to overcorrection in the future. It is also important to note that 12 of the 13 papules reported in the original Blue Pacific study<sup>13</sup> resolved spontaneously over the 36-month combined study period. This observation is encouraging in that the vast majority of papules appear to be self-limiting.

The absence of a prespecified threshold to determine the need for retreatment limited the study design. This may have contributed to the large number of patients (36 of 75) opting to have their first retreatment at the time of their month-12 on-site follow-up from the original Blue Pacific study. These patients were already at the study site, were eligible for retreatment, and may have elected to undergo retreatment with the goal of maintaining correction rather than waiting for a decrease in the degree of correction before retreatment. In addition, the study protocol did not limit treatment to areas previously treated. A few patients did not *objectively* require retreatment because they had the same or greater caliper measurements but requested treatment mainly in areas not previously treated in the Blue Pacific study; because they were undergoing treatment, they also requested retreatment in areas previously treated for fear of loss of correction (Figure 4). Consequently, an exact answer to the rate of loss of correction over time is not possible from this study, although we feel that the data provide a clinical picture of when and how many retreatments are required for various patients with HIV-associated facial lipotrophy included in this study.

This study was a continuation study of the Blue Pacific study. The manufacturer provided all study material, and patients paid a reduced injection fee. Although 12 treatments was the maximum available to each patient, only three patients with the most severe facial wasting at the start of the Blue Pacific study required all 12 treatments. The majority of patients required or asked for four treatments or less



**Figure 4.** Representative patient who received injectable poly-L-lactic acid at month 12 mainly in previously untreated areas. During the Blue Pacific study, treatment was in the buccal fat pad and perizygomatic areas, but at month 12 follow-up, he mainly needed treatment in the nasolabial folds and lower cheeks (but also received retreatment in the originally treated areas); at month 28 after last retreatment, he received treatment in the infraorbital, lower face, nasolabial folds, and buccal fat pad areas. Labels (A) to (D) indicate progression of photographs.

over a period of 24 months. In general, in the authors' experience, non-HIV patients require significantly fewer total treatments, including

retreatments, than HIV-positive patients. Therefore, direct cost comparisons for other patient populations are not possible based on the results of this study.

This was an investigator-initiated trial conducted in a small, non-university-based clinic office. As such, we did not have access to other, validated means of objectively measuring efficacy, such as cutaneous ultrasound<sup>11</sup> or three-dimensional photography.<sup>16</sup> The use of skin calipers during the initial efficacy trial led us to continue using this measurement throughout the retreatment (extension) study. Nevertheless, the photographic and patient satisfaction data were all consistent with the skin-caliper measurements in support of the beneficial effects of injectable PLLA over the duration of the retreatment study. Furthermore, although potential bias might have been avoided by having one individual perform the skin-caliper measurements and another perform the injections, using the same individual to consistently obtain his or her own patient's measurements ensured inpatient consistency in measurement technique.

Nine of the 10 eligible patients who did not enroll in the retreatment study reported persistent correction (> 36 months) when contacted over the telephone for assessment of adverse events, and the additional patient was treated privately at month 30. The study protocol did not require patients to return to the study site for final measurement. Because these patients were not measured physically, their data could not be included in the quantitative final results, but their continued correction and satisfaction would only tend to further support the longevity of results with injectable PLLA. In fact, according to patient report, approximately 10% of the patients who took part in the original Blue Pacific study had more than 36 months of persistent satisfaction and, therefore, presumed sustained correction. Finally, the demographics of this trial (heavily weighted to white men) is similar to the demographics reported in other studies of HIV-associated facial lipoatrophy.<sup>1,10,11</sup> A 5-year manufacturer-sponsored registry study is currently underway to better elucidate response to

injectable PLLA and the rate of side effects in women and people of color.

In conclusion, injectable PLLA was shown to be a safe and effective long-term treatment option for HIV-associated facial lipoatrophy. The results may not be completely generalizable to a non-HIV-infected population because host response may partially affect treatment outcome.<sup>17</sup> Patients with milder facial lipoatrophy required fewer injections and had more sustained correction than those with severe facial lipoatrophy. All patients receiving treatment of facial lipoatrophy with injectable PLLA were highly satisfied with the results of the therapy.

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February 16, 2009

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*Submitted Electronically*

**Re:** Reconstructive Treatments for Facial Lipodystrophy Syndrome

To Whom It May Concern:

The American Society of Plastic Surgeons (ASPS) is the largest association of plastic surgeons in the world, representing surgeons certified by the American Board of Plastic Surgery. Plastic surgeons provide highly skilled surgical services that improve both the functional capacity and quality of life of patients. These services include the treatment of congenital deformities, burn injuries, traumatic injuries, and cancer. ASPS promotes the highest quality patient care, professional, and ethical standards and supports education, research and public service activities of plastic surgeons.

As such, the ASPS recommends the use of the following definitions for cosmetic and reconstructive surgery, adopted by the American Medical Association: “**Cosmetic** surgery is performed to reshape normal structures of the body in order to improve the patient's appearance and self esteem.

**Reconstructive** surgery is performed on abnormal structures of the body, caused by congenital defects, developmental abnormalities, trauma, infection, tumors, or disease. It is generally performed to improve function, but may also be done to approximate a normal appearance.” With that said, ASPS believes that facial lipodystrophy syndrome is a cosmetic side effect of a medication used for the treatment of Human Immunodeficiency Virus (HIV), and the injection of fillers do not result in a functional improvement.

We appreciate your consideration. Should you have any questions please contact Jenny Jackson, ASPS Health Policy Associate, Department of Health Policy and Advocacy, by email at [jjackson@plasticsurgery.org](mailto:jjackson@plasticsurgery.org) or phone at (800) 283-9600 ext. 312.

Sincerely,

Scott Oates, MD, F.A.C.S.  
Chair, ASPS Coding and Payment Policy Committee