HIV-associated lipodystrophy syndrome affects approximately 50% of HIV-positive patients, particularly those receiving antiretroviral therapy based on nucleoside reverse transcriptase inhibitors and protease inhibitors. Growing evidence suggests that certain antiretroviral drugs may precipitate or exacerbate lipoatrophy and associated metabolic abnormalities, and this is an important consideration when selecting appropriate treatment regimens. However, because of problems of cross-resistance among antiretroviral drug classes and other treatment-related toxicities, it is likely that, at some stage, the HIV-infected patient will have to take drugs that confer a risk of development of lipodystrophy syndrome.

Combination therapy for HIV, known as highly active antiretroviral therapy (HAART), has dramatically altered the prognosis for the HIV-infected individual. With optimal use of HAART, which includes regular monitoring of viral load, viral resistance, and compliance with medication, HIV infection has changed from being a fatal disease to a lifelong infection. However, HAART-related lipodystrophy syndrome, and especially facial lipoatrophy, is of great concern for patients and physicians involved in HIV care. For the patient, facial lipoatrophy is a major stigma that affects self-esteem and social interaction, and in some cases, it is a cause of noncompliance with HAART.

Accordingly, many treatment-experienced HIV patients are requesting, and being treated with, various dermal fillers for cosmetic correction of facial lipoatrophy. Prior to the introduction of HAART, when life expectancy for the HIV-infected individual was severely limited, permanent fillers were widely used for this purpose. Because these products remain in situ indefinitely and the facial soft tissues change over time, the permanent fillers are no longer a satisfactory treatment option. Now that HIV infection has been transformed into a chronic but not necessarily life-threatening disease, there is an urgent need for a safe, biodegradable, and biocompatible alternative dermal filler for treating HIV-associated facial lipoatrophy.

(Aesthetic Surg J 2006;26(suppl):S35-S40.)

Following the introduction of highly active antiretroviral therapy (HAART) in 1996, the prognosis for patients infected with human immunodeficiency virus (HIV) has changed dramatically. Whereas patients could previously expect to live for another 10 to 15 years after being diagnosed with acquired immune deficiency syndrome (AIDS), they now face the prospect of coping with a life-long infection that requires continuous antiretroviral therapy but does not necessarily shorten their survival. However, antiretroviral therapy must be taken on a regular basis, with strict attention to the recommended treatment schedule. Poor adherence to HAART is likely to result in suboptimal virologic suppression and, consequently, to promote the development of drug-resistant viral strains.

Not only can the consequences of poor compliance with antiretroviral therapy be devastating, the medication itself causes severe symptomatic and metabolic side effects in many patients. For the HIV-infected patient receiving HAART, one of the more dreaded sequelae is lipoatrophy of the face—perhaps the most obvious outward sign of HIV infection. This condition is distressing to the patient and, in many cases, leads to low self-esteem, depression, and social withdrawal. Studies suggest a strong causal relationship between the use of protease inhibitors and certain nucleoside analogues (most notably stavudine and didanosine) and the development of facial lipoatrophy.

Facial lipoatrophy is only one of several clinical manifestations of the metabolic changes associated with HAART, which collectively make up the lipodystrophy syndrome. This comprises dyslipidemia, insulin resistance, and abnormal glucose homeostasis, as well as altered fat distribution—loss of subcutaneous fat in the head, shoulders, and upper arms. The extent of these changes varies greatly from person to person but can be severe enough to cause significant disfigurement...

(Aesthetic Surg J 2006;26(suppl):S35-S40.)
face, limbs and buttocks, and relative accumulation of fat in the abdomen and dorso-cervical fat pad (the so-called “buffalo hump”). Although there is an initial increase in fat deposits in the limbs during the first few months of HAART in antiretroviral-naïve patients, this is followed by a progressive decrease over the long term.

Abnormalities of body-fat composition have been reported in 40% to 50% of ambulatory HIV-infected patients. Estimates of the prevalence of lipodystrophy syndrome are more variable, ranging from 10% to more than 80% in cross-sectional studies. Facial lipoatrophy rates may be even higher, depending on the sex and age of the patient population and the type and duration of antiretroviral therapy.

**Pathogenesis of Facial Lipoatrophy**

The type and duration of HAART strongly influence the severity of facial lipoatrophy in HIV-infected patients, with protease inhibitor/nucleoside reverse-transcriptase inhibitor combinations producing the most pronounced changes.

Protease inhibitors can inhibit lipogenesis and adipocyte differentiation, stimulate lipoysis, and impair expression of the adipogenic factor sterol regulatory element-binding protein-1 (SREBP1). Nucleoside-induced lipoatrophy may be partly due to mitochondrial injury resulting from inhibition of mitochondrial DNA polymerase gamma within the adipocyte and depletion of mitochondrial DNA, although the exact mechanisms underlying this effect remain unclear.

Combinations of nucleoside analogues and protease inhibitors also exert synergistic inhibitory effects on adipocyte differentiation and adipogenesis, both in vitro and in vivo. The possible mechanisms underlying the lipoatrophy syndrome have recently been comprehensively reviewed.

**Assessment of Lipodystrophy**

Peripheral fat loss in HIV-infected patients has been evaluated in several studies. Visceral fat accumulation can be assessed by computed tomography, but since this procedure involves exposure to ionizing radiation, it should not be used without good reason. To date, there are no validated techniques for assessing the severity of facial lipoatrophy, although ultrasonography has been used successfully for this purpose.

A system for classifying the severity of facial lipoatrophy, based on a 4-grade rating scale, has been proposed. According to this system, facial lipoatrophy is graded as follows:

- Grade 1 – mild and localized facial lipoatrophy, with near-normal facial appearance.
- Grade 2 – deeper and longer central cheek atrophy, with early signs of the facial muscles (especially zygomaticus major) showing through the skin.
- Grade 3 – even deeper and wider areas of atrophy, with the muscles clearly showing through the skin.
- Grade 4 – atrophy covering a wide area and extending towards the orbit; the facial skin lies directly on the muscles and bone structures over wide areas.

**Treatment Options**

Although there are a number of treatment options for the patient with facial lipoatrophy, the physician’s first priority should be to prevent development of this condition by selecting an appropriate antiretroviral drug regimen. With the expanding choice of drugs available for initiating HAART, the goal of averting facial lipoatrophy has now become more feasible. However, because of the problem of poor patient compliance with HAART and the potential risk of viral resistance to first-line therapy, situations will continue to arise whereby patients are necessarily placed on antiretroviral therapies that increase the risk of lipoatrophy.

For the patient showing early signs of facial lipoatrophy, modification of existing antiretroviral therapy—usually by replacing stavudine or zidovudine with a less toxic agent such as abacavir—is one possible option. Another approach is to increase the volume of facial subcutaneous tissue through pharmacological means. This involves the use of glitazones—ligands for the transcription factor peroxisome proliferator-activated receptor gamma, which is essential for adipocyte differentiation. In patients with type 2 diabetes, rosiglitazone has been shown to increase body fat mass (predominantly in the subcutaneous compartment) by ~4 kg over a 12-week treatment period. This effect is accompanied by an improvement in insulin sensitivity, but these benefits are partly offset by a significant elevation of plasma lipids. For this reason, use of glitazones for treatment of HAART-associated lipoatrophy cannot be recommended outside the clinical trial setting.

**Dermal fillers**

An alternative approach to the treatment of facial lipoatrophy is the use of dermal fillers to restore lost facial volume. During the last decade, dermal fillers (both degradable and nondegradable varieties) have been widely used for correction of age-related wrinkles and restoration of lost facial volume. The first fillers to be launched on the market more than 20 years ago were collagens of...
animal origin; these have since been supplemented by human collagen–based products.21 Today there are safer, biocompatible fillers that are associated with a very low risk of granuloma or inflammatory reactions.22

Before the HAART era, nonbiodegradable fillers were widely used for treatment of facial lipoatrophy and, given the limited life expectancy that HIV-infected individuals faced at that time, this approach was not entirely unacceptable. However, now that life expectancy for the HIV-infected individual has improved to a level comparable to that for the seronegative individual, we must reconsider this approach.

Nonbiodegradable dermal fillers (eg, polyalkylimide, polymethylmethacrylate, and silicone) remain in situ indefinitely, which is an unsatisfactory treatment option since facial soft tissues change over time. After modification of HAART in response to the onset of facial lipoatrophy, the patient might potentially regain some lost subcutaneous fat; under these circumstances, the use of a permanent filler could result in an unacceptable degree of over-correction to the previously lipoatrophic face.

Among the currently available biodegradable dermal fillers are poly-L-lactic acid (PLLA), hyaluronic acid, and collagen. Autologous fat can also be used to correct facial lipoatrophy, although the transplantation procedure is more invasive and time-consuming than that for injectable fillers. Moreover, in HIV-infected patients undergoing HAART it may prove difficult to harvest sufficient quantities of fat. The recovery time following fat transplantation is also prolonged compared to the instant result provided by the injectable products.

Biodegradable fillers

The first dermal filler to be approved by the Food and Drug Administration (FDA) for the treatment of HAART-associated facial lipoatrophy was the PLLA product, Sculptra (Dermik Laboratories, Berwyn, PA). This currently remains the only approved product on the US market for use in the treatment of HAART-associated facial lipoatrophy. In the VEGA trial, an open-label, noncomparative pilot study involving 50 HIV-infected patients with diminished subcutaneous facial fat, Sculptra was demonstrated to improve facial cutaneous thickness.18 The proportion of patients achieving a cutaneous thickness >10 mm was 19% at week 6 and 61% at week 48, and this therapeutic endpoint was maintained at week 96 in 43% of patients. Treatment complications were mild in nature, although palpable subcutaneous micronodules were observed in 22 (44%) patients; in 6 of these patients, the nodules resolved spontaneously after 2 years.

In another study focusing on quality-of-life issues, PLLA treatment had a positive effect on anxiety/depression, as measured on a visual analogue scale, over the 24-week study period.23 For cosmetic correction of facial scars, the estimated duration of clinical effect of PLLA is ~18 months.24 However, the durability of effect of PLLA in the treatment of HAART-associated facial lipoatrophy remains to be established. In a recent study in which patients underwent repeated treatment with PLLA over a 5-month period, the cosmetic effect was maintained for up to 2 years in some cases.25 However, late-onset foreign-body granulomas have been reported after PLLA treatment.26

Non-animal stabilized hyaluronic acid (NASHA) approaches the ideal dermal filler material for the treatment of facial lipoatrophy on account of its biodegradable nature and biocompatibility. Extensive clinical experience gained from intradermal application of NASHA in over 3 million instant aesthetic treatments for correction of facial wrinkles and folds confirms its effectiveness, safety, and extremely low allergic potential. In the US, the NASHA product Restylane was granted FDA approval in 2003 for the treatment of facial wrinkles. The new NASHA product Restylane SubQ allows larger volumes to be injected in the cheek and malar regions, and on the basis of our initial clinical experience, it appears to be an attractive treatment option for facial lipoatrophy. To date, we have treated 13 patients (3 females and 10 males) with HIV-associated facial lipoatrophy with Restylane SubQ. Of these, 9 patients received single injections of 2 mL of Restylane in each cheek, and the other 4 patients required repeated treatment. The product was administered using a multiple tunneling technique to place ~0.1 to 0.2 mL of product in each tunnel (~5–6 cm in length). All of the patients experienced good cosmetic improvement and were well satisfied with the results. One patient had clumping of the product, 1 patient had swelling of the left cheek that lasted for 1 week, and 1 patient showed volume loss after 6 months.

We present two case studies that illustrate the aesthetic results obtained with Restylane SubQ in the treatment of facial lipoatrophy in HIV-infected patients.

The patient depicted in Figure 1 is a 42-year-old woman who had been receiving HAART for 9 years, and had undergone successful treatment with PLLA for facial lipoatrophy 2 years prior. The patient received 2 mL of Restylane SubQ in each cheek, and the procedure was repeated 6 weeks later (total injection volume 4 mL in each cheek) to produce a natural looking appearance.
The patient shown in Figure 2 is a 47-year-old man who had been receiving HAART for 11 years and had experienced progressive facial lipoatrophy for the past 4 years. He was treated with Restylane SubQ (2 mL in the lower and upper cheek on each side), and this treatment was repeated 2 weeks later (total injection volume 4 mL in each cheek), resulting in a very satisfactory cosmetic outcome.

**Nondegradable fillers**

Bio-Alcamid (Polymekon, Milan, Italy) is a nonreabsorbable polyacrylamide hydrogel composed of polyalkyl-imide-groups. A published study has demonstrated the efficacy and tolerability of Bio-Alcamid in a cohort of 73 patients with HAART-associated lipoatrophy. Although this is a nonbiodegradable filler, it is reported to be relatively easy to remove from the implantation site, if necessary.

Silicone has been used for soft-tissue augmentation, but it cannot be recommended because of its potential adverse effects, such as inflammation and granuloma formation, and the risk of product migration. A recently published open-label pilot study evaluated standard-viscosity (1000 cSt) silicone oil in the treatment of 77 patients with HIV-associated facial lipoatrophy and found this highly purified product to be safe and effective. However, its long-term effects remain to be established.

**Autologous fat transplant**

The techniques of autologous fat transplantation have recently been comprehensively described by Sydney Coleman. Harvesting, refining, and re-injecting autolo-
gous fat is a time-consuming procedure that requires general anesthesia and, occasionally, hospitalization, and involves prolonged down-time for the patient compared to other injectable treatments. Nevertheless, autologous fat transplantation has been used successfully in the treatment of HAART-associated lipoatrophy; structural fat grafts placed in the malar pockets using a transoral approach are reported to provide a sustained cosmetic effect for 12 to 24 months posttreatment.31

Conclusion

The improvement in survival that has resulted from the adoption of HAART for HIV-infected individuals is achieved at the expense of a number of metabolic alterations that are collectively referred to as “lipodystrophy syndrome.” Facial lipoatrophy is the most stigmatizing manifestation of this syndrome, and it presents a difficult therapeutic challenge. Erosion of self-image and self-esteem, problems with social and sexual relations, anxiety, depression, social withdrawal, and unintentional HIV disclosure are commonly reported complaints in studies of the impact of lipodystrophy. Possible approaches for management of this condition include switching HAART, usually from didanosine-, stavudine- and zidovudine-containing regimens to abacavir- and tenofovir-based regimens. Glitazones are effective in increasing subcutaneous fat stores, but have the drawback of elevating plasma lipid levels. Facial soft tissue augmentation through the use of dermal fillers (biodegradable and nonbiodegradable) and autologous fat transplants is an alternative treatment option. Since HIV infection is now chronic and treatable, rather than fatal, biodegradable and biocompatible dermal fillers should be considered as the treatment of choice for patients with HAART-associated facial lipoatrophy. To date, the only dermal filler that has been approved by the FDA for the treatment of HAART-associated facial lipoatrophy is PLLA (Sculptra). However, this product requires repeated injections over several weeks to months. In contrast, the new NASHA product Restylane SubQ offers an instant cosmetic result, and appears to be a promising treatment for HAART-associated facial lipoatrophy. ■

References

19. John M, McKinnon EJ, James IR, Nolan DA, Hermann SE, Moore CB, et al. Randomized, controlled, 48-week study of switching stavudine and/or protease inhibitors to combivir/abacavir to prevent or reverse


This supplement is funded through sponsorship by Q-Med.

Restylane SubQ is not approved for any use by the US Food and Drug Administration.

Accepted for publication August 10, 2005.


Copyright © 2006 by The American Society for Aesthetic Plastic Surgery, Inc.

1090-820x/$32.00