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HIV-associated Facial Lipoatrophy – Review of Current Therapy Options

F. G. Bechara, M. Sand, A. Potthoff, P. Altmeyer, N. H. Brockmeyer, German Competence Network for HIV/AIDS

Department of Dermatology and Allergology, Ruhr-University Bochum, Germany

Abstract
Highly active antiretroviral therapy (HAART) has dramatically improved the life expectancy for HIV-infected patients. Long-term complications of both HIV-infection and antiretroviral agents are therefore of increasing concern. Facial lipoatrophy (FLA) is a stigmatising complication associated with sever social impact and a reduced quality of life for the patient.

We aimed to review the treatment options of HIV-associated FLA. The current treatments available for treating FLA are limited and can be classified in three main categories: I. Medial therapy, II. Injectables with different duration of effect, and III. Surgical treatment options. Medical therapy can provide a small benefit but improvement is, at best, slow and partial. Injectables can yield marked results but are costly, time consuming and may be associated with complications such as granuloma formation. Surgical options such as augmentation with specially designed silicone implants may be of benefit for severe cases of FLA, however, they are associated with higher surgical complications and do not account for the dynamic process of FLA.

To summarize, until today no ideal strategies for treatment of HIV-associated FLA are available, and new therapies are strongly required.

Key words: HIV, facial lipoatrophy lipodystrophy syndrome

Introduction

The introduction of highly active antiretroviral therapy (HAART) in 1996 has dramatically improved the clinical prognosis of patients with human immunodeficiency virus (HIV) with significant reduction in disease-associated morbidity and mortality [1]. The use of protease inhibitors (PI) with nucleoside reverse transcriptase inhibitors (NRTIs) has become a standard drug regimen for patients infected with HIV [2]. However, HAART has also led to undesirable sequelae such as HIV-associated lipodystrophy syndrome with possible lipoatrophy, consisting of peripheral fat wasting (face, arms, legs, buttocks) [3, 4]. Occasionally it is associated with a lipohypertrophy, clinically visible as fat accumulation in the dorsocervical neck ("buffalo hump"), breast, and trunk [1, 5, 6]. The estimated prevalence of lipodystrophy syndrome varies widely in the literature, ranging from 15% to over 80% [7, 8]. Although the pathogenesis of lipodystrophy syndrome is not fully understood, recent hypotheses and evidence suggest that impairment of adipocyte differentiation, unopposed production of proinflammatory cytokines, and mitochondrial toxicity may play roles in lipodystrophy [9, 10].

The facial lipoatrophy (FLA) is most prominent in the midface affecting the malar, buccal, and nasolabial areas in varying degrees. The loss of the buccal fat pads may cause significant psychological impact in the patient [11]. It can affect self-esteem and may lead to social withdrawal, depression, or even noncompliance with the antiretroviral medication [7, 12].

To evaluate the degree of FLA, and specify therapeutic effects, a severity score has been proposed by James and colleagues for FLA: Grade 1 with mild and localized FLA; Grade 2 consisting of deeper and longer areas of central cheek atrophy; Grade 3 with even deeper atrophic areas allowing recognition of underlying facial muscles; Grade 4 facial atrophy displaying a wide area of atrophy and extending toward the orbit with only skin overlying the facial musculature causing a "skull-like" appearance [13].

In recent years a variety of treatment strategies has been reported for therapy of FLA, and the search for an ideal option is still on-going.

In this review we present a summary of current strategies for the treatment of FLA. We differentiated treatment options into three categories: I. Medical therapy, consisting of switching HAART or the additional use of non-HIV medication, II. Injectables with different duration of effect and III. Surgical treatment options (Table 1).

I. Medical Therapy

Medical therapy can be divided into two main parts: the modification of HAART, also known as switching therapy, and the additional use of non-HIV drugs. The switching therapies aim to minimize toxic effects of HAART by switching the agent presumed to be most toxic. The use of non-HIV drugs is based on the notion that lipohypertrophy (mainly visceral fat) is reduced while lipoatrophic areas (face, limbs) are augmented by fat increasing.

I.1. Switching Therapy

With regard to its impact on lipodystrophy syndrome, substitution of PIs and NRTIs with alternative medications of the same class has been investigated in several studies [14]. In this review we focus only on their

Table 1. Classification of treatment options for HIV-associated facial lipoatrophy.

I.	Medical therapy
I.1.	Switching therapy
I.2.	Additional non-HIV drugs
I.2.a.	Antidiabetic drugs
I.2.b.	Human growth hormones
I.2.c.	Anabolic steroids
II.	Injectables
II.1.	Temporary injectables
II.1.a.	Bovine collagen
II.1.b.	Human collagen
II.1.c.	Hyaluronic acid
II.1.d.	Human fascia
II.1.e.	Fat transplantation
II.2.	Semipermanent injectables
II.2.a.	Polylactid acid
II.2.b.	Calcium hydroxylapatite
II.3.	Permanent injectables
II.3.a.	Liquid silicone
II.3.b.	Polymethylmethacrylate
II.3.c.	Polyacrylamide Gel
II.3.d.	Polyalkylamide
III.	Surgical treatment options
III.1.	Lifting procedures
III.2.	Polytetrafluoroethylene (PTFE) implants
III.3.	Other alloplastic implants

efficacy in correcting the fat distribution. Most studies lack objective measurements, making it difficult to determine the outcome. Some PI switch studies could show a trend towards reduction of visceral fat accumulation [14], however no study could demonstrate any benefit for the loss of fat (lipoatrophy). NRTI switch studies mainly focus on the replacement of stavudine, and could show a modest gain in peripheral fat after switching. Facial lipoatrophy in contrast did not improve [15, 16].

To summarize, at present switch studies do not demonstrate effectiveness for treatment of FLA.

I.2. Additional non-HIV drugs

I.2.a. Antidiabetic agents

Depending on the substance class, desirable effects of antidiabetic agents are an improvement in insulin sensitivity, an increase of subcutaneous fat, and a reduced cardiovascular risk. However, effectiveness of administrating anti-diabetic medications on HIV-associated lipodystrophy is inconclusive [14]. Currently they cannot be recommended for the treatment of HIV-associated FLA.

Rosiglitazone, a novel insulin-sensitizing anti-diabetic agent of the thiazolidinedione group, is available for treatment of type 2 diabetes. Most studies show predominantly metabolic effects with continued reduction in peripheral fat and no improvement of facial fat loss [17-19]. A possible side effect is the significant increase in blood lipids.

Metformin, an anti-diabetic drug from the biguanide class of oral antihyperglycemic agents, has been evaluated as one of the first possible drugs for lipodystrophy. A recent study could show that metformin only improves visceral fat accumulation [20].

I.2.b. Human growth hormones

The use of recombinant human growth hormone is capable of decreasing the visceral adipose accumulation but most studies indicate that it may worsen the lipoatrophy and possibly precipitate diabetes [21]. Recently, a study reported positive effects of recombinant human growth hormone (rhGH) in patients with moderate to severe FLA following daily administration of 5 mg rhGH for 6 months. The authors reported a positive effect in 24 of 25 patients as evaluated by computer tomography [22]. However, due to the overwhelmingly inconclusive data of previous studies, rhGH is still not recommended for FLA today.

I.2.c. Anabolic steroids

The use of anabolic steroids has been described for lipodystrophy. However, the treatment seems only to result in augmentation of muscle mass, thus masking the fat loss instead of resolving it [23]. No positive effect of FLA has been demonstrated to date. Hepatic toxicity is a frequent side effect.

II. Injectables

Injectables are drugs or medicine that can be injected. In aesthetic and reconstructive medicine the term injectable or filler is used for products which are used for soft-tissue augmentation. They can be classified by their longevity or their substances of content. In the following we use an established classification of temporary, semipermanent, and permanent injectables.

II.1. Temporary Injectables

Temporary injectables are completely resorbable soft-tissue fillers. Therefore they have a lower risk of side effects compared to permanent products. Their main disadvantage is the necessity of repeat application, resulting in high treatment costs. In this section we have designated autologous fat transplantation as temporary treatment, since several studies have shown that in HIV-associated FLA, the transplanted fat is reabsorbed.

II.1.a Bovine collagen

Bovine collagen (Zyderm™, Zyplast™, Inamed Aesthetics, Santa Barbara, CA, USA) has been successfully used for volume augmentation, although the results are temporary, and repeated injections are required [24, 25]. It is easy to use and has a good safety profile; however it appears to be degraded more quickly than hyaluronic acid, with some patients thus treated describing an unnatural feel of the product beneath the skin [26]. Because the product is based on animal protein, double intradermal testing is recommended because up to 5% of the population may develop hypersensitivity, despite a negative initial test [27].

II.1.b. Human collagen

To avoid skin testing and reduce the risk of allergic reactions, human collagen (CosmoDerm and CosmoPlast, Inamed) or allogeneic collagen sources, harvested from cadaver tissue, have been proposed (AlloDerm, LifeCell, Branchburg, NJ, USA). The advantage of these products is a reduced risk of hypersensitivity

reaction, but they are limited due to high costs, large-gauge needle size, and the frequent necessity of touch-up treatments. In a study of twenty-five (n = 25) HIV patients treated with AllodDerm™, most patients had returned to their pre-treatment lipoatrophy baseline within 3 months after an injected volume ranging from 6 to 12 cc [28, 29]. Cymetra (LifeCell, Branchburg, NJ, USA) is a micronized particulate form of AlloDerm made for easier injection.

II.1.c Hyaluronic acid

Hyaluronic acid (HA) is a naturally existing substance of different human organs including the skin. The main disadvantage of HA has to be seen in its short durability. Manufacturers are attempting to lengthen durability by using novel stabilization and cross-linking techniques. Compared to bovine collagen, the absence of animal protein in HA decreases the risk of a hypersensitivity reaction, hence no skin testing is required for its use. Side effects of HA are generally considered to be mild and include redness, swelling, and bruising.

HA, has been investigated for the augmentation of HIV associated lipoatrophy in some smaller studies [30-32]. Restylane™ (Q-Med, Uppsala, Sweden) has been shown to last approximately 6 months after injection [32]. The nonanimal hyaluronic acid Perlane™ (Q-Med, Uppsala, Sweden) has also been used for correction of FLA; however, the results were only evaluated for 6 months and frequently required touch-ups [28].

Currently two pure hyaluronic acid products with assumed long-lasting properties are available: SubQ™ (Q-Med AB, Uppsala, Sweden) and Voluma™ (Allergan Inc., Irvine, CA, USA). SubQ™ has been reported to be effective in the treatment of HIV-associated lipoatrophy, although the data has yet to be peer reviewed [30]. In a small cohort of eighteen (n = 18) HIV-positive patients the longevity of the product was reported to range from 6 to 12 months after implantation with a 16 G Coleman cannula [30].

Voluma™ is a relatively new product that has not been evaluated for lipoatrophy so far. Compared to SubQ™ and dermal grafts it has the important advantage of allowing implantation with a needle without the need for a special cannula.

II.1.d. Human fascia

Fascian™ (Fascia Biosystems, CA, USA) is preserved particulate fascia lata from human cadavers, thus no testing for allergic response is necessary before injection. Side effects of Fascian™ seem to be low [33, 34]. However, an observation on thirty patients (n = 30) with HIV lipoatrophy was disappointing, with fast resorption of the product [28].

II.1.e. Fat transplantation

The idea of autologous fat transplantation seems tempting, as it carries no risk of allergic reactions. Therefore fat injections have been used previously in several trials to treat HIV-associated FLA. There have been reports of successful liposuction for dorsocervical fat pad accumulation serving as donor site [35]. The abdominal fat accumulation is less accessible for this therapy as most of the fat is located visceral. However, the excess fat deposits in the neck do not usually accompany FLA and affected individuals with FLA often do not have sufficient fat for harvesting [36]. Additionally, these hypertrophied areas frequently have extremely fibrous fat that requires ultrasonic liposuction for removal and is generally unsuitable for transfer and injection [35]. One study demonstrated that this fat seems to reabsorb after the first month of implantation, whereas another study utilized MRI to show fat preservation after implantation at 6 months [37, 38]. Others report that 50% of injected fat will disappear after 6 months. Moreover, fat injections may have unpredictable results leading to irregularity, particularly if the patient is continuing highly active antiretroviral therapy [13, 39, 40]. An alternative to exclusive fat transplantation is the augmentation with a derma-fat graft [41].

In our opinion, however, the supply of fat is the most limiting factor in this population, since most patients have lost peripheral fat donor sites.

II.2. Semipermanent Injectables

Semipermanent products consist of resorbable components. However, they induce reactions in surrounding tissue, thus serving as a scaffold for long-lasting natural collagen production. Therefore they have a special status between permanent and temporary injectables. However, some authors refuse this additional classification, calling them temporary fillers. The most common semipermanent fillers are polylactid acid (PLA) and calcium hydroxylapatite microspheres.

II.2.a. Polylactid acid (PLA)

PLA (Sculptra™, SanofiAventis, Paris, France) has been used in Europe for HIV-associated FLA since 1999 and was approved by the FDA specifically for this indication in August of 2004. It seems to be a promising and longer-lasting semipermanent filler [42]. However, multiple injections with large volumes over a longer period are mandatory. When PLA is injected into the deep dermis or subcutaneous-deep dermal plane, it causes an immediate tissue expansion due to the carrier solution. Once the carrier solution is reabsorbed, a slow process of biodegradation of the microspheres occurs. This process is followed by a fibroblastic response with collagen neogenesis. The polylactides are eventually broken down to carbon dioxide after 12 to 18 months. The esthetic results of PLA are believed to last anywhere from 12 to 24 months. Studies have demonstrated that approximately 3 to 6 cc of PLA should be injected into each cheek and 0.5 to 1 cc into the temporal area every 2 to 4 weeks over 3 to 6 sessions to obtain a good cosmetic result [43-45]. Palpable, but generally not visible, micronodules have been reported in a minority of patients. Often a too superficial placement of the product is responsible for this granuloma formation.

II.2.b. Calcium hydroxylapatite

Calcium hydroxylapatite microspheres (Radiesse™, BioForm Medical, San Mateo, CA, USA) have also been used in the treatment of HIV-associated FLA. The product contains the synthetic form of a natural

substance found in bones and teeth, and it consists of 30 percent calcium hydroxylapatite microspheres and 70 percent sodium carboxymethylcellulose gel carrier. The microspheres measure 25 to 40 μm in diameter, and are believed to function as a scaffold for natural collagen.

The first observation reported on its use for FLA in three patients with a good cosmetic enhancement lasting 7 to 10 months [46]. It is injected in the space between the deep dermis and the subcutaneous layers, and is reported to be a safe augmentation option without observed migration. Recently, a persistent complication (foreign body reaction) was reported after use of Radiesse for augmentation of the lips [47]. A recent larger study on 100 HIV-positive patients reported good cosmetic outcome over 12 months with a low rate of minor side effects (ecchymosis, edema, erythema, pain, and pruritus) [48]. In December 2006 Radiesse was approved by the FDA for augmentation of HIV-associated FLA.

II.3. Permanent Injectables

Although permanent fillers can provide the patient with a lasting result, an error in placement of the material can lead to irreversible disfigurement [39]. The patient must be advised that, though permanent, further injections may be required as the underlying atrophy continues.

II.3.a. Liquid silicone

Limited experience with silicone injection for HIV-associated FLA has been documented. High-grade liquid silicone (SilSkin™, R.J. Development Corp., Peabody, MA, USA) is currently being investigated in the United States but is not yet available for this indication and is therefore an off-label use [28, 32, 49]. The most frequently used products are Silikon 1000 (Alcon Laboratories, Inc., Fort Worth, TX, USA) and Adatosil 5000 (Bausch & Lomb, Rochester, NY, USA), which have been approved by the FDA for eye surgery to prevent and treat detached retina [50]. However, no approval for cosmetic use has been obtained. Because the silicone is chemically inert, it remains liquid in the skin and is held in place by the formation of a collagenous capsule around each droplet [27]. The risks associated with this procedure include granuloma formation, difficult revisions, induration, ulceration, discoloration of the overlying skin, and migration of the droplets [39]. For FLA the product has to be placed in the subcutaneous plane, not exceeding 1 cc per side, and multiple injections are necessary with a least one-month intervals in between, as fibroplasia must be evaluated before the next treatment. This so-called micro droplet technique seems to be mandatory to reduce the rate of complications.

Recently a pilot study by Jones and colleagues evaluated the use of SilSkin in 77 patients with HIV-associated FLA [26]. They reported a good cosmetic outcome in all patients, without any severe side effects. However, long-term safety data are not available so far. This is particularly important, as complications after silicone injections may appear years after implantation due to its permanent nature.

II.3.b. Polymethylmethacrylate

Artecoll™ (Rofil Medical International, Breda, Netherlands) is a permanent filler substance composed of polymethylmethacrylate microspheres delivered in a collagen suspension and therefore requires skin testing prior to use [27, 39, 51]. It is injected into the subdermal space, where the collagen vehicle is eventually degraded, and the microspheres develop individual fibrous capsules over the next 2 to 4 months. As the collagen fraction of the product is temporary, the permanent volume is believed to be about 50% of the injected volume [13].

A major disadvantage is the risk of granuloma formation or lumps owing to superficial placement of the product [39]. Although Lemperle et al. hypothesize that all injectable filler substances can cause normal foreign body-type reaction leading to granuloma, the risk is substantially higher when using permanent fillers [52]. Peer-reviewed data on the use of polymethylmethacrylate for HIV-associated FLA is currently not available.

II.3.c. Polyacrylamide gel

Polyacrylamide Gel (Aquamid™, Contura International A/S, Soeborg, Denmark) is a soft tissue filler that has been used since 1997 in Europe and Asia. It has been used solely or in combination with other implants for augmentation of FLA [53, 54]. In a study comparing Aquamid™ with polylactid acid and fat transplantation, all three methods were efficacious for correcting FLA [54]. However, Cheng and colleagues reported complications in 15 patients due to serious gel migration possibly due to muscular activity [25]. For this reason they do not recommend the product for subcutaneous areas with active movement, which clearly limits its use in HIV-associated FLA of the malar region.

Currently a single-blind, randomized, CT-scan controlled phase III study (ANRS 132 SMILE) is ongoing, comparing a polyacrylamide gel (Eutrophill, Pro-Cytech, Bordeaux, France) vs PLA (Sculptra™, SanofiAventis, Paris, France) for treatment of HIV-associated FLA.

II.3.d. Polyalkylamide

The product Bio-Alcamid™ (Polymekon, Milan, Italy) consists of permanent polymeric material. An Italian study on 73 patients with HIV-associated FLA reported a good cosmetic outcome without major complications [55]. However, over correction or wrong application may necessitate removal of the product, and long-term complications (e.g. migration, granuloma formation) have been described [56, 57].

III. Surgical Treatment Options

III.1. Lifting Procedures

No pertinent peer-reviewed data about lifting procedures are available for the treatment of FLA. From the authors' experience lifting procedures have an important disadvantage for this indication. FLA develops due to a loss of volume and not due to skin excess or muscle slackness. Therefore lifting leads to tightened

skin over the untreated area of volume loss, which may even accentuate the "skull-like" appearance of FLA.

III.2. Polytetrafluoroethylene (PTFE) Implants

Polytetrafluoroethylene (PTFE) is a synthetic fluoropolymer used as permanent filling substance. The inert biomaterial has a porous structure that allows the penetration of cells and vessels after implantation [58]. Compared to larger silicone implants these can usually be inserted in topical anesthesia. Recently, Mole reported about the use of expanded polytetrafluoroethylene (ePTFE; GORE S.A.M., W. L. Gore & Associates, Flagstaff, AZ, USA) malar implants for augmentation of FLA in HIV patients [53]. 11 patients were treated solely with ePTFE implants, and another 11 patients were treated with a combination of implants and a 2.5% polyacrylamide hydrogel (Eutrophill, ProCytech, Bordeaux, France). Three cases of chronic inflammation with the implants, and light bulgings with acrylamid injections were observed. With a mean follow-up of 17 months the cosmetic outcome was evaluated as positive.

III.3. Other Alloplastic Implants

Surgical volume augmentation using permanent silicone implants is mostly performed in general anesthesia. This implies a much higher surgical risk (e.g. extrusion, movement, infection) and a considerable effort; also the procedure is limited to performance by facial or plastic surgeons. Although some studies have shown a good cosmetic outcome after such implants, often additional augmentation with filling substances is required to obtain satisfying results [31]. A recent study on 39 HIV-positive patients could show that only Grade 1 patients were completely satisfied with a malar implant, but with higher grades additional injections with fillers proved necessary. The authors report that Grade 3 disease patients almost always needed injections after implantation, while Grade 4 patients uniformly required filler injections after malar implantation [31].

Another small study compared fat transplantation with implantation of silicon implants in 12 patients. Both techniques gave long-lasting results in facial contour reshaping ranging from good to very good during a mean follow-up period of 2 years [59].

In a small cohort of twenty-two (n = 22) patients submalar implants were used in case of moderate FLA, whereas severe cases received custom-designed implants, with both methods leading to good restauration of facial appearance [60].

Conclusion and Outlook

Currently, no ideal technique is available for the treatment of FLA. This option would consist of a risk-free, permanent, easy to apply, and cost-effective therapy. As reported above, most techniques provide some of these desired effects.

Unfortunately, medical therapy has been unable to show sufficient effectiveness to date. A positive effect on some parts of the complex FLA syndrome seem to be evident, nevertheless stigmatizing features are barely improved. Hence, reconstructive methods alone seem to offer the only possibility for improving the facial anatomic contour. Although personal preferences and experience of the treating physician ultimately determines the method, evidence based guidelines are missing. For two reasons primarily, the authors reject the usage of permanent injectable fillers. First the risks of permanent fillers are unacceptably higher. Secondly FLA must be seen as a dynamic process influenced by various factors. Therefore we do not know, whether the permanent implant that offers a cosmetically positive result initially will ultimately disfigure the patient's face. Finally, an implanted permanent filler is extremely difficult to remove by surgical means.

Surgical treatment with solid implants may provide a fast and permanent effect, although the same disadvantages as with permanent injectables apply here. Moreover the procedure is often limited to plastic surgeons, and expenses and surgical effort can be enormous. Therefore we favor temporary or semipermanent injectables. We have achieved good results with long-lasting high density HA (temporary) as well as with PLA (semipermanent). The choice of product is based primarily on a pre-treatment discussion with the patient. We have observed that some patients are willing to receive multiple injections over a longer period with a "little by little" augmentation. These patients are appropriate to PLA treatments. If an impressive augmentation is desired directly after the first injection we use HA. However, we do realize that these procedures must often be repeated and are very cost-intensive.

To summarize, both patients and physicians are still waiting expectantly for the ideal treatment option in the future – when ever it will be discovered.

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Address for correspondence:
Falk Georges Bechara, MD
Department of Dermatology and Allergology
Ruhr-University Bochum
St. Josef Hospital
Gudrunstr. 56
44791 Bochum
Germany
Tel.: +-49-234-509-0
Fax: +-49-234-509-3445
E-mail: f.bechara@derma.de