# Restorative Interventions for HIV Facial Lipoatrophy

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## Abstract

*Facial lipoatrophy is a common and distressing manifestation of HIV lipodystrophy. The changes in facial appearance can reduce quality of life, self esteem and antiretroviral adherence. Apart from the modest benefits of thymidine-based nucleoside analog cessation, there are no proven therapies for lipoatrophy. Management of established fat loss can be challenging as restoration of lost fat mass is extremely gradual. Plastic surgery and cosmetic procedures can restore lost facial volume. Both biodegradable and permanent filling agents have been investigated for HIV facial lipoatrophy. Biodegradable products offer a good safety profile, but maintenance of aesthetic benefits necessitates reinjection over time. Although permanent products offer longevity and lower treatment costs, adverse events should they occur can be serious and of long duration. Despite the substantial increase in options for soft-tissue augmentation in recent years, well-performed clinical studies in HIV-infected adults with facial lipoatrophy are scarce, and long-term clinical safety data are lacking. This review will summarize available efficacy and safety data of the biodegradable and permanent agents utilized for soft-tissue augmentation in this population. Difficulties associated with comparing treatment efficacy data, assessment of facial lipoatrophy presence and severity, and measurement of facial fat will be discussed. Available data indicate that in HIV-infected adults, most filling agents have short-term clinically safety, and can provide aesthetic improvement and improve well-being, social functioning and quality of life. However, well-designed studies with objectively assessed endpoints are needed to elucidate optimal treatments for this distressing condition.* (AIDS Rev. 2008;10:116-24)
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# Introduction

Lipoatrophy of subcutaneous adipose tissue is a distressing manifestation of HIV lipodystrophy, severely affecting quality of life and self-esteem, and may result in reduced antiretroviral adherence[1,2]. Facial lipoatrophy, which is associated with loss of buccal fat pads and dermal/subcutaneous layers, is a common manifestation[3]. As the severity increases, underlying facial musculature becomes more visible, and the atrophy extends to the orbits and temples, giving rise to a cachectic appearance (Fig. 1a, 1b and 2). These changes in facial appearance can lead to unmasking of HIV status and social stigmatization[4]. Although use of the newer non-thymidine nucleoside reverse transcriptase inhibitors is associated with less lipoatrophy[5], in the absence of proven therapies, management of established fat loss can be challenging as reversal is extremely slow[6-8].

Plastic surgery and cosmetic interventions are able to restore lost facial volume. An array of injectable filling agents has been marketed for soft-tissue augmentation and facial rejuvenation procedures, and many of these are used for HIV facial lipoatrophy. Randomized

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**Figure 1.** *A: Severe facial lipoatrophy in an HIV-infected male. B: Severe facial lipoatrophy in an HIV-infected male.*



**Figure 2.** *Computed tomography image at level of maxillary antrum in A: HIV+ male with severe facial lipoatrophy demonstrating severe loss of dermal/subcutaneous layers, and B: sex- and aged-matched control.*

clinical trials have demonstrated acceptable safety and efficacy of soft-tissue filling agents in the general population[9,10]. However, HIV facial lipoatrophy commonly encompasses substantially larger atrophic surface areas and volumes and so treatment outcomes are not comparable. Although two filling agents have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of HIV facial lipoatrophy, scientifically valid data that relate to this treatment approach are scarce. A number of filling agents appear clinically safe, at least in the short-term, but efficacy data are derived from a small number of short-term cohort and case series.

Comparison of treatment efficacy data is complicated by study heterogeneity. Assessment of HIV facial lipoatrophy presence and severity are particularly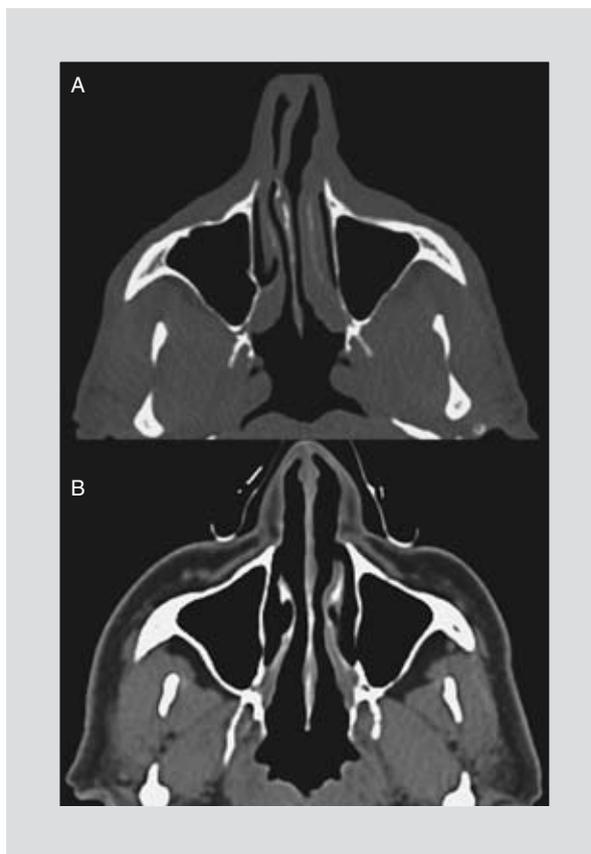 problematic. Objective methods have been used rarely to assess lipodystrophy presence. Moreover, lipoatrophy severity is commonly assessed utilizing site-specific scales with patient and/or clinician assessment. Use of a validated lipodystrophy assessment tool[11] to assess facial lipoatrophy severity is rare[12,13]. Measurement of facial fat is challenging. Currently, there are no widely accepted measurement methods. Treatment efficacy has predominantly been subjectively assessed by clinicians and/or patients, or by non-standardized photography, or the use of non-validated methods such as calipers or sonography to measure facial thickness.

Soft-tissue filling agents are derived from either natural or synthetic sources. Natural products originate from autogenic, allogeneic, or xenogeneic sources that biodegrade over time and so provide temporary correction that may persist for weeks to months, depending on the amount and type of agent injected[14]. Synthetic materials can be slowly biodegradable, providing semi-permanent correction up to a few years, or non-biodegradable providing permanent augmentation[14]. Although injectable fillers are employed most commonly, surgical augmentation with alloplastic implants

may provide a permanent option. Fat/dermal transplantation also necessitates a surgical procedure.

Most filling agents are well tolerated, but all are associated with the risk of both acute and delayed adverse reactions[15,16]. Reactions can be attributed to the procedure itself, the filling agent, or the procedural technique. Acute events are common, occurring up to several days post procedure, but are usually transient and of minor severity. They are predominantly procedure-related and include injection site reactions such as edema, pain/tenderness, erythema, pruritus, ecchymosis, and injection site bleeding[15,17]. More serious acute events include asymmetry, hematoma, lumps caused by product maldistribution, and rarely immediate hypersensitivity reactions, infection or tissue necrosis[16,18]. In contrast, delayed events can occur weeks to years after the procedure. Less frequently they include minor complications such as small nodules and delayed hypersensitivity reactions[17]. Major delayed events include infection, asymmetry, implant dislocation or migration, persistent scarring or discoloration, and rarely inflammatory or granulomatous reactions[15,16,18].

## Biodegradable products

Biodegradable agents offer a greater safety profile, having a lower incidence of adverse effects compared to non-resorbable products[19]. Their main limitation is short longevity, and hence the need for reinjection to maintain aesthetic benefits over time which increases treatment costs. Biodegradable fillers are preferable where there is potential for recovery of the underlying condition, which would appear the case for HIV facial lipoatrophy[20].

### *Autologous fat*

Autologous fat has been used as a volume replacement agent for many decades. The Coleman technique, which comprises methods for fat tissue harvesting, refining, transfer and placement, has demonstrated improved grafting outcomes relative to earlier procedures and is employed most commonly[21]. Autologous fat is non-immunogenic, and in the general population readily available from donor sites such as the abdomen, suprapubic region, thighs and flanks[21]. In adults with HIV lipodystrophy, the coexistence of central fat would appear an ideal fat source, but its fibrous nature may render it unsuitable[22]. Additionally, hypertrophy has been reported following facial augmentation with dorso-cervical fat[23]. Consequently, in many HIV lipoatrophic individuals, autologous transplantation is limited by insufficient donor sites to achieve the desired corrections. In contrast to injectable fillers, fat transplantation requires invasive surgical procedures with either general anesthesia or regional block and has a longer post-procedure recovery period.

A number (n = 5) of small, open-label, single-site case series have demonstrated the safety of the Coleman technique of autologous fat transplantation for HIV facial lipoatrophy[23-28]. However, efficacy was objectively assessed in only one series of 15 patients[25]. The mean increase in facial fat thickness assessed by transverse magnetic resonance imaging (MRI) at the level of the dental apices six months posttransplantation was 10.5 mm (range 3-22 mm) in the left cheek and 10 mm (range 3-21 mm) in the right cheek[25]. Using sonography, a mean increase in cheek thickness of 5.5 ± 2.4 mm was reported 17.5 months post-procedure in 41 patients[23]. In the remaining studies, clinically assessed good improvements in lipoatrophy severity were reported in 36-74% of patients at 6-12 months posttransplantation[24,27,28]. Despite initial surgical overcorrection, 26-32% of patients required re-grafting due to fat resorption during the six-month period post-surgery[24,26,28]. Derma-fat grafting in five patients has also been reported[29]. Following initial overcorrection, the final volume was attained 3-5 months post-surgery, with clinicians assessing no subsequent loss of volume during follow-up periods that ranged from 14 to 30 months[29].

Two prospective, open-label, single-site studies compared the efficacy of autologous fat transfer with two injectable soft-tissue filling agents, one biodegradable (poly-L-lactic acid, PLLA), and one permanent (polyacrylamide hydrogel)[30,31]. Only 24 (41%) and eight (6%) participants, respectively, had sufficient subcutaneous fat for transfer, with the remainder allocated to receive one of the synthetic agents[30,31]. Heterogeneity makes inter-study efficacy comparisons difficult. Facial lipoatrophy severity was subjectively assessed, while the volume of fat transferred was either subjectively assessed by surgeons based on pre-lipodystrophy photographs[30], or based on subjectively assessed baseline facial lipoatrophy severity and surgical criteria[31]. Additionally, injected volumes of the filling agents were not fixed but adjusted to achieve optimal facial correction. In the study by Guaraldi, et al., mean increases in cheek thickness, assessed by ultrasound at 24 weeks, did not differ between study groups, being 3.3 ± 4.1 mm in fat recipients, 3.5 ± 4.0 mm for PLLA, and 2.1 ± 3.0 mm in polyacrylamide recipients (p = 0.69). In the study by Negredo, et al., efficacy was subjectively

assessed following treatment and at week 48[31]. After treatment completion, 97% of participants perceived an aesthetic improvement, but by week 48 clinically assessed facial lipoatrophy severity had returned to baseline levels in seven (88%) fat, 17 (85%) PLLA, and five (8%) polyacrylamide recipients[31].

Although most authors reported treatment/procedure-related adverse events, frequency and duration data are lacking. Common adverse events include facial edema, pain at donor and facial injection sites, and facial asymmetry or asymmetric fat resorption necessitating reinjection[25-28,30,31]. Significant facial disfigurement, the result of continual graft hypertrophy, has also been reported[23,27], demonstrating that transferred vascularized fat can respond metabolically as if it were in its original location. To date, no scientific data on long-term graft survival in either the general population or HIV-infected individuals have been published. As the long-term unpredictability of volume maintenance is one of the major limitations of fat transplantation, these data are needed urgently.

## Collagen

A key constituent of connective tissue, collagen has been used extensively in soft-tissue augmentation over several decades[32]. FDA-approved for correction of contour deformities of the dermis, bovine collagen was one of the early products evaluated for correction of HIV facial lipoatrophy. The immunogenicity of bovine collagen is high relative to other fillers, necessitating pretreatment screening and intradermal testing[33]. Local hypersensitivity reactions have been reported in 1-2% of patients following a single negative skin test[33], and so double testing over a four-week period is recommended[34]. Although widely available and frequently used for correction of rhytids, furrows, and other contour defects, collagen is not indicated for HIV facial lipoatrophy because of its short durability (3-4 months) and the need for large volumes to restore facial appearance[35]. Human-based collagen homologs are also available. These products do not require pretreatment allergy testing, but volume correction is more expensive than with bovine collagen and improved durability has not been demonstrated, particularly in HIV-infected individuals[32].

## Hyaluronic acid

Hyaluronic acid, a naturally occurring polysaccharide, is a component of all connective tissue with no species or tissue specificity, and thus has a lower potential for immunogenicity[36]. As hyaluronic acid rapidly regrades following injection, it is chemically modified to improve stability[36]. Formulations of synthetic hyaluronic acid from both animal and non-animal sources with varying viscosities and concentrations or particle size are available for soft-tissue augmentation. Several products have been FDA approved for the correction of facial soft-tissue deficiencies such as rhytids and folds. Clinical trial data from HIV-uninfected populations suggest hyaluronic acid-based fillers provide greater durability than collagen-based fillers[9]. Adverse events associated with hyaluronic acid are generally mild and transient injection site reactions, while localized hypersensitivity to non-animal hyaluronic acid gels have decreased in frequency following improved purification of raw hyaluronic acid and are now rare[37]. Localized granulomatous reactions, both acute and late-onset, have occasionally been reported[37].

Small, open-label, predominantly descriptive studies have reported the use of hyaluronic acid for mild to moderate HIV facial lipoatrophy[38-41]. In one study (n = 20), mean total cutaneous thickness assessed by sonography increased from 6 ± 1 mm at baseline to 15 ± 3 mm at week 6, but had reduced to 10 ± 2 mm at week 52[41], and response rates, defined as a total cutaneous thickness > 10 mm, were 85% at week 24 and 60% at week 52[41]. In the remaining studies, subjectively assessed durability ranged from six to 12 months; however, optimal correction required large injection volumes[38-40]. No serious adverse events were reported, but eight (40%) patients developed palpable lumps, which were still present in three (15%) patients at week 52[41].

## Poly-L-lactic acid

Poly-L-lactic acid (PLLA) is a synthetic, biodegradable, immunologically inert, resorbable polymer. It has been widely and safely used for many years within fixative devices for craniofacial and orthopedic surgery and as vectors for injectable slow-release drug delivery systems[42,43]. Poly-L-lactic acid (Sculptra™, Dermik Laboratories, USA) has been approved in Europe and the USA for use in HIV facial lipoatrophy. Following injection, PLLA microspheres produce a foreign body inflammatory response with increased deposition of fibroblasts and collagen fibers that leads to a gradual and progressive increase in volume of the lipoatrophic area[14,44].

Open-label studies have demonstrated the safety of PLLA injections in HIV-infected adults[12,13,30,31,45-50]. However, to date, the efficacy of PLLA in HIV-infected
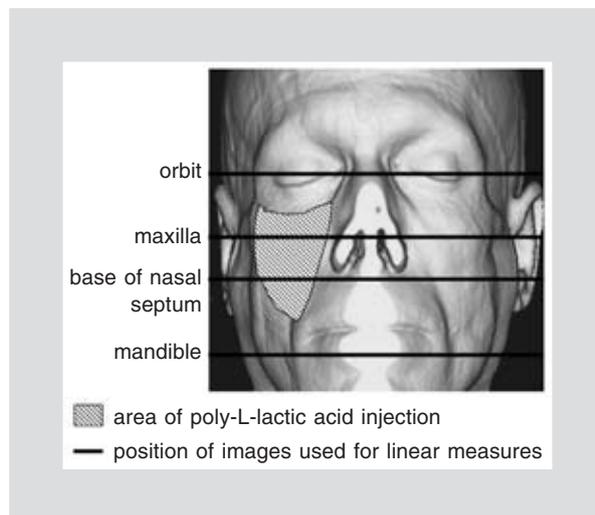
**Figure 3.** *Area of poly-L-lactic acid injection and position of computed tomography images. Note: orbit and mandible levels form upper and lower margins of facial soft-tissue volume, respectively* (adapted from Carey, et al.[13] with permission of Lippincott Williams & Wilkins, 2008).

adults has been objectively assessed in only one randomized clinical study[13]. This multicentre study randomized 100 adults with moderate/severe HIV facial lipoatrophy to receive four open-label PLLA treatments, either two weekly from week 0 (immediate group; n = 51) or after week 24 (deferred group; n = 50). The primary endpoint was mean change in facial soft-tissue volume by spiral computed tomography (CT) at week 24 (Fig. 3). Using an intent-to-treat analysis, mean changes in facial soft-tissue volume at week 24 were 0 $cm^3$ in the immediate group and –10 $cm^3$ in the deferred group (between-group difference, 10; 95% CI: –7 to 28 $cm^3$; p = 0.24). Improvements in objectively assessed soft-tissue thickness around the planes of injection (Fig. 3) were demonstrated in the immediate group compared to untreated individuals, with a mean change of 2.2 mm (95% CI: 1.6-2.9; p < 0.0001) at the maxillary level, and 1.0 mm (95% CI: 0.3-1.6; p = 0.003) at the base of nasal septum. Despite only modest improvements in soft-tissue thickness, patients and physicians perceived significant improvements in facial lipoatrophy severity (p < 0.0001). Additionally, some Short Form-36 Health Survey and Multidimensional Body-Self Relations Questionnaire-Appearance Scales domains improved significantly. The PLLA injections were safe and well tolerated. The majority of adverse events were low-grade, transient injection-site reactions[13]. The incidence of injection-site nodules (12%) was comparable with previous clinical studies[31,46,49].

Other open-label clinical studies (n = 8) have evaluated the efficacy of PLLA in HIV-infected individuals;

however, all were performed at a single site, most were small, and all were either uncontrolled or had subjective efficacy endpoints[12,30,31,45,46,48-50]. The heterogeneity of these studies in terms of the number of PLLA treatments, study subjects, facial lipoatrophy severity and its assessment, and a variety of subjective measurement methods makes efficacy comparisons difficult.

## Calcium hydroxylapatite

Calcium hydroxylapatite, the major mineral component of bone and teeth, has a long-standing safety profile in reconstructive surgery and dentistry[51,52]. Synthetic calcium hydroxylapatite (CaHA; Radiesse™ Bio-Form Medical Inc. USA) was the second product to receive FDA approval for the restoration and/or correction of HIV facial lipoatrophy[53]. Synthetic CaHA is a sterile, non-pyrogenic, biodegradable, cohesive subdermal implant containing calcium hydroxylapatite microspheres 25-45 μm in diameter suspended in a water-based gel. Following injection, the gel is slowly resorbed but, due to low solubility, the microspheres remain, supporting the growth of fibroblasts and the formation of new collagen[54].

Use of CaHA for the treatment of moderate to severe HIV facial lipoatrophy was investigated in a prospective, open-label, three-site study[55]. A total of 100 subjects received initial treatment (baseline injection with an additional injection at one month if required) and an optional top-up at six months such that the volume injected at each time point achieved adequate lipoatrophy correction. Most patients (78%) required three treatments (baseline, months 1 and 6), while the remainder received two (4% patients) or three (18%) treatments. The mean total volume of CaHA injected over six months was 8.4 ml (range 2.0-20.4). At six months the mean increase from baseline in cheek thickness assessed by calipers was 2.7 mm on the right side and 2.4 mm on the left[53]. At 12 months, 100% (n = 98) of subjects rated an improvement in facial lipoatrophy severity, but at 18 months, 10% (n = 9) perceived severity had returned to baseline levels[55]. Most commonly reported adverse events included edema (99%), ecchymosis (64%), erythema (55%), pain (37%), and pruritus (21%)[53]. The majority of events were mild (58%) to moderate (39%) in severity. No serious adverse events and no granulomas or nodules were reported[55]. Nodularity both palpable and visible has been reported in HIV-uninfected subjects following lip augmentation with CaHA, suggesting its use may be problematic for some facial soft-tissue corrections[56].

## Non-biodegradable products

Non-resorbable fillers include homogenously constructed liquids such as silicone, and resorbable liquids that contain either non-resorbable microspheres or particles. These products offer longevity and lower treatment costs, but adverse events, should they occur, can be serious and of long duration.

### *Silicone*

Only purified medical-grade liquid silicone approved for injection into the human body should be employed for soft-tissue augmentation[57]. Its use necessitates specific techniques to achieve favorable outcomes and to prevent migration and nodule formation. Additionally, corrections where total treatment volumes can be high, such as in HIV facial lipoatrophy, require multiple injection sessions at intervals of at least one month to allow adequate collagen deposition around injected microdroplets[57]. Adverse reactions include foreign-body granulomas appearing up to many years following treatment[58].

Use of highly purified silicone oil has been described in a cohort of 77 HIV-infected patients with predominantly (87%) mild or moderate facial lipoatrophy[59]. Overall, the mean injection volume for complete lipoatrophy correction was 8.4 ml, but in patients with severe lipoatrophy the mean volume was 16.9 ml, necessitating a mean treatment duration of 60 weeks. No major adverse events were observed during treatment or the 27-week mean follow-up period[59]. However, given the controversial history of injectable liquid silicone use in soft-tissue augmentation[57], rigorous, well-designed studies are essential to evaluate the long-term safety of newer, highly purified silicone products for correction of HIV lipoatrophy.

### *Polymethylmethacrylate*

Polymethylmethacrylate (PMMA) is biocompatible and non-degradable and has been used over many years for medical applications, contact lenses, artificial joints, and pacemakers. Polymethylmethacrylate (Artefill®; Artes Medical Inc, USA) as microspheres suspended in a bovine collagen-containing gel has FDA approval for correction of nasolabial folds. Following injection, the collagen biodegrades over 1-3 months, and the non-resorbable PMMA microspheres remain acting as a matrix to promote new collagen deposition[14]. The bovine collagen component necessitates pretreatment skin testing[34].

Use of PMMA for HIV facial lipoatrophy was reported in a series of open-label case studies, but both overall efficacy and safety data were lacking[60]. Some patients, particularly those with severe lipoatrophy, required retreatment after 12-18 months, although one series reported ultrasound-assessed increases in cheek thickness that was maintained for up to five years. The procedure appeared safe, with no reported unexpected adverse effects, infections, or severe inflammation[60]. However, good long-term safety data in HIV-infected populations are needed as late-onset nodules, appearing 2-5 years following correction of rhytids, have been reported in HIV-uninfected individuals[61].

### *Acrylic polymer gels*

Acrylic polymer gels contain cross-linked polymers formed from acrylamide. The quantity and nature of the cross-linking agent influence gel characteristics and biological properties. Hydrogels have a high water content and are biocompatible. Following injection they are well tolerated and are absorbed slowly over many years, either dissolving or remaining in place by means of a connective capsule[14]. Both polyacrylamide and polyalkylimide hydrogels are used as soft-tissue filling agents.

Polyacrylamide gel contains 2.5% cross-linked polyacrylamide bound to 97.5% pyrogen-free water. The efficacy of polyacrylamide for the treatment of HIV facial lipoatrophy was assessed in two comparative, open-label, single-site studies discussed previously under autologous fat[30,31]. The number of treatments was based on subjectively assessed surgical criteria and either patient desire[30] or subjectively assessed baseline facial lipoatrophy severity[31]. Efficacy at 24 weeks assessed by ultrasound indicated cheek thickness in polyacrylamide-treated subjects was not different to cheek thickness in subjects who received either autologous fat or PLLA (p = 0.69)[30]. The second study indicated increased durability in polyacrylamide recipients, with only 8% clinically assessed as requiring retreatment at week 48 compared to 88 and 85% of autologous fat and PLLA recipients, respectively[31]. Although no serious adverse events were reported, overcorrection necessitated polyacrylamide removal in two (2%) recipients[31].

Polyalkylimide hydrogel is comprised of alkylimide-amide groups (4%) bound to pyrogen-free water (96%). The efficacy and safety of immediate versus delayed polyalkylimide gel for correction of HIV facial lipoatrophy was investigated in a small, open-label, single-site,

randomized study[62]. Participants, 74% of whom were assessed as having moderate to severe facial lipoatrophy, were randomly assigned to receive either immediate treatment (day 0 with touch-up at week 6; n = 15), or delayed treatment (week 12 with touch-up at week 18; n = 16), although additional treatment could be given to achieve optimal correction. At week 12, subjectively assessed lipoatrophy severity was perceived by both clinicians and patients as improved in the immediate treatment group relative to the delayed group (p < 0.0001 and p = 0.002 respectively). Scores for both quality of life and anxiety improved in the immediate treatment group compared to untreated participants (p = 0.01 and p = 0.02 respectively). Adverse events were of short duration, with no serious adverse events and no cases of nodules, necrosis, or infection reported over 48 weeks. At week 48, there was no between-group difference for any efficacy or safety endpoint. Facial lipoatrophy severity was perceived as unchanged from week 12 in the immediate group. In total, 13 (42%) participants (9 immediate, 4 delayed) required supplementary treatment as the baseline and single top-up injections were insufficient for lipoatrophy correction. The median volume of polyalkylimide injected over 48 weeks was 16.0 ml (IQR 12-20)[62].

Use of polyalkylimide gel has also been described in several HIV-infected cohorts. In one cohort of 73 adults, volumes of up to 35 ml were injected without any major adverse effects[63]. In a small cohort (n = 11), adverse effects were minimal and aesthetic benefits were perceived to persist 18 months posttreatment[64]. The absence of infection and/or inflammation may reflect the use of post-procedure antibiotic prophylaxis[62-64]. Following injection, polyalkylimide gel acts as an endoprosthesis and so it can be relatively easily removed by percutaneous puncture and manual pressure[65] should facial fat recover.

### *Implants*

Malar and sub-malar augmentation with alloplastic implants has been used over many years to restore facial structure and may be beneficial in HIV-infected individuals, provided fat loss is not profound. In contrast to injectable fillers, which are minimally invasive, implantation necessitates a surgical procedure usually under general anesthesia. Polymeric silicone implants and more recently expanded polytetrafluoroethylene (e-PTFE) and high-density porous polyethylene implants are utilized[66]. Potential implant problems include incorrect positioning, implant migration, displacement,

or extrusion and infection[66]. Worsening fat loss post-implantation may also produce a lumpy appearance.

Silastic® malar implantation has been described in a cohort of 39 patients with HIV-associated facial lipoatrophy, with seven (18%) also receiving postoperative augmentation with a soft-tissue filler[67]. Although no major surgical complications were reported, there were four late-onset events, one incorrectly positioned implant, and three delayed infections[67]. In a retrospective case series, eight patients received sub-malar implants and 14 with more severe lipoatrophy received larger, custom-made silicone implants[68]. Adverse events included two wound infections, one postoperatively and one delayed, both of which necessitated implant removal[68]. Subcutaneous augmentation material implants manufactured from e-PTFE have been used alone and in concert with soft-tissue filling agents for HIV facial lipoatrophy[69]. Implants composed of low-porosity e-PTFE materials may be preferable to solid Silastic® or high-density porous polyethylene for correction of HIV lipoatrophy, as capsule formation and fibrous tissue in-growth are limited with e-PTFE, thereby enabling easier removal should facial fat recover over time[66].

## Conclusions

Despite the substantial increase in options for soft-tissue augmentation in recent years, well-performed clinical studies in individuals with HIV facial lipoatrophy remain sparse. Available data indicate most products are clinically safe, at least in the short term, and can provide aesthetic improvement and improve well-being, social functioning, and quality of life. Comparative studies are few, and to date only three prospective, randomized controlled studies, one with objective endpoints, have evaluated the efficacy of soft-tissue filling agents in HIV-infected adults.

Research to define and compare the most appropriate and efficacious soft-tissue filling agents has been hindered by a number of factors. Firstly, there is a lack of consensus on how to best define and assess HIV facial lipoatrophy. Currently, there are no universally accepted validated diagnostic criteria and/or tools to assess lipoatrophy severity. Secondly, the lack of validated measure/s of facial soft-tissue thickness or volume makes evaluation of treatment efficacy problematic. Although standard objective methods such as dual-energy X-ray absorptiometry (DEXA) and abdominal CT have been developed to assess body composition, facial fat is not quantitated. Newer methods such as three-dimensional laser scans[20] and MRI[70] appear

promising and require further evaluation in clinical trials of interventions for HIV facial lipoatrophy. Additionally, efficacy and safety endpoints should be comparable across studies, with subjects followed for at least two years to assess durability and long-term safety.

Currently available filling agents can provide cosmetic improvement, but they are not a panacea and do not address fat loss in other body regions. Restoration of lost fat mass is very gradual, necessitating long-term facial lipoatrophy correction. Biodegradable fillers require ongoing maintenance for continued aesthetic benefits, making them an expensive and at times unaffordable option. Limited data indicate permanent fillers can provide long-term correction, but their permanence may become problematic should lipoatrophy resolve. Given that the future outcome for individuals with HIV facial lipoatrophy is unknown, further well-designed, comparative studies with objectively assessed endpoints are needed to ascertain optimal treatments for this distressing condition.

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