NATAP NATIONAL AIDS TREATMENT ADVOCACY PROJECT
EDUCATING COMMUNITIES ABOUT HIV AND HEPATITIS

580 Broadway, Suite 1010
New York, NY 10012
1-212-219-0106
1-888-26-NATAP
www.natap.org

Living with HIV Therapy: Effects of HIV Infection and Treatment on Physical Appearance and Body Image

Written by: Brett Moskowitz, New World Health (bmoskowitz@whcom.com)

Introduction by Jules Levin
Living with HIV has an emotional impact that is further complicated by the effects of body changes many individuals are experiencing. The body changes appear to be due to a combination of risk factors, which include the effect of HIV and a compromised immune system, the effect of ART in reversing the compromised immune system, advancing age, poor diet, history of obesity in the family, the shape of one's body before starting ART, diabetes or a genetic predisposition to diabetes or insulin resistance, lack of exercise, and extended periods on HIV therapy. Despite much research to date, the precise reasons why the body changes occur remain unknown. This article provides insight into the emotional lives of those experiencing body changes on HIV therapy, and provides an analysis of therapeutic interventions used in an attempt to alleviate these body changes.

Interviews were conducted with two HIV-infected individuals who are also educators and advocates, Dawn Averitt and Nelson Vergel. As well, an interview was conducted with Michael Saag, MD, a long time leader in HIV research and treatment. The topic for discussion was body changes, lipoatrophy and fat accumulation. Dawn and Nelson relate their personal experiences with body changes and discuss their experiences in working with patients and in their advocacy work. Dr Saag discusses his experiences in working with patients and shares his opinions based on research and experience. This is followed with a discussion by me, on what we call lipodystrophy. I talk about what we know about its causes and research findings, and what we know & don't know about addressing this problem for patients struggling with it.

A Tale of Two HIV Positive People
Over the years Dawn Averitt took many antiretroviral drug combinations, but it wasn't until she started on combination therapy with both nucleosides and protease inhibitors that body changes became noticeable. In the spring of 1996, after 2 years of combination therapy with stavudine, lamivudine, and indinavir, some of Averitt's family members complemented her on the significant thinning they noticed in her legs. Averitt had always carried extra weight in her legs, so the change was quite noticeable. Eventually, though, she became shocked by her emaciated legs. But because she was doing well on her treatment, she was advised not to let the physical changes bother her.

"I was thick through the middle, starting to get fat pads in the back, my necklaces stopped fitting, and I had really skinny arms and legs, says Averitt, an HIV-positive community advocate and educator. "I weighed the same as I had before, within 5 pounds, but what had

changed is that I lost all the fat in my arms and legs and it was redistributed to my middle. My cheeks were sunken, too. I was very self conscious. People would turn and stare in public places. It was, for me, and for many people I've spoken with, the 90s version of Kaposi's sarcoma– it was like a sign that says, 'I have AIDS'. It was really frustrating."

Nelson Vergel, a treatment advocate for HIV-related wasting/lipodystrophy in the Houston, Texas area, was diagnosed with HIV in 1986. He also noticed body changes several years after treatment with triple-combination HIV therapy. "When I was taking a regimen that included stavudine, indinavir/ritonavir and efavirenz, I began to notice body changes. Within a month my face sunk in and I lost weight. I got off this regimen soon after. I became depressed when these changes occurred. I couldn't look in the mirror. But I never stopped working out and eventually the body changes stopped when I changed therapy. I achieved the best viral load I ever had but I was so depressed that I could not continue."

Learning to Live with HIV and Body Changes

An HIV diagnosis may have had a different emotional impact in the 1980s than it does today. Now fifteen years after learning of her HIV positive status, Averitt remembers the moment of diagnosis as if it were yesterday. "My first goal was to reach 20, which was 6 months away." Before she was diagnosed, Averitt was a typical 19-year-old college student. She was living and working in Europe while taking a year break from attending New York University when she became very sick and discovered golf-ball size lymphnodes in her neck. When she returned home to Georgia, she saw an infectious disease doctor in Atlanta, but he was reluctant to test her for HIV--he thought it was unnecessary and too expensive. Just before a biopsy looking for non-Hodgkin's lymphoma, the headstrong and progressive Averitt persisted with her request for an HIV test. The results were confirmed on June 28, 1988.

Like Averitt, Nelson Vergel took various anti-HIV drugs in various combinations as they came available over the years. He did not notice body changes at first. He was worried about wasting, especially after losing several friends to severe wasting syndrome, and seeing his own weight drop about 30 pounds. It goes without saying that when he was diagnosed and first began treatment, Vergel was worried about his life and not his appearance.

Today, newly diagnosed patients don't have to consider HIV infection a death sentence. They have more than 20 antiretroviral drugs to choose from, and benefit from doctors' accumulated years of experience treating patients like them.

Averitt and Vergel now needed to deal with the problems associated with a chronic disease—including the body changes associated with certain anti-HIV medications. After finishing college and working on Capital Hill in the office of Georgia Senator, Sam Nunn, Averitt became involved in HIV education and attended a September 1997 meeting with representatives of the pharmaceutical industry (Roche, Merck, and Abbott), the HIV community, and the medical community. It was the first meeting of its kind to address long-term metabolic complications of protease-inhibitor use, which was considered the cause of lipodystrophy. At first, there was reluctance by industry to accept the idea that drug treatment caused lipodystrophy, but as the problem became more common, patients became increasingly vocal on the subject and the pharmaceutical industry and medical community soon began to focus on the issue. "Over time I noticed other people with body changes. When triple combination regimens became more widely used, there was a lot of discussion about this problem," Averitt recalled.

Defining The Syndrome

There is no standard definition of a single "lipodystrophy syndrome."
"I don't think we have a clear description of how to characterize body changes," says Michael Saag, MD, deputy director of the Center for AIDS Research at the University of Alabama at Birmingham. "There has been an assumption in the past that body changes are grouped into one syndrome. Healthcare professionals have to do a better job of first describing what we are seeing; only then can researchers go back and try to find out what is causing these changes."

Specific body changes include generalized subcutaneous fat loss (lipoatrophy), which is most evident in the face, limbs, and buttocks. Fat accumulation (lipohypertrophy) is characterized by accumulation of fat in the midsection and neck, and by breast enlargement. "The most common thing we see in the clinic is general fat atrophy, in varying degrees, says Dr Saag. "The FRAM study showed that there is a universal theme of less total body fat in HIV-infected versus non-HIV infected persons. This is independent of whether patients are on therapy or not, although facial fat loss tends to be seen more with treatment, especially d4T-containing regimens. Visceral [trunk of the body] fat accumulation is less common generally, and does not seem to be linked with peripheral [face, buttock, and limb] fat loss. There is a subset of people with fat loss in limbs and fat gain in the viscera. Breast enlargement can be seen in women, and even some men."

Ten years after finding out about her status, in February 1998, after some time off therapy, Averitt changed to the combination of saquinavir, ritonavir (800/200 mg BID), efavirenz, didanosine, and hydroxyurea. The following year, she undertook a 2000+ mile hike and experienced a dramatic improvement in her body changes. Although she is not physically the same as she was before, her body changes have normalized somewhat. She has no explanation for this unusual change, although after finishing the hike there was no further improvement, and even some regression.

Unlike Averitt, most patients who experience body changes do not see such dramatic improvement, and the fear of dying from AIDS is joined or replaced by a fear of becoming alienated from one's own body. Nelson Vergel says that patients today are more demanding about their treatment and some are really concerned about the way they look, especially with subcutaneous fat loss or lipoatrophy. "People are outed by their faces," says Vergel. "Men don't mind the lipoatrophy as much as women, particularly African-American women. Although women have many emotional issues with body changes, gay men have the most difficult time dealing with body changes within their community.

"People are stopping treatment because they are terrified of the way they look," Vergel adds. "Doctors tell them they should be happy if there viral loads are undetectable and T-cell counts are high. But people experiencing these changes are still very distressed."

What Causes Lipodystrophy Syndrome?

It remains unclear what causes these changes in those who are HIV positive, although there appear to be certain risk factors associated with both HIV infection and treatment.

The immune system of HIV positive people may be causing body changes, according to Dr Saag. Because some parts of the immune system are selectively compromised, other components of the immune system may overcompensate, causing a chain of events that

impact on metabolism and, ultimately, body fat. “These body changes are not unique to HIV,” comments Dr Saag. “Patients with malignancies have wasting, much like is seen with advanced HIV disease. In HIV, there is a selective immune deficiency of some cellular immune processes. When one part of an immune response is weakened, other parts that are unaffected tend to overcompensate. One way to think about this is to take the case of partial paralysis. When a person with partial paralysis of the arm tries to lift that arm, you can see the rest of the body contort to help compensate for the arm. That is what the rest of the immune system is doing to the part that is affected by HIV infection. This overcompensation can burn more weight, produce more cytokines, and create metabolic changes. With therapy, this process may perhaps be accelerated.” Although it has not been substantiated, the possibility that significant body changes may be associated with a strong immune response is disconcerting, especially given the fact that many patients are hesitant about starting treatment to begin with.

It may be that HIV infection and treatment accelerate the aging process in some ways. “The majority of people over 50 years of age develop a belly,” notes Dr Saag. “A lot of that is associated with increasing insulin resistance, a normal part of the aging process. HIV may accelerate the aging process, causing some of these fat changes seen with aging to come on sooner in life. You don’t see severe lipoatrophy with aging alone.”

How Patients React to Body Changes

The current feeling among many patients about treatment, based on the available information today, varies considerably. Dawn Averitt says that in her experience working with patients, there are no clear predictors of how people will approach and react to treatment. However, for those patients who worry about body changes, there are certain concerns that are common. “It has more to do with disclosure than anything else for many people of all demographics.” Averitt says that women have an especially hard time trying to deal with body changes while continuing to function in society. “You are already treated differently in the world as a woman, and if you add HIV and noticeable body changes, many women end up feeling totally alienated and depressed.”

Providers who take the time to understand the obstacles their patients are hurtling may be able to help patients overcome those obstacles. According to Averitt, “those clinicians who are HIV specialists understand the difficulties associated with the physical changes their patients experience better than those who do not treat a lot of HIV patients.”

Dr Saag says that it is rare to find patients who are concerned about body changes when they first enter treatment. “Well-informed patients who ask questions about body changes when they first come in are not the norm. Most patients want to know what it’s like taking pills every day and the immediate side effects. Providers are more concerned with body changes from the outset. There are some patients with profound changes, such as lipomas, that will interfere with their willingness to continue therapy, but this is rare. Most patients don’t experience that much of a change to where they will want to change therapy.”

But Averitt has found that many HIV-positive women she talks to don’t feel they have any treatment choices, simply because they do not want to experience body changes. “In a society where women are judged by appearance, this is a particularly strong and devastating blow to a community of people trying to figure out how to be in the world with this disease.”

What People Seeking Treatment Should Know

Nelson Vergel sees a need for information on combination regimens that have not been studied for their metabolic effects. “I am a proponent of counseling patients on what treatments to use. I am looking for data on metabolically friendly combinations. The combination of tenofovir, lamivudine, and nevirapine, for instance, has not been studied for its metabolic effects. Nucleoside-free and ritonavir-boosted single protease combos also need to be researched more. There needs to be more research into the metabolic effects of different treatment combinations.”

Many studies have been done to understand the effects of particular NRTIs or PIs, but there are little data studying the effects of using both NRTIs and PIs in the same regimen. According to Dr Saag, the effects of using NRTIs and PIs together have not been determined and need to be studied.

Dawn Averitt agrees with the need for more studies. “My work around this issue has been focused on planning trials to study these effects,” says Averitt. “I don’t have any great claim other than trying to find ways to support people while the research community tries to understand the causes of these body changes. Every time patients begin to feel comfortable with one issue, there is another issue. People take risks with the virus and take risks with the meds as well. Providing new research findings has enabled HIV-positive people to begin to see that the lipodystrophy story is bigger than protease inhibitors. Yet, they are still hesitant about using PIs. There are data on stavudine and efavirenz, for example, that have not really penetrated the mainstream yet.”

Management Strategies

Management strategies to treat body changes remain experimental.

There appears to be a clear correlation between exercise and improvement of body changes. “Exercise, believe it or not, helps the most,” believes Dr Saag. “Aerobic exercise is protective against visceral fat accumulation and will increase some fat in the periphery. Diet changes also help.”

Another strategy, for which there is some supporting data, to combat existing body changes is to switch antiretrovirals. “There is a study showing that switching from d4T to abacavir had a partial reversion where some fat came back after lipoatrophy, and it did not progress further,” notes Dr Saag. “However, lipoatrophy is not exclusive to d4T, and at this time we can’t say there is any NRTI regimen that will not cause lipoatrophy.”

Elective surgery has been used by some patients to reverse certain body changes. For those who want or need an intervention for their body changes, there are options to consider, but these may come at a considerable cost and risk. “Our biggest challenge in all of this is that patients, counselors, advocates, and providers, are not informed about the spectrum of issues involved. Plastic surgery is an intensely personal decision but there are risks,” says Averitt. “I would personally consider cosmetic surgery if I had no other options, but it is impossible to know unless you are in someone’s shoes how these changes impact a person. I don’t second-guess people’s choices. As long as people know the risks and benefits, it is their decision.”

The most obvious risk for any surgery is that complications can ensue. There is also the possibility that the surgery will not be effective over the long term or will not have the

expected results. In addition, some procedures are not covered by insurance and therefore come at a great expense to the patient.

"We're more than a body, but we are judged by the way we look," says Vergel. "I tell people who are experiencing body changes that they need to take charge. Exercise, the use of hormones, dietary changes, and other things can help patients take charge of their situation and not accept the changes as inevitable. But patients are paying several thousand dollars for treatments. My main goal as an advocate is to change the protocol so these products are made available to patients, and to change attitudes so that exercise is a priority. Patients want services that are not available to them."

Dr Saag believes that elective surgery for facial wasting does not have long-term benefits for most people, although surgeries for other types of body changes may be successful for some patients. "We have had more than a handful of people who have undergone surgery for fat accumulation. Lipoma extractions and breast reductions can benefit some patients. Operations are sometimes done to remove fat accumulation around the neck, not just for cosmetic reasons, but for sleep apnea as well. Facial implants have been done, but I've not seen a lot of people with long-term success with this intervention. They feel good for a few months and then have to go back for further surgery or are unhappy with the results within a year or so. We've not been recommending facial surgery, because I'm not sure anything really works in the long term. There has been some success with other types of surgeries."

It must be remembered that HIV infection and treatment are not the only predictors of body changes, as Dr Saag points out. "We are a product of our genes. You can look at an individual's parents and see what their body type might be like." In addition to genetic predispositions, behaviors such as proper diet and exercise can have an effect on the body, as can aging.

Multiple influences make it hard to determine what exactly may be causing body changes. It is important for patients and their healthcare providers to engage in frank discussions about the current or potential physical effects of HIV infection, therapy, age, and behaviors. The management of body changes may require any of several possible interventions including dietary and exercise changes, changing of antiretrovirals, or even elective surgery, although this last option comes with financial challenges and potential health risks.

(The development of this article was supported by an independent grant from GlaxoSmithKline.)

Commentary: Jules Levin

I have had HIV for 20 years. I had hepatitis C also for 20 years, but successfully completed my second course of HCV therapy in the summer of 2002, using pegylated interferon plus ribavirin combination therapy. My HCV RNA (viral load) was undetectable (<50 copies/mL) at the end of therapy and 1 year after stopping therapy. Several studies show that at least 95% of patients achieving and sustaining undetectable HCV RNA 6 months after stopping therapy still have no HCV RNA in their blood for as long as they have followed patients, which is now up to 11 years for a small group of patients. They've followed several thousand patients for 4-5 years so far. Additional Long-term followup is important.

Unlike HCV, HIV is not curable and ongoing therapy is required for HIV unless new drugs are developed that address the barriers to eradicating HIV. Therefore, the side effects and toxicities of HIV antiretroviral drugs are a concern. The two biggest health concerns today for people with HIV are co-infection with hepatitis B and C and lipodystrophy. I use lipodystrophy as a catchall term, which includes reference to metabolic abnormalities (cholesterol, triglycerides, glucose), as well as body changes (fat loss, fat accumulation). Fat loss, also called lipoatrophy, is the main concern patients have. I have personally experienced lipoatrophy and still have it in the butt, face, arms, and legs, although since clearing HCV from my blood friends say they see an improvement. Several small studies find that patients co-infected with HIV and hepatitis may be more likely to experience body changes and metabolic abnormalities. This could be due to an impaired liver.

Researchers still do not know the precise causes of this syndrome of body changes in HIV. They have been unable to construct the proper studies that could precisely identify the cause. Instead we have numerous studies that show associations with the manifestation of lipoatrophy. Associations cannot precisely pinpoint cause but only suggest causation. As referred to above by Dr Saag, some of the key associations that have been found include the affect of HIV on the immune system, the affect of successful ART or HAART in partially reversing immune deficiency and dysregulation, genetic predisposition, diet and exercise. A number of studies have found d4T use associated with fat loss. One ongoing study reports slow improvement in fat loss over the course of several years after switching from d4T to abacavir. A second recently completed study following patients who switched from d4T to abacavir found a percentage of patients improved fat loss and a percentage reported fat loss stopped, while other patients reported no improvement. Patients were asked to self-assess body changes. After 48 weeks, the percentage of subjects reporting positive body changes for face, legs, arms, and buttocks were 27%, 20%, 22%, and 19%. The majority of the remaining subjects reported stabilization of their body fat.

NRTIs (d4T, AZT, 3TC etc) can lead to mitochondrial toxicity which studies show may be associated with lipoatrophy. There has been discussion among researchers about the possibility of not using NRTIs in HAART regimens; but to do this, another class of HIV drugs would be needed. The successful development of entry inhibitors might promote this strategy.

Another interesting association found is that if a patient was skinny before starting HAART, they tended to be more likely to develop lipoatrophy. If a person was overweight they tended to develop fat accumulation.

If a patient had a low CD4 count and higher viral load before starting therapy, and had a very good response to HAART with nicely improved CD4 count and undetectable HIV, study findings report they tend to have a greater risk for developing body changes. The more emphatic and greater reversal in immune deficiency appeared to promote a greater risk for developing body changes.

It's possible that a combination of factors present in any one individual may result in lipoatrophy. For a given person, multiple factors--genetic predisposition (a family history of diabetes), a better response to HAART after more full immune depletion, lack of exercise, fat laden diet—may increase the risk for body changes.

Studies suggest that lipoatrophy can result from regimens that include AZT and 3TC but studies show that use of d4T may be more likely to increase the risk for body changes. The use of d4T and ddI together has been found to also be more likely to result in body changes. Findings from studies suggest that the use of abacavir (Ziagen) and tenofovir (Viread) appear less of a risk in causing lipoatrophy. The use of Trizivir, which is a one pill twice-daily combination of AZT, 3TC, and abacavir, appears less likely to cause body changes. This does not mean that use of these drugs excludes the possibility of developing fat loss.

A few studies have looked at patients taking efavirenz and AZT/3TC. On average, patients in the study did not develop body changes. Does this mean that patients taking this regimen will not develop fat loss? There is no guarantee, and probably some patients may develop some fat loss. But fewer patients appear to develop fat loss and the degree of fat loss appears to be less.

Studies show that nevirapine (Viramune) is beneficial to lipids. Studies in patients with elevated lipids who switched from a PI regimen to nevirapine showed improvements in lipids.

A new protease inhibitor called Reyataz has been studied in combination with AZT and 3TC. Reyataz studies with 108 weeks of patient follow up do not see metabolic abnormalities (cholesterol, triglycerides, glucose). Researchers followed study patients receiving Reyataz plus AZT/3TC for one year and found that on average patients did not develop fat loss. These patients need another year of follow up because we know that lipoatrophy often occurs in the second year of therapy. Again, this does not necessarily mean that no patients in the study developed fat loss of some degree or that there is no risk of fat loss with this regimen. The study results suggest it appears much less likely to develop body changes when using this regimen.

Does this mean that elevations in cholesterol and triglycerides cause lipoatrophy? We don't have an answer to this question. Elevated lipids are associated with body changes but there is no clear evidence that elevated lipids cause fat loss. The cause-effect relationship between body changes and lipid abnormalities is unclear. The body changes that accompany lipid abnormalities may actually cause those lipid abnormalities. To me, a plausible but unconfirmed explanation is that HIV and ART affect the network of cell interactions and communications (immune dysregulation), the liver (through which much direction of function occurs), fat cells, glucose metabolism, and cell functioning. This effect may lead to body changes, and an accompanying affect is elevated lipids.

A few studies have found that protease inhibitors can have metabolic affects. Indinavir has been found to lead to elevations in glucose. Ritonavir and nelfinavir have also been found to affect the interactions and function of cells. Lipid elevations often occur when taking most PI regimens, except for Reyataz.

Ongoing research examines anti-diabetic drugs like rosiglitazone and its potential for benefit regarding fat loss. Interim study results suggest rosiglitazone may benefit fat loss in patients with glucose abnormalities such as diabetes and insulin resistance. Studies of pioglitazone and rosiglitazone are in progress. In studies, rosiglitazone increased lipids but this has not been observed with pioglitazone. For individuals with diabetes or insulin resistance and body changes, these anti-diabetic drugs may prove to be more effective than for individuals without glucose abnormalities. This may be because body changes in diabetics may occur for different reasons or mechanisms of action.

Treatment switching is another approach that can be considered. Switching from a PI regimen to a PI sparing regimen has been studied. Although lipids often improve for patients with lipid elevations, so far studies have not found this approach improves fat loss. It's possible the studies were not conducted in a way to discern when and how a switch may be most beneficial. As mentioned above, a switch from d4T to abacavir appeared to reverse or stop fat loss for many patients.

Tenofovir is a relatively new drug as it was FDA approved 2 years ago. Study results suggest tenofovir may have beneficial effects regarding body changes. Presence or emergence of lipodystrophy was determined in the study by the subjective opinion of the investigator. Researchers prefer the use of objective tests measuring the presence of body changes, such as an MRI or CT scan. Lipodystrophy was reported for 12% of patients taking the d4T regimen compared with 1% for patients taking tenofovir. The other drugs used in the study were 3TC and efavirenz.

As you can see, we do not yet understand very well what causes lipoatrophy and how to prevent or treat it. Although a good deal of research has been conducted in this area, we have not been able to identify the precise mechanisms of action nor how we can successfully prevent or treat body changes. We need better research and we also need safer anti-HIV drug therapy. New research directions are discovering entry inhibitors and perhaps integrase inhibitors. The current classes of drugs prevent replication of HIV in the CD4 cell. Entry inhibitors prevent HIV from entering the CD4 cell. Perhaps this difference will have some effect on the development of body changes. Successful ART with entry inhibitors will still allow partial reversal of immune deficiency similar to that seen with combination therapy using the current classes of drugs.

Further Information

Nelson Vergel is the director of the Program for Wellness Restoration (PoWeR), a non profit all volunteer organization that disseminates information about side effect management and wellness in HIV. The web address is http://www.powerusa.org. Mr. Vergel moderates a free listserve called lipodystrophy at yahoo. Those who are interested can join by sending an email to lipodystrophy-subscribe@yahoogroups.com. He has also started a website, www.facialwasting.org, with information on facial fillers.

Dawn Averitt is one of the nation's most prominent HIV and AIDS treatment advocates, an accomplished speaker and trainer, and a published scientific writer. Dawn's latest initiative is The Well Project at http://www.thewellproject.com. The Well Project's mission is to improve the lives of women living with HIV and AIDS, by developing and nurturing a community created for all people supporting women living with HIV disease– from the HIV+ woman and her caregivers to the physicians treating women living with HIV. In the year 2000, Dawn undertook and completed a 2,167 mile hike of the entire Appalachian Trail – from Maine to Georgia – to celebrate 12 years of *living* with HIV disease.