



HIV-associated lipodystrophy syndrome:

An accelerated form of the metabolic syndrome of insulin resistance due to altered fat distribution

By Ashok Balasubramanyam, MD and Rajagopal V. Sekhar, MD

Highly active antiretroviral therapy (HAART) has greatly reduced AIDS-related morbidity and mortality. However, its widespread use has been associated with a marked rise in the frequency of insulin resistance, a metabolic syndrome that increases cardiovascular risk in these patients.¹ Some HIV-positive patients receiving HAART also develop “lipodystrophic” features, that is, loss of fat in some parts of the body (especially the face, arms, and legs)^{2,3} as well as accumulation of fat in other parts of the body (such as the dorsocervical area,^{4,5} trunk, and abdomen.^{6,7})

Altered fat distribution may affect 14% to 32% of the HIV-positive population. Features of metabolic syndrome (abdominal obesity, reduced high-density lipoprotein [HDL] cholesterol, hypertension, and elevated triglycerides and glucose) are even more frequent, affecting as many as 69% of men receiving HAART.⁸ An important issue, hitherto unresolved, is whether the so-called “metabolic” complications (features of the metabolic syndrome) are linked to the body fat alterations, or indeed if the various aspects of fat “redistribution” (lipoatrophy and lipohypertrophy) are due to the same or different pathophysiologic processes.⁹

HOW CAN WE DEFINE HIV-ASSOCIATED LIPODYSTROPHY?

There is as yet no widely accepted and practical case definition for HIV-associated lipodystrophy.¹⁰ Numerous reports of widely varying descriptions of body habitus changes and of their frequencies have used different methods of measuring total body fat

(as well as specific fat depots), and have largely relied on cross-sectional analyses, self-reports of body changes, or less than objective measurements by clinical observers.¹¹ In 2003, an HIV Lipodystrophy Case Definition Study Group developed a multifactorial statistical model to improve accuracy in diagnosing HIV-associated lipodystrophy.¹² However, this model has limitations in that it emphasizes lipoatrophy rather than fat accumulation as the chief manifestation of altered fat distribution; it also relies on imaging techniques to quantify fat in different regions of the body, making it less than practical for routine medical practice.

There has been a general bias in reporting peripheral fat loss (lipoatrophy) over central fat accumulation as clinical evidence of HIV-associated lipodystrophy. To some extent, this is because visceral abdominal obesity is markedly on the rise worldwide in virtually all populations, hence it is difficult to impute increases in abdominal fat to specific effects of HIV infection or its treatment. Nevertheless, several cohort studies have noted that a significant proportion of HIV-infected patients develop increased abdominal fat following HAART.^{6,13-19} The Fat Redistribution and Metabolic Changes in HIV Infection (FRAM) Study set out to examine rigorously, albeit with a cross-sectional design, the relative contributions of peripheral lipoatrophy and central fat accumulation to the phenotype of HIV-associated lipodystrophy. The investigators found, both by self-report and detailed examination, that HIV-positive men had peripheral fat loss, but observed equivalent increas-

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es in central fat in both HIV-positive men and HIV-negative controls, as well as an absence of correlation between changes in central fat accumulation and peripheral fat loss in the HIV-positive men.³ Hence, peripheral fat loss and central fat “gain” may not be pathophysiologically linked.

HOW COULD FAT DISTRIBUTION CHANGES BE LINKED TO THE DEVELOPMENT OF METABOLIC SYNDROME?

In many populations, increase in visceral fat is linked to the development of insulin resistance and the metabolic syndrome, in turn leading to greater cardiovascular risk. Increased visceral fat is associated with further deposition of fat in the liver and muscle, causing local tissue insulin resistance, as well as a rise in circulating factors that are atherogenic and thrombogenic (eg, free fatty acids, tumor necrosis factor- α [TNF- α], interleukin-6 [IL-6], and plasminogen activator inhibitor type-1 [PAI-1]), and a decline in factors linked to insulin sensitivity (eg, adiponectin, leptin). The question in regard to HIV-associated lipodystrophy is *if* and *how* peripheral fat loss is also linked to the development of insulin resistance and the metabolic syndrome, and whether these effects are linked to those of visceral fat accumulation.

On the basis of kinetic metabolic studies in the fasting and fed states in patients with HIV-associated lipodystrophy, Sekhar et al^{20,21} identified basic defects in adipocyte function that result in a marked acceleration of *lipolysis*, or hydrolysis of stored triglycerides leading to a net release of free fatty acids into the circulation. This causes a decrease in the size of some fat depots, and increases the flow of fatty acids to the liver where they undergo increased re-esterification, leading to high levels of very-low-density lipoprotein (VLDL)-triglyceridemia. Furthermore, a profound defect in the clearance of dietary triglycerides leads to hyper-

chylomicron triglyceridemia. This scenario explains the typical dyslipidemia observed in patients with HIV-associated lipodystrophy, as well as their tendency to develop fatty liver, fatty muscle, and insulin resistance. However, it does not explain why they might develop visceral adiposity, but this could be due to differential turnover rates of lipids in visceral adipocytes (higher) compared to peripheral adipocytes (lower). As to the mechanisms underlying adipocyte dysfunction, they are likely complex and multifactorial, and probably include one or more HAART agents, increased proinflammatory cytokine activity,²² or proteins expressed by HIV itself.

An altered milieu of endocrine or paracrine hormones in the setting of HIV infection or its treatment may also contribute to adipocyte dysfunction. Proinflammatory cytokines (eg, TNF- α , IL-6) released by HIV-infected immunocytes, or by the adipocytes themselves when exposed to these HIV-infected cells, may lead to increased apoptosis (programmed cell death). Mitochondrial toxicity due to drugs of the nucleoside reverse transcriptase inhibitor (NRTI) class may add to this effect,²³ resulting in lipoatrophy. The mechanisms leading to central fat accumulation are more difficult to rationalize, but attention is turning to dysregulation of the enzyme 11-beta-hydroxysteroid dehydrogenase type 1 (11- β -HSD1), which is expressed more in visceral than peripheral fat. 11- β -HSD1 converts inactive cortisone to the active glucocorticoid hormone cortisol. There is evidence that 11- β -HSD1 activity is increased in many forms of visceral obesity, leading to a localized “Cushing’s syndrome of the abdomen,” with its attendant insulin resistance, fatty liver, and dyslipidemia.²⁴

A well-documented hormonal defect that is linked with HIV-associated lipodystrophy is partial or complete growth hormone (GH) deficiency, and

this may contribute to its pathophysiology of the syndrome overall. Indeed, this condition may occur in about a third of patients with HIV lipodystrophy.²⁵ Rietschel et al assessed the function of the growth hormone axis through careful analysis of the pulse-frequency of GH release, and they observed reductions in basal GH concentration and GH pulse amplitude, associated with normal insulin-like growth factor-1 (IGF-1) and increased visceral fat. Levels of IGF-binding protein 3 (IGFBP3), the chief IGF-1-specific binding protein, are also high relative to the low GH concentrations in these patients.²⁶ While the reasons for this “disconnect” between GH levels/kinetics and IGF-1 levels remain unclear, these data do imply that GH sensitivity is retained in patients with HIV-associated lipodystrophy, suggesting a rationale for treatment of the condition with GH. Although treatment approaches are beyond the scope of this review, it is worth mentioning that high-dose GH treatment has resulted in significant (if temporary) improvement in the lipodystrophic features,²⁷ and similar benefits, with fewer side effects, have been noted with treatments aimed at restoration of plasma GH levels to a physiologic range.²⁸

Visceral adiposity may represent an effort to retain fat within adipocytes, rather than permit fatty acids and triglycerides to accumulate in energetic tissues such as muscle and liver, as well as in triglyceride-rich lipoproteins. Unger has suggested that the lipotoxicity associated with “ectopic” accumulation of fat is greatly increased when the synthesis and secretion of the adipocyte hormone leptin is inadequate to meet the challenge of increased flow of fatty acids from the periphery or the gut.²⁹ Thus, in a low-leptin state that occurs in HIV-positive patients with marked peripheral lipoatrophy,³⁰ a kind of “systemic steatosis” occurs.³¹ Increased lipolysis, the key biochemical marker of lipodystro-

phy, causes increased flow of fatty acids to the liver, promoting the synthesis of triglycerides, reducing degradation of apolipoprotein B, and causing increased synthesis and secretion of VLDL-triglycerides. Lipid uptake within the central fat depots is higher than in peripheral fat depots (specifically the femoral-gluteal regions), perhaps because of increased sensitivity to lipoprotein lipase (LPL)-activating hormones (eg, cortisol in omental adipocytes), so that fatty acids transported to this site are consequently taken up and stored as diglycerides and triglycerides. The result is preferential deposition of fat in abdominal visceral fat depots, central obesity, and the clinical picture of HIV-associated lipodystrophy.

Perhaps because of a “spillover” from intra-abdominal fat depots (possibly caused by leptin deficiency or leptin resistance), fat accumulates “ectopically” in patients with HIV-associated lipodystrophy. Both total abdominal fat and intrahepatic lipid content were greater in HIV-positive men than in healthy controls, and were associated with dyslipidemia.³² This reflects insulin resistance at the level of the liver, as shown in a detailed study by Sutinen et al³³ The severity of insulin resistance was related to the accumulation of fat in the liver rather than to the accumulation of intra-abdominal fat; the same relationship between liver fat and dyslipidemia has also been found in HIV-negative men.³⁴ The data of Sekhar et al^{20,21} would suggest that the source of the fat that accumulates in the liver is from excessive lipolysis; indeed Hadigan et al showed that blocking lipolysis acutely with acipimox improved insulin sensitivity in patients with HIV-associated lipodystrophy and visceral obesity.³⁵ Fatty infiltration of muscle also occurs and is linked to insulin resistance at the level of skeletal muscle.³⁶

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WHAT ARE THE ETIOLOGIC FACTORS THAT LEAD TO ADIPOCYTE DYSFUNCTION, AND HENCE TO HIV-ASSOCIATED LIPODYSTROPHY?

Although much attention has been focused on one or more HAART drugs as the inciting cause of HIV-associated lipodystrophy, its etiology is very likely multifactorial. Intrinsic host factors and disease status, as well as treatment duration and type, probably play key roles.³⁷ Multivariate analyses of data from the HIV Out-Patient Study (HOPS) cohort²³ indicate that the following are risk factors for lipodystrophy: exposure to and duration of thymidine analogs (particularly stavudine and zidovudine), age, CD4 T-cell count, viral load, duration of therapy in general, and White race. Risk factors for fat accumulation are: duration of therapy, CD4 T-cell count, viral load, age, exposure to HIV protease inhibitors (PIs), and female sex. While such epidemiologic risk factor assessments are helpful in understanding the heterogeneity and multiplicity of possible causes of HIV-associated lipodystrophy, they cannot serve to define etiologies or mechanisms. Regarding fat distribution abnormalities and their relation to the development of the metabolic syndrome, it is unfortunate that few mechanistic hypotheses have been tested to date.

WHAT ARE THE PATHOLOGIC CONSEQUENCES OF HIV-ASSOCIATED LIPODYSTROPHY?

Patients with HIV-associated lipodystrophy frequently complain of cosmetic alterations in more noticeable parts of the body such as the face. This may lead patients to attempt cosmetic surgery or to discontinue some or all of their antiretroviral medications in the belief that the drugs are chiefly responsible for the disfiguration. Severe, sometimes rapid, accumulation of fat in the abdomen may lead

to abdominal discomfort or respiratory difficulty, umbilical herniation, or gastro-esophageal reflux.³⁸ Most significantly, in relation to long-term metabolic morbidity and cardiovascular risk, the lipid kinetic and fat storage abnormalities that underlie fat maldistribution are strongly associated with rapid development of the metabolic syndrome.³⁹ Components of the metabolic syndrome are increased waist circumference, increased triglycerides, reduced HDL-cholesterol, high blood pressure, and elevated fasting glucose. This cluster of cardiovascular risk factors predisposes HIV-positive patients receiving HAART, and especially patients with HIV-associated lipodystrophy, to premature cardiovascular disease.^{40,41}

Insulin resistance is increased in patients with HIV-associated lipodystrophy

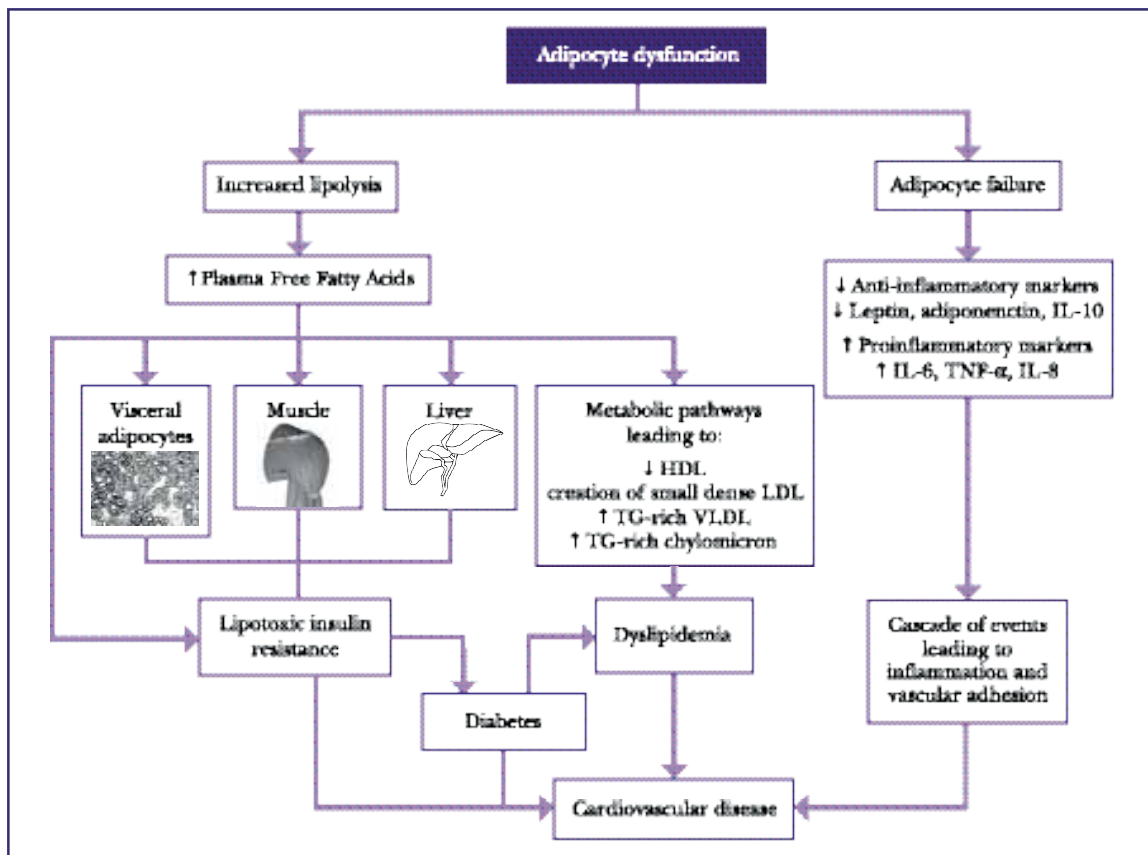
The basis of the metabolic syndrome is insulin resistance, and central fat accumulation is the primary consequence of insulin resistance, acting as the driving force for other risk factors.^{6,42-44} About 30% to 90% of HIV-positive patients treated with PIs develop insulin resistance; the incidence of frank diabetes is about 10%.⁴⁵ PIs induce insulin resistance in muscle by inhibiting the function of the Glut 4 transporter.⁴⁶ Among non-diabetic, HIV-positive patients receiving HAART (PIs in particular), fasting glucose levels are not elevated, but levels of fasting insulin, 2-hour insulin, and 2-hour glucose on-challenge are elevated.⁴⁷ NRTIs, especially the thymidine analogs, may also induce lipotoxic insulin resistance in muscle and liver by disrupting mitochondrial function; this is linked to the inability of these tissues to oxidize fat. These effects of PIs and NRTIs, together with those of adipocyte lipolysis causing visceral adiposity and increased intrahepatic and intramyocellular fat deposition, may account for the insulin resistance observed in HIV-positive patients.⁴⁸

Cardiovascular risk is increased because of the metabolic syndrome resulting from insulin resistance

HIV-positive patients receiving HAART and patients with HIV-associated lipodystrophy have an elevated risk of cardiovascular disease.^{40,49} Patients receiving HAART may be at increased risk of myocardial infarction (MI) or coronary heart disease compared with the general population or with HIV-positive patients not receiving HAART. Insulin resistance and diabetes mellitus, hypertension, and the presence of a chronic inflammatory state (such as seen in HIV disease) could predispose

a patient to accelerated atherosclerosis, endothelial dysfunction, and a chronic prothrombotic state. The degree of cardiovascular risk induced by HIV infection or its treatment remains controversial. The largest data set to date is that of the prospective D:A:D Study, a clinical study of more than 23,000 patients, in which 207 patients had a total of 268 cardiovascular or cerebrovascular events. There was a gradual increase in the incidence of MI with duration on therapy. Combination therapy was associated with a small annual increase (5 events per 1000 patient years) in the risk of myocardial infarction.^{50,51}

Figure: Model of causes and consequences related to adipocyte dysfunction as seen in HIV-associated lipodystrophy



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CONCLUSIONS

The precise pathophysiologic mechanisms underlying the heterogeneous manifestations of HIV-associated lipodystrophy remain unclear. Much data have been acquired from human epidemiologic and metabolic studies; but these now need to be translated into mechanistic studies in animal or cellular models. Meanwhile, there is a pressing need to diagnose and treat patients for the lipodystrophic changes and the attendant dyslipidemia, if only to alleviate the metabolic syndrome and its associated cardiovascular risks. In this regard, the lack of a reliable and practical case definition of HIV-associated lipodystrophy is a problem, as it leads to marked variability in estimates of prevalence and

risk factors, and difficulties in interpreting results of clinical trials in heterogeneous patients. Important future developments in the area of HIV-associated lipodystrophy should include a more thorough comprehension of the molecular pathogenesis, as well as the availability of rational treatment options. Until then, clinicians should continue to use best practice guidelines for the treatment of the metabolic syndrome and reduction of cardiovascular risk factors, utilizing both lifestyle (diet and exercise) and pharmacologic approaches. Nevertheless, the latter must be based on a good understanding of their interactions with HAART agents and effects on other medical conditions that are common in patients with HIV infection.



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HEART POSITIVE: Looking for study volunteers

Diet/exercise, Niacin, Fenofibrate for HIV Lipodystrophy (ie, “Heart Positive”) is an NIH-funded study conducted by Baylor College of Medicine in coordination with Legacy Community Health Services. Its goal is to find new ways to reduce the risk of heart disease and diabetes in HIV-positive adults suffering from the effects of lipodystrophy.

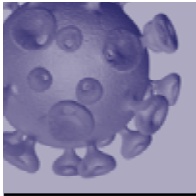
The mechanisms leading to the dyslipidemia, insulin resistance, and anthropomorphic changes—collectively termed “HIV-associated lipodystrophy”—have been unclear. Numerous small studies have failed to delineate a course of therapy that can clearly reverse the dyslipidemia and attendant cardiovascular risk in the majority of patients. There is an urgent need for evidence-based, rational, effective therapy of this condition.

Based on 1) our recent data on key mechanisms of altered lipid kinetics in HIV-associated lipodystrophy; 2) evidence that diet and exercise patterns of HIV-positive patients are suboptimal to manage cardiovascular risk factors; and 3) the latest treatment recommendations for dyslipidemia and insulin resistance, we propose a randomized, placebo-controlled trial of intensive lifestyle modification and 2 lipid-lowering agents.

We are looking for: HIV-positive adults with a fasting serum triglyceride level >150 but <1000 mg/dL and BMI <35 , who have been taking a stable HAART regimen for at least 6 months. A “stable HAART regimen” is defined as one that is tolerated and adhered to by the patient, has caused no demonstrated adverse effects, and has resulted in a CD4 count >100 /cc and HIV viral load by PCR or branch-chain DNA maintained below 5000 copies/cc.

Patients who join the study may receive 2 weeks worth of food at the beginning of the study, a 6-month gym membership with a personal trainer, and the opportunity to work closely with a dietitian to improve eating habits, all at no cost to the patient.

For more information about **Heart Positive**,
go to **www.heartpositive.org**.



Body shape changes: Where are we?

By Robert Munk, PhD

In 1997, people taking the recently introduced protease inhibitors (PIs) reported rapid enlargement of their abdomens. The condition picked up the name “Crix belly,” most likely from the large market share of indinavir (Crixivan) at that time. In June 1997, the Food and Drug Administration (FDA) issued an advisory about cases of diabetes and hyperglycemia in patients receiving PIs.¹ A few months later, Carr and colleagues published a paper identifying a syndrome of “lipodystrophy,” which they defined as fat wasting of the face, limbs, and upper trunk.² This was the first published use of the term “lipodystrophy” in conjunction with HIV-associated metabolic and morphologic disturbances.

Defining Lipodystrophy

Prior to these reports of lipodystrophy in HIV-infected patients, the clinical condition of lipodystrophy was considered to be a cluster of rare genetic or acquired disorders (non-HIV-related) characterized by a near-total absence of body fat, or by fat loss in the extremities (although sometimes not in the legs) and fat deposition around the head and neck areas. HIV-associated lipodystrophy affects many more people and differs from the “non-HIV” lipodystrophies, as many with this condition have increased fat deposition in the abdomen.

Unfortunately, many research studies in HIV rely on clinician-defined lipodystrophy as an endpoint. In some cases, researchers have combined lipid changes with morphologic (body shape) changes as their definition. Fat gain and fat loss are commonly combined, although the processes responsi-

ble for each may be quite separate. The inaccurate term “fat redistribution” is often used to describe HIV-associated lipodystrophy, implying a movement of adipose tissue or cells from the periphery to the abdomen or other areas, an idea for which there are no supportive data.

While laboratory abnormalities are objective and easily quantifiable, the same is not true for the morphologic changes associated with lipodystrophy. Patient self-report has been used as an indicator, confirmed in some cases by clinical observations. However, disagreements or discrepancies on the severity of fat loss or accumulation are common. Anthropometric measurements are fraught with both inter- and intra-rater unreliability, despite the availability of detailed instruction manuals. Bioelectric impedance analysis is useful only to measure overall body composition and cannot generate regional body composition data. Dual-energy X-ray absorptiometry (DXA) scans can provide data on regional body composition, and abdominal computed tomography (CT) scan slices provide quantifiable data on subcutaneous and visceral fat. However, these techniques are not widely available largely due to cost, and norms for interpreting their results have yet to be established.

With causative factors still unclear, lipodystrophy remains little more than a collection of symptoms mainly observed in people taking antiretroviral medications for HIV (see Table). As more side effects are identified and associated with antiretroviral therapy, new symptoms or related conditions (including lipodystrophy) are added by various

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TABLE: Symptoms often associated with lipodystrophy

Fat accumulation (hypertrophy)	Fat wasting (atrophy)	Lipid and glucose metabolism	Other symptoms
<ul style="list-style-type: none"> ↑ visceral fat ↑ abdominal girth ↑ dorsocervical fat pad (buffalo hump and/or horse collar) ↑ breast hypertrophy (gynecomastia) ↑ lipomas 	<ul style="list-style-type: none"> ↓ subcutaneous fat in legs and arms ↓ gluteal fat ↓ buccal fat pad ↓ fat at temples 	<ul style="list-style-type: none"> ↑ triglycerides ↑ LDL cholesterol ↑ HDL cholesterol ↑ blood glucose ↑ insulin resistance 	<ul style="list-style-type: none"> • hypertension • dry skin • brittle hair and nails • sexual dysfunction • loss of bone mineral density (osteoporosis and osteonecrosis) ↑ serum lactate ↑ lactic acidosis

researchers to the list of conditions considered part of HIV and/or its treatment. Because of the confusion about a definition of lipodystrophy, its prevalence has been variably reported from as low as 13% to as high as 84%.

The idea for an overall definition of HIV-associated lipodystrophy is based on the assumption that the various elements of lipodystrophy are in fact inter-related and may have a common etiology. However, clinicians do not need an overall definition to treat their patients. They continue to diagnose and treat individual symptoms, while researchers continue to look for their causes.

Newer Approaches to Understanding Body Shape Changes

In 2002, at the *International AIDS Conference* in Barcelona, Grunfeld³ first suggested that in lipodystrophy, peripheral fat loss is actually associated with central fat *loss* and is clearly greater in HIV-infected patients with lipodystrophy than in HIV-infected patients without lipodystrophy or in HIV-negative controls. Further, he stated that a “mixed” syndrome of peripheral fat loss and central fat gain does not exist and that visceral adipose tissue was lower in HIV-positive patients compared to controls. His comments were based on a preliminary

analysis of data on men only from the Fat Redistribution and Metabolic Change in HIV Infection or FRAM study,⁴ a cross-sectional comparison of HIV-infected patients with or without lipodystrophy and HIV-negative controls. The FRAM study was the first major research report to suggest that fat loss and fat gain were distinct syndromes, perhaps with independent causes, and that central fat gain should not be considered a feature of lipodystrophy. Later analysis of data on women in the study showed parallel results: lipoatrophy was not related to central fat gain, but rather to central fat loss. This finding went against many researchers’ assumptions and called into question the concept of “fat redistribution.” Further analysis of FRAM data and additional studies are needed to clarify this controversy.

Initial efforts to define lipodystrophy were based on the assumption that the syndrome was related to the use of PIs, despite the fact that many symptoms—including half of the cases reported in the first paper on buffalo humps⁵—were seen in patients who had never taken PIs. Brinkman introduced nucleoside reverse transcriptase inhibitor (NRTI)-induced mitochondrial toxicity as a potential cause of lipodystrophy.⁶ This hypothesis reinforced the view that lipodystrophy might represent

2 syndromes: fat accumulation (probably caused by PIs) and fat wasting (most likely caused by NRTIs).

Because the PIs were blamed for visceral fat accumulation, a series of “switch” studies examined the impact of changing from PIs to non-nucleoside reverse transcriptase inhibitors (NNRTIs). Although these studies showed improvements in blood lipid levels, the effects on visceral fat were very modest. However, switching away from certain NRTIs—particularly d4T (stavudine or Zerit)—in several studies proved helpful in decreasing the rate of peripheral fat loss, or even in restoring it. Demonstrating any link between specific drugs and body shape changes is complicated because people do not remain on a particular regimen for long, and the effects from various components of each regimen may be difficult to separate.

Alternatively, lipodystrophy may not be significantly related to individual medications. The HIV Outpatient Study (HOPS) has consistently reported that in new cases of lipoatrophy identified during a 21-month study, neither drug class nor individual agents were significantly related to the development of lipoatrophy.⁷ Instead, patient characteristics such as White race, a less robust treatment-induced CD4 lymphocyte increase, CD4 lymphocyte count below 100, and lower body mass index (BMI) were found to be significantly associated with fat loss. More recently, a series of analyses has examined the link between patient genetic profiles and the development of fat loss and fat accumulation, with suggestive results that point to the need for larger trials to confirm these findings.⁸

Additionally, there are several reports of gender differences in the manifestations of lipodystrophy.⁸ The SALSA study found that male patients started with less body fat and were more likely to report fat loss, while female patients (with greater initial fat) were more likely to report fat gain. Engelson and Kotler’s group used magnetic resonance imaging (MRI) and DXA scans to define changes in body

composition in HIV-infected men and women compared to uninfected controls.⁹ Commenting on this study, Kotler noted that only men had a significant decrease in subcutaneous adipose tissue, while both men and women had increased visceral adipose tissue. Disagreeing with the FRAM study findings, he suggested that visceral fat increase is the primary element of lipodystrophy, while subcutaneous fat loss may be caused by other factors.¹⁰

Most studies of lipodystrophy have been cross-sectional rather than longitudinal, the former design being unable to capture rates of change for various parameters. An HIV-positive population with several years of experience on antiretroviral medications might appear similar to HIV-negative controls in certain respects, but longitudinal study might show very different patterns of change. The datasets for some longitudinal studies clearly show that cross-sectional analyses at different time points would have yielded very different results.¹¹

Questions also have been raised concerning whether the HIV-negative controls used in the FRAM study were selected appropriately. Data were collected at one time point from age-matched patients from the national CARDIA study of cardiovascular disease. Some researchers are concerned that this is a poor comparator for the body shape changes that sometimes occur within a fairly short time frame in people with HIV. Certainly, the experience of patients and clinicians dealing with lipodystrophy suggests that it is characterized by sometimes rapid changes in body shape, particularly in abdominal girth. Fat atrophy and fat hypertrophy may often appear simultaneously, even if they are not both statistically linked to a single cause. Clinicians and patients might be ill-served if the definition of HIV-associated lipodystrophy, for example, were to exclude abdominal fat accumulation as not being statistically linked to HIV disease. Conceivably, such a definition might lead to reduced research attention to the diagnosis and treatment of abdominal fat accumulation, or to

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reduced third-party reimbursement for related treatments or procedures.

Treatments for Body Shape Changes

As noted earlier, clinicians do not need an overall definition to treat their patients. They diagnose and treat individual symptoms, and much research has focused on this topic. For example, great attention is being paid to central fat accumulation as part of an overall, clinically defined metabolic syndrome that has been observed in the general population (usually associated with aging, development of diabetes, central fat gain, etc). Along that line, medications used to normalize glucose levels such as metformin and pioglitazone have been studied, but with limited benefit in reducing fat accumulation.¹² A difficulty in many such studies is the lack of clear baseline values for study participants. Studies investigating the effects of diet and exercise changes have also been conducted in patients with HIV-associated lipodystrophy (see article on page 20 of this issue).

More work is also underway in treating lipoatrophy. Switching away from d4T has shown benefits, although often slow and modest. Newer studies are

trying to correct mitochondrial depletion through the use of the supplement uridine, which has been shown effective in treating mitochondrial toxicity caused by d4T and AZT (zidovudine or Retrovir).

Non-drug treatments include the use of liposuction to remove fatty accumulations behind the neck (dorsocervical fat pads). Liposuction, however, cannot be used to reduce visceral fat accumulations, which are deep in the body and surround internal organs. A more dramatic treatment is the use of facial fillers or implants to correct fat loss. Much work continues to be done to investigate the safety and effectiveness of such interventions. Sculptra, an injectable form of poly-L-lactic acid that is a biodegradable and biocompatible synthetic polymer, was FDA-approved in 2004 for facial use and has been used as extensively as patient financial resources allow.

There is little doubt that research will continue into both drug and cosmetic treatments for the body shape changes associated with HIV disease and its treatment. However, these efforts are hampered by a continuing lack of clarity on the pathogenesis of these morphologic changes.



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Bone problems and HIV:

An interview with Steven Petak

Steven Petak MD, JD, FACE, FCLM is an Associate at the Texas Institute for Reproductive Medicine and Endocrinology in Houston and President of the American Association of Clinical Endocrinologists.

RITA:

Certainly for the past 10 years, almost since the beginning of widespread use of highly active anti-retroviral therapy (HAART), we have known about changes in fat metabolism in the setting of HIV/AIDS that result in a cluster of symptoms commonly called lipodystrophy. What we have not heard as much about are HIV-related bone disturbances, but these are well-documented in the clinical literature. Are these bone problems also related to metabolic disturbances or irregularities?

SP:

We have not seen any direct evidence that these bone problems are related to the metabolic disturbances observed in HIV-positive people. However, HIV-positive patients with dyslipidemia, insulin resistance, and central adiposity appear to be more vulnerable to having decreased bone mineral density (BMD). In fact, these patients don't have to be very ill to experience bone problems—it isn't just patients with AIDS-related wasting. There are also some data suggesting that the hormone leptin, which is involved in regulating body weight and appetite, increases bone resorption (the process of losing bone). This hormone could provide a link between lipodystrophy and bone problems in HIV-positive people, but there is no direct evidence yet. To complicate matters, several studies have used a variety of different methodologies to assess BMD. For example, studies using quantitative computed

tomography (QCT) report somewhat disparate findings from studies using dual X-ray absorptiometry (DXA) to measure BMD. CT is somewhat affected by marrow fat and this may complicate the findings further. This is a fascinating controversy, and much research is being done to figure out which method is the most accurate.

RITA:

In your opinion as a researcher and clinician, is there any direct relationship between these bone changes and the changes in fat metabolism?

SP:

At this point, it isn't clear whether there is a direct relationship. As mentioned earlier, one interesting area of research focuses on the hormone leptin. In addition, cytokines may be involved in inhibiting new bone formation and stimulating bone resorption, therefore resulting in decreased BMD. People with HIV have elevated levels of certain cytokines, such as tumor necrosis factor (TNF) and interleukin-1 (IL-1), and these elevated levels may be partly responsible. Because both healthy HIV-positive patients and patients with AIDS-related wasting have increased levels of cytokines, all HIV-positive patients are at risk.

RITA:

So are bone changes in HIV disease caused by HIV medications, HIV itself, both of these, or some other factors (eg, host factors or risk factors)?

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SP:

The majority of studies indicate that these bone problems are not caused by HIV medications. While it is common to see a loss of BMD in patients when they initially start taking HIV medications, especially protease inhibitors, this loss is typically transient and stabilizes over time. Instead, researchers believe that HIV disease itself leads to an imbalance between bone formation and bone resorption, possibly via increased cytokine levels.

RITA:

What are the clinical manifestations or symptoms of these types of bone changes?

SP:

Decreased BMD as shown by DXA (or another methodology) is an obvious feature. Unfortunately, osteoporosis is typically asymptomatic until a patient experiences a bone fracture. Malnourished patients, such as those with a calcium and/or vitamin D deficiency, can experience osteomalacia. In this situation, the bone mass is present, but the bone tissue is soft. Patients with osteomalacia frequently experience bone aches. Fragility fractures are also a common symptom and can be a strong predictor of recurrent fractures.

RITA:

Are there any warning signs of these types of bone problems? If so, what are they? What should patients look for and when should they discuss any signs or symptoms with their doctor?

SP:

Warning signs include bone aches, fragility fractures, or bone fractures. In addition, patients with calcium and/or vitamin D deficiencies will have muscle weakness and balance problems. Any patient with signs of AIDS-related wasting should definitely be assessed for loss of BMD. However, even healthy HIV-positive patients are at risk for

these bone problems, especially if they have a low body weight and a low body mass index (BMI). Patients having any of these symptoms or risk factors should discuss these issues immediately with their doctor.

RITA:

As an endocrinologist, how have you become involved or interested in the issues around HIV and bone disease? Are HIV-positive patients with these types of bone problems referred to you?

SP:

I am part of a specialty practice that focuses on general endocrine and nonsurgical reproductive system disorders affecting men and women. Approximately 60% of the patients in my practice have bone disease. In addition to seeing HIV-positive patients with bone disease, I also see patients whose bone disease is caused by other factors such as renal disease, steroid use, or unknown factors. Unfortunately, while the HIV-positive population is extremely vulnerable to bone disease, bone health status is often overlooked in clinical exams. As a result, these problems are not being addressed adequately. Since many of these patients are young, their fractures risks may be offset by their age in part—but there is much we don't know.

RITA:

What are the standard treatments or interventions for these types of bone problems?

SP:

First, patients must be assessed for a calcium and/or vitamin D deficiency and be treated with the appropriate supplements. Surprisingly, vitamin D insufficiency is common even in developed countries. In addition, patients can also be treated off-label with bisphosphonates like alendronate (Fosamax) if risk factors indicate that they have a high fracture risk.

RITA:

Are there any preventive measures an HIV-positive person can take to stop or delay the onset of these symptoms?

SP:

Good nutrition is imperative. As discussed earlier, deficiencies in calcium and/or vitamin D are well-documented risk factors. Maintaining a proper body weight is also important because being underweight is a risk factor. Patients have to control their HIV disease with available medications that suppress viral replication. In particular, minimizing irregularities in cytokine levels is important because there is strong evidence that cytokines affect bone resorption. Also, HIV-positive patients with hypogonadism are at increased risk for bone disease, and patients should be tested for this. In addition, I would recommend that any HIV comorbidities, such as liver or kidney disease, be treated or controlled as best as possible. There are also some data to suggest that smoking and alcohol use can increase a patient's risk for developing bone problems. Overall, I would recommend that HIV-positive patients do their best to stay as healthy as possible and focus on the conventional risk factors, in addition to controlling their disease.

RITA:

What are the hot areas of research now in this field? Is it applicable or specific to HIV?

SP:

Cytokines are a very interesting area of research. In

addition, looking at new ways to measure or assess bone loss is another fertile area of research. These would include micro-magnetic resonance imaging (micro-MRI), micro-computed tomography (micro-CT), and ways to actually assess bone structure. Also, in 2007, the World Health Organization will be publishing an updated set of guidelines to assess fracture risk that will help identify at-risk populations in older men and women, but will not be directly applicable to secondary causes for low bone density such as HIV. Clearly, there is a need for further research.

RITA:

As an endocrinologist, what interested you in disorders related to HIV?

SP:

In the past, I would see these patients as part of a consultation and I realized that not a lot of information was known about this particular condition. I also believe that this condition is often overlooked in the HIV-positive population. Today, with the use of HIV medications, HIV-positive patients are living more normal lives. Unfortunately, these patients are getting other diseases now, including bone disease. We need to keep their bones healthy, especially those patients with risk factors.

**Suggested resources:**

- Amorosa V, Tebas P. *Clin Infect Dis*. 2006;42(1):108-114.
- Brown TT, Ruppe MD, Kassner R, et al. *J Clin Endocrinol Metab*. 2004;89(3):1200-1206.
- The Surgeon General Report on Bone Health and Osteoporosis at www.surgeongeneral.gov
- The International Society for Clinical Densitometry (ISCD) website for updates and guidelines on densitometry at www.iscd.org
- The American Association of Clinical Endocrinologists (AACE) website for AACE guidelines at www.aace.com



Thinking outside of the (pill) box:

Alternative approaches to combating lipodystrophy

By Jennifer Newcomb-Fernandez, PhD

HIV-associated lipodystrophy is a significant problem affecting those living with HIV disease and encompasses both morphologic (body shape) changes and metabolic abnormalities (such as dyslipidemia). Currently, a number of components of dyslipidemia are managed pharmacologically: statins to treat high cholesterol, fibrates for high triglycerides, and various medications to treat insulin resistance (a related metabolic disturbance). While these agents have had some success, they can potentially interact with antiretroviral medications.^{1,2} But not all agents can successfully treat disturbances related to HIV-associated lipodystrophy. For example, data on the use of the glitazones (eg, troglitazone, rosiglitazone, pioglitazone) to treat HIV-associated lipodystrophy have been conflicting and somewhat disappointing.² Consequently, lifestyle changes such as modifying diet and exercise habits may be one way to ameliorate HIV-associated lipodystrophy.

Regarding diet, dramatic differences exist between HIV-positive people with lipodystrophy and HIV-positive patients who do not have lipodystrophy. An almost universal finding has been that dietary fiber prevents (or reverses) dyslipidemia, central fat accumulation, and insulin resistance in HIV-positive individuals.³⁻⁵ Though the American Dietetic Association recommends that adults consume 20 to 35 grams of dietary fiber daily from a variety of plant foods, many Americans (regardless of HIV status) do not meet this requirement.⁶ In one study cohort, the average fiber intake among HIV-positive patients with lipodystrophy was 7 grams a day.³ Likewise, another group reported that 53% of their study participants consumed less than 20 grams of fiber daily.⁵ Increased intake of soluble

fiber is also associated with lower levels of total cholesterol and non-high density lipoprotein (non-HDL) cholesterol.³ In one particular study, a 1-gram increase in total dietary fiber was associated with a 7% reduction in the risk of developing central fat deposition.⁴ On the other hand, low dietary fiber intake, in addition to a high polyunsaturated fat:saturated fat ratio, is a strong predictor of hyperinsulinemia,⁵ though other studies have reported no relationship between fat or dietary fiber intake and insulin resistance.⁷

Data also indicate that fat intake, and particularly the type of fat ingested, may have an effect on the development of HIV-associated lipodystrophy. A large, multicenter study analyzed the short-term effects of a Mediterranean-style diet rich in unsaturated fats versus a low-fat diet in HIV-negative adults at high risk for cardiovascular disease.⁸ Adults who consumed a Mediterranean-style diet (see Table) improved their lipid profile and lowered their insulin resistance, blood pressure, and concentrations of inflammatory markers compared with adults who consumed the low-fat diet. Along these lines, a pilot study conducted in HIV-positive patients with lipodystrophy assessing the combination of dietary and exercise counseling with or without fish oil (omega-3 fatty acid) supplementation reported a significant decline in triglyceride levels at week 4 in patients receiving fish oil, that was no longer significant at week 16.⁹ Treatment was well tolerated, but patients receiving fish oil did experience an increase in low-density lipoprotein (LDL) cholesterol at both time points. While these values are higher than expected, fish oil has been reported to increase LDL cholesterol levels.¹⁰

TABLE: Examples of foods included in a Mediterranean-style diet

High intake of:	Low intake of:
Virgin olive oil Vegetables Fruits Tree nuts (eg, walnuts, hazelnuts, almonds) Whole grains Legumes Fish and shellfish Wine (in moderation)	Meat or meat products Poultry High-fat dairy products Desserts (cakes, pastries, or other sweets)

Not surprisingly, the data are conflicting and some studies have failed to observe any differences in fat intake between HIV-positive patients with and without lipodystrophy, specifically with regard to total or saturated fat intake.^{3,4,11} Gavrilla and colleagues⁷ reported no significant associations between any dietary component and levels of triglycerides, LDL, HDL, or total cholesterol in their study of HIV-positive patients. Interestingly, in this study, total intake of vitamin E was negatively associated with body fat percentage and subcutaneous abdominal fat. Shah and colleagues³ observed that in their study cohort, patients with HIV-associated lipodystrophy consumed higher than recommended amounts of saturated fat and trans fat, and lower than recommended amounts of unsaturated fats. Levels of total cholesterol, triglycerides, and non-HDL cholesterol were positively associated with increased daily intake of total protein and animal protein; triglyceride level was positively correlated with increased daily intake of trans fats. However, daily intake of total fat, satu-

rated fat, dietary cholesterol, and various unsaturated fats were not related to any metabolic parameter. Hendricks et al⁴ reported no differences in intake of carbohydrates, fats, cholesterol, or any specific micronutrient between HIV-positive patients with fat deposition and HIV-positive patients without fat deposition, but did find that patients with fat deposition consumed less total protein than those subjects without fat deposition.

Many of these same studies that have analyzed patients' diets have also analyzed patients' exercise habits. As with diet, differences in exercise habits exist between HIV-positive individuals with and without lipodystrophy. One study observed that HIV-positive men without fat deposition tend to participate in resistance training types of exercise more frequently than men with fat deposition.⁴ HIV-positive patients who regularly participated in aerobic exercise or a combination of resistance training and aerobic exercise had a higher percentage of lean body mass.⁷ Moreover, these

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patients had significantly reduced triglyceride levels and insulin resistance, though the latter was not statistically significant. However, exercise did not seem to affect levels of LDL, HDL, or total cholesterol. Likewise, Shah et al³ observed that only aerobic exercise of a moderate or heavy intensity was associated with higher values of HDL cholesterol, though this association was not statistically significant.

In contrast to the observational studies discussed above, numerous studies have examined the effect of prescribing specific dietary changes or exercise regimens in people with HIV-associated lipodystrophy. Prescribed exercise regimens have included either aerobic or resistance training, or a combination of both.¹² Though there is some variability, aerobic exercise regimens typically have consisted of stationary cycling or treadmill walking for 20 to 60 minutes per session, 3 times a week. Resistance training usually has been performed 3 times a week with each session comprising 3 sets of 8 repetitions for each exercise. Studies that combined aerobic and resistance training usually involved 20 minutes of aerobic activity, followed by 35 to 40 minutes of resistance training, and then stretching.

A consistent regimen of aerobic exercise is beneficial in treating many of the symptoms of HIV-associated lipodystrophy. HIV-positive patients who exercised 3 times a week for 12 weeks improved their exercise capacity and experienced a significant reduction in body weight, body mass index (BMI), subcutaneous fat, and waist circumference compared with HIV-positive patients who continued their normal level of activity during the study.¹³ Patients in the exercise group did reduce their percentage intake of dietary fat from 35% to almost 30%, although reducing fat intake was only a recommendation and not a planned intervention. In contrast, another study found that all subjects experienced similar decreases in body weight, body fat, and waist-to-hip ratio, regardless of whether

they participated in an aerobic exercise regimen.¹⁴ HIV-positive patients with lipodystrophy received nutritional counseling, but one group participated in a 45-minute routine of light stretching and relaxation exercises 3 times a week while the other group participated in 60 minutes of aerobic exercise 3 times a week. No significant changes in serum lipid levels were observed in either group, though patients in the aerobic exercise group showed a significant improvement in exercise capacity. The researchers speculated that morphologic changes were probably caused by dietary changes (ie, reducing total fat and saturated fat and increasing unsaturated fat) and questioned if a more intensive or long-term exercise program would have led to more dramatic changes in terms of dyslipidemia.

Resistance training may also offer a non-pharmacologic way to treat HIV-associated lipodystrophy. Following 16 weeks of progressive resistance training, HIV-positive men had a reduction in serum triglyceride levels, but no effect was seen on levels of relevant markers including total cholesterol, HDL cholesterol, LDL cholesterol, insulin, C-peptide, proinsulin, or glucagon.¹⁵ Nonetheless, the regimen led to increased strength, body weight, and lean mass in the whole body, trunk, and arms, though no reduction in whole-body adiposity or trunk, arm, or leg adiposity was observed. The authors speculated that the absence of aerobic exercise was a likely explanation. In another small study, patients followed a highly intensive and progressive resistance training regimen for 8 weeks in conjunction with nutritional counseling.¹⁶ To monitor any changes in strength and body composition, the subsequent 8 weeks were self-directed and patients were not required to exercise but permitted to do so. After the initial 8 weeks, both male and female patients had a significant increase in strength and lean body mass and a decrease in body fat. At 16 weeks, most patients still retained increased strength for most of the exercises and lean body mass was maintained, though the

decrease in fat mass was no longer significant. For those who continued to exercise for the study duration, lean body mass continued to increase and body fat continued to decrease.

A combination of aerobic exercise and resistance training may provide the best strategy for treating HIV-associated lipodystrophy.¹⁷ Several small pilot studies have assessed this strategy. For instance, following 16 weeks of combined aerobic exercise and resistance training, HIV-positive men experienced a significant reduction in total body and trunk fat.¹⁸ Nevertheless, body weight, BMI, and lean mass were not affected. Another study performed in 6 HIV-positive patients (5 men and 1 woman) reported that after 10 weeks of combination exercise, total cholesterol and triglycerides decreased significantly, along with a slight (but not statistically significant) increase in HDL cholesterol.¹⁹ This exercise regimen was associated with a significant increase in muscle strength, exercise capacity, and body mass, in conjunction with a decline in body fat.

A case report of a 44-year-old, HIV-positive man with lipodystrophy described such dramatic results after modifying his diet (eg, increasing dietary fiber consumption, as well as lowering consumption of saturated fat and simple sugars) and exercise habits, the authors recommended that these types of lifestyle changes be considered standard treatment for HIV-associated lipodystrophy.²⁰ Though it is not feasible to tease out the effect of diet versus exercise, this patient experienced significant reductions in abdominal fat, BMI, waist-to-hip ratio, and body fat percentage while increasing exercise capacity and lean body mass (though there was no effect on peripheral fat atrophy). In addition, levels of total and LDL cholesterol were reduced, though HDL cholesterol levels also decreased. Insulin resistance and levels of fasting insulin in this patient decreased.

Along the same lines, a recent randomized study examined the effects of a 6-month “lifestyle modification” program.²¹ Patients in the lifestyle modification group attended weekly counseling sessions on improving their diet and participating in at least 3 hours of moderate exercise a week. These patients experienced a significant decrease in blood pressure, waist circumference, and various markers of cardiovascular disease. Exercise capacity increased, but (like several of the studies discussed) there was no effect on total, HDL, or LDL cholesterol.

Overall, these data strongly suggest that diet and exercise have a great impact on the morphologic and metabolic changes that characterize HIV-associated lipodystrophy. Though the published reports all differ somewhat in terms of patient populations, parameters examined, and the specific dietary or exercise recommendations, a common theme is the importance of “healthy living”—eating a balanced diet rich in plant-derived foods and fiber as well as participating in aerobic and strength-training exercises. This research emphasizes the importance of patient education for making these lifestyle changes. Teaching patients that healthy behaviors can have dramatic effects, not only in controlling HIV disease and limiting risk of cardiovascular disease, but on physical appearance as well, is essential to help them succeed in making these lifestyle changes.

But evidence also suggests that certain other habits may predispose HIV-positive patients to developing lipodystrophy. For example, Hendricks et al⁴ reported that cigarette smoking was more prevalent in HIV-positive patients with fat deposition compared with patients without fat deposition. However, another study observed no relationship between smoking and dyslipidemia, though the sample size was limited.³ Alcohol consumption also has been shown to be a positive predictor of

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increased LDL and HDL cholesterol levels and insulin resistance in HIV-positive patients with lipodystrophy.⁵ Still, other studies have failed to show differences in terms of alcohol intake between HIV-positive men with fat deposition and without fat deposition.⁴

The importance of building strength and muscle mass cannot be underestimated as a means of staying healthy and avoiding injury or disabling events, and there is some suggestion that working with an exercise trainer may be even more beneficial to patients.¹⁶ An encouraging finding was that for people with HIV in otherwise good overall health, regular exercise had no negative impact on a

patient's immune system, as shown by stable CD4 cell counts and percentages and HIV viral load levels.^{13,14,16,17,21} Unfortunately, in the midst of these positive data, another common theme in many of these studies was that the resultant dyslipidemia in those living with HIV may be too much to overcome with lifestyle changes. Many researchers speculate that diet and exercise are not enough for treating HIV-associated lipodystrophy, particularly in the presence of HIV antiretrovirals.^{14,21} Thus, pharmacologic treatment may need to be combined with these interventions to achieve desirable measures that fall within general guideline recommendations for cardiovascular health.



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A farewell message

One thing I have learned in my time working at The Center for AIDS (CFA) is that nothing is permanent. Perhaps change is the only constant. Research continues to advance, thoughts and ideas evolve, and treatments are replaced or improved. People, too, are transient. They come in and out of our lives through so many different channels.

That is why this piece is particularly difficult to write. After more than 6 years with The CFA, I have stepped down as Executive Director and Senior Editor (effective July 21, 2006) to move back to my native Connecticut so that I can be closer to my family. I would never have dreamed in 1994, when I moved to Texas to attend graduate school, that Houston would become my beloved home for 12 years. I also never would have dreamed that HIV would become such an important force in my life. To me, being part of The CFA has meant the opportunity to share in the dream of a cure for AIDS and to take part in the work we all must do to make sure that happens.

In my work here, I have been inspired and disheartened, angered and overjoyed. Yet I never lost hope, nor will I ever, that I will live to see an end of AIDS. Perhaps hope is also permanent.

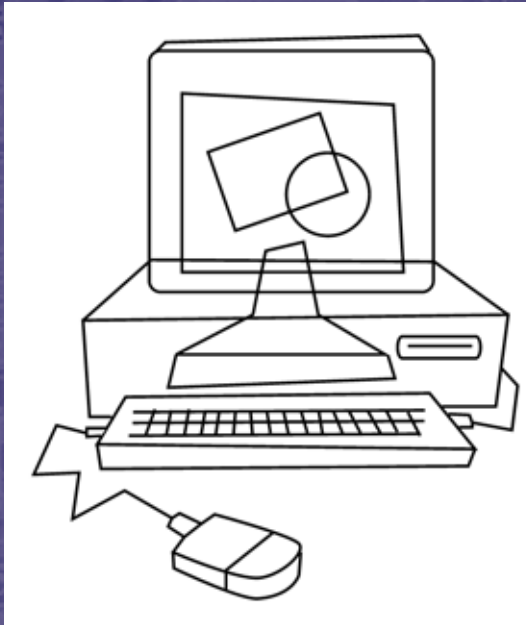
Although this message is about my departure and an end to my current role at The CFA, it is also

about a new beginning. The CFA remains a strong and focused organization with unique HIV/AIDS information, education, and advocacy roles both locally and nationally. A new leader will be hired to guide the organization to the next level of excellence in fulfilling The CFA's mission until there's a cure.

Over the past several years, CFA publications have benefited from the talents of our editor, Jennifer Newcomb-Fernandez, who will continue in her role to write for and produce The CFA's quality publications. She has been contract editor with The CFA since 2003 and will now assume full responsibility for creating and producing publications. Jennifer and all the wonderful staff at The CFA have been my friends and allies both within and outside of the office. I will miss everyone dearly, but never plan to stray too far from this inspiring and vital work.

In closing, I wish you well and thank you, as always, for your readership and support.

Thomas Gegeny



Publications online

- RITA!
- HIV Treatment Alerts!
- Houston-area HIV/AIDS Clinical Trials Directory
- The Top 25 Things You Should Know if You Are HIV+
- HIV medication factsheets
- RITA! Weekly Newsletter (by e-mail)

interforaids.org

The CFA has retained a search consultant to conduct a **national search** for the newly created position of **Information and Advocacy Director**, the national program director.

This executive-level position will direct organizational activities with regard to vision, mission, and goals with an emphasis on the science of HIV/AIDS and The CFA's programs and services; and will work in partnership with the Managing Director to achieve the organization's goals.



All inquiries are being directed to
cclarose@mindspring.com.
 Please put CFA Search in subject line.

Note: No calls, resumes, emails, or faxes will be accepted at The CFA office.

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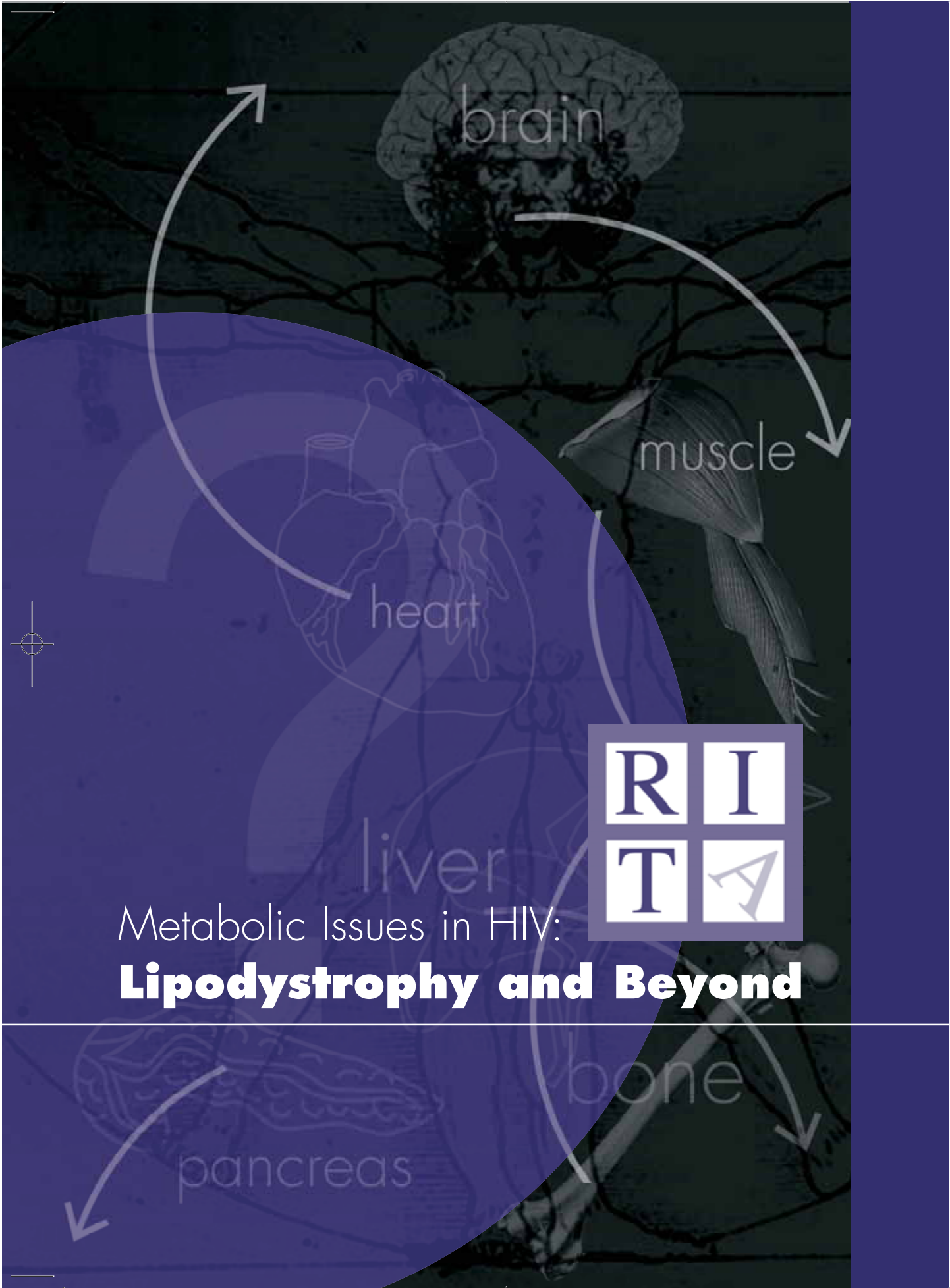
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brain

muscle

heart

liver

pancreas

bone



Metabolic Issues in HIV:

Lipodystrophy and Beyond