Lipodystrophy in the Patient with HIV: Social, Psychological, and Treatment Considerations

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According to the World Health Organization (WHO), there are currently 1.3 million people in the United States living with HIV. Worldwide, the WHO estimates that 33.2 million people are infected with HIV.

Previously, HIV/AIDS was considered to be uniformly fatal. With the introduction of highly active antiretroviral therapy (HAART), HIV has become a chronic, manageable disease in countries that are able to provide this therapy. The preservation of lives has not been without complications. In these patients, metabolic and stereotypical body disfiguring fat changes have emerged and have been lumped under the term lipodystrophy. Lipodystrophy and fat accumulation are generally thought to be separate yet overlapping phenomena. The prevalence rates for lipodystrophy may be as high as 25% to 38%; estimates for fat accumulation vary widely (from 14%–63%). Far from being “purely cosmetic,” these fat changes can have a profoundly negative social and psychological impact, causing patients to feel disfigured, isolated, and stigmatized. Further, lipodystrophy may also negatively impact compliance with HAART. While there is evidence that the use of new HIV medications can prevent the development of these fat changes, many patients already manifest fat abnormalities; switching HAART, especially after lipodystrophy has progressed, offers only limited benefit. In addition, many resource-poor nations continue to rely on older HAART out of necessity. Because of this, methods are needed to address disfiguring body shape changes. The authors review the prevalence of lipoatrophy and lipohypertrophy, focusing on the impact on patients as well as reviewing available treatment options. (Aesthetic Surg J 2008;28:443–451.)

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Initially, these metabolic and body fat changes were lumped under the term lipodystrophy, first described in 1998. Early studies reported reciprocal changes in peripheral lipodystrophy with central fat accumulation, frequently called “redistribution syndrome.”

Prevalence estimates varied widely, from 11% to 83%, in part because of variable definitions and methodology employed by researchers. More recently, there is growing consensus that lipoatrophy and fat accumulation are separate, though frequently overlapping, phenomena.

The metabolic changes carry cardiovascular risk. Equally important, the physical changes are associated with poor body image and, even worse, a general perception of ill health and, potentially, a reduced adherence to antiretroviral therapy. Here, we review the prevalence of lipoatrophy and lipohypertrophy, focusing on impact on patients and available treatment options.

DEFINITIONS AND PREVALENCE

Lipodystrophy was initially described as a syndrome that involved the redistribution of visceral and subcutaneous fat along with associated metabolic abnormalities, including dyslipidemia and insulin resistance.

Data suggest that patients with both peripheral lipoat-
rophy and central fat accumulation have defective postprandial fatty acid disposal and storage by peripheral adipocytes. Although there are hypothetical links, most consider the fat changes to be distinct processes of lipoatrophy and lipohypertrophy, with overlapping incidence. The cross-sectional Fat Redistribution and Metabolic Change in HIV Infection (FRAM) study was of 425 HIV-infected men and 152 age-matched controls. Using the concordance of patient-reported fat change over the previous 5 years with a researcher’s determination that the patient had more/less fat at a given site compared with healthy people, along with visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) measured with magnetic resonance imaging (MRI), FRAM found no correlation between changes in central fat and peripheral fat in HIV-infected men. MRI measurements showed that HIV-infected men with clinical lipoatrophy had a smaller volume of adipose tissue in central sites and less VAT than did HIV-positive men without clinical lipoatrophy. The presence of peripheral lipoatrophy did not positively correlate with the presence of central lipohypertrophy. FRAM data argue strongly for separate processes determining peripheral lipoatrophy and central lipohypertrophy. Other studies have drawn similar conclusions. Diagnosis is typically made by patient and provider description. Studies employing anthropometrics, computed tomography, and/or MRI scans for quantification of central and visceral fat, and dual energy X-ray absorptiometry (DEXA) for quantification of limb fat can be completed but are frequently cost prohibitive and rarely yield meaningful results in clinical practice.

Because radiographic studies generally are not the basis for diagnosis, the staging and documentation of progression of disease become important. A grading scale for the classification of the severity of lipoatrophy was developed by James et al. and is clinically useful to document deterioration. Grade 1 is considered localized with minimal lipoatrophy and near normal appearance. Grade 2 involves central cheek atrophy with minimal appearance of facial muscles. Grade 3 involves more prominent cheek atrophy with facial muscles clearly visible. Grade 4 atrophy extends up to the eye socket with facial muscles approximating the skin directly (Figure 1).

**Figure 1.** A, Lipoatrophy grade 1 with limited fat loss and near normal appearance. B, Lipoatrophy grade 2 with limited visualization of facial muscles. C, Lipoatrophy grade 3 with visible facial musculature and marked buccal fat atrophy. D, Lipoatrophy grade 3 to 4 with extensive fat atrophy extending up the face with skin just overlying the musculature.
LIPOATROPHY
Lipoatrophy refers to the loss of subcutaneous fat noted after the initiation of HAART.\textsuperscript{16} Loss occurs in the face (impacting the full face, but especially the buccal fat pads); extremities (with lower extremity loss generally more pronounced than upper); and the buttocks as well as abdominal areas. The face appears to be “wasted,” the veins in the extremities more pronounced, and the buttocks appear to have sagging skin because of a profound reduction of fat. Population-based prospective studies documenting incidents of lipodystrophy-associated symptoms, as well as prospective cohort studies confirmed by DEXA scans, suggest that lipoatrophy has a 22\% to 38\% prevalence within 1 to 2 years of initiation of HAART.\textsuperscript{17–19} Data based on concordance of patient self-report and physical examination from the FRAM study indicate that prevalence rates for lipoatrophy at different sites (cheeks, face, arms, buttocks, and legs) range from 11\% to 24\% in men and from 11\% to 16\% in women.\textsuperscript{4,20}

Pathogenesis likely involves mitochondria dysfunction leading to adipose cell loss and adipocyte dysfunction.\textsuperscript{21–23} Proinflammatory cytokines such as tumor necrosis factor–\textalpha may play a role.\textsuperscript{24} Ultimately, it is a multifactorial phenomenon involving metabolic dysregulation, HAART, immune restoration, and the virus itself.\textsuperscript{25–28} The use of thymidine analogues and stavudine in particular have been the most strongly associated with lipoatrophy and mitochondria dysfunction.\textsuperscript{27,29,30}

It is critically important to differentiate lipoatrophy caused by HIV treatment from HIV wasting syndrome, a consequence of advancing disease. With HIV-associated wasting, there is a loss of muscle and a generalized loss of fat thought to be secondary to the metabolic effects of the virus itself. Hormonal disturbances have also been noted in men, with decreased levels of testosterone contributing to muscle wasting and decreases in bone density. The treatment for disease-induced wasting is distinguished from treatment-induced lipoatrophy and includes HAART, testosterone replacement if indicated, and anabolic steroids in some cases.\textsuperscript{31,32}

FAT ACCUMULATION
Lipohypertrophy involves abnormal accumulation of neck fat and hypertrophy of the dorsal cervical fat pad (“buffalo hump”) with accumulation of visceral adipose tissue. Lipoma formation and excessive fat deposition in the breasts and mons pubis can also occur (Figure 2).\textsuperscript{21} While most practitioners agree about the prevalence of lipoatrophy in HIV-infected individuals, there is increas-

**Figure 2.** A, Breast tissue fat accumulation. B, Mons pubis fat accumulation. C, Facial lipoatrophy and neck tissue fat accumulation. D, Accumulation of fat in the upper back (“buffalo hump”).
ing debate about the prevalence of fat accumulation in these patients. Longitudinal data from the MultiCenter AIDS Cohort Study (MACS) indicate that changes in waist circumferences occurring over 4 years did not differ between HIV-positive and -negative subjects.\textsuperscript{30} Similarly, the Women’s Interagency HIV Study found that the incidence of central lipohypertrophy was similar in HIV-positive women and HIV-negative controls.\textsuperscript{53} It is challenging to separate abnormal fat accumulation caused by HIV and/or HAART from reconstitution of body fat in a patient previously sick with AIDS and now better on HAART, as well as changes typically associated with aging. Though the prevalence of this phenomenon is increasingly debated, most clinicians can recognize its presence. Cross-sectional studies involving DEXA and computed tomography indicate that 14% to 63% of patients initiating HAART experienced central lipohypertrophy within 1 to 2 years.\textsuperscript{34,35}

Given the controversy surrounding fat accumulation and various inclusion criteria for studies, along with different methods used to quantify visceral fat accumulation, a discussion of the causes of lipohypertrophy are challenging.

Lipohypertrophy has been variably linked with use of some PIs via the inhibition of proteins involved in lipid metabolism such as the low-density lipoprotein receptor–related protein and cytochrome p450 3A.\textsuperscript{36,37} However, the effects of antiretroviral therapy on specific fat deposits might not be linked to a single drug class. Pathogenesis involves adipocyte hypertrophy and increased cell numbers. It is most likely a multifactorial phenomenon involving metabolic and cytokine dysregulation, HAART, immune restoration, and HIV disease itself.

**SOCIAL, PSYCHOLOGICAL, AND TREATMENT IMPACT OF LIPOATROPHY**

It is important to understand that these fat changes can have a profoundly negative social and psychological impact. Patients see themselves as disfigured, isolated, and stigmatized. Such concerns cannot be considered “purely cosmetic.” Studies of both men and women with HIV-related body shape changes (fat atrophy or hypertrophy) showed significantly poorer body image compared with HIV-infected patients without lipodystrophy.\textsuperscript{5,10} A 2006 study based on focus groups of patients with HIV found that patients’ primary concerns across groups was with physical discomfort, impairment, and psychological and social distress caused by their lipodystrophy, including a fear that fat changes represented disease progression and fear of unintentional disclosure of their disease.\textsuperscript{38} Low self-esteem, poor body image, and depression are common sequelae of lipodystrophy. A 2004 study assessing quality of life issues associated with lipodystrophy found that 49% of patients with lipodystrophy experienced feelings of shame and 27% experienced a disruption of their sexual life.\textsuperscript{35} In addition, patients often feel stigmatized by the characteristic facies resulting from lipodystrophy.\textsuperscript{39} Data specifically pertaining to HIV patients with excess truncal fat show significantly worse general perceived health scores than in age- and sex-matched HIV-negative patients with other chronic conditions known to adversely affect quality of life.\textsuperscript{41}

Adherence to HAART is critical to successful treatment and the prevention of emerging resistance, which is permanent. Although some studies do not support an association of lipodystrophy with worsening adherence to HAART, this remains a concern.\textsuperscript{40} Some studies have suggested that patients’ perception of alterations in body fat distribution are associated with reduced adherence to antiretroviral therapy.\textsuperscript{12,13,41–43}

**Medical Treatments**

Although medical treatments for the metabolic complications associated with HAART have shown promise, medical treatments for fat changes have generally been disappointing. Diet and exercise reduces systolic blood pressure and weight and may somewhat diminish central fat accumulation; it may also worsen fat loss.\textsuperscript{44}

Modifying HAART has long been a popular technique for trying to reverse fat changes. The elimination of the thymidine analog may improve limb fat (approximately 0.4 kg limb fat at 12 months) but generally has no impact of visceral fat accumulation.\textsuperscript{45–47} The TARHEEL study, as one example, demonstrated moderate improvement in lipodystrophy by DEXA scan when patients were switched from stavudine containing HAART regimens to abacavir or zidovudine.\textsuperscript{30} However, the Mitox study ultimately found that in spite of calculable improvements in lipodystrophy, self-perception of lipoatrophy remained unchanged, suggesting that while switching medications may have some benefit, the psychosocial issues may remain.\textsuperscript{48} Switching PIs to another class often improves metabolic parameters but has very limited utility in reduction of central fat accumulation, seen only in a few studies, and no impact on lipoatrophy.\textsuperscript{47,48} When changing HAART, providers must be careful not to lose virologic control, and switching is not always an option for patients. An older approach of discontinuing HAART\textsuperscript{49} is not a therapeutically viable option.

The use of medications to directly treat fat changes have been equally disappointing, occasionally with worsening of some fat parameters. The utility of insulin sensitizing agents, such as thiazolidinediones, have been studied. There may be small improvement in fat with pioglitazone; rosiglitazone may raise triglyceride and low-density lipoprotein C levels and may not help with lipoatrophy.\textsuperscript{47,50,51} Metformin may have a modest effect on decreasing visceral fat, but at the cost of worsening subcutaneous fat.\textsuperscript{5} Both human recombinant growth hormone and growth hormone releasing hormones show promise for decreasing visceral fat; however, both compounds are expensive, require daily injections, and have potential toxicities.\textsuperscript{52–56} Finally, uridine is being studied to help with lipoatrophy for patients still on thymidine analog medications.\textsuperscript{57}
Restorative Treatments

Because medical treatment for lipoatrophy and fat accumulation have largely failed, and many patients already have deforming changes in fat, restorative procedures are needed. Facial lipoatrophy is an especially important issue for many patients, and facial filler products have become increasingly popular. They are generally divided into temporary and permanent fillers. In the United States, only poly-L-lactic (Sculptra; Sanofi-Aventis, Bridgewater, NJ) and injectable calcium hydroxylapatite implant in the form of a gel (Radiesse; Bioform Medical, San Mateo, CA) have been approved for use in HIV lipoatrophy. However, many other types of filler products are also employed, especially outside of the United States (Table). With all fillers, the purity of the injectable product and skill of the provider are very important factors to decrease risk of infection and disfigurement. Combinations of fillers and surgical procedures are often used to achieve the best aesthetic result.

Temporary fillers can last from 3 months to more than 24 months and usually require reinjection to maintain cosmetic results. Permanent fillers are not reabsorbed and induce fibroplasia around the injection sites. They are synthetic materials and are approved by the U.S. Food and Drug Administration (FDA) for dermal augmentation. Even though immediate results may be satisfactory, a gaunt appearance may become pronounced if lipoatrophy progresses. Few fillers have been formally tested in HIV patients and, among those tested, case series often report a relatively small number of subjects and often lack objective outcome measurements.32 Poly-L-lactic acid is a biocompatible and immunologically inert synthetic product that has been used extensively in HIV-infected patients.58 Its benefits include that it is effective in most cases, often lasts up to 96 weeks, and can be easily injected in the office. However, it requires multiple sessions (up to 5 treatment sessions spaced 4 to 6 weeks apart) and can be very expensive for patients who do not qualify for the patient assistance program.19,59 In an open-label, single-arm pilot study of 50 patients with severe facial lipoatrophy, 4 sets of injections, given every 2 weeks for 6 weeks, led to a median cutaneous thickness increase (6.8-mm increase at week 96) with no adverse events reported. However, 44% of patients had palpable but non-visible subcutaneous nodules.60 Figures 3 and 4

Table. Facial filler compounds

<table>
<thead>
<tr>
<th>Fillers</th>
<th>Compound</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poly-L-lactic (Sculptra)63</td>
<td>Biologically inert synthetic</td>
<td>1. Does not require intradermal testing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Rapidly effective, but requires multiple injections</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Can last up to 24 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. Can be administered in office setting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. Expensive</td>
</tr>
<tr>
<td>Injectable calcium</td>
<td>Injectable implant in form of a gel</td>
<td>1. Does not require intradermal testing</td>
</tr>
<tr>
<td>hydroxylapatite implant</td>
<td></td>
<td>2. Lasts 7–12 months</td>
</tr>
<tr>
<td>(Radiesse)19</td>
<td></td>
<td>3. Expensive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. Nodule formation in up to 5% of patients</td>
</tr>
<tr>
<td>Particulate fascia lata31</td>
<td>Cadaveric fascia fragments</td>
<td>1. Does not require intradermal testing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Expensive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Requires reinjections 2–3 months</td>
</tr>
<tr>
<td>Micronized allograft51</td>
<td>Cadaveric dermis</td>
<td>1. Intradermal testing recommended</td>
</tr>
<tr>
<td>Hyaluronic acid31</td>
<td>Hyaluronic acid</td>
<td>1. Does not require intradermal testing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Can last 6 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Requires large volumes—expensive option</td>
</tr>
<tr>
<td>Permanent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Artefill; Artecoll31</td>
<td>PMMA polymer suspended in bovine collagen</td>
<td>1. Intradermal testing recommended</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Risk of granuloma formation</td>
</tr>
<tr>
<td>Polyalkylamide31</td>
<td>Polyalkylamide</td>
<td>1. Non-reabsorbable, easily injected, and easily removed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Not generally available</td>
</tr>
<tr>
<td>1000 c-ST silicone (SilSkin)31</td>
<td>Silicone</td>
<td>1. Migration can occur if microdroplet serial puncture technique is not used</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Rejection can occur if compound is not pure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Granuloma and cyst formation can occur</td>
</tr>
</tbody>
</table>

ArteFill and Artecoll are manufactured by Artes Medical (San Diego, CA). Captique is manufactured by Inamed Aesthetics (San Francisco, CA). Juvederm is manufactured by Allergan, Inc. (Irvine, CA). Radiesse is manufactured by Bioform Medical (San Mateo, CA). Restylane and Perlane are manufactured by Medicis Aesthetics, Inc. (Scottsdale, AZ). Sculptra is manufactured by Sanofi-Aventis (Bridgewater, NJ). SilSkin is manufactured by RJ Development (Peabody, MA). PMMA, polymethyl metacrylate.
show the results of patients with mild to moderate facial lipoatrophy treated with Sculptra injections.

Transfer of autologous fat to the face is another popular and effective method. However, up to 40% of patients lack suitable donor sites, limiting its utility. One study of 29 HIV-positive subjects found the graft durable after 6 months.61 Touch-ups are frequently required. In approximately 10% of patients, there can be hypertrophy of the cheeks, creating a “hamster cheek” appearance, especially if the donor site is the dorso-cervical area and fat reaccumulates.62 The most common complications include bleeding, bruising, facial erythema and swelling, contour irregularities, and infections.63

Radiesse, which is made of calcium hydroxylapatite, is the other product that is also approved by the FDA for volume replacement in the face of HIV-positive individuals. The product is thicker and longer lasting as compared with Sculptra; therefore, good results are achieved with only one or two sessions. However, the syringes are only 1.3 mL in volume; therefore, this product is best recommended for people with grades 1 and 2 facial lipoatrophy not in need of too much volume for adequate correction. This product is also very good for correction of the nasolabial folds that are often seen when the degree of lipoatrophy is very pronounced and it should be used concomitantly with Sculptra for best results.

Of the permanent products currently available in the United States, highly purified 1000-cSt silicone oil is the most commonly used. It is injected using a very specific technique called serial puncture microdroplet technique. Because of this technique, there is no migration of the silicone oil. This treatment is approved by the FDA for the treatment of retinal detachment but not for intradermal or subcutaneous injections. The only permanent tissue filler approved by the FDA is ArteFill (Artes Medical, San Diego, CA), which is composed of polymethyl metacrylate (PMMA) in a mesh of collagen. PMMA has been used extensively in Europe and South America for the correction of HIV-associated lipoatrophy, but it has not yet been approved for this indication in the United States.

A face lift procedure accompanied by implant insertion is another popular option that generally achieves good results. However, as the lipoatrophy progresses, implants may become very obvious and eventually need

Figure 3. A, Pretreatment view of a 49-year-old man with grade 2 lipoatrophy. B, Posttreatment view 6 months after 3 treatments with Sculptra (Sanofi-Aventis, Bridgewater, NJ).

Figure 4. A, Pretreatment view of a 45-year-old man with grade 2 lipoatrophy. B, Posttreatment view 2 months following 1 treatment with Sculptra (Sanofi-Aventis, Bridgewater, NJ).
removal. Face lift procedures improve the sagging appearance of the skin; they do not, however, replace the lost volume. Therefore, concomitant volume augmentation with facial fillers is also required. These procedures are much more expensive and are generally reserved for severe lipoatrophy. Implants include polytetrafluoroethylene and silastic malar implants. Both are highly porous materials allowing cells and blood vessels to develop without granuloma formation.64,65

Removal of excessive fat can be successful if the patient, body location, and procedures are properly selected. Unfortunately, because abdominal fat accumulation with HIV is visceral, lipoplasty is not an option. Similarly, many other areas of fat accumulations associated with HIV do not lend themselves to lipoplasty. However, suction-assisted lipectomy, or lipoplasty, may be a good option for removal of fat in the dorsocervical area (“buffalo hump”) and submental areas.60 Lipoplasty can be performed with tumescent and ultrasound-guided techniques, with the tumescent technique helpful for the dorsocervical area as it is often fibrotic.32 Unfortunately, the “hump” may reaccumulate.62

CONCLUSION

HIV, once a near uniformly fatal disease, has been transformed into a chronic medical condition provided that HAART can be obtained and the patient is able to maintain adherence. In ideal circumstances and with early proper treatment and monitoring, many patients can have a near normal life expectancy.66,67 However, especially with the medications used in earlier HAART, stereotypical fat changes occur. There is evidence that use of new HIV medications may prevent the development of these fat changes.68,69 Unfortunately, many patients already manifest fat abnormalities. Switching HAART, especially after lipodystrophy has progressed, offers only limited benefit. Medical therapies for both facets of lipodystrophy have largely failed. Finally, many resource poor nations continue to rely on older HAART out of necessity. Because of this, methods are needed to address the disfiguring body shape changes.

The evidence indicates that these body changes cause real and significant psychosocial problems. Both lipoatrophy and fat accumulation can be devastating, creating feelings of stigmatization, depression, isolation, and poor body image. Potentially, they can lead to poorer adherence with HAART and therefore a loss of virology control. Fortunately, a number of restorative treatments are currently available, although insurance companies remain reluctant to cover them, deeming them “purely cosmetic.”

Current facial fillers have proven to be quite helpful. Certain areas of fat accumulation are amenable to removal. However, much work remains to develop additional treatments, both medical and surgical, to address these issues. Future studies will need to further delineate the pathophysiology of the fat loss and gain in order to develop new approaches. Until then, many patients turn to restorative dermatologic and surgical techniques to restore a normal appearance and lifestyle. We can manage and control HIV; we need to do so without creating additional stigma and psychosocial distress.6

DISCLOSURES

The authors have no financial interest in and received no compensation from manufacturers of products mentioned in this article.

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