

HIV lipodystrophy: risk factors, pathogenesis, diagnosis and management

Andrew Carr

HIV lipodystrophy is a heterogeneous syndrome, which has yet to be objectively defined, comprising peripheral lipoatrophy, central fat accumulation and lipomata, along with hyperlipidaemia, insulin resistance and lactic acidemia. Both nucleoside analogues and protease inhibitors are involved, but there are also host factors that probably place some patients at greater risk. The pathogenesis is increasingly understood, with evidence of interference of several regulatory proteins such as sterol regulatory enhancer binding protein-1, the proteasome, mitochondrial DNA polymerase gamma and GLUT-4. Along with the issues of cosmetics and stigmatization, a principal clinical concern that arises with lipodystrophy is a possible increased risk of accelerated atherosclerosis. A variety of therapeutic interventions, designed to limit these risks, are under evaluation, but none is conclusively shown to be of value.

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Clinical and metabolic features

Lipodystrophy affecting HIV-infected patients was first described 4 years ago. The main clinical features are peripheral lipoatrophy of the face, limbs and buttocks, and central fat accumulation [within the abdomen, breasts and over the dorso-cervical spine (so-called 'buffalo hump'), as well as other lipomata] [1–6]. Dual-energy X-ray absorptiometry and abdominal computerized tomography have objectively confirmed these clinical findings, demonstrating peripheral fat loss, increased visceral fat, overall fat loss, and preserved lean body mass.

The overall prevalence of at least one physical abnormality is about 50% in otherwise healthy outpatients [1,7–19]. The differences between these prevalence rates (which ranged from 18 to 83%) may also have been confounded by patient sex, age, and type and duration of antiretroviral therapy, and the lack of an objective and validated case definition. Two prospective studies of previously antiretroviral-naive adults found a prevalence of 20 and 35% at 18 and 12 months of protease inhibitor-containing therapy, respectively, suggesting clinical variability in diagnosis may be another confounding factor [20,21].

Metabolic features significantly associated with lipodystrophy include hypertriglyceridaemia, hypercholesterolaemia, low levels of high-density lipoprotein cholesterol, insulin resistance (elevated C-peptide and insulin), type 2 diabetes mellitus, lactic acidemia and elevated hepatic transaminases [1,11,12,14–26]. Protease inhibitor therapy has been linked mainly to insulin resistance and hypercholesterolaemia, and nucleoside analogues to lactic acidemia. These metabolic abnormalities are more profound in those with more severe physician-assessed lipodystrophy [1,9,14]. Lipodystrophy has been associated in one study with low serum testosterone, but not with significant differences in sex hormone binding globulin, prolactin, cortisol, complement or tumour necrosis factor-alpha levels, all of which are involved in adipocyte homeostasis. Leptin levels are low, consistent with reduced fat mass [1].

Dyslipidaemia at levels associated with increased risk of cardiovascular disease occurs in about 70% of patients, although this occurrence is probably not totally a result of lipodystrophy [1,15,17,27]. Hypertriglyceridaemia and low levels of high-density lipoprotein cholesterol are seen in untreated HIV infection, and there is also very probably a background level due to genes, diet and pre-morbid body habitus.

From the HIV, Immunology and Infectious Diseases Clinical Services Unit, St Vincent's Hospital, Sydney, Australia.

Requests for reprints to Associate Professor Andrew Carr, HIV, Immunology and Infectious Diseases Clinical Services Unit, St Vincent's Hospital, Sydney 2010, Australia. Tel: +61 2 8382 3359; fax: +61 2 8382 3893; e-mail: acarr@stvincents.com.au

The prevalence of diabetes mellitus is about 8–10%, with most cases identified after oral glucose loading [1,9,22–26]. Few cases appear to have symptoms such as polyuria, blurred vision or weight loss, and ketoacidosis is rare. A further 15% of patients have impaired glucose tolerance. Most diabetes has been identified in protease inhibitor recipients, but a causal relationship has not been established. No risk factor for developing diabetes in protease inhibitor recipients has been identified. Why diabetes is less common than the physical changes and dyslipidaemia is unclear, although development of type 2 diabetes usually involves both insulin resistance and impaired insulin secretion.

Potential risk factors

Several large cross-sectional studies and two prospective cohort studies have identified factors associated with lipodystrophy (Table 1). Factors seen consistently in cohorts include increasing age, current use and total duration of antiretroviral therapy, including nucleoside analogue reverse transcriptase inhibitors (NRTI) and of protease inhibitors, but not non-nucleoside reverse transcriptase inhibitors. Less clear associations include gender, AIDS diagnosis, greater CD4 lymphocyte and HIV RNA responses to antiretroviral treatment, low body weight pre-therapy, elevated C-peptide and triglyceride levels after about 1 year of therapy, use of the dual protease inhibitor combination ritonavir-saquinavir, and use of the thymidine analogues, particularly stavudine. Whether there is a definite hierarchy of responsible drugs is not clear as this has not been disentangled from the duration of therapy with each drug and class.

Pathogenesis

The pathogenesis of HIV lipodystrophy is unknown. Risk factors identified in cohort studies, and several *in vitro* studies of adipocytes, skeletal muscle and hepatocytes, suggest a complex model to explain the pathogenesis of HIV lipodystrophy, involving antiretroviral therapies, and host and environmental factors (Fig. 1).

Lipodystrophy

Lipodystrophy secondary to protease inhibitors may be due to inhibition of lipid and adipocyte regulatory proteins that have partial homology to the catalytic site of HIV-1 protease, to which all protease inhibitors bind [28]. *In vitro* studies have demonstrated that protease inhibitors can inhibit lipogenesis [29–35] by inhibiting the differentiation of proliferating pre-adipocytes to mature adipocytes, which have substantially lower levels of the transcription factors sterol regulatory

Table 1. Factors associated with lipodystrophy in cohort and prospective studies.

Cohort [reference]	n	Antiretroviral therapy				HIV disease		Demographics				Metabolic parameters (increases)			
		PI now	↑ PI duration	NRTI now	↑ NRTI duration	NNRTI	CD4 cell	↑ HIV RNA	↑ Age	AIDS	Sex	Caucasian	Lactate	Lipids	Insulin resistance
Sydney [14]	221	+	+	+	+	–	–	–	–	ns	ns	+	+	+	
Australia [15]	1348	+	+	+	+	–	–	+	+	LA, male	ns	–	+	+	
HOPS [10]	1077	IDV	IDV	d4T	d4T	–	+	+	+	–	+	ns	ns	ns	
Swiss [16]	1480	+	+	+	+	–	–	–	–	ns	ns	+	+	+	
Aquitaine [17]	581	ns	+	ns	+	ns	–	LA	+	ns	ns	ns	+	+	
Italian [18]	2250	+	+	+	+	–	+	–	–	ns	ns	+	ns	+	
Vancouver [19]	221	+	+	+	+	–	–	–	–	–	ns	ns	+	ns	
Barcelona [20]	462	ns	+	ns	+	na	–	+	–	Female	ns	ns	ns	+	
Germany [21]	115	–	+	–	+	–	–	+	–	–	+	ns	ns	ns	

↑, Increase; ↓, decrease; +, positive association with presence of HIV lipodystrophy; –, negative association with presence of HIV lipodystrophy; d4T, stavudine; HOPS, HIV Outpatient Study; IDV, indinavir; LA, lipodystrophy; na, not applicable (no patient in this cohort received a NNRTI); NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; ns, not studied; PI, protease inhibitor; PI/NRTI now, subject on PI/NRTI containing regimen at time of study; PI/NRTI duration, total length of exposure to stated class of drug.

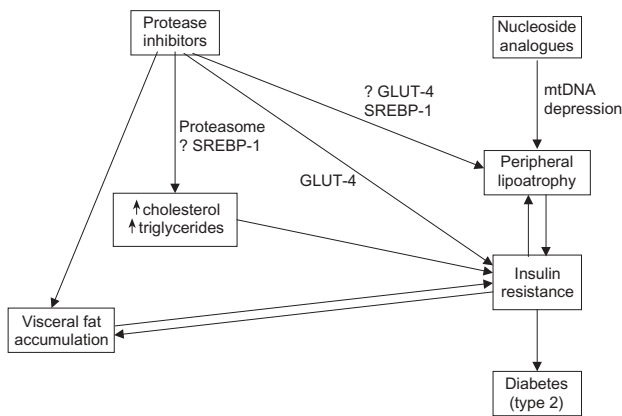


Fig. 1. Possible pathogenesis of lipodystrophy, dyslipidaemia and insulin resistance.

element binding protein (SREBP)-1 and peroxisome proliferator activating factor- γ , with obvious defective maturation of SREBP-1 [33]. Indinavir did not affect pre-adipocyte growth or insulin responsiveness, nor the initial step of adipocyte cell differentiation. Cells that did develop were insulin resistant, which implies their capacity to store triglyceride would be impaired. Nevertheless, rosiglitazone, a peroxisome proliferator activating factor- γ agonist, can reverse these effects of indinavir.

Several lines of evidence suggest that some lipodystrophy may represent a mitochondrial toxicity caused by NRTI. Nucleoside analogues also inhibit adipogenesis and promote lipolysis, and may exert strong synergistic toxicity with protease inhibitors *in vitro* [36]. Second, lipodystrophy and buffalo hump have been reported in patients who have received only NRTI [13–16], and both can occur in HIV-uninfected patients with mitochondrial defects [37]. Third, lipodystrophy is linked with lactic acidemia and, indeed, the presence of lactic acidemia is associated with a higher risk for subsequent lipodystrophy [14,16]. Also, stavudine can deplete mitochondrial DNA in white fat of obese, but not lean, mice [38]. Finally, lipodystrophic men receiving NRTI show evidence of mitochondrial DNA depletion (but not mutation [39,40]). However, short-term adipocyte culture in the presence of a NRTI does not cause mitochondrial depletion or reduced adenosine triphosphate production [36].

It is less likely that the syndrome is a direct effect of HIV. Lipodystrophy is almost exclusive to patients receiving antiretroviral therapy, and has not been observed in patients with long-term, non-progressive HIV infection. Lipodystrophy has not been reported in untreated patients, even in the presence of high plasma HIV RNA load, and yet can occur in patients who receive antiretroviral therapy after primary HIV infection [41]. Also, visceral fat accumulation and lipoatro-

phy can improve after protease inhibitor and NRTI switching, respectively, without change in viral load [42,43]. Finally, most cohorts have found either a negative association between increasing HIV RNA and lipodystrophy or no association at all.

Growth hormone levels are significantly lower in lipodystrophic HIV-infected patients with visceral adiposity, as is seen in growth hormone deficiency [44]. Paradoxically, insulin-like growth factor type 1 levels were not increased, as would be expected with true growth hormone deficiency.

There are other unlikely mechanisms. Although many features of lipodystrophy are suggestive of Cushing's syndrome, this appears to have been excluded [4]. Fat accumulation could be a refeeding effect associated with improved appetite in the setting of suppression of HIV-1 replication; this would not explain lipoatrophy, however.

Hyperlipidaemia

Ritonavir therapy for 2 weeks in HIV-uninfected adults resulted in increased cholesterol, triglycerides, lipoprotein(a) and apolipoprotein B, with evidence of increased lipid production [45], establishing that these abnormalities can occur independently of HIV infection.

In hepatocyte cell lines, protease inhibitors interfere with the cholesterol synthesis, perhaps by inhibition of the proteasome, which regulates apolipoprotein B production. Interestingly, SREBP-1 is important in hepatic very-low-density lipoprotein production [46], and it has been hypothesized that SREBP-1 inhibition is the cause of increased hepatic lipid production [47]. In keeping with these data, a polymorphism in the SREBP type 1c gene is significantly associated with the presence of hypercholesterolaemia on protease inhibitor therapy, suggesting that this pathway is interrupted by protease inhibitors both within adipocytes (fat storage) and the liver (fat synthesis) [48].

Dyslipidaemia may also be a consequence of insulin resistance, of visceral fat accumulation and of lipoatrophy (release of stored lipid, and an inability to take up circulating triglycerides), as is the case in lipodystrophic adults without HIV infection [49].

Insulin resistance

Treatment of HIV-uninfected adults with indinavir resulted in rapid onset of insulin resistance but not hyperlipidaemia or changes in body composition, although treatment was only for 4 weeks [50].

Obesity and lipoatrophy may also play a part. In obesity-related insulin resistance, intra-abdominal fat mass correlates positively with insulin resistance [9,26];

Table 2. Possible interventions and outcomes for various features of lipodystrophy. Refs 42, 43, 69–81

Intervention	Lipodystrophy		Metabolic complications				Risk	Preferred current use
	Peripheral fat	Central fat	Trigs	Cholesterol	Insulin resistance	Lactic acidaemia		
Diet	May ↓	May ↓	↓	↓	May ↓	No Δ likely	↑ lipoatrophy	Visceral fat accumulation
Exercise	May ↓	May ↓	↓	↓	May ↓	No Δ likely	↑ lipoatrophy	Visceral fat accumulation
Switch PI to NNRTI/abacavir	No Δ or ↓	↓	↓	↓ LDL , ↑ HDL	No Δ or ↓	No Δ likely	Adverse event, virologic failure	Hyperlipidaemia or visceral fat accumulation
Switch NRTI	↑	No change?	May ↓	No Δ	Unclear	May improve	Adverse event	Research
Metformin	↓	↓	No Δ	No Δ	↓	No Δ	More lipoatrophy	Diabetes or visceral fat accumulation
Thiazolidinediones	May ↓	May ↓	?	↓ <i>HDL</i> , ↑ <i>LDL</i>	<i>Improves</i>	No Δ likely	P450 interaction, hepatitis	Research
Fibrates	No Δ likely	No Δ likely	↓	No Δ	No Δ	No Δ likely	None	Isolated hypertriglyceridaemia*
Statins	No Δ likely	No Δ likely	↓	↓	No data	No Δ likely	Adverse event, P450 interaction	Isolated hypercholesterolaemia*
Testosterone	May ↓	No data	No data	↓ HDL	No data	No Δ likely	Unknown	Male hypogonadism at physiological dose
Anabolic steroids	May ↓	No data	No Δ likely	No Δ likely	No Δ likely	No Δ likely	↑ lipoatrophy	Unknown
Growth hormone	↓	↓	?	↑ HDL	May ↑	No Δ likely	↑ lipoatrophy	Research; limited by cost and other side effects
Plastic surgery	Improved facial appearance	Transient ↓ buffalo hump	No Δ	No Δ	No Δ	No Δ likely	Surgery, recurrence	Unknown; recurrence likely

↑, Increase; ↓, decrease; Δ = change; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Bold, confirmed effect in randomized studies of HIV-uninfected adults; roman, effect in non-randomized studies of HIV-uninfected adults; italic, confirmed effect in HIV-uninfected adults, but no data in HIV-infected adults.

*Only recommended if causative antiretroviral cannot be substituted without compromising control of HIV replication.

while in lipodystrophies not associated with HIV, there is a correlation between loss of subcutaneous adipose tissue and insulin resistance [49]. Levels of leptin, a hormone secreted by adipocytes, are low in congenital and HIV lipoatrophy, and in mouse models of lipodystrophy, and leptin infusions and fat transplantation improve insulin resistance in such mice [1,49,51–53]. Lipoatrophic patients also have increased intramyocellular lipid in direct proportion to their degree of insulin resistance [53].

Protease inhibitors inhibit insulin-mediated glucose uptake via the GLUT-4, but not the GLUT-1, receptor in skeletal muscle, adipocytes and transfected oocytes [34,54–56]. This may be a result of reduced GLUT-4 translocation to the cell surface. Of note, GLUT-4 knockout mice are also lipoatrophic.

Diagnosis

Lipodystrophy is diagnosed subjectively, generally by the presence of lipoatrophy and/or fat accumulation on physical examination and/or patient report (preferably both). No objective parameter obtained by dual-energy X-ray absorptiometry or computerized tomography has been reported to reliably diagnose lipodystrophy, perhaps because of the large natural variability in body fat mass (and also in distribution). In addition, the presence of abdominal obesity, insulin resistance or hyperlipidaemia in isolation are not useful individually for diagnosis, as these are common in the general population.

There is a clear need for objective criteria by which to diagnose lipodystrophy. Such criteria should assist industry, regulators and researchers in the standardization of recruitment to lipodystrophy studies and the reporting of lipodystrophy, in the assessment of drugs, drug combinations, drug classes and of different patient populations, and in the identification of risk factors. Also, such criteria would assist less experienced clinicians in making a diagnosis.

Five working case definitions or classification systems have been proposed [9,10,57–59]. These definitions are limited in that they were generated from studies performed in relatively few sites in selected (mostly male) patients. Furthermore, two studies had no objective body composition data and, importantly, no definition has been validated. One recent study has found that the presence of only one mild lipodystrophy feature identified on patient assessment was not reliable for diagnosis [59]. Although body composition and metabolic parameters differ in subjects with lipodystrophy, no objective physical or metabolic feature has been identified that reliably distinguishes lipodystrophy from healthy HIV-infected subjects. Consensus at the

1st International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV was that the presence of at least one patient-reported physical change confirmed on physical examination may be useful for diagnosis, but it was agreed that this consensus was opinion based rather than evidence based.

Additional factors need to be addressed to develop an objective case definition for HIV lipodystrophy. These include the high variability in normal body composition, the fact that metabolic abnormalities common to lipodystrophy are also common in the general population, and the fact that both NRTI and protease inhibitors are implicated in lipodystrophy. It is also uncertain whether some probable toxicities of antiretroviral therapy (e.g. ingrown toenails, loss of libido, dry skin) are features of lipodystrophy, or represent unrelated, albeit drug-related, events.

Clinical significance

There are several possible sequelae of lipodystrophy. First, adherence to antiretroviral therapy may be compromised because of the cosmetic effects, leading to virological and even clinical failure [60]. Second, lipodystrophy could be stigmatizing in the same way as Kaposi's sarcoma and wasting once were.

The metabolic effects could lead to an increase in cardiovascular disease, and there are now several case reports of premature coronary artery disease in patients with few or no risk factors that were receiving protease inhibitor therapy [61–64]. However, a causal link has not been demonstrated and there are no data estimating prevalence or risk factors of cardiovascular disease in patients receiving highly active antiretroviral therapy. Some cases have developed in patients with very brief protease inhibitor therapy and may represent a prothrombotic effect of therapy rather than an atherosclerotic effect. The increase in risk has been estimated from available metabolic data using the Framingham equations to be 1.4 cardiac events per thousand years of therapy [65], although the risks will probably also depend on the presence and severity of other cardiac risk factors [66]. A global cohort study sponsored by pharmaceutical industry and the European Medicines Evaluation Agency is currently addressing this issue.

One further risk of occasionally severe hypertriglyceridaemia (levels > 20 mmol/l) seen with protease inhibitor therapy may be pancreatitis, but this association remains unproven [67].

Patients with diabetes mellitus or impaired glucose tolerance are at increased risk of microvascular diabetic disease such as retinopathy, neuropathy and nephro-

pathy over the medium to long term. Whether it is appropriate to monitor patients on long-term protease inhibitor therapy for these conditions is not clear at present.

Management

There is no clinically proven therapy for any feature of lipodystrophy (Table 2). Factors that would affect a decision to treat any feature would include presence of symptoms, the status of HIV disease, the likelihood that a particular antiretroviral regimen would be long term, the severity of any feature, and the presence of one or more cardiovascular risk factors. In particular, it should be remembered that the efficacy and safety of metabolic interventions designed to prevent cardiovascular disease cannot be extrapolated at this time from studies of healthy adults. It may be that non-HIV lipodystrophy is a more relevant model, in which lipid-lowering and diabetic therapies tend to be far less effective, probably because of the lipotrophy and central obesity that underlie these disorders.

Increased exercise can reduce central fat accumulation, but at the expense of increased peripheral fat wasting [68]. The role of diet has not been evaluated. Certainly, no diet should interfere with antiretroviral drug absorption or overall patient well-being. Gemfibrozil treatment in a randomized, placebo-controlled study resulted in a modest reduction in triglyceride levels, but without change in cholesterol, and appeared safe [69]. Atorvastatin may be safe and have some efficacy in lowering lipids, although pravastatin may be a better alternative in protease inhibitor recipients as it is not metabolized by cytochrome P450 3A4 [70,71]. Statins such as simvastatin that are metabolized by P450 3A4 should be avoided. Treatment of lipids alone may not affect cardiovascular risk, however, if diabetes is not also addressed (and *vice versa*). Metformin effectively improves insulin sensitivity and reduces visceral adiposity, without appearing to aggravate lactic acidemia but also reduced peripheral fat [72,73].

Some agents may be inappropriate. Anabolic steroids are anabolic for muscle not fat, although increased muscle mass may partially disguise fat loss. Subcutaneous or intralesional growth hormone can reduce intra-abdominal adiposity and the size of buffalo humps, respectively, but if given parenterally may worsen lipotrophy or precipitate diabetes [74–76]. Some statins and glitazones (insulin sensitizers and possible peripheral adipocyte growth factors) are metabolized by cytochrome P450 3A4, and their use with protease inhibitors could therefore increase the risks for myositis and hepatitis, respectively. Studies with rosiglitazone, which is not P450 metabolized, are underway.

Surgery (excision or liposuction) has been performed on some patients with severe fat accumulation, although fat may re-accumulate within months [77]. There is no report of implant surgery for fat wasting, an approach used for some forms of congenital lipodystrophy.

One theoretical treatment option is withdrawal or substitution of protease inhibitors or NRTI. Again, data suggest that protease inhibitor substitution with nevirapine, efavirenz, or abacavir, and stavudine withdrawal or cessation for at least 6 months may improve fat accumulation and/or insulin resistance (protease switching) and lipotrophy (stavudine), respectively [42,43,78–81]. Nevertheless, lipotrophy did not resolve some patients' experienced virological rebound and it is unclear whether metabolic parameters can normalize. Furthermore, given the other issues that lead to virological failure, such as other adverse effects and human behaviour, it would seem probable that most patients will receive all antiretrovirals at some stage.

Conclusion

There has been significant progress in understanding the pathogenesis of HIV lipodystrophy. A case definition should be available shortly. The area of greatest need remains therapy and prevention.

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