HIV-associated facial lipoatrophy has been strongly associated with treatment of protease inhibitors and nucleoside reverse transcriptase inhibitors for HIV. Some studies have found that up to 80% of patients on highly active antiretroviral therapy develop facial lipoatrophy within 10 months of starting therapy. This can have a profound effect on the patient’s mental and psychological well being. The outward physical signs can make patients feel stigmatized and experience depression and anxiety over their condition. Overall, quality of life has been found to be poorer in patients with lipoatrophy. Patients have been so negatively affected by this condition that some have even stopped taking their antiretroviral medications to avoid facial atrophy.

**TREATMENT OPTIONS**

Over the years, many treatments for facial lipoatrophy have been investigated, with varying results. Autologous fat transfer is one option that has been helpful for some patients, but disadvantages include difficulty in finding harvestable fat in the HIV population and the possibility of resorption of the transferred fat. In addition to fat, many temporary, semipermanent, and permanent fillers have been investigated. Human and bovine collagen (Cosmoderm or Cosmoplast [Allergan, Inc., Irvine CA]; and Zyderm or Zyplast [Inamed Corp., Santa Barbara, CA]) and hyaluronic acid dermal fillers (Restylane Medicis Aesthetics, Inc., Scottsdale, AZ; Juvederm [Allergan]; and Hylaform [Inamed]) offer many advantages but suffer the significant disadvantage of having the results last less than 1 year on average, making these fillers a suboptimal choice.

**BACKGROUND:** Most HIV-positive patients receiving highly active antiretroviral therapy develop facial lipoatrophy soon after commencing treatment. Attempts to correct lipoatrophy through autologous fat transfer or the use of temporary, semipermanent, or permanent fillers have achieved some benefits, but either do not have lasting effects, do not treat some areas effectively, or have other disadvantages.

**OBJECTIVE:** The purpose of this article is to outline the treatment principles for use of poly-L-lactic acid (PLLA) in HIV-associated facial lipoatrophy since its emergence in 1999 and review the relevant literature, with particular emphasis on investigations of the incidence of subcutaneous papule formation after PLLA treatment.

**METHODS:** The principles of treating facial lipoatrophy with PLLA, including product preparation, patient preparation, and injection technique, are reviewed. Two case studies and results are presented as typical examples of treatment and results. A literature discussion focuses on changes in the incidence of papule formation after PLLA treatment.

**RESULTS:** In the representative cases presented, 2 white men in their forties with facial lipoatrophy who had been HIV-positive for more than 10 years received 2 vials of PLLA in each of 5 treatments spaced 4 weeks apart. Results are shown 4 weeks after the final treatment. No papules were reported in the 12-month follow-up period.

**CONCLUSIONS:** Early investigations of PLLA for the treatment of HIV-associated facial lipoatrophy reported a significantly high incidence of subcutaneous papule formation. As experience with PLLA has increased, the incidence of papule formation has dropped dramatically. The proper dilution, adequate hydration time, proper placement of the product, sufficient intervals between treatments, and posttreatment massage all have contributed to this decrease.
Calcium hydroxylapatite (Radiesse; BioForm Medical, Inc., San Mateo, CA), which is considered a semipermanent filler, has recently gained US Food and Drug Administration (FDA) approval for the treatment of HIV-associated facial lipoatrophy and has proven to be a safe and effective option. The results typically last from 12 to 18 months. Augmentation with this filler provides very good results in the nasolabial folds and lower face, among other areas. The one major drawback of calcium hydroxylapatite is that it is not the optimal treatment for volumizing the bulk of the cheeks and the temple region, areas that are typically affected in lipoatrophy patients.

Of the permanent fillers, none are currently approved by the FDA for the treatment of HIV-associated facial lipoatrophy. Two are currently under review for FDA approval: polydimethylsiloxane (Silikon 1000, Alcon Laboratories, Fort Worth, TX) and polymethylmethacrylate (ArteFill or Artecoll [Artes Medical, San Diego, CA]). Both products rely on the host response to produce collagen. The main disadvantages of these products are that a steep learning curve is necessary in order to use permanent fillers safely and satisfactorily, and that permanent products may not accommodate the changes in appearance that occur with natural aging. In addition, the issue of using silicone for cosmetic treatments is still widely debated.

Poly-L-lactic acid (PLLA) is a synthetic polymer derived from the alpha-hydroxy-acid family that is both biodegradable and biocompatible. Polymers of lactic acid have been widely used in the medical field for many years in devices such as pins and screws, but are most familiar to dermatologists and plastic surgeons as resorbable sutures. The mechanism of action of injectable PLLA involves the degradation of the microsphere particles, in which an inflammatory tissue response is initiated and a fibrous capsule surrounds the polylactides. Over time, the product degrades, the inflammatory response wanes, and the ensuing collagen deposition increases. This dermal fibroplasia produces the desired cosmetic result and increase in dermal thickness.

Sculptra (injectable PLLA; Sanofi-Aventis, Paris, France) was approved by the FDA in August 2004 for the restoration and correction of the signs associated with HIV-associated facial lipoatrophy and has proven to be a long-lasting, well tolerated treatment option. In Europe, PLLA was originally marketed as New-Fill and has been used since 1999. It is estimated that it has been used to treat more than 150,000 patients worldwide. One of its unique characteristics is that unlike traditional fillers, it can replace significant volume loss. The effects of this semipermanent filler last significantly longer than other fillers, with typical results lasting up to 2 years and longer in some patients. Since PLLA has emerged onto the treatment arena for HIV-associated lipoatrophy, dramatic improvement in appearance, psychosocial aspects, and overall quality of life has been experienced by patients able to restore their facial appearance. A significant adverse effect of injectable PLLA, the formation of posttreatment subcutaneous papules, has been largely overcome. In this paper, we summarize the principles of treatment of HIV-associated lipoatrophy with PLLA, discuss two cases of patients treated with PLLA that showed significant results after several treatment sessions, and review the medical literature on papular formation after treatment with PLLA.

**PRINCIPLES OF TECHNIQUE**

When treating HIV-associated facial lipoatrophy with PLLA, an individualized treatment plan is necessary. Typically, a series of injections is required to achieve the desired result. The number of injection sessions varies between patients and is somewhat dependent on the severity of lipoatrophy. On average, most patients will require 3 to 5 sessions. Treatment sessions are usually spaced 2 to 6 weeks apart, using the mantra of treat, wait, and assess as a general rule of thumb.

**Preparation**

Each vial contains 90 mg sodium carboxymethylcellulose, 150 mg freeze-dried PLLA powder, and 127.5 mg pyrogen-free mannitol. Preparation of the PLLA requires reconstitution with 3 to 5 mL of sterile water for injection to each vial. Do not shake the vials and let them stand at room temperature during hydration. There is no need for refrigeration during the hydration period. Preparation must be done at least 2 hours before the injection, but many experienced injectors have found that for optimal results at least 12 hours is needed. The longer the PLLA is in the water, the better hydrated the particles become (12 to 72 hours). Before injection, agitate the mixture until a uniform suspension is obtained. In addition, 1 to 2 mL of 1% lidocaine, with or without 1:100,000 epinephrine, can be added to the solution for patient comfort.

Patient preparation includes setting realistic expectations for the patient and patient comprehension of the gradual nature of the product. Before setting up the first treatment session, the patient needs to understand that it will require multiple sessions and will take several months to achieve optimal correction. In clinical trials, patients with moderate HIV-associated lipoatrophy required 3 treatment sessions, with 2 vials at each session. Patients with severe HIV-associated lipoatrophy typically had 4 to 5 treatment sessions, with two vials at each session.

Topical anesthetics (LMX, Ferndale Labs, Ferndale, MI; Pliagis, Galderma Laboratories, Fort Worth, TX; EMLA, AstraZeneca, Wilmington, DE) are usually used for procedural pain management. In addition, adding local anesthetics and 1% lidocaine (with or without 1:100,000 epinephrine) to the vial before injection adds additional pain relief. Most injectors rarely find it necessary to perform nerve blocks for patient comfort. Patient feedback suggests that PLLA injections seem to be the least painful of all the injectables. Lastly, in patient preparation, the patient’s skin must be well cleansed and disinfected before injection.
Injection Methods
Injection techniques for PLLA differ from those of other injectables. Sculptra is injected into the deep dermis or into the subcutaneous layer in most areas. Superficial injection must to be strictly avoided to minimize complications. Depot injections are made under the temporalis muscle and on the periosteum on the upper zygoma.

There are 2 basic techniques for injecting PLLA—the tunneling cross-hatch technique and the depot technique—and a third more advanced fanning technique (Figure 1). The tunnel cross-hatch technique works well in the lower face (ie, cheeks and nasolabial folds). Using a 25- or 26-gauge sterile needle, 1 inch or less, small trails of approximately 0.1 to 0.2 mL of Sculptra are injected into the deep dermis in a grid-like fashion to produce the cross-hatched pattern.

The depot technique is used for injecting the upper zygoma and temporal areas. Small deposits of approximately 0.05 mL are injected underneath the muscle, directly on the periosteum. After each deposition, the site should be vigorously massaged or moulded. Careful aspiration should be practiced in the temporal region to avoid any vessels.

The fanning technique tends to be reserved as a more advanced technique. The primary advantage to this technique is that it requires fewer needle sticks, using approximately 0.1-mL trails of material deposited on each fan. However, extreme care must be used not to unintentionally overlap a serial fan.

POSTTREATMENT INSTRUCTIONS
Following the treatment, patient massage at home is vital to optimize results and to minimize any injection-related side effects. The importance of self-massage should be stressed to the patient, and the patient should be given instructions on how to massage the treated area. To further enhance the distribution of the product, the patient should be instructed to massage using the “rule of 5s”: 5 minutes, 5 times a day, for 5 days. A mild lotion is used to lubricate the skin during the massage.

CASE REPORTS
The two patients (Figures 2 and 3) are white men in their 40s who were HIV-positive for more than 10 years. Neither patient had received previous treatment for lipoatrophy. Both were treated with PLLA diluted with 5 mL sterile water for injection and left to hydrate overnight. Immediately before injection, 1 to 2 mL of 1% lidocaine without epinephrine was added. Treatments were administered with either a 25-gauge 1 1/2-
inch needle (cheeks) or a 26-gauge 5/8-inch needle (temples and chin) and a 3 mL syringe. Product was deposited into the deep dermis/subcutaneous junction in the cheeks and chin using the fanning and cross-hatch tunneling techniques. A depot technique with supraperiosteal placement was used in the temples and the infraorbital area. Care was taken not to insert the needle through the orbicularis muscle, because this can lead to clumping and subsequent papule formation. The periocular area was instead approached from a site in the mid-cheek distal to the insertion of the orbicularis oculi muscle. Both patients received 2 vials per treatment, and all treatments were spaced approximately 4 weeks apart. Both patients were instructed to massage the treated areas for 5 minutes, 5 times daily, for 5 days after treatment. All final follow-up photographs were taken 4 weeks after the final treatment. Treatments were associated with mild swelling with each treatment session that resolved within 5 to 7 days. Bruising was not observed. No papules were reported in the follow-up period of 12 months.

**DISCUSSION**

Various studies have been conducted to look at the clinical application of PLLA in the treatment of HIV-associated facial lipoatrophy. Earlier studies with PLLA in Europe—the Chelsea and Westminster (2004) and the VEGA (2003) studies—had much higher adverse event rates, with papule formation of 31% and 52%, respectively. In these studies, the dilutions were lower (2 to 4 mL) than are typically standard now and, in addition, mixtures were prepared immediately before injection. Patients in these two studies were also injected at 2-week intervals. These factors—more concentrated solutions, no hydration time, and short injection intervals—may account for the high papule formation rates in these studies.

Later patient studies in the United States and elsewhere have found papule formation to be significantly...
In the Blue Pacific Aesthetic Medical Group study, the papule rate was decreased to 13.1%, while the APEX002 study reported a papule rate of 6%.23,24 In 2005, Burgess and Quiroga published data reporting papules in only 3.2% of patients. Another 2005 study from France by Laufaurie et al reported a rate of 13%. In a pilot study by Borelli et al.14 patients reported no incidence of papule formation. In 2006, Cattelan et al also reported no papules or nodules in their patient series. Bodokh and Simonet that same year reported a low rate of 4.8% of patients. In a study by Piquet et al., the papule rate was 4% of patients. In a recent 2007 study, Hanke and Redbord reported a papule rate of 7%.

Noninflammatory papules are typically nonvisible, small, mild, and not bothersome to the patient. Papules

Table 1. Summary of HIV-associated facial lipoatrophy studies

<table>
<thead>
<tr>
<th>Study (yr)</th>
<th>No. of patients</th>
<th>Treatment interval (wks)</th>
<th>Reconstituted volume</th>
<th>Hydration time</th>
<th>No. of patients with papules (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGA (2003)</td>
<td>50</td>
<td>2</td>
<td>3-4 mL</td>
<td>0 hours</td>
<td>26 (52%)</td>
</tr>
<tr>
<td>Chelsea and Westminster (2004)</td>
<td>30</td>
<td>2</td>
<td>2 mL; 1 mL lidocaine</td>
<td>0 hours</td>
<td>89 (31%)</td>
</tr>
<tr>
<td>APEX002 (2004)</td>
<td>99</td>
<td>4–6</td>
<td>3-4 mL</td>
<td>Not specified</td>
<td>6 (6%)</td>
</tr>
<tr>
<td>Blue Pacific (2004)</td>
<td>99</td>
<td>3</td>
<td>3 mL</td>
<td>30 minutes*</td>
<td>13 (13.1%)</td>
</tr>
<tr>
<td>Burgess and Quiroga (2005)</td>
<td>61</td>
<td>3–6</td>
<td>4–6 mL</td>
<td>At least 1 hour</td>
<td>2 (3.2%)</td>
</tr>
<tr>
<td>Laufaurie et al. (2005)</td>
<td>94</td>
<td>2</td>
<td>3 mL; 1 mL lidocaine</td>
<td>Not specified</td>
<td>12 (13%)</td>
</tr>
<tr>
<td>Borelli et al. (2005)</td>
<td>14</td>
<td>4–6</td>
<td>4–5 mL; 1 mL lidocaine</td>
<td>2 hours</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Cattelan et al. (2006)</td>
<td>50</td>
<td>2–4</td>
<td>3-4 mL</td>
<td>Not specified</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Bodokh and Simonet (2006)</td>
<td>83</td>
<td>Not found</td>
<td>5 mL (? amount SW vs. lidocaine)</td>
<td>Not found</td>
<td>4 (4.8%)</td>
</tr>
<tr>
<td>Piquet (2007)</td>
<td>25</td>
<td>4</td>
<td>5 mL</td>
<td>Not found</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Hanke and Redbord (2007)</td>
<td>27</td>
<td>4–6</td>
<td>3 mL; 2 mL lidocaine</td>
<td>Night before procedure</td>
<td>2 (7%)</td>
</tr>
</tbody>
</table>

SW, Sterile water.

*Verbal communication from Dr. Mest.
typically form between the third and fourth month, but can form as early as the first month and up to 12 months later.\textsuperscript{32}

As study design evolved and increased experience with the product was gained, the incidence of subcutaneous papules decreased. With the later studies, the reconstituted dilution volumes increased to 3 to 5 mL of sterile water on average in each vial and hydration time was a minimum of 1 to 2 hours and usually several hours. In addition, the interval between injections lengthened. These more dilute concentrations and better hydrated products may have resulted in more even distribution and greater dispersion of the product, resulting in a lower incidence of papule formation.

CONCLUSION

In early reports on the treatment of HIV-associated lipoatrophy with PLLA, the incidence of subcutaneous papules was significantly high, at 31\% to 52\% of patients.\textsuperscript{21,22} Over time, as experience with PLLA increased, the occurrence of these adverse events has dropped dramatically, to 0\% to 13\%.\textsuperscript{23–31} Proper dilution, adequate hydration time, proper placement of product, sufficient intervals between treatments, and massage after treatment have contributed to the dramatic decrease in papule formation. As demonstrated by these cases, PLLA is an excellent choice for volume restoration in the HIV-associated facial lipoatrophy patient with long-lasting results.

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DISCLOSURES

Dr. Kates and Dr. Fitzgerald are consultants for Dermik Laboratories/Sanoﬁ-Aventis. Dr. Fitzgerald is also a speaker for Dermik Laboratories/Sanoﬁ-Aventis.

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