HIV Lipodystrophy: Where are we after ten years?

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Ten years have passed since the first report of lipodystrophy at an HIV conference. The excitement and hope for a longer life that accompanied the arrival of Highly Active Anti-Retroviral Therapy (HAART) has been tempered by accounts of humps, bellies, and facial wasting. A decade on, many unanswered questions and misconceptions about HIV associated lipodystrophy persist with only a limited number of treatment options available. Frustrated and tired of waiting for answers from the medical community many people living with lipodystrophy have turned to the internet for advice, treatment and support in hopes of reversing some of the devastating effects of this stigmatizing syndrome.

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Lipodystrophy is a condition of abnormal fat redistribution that can lead to either **lipohypertrophy** (fat accumulation in specific areas of the body such as the neck, belly, upper torso, and breasts) or **lipoatrophy** (fat loss in the face, buttocks, arms and legs). An online survey of 695 people (predominantly white men, over the age of forty, living with HIV for over 10 years and with exposure to HAART for at least that long) found that 20% had considered suicide because of body shape changes associated with lipodystrophy. Almost 90% of respondents believed that their HIV medications caused lipodystrophy and 20% had stopped taking their HIV medications altogether due to this concern. Further, over 60% of respondents reported being rejected by potential sexual partners because of the syndrome. A similar number of respondents indicated that they had stopped looking into the mirror because of crippling body dissatisfaction. Nearly all of the respondents attempted to curb the effects of lipodystrophy with diet and exercise or by using costly facial reconstruction procedures, supplements and hormones—treatments not typically covered by insurance companies or drug assistance programs.

Lipoatrophy and HIV Medications

In 1999, the HIV drug Zerit was correlated with the development of lipoatrophy related fat loss under the skin.1 Since then, several studies have concluded that Zerit can affect the way our mitochondria (think: energy factories in our cells) work and multiply. Later studies also linked lipoatrophy to AZT, although at a lower rate than Zerit. Nucleoside reverse transcriptase inhibitors (NRTIs) like Zerit and AZT, keep HIV from altering the genetic material of healthy T-cells, thereby halting the reproduction of new virus cells. Additionally, NRTIs affect the mitochondria in fat cells under the skin, preventing them from multiplying and causing them to die. Also, those who have taken Zerit and Videx (another NRTI) together report more lipoatrophy than those taking Zerit alone. This combination is not recommended by guideline groups. It appears that Zerit and AZT make fat accumulation worse in the presence of protease inhibitors or non-nucleoside analogs (NNRTIs) like Sustiva, leading researchers to suspect that their negative effect may play a combined role. However, Sustiva taken with Viread (Tenofovir) and Epivir (3TC) seems to cause less lipoatrophy. Due to the high risk of developing lipoatrophy and neuropathy, the U.S. Department of Health and Human Services guidelines committee dropped Zerit from the list of recommended drugs for first line therapy for people new to HAART.

Viread (Tenofovir) and Ziagen (Abacavir), two other NRTIs in the same drug class as Zerit and AZT, do not seem to strongly correlate with the development of lipoatrophy. Some people have even reported a slow reversal of the fat loss after switching from Zerit or AZT to either Ziagen or Viread. However, even after a number of years most patients do not experience re-accumulation of fat in their faces after going off AZT or Zerit. It is also important to note that puzzling new data from a recent study by the AIDS Clinical Trials Group[2] showed that 20% of subcutaneous fat loss (loss in body fat closer to the skin's surface) occurred in a small percentage of patients starting HAART for the first time with a combination of Sustiva, Viread and Epivir. More studies are needed to determine why lipoatrophy still occurs in some patients in the absence of Zerit or AZT.

The sales of Zerit and AZT in the industrialized world have dropped considerably in the past years due to their effects on lipoatrophy. Unfortunately, these two drugs are among the primary HIV medications used in the developing world, so millions of people in poorer countries will continue to suffer with body changes.

Treatment Options for Lipoatrophy

In recent years many men have relied on an off-label injectable anabolic steroid called nandrolone decanoate (old trade name: Deca Durabolin), to "balance out" their bodies and add muscle to their thin extremities and buttocks affected by lipoatrophy. Even though Watson Laboratories ceased production of nandrolone in March of 2007, it is still available through prescription at compounding pharmacies for a low cost.[3]

Uridine (Nucleomaxx), a supplement made of sugar cane and available through a German supplier[4] may lessen lipoatrophy in patients taking Zerit, however it may also cause abdominal fat and high triglycerides. These side effects, along with high cost and bad taste, make Uridine an unpopular choice. However, for those who must take Zerit, Uridine may be a viable option to prevent or reverse lipoatrophy. Additionally, for those who are no longer taking Zerit, the diabetes drug Rosiglitazone (Avandia) works well for reversing lipoatrophy. There are side effects however, including weight gain and high triglycerides.

Since 2002 there have been a couple of non-permanent reconstruction procedures available to treat facial lipoatrophy. The face wasting reconstruction option, Sculptra (polylactic acid, old name: NewFill) entails an expensive series of multiple sessions, requiring additional touch ups that can be used to treat those moderately affected by lipoatrophy. Radiesse, another FDA approved option, seems to last a little bit longer but is also costly, requiring 3–5 sessions and yearly touch ups. Some patients treated with face wasting fillers experience side effects such as bruising and treatable granulomas (hardened pimple-like nodules). There are patient assistance programs available for both Sculptra and Radiesse.[5]

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There are no FDA approved permanent solutions for facial lipoatrophy, yet many in the U.S. seek tiny injections of silicone (Silikon 1000) from their doctors. Silikon 1000 can be used legally in an off-label manner for facial lipoatrophy. Silikon 1000 micro-injections can reconstruct patients' faces slowly over five sessions spaced one month apart. There is no patient assistance program for this option and sessions cost anywhere from $600 to $900 and here too, multiple sessions are required. Beware that very few U.S. doctors are well trained in this procedure.

Another permanent product, Polymethylmethacrylate (PMMA), has been used in Brazil for eight years and in Mexico for three with relatively positive results, though more time is

needed to determine the long term effects of this procedure. Usually 2-4 sessions are required and no yearly touch ups are needed. Short term, we have seen that PMMA can harden and be lumpy in certain patients, but many people seem pleased with the results. Artefill, a PMMA based product, is FDA approved for cosmetic purposes but not for HIV related lipoatrophy. Artefill is extremely expensive for the amount required to treat lipoatrophy so some HIV positive people in the U.S. go to Mexico or Brazil for the procedure where costs can range from $2000 to $6000. PMMA is not removable.

BioAlcamid (poly-alkylamide gel), also permanent, is an injectable filler unavailable in the U.S. (some patients travel to Mexico or Canada for injections). Unfortunately, BioAlcamid forms a "pocket" in the face and buttocks enabling bacteria to penetrate and posing a high risk of infection. As such, extreme caution is warranted before pursuing this option.

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It is critical to remember that no long-term data on these experimental facial reconstruction treatments are available, so one must weigh the risks of injecting a foreign substance into their body. Sadly, many people find that the emotional, psychological and social toll of living with lipoatrophy is so great as to justify these risks.

Experimental Treatment Options for Lipohypertrophy

Unlike lipoatrophy, researchers have not been able to attribute lipohypertrophy (fat gain in the belly, back of neck and breasts) to any specific medication or drug class. Protease inhibitors were once thought to be the main culprits, however researchers have recently discovered that fat gain in the belly may relate to inflammatory responses in the immune system when CD4 cells increase in number. This means that those who start HAART with a lower baseline CD4 count may see greater lipodystrophy. Moreover, recent data shows that patients with a CD4 count of over 250 who start a HAART regime with protease inhibitors boosted with Norvir plus Viread and Epivir, do not experience a gain in visceral fat (fat surrounding the internal organs). It is still too early to tell what happens to those on this particular regimen who start with lower CD4 counts. Some studies have shown that those who begin taking protease inhibitors in combination with Zerit, AZT or Zerit plus Videx, seem to have more visceral and hump fat gain than those who start on protease inhibitors with other drugs. It may be that the same drugs that are linked to lipoatrophy may also make fat gain worse, especially in patients who start HAART with fewer CD4 cells.

A common misconception promoted by a few pharmaceutical companies and echoed by some doctors is that HIV medications that do not increase cholesterol and triglycerides do not cause fat gain. On the contrary, several studies have shown that people taking lipid friendly drugs like Reyataz with Viread also gain fat in the belly after starting HAART.

Dr. David Nolan, a clinician and researcher at Royal Perth Hospital in Western Australia and an expert on fat metabolism and HIV, was asked about why visceral fat does not get "burned off" by Zerit and AZT like subcutaneous fat does. Dr. Nolan hypothesized that fat cells in the organ cavity may not be as susceptible as subcutaneous fat cells to the mitochondrial toxicity caused by Zerit and AZT.

Fat gain may also be linked to insulin resistance. Insulin resistance can cause glucose intolerance, which has been associated with fat gain, increased triglycerides, and the development of diabetes. Insulin is a hormone produced by the pancreas to control blood sugar-glucose. HIV medications may block or slow down the process by which insulin converts glucose to energy. In laboratory studies, Crixivan and higher doses of Norvir and Zerit have been shown to impair the action of insulin in fat and muscle cells. In this scenario the pancreas will tend to produce more and

more insulin to compensate for the decrease in function. High insulin levels may be present for years before type 2 diabetes develops. A glucose tolerance test (GTT) may reveal that problem easily but it is hardly used in clinical practices. Additionally, some people may have a genetic predisposition to insulin resistance. A sedentary lifestyle and a diet rich in sugars and animal fats may also compound this problem. In any case, insulin resistance may just be a part of the mystery of lipohypertrophy. There is no agreement among researchers whether or not monitoring insulin levels in HIV-positive people is justifiable or dependable as a tool to assess insulin resistance and fat gain.

The full body dual x-ray absorptiometry (DEXA) scan is the gold standard test in lipodystrophy. It is a highly valuable test that can provide information about body fat, muscle mass and bone density (low bone density has been associated with HIV in several studies.) Both Medicare and private insurance often cover this inexpensive test. While the scan cannot differentiate between fat accumulated in the belly on under the skin in the abdominal area, it can be useful as a baseline to assess body changes and to justify reimbursable therapies for fat, muscle, and bone mass.

Treatment Interventions for Lipohypertrophy

Some people have switched from protease inhibitors to Viramune or Sustiva to combat visceral fat gain, but this has not been shown to make a difference. It is not yet known what happens to belly fat when a patient switches from Zerit or AZT to Viread or Ziagen while taking protease inhibitors or non-nucleoside analogs like Sustiva or Viramune.

The recombinant human growth hormone Serostim is a daily injectable drug approved by the FDA for HIV associated wasting. At approximately $3000 a month, it is an expensive option for treating lipodystrophy. Serostim works well in lowering abdominal fat but has many side effects including joint pain, water retention, carpal tunnel syndrome, and irreversible diabetes. These side effects and the lack of proven longterm health benefits are why the FDA has not approved Serostim for the treatment of HIV related fat accumulation.

Tesamorelin- TH9507 made by Theratechnologies, is a daily injectable growth hormone precursor that is in its last stages of FDA approval. Tesamorelin appears to have fewer side effects than Serostim, but may take a longer time to show benefits in patients. Disappointingly, fat gain returns after discontinuation of both Serostim and Tesamorelin.

Leptin, a hormone that produced by fat cells, is another new contender in the search to decrease visceral fat. Researchers have found that leptin levels in the blood are proportional to an individual's level of body fat. Leptin works in the part of the brain that controls appetite and other basic functions. High levels of leptin generally suppress the appetite and stimulate the burning of fat. Leptin does not appear to have a negative impact on glucose tolerance.

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Nowadays, physicians are likely to prescribe testosterone gels, injections, and subcutaneous pellets. A testosterone gel applied to the belly can reduce the waist size in HIV-positive men. This decrease is usually as a result of a reduction in subcutaneous fat, not in visceral fat. In contrast, a small pilot study of Oxandrin (an oral anabolic steroid) has yielded encouraging results in decreasing visceral fat. Increases in the low density lipoprotein (the "bad" cholesterol) and decreases in the high density lipoprotein (the "good" cholesterol) correspond to a small decrease in subcutaneous fat. There is no data yet on a connection with the popular anabolic, nandrolone decanoate and visceral fat reductions

Some individuals who have been looking elsewhere for fat burners have fallen prey to advertisements pushing growth hormone supplements or fat burners. These products do lit-

tle but increase blood pressure and anxiety and are generally considered scams.

Metformin (trade name, Glucophage), is a generic diabetes drug that has been shown to improve glucose tolerance and lower visceral fat. Its effects may be enhanced by exercise. Metformin improves insulin sensitivity, triglycerides and fatty liver but can also cause diarrhea and weight loss. There have also been reports of low blood sugar and dizzy spells associated with this drug.

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In addition to the aforementioned treatments many patients explore liposuction. Ultrasound-assisted liposuction can be used to successfully remove fat accumulated in buffalo humps and around the neck.

Some patients complain about the enlargement of salivary glands on each side of the face commonly referred to as the "chipmunk look." While only a few radiologists know how to use it for this purpose, low dose electron radiation has worked very effectively in treating the enlargement of salivary parotid glands. It is unknown whether the "chipmunk look" is related to lipodystrophy or caused by immune reconstitution.

Another under explored intervention is diet and exercise. A study at Tufts University revealed a trend towards less lipodystrophy in those who had higher consumption of soluble fiber (fruits and vegetables) and who exercised. However more research is needed with the use of diets lower in simple carbohydrates . These diets have been shown to improve insulin resistance and visceral fat in non- HV studies. One observational cohort showed that HIVers eat more saturated fats. A small pilot on a combination of cardiovascular and resistance exercise showed decreased in triglycerides and visceral fat. However, adherence to exercise remains a challenge to many people and exercise research in HIV generally remains in its infancy.

Increased Lipids: Low density lipoprotein (LDL) and triglycerides)

The most common lipid abnormalities in HIV are high triglycerides and LDL, "bad" cholesterol, and low High Density Lipoprotein (HDL), "good" cholesterol. Before HIV-positive people start HIV medication for the first time, both their high and low density lipoprotein may be lower than normal. However, after HIV drugs are started, low and high density lipoproteins and triglycerides increase in some people. Some studies have shown that LDL increases to "pre-HIV" levels while HDL never returns to normal levels. Increased triglycerides is the most strongly associated lipid change caused by HIV medications such as protease inhibitors, Zerit, AZT, or Sustiva. Among protease inhibitors, Reyataz seems to correlate with the lowest lipid increases.

Many people want to start supplements before they start lipid lowering medications. The only supplements with solid emerging data on lipids are omega-3 fatty acids (fish oils), and niacin (also available as Niaspan). Fish oils can decrease triglycerides but some patients' stomachs cannot tolerate them. Niacin is better than any lipid lowering drug in increasing the "good" cholesterol (HDL). It can cause flushing of the face and a hot sensation for a half an hour at a time, but most people get used to it. Non-flush versions are available but their effectiveness is unknown.

It is not clear if Raltegravir (Isentress, the first integrase inhibitor) or Maraviroc (Celsentry- a CCR5 entry inhibitor) have any effect on body composition. So far, they appear to be lipid friendly when taken with Viread and Epivir. Fuzeon (an injectable entry inhibitor) also seems to be lipid friendly, but it is usually used with boosted protease inhibitors that can cause increases in lipids. It seems that there may be genetic factors that make some patients more prone to increased low density lipoprotein (bad) cholesterol and triglycerides.

Lipid lowering agents like statins (Lipitor etc) or fibrates (Tricor, etc) can work wonders

in many, but even with their use, some patients never reach "normal" lipid levels. A combination of niacin, lower sugar and animal fat intake, exercise, fish oil supplements or an increase in fatty cold water fish consumption (salmon) and soluble fiber (fruits, vegetables, oats) are sometimes used to treat lipids. Some individuals have tried combining statins and fibrates, but this combo can lead to an increase in muscle related disorders in some patients.

Conclusion:

We have learned a lot during the past 10 years about body changes associated with HIV, but many more questions remain. It is the hope that those new to HAART therapy will not have to suffer the devastating drug side effects that their predecessors have had to contend with in the past 20 years. As patients, it is our responsibility to stay educated and learn from others about emerging options that may make it possible one day to live fully without HIV related body changes and other side effects.

For more information visit: www.facialwasting.org or to subscribe to the largest internet HIV health discussion group send a blank email to pozhealth-subscribe@yahoogroups.com

1 *A syndrome of peripheral fat wasting (lipodystrophy) in patients receiving long-term nucleoside analogue therapy. Saint-Marc T, Partisani M, Poizot-Martin I, Bruno F, Rouviere O, Lang JM, Gastaut JA, Touraine JL. AIDS. 1999 Sep 10;13(13):1659-67.*

2 *Metabolic Outcomes of ACTG 5142: A Prospective, Randomized, Phase III Trial of NRTI-, PI-, and NNRTI-sparing Regimens for Initial Treatment of HIV-1 Infection. Richard H. Haubrich, S Riddler, G DiRienzo et al.*

3 *More information is available at www.medibolics.com*

4 *More information is available at www.nucleomaxx.com*

5 *More information is available at www.facialwasting.org.*

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Migration and HIV in Africa: Challenges and Recommendations

Anthony Rutabanzibwa

Increasingly, global responses to migration and to migrants are influencing responses to the HIV/AIDS epidemic itself. African migrants in particular have borne the brunt of xenophobia and discrimination directed toward outsiders. Those who are undocumented have little or no legal protections and limited access to basic health and social services that are fundamental to successful integration into a foreign environment. These barriers, coupled with the complex social, behavior and psychological dynamics of migrancy form a constellation of risk factors that heightens vulnerability for contracting HIV/AIDS.

The African population has always been extremely mobile. Pre-colonial migratory patterns occurred without barriers or legal restraint, driven by agricultural resources, trade and labor. Similarly, in the post-colonial period migration has become a vehicle for economic betterment as well as an escape valve to overwhelming tensions caused by displacement, conflict, poverty, and resource deprivation. Today, international labor migration is commonplace.

With the increased sophistication of globalization a common pattern of regional and international African migration has emerged. The vast majority of migratory routes now steer northwards towards Europe and westwards towards the Americas. Migratory highways extend from as far as Somalia through Sudan, Libya to Tunisia and across the Mediterranean into Spain and Italy.

According to the International Labor Organization (ILO), over 20 million African men