Comparison of Poly-L-lactic Acid and Calcium Hydroxylapatite for Treating Human Immunodeficiency Virus–Associated Facial Lipoatrophy

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Human immunodeficiency virus (HIV)–associated lipodystrophy syndrome is a condition that may affect patients with HIV infection. It is characterized by both metabolic disturbances and changes in distribution of adipose tissue, including lipoatrophy of the face. Poly-L-lactic acid and calcium hydroxylapatite are commonly used, long-lasting, nonpermanent fillers that are approved by the US Food and Drug Administration to treat facial lipoatrophy. This article reviews the current literature on, and compares the use of, these products in HIV-associated facial lipoatrophy. Both poly-L-lactic acid and calcium hydroxylapatite appear to be safe and effective for treating HIV-associated facial lipoatrophy, and both are viable treatment options.

Human immunodeficiency virus (HIV)–associated lipodystrophy syndrome is a condition that may affect patients with HIV infection, especially those taking highly active antiretroviral therapy. First described in 1998, the syndrome is characterized by hyperlipidemia, insulin resistance, and lipodystrophy.[1] The lipodystrophy manifests as lipoatrophy of the face, arms, legs, and buttocks and lipohypertrophy of the abdominal viscera, breasts, and dorsocervical neck (buffalo hump). Patients with the syndrome may have different combinations of these conditions with varying degrees of severity.[2]

The etiology of HIV-associated lipodystrophy has been studied extensively and has been linked to the use of protease inhibitors[1,3,4] and nucleoside reverse transcriptase inhibitors,[5] with synergy from the combination of the antiretroviral classes.[4] In addition, drug-independent risk factors such as disease length and severity have also been linked to expression of the syndrome.[6] A study by Miller et al[7] found that approximately half of patients on highly active antiretroviral therapy met the criteria for lipodystrophy. It also affects patients with HIV infection who are not on antiretroviral therapy, though less commonly.[8]

Although HIV-associated lipodystrophy syndrome has several manifestations, the most distressing to the patient is often facial lipoatrophy, which patients feel stigmatizes them. In addition, quality of life has been shown to be worse in patients with lipoatrophy,[9,10] and fear of developing the syndrome may lead to medication noncompliance.[11]

Several medical therapies have attempted to reduce or reverse lipodystrophy. Interventions include administering insulin-sensitizing diabetic agents in the thiazolidinedione class,[12-17] modifying or switching antiretroviral therapies,[18-22] and using hormonal therapy.[23-26] Treatments thus far have been ineffective or only marginally

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effective, prompting patients to seek reconstructive therapy options.

Several reconstructive options are available to treat facial lipoatrophy in patients with HIV-associated lipodystrophy syndrome. These include surgical device implantation,[27-30] autologous fat transfer,[31,32] and injectable fillers.[33,34] Injectable fillers can be classified as temporary, such as collagen, cadaveric dermal tissue, and hyaluronic acid (lasting ≈3–24 months); semipermanent, including poly-L-lactic acid (PLLA) and calcium hydroxylapatite (CaHA) (lasting 1–2 years); and permanent, such as liquid injectable silicone (lasting several years).

This article will compare 2 semipermanent fillers: CaHA and PLLA. Both are approved by the US Food and Drug Administration (FDA) for soft tissue filling and volume augmentation and are used in the treatment of HIV-associated facial lipoatrophy.

POLY-L-LACTIC ACID

PLLA is a soft tissue filler approved by the FDA for treating HIV-associated facial lipoatrophy.[35] Its FDA approval came in August 2004, but it is not new to medicine, as it has been used safely for the past 30 years in sutures, reconstructive surgery pins, screws, soft tissue implants, and other medical devices.[36] In addition, its use in cosmetic applications has been prevalent outside the United States since 1999, when it was approved in the European Union for restoring volume to depressed areas, including scars, creases, wrinkles, and folds.[37] In February 2004, the European indication for large-volume application of PLLA was added, allowing practitioners to address facial lipoatrophy. PLLA has been used in an estimated 150,000 people in more than 30 countries for facial volume and contour deficiencies.[37]

PLLA is biodegradable and biocompatible, derived from corn dextrose fermentation. One vial contains 90 mg sodium carboxymethylcellulose, 150 mg freeze-dried PLLA powder, and 127.5 mg pyrogen-free mannitol, to which sterile water (usually 3–5 mL) is added preinjection. Different amounts of liquid may be added to dilute the solution; using larger amounts may decrease the frequency of adverse reactions. Because PLLA is composed of heavy, crystalline-shaped particles, bioresorption occurs slowly over 18 months.[35] PLLA has been shown to last for up to 2 years postinjection.[36] It is metabolized via the lactate pathway but does not cause a change of total body lactate. Metabolism is completed by macrophage-mediated conversion of lactate to carbon dioxide, which is expelled through respiration.[35,36] The result immediately postinjection is a soft tissue enhancement that lasts a few days before a return to baseline. This is followed by a more delayed effect visible for approximately 2 months postinjection.[38] The net filling effect of atrophic areas is thought to be from neocollagenesis that is stimulated by a foreign-body reaction, which is balanced by the slow metabolism of PLLA, leaving new type I collagen in facial defects.[36,37]

Multiple clinical trials have been conducted to analyze the efficacy, safety, and durability of PLLA for treating HIV-associated facial lipoatrophy (Table 1). In all studies, patient and physician satisfaction were high. Several objective measures have also been used to quantify the results.

The Chelsea and Westminster study analyzed 30 patients over 24 weeks who underwent 3 injection sessions of PLLA every 2 weeks.[39] Half the patients received delayed treatment 12 weeks after the immediate treatment group, thus serving as an initial control. As expected, patients had a significant ($P<.001$) increase in skin thickness only after PLLA administration, supporting the idea that the increased volume was from the PLLA injections. A Hospital Anxiety and Depression Scale was administered and showed that PLLA treatment decreased depression and anxiety.[39] In their long-term safety and efficacy follow-up, the authors concluded that the physical and psychological benefits of PLLA treatment may be sustained for up to 18 months or longer. [40]

The APEX002 study involved 99 patients who underwent 1 to 6 injection sessions every 4 to 6 weeks.[41] Patient and investigator satisfaction, as well as patient rating of lipoatrophy, showed positive results that were sustained 12 months posttreatment. Adverse reactions included subcutaneous papules in 6 patients. In another single-center study, Burgess and Quiroga[38] showed successful results in 61 patients with HIV infection who underwent an average of 3 injection sessions every 3 to 6 weeks. At the 6-month follow-up, all patients reported an excellent response, and the improvement was sustained an average of 18 months. The beneficial effects lasted up to 2 years in 5 patients, and no serious adverse reactions were recorded.

The VEGA open-label pilot study used ultrasound to measure changes in cutaneous thickness and a visual analog scale to assess changes in quality of life in 50 patients with an initial median facial fat thickness of 0 mm. The patients underwent a total of 4 injections every 2 weeks for 6 weeks.[42] An additional injection was given at week 6 if the transcutaneous thickness was less than 8 mm. Results showed improved quality of life in all patients treated and a statistically significant ($P<.001$) increase in skin thickness from baseline at all monitoring points, including week 96. Thus, the primary end point of transcutaneous thickness greater than 10 mm at 24 weeks was met by 41% of patients; at 96 weeks, 43% of patients met this end point. Twenty-two patients developed palpable subcutaneous nodules, which resolved in 6 patients by week 96.

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Table 1

Summary of Major Studies With Poly-L-lactic Acid Treatment

	Chelsea and Westminster[39]	APEX002[41]	Burgess and Quiroga[38]	VEGA[42]	Lafaurie et al[43]	Blue Pacific Aesthetic Medical Group[45]
Patients, n	30	99	61	50	94	99
Treatments	3 injection sessions every 2 wk	1–6 injection sessions every 4–6 wk	Average of 3 injection sessions every 3–6 wk	4 injection sessions every 2 wk	Median of 5 injection sessions every 2 wk	1–6 injection sessions every 3 wk
Reconstitution volume	3 mL (2 mL sterile saline, 1 mL lidocaine)	3–4 mL	4–6 mL	3–4 mL	4 mL (3 mL sterile saline, 1 mL lidocaine)	3 mL
Primary findings	Statistically significant increased visual analog scale; patient-perceived increase in skin thickness at 24 wk posttreatment	Significantly improved patient satisfaction sustained at 6 and 12 mo posttreatment	At 6 mo, 100% of patients reported an excellent response	Significantly improved total cutaneous thickness at 6, 24, 48, 72, and 96 wk (ultrasound)	Statistically significant increase in visual analog scale (0–10, where 0=total dissatisfaction and 10=total satisfaction) of patients' perception of lipoatrophy: 3.4 at baseline to 6.8 at the end of treatment (average, 2.3 mo) and 7 at last follow-up	Increased mean skin thickness by 68.8% and 73% at 6 and 12 mo, respectively, posttreatment (skin calipers)
Additional findings			37 (60%) patients had significant increase in dermal thickness at 6 mo; 9 (14%) at 18 mo; 5 (8%) at ≥2 y	Average cheek thickness increased 6.8 mm at 96 wk	Median skin thickness increased to 2.3 mm at last follow-up (3-dimensional photography)	All patients who completed the study said they would recommend the treatment
Patients with subcutaneous nodules, n (%)	9 (31)	6 (6)	2 (3.2)	22 (44)	12 (13)	13 (13.1)

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Other studies have also looked at the objective change in skin thickness posttreatment with PLLA. Lafaurie et al[43] studied 94 patients with HIV infection who received a median of 5 treatments every 2 weeks. They found that mean dermal thickness increased by 2.3 mm at a median of 6 months after the last treatment. As for adverse reactions, 1 patient experienced an anaphylactic reaction with generalized edema and macular rash, and 12 patients developed asymptomatic subcutaneous nodules at the injection site. Another study of 26 patients with HIV-associated facial lipoatrophy who were injected with PLLA found a 196% increase in dermal thickness measured by ultrasound at 24 weeks after 4 treatments.[44]

The first US formal prospective study of patients with HIV-associated facial lipoatrophy treated with PLLA was conducted by the Blue Pacific Aesthetic Medical Group, which enrolled 99 patients between July 2002 and August 2003.[45] In this single-site, open-label study, patients received 1 to 6 treatments of PLLA every 3 weeks. A typical session involved injection of 6 mL PLLA (2 vials, each reconstituted with 3 mL sterile water). Ninety-seven patients completed the treatment series. Mean change in skin thickness, measured by calipers, increased by 68.8% at 6 months and 73% at 12 months after the last treatment. In addition, mean physician satisfaction, with overall correction, was 4.8 out of 5 (1=dissatisfied, 5=satisfied) at the 12-month follow-up.[45] Of the 76 and 54 patients who completed the 6-month and 12-month follow-ups, respectively, 100% said they would recommend this treatment to a friend.

Adverse reactions to PLLA are generally mild and without visible consequence. However, small subcutaneous papules, generally less than 5 mm, have been reported by the authors of the Chelsea and Westminster,[39,40] APEX002,[41] VEGA,[42] and Blue Pacific Aesthetic Medical Group[45] studies, as well as by Jones,[33] Burgess et al,[38] Lafaurie et al,[43] Bauer,[46] and Vleggaar.[47] These papules are thought to result from uneven dermal dispersion of injected PLLA leading to patchy overstimulation of fibroblasts. The Blue Pacific Aesthetic Medical Group study, which used 3-mL concentrated injections, reported a 13.1% rate of papule formation, with most appearing between 3 and 4 months after the initial treatment.[45] Seven of the 13 papules resolved within 6 months. Other studies have reported 3% to 44% incidences.[38,39,42,43,45] This wide variance might be attributed to injection technique, as the study resulting in the highest incidence used a more concentrated injection of 3 mL. Studies with a lower incidence of papules have reported that a more diluted mixture of 5 mL may allow a more even distribution of product and greater dispersion throughout atrophic areas. Most nodules are reported as not bothersome and are not visibly apparent.[40]

More common adverse reactions reported by multiple authors relate to injections in general and include bruising, discomfort, erythema, inflammation, and infection.[38,39,42,43,45] These reactions were localized to the injected tissue. No change in lactate or serum transaminase levels have been shown with PLLA injections, nor have viral-load or CD4-count changes been reported.[41]

In summary, PLLA is an FDA-approved treatment for HIV-associated facial lipoatrophy that has been proven to be efficacious in many clinical trials and has a well-understood safety profile. Although adverse reactions, such as subcutaneous papule formation, are not uncommon, they tend to be mild and without visible consequence.[46] Although the filling effects are not immediate, they are long-lasting. High patient satisfaction, along with decreased depression and anxiety scores, show that PLLA injections have positive effects for patients with HIV-associated facial lipoatrophy.

CALCIUM HYDROXYLAPATITE

An FDA-approved dermal filler consisting of 30% CaHA microspheres in a 70% carrier gel made up of sodium carboxymethylcellulose is commercially available. The long-lasting biomaterial in the filler is CaHA, a synthetic form of a substance found in bones and teeth. CaHA has been used in a variety of forms in dentistry and reconstructive and orthopedic surgery for many years.[48] After the material is injected into the deep dermis, the CaHA particles remain at the injection site and slowly degrade via enzymatic breakdown.[49] In addition, collagen formation occurs around the microspheres, prolonging the correction.[50] As this material is a normal component of our bones, it is nonimmunogenic, and granuloma formation has not been reported.[50] Furthermore, it should not ossify if correctly placed out of contact with bone. Although patients should be informed that CaHA is radio-opaque and visible on X-rays, it has not been shown to interfere with imaging.

CaHA was granted FDA approval in December 2006 for treating moderate to severe facial wrinkles and folds and for restoring volume lost as a result of HIV-associated facial lipoatrophy.[51] CaHA had previously been approved by the FDA for treating vocal cord insufficiency and oral and maxillofacial defects and also for radiographic tissue marking. Before the new indication, it had been used off label for treating rhytides and for facial soft tissue augmentation. CaHA has also been approved in Europe for aesthetic use. It creates an immediate augmentation that generally lasts 1 to 2 years.[52,53] Overall, CaHA has an excellent safety record, with the exception of a small but significant number of patients reporting nodule formation when the product was injected into the body of the lips.[52-54]

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HIV-Associated Facial Lipoatrophy

An open-label study was published in 2006 evaluating the safety and efficacy of CaHA for facial soft tissue augmentation in patients with HIV-associated facial lipoatrophy.[55] A total of 100 patients participated in this multicenter study. Patients received an initial injection and were permitted touch-ups at 1 month, 6 months, and 18 months if deemed necessary by the treating physician. Patients were evaluated by several criteria, and the primary end point was evaluation of the correction of facial lipoatrophy at 3 months by comparing changes from baseline on the 5-point Global Aesthetic Improvement Scale (GAIS) (1=highest, 5=lowest).

In the trial, all patients were rated as improved or better at 3 months, with 72% much improved (GAIS 2) and 26% very much improved (GAIS 1). Most patients (78%) did receive touch-ups at 1 month and 6 months, albeit with much smaller amounts injected than at their initial treatment. At the 18-month follow-up (1 year after the last CaHA injection), 91% of the patients reported they were still improved or better compared with baseline (S.L. Silvers, J.A. Eviatar, M.I. Echavez, unpublished data, 2006). In addition, cheek thickness was shown to have increased substantially (mean: baseline, 4.8 mm; 3 months, 7.65 mm; 6 months, 7.3 mm; 12 months, 6.95 mm).[55] Patient satisfaction was assessed at 12 and 18 months, with 99% of patients reporting that they would recommend treatment with CaHA. Adverse reactions were mostly of short duration and included ecchymoses, edema, and pain. Of note, no granulomas, nodules, necrosis, infections, or hematomas were reported. Table 2 summarizes this trial.

A small case series of patients with HIV-associated facial lipoatrophy by Comite et al[56] reported 75% to 90% improvement following the initial treatment with CaHA and significant persistence at follow-up 6 to 9 months later. No adverse reactions were reported.

In a larger study, Jansen and Graivier[53] treated 609 HIV-negative patients for facial soft tissue augmentation, including the lips, nasolabial folds, and cheeks. Patient satisfaction was then assessed by questionnaires. The majority of patients (77%) responding to the questionnaire said that they were still satisfied with their results between 12 and 24 months after the initial treatment, and they estimated that a mean of 57% of the filler still remained present. Adverse reactions were mostly minimal and included edema, temporary pain, and bruising. Nodule formation was not reported except when the product was injected in or around the lips (12.4%, lip mucosa; 3.7%, radial lip lines).[53] The majority of lip nodules responded positively to steroid injections or massage.

Multiple studies in HIV-negative patients have shown that CaHA is safe and effective for soft tissue augmentation. Sklar and White[48] studied CaHA in 64 consecutive patients undergoing aesthetic soft tissue augmentation. The authors treated 8 areas of the face, including nasolabial folds, the tear trough area, the lips, and the infraoral region. Patient and physician satisfaction was high. Notably, however, the authors no longer use CaHA in the lips because of nodularity that developed in 3 of 15 patients treated in this area. A study of 90 patients undergoing soft tissue augmentation with CaHA reported similar satisfaction and improvement at the 6-month follow-up.[57] One author retrospectively reviewed his patients' charts for soft tissue augmentation and found CaHA to be cost effective and long lived for isolated nasolabial fold and glabellar rejuvenation.[58]

Other studies confirm the high patient and physician satisfaction with CaHA. Roy et al[59] treated 82 HIV-negative patients in the melolabial folds, upper and lower lips, infracommissural folds, and chin-lip crease, with

TABLE 2

Calcium Hydroxylapatite Treatment in HIV-Associated Facial Lipoatrophy[55]*

No. of Patients	Treatments	Amount Injected	Primary Findings	Additional Findings	Patients With Subcutaneous Nodules, n (%)
100	Majority with 3 injection sessions	Mean of 8.4 mL over 3 sessions	All patients improved at 3 and 6 mo, using the GAIS	Mean skin thickness increased by 45% at 6 mo	0 (0)

*GAIS indicates Global Aesthetic Improvement Scale; HIV, human immunodeficiency virus.

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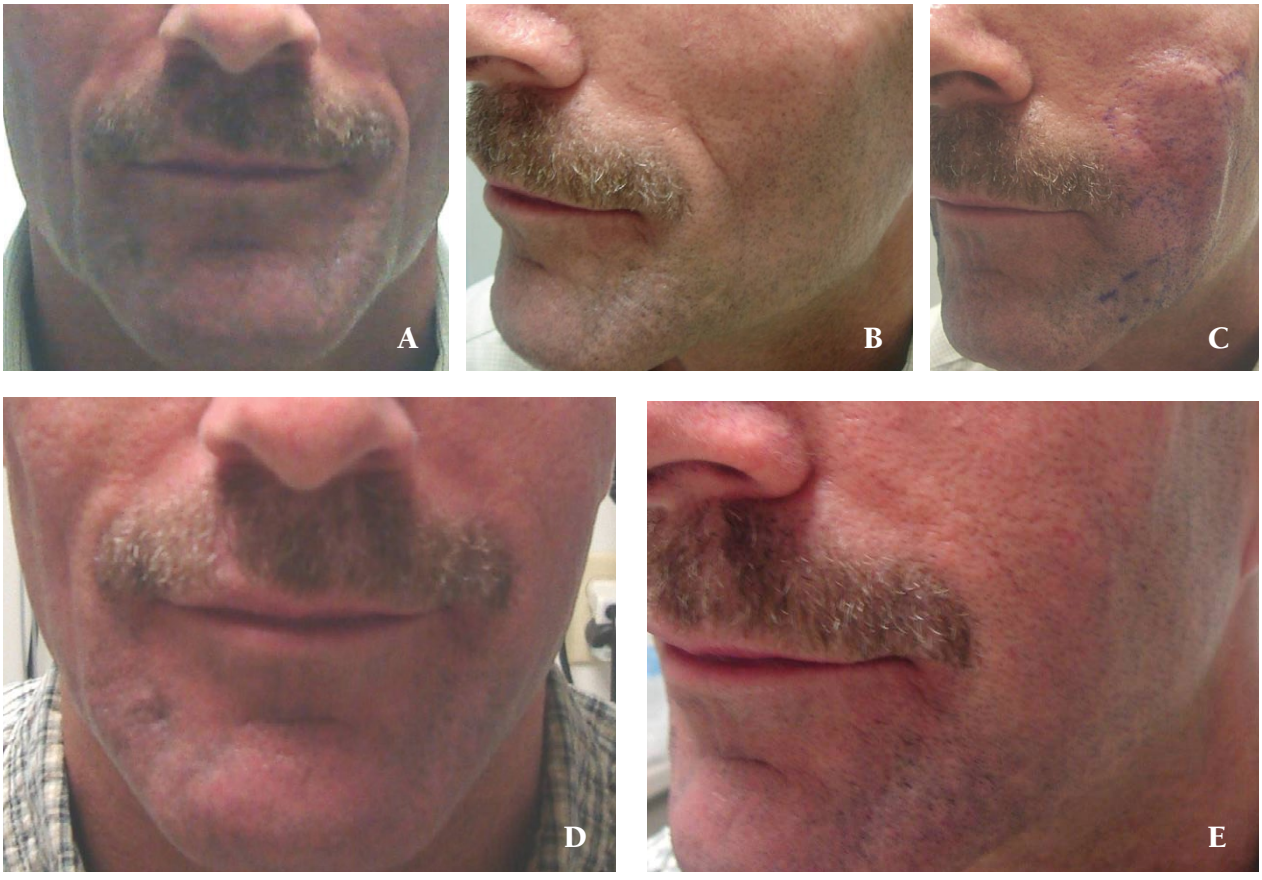

Patient with human immunodeficiency virus–associated facial lipoatrophy before (A, B), immediately after (C), and 3 weeks after (D, E) injection of 2.9 mL of calcium hydroxylapatite in the right cheek and 1.9 mL of calcium hydroxylapatite in the left cheek.

follow-ups at 3 and 6 months. The 6 patients who developed lip nodules had prior lip augmentation procedures and were successfully treated with excision or intralesional corticosteroids. A study by Godin et al[60] investigated the use of CaHA with Restylane® for facial augmentation. Patients treated with CaHA reported high overall satisfaction (7.6 out of 10, where 1=very poor and 10=excellent), whereas patients treated with both products reported an even higher (but not statistically significant) satisfaction score. Cuevas et al[61] also demonstrated a high rate of complete patient and physician satisfaction in their series of patients 1 year after facial augmentation with CaHA. Additional uses for CaHA have included correction of minor nasal irregularities[62] and correction of defects along the perichondrium of the ears and nose from skin cancer surgery.[63]

CaHA is a biologically inert, semipermanent filler that appears to be safe and effective for soft tissue augmentation, including the treatment of HIV-associated facial lipoatrophy. Its biggest strength is that it provides both immediate and long-lasting effects with few injections. In addition, no granulomas or nodules have been reported when the product is injected in areas other than the lips. CaHA is now FDA approved for treating HIV-associated facial lipoatrophy and certainly appears to be a safe treatment option with high patient and physician satisfaction sustained at 1 to 2 years. The Figure depicts a patient who received CaHA treatment for HIV-associated facial lipoatrophy.

COMMENT

Both PLLA and CaHA are biodegradable, biocompatible, long-lasting, nonpermanent fillers that have been shown to be effective for treating HIV-associated facial lipoatrophy. Neither product requires allergy testing. When used in patients with HIV-associated facial lipoatrophy, PLLA and CaHA both require multiple treatments, with an average of 3 to 5 injection sessions for PLLA and 3 sessions for CaHA. Both PLLA and CaHA have an immediate filling effect related to the amount injected plus additional edema and hemorrhage. After the edema and hemorrhage resolve in approximately 1 week, patients who receive CaHA will retain volume from the effects of the product in combination with the carrier gel. However, patients who receive PLLA will usually return to baseline or close to it 1 week postinjection, and the increase in volume will occur slowly secondary to the body's reaction to PLLA. The volume enhancement from

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Table 3

Comparison of Poly-L-lactic Acid and Calcium Hydroxylapatite*

	Poly-L-lactic Acid	Calcium Hydroxylapatite
Packaging	Vial requiring reconstitution (must let stand ≥2 h before use)	Prefilled 1.3-mL syringes
Injection site	Deep dermis/subdermis	Deep dermis/subdermis
FDA status	2004 approval for HIV-associated facial lipoatrophy	2006 approval for HIV-associated facial lipoatrophy
Average treatments, n	3–5	3
Onset	≈2 mo postinjection	Immediate
Durability	12–24 mo	12–18 mo
Adverse reactions	Nodule formation in 3%–44%; local effects (ecchymoses, pain)	Local effects (ecchymoses, pain)
Cost per unit	$480	$295
Estimated cost of treatment	$3840 (4 treatments)	$2065 (3 treatments)

*FDA indicates US Food and Drug Administration; HIV, human immunodeficiency virus.

neocollagenesis usually becomes apparent 2 months posttreatment. Although CaHA appears to maintain filling effects 12 or more months posttreatment series, PLLA may last slightly longer. Longer-term data collection on CaHA treatment for HIV-associated facial lipoatrophy are under way. Table 3 compares PLLA with CaHA.

Comparing the effectiveness of the 2 products is challenging without a head-to-head study. Most studies that have examined changes in cheek thickness posttreatment with PLLA used varying methods of measuring thickness, including ultrasound, 3-dimensional photography, and skin calipers.[38,41,42,44] The Blue Pacific Aesthetic Medical Group study[45] of PLLA and the study by Silvers et al[55] of CaHA used identical methods of assessing cheek thickness, thus making it logical to compare the 2 studies. Both measured cheek thickness at each visit using calipers at the same fixed point: the intersection of the vertical axis through the lateral canthus and the horizontal axis of the nares. In the Blue Pacific Aesthetic Medical Group study, 80% of the patients had 4 to 6 treatments with PLLA, and at 6 months posttreatment, they had a 69% mean increase of skin thickness.[45] In the study by Silvers et al,[55] 78% of the patients received 3 injections with CaHA and at 6 months had a 45% mean increase of skin thickness. Patients and physicians have been pleased with the effects of both products.

The most common adverse reactions with PLLA and CaHA are local and include injection-site bruising, discomfort, and edema. However, subcutaneous nodule formation has been reported in 3% to 44% of PLLA-treated patients with HIV-associated facial lipoatrophy.[38,39,41,42,44] Generally, these nodules are palpable and not visible. The formation of these nodules is not predictable, and they may develop within weeks or 6 or more months postinjection. Many appear unresponsive to treatment. Although using larger amounts (≈5 mL sterile water) to reconstitute PLLA may decrease the rate of nodule formation substantially, this adverse reaction still remains a concern to physicians and patients.[40] When CaHA is injected in or around the lips, the incidence of nodule formation has been reported to be approximately 12%.[40] However, subcutaneous papules have not been reported from CaHA injections into the cheeks of patients with HIV-associated facial lipoatrophy.[55,56]

When comparing the costs of the 2 products, it appears that CaHA is the least expensive. The average amount of CaHA used by Silvers et al[55] for all 3 injections was 8.4 mL. This would require 7 prefilled, 1.3-mL syringes ($295 each), bringing the product cost to $2065. The cost of PLLA for the entire treatment is harder to estimate because most of the studies on treating HIV-associated facial lipoatrophy with PLLA do not mention the precise

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amount of product used. Estimating 2 vials ($480 each) per treatment with 4 total treatments, the cost of PLLA would be approximately $3840.

In conclusion, 2 viable, long-lasting, nonpermanent filler options are available for treating HIV-associated facial lipoatrophy. CaHA appears to be slightly less expensive, with no reported subcutaneous nodule formation associated with lipoatrophy treatment. It also has the benefit of an immediate and long-lasting effect. PLLA has been used much more extensively and may have a longer-lasting filling effect than CaHA, but longer-term data are needed. The choice of filler should be individualized, based on physician experience and preference, as well as patient preference.

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