

## Perspective

# Pathogenesis and Treatment of Lipodystrophy: What Clinicians Need to Know

The pathogenesis of lipodystrophy in HIV-infected patients is likely multifactorial, involving effects of antiretroviral medications, HIV itself, as well as genetic and other host factors. Protease inhibitors have been associated with fat accumulation, and the nucleoside analogue reverse transcriptase inhibitors (nRTIs) stavudine, didanosine, and zidovudine have been associated with fat loss (lipoatrophy). Strategies that have met with some success in reducing central fat accumulation include treatment with growth hormone or growth hormone-releasing hormone. Strategies that have met with some success for lipoatrophy include switching from nRTIs associated with lipoatrophy or starting treatment with regimens that include drugs associated with lower risk of lipoatrophy (tenofovir, abacavir, lamivudine, emtricitabine). This article summarizes a presentation on lipodystrophy made by Fred R. Sattler, MD, at an International AIDS Society–USA Continuing Medical Education course in Washington, DC, in May 2008. The original presentation is available as a Webcast at [www.iasusa.org](http://www.iasusa.org).

Lipodystrophy is a disorder of fat metabolism that may be clinically evident as adipose tissue accumulation (eg, in intraabdominal, dorsocervical, or breast tissues, and lipomas), lipoatrophy (loss of fat mass, eg, of the face, limbs, buttocks), and metabolic abnormalities (eg, insulin resistance, diabetes, dyslipidemia, hypertension, or lactic acidemia). The pathogenesis of lipodystrophy in HIV-infected patients is multifactorial (Mallon, *AIDS Rev*, 2007) and includes effects of antiretroviral therapy, HIV itself, and genetics and other host factors. Evidence suggests that the nucleoside analogue reverse transcriptase inhibitors (nRTIs) stavudine, didanosine, and zidovudine may cause mitochondrial toxicity by inhibiting mitochondrial DNA polymerase- $\gamma$  in fat and other tissues and thus interfering with respiratory chain complexes (Figure 1). The result is impaired fatty acid oxidation and intracellular accumulation of triglycerides and lactate, which can enter the systemic circulation.

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Protease inhibitors (PIs) inhibit maturation of sterol response element binding proteins (SREBPs, Figure 2A), which affect intracellular fatty acid and

glucose metabolism and adipocyte differentiation (Mallon et al, *J Infect Dis*, 2005). The PIs also down-regulate peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ), an important nuclear transcription factor that is affected by SREBPs and is necessary for adipocyte differentiation and function and fatty acid metabolism (Figure 2B). The HIV viral protein R (vpr) accessory protein also inhibits PPAR $\gamma$ , and PPAR $\gamma$ -deleted mice exhibit lipoatrophy, hepatic steatosis, and increased triglyceride levels. In addition, the duration of HIV infection and its treatment as well as nadir CD4+ cell count have been implicated in lipodystrophy. Lipodystrophy is also observed in acute HIV infection, lending support to a direct viral role as well.

Potential host risk factors include age, sex, and race or ethnicity. Lipodys-

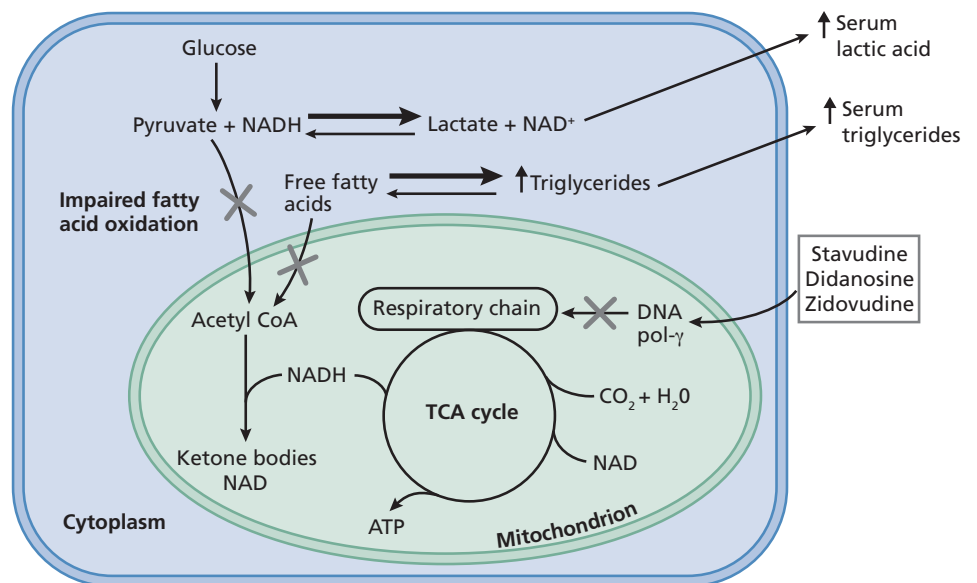
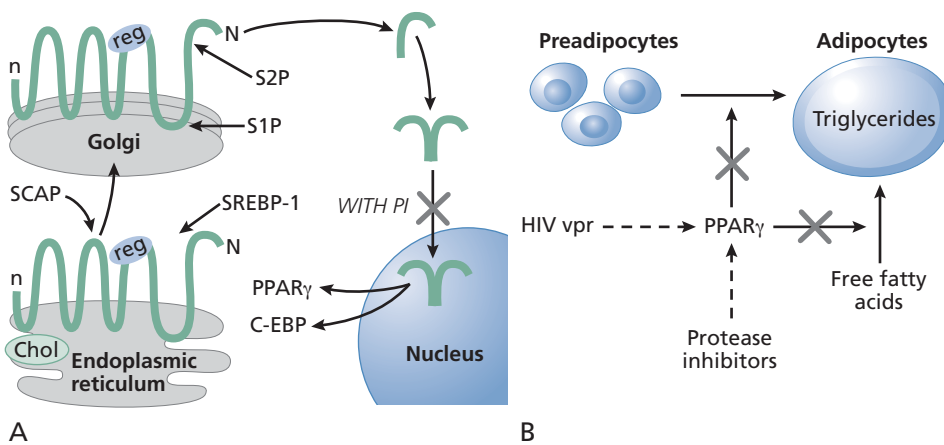


Figure 1. Major intracellular metabolic pathways associated with increased triglyceride and lactic acid production and impaired adenosine triphosphate (ATP) energy production that may contribute to cell death in adipocytes in subjects with lipodystrophy. The nucleoside analogue reverse transcriptase inhibitors stavudine, didanosine, and zidovudine inhibit DNA polymerase gamma (DNA pol- $\gamma$ ), which is necessary for replication of mitochondrial DNA and synthesis of respiratory chain enzyme complexes required in the tricarboxylic acid (TCA) cycle used to generate ATP. Acetyl CoA indicates acetyl coenzyme A; NAD, nicotinamide adenine dinucleotide; NADH, reduced NAD.



**Figure 2.** A: potential effects of HIV protease inhibitors (PIs) on sterol response element binding protein (SREBP) metabolism. These sterol-sensing transcription factors, which affect intracellular lipid metabolism and transcription of a number of gene products including peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) are complexed in an inactive form with SREBP cleavage-activating protein (SCAP). In response to intracellular sterol depletion, both are transported to the Golgi apparatus, where the amino terminus is released by site proteases (S1P, S2P). At the nucleus, the process of signal transduction (which may be inhibited by PIs) results in synthesis and translocation of PPAR $\gamma$  to the cytoplasm. Chol indicates cholesterol; EBP, enhancer-binding protein; reg, regulatory domain that interacts with SCAP. Adapted from Mallon, *AIDS Rev*, 2007. B: both HIV protease inhibitors and HIV viral protein (vpr) accessory protein may inhibit intracellular PPAR $\gamma$ , which is necessary for differentiation of preadipocytes to mature adipocytes and their accumulation of lipid.

trophy is more common in older patients; fat accumulation is more common in women and lipoatrophy in men; and non-Hispanic black patients appear to be at lower risk of lipoatrophy. A genetic component is indicated by a recent analysis in AIDS Clinical Trials Group (ACTG) study 5005s, suggesting either predisposition or protection associated with mitochondrial DNA polymorphisms. Patients homozygous for C/C at the HFE187 locus ( $n = 71$ ) had a 0.6-kg and 12.5% loss of limb fat at weeks 48 to 64, with 37 (52%) of the 71 patients diagnosed with clinical lipoatrophy. By comparison, heterozygous patients with HFE187C/G had a 0.2-kg and 6.1% increase in limb fat, with 6 (26%) of 23 patients having clinical lipoatrophy ( $P < .05$  for all comparisons) (Hulgan et al, *J Infect Dis*, 2008).

### Body Composition Changes

The Fat Redistribution and Metabolic Change in HIV (FRAM) study (Bacchetti et al, *JAIDS*, 2005) showed that HIV-infected men with lipoatrophy had less peripheral and central subcutaneous

adipose tissue (SAT) and less visceral adipose tissue (VAT), contrary to the early impression that peripheral lipoatrophy was frequently accompanied by central fat accumulation. The study included 425 HIV-infected patients and 152 HIV-seronegative subjects. All underwent total body magnetic resonance imaging (MRI), and diagnosis of lipoatrophy was based on the concordance of self-report and HIV Out-patient Study (HOPS) criteria. Relative to noninfected patients, HIV-infected patients with clinical lipoatrophy had markedly greater reductions in adipose tissue volume in the leg, lower trunk, upper trunk, and arm, and in VAT than did HIV patients without clinical abnormalities. Among HIV patients, there was no difference in frequency of peripheral lipoatrophy according to the presence or absence of central fat accumulation. Of patients with central lipoatrophy, however, 90% also had peripheral lipoatrophy, compared with less than 40% of those without central lipoatrophy (odds ratio, 18.9;  $P < .001$ ).

In a study in the Women's Interagency Health Study (WIHS) popula-

tion, dual-energy x-ray absorptiometry (DEXA) scans were performed in 359 mostly overweight or obese women, and differences in fat distribution were compared among 88 women who were HIV-seronegative, 70 who were HIV-infected but receiving no antiretroviral therapy, 48 receiving PI-containing antiretroviral therapy, and 53 receiving antiretroviral therapy with no PI (Mulligan et al, *JAIDS*, 2005). Overall, HIV patients receiving either type of antiretroviral therapy had greater decreases in leg fat than in trunk fat relative to non-HIV-infected women or those not receiving antiretroviral therapy. Trunk fat appeared to be retained in women receiving PI-containing antiretroviral therapy but significantly reduced in those not receiving a PI ( $P < .05$ ).

### Insulin Resistance

Numerous studies have shown that fat loss in the extremities is accompanied by insulin resistance. An early study comparing fasting insulin levels in 71 HIV patients with lipodystrophy versus those in 213 control subjects from the Framingham cohort that were matched for age, sex, and body mass index showed statistically significantly higher levels in HIV patients but no difference between HIV patients with lipodystrophy and those with fat accumulation (Hadigan et al, *J Clin Endocrinol Metab*, 2001).

In the FRAM study (Grunfeld et al, *JAIDS*, 2007), increased values of VAT and upper trunk SAT were independently associated with insulin resistance as assessed by the homeostasis model assessment of insulin resistance (HOMA-IR) in non-HIV-infected control subjects and in HIV patients (Table 1). The finding of a strong association of insulin resistance with upper trunk SAT as well as VAT was somewhat surprising because previous assumptions were that the predominant association is between insulin resistance and VAT accumulation.

Insulin resistance is part of the metabolic syndrome, which poses increased risk of cardiovascular disease complications (eg, heart attack, stroke, peripheral vascular disorders). It is noteworthy that other features of the metabolic syndrome, including cen-

**Table 1.** Association Between Increased Fat Volume and Insulin Resistance in Non-HIV-infected and HIV-infected Patients in the FRAM Study

	Non-HIV-infected Patients (n = 248)		HIV-infected Patients (n = 926)	
	HOMA-IR value > 4	Odds Ratio (P value)	HOMA-IR value > 4	Odds Ratio (P value)
<b>Visceral Adipose Tissue</b>				
3rd vs 1st tertile	63%	12.1 (<.001)	55%	3.1 (<.001)
2nd vs 1st tertile	18%	1.9 (.31)	38%	1.9 (.002)
1st tertile (reference)	6%	--	22%	--
<b>Upper Trunk Subcutaneous Adipose Tissue</b>				
3rd vs 1st tertile	61%	9 (.001)	57%	2.1 (.001)
2nd vs 1st tertile	20%	2.4 (.26)	36%	1.2 (.33)
1st tertile (reference)	5%	--	27%	--

FRAM indicates Fat Redistribution and Metabolic Changes in HIV; HOMA-IR, homeostatic model assessment of insulin resistance. Adapted from Grunfeld et al, *JAIDS*, 2007.

tral obesity, hypertension, and dyslipidemia (hypertriglyceridemia and low high-density lipoprotein [HDL] cholesterol level), frequently are present in HIV patients with lipodystrophy.

### Effects of Antiretroviral Therapy

Of commonly used drugs, stavudine (a thymidine analogue) is the nRTI most frequently associated clinically with lipoatrophy. The fact that some patients have received stavudine for years and do not develop lipoatrophy suggests that host and genetic factors may be contributing to the pathogenesis of (or protection from) the syndrome. Didanosine, which is now used infrequently, has been clearly associated with the occurrence of clinical lipoatrophy. Zidovudine (a thymidine nRTI) has also been implicated but to a lesser degree than the other 2 nRTIs. A good example of body composition changes associated with antiretroviral therapy is demonstrated in several substudies performed by Dube and colleagues in ACTG study 384 (Dube et al, *AIDS*, 2005; Mulligan et al, *JAIDS*, 2006; Dube et al, *JAIDS*, 2007), in which antiretroviral therapy-naïve patients received nelfinavir or efavirenz plus either didanosine/stavudine or zidovudine/lamivudine. Analysis of trunk fat

changes at 64 weeks showed statistically significantly greater increases with efavirenz versus nelfinavir (16.5% vs 8.1%;  $P = .01$ ) and with zidovudine/lamivudine versus didanosine/stavudine (13.5% vs 5.3%;  $P = .02$ ). However, nelfinavir (approximately  $-15\%$  vs  $+3\%$ ;  $P = .003$ ) and didanosine/stavudine (approximately  $-17\%$  vs  $+5\%$ ,  $P < .001$ ) were associated with a statistically significantly greater loss in limb fat. These losses plateaued at approximately 80 weeks and amounted to a loss of approximately 0.90 kg.

### Treatment

#### Strategies to Reduce Central Obesity

A number of strategies for reducing central obesity have been investigated. Stopping PI treatment has not been effective. Changes in diet and exercise have produced improvements, but adherence to a regimen of lifestyle change is difficult for most patients. Liposuction has produced acceptable results (particularly with dorsocervical fat accumulation, ie, "buffalo hump"). Results of 7 studies of thiazolidinediones (Walli et al, *Res Exp Med* (Berl), 2000; Sutinen et al, *Antivir Ther*, 2003; Hadigan et al, *Ann*

*Intern Med*, 2004; van Wijk et al, *Ann Intern Med*, 2005; Gavrila et al, *Clin Infect Dis*, 2005; Feldt et al, *Infection*, 2006; Mulligan et al, *AIDS*, 2007) have shown no change in VAT. Five studies of metformin (Hadigan et al, *JAMA*, 2000; Martinez et al, *Antivir Ther*, 2003; Driscoll et al, *J Clin Endocrinol Metab*, 2004; Hadigan et al, *Ann Intern Med*, 2004; Mulligan et al, *AIDS*, 2007) showed no change in VAT, and 1 (van Wijk, *Ann Intern Med*, 2005) showed a decrease of 25 cm<sup>2</sup> compared with no change with rosiglitazone ( $P < .05$ ).

Testosterone replacement to physiologic levels reduces VAT, total fat, and abdominal fat and improves insulin sensitivity and lipid profile in older, non-HIV-infected men with upper body obesity and low testosterone levels. In a recent study, 88 HIV-infected men with central obesity (waist circumference > 100 cm) and low testosterone levels (< 400 ng/dL) underwent randomization to testosterone as a transdermal gel at a dose of 10 g daily or placebo for 24 weeks (Bhasin et al, *J Clin Endocrinol Metab*, 2007). The testosterone group had statistically significant reductions in abdominal fat ( $-1.5\%$  vs  $+4.3\%$ ), abdominal SAT ( $-7.2\%$  vs  $+8.1\%$ ), trunk fat ( $-9.9\%$  vs  $+4.6\%$ ), and limb fat ( $-10.1\%$  vs  $+3.1\%$ ); the latter finding is of potential concern in a population predisposed to lipoatrophy. No statistically significant difference in change in VAT ( $+0.9\%$  vs  $+2.3\%$ ) was observed, and no statistically significant differences were observed in changes in lipid levels, fasting blood glucose levels, insulin levels, or insulin resistance.

Like testosterone, growth hormone (GH) has fat-oxidizing and lipolytic properties. A substantial proportion of HIV patients with central obesity (approximately 30%-40%) have impaired GH biology, including reduced GH mass secretion, reduced response to GH-releasing hormone (GHRH) and free fatty acids, and increased somatostatin tone, which suppresses GH. A number of recent studies have assessed GH treatment in HIV patients with fat accumulation. In 1 study, 325 HIV patients with increased waist:hip ratios and increased VAT measurements received

**Table 2.** Metabolic Changes in HIV Patients With Increased Waist:Hip Ratios and Visceral Adipose Tissue Measurements After Treatment With Recombinant Human Growth Hormone (rhGH)<sup>a</sup>

	Change at 12 Weeks (P value)	Change at 36 Weeks (P value)	Change at 36 Weeks (P value)
	rhGH 4 mg/day Weeks 0-12	rhGH 4 mg/day Weeks 0-12+	rhGH 4 mg/day Weeks 0-12+
		rhGH 2 mg/day Weeks 13-36	Placebo rhGH Weeks 13-36
Visceral adipose tissue, cm <sup>2</sup>	-32.6 (<.001)	-15.7 (.001)	-7.9 (.03)
Abdominal subcutaneous adipose tissue, cm <sup>2</sup>	-14.3 (<.001)	8.5 (.67)	5.1 (.82)
Limb fat, kg	-0.4 (<.001)	0.0 (.63)	0.1 (.19)
Non-HDL cholesterol, mmol/L	-13.0 (<.001)	-6.7 (.03)	-4.3 (.61)
Triglycerides, mmol/L	-11.3 (.63)	4.5 (.42)	-7.8 (.84)
Fasting blood glucose, mg/dL	6.0 (<.001)	-0.4 (.29)	-0.3 (.89)
Insulin AUC, $\mu$ IU/mL	1466 (<.001)	30.7 (.31)	-1070 (.008)

AUC indicates area under the concentration curve; HDL, high-density lipoprotein.

<sup>a</sup>Study subjects were treated with supraphysiologic doses (4 mg/day) of rhGH for 12 weeks, followed by alternate-day treatment with either rhGH (2 mg/day) or placebo for 24 weeks.

Adapted from Grunfeld et al, *JAIDS*, 2007.

supraphysiologic doses of recombinant human GH (rhGH) consisting of 4 mg daily for 12 weeks and then alternate-day treatment with either 2 mg rhGH or placebo for an additional 24 weeks (Grunfeld et al, *JAIDS*, 2007).

As shown in Table 2, after 12 weeks, there were statistically significant reductions in VAT and abdominal SAT, and a statistically significant decrease in limb fat. Non-HDL cholesterol level was modestly reduced. However, there was also a statistically significant decrease in limb fat and statistically significant increases in fasting blood glucose levels and the insulin area under the concentration curve (indicating increased insulin resistance).

After an additional 24 weeks of alternate-day treatment, the reduction in VAT was reduced by half and the reduction in abdominal SAT was lost, but the adverse effect on glucose metabolism resolved. In the group receiving placebo for 24 weeks, the overall reduction in VAT was modest (about one-fourth of that achieved after 12 weeks with 4 mg/

day) but remained statistically significant, and there was a statistically significant improvement in insulin sensitivity. Thus, there are early adverse effects associated with supraphysiologic doses of rhGH (namely loss of limb fat, decreases

in HDL-cholesterol, and impaired carbohydrate metabolism). Although these appear largely to abate with longer therapy at lower doses, the improvements in trunk fat have been modest.

A second study evaluated the effects physiologic doses of rhGH in 56 HIV patients with lipodystrophy and low GH levels after a GHRH/arginine stimulation test (Lo et al, *CROI*, 2008). Patients received either placebo or rhGH sufficient to increase levels of insulin-like growth factor 1 (IGF-1) into the upper quartile. The dose was 2.1  $\mu$ g/kg, approximately one-thirtieth the dose used in the study of supraphysiologic doses. As shown in Table 3, patients receiving rhGH had large and statistically significant reductions in VAT, smaller but statistically significant reductions in trunk fat, no loss of extremity fat, and statistically significant reductions in diastolic blood pressure. Unfortunately, there was no overall reduction in carotid intima-media thickness, and rhGH treatment was again associated with evidence of insulin resistance.

In a potentially more promising approach to GH modulation, another study evaluated treatment with 2 mg daily of an investigational GHRH agent, tesamorelin, versus placebo in 412 HIV patients with high waist circumferences (Falutz et al, *N Engl J Med*, 2007). Table 4 shows that GHRH treatment was associated with a large and statistically

**Table 3.** Metabolic Changes in HIV Patients with Lipodystrophy and Low Growth Hormone Levels Receiving Recombinant Human Growth Hormone (rhGH)<sup>a</sup>

	rhGH (2.1 $\mu$ g/kg)	Placebo	P Value
Visceral adipose tissue, cm <sup>2</sup>	-22	-4	<.001
Trunk fat, kg	-0.5	0.2	.04
Extremity fat, kg	0.3	0.3	.94
Diastolic blood pressure, mmHg	-3	4	.006
Intima-media thickness, mm	0.003	-0.003	.78
2-hour glucose (OGTT), mg/dL	16	-4	.009

OGTT indicates oral glucose tolerance test.

<sup>a</sup>Subjects (n = 56) were treated with rhGH or placebo for 18 months.

Adapted from Lo et al, *CROI*, 2008.

significant reduction in VAT with only a marginal reduction in abdominal SAT, and a statistically significant reduction in triglyceride levels and improvement in adiponectin; there was no apparent adverse effect on glucose metabolism. Although the change in limb fat was statistically different from that in the placebo group, the absolute change (0.02 kg) was quite small and unlikely to be of clinical importance. As with rhGH, 24 weeks after discontinuation of treatment, improvements in VAT dissipated, indicating that long-term suppressive therapy will be necessary to sustain these improvements (Falutz et al, CROI, 2008).

Although the GH and GHRH therapies show some promise, there are limitations to their use. They are parenteral therapies and either expensive (rhGH) or not FDA-approved (tesamorelin). Thus far, there is evidence of waning durability of the reduction in VAT after their discontinuation, short-term increases in insulin resistance with rhGH, and small short-term reductions

in SAT and limb fat, especially with high-dose rhGH. Short-term reductions in VAT have thus far not been associated with reductions in carotid intima-media thickness. The long-term safety of such treatments also has not been established, and it is uncertain whether there is increased risk of cancer if IGF-1 levels are excessively elevated. This latter issue is of theoretical concern, but in fact, when rhGH is used to treat other conditions and IGF-1 levels are increased, there has not been a demonstrable increase in risks of cancer, but those studies are relatively small. Further, the potential benefits in reducing cardiovascular risks through these strategies (eg, through beneficial effects on blood pressure and lipid levels) remain undefined.

#### Strategies to Increase Subcutaneous Fat

Strategies to increase SAT in patients with lipodystrophy include facial implants, uridine treatment to replenish

intracellular pyrimidines, switching from stavudine, didanosine, or zidovudine, treatment with a thiazolidinedione, and initial antiretroviral therapy with “lipoatrophy-friendly” drugs such as tenofovir, abacavir, lamivudine, or emtricitabine.

The benefits of switching antiretroviral therapy were shown in the Mitochondrial Toxicity (MITOX) study (Martin et al, *AIDS*, 2004). In that study, 111 patients who developed lipodystrophy while receiving stavudine or zidovudine underwent randomization to continue treatment or switch to abacavir. At week 24, control patients were permitted to switch to abacavir. At week 104, results of DEXA measurements showed that the abacavir group gained 1.26 kg of limb fat versus 0.49 kg in control subjects ( $P = .008$ ). No statistically significant differences were found in change in VAT, nor was there clinical evidence of lipoatrophy.

In the Randomized Abacavir Versus Viread Evaluation (RAVE) study (Moyle et al, *AIDS*, 2006), thymidine nRTIs were replaced with tenofovir or abacavir in 105 patients with lipodystrophy. After 48 weeks, there were statistically significant within-group reductions in lipoatrophy, with limb fat gains of 0.33 kg in patients taking tenofovir ( $P = .01$ ) and 0.48 kg in those taking abacavir ( $P = .0001$ ). There were no changes in trunk fat or VAT measures. Tenofovir treatment was associated with modest reductions in levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides, whereas there were no lipid changes with abacavir treatment.

In a study of patients with advanced HIV disease, 62 patients (with plasma HIV RNA levels < 200 copies/mL) were switched to an nRTI-sparing regimen of lopinavir/ritonavir plus efavirenz versus a PI-sparing regimen of efavirenz plus 2 nRTIs for 48 to 104 weeks (Tebas et al, *JAIDS*, 2007). At 48 weeks, there was a statistically nonsignificant increase in limb fat of approximately 0.6 kg in patients taking the nRTI-sparing regimen, and a marginally statistically significant ( $P = .05$ ) decrease of more than 0.2 kg in patients taking the PI-sparing regimen. At week 104, there

**Table 4.** Metabolic Changes in HIV Patients with High Waist Circumferences Receiving Investigational Growth Hormone–Releasing Hormone (GHRH)<sup>a</sup>

	GHRH	Placebo	P Value
Visceral adipose tissue, cm <sup>2</sup>	-27.8	5.1	<.001
Abdominal subcutaneous adipose tissue, cm <sup>2</sup>	-3.3	2.3	.05
Limb fat, kg	-0.0	0.2	.006
IGF-1, ng/mL	109	-16	<.001
Triglycerides, mg/dL	-50	9	<.001
Total cholesterol, mg/dL	-10	-3	.2
Adiponectin, µg/mL	0.5	-0.1	.03
Fasting blood glucose, mg/dL	3	1	.28
Insulin, µU/mL	2	3	.93

IGF-1 indicates insulinlike growth factor 1.

<sup>a</sup>Subjects (n = 412) received the investigational GHRH tesamorelin 2 mg/day or placebo for 26 weeks.

Adapted from Falutz et al, *N Engl J Med*, 2007.

was an increase of 0.8 kg in the nRTI-sparing group ( $P = .07$ ), compared with a decrease of 0.85 kg ( $P = .07$ ) in the PI-sparing group ( $P = .002$  for between-group comparison). However, the gain in fat associated with the nRTI-sparing regimen was accompanied by greater increases in triglyceride levels and total cholesterol levels. No changes in trunk fat, insulin, glucose, or insulin resistance (as measured by HOMA-IR values) were observed.

The thiazolidinediones may be of benefit in lipoatrophy by stimulating adipogenesis through an agonist effect on PPAR $\gamma$ . A number of studies have shown no effect of rosiglitazone on lipoatrophy (Sutinen et al, *Antivir Ther*, 2003; Carr et al, *Lancet*, 2004; Cavalcanti et al, *J Infect Dis*, 2007). Others have shown partial effects, including increased abdominal SAT (Gelato et al, *JAIDS*, 2002), increased abdominal SAT and VAT (van Wijk et al, *Ann Intern Med*, 2005), and increased limb fat (Hadigan et al, *Ann Intern Med*, 2004; Mulligan et al, *AIDS*, 2007).

In a recent study (Mulligan et al, *AIDS*, 2007), 105 patients with increased waist:hip ratios and evidence of insulin resistance received metformin, rosiglitazone, a combination of the 2, or double placebo for 16 weeks. Among patients receiving only rosiglitazone 4 mg daily, there was a 4.8% increase in leg fat (approximately 0.22 kg) from pretreatment ( $P = .03$ ), no change in VAT, an increase in adiponectin levels (3.0  $\mu\text{g}/\text{mL}$ ;  $P < .001$ ), and a reduction in insulin area under the concentration curve (25.7  $\mu\text{U}/\text{mL}$ ;  $P = .01$ ), indicating improved insulin sensitivity. However, there was also a decrease in HDL cholesterol level (5 mg/dL;  $P = .005$ ) and an increase in LDL cholesterol level (7 mg/dL;  $P = .048$ ). In addition to the short duration of the study, another limitation is that the study was not controlled for use of thymidine nRTIs.

Promising results have been observed with pioglitazone. In a study comparing pioglitazone 30 mg daily ( $n = 64$ ) with placebo ( $n = 66$ ) in patients with lipodystrophy (Slama et al, *Antivir Ther*, 2008), pioglitazone

was associated with an increase in limb fat of 0.38 kg versus 0.05 kg ( $P = .051$ ), respectively, at 48 weeks. Among patients not receiving stavudine ( $n = 48$  vs 46), the increase was 0.45 kg versus 0.04 kg ( $P = .013$ ), respectively, whereas the increase was 0.17 kg versus 0.07 kg ( $P = .40$ ), respectively, among those receiving stavudine ( $n = 16$  vs 20). Pioglitazone was also associated with an increase in thigh circumference (1.4 cm vs 0.2 cm;  $P = .017$ ), with no statistically significant differences observed between groups in changes in VAT (5.3  $\text{cm}^2$  vs 7.7  $\text{cm}^2$ ) or abdominal SAT (16.3  $\text{cm}^2$  vs 7.8  $\text{cm}^2$ ). High-density lipoprotein cholesterol level increased in pioglitazone patients (3.3 mg/dL vs -3.2 mg/dL;  $P = .005$ ). There were no statistically significant differences in clinical manifestations of lipodystrophy or changes in other lipid levels or in glucose metabolism. Pioglitazone, unlike rosiglitazone, is metabolized by cytochrome P450 3A4 enzymes and thus has potential for pharmacokinetic interactions with PIs.

A successful strategy in antiretroviral therapy-naïve patients is selection of initial regimens less likely to be associated with lipoatrophy. For example, 2 studies have shown benefit in this regard with use of initial regimens including tenofovir/emtricitabine versus zidovudine/lamivudine; the results suggested that tenofovir causes less lipoatrophy than zidovudine. In 1 study (Gallant et al, *JAMA*, 2004) involving 753 patients, use of tenofovir/emtricitabine statistically significantly reduced the rate of clinical lipodystrophy at 3 years to 3% versus 19% with zidovudine/lamivudine ( $P < .001$ ). Limb fat measurements showed greater fat with tenofovir/emtricitabine at week 96 (7.9 kg vs 5.0 kg;  $P < .001$ ;  $n = 262$ ) and at week 144 (8.6 kg vs 4.5 kg;  $P < .001$ ;  $n = 232$ ). In another study (Gallant et al, *N Engl J Med*, 2006) involving 517 patients, weight gain was similar with tenofovir/emtricitabine and zidovudine/lamivudine (2.1 vs 1.1 kg, respectively;  $P = .14$ ), and limb fat was statistically significantly greater (8.9 kg vs 6.9 kg;  $P = .03$ ) among 100

patients with measurements taken at 48 weeks. These studies were limited by the absence of pretreatment DEXA measurements, although pretreatment body weights were comparable in the 2 groups in both studies.

## Summary

Fat accumulation and lipoatrophy syndromes in HIV patients most likely differ mechanistically. The pathogenesis of these syndromes is not established, but it is clear that thymidine nRTIs and PIs contribute to lipodystrophy. For treatment of fat accumulation, (1) stopping PIs is not effective; (2) diet and exercise adjustments are effective, but long-term maintenance is difficult; (3) liposuction works for dorsocervical fat; (4) metformin and testosterone administration do not appear to be effective in reducing VAT; and (5) rhGH and GHRH treatments decrease VAT and improve lipid levels—although rhGH is associated with musculoskeletal adverse effects, insulin resistance, and reduced limb fat, maintenance treatment is required, and benefits in terms of cardiovascular risk reduction have not been defined.

For treatment of lipoatrophy, (1) facial implants are successful (although poly-L-lactic acid implants may be lumpy, and the radiopacity of synthetic calcium hydroxylapatite needs to be noted); (2) the effectiveness of uridine treatment remains to be established; (3) switching from thymidine nRTIs is partially effective; (4) thiazolidinedione treatment is minimally effective; and (5) initial therapy with tenofovir, abacavir, lamivudine, or emtricitabine should minimize risk. A primary goal of current and future study is improved understanding of the mechanisms of and genetic predilections for lipodystrophy.

*Presented by Dr Sattler in May 2008. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Sattler in September 2008.*

*Dr Sattler has no relevant financial affiliations to disclose.*

## Suggested Reading

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