HIV-associated lipodystrophy: a review of underlying mechanisms and therapeutic options

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Lipodystrophy (LD) is a common adverse effect of HIV treatment with highly active antiretroviral therapy, which comprises morphological and metabolic changes. The underlying mechanisms for LD are thought to be due to mitochondrial toxicity and insulin resistance, which results from derangements in levels of adipose tissue-derived proteins (adipocytokines) that are actively involved in energy homeostasis. Several management strategies for combating this syndrome are available, but they all have limitations. They include: switching from thymidine analogues to tenofovir or abacavir in lipodystrophy, or switching from protease inhibitors associated with hyperlipidaemia to a protease-sparing option; injection into the face with either biodegradable fillers such as poly-L-lactic acid and hyaluronic acid (a temporary measure requiring re-treatment) or permanent fillers such as bio-alcamid (with the risk of foreign body reaction or granuloma formation); and structured treatment interruption with the risk of loss of virological control and disease progression. There is therefore a need to explore alternative therapeutic options. Some new approaches including adipocytokines, uridine supplementation, glitazones, growth hormone (or growth hormone-releasing hormone analogues), metformin and statins (used alone or in combination) merit further investigation.

Keywords: adipocytokines, antiretroviral therapy, protease inhibitors, nucleoside reverse transcriptase inhibitors

Introduction

The success of controlling HIV infection with antiretroviral drugs (ARVs) and the resultant reduction in morbidity and mortality has been marred somewhat by the development of significant adverse effects in some patients, which include metabolic and morphological changes. Lipodystrophy (LD) is a term used to embrace these changes that comprise peripheral lipodystrophy, localized fat accumulation (visceral, back of neck and lipomata), hyperlipidaemia, insulin resistance and hyperglycaemia.1 The prevalence rate of LD in patients on highly active antiretroviral therapy (HAART) is reported to be up to 40%.1,2 The frequency of LD, not unexpectedly varies with the drugs used. Nucleoside reverse transcriptase inhibitors (NRTIs), particularly thymidine analogues (zidovudine and stavudine), have been associated with morphological changes, particularly extremity fat loss,3 while protease inhibitors (PIs) have been associated with biochemical derangements of glucose and lipids as well as with localized accumulation of fat.4 NRTIs such as stavudine have also been shown to be associated with dyslipidaemia.5 Since the drugs are often used together as part of HAART, clinical data suggest that they act synergistically in causing LD. The body changes of LD are distressing and can be stigmatizing for sufferers. The metabolic effects have been associated with an increased risk of cardiovascular disease.6–9 Mitochondrial toxicity, insulin resistance, adipose gene expression derangements, genetic polymorphisms and cellular dysfunction are thought to be important pathophysiological mechanisms underlying the development of LD.8,10–16

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The mechanisms of HIV LD

Mitochondrial toxicity

Mitochondrial toxicity occurs through inhibition of mitochondrial DNA polymerase-γ leading to hyperlactataemia and organ-based toxicities involving the liver, pancreas, peripheral nerves and skeletal muscle in particular.11 Walker and Brinkman10 have also shown a link between peripheral lipoatrophy and mitochondrial toxicity in that patients with lipoatrophy had more pronounced mitochondrial depletion in biopsies from subcutaneous lipoatrophic tissues. The degree of mitochondrial toxicity depends on the drugs used, with in vitro studies using HepG2 human hepatoma cells showing the worst effects with zidovudine, didanosine and stavudine in reducing order. Tenofovir and lamivudine show minimal or no mitochondrial toxicity. Zidovudine, emtricitabine and abacavir impair cell proliferation and increase lactate and lipid production but show no mitochondrial depletion. Combinations of the drugs show that they act synergistically to cause mitochondrial toxicity, with pyrimidine combinations (such as zalcitabine and stavudine) being the worst offenders.17–20

The level of affinity of the active metabolites of the drugs for mitochondrial DNA (mtDNA) polymerase-γ is thought to underlie these differences.20

Insulin resistance and adipose tissue-derived cytokines

Derangement in the function of adipocytes in adipose tissue is thought to result in insulin resistance. Studies have shown that the insulin resistance associated with obesity and type II diabetes is mediated at the level of the adipocyte and adipose tissue. The adipocyte has been shown to be actively involved in energy homeostasis by secreting hormones or proteins that have collectively been termed adipocytokines (adiponectin, leptin, resistin and visfatin).21–23 Adipocytes also secrete pro-inflammatory cytokines such as tumour necrosis factor-α (TNF-α) and interleukin-6 (IL-6).21,24 These cytokines are known to affect glucose and lipid metabolism and may also alter body habitus.8,21,25 Obese and type II diabetic patients have raised levels of TNF-α, IL-6 and leptin; they also show reduced levels of adiponectin while levels of resistin have been variable.24

Altered levels of adipocytokines and pro-inflammatory markers have also been demonstrated in in vitro (in murine and human adipocyte cell lines) and in vivo studies with the use of NRTIs (particularly zidovudine and stavudine) and PIs in HIV patients.25–29 PIs led to the following changes in these studies:

(i) A reduction in lipid accumulation in adipocytes.
(ii) Increase in adipocyte apoptosis leading to a reduction in cell numbers.
(iii) Induction of insulin resistance by:

(a) Inhibition of insulin-stimulated glucose uptake via inhibition of the glucose transporter (GLUT-4).
(b) Induction of IL-6 and TNF-α.
(c) Reduction in gene expression and secretion of adiponectin.
(d) Increased lipolysis.

The ability of PIs to induce these changes varies between the individual drugs, with lopinavir, ritonavir, saquinavir and nelfinavir being the worst offenders.25,26 The newer PI atazanavir has a much reduced effect.27,28 Indinavir did not have much effect on cell viability or lipogenesis but inhibited glucose uptake to a greater extent than the other PIs.24,25 With regard to NRTIs, Jones et al.25 and Janneh et al.26 showed in murine adipocyte cell lines (3T3-L1 and 3T3-F442A) that zidovudine and stavudine were not cytotoxic, did not affect adipogenesis or induce lipolysis and did not up-regulate the expression of IL-6 and TNF-α. However, Lagathu et al.29 working with the same murine cell lines found that zidovudine and stavudine raised levels of IL-6 and TNF-α. These two thymidine analogues also reduced the levels of adiponectin, which could contribute to insulin resistance.24,25 Pacenti et al.30 also found that zidovudine and lamivudine (3TC), either alone or in combination, did not significantly alter the viability and adipogenesis of 3T3-L1 cells. The differences in findings in these studies may be due to differences in drug concentrations used, origins of cell lines and methodology.

In studies involving HIV patients, lipodystrophic patients show morphological alterations of the adipose tissue with abnormal expression of adipocytokines and pro-inflammatory cytokines, as well as adipocyte transcription factors.29 Patients have elevated circulating levels, and increased tissue mRNA expression, of TNF-α and IL-6.12,31,32 Lipoatrophic fat from patients has also been shown to have reduced adipogenic transcription factors such as sterol regulatory element-binding protein (SREBP-1c), CAAT enhancer-binding protein-α (CEBP-α) and peroxisome proliferator activated receptor-γ (PPAR-γ), which are all involved in adipocyte differentiation.12,15,33 Additionally, lipodystrophic HIV patients also have reduced mRNA expression of adiponectin and leptin, and decreased levels of these proteins.12,29,31 Taken together, all these changes probably account for the increased apoptosis, and decreased differentiation, of adipocytes seen in these patients, which ultimately lead to lipoatrophy and insulin resistance.29 It is interesting to note, however, that similar changes (up-regulation of TNF-α and down-regulation of adiponectin and leptin) have also been found in HIV patients not on treatment, suggesting that HIV itself may have a role in the aetiology of LD.34

Adipose gene expression derangements

Whole genome expression analysis using microarrays have provided interesting insights into the derangements that occur in the genes involved in adipocyte differentiation and lipid metabolism on exposure to antiretrovirals.30 An in vitro study with 3TC-L1 cell showed that PIs (indinavir, saquinavir and lopinavir) induced or up-regulated genes that inhibit adipocyte differentiation, and down-regulated the expression of master adipogenic transcription factors as well as several genes mainly involved in lipid metabolism.22 These are summarized in Table 1. The same study showed that NRTIs (zidovudine, lamivudine, stavudine and zalcitabine) showed a milder effect on these genes though they were found to induce a gene, Aehp-I (adipocyte enhancer-binding protein 1), the overexpression of which could inhibit adipogenesis.22 The PI suppression of adipogenesis and lipogenesis genes has been replicated in vivo in the subcutaneous adipose tissue (SAT) from lipodystrophic HIV-infected patients.12–15
Proteasome dysfunction

Dysfunction of proteasome activity in cells has been implicated in the pathogenesis of HIV LD. Proteasomes are multi-subunit protease complexes engaged in the turnover of short-lived proteins that regulate a variety of cellular processes including signal transduction, stress response, transcription control, chromosomal segregation, DNA repair and cell cycle progression. Proteasome activity coordinates protein handling in the endoplasmic reticulum (ER) by removing misfolded proteins; disruption of this process leads to an ER stress response. An in vitro study by Parker et al. [working with a human hepatoma cell line (HepG2) and 3T3-L1 mouse cells] found that PIs inhibited proteasome chemotryptic, and to a lesser extent tryptic, activity. The ER stress response induced differed between the hepatocytes and the adipocytes as outlined in Table 2.

Adipose tissue pro-inflammatory cytokines and adipocytokines

The effects of the individual pro-inflammatory cytokines and some of the adipocytokines can be summarized as follows:

Tumour necrosis factor-α

TNF-α is a pro-inflammatory cytokine. The level of TNF-α in adipocytes is increased in obesity and type II diabetes. With regard to obesity, overexpression of TNF-α is higher in omental, compared with subcutaneous fat. Visceral fat comprises omental and mesenteric fat and has been linked in epidemiological studies to the development of insulin resistance, dyslipidaemia, type 2 diabetes and cardiovascular disease. TNF-α may be the link between visceral obesity and development of these complications.

TNF-α mediates insulin resistance via reduction of insulin receptor kinase activity. It induces lipolysis and down-regulates insulin receptor substrate (IRS)-1 and the insulin-sensitive glucose transporter (GLUT)-4. It may act in an autocrine manner thereby profoundly altering adipose tissue biology. It also induces apoptosis, which might underlie the lipodystrophy caused by NRTIs. The secretion of TNF-α is, at least partly, under genetic control. The TNF-α gene contains numerous polymorphisms and exhibits a complex haplotype structure. Many of these polymorphisms are thought to be functionally important, including the promoter region polymorphisms at positions −308 and −238, which have been the most widely studied. Maher et al. showed an increased frequency of the −238 G→A transition in LD patients compared with those without LD. The patients were on both PIs and NRTIs. This effect was thought to be attributable to the PIs, although the authors acknowledged that the NRTIs might also have contributed. This study, taken together with the replication of the findings in an Australian cohort, suggests that TNF-α −238 promoter region gene polymorphism, which is functionally active, increases the risk of developing antiretroviral-related LD.

Adiponectin

Adiponectin is a 30 kDa cytokine synthesized and secreted exclusively by adipose tissue. It is a potent insulin sensitizer
acting in adipose tissue, muscle and liver. It has also been shown to have anti-atherogenic, anti-inflammatory, anti-angiogenic and anti-tumour functions. The level of adiponectin is reduced in obesity, particularly in visceral obesity, and in insulin resistant states. It has been shown from epidemiological studies that low levels of adiponectin are an independent predictor for developing type 2 diabetes and myocardial infarction. Adiponectin profoundly influences endogenous insulin sensitivity: it reduces plasma glucose concentration (by reducing liver output of glucose), increases fatty acid oxidation in muscle and inhibits hepatic gluconeogenesis through its activation of 5'-AMP-activated protein kinase (AMPK). Adiponectin knockout mice have impaired insulin sensitivity providing further evidence of its important role in the metabolic diseases that afflict a huge proportion of the global population. Adiponectin acts via the adiponectin receptor 1 (AdipoR1) in skeletal muscle and adiponectin receptor 2 (AdipoR2) in the liver. An additional receptor for hexameric adiponectin is T-cadherin. HIV-associated LD is associated with low plasma adiponectin levels and low expression of adiponectin in adipose tissue, particularly after administration of PIs (via inhibition of adipogenesis), but has also been seen with stavudine and zidovudine. However, it is thought that the low levels seen with NRTIs may be due to a reduction in adipose tissue mass (seen in peripheral lipatrophy) rather than a direct effect of the drugs. Consistent with this, in vitro studies (microarray studies and proteasome pathway) have shown that adiponectin gene expression is down-regulated by PIs rather than by NRTIs. However, it is important to bear in mind that feedback loops operate with regard to cytokine expression and levels with in vitro studies in mouse and human adipocytes, showing that the levels of adiponectin can also be reduced by the pro-inflammatory cytokines TNF-α and IL-6.

Interleukin-6

IL-6 is a pro-inflammatory protein; 30% of systemic IL-6 is derived from adipose tissue and mediates insulin resistance. IL-6 levels are raised in obesity and insulin resistance, and independently predict future development of type 2 diabetes. IL-6 stimulates or induces hepatic gluconeogenesis with resultant hyperglycaemia and compensatory hyperinsulinaemia. It also induces hepatic triglyceride secretion. In murine adipocytes and hepatocytes, IL-6 directly impairs insulin signalling with decreased activation of IRS-1 and phosphatidylinositol 3-kinase. Studies in HIV treatment-induced LD show conflicting results with respect to the levels of this cytokine; with some showing higher levels compared with HIV-negative controls, while others have shown no difference. However, in vitro studies using both murine and human adipocytes have demonstrated that there is increased expression and secretion of this cytokine in response to both PIs (such as lopinavir, nelfinavir and ritonavir) and NRTIs (zidovudine and stavudine).

Resistin

There is conflicting evidence as to whether resistin plays a major role in obesity and insulin resistance. It has been suggested that resistin impairs glucose tolerance by inducing severe hepatic but not peripheral insulin resistance. However, conflicting data from other studies suggest that it may not have a major role in glucose homeostasis. For instance, while some studies have shown high levels of resistin in obesity, others have shown low levels. Data on the effects of ARVs on resistin are scanty. A study in HIV patients showed that single nucleotide mutations in the resistin gene (C→T transition in the second intron of the gene) were associated with the development of adverse metabolic changes on HAART.

Leptin

Leptin is mostly expressed in adipose tissue and is found both in the circulation and cerebrospinal fluid. It acts centrally to increase energy expenditure, inhibit appetite and weight gain by decreasing appetite-enhancing and increasing appetite-inhibiting peptide expression in the arcuate nucleus of the hypothalamus. It also has peripheral effects on skeletal muscle, liver, pancreas, adipose tissue and other cell types where it acts via 5'-AMP-activated protein kinase to decrease anabolic pathways (such as glucose, lipid and protein synthesis) and increase catabolic pathways (glucose and lipid utilization). Its levels are raised in obesity and have also been found to positively correlate with body mass index in HIV patients on HAART, although plasma levels of leptin did not differ between patients on or off treatment. However, in vitro studies have demonstrated that leptin levels increase when human adipocyte stem cells are exposed to the PIs ritonavir, lopinavir and amprenavir.
Visfatin

This is a visceral fat adipocytokine that was previously identified as pre-B cell-colony-enhancing factor.\textsuperscript{22,63} It exerts insulin-mimetic effects in cultured cells and in mice, leading to a lowering of plasma glucose levels, triglyceride accumulation in preadipocytes in both fat depots and accelerated triglyceride synthesis from glucose.\textsuperscript{22} It binds to and activates the insulin receptor, at a site different from where insulin binds.\textsuperscript{22} Visfatin levels are high in obese people,\textsuperscript{63} particularly in those with increased visceral adiposity.\textsuperscript{22} A recent study also found that visfatin levels increased by ~7-fold in HIV-positive patients who were on HAART for 1 year compared with HIV-negative individuals, although other parameters of glucose metabolism and body fat mass were unchanged.\textsuperscript{64}

Plasminogen activator inhibitor type I (PAI-1)

PAI-1 plays a regulatory role in fibrinolysis by limiting the production of plasmin.\textsuperscript{65} It neutralizes the endogenous tissue plasminogen activator (t-PA) that converts plasminogen to active plasmin, and thereby degrades fibrin. PAI-1 therefore reduces the risk of bleeding.\textsuperscript{65} It is produced by activated platelets, vascular endothelial and smooth muscle cells, liver, spleen and adipose tissue.\textsuperscript{65} High levels of PAI-1 are therefore prothrombotic.\textsuperscript{65} Raised levels of PAI-1 have been found in insulin-resistant states and type II diabetes.\textsuperscript{66} Elevated plasma levels of PAI-1 are associated with an increased incidence of coronary events such as unstable angina, myocardial infarction and sudden cardiac death as well as chronic coronary artery disease.\textsuperscript{66–70} It has also been shown to contribute to other thromboembolic disorders such as cerebrovascular accidents,\textsuperscript{66,71} peripheral vascular disease,\textsuperscript{66,72} pulmonary embolism, deep vein thrombosis,\textsuperscript{66,73} and primary or secondary pulmonary hypertension.\textsuperscript{74,75}

A study by He et al.\textsuperscript{76} in 18 HIV patients with LD found significantly higher levels of PAI-1 in those with LD (P < 0.05) when compared with 18 patients without LD, although there was no difference in PAI-1 mRNA expression in adipose tissue between the two groups. They also found that high levels of PAI-1 were associated with insulin resistance in the LD patients.\textsuperscript{76} Levels of PAI-1 were also positively correlated with plasma TNF-\(\alpha\), TNF-\(\alpha\) mRNA and TNF receptors I and II, suggesting that TNF-\(\alpha\) may be involved in the regulation of plasma PAI-1 levels in HIV LD patients.\textsuperscript{76}

Monocyte chemoattractant protein-1 (MCP-1)

MCP-1 is a member of the CC chemokine family and is an important mediator recruiting monocytes and T lymphocytes into different tissues during infection and inflammation.\textsuperscript{77} Inflammation underlies the development of atherosclerosis, and therefore MCP-1 may play an important role in atherosclerosis and ultimately, in cardiovascular events.\textsuperscript{78,79} MCP-1 induces insulin resistance by strongly decreasing insulin-stimulated glucose uptake and down-regulating adipogenic genes such as adipin, GLUT4, \(\beta\)-adrenergic receptors and PPAR-\(\gamma\) in murine adipocytes in vitro.\textsuperscript{54,80} Its expression is up-regulated in genetically obese mice compared with lean controls and its secretion is stimulated by insulin, TNF-\(\alpha\), IL-6 and growth hormone (GH).\textsuperscript{54,80} In human non-diabetic subjects, MCP-1 mRNA positively correlates with body mass index (BMI)\textsuperscript{81,82} and circulating levels correlate with waist-to-hip ratio.\textsuperscript{82} It is up-regulated in patients with type II diabetes.\textsuperscript{82–84}

HIV infection is a chronic inflammatory disease associated with low grade levels of atherosclerosis.\textsuperscript{83} High levels of MCP-1 were found in a study in HIV patients with LD.\textsuperscript{85} These patients also had increased carotid intimal thickness, a marker of atherosclerosis,\textsuperscript{83,85} which correlated with levels of MCP-1.\textsuperscript{83} This adds to the knowledge that HIV LD patients are at increased risk of atherosclerosis.

Vaspin

This is an adipocytokine designated as visceral adipose tissue (VAT)-derived serpin (Vaspin), a member of the serine PI family.\textsuperscript{86} It has been isolated from visceral white adipose tissue of a rat model with obesity and type II diabetes.\textsuperscript{54,86,87} Tissue expression and serum levels of vaspin decrease with worsening diabetes in these rats.\textsuperscript{86} Treatment of rats with insulin or pioglitazone (an insulin-sensitizing agent) normalized the expression and serum levels of the cytokine.\textsuperscript{86} Additionally, administration of vaspin to another obese rat model fed on high-fat high-sucrose diet improved glucose tolerance and insulin sensitivity.\textsuperscript{86} These studies indicate that vaspin exerts an insulin-sensitizing effect on white adipose tissue.\textsuperscript{54,86} In humans, vaspin mRNA was not detected in lean subjects (BMI < 25) and was more frequently detected in patients with type II diabetes.\textsuperscript{87} Visceral vaspin expression correlated with BMI and % body fat, while subcutaneous vaspin expression correlates with insulin sensitivity.\textsuperscript{54,86,87} The level of this cytokine in HIV patients on treatment, with or without LD has not been studied.

Therapeutic options with non-ARVs

Treatment of LD can be difficult and the changes slow to reverse if at all. Patients may not be able to switch regimens, and cosmetic options (such as injection of fillers) may not be successful. It is not within the scope of this review to discuss modifications of antiretroviral treatment to treat HIV LD. This is adequately covered in the European AIDS Clinical Society (EACS) guidelines on the prevention and management of metabolic diseases in.\textsuperscript{88} Future options may include therapy revolving around adipocytokines and other drugs to correct the metabolic derangements and/or the physical changes of LD.

Adipocytokines, adipocyte transcription factors and nuclear receptors

Some of the studies looking at the use of cytokines such as leptin and PPAR-\(\gamma\) agonists in HIV LD are summarized in Table 3. Leptin therapy has been used successfully in cases of congenital and acquired non-HIV-related LD with resultant improvements in glycaemic control, hypertriglyceridaemia and a decrease in fatty infiltration of the liver.\textsuperscript{89,96} In HIV LD, leptin administration improves lipid profiles, insulin resistance and fat accumulation and is well tolerated, but the studies were small.\textsuperscript{91,92,137} Adiponectin as well as its receptors AdipoR1 and AdipoR2 are attractive future targets for drug development.\textsuperscript{54} Studies with TNF-\(\alpha\) antagonists designed to improve insulin sensitivity have not been promising in humans with obesity and
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<th>Research studies</th>
<th>Patient population</th>
<th>Treatments and duration</th>
<th>Results</th>
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<td><strong>Leptin</strong></td>
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<tr>
<td>Riddle <em>et al.</em> 91 <em>(in vitro study)</em></td>
<td>ritonavir-treated mice</td>
<td>leptin administration or polyunsaturated fatty acid (PUFA) diet</td>
<td>leptin use showed:</td>
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<td>– reversal of raised TC</td>
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<td>– ↓ in Rit-induced interscapular fat</td>
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<td>– improved liver steatosis</td>
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<td>Lee <em>et al.</em> 92 <em>(randomized, placebo-controlled, double-blinded, crossover study)</em></td>
<td>7 men with HAART-induced LA, low leptin and hypertriglyceridaemia</td>
<td>recombinant human leptin 0.04 mg/kg daily or placebo for 2 months</td>
<td>leptin improved insulin resistance, HDL, trunkal fat mass</td>
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<td>Mulligan <em>et al.</em> 137 <em>(open-label, proof-of-principle study)</em></td>
<td>8 men with HIV-induced LA, low leptin, insulin resistance</td>
<td>recombinant methionyl human leptin for 6 months (0.01 mg/kg twice daily for 3 months, followed by 0.03 mg/kg twice daily for 3 months)</td>
<td>– 30% ↓ in visceral fat (P = 0.001)</td>
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<td>– ↓ in TC, LDL-C, non-HDL-C, TGs</td>
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<td>– improved hepatic insulin sensitivity</td>
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<td>– ↓ in lipolysis</td>
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<td><strong>Thiazolidinediones</strong></td>
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<tr>
<td>Carr <em>et al.</em> 95 <em>(randomized, double-blind, placebo-controlled study)</em></td>
<td>108 patients with HIV LA</td>
<td>rosiglitazone 4 mg bd po or placebo for 48 weeks</td>
<td>rosiglitazone:</td>
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<td>– improved insulin sensitivity</td>
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<td>– no improvement of LA</td>
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<td>– ↑ in TC, TGs</td>
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<tr>
<td>Slama <em>et al.</em> 99 <em>(randomized, double-blind, placebo-controlled study)</em></td>
<td>130 HIV patients with LA</td>
<td>pioglitazone 30 mg od or placebo for 48 weeks</td>
<td>pioglitazone group:</td>
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<td>– ↑ in limb fat (patients not on d4T)</td>
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<td>– ↑ in HDL-C</td>
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<td>– no change in other lipid fractions</td>
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<td>Calmy <em>et al.</em> 98 <em>(open-label, prospective study)</em></td>
<td>11 HIV patients (all on d4T)</td>
<td>pioglitazone 30 mg od × 3 months, then 45 mg od × 3 months</td>
<td>– ↑ in body fat mass (total and leg)</td>
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<td>– no change to lipids</td>
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<td>Gavrila <em>et al.</em> 100 <em>(2 × 2 factorial, randomized, double-blinded, placebo-controlled study)</em></td>
<td>14 HIV patients with HAART-induced metabolic side effects</td>
<td>pioglitazone 30–45 mg od po versus finofibrate 200 mg od for 12 months</td>
<td>pioglitazone (but not finofibrate):</td>
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<td>improved insulin resistance, blood pressure and lipid profile</td>
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↑, increase; ↓, decrease/reduction; HAART, highly active antiretroviral therapy; Rit, ritonavir; bd, twice daily; od, once daily; TC, total cholesterol; TGs, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; d4T, stavudine; po, orally.
type II diabetes.93 Use of TNF-α antagonists such as infliximab in Crohn’s disease and rheumatoid arthritis does not improve insulin sensitivity.54 However, use of TNF-α antagonists has not been studied in HIV-treatment-associated LD since there is a risk of activation of opportunistic infections such as tuberculosis.

Thiazolidinediones or glitazones (such as rosiglitazone and pioglitazone) are ligands for the transcription factor PPAR-γ and are used in type II diabetes to improve insulin sensitivity.94 Use of rosiglitazone in HIV LD appears not to be a viable option with its inability to improve peripheral lipatrophy as well as its adverse effects on lipids,95 particularly in light of recent data on increased risk of cardiovascular events in type 2 diabetes patients with use of rosiglitazone.96,97 Pioglitazone may have a place in the treatment of HIV LD in that it may increase limb fat though its effects on lipids is conflicting, with some studies showing no change and others showing improvement.98–100

Non-ARV drugs

Various drugs have been studied in the treatment of HIV LD. These include, among others, GH and GH secretagogues, metformin, statins and uridine supplementation. Table 4 summarizes the results of studies looking at the use of these drugs in HIV LD patients.

**GH and GH-releasing hormone (GHRH) analogues.** GH deficiency in HIV-negative patients is associated with increased cardiovascular mortality.101 Effects of recombinant GH (rGH) therapy have been studied in patients with adult GH deficiency, obesity and HIV wasting. In these patients, GH replacement increases lean body mass; reduces fat mass with reductions in abdominal subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT); and increases energy expenditure, exercise performance and cardiac function.102–105 There may be a tendency for lipids to decrease.102 GH therapy has, however, been thought to increase the risk of cancers, though extensive studies of the outcome of GH replacement in childhood cancer survivors showed no evidence of an excess of de novo cancers.106

In HIV LD, patients have markedly reduced GH levels in association with excess visceral adiposity.107,108 Impaired GH secretory patterns in these patients are influenced by gender, race and fat redistribution (increased waist–hip ratio).109 GH therapy in HIV LD increases lean body mass; decreases trunk or visceral fat and limb fat; and improves facial lipatrophy with little or no effects on lipid profiles. The most common adverse effects of GH therapy are fluid retention, arthralgia, muscle pains, carpal tunnel syndrome and a decrease in insulin sensitivity. These effects return to baseline levels after treatment with GH stopped.110–112 The long-term effects of GH therapy on visceral fat, limb fat, insulin sensitivity, lipid profiles and the risk of carcinogenesis are not known. The possible worsening of insulin resistance may expose patients to an increased risk of cardiovascular disease, and the risk of further limb fat loss may be intolerable to patients.

Other studies have looked at use of GH secretagogues such as GHRH analogues to induce a more physiological release of GH to avoid the side effects associated with treatment with GH.113,114 Compared with placebo, GHRH analogues (Geref or GHRH 1–29 and Tesamorelin or TH9507) significantly increase levels of IGF-1, increase lean body mass, decrease visceral and trunk fat and improve the ratio of visceral to lower extremity fat. There are no significant changes in levels of glucose and insulin. Adverse effects associated with GH excess are not seen.113–115 The effects on lipids vary, with some studies finding no significant changes113 and others115 finding significant reductions in triglyceride and cholesterol to HDL ratio. Use of GHRH analogues appears to require long-term treatment for continued benefit, as patients who stop treatment regain their VAT.115

Both GH and GHRH analogues have to be given by injection, which might not be acceptable to some patients and, additionally, the cost of both drugs is prohibitive.

**Metformin therapy.** Metformin is a biguanide oral anti-diabetic agent, which is widely used in type 2 diabetes, particularly in patients with obesity. It acts by reducing endogenous glucose production by the liver and by sensitizing the liver and peripheral tissues to insulin by acting partly through the activation of AMPK.116–118 Metformin has been shown to reduce cardiovascular risk in patients with type 2 diabetes through its reduction of lipids and markers of lipid peroxidation and platelet activation (isoprostanes and thromboxanes), and increases tissue antioxidants (vitamins A and E), which leads to a reduction in atherosclerosis.119,120 Metformin therefore represents an interesting therapeutic option in HIV LD, in which fat redistribution and insulin resistance are prominent features.121 Indeed, studies do show that metformin may have a place in the management of HIV LD with reductions in VAT, total adipose fat and waist-to-hip ratio.122,123 However, some studies show no change in waist-to-hip ratio and, rather worryingly, further loss in limb fat.124,138,139

**Statins.** Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are used in the treatment of hyperlipidaemia and established cardiovascular disease in the general population. They have anti-inflammatory, anti-thrombotic and endothelial effects that contribute to their overall beneficial effects on reducing mortality from cardiovascular disease in both healthy people and diabetics.125–128 The effects of statins on insulin resistance are contradictory with some studies showing beneficial, neutral or worsening effects.129,130 The use of statins to treat the hyperlipidaemia associated with HAART has been extensively studied, showing efficacy in lowering total and LDL cholesterol and triglycerides.131,132 However, few studies exist that have looked at whether statins have beneficial effects on the physical aspects of HIV LD. A study by Mallon et al.133 showed that apart from lowering lipids, pravastatin also increased subcutaneous fat and limb fat in patients when compared with placebo. There was no significant effect on visceral fat, trunk fat and body mass index.

**Uridine.** In vitro studies show that the pyrimidine precursor uridine reverses the mitochondrial toxicity induced by pyrimidines such as zalcitabine and stavudine with restoration of cell proliferation. Uridine also reverses the cell depletion and lactic acidosis seen with zidovudine and lamivudine combination. It, however, does not reverse similar effects caused by didanosine (a purine analogue).17 Use of uridine in HIV patients shows that it may be of benefit, with the improvement of lipatrophy, and being well tolerated.134,135
<table>
<thead>
<tr>
<th>Research studies</th>
<th>Patient population</th>
<th>Treatments and duration</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recombinant GH</strong></td>
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</table>
| Luzi *et al.* | 30 HIV patients with fat redistribution and metabolic derangement | rGH 0.2 IU/kg per week SC versus placebo ×6 months | rGH group:  
- ↓ in truncal fat ($P = 0.048$)  
- ↓ in limb fat ($P = 0.0248$)  
- ↓ in TC, TGs (non-significant) |
| Lo *et al.* | 8 men with HIV-associated fat accumulation | GH 3 mg/day SC × 6 months | – ↓ in total body fat ($P = 0.05$); primarily in the trunk region  
- ↑ in lean body mass ($P = 0.03$) |
| Honda *et al.* | 25 HIV-1 patients with moderate to severe facial lipoatrophy | rGH 5 mg alternate days SC × 6 months; further 1 month follow-up | – ↑ soft tissue thickness at the level of zygomatics sustained at month 12 ($P = 0.021$) |
| **GHRH analogues** |                    |                         |         |
| Falutz *et al.* | 412 patients with HIV with abdominal fat accumulation | Tesamorelin 2 mg od SC (or placebo) ×26 weeks | Tesamorelin group:  
- ↓ VAT by 15.2% in the Tesamorelin group (versus ↑ by 5.0% in the placebo group)  
- ↓ TC, TGs, TC:HDL-C ratio  
- ↑ HDL-C |
| Koutkia *et al.* | 31 HIV-infected men with lipodystrophy | Geref or GHRH 1–29 1 mg bd SC or placebo ×12 weeks | Geref group:  
- ↑ lean body mass with GHRH ($P = 0.04$)  
- trunk fat ($P = 0.03$)  
- improved ratio of trunk:lower extremity fat ($P = 0.005$)  
- levels of glucose, insulin and lipids unchanged |
| **Metformin** |                    |                         |         |
| Hadigan *et al.* | 26 HIV, non-diabetic patients with fat redistribution and abnormal OGTT, hyperinsulinaemia, or both | metformin 500 mg bd po placebo ×3 months | Metformin group:  
**pilot phase**  
- ↓ insulin resistance (↓ insulin area under curve by 20%) ($P = 0.01$)  
- ↓ weight ($P = 0.005$)  
- ↓ diastolic blood pressure ($P = 0.009$)  
- VAT:SAT ratio unchanged  
**continuation phase**  
- sustained ↓ in insulin levels, weight circumference  
- ↓ t-PA and PAI-1 |

*Continued*
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<th>Patient population</th>
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</tr>
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<tbody>
<tr>
<td>Saint-Marc and Touraine\textsuperscript{123} (randomized, controlled study)</td>
<td>29 HIV patients with central adiposity and hyperinsulinaemia on PI-based HAART</td>
<td>metformin 850 mg TDS po or no treatment (control group) $\times$ 2 months</td>
<td>metformin group: $\downarrow$ basal plasma glucose, insulin, C-peptide $\downarrow$ triglycerides by 30.1% $\downarrow$ VAT, total adipose tissue and waist-to-hip ratio (increase of these in control group)</td>
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<tr>
<td>Mulligan \textit{et al.}\textsuperscript{139} (randomized, controlled study)</td>
<td>105 HIV patients with $\uparrow$ waist-to-hip ratio and hyperinsulinaemia</td>
<td>metformin (500–1000 mg bd) or rosiglitazone (4 mg od) or combined versus placebo</td>
<td>$\downarrow$ no significant changes in VAT, SAT or total extremity fat among the groups ($\uparrow$ in lower extremity fat with rosiglitazone)</td>
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<tr>
<td>Kohli \textit{et al.}\textsuperscript{138} (randomized, double-blinded, placebo-controlled study)</td>
<td>48 HIV patients with lipodystrophy ($\uparrow$ abdominal girth and waist-hip ratio) and normal glucose tolerance</td>
<td>metformin 1500 mg daily or placebo $\times$ 24 weeks</td>
<td>metformin group: $\downarrow$ appendicular fat mass compared with placebo ($P = 0.03$) $\downarrow$ no change in VAT and lipids</td>
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<tr>
<td>Martinez \textit{et al.}\textsuperscript{124} (randomized, blinded, placebo-controlled study)</td>
<td>108 HIV patients on PI-based HAART with abdominal obesity and $\uparrow$ TGs</td>
<td>metformin 850 mg, gemfibrozil 600 mg or placebo bd $\times$ 1 year</td>
<td>in both groups: $\downarrow$ loss of total and regional fat in all three groups (less with gemfibrozil) $\downarrow$ no significant change in waist-to-hip ratio</td>
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<tr>
<td>\textbf{Statins}</td>
<td>\textbf{Mallon \textit{et al.}\textsuperscript{133} (randomized, placebo-controlled study)}</td>
<td>33 HIV-positive men $\uparrow$ TC ($&gt;6.5 \text{ mmol/ L}$) on PI-based HAART</td>
<td>pravastatin (40 mg each night) or placebo $\times$ 12 weeks</td>
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<tr>
<td>\textbf{Uridine}</td>
<td>\textit{McComsey \textit{et al.}\textsuperscript{135} [pilot study (safety and effectiveness)]}</td>
<td>16 patients with lipoatrophy on stavudine-containing ART</td>
<td>Nucleomax\textsuperscript{a} 36 g TDS every other day $\times$ 16 weeks</td>
</tr>
<tr>
<td>\textit{Sutinen \textit{et al.}\textsuperscript{134} (randomized, double-blinded, placebo-controlled study)}</td>
<td>20 patients with HAART-associated LA</td>
<td>dietary uridine supplement (36 g TDS for 10 consecutive days/month) or placebo, $\times$ 3 months</td>
<td>uridine group: $\uparrow$ total limb fat ($P &lt; 0.001$) $\uparrow$ intra-abdominal fat ($P &lt; 0.05$) $\uparrow$ total body fat ($P &lt; 0.001$)</td>
</tr>
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</table>

\textsuperscript{a}Nucleomax\textsuperscript{a} (dietary supplement containing uridine).

$\uparrow$, increase; $\downarrow$, decrease/reduction; HAART, highly active antiretroviral therapy; TDS, three times daily; bd, twice daily; od, once daily; TC, total cholesterol; TGs, triglycerides; HDL-C, high-density lipoprotein cholesterol; OGGT, oral glucose tolerance test; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; mtDNA, mitochondrial DNA; PBMC, peripheral blood mononuclear cells; t-PA, tissue plasminogen activator; PAI-1, plasminogen activator inhibitor type 1; SC, subcutaneously; po, orally.
Conclusions

HIV/HAART-induced LD is a difficult condition to manage. There are well-established treatment modalities, but all have limitations. Therefore, it is important to look into new ways of treating this condition. The role of adipocytokines in the pathogenesis of LD is now well understood, and research into the use of adipocytokines such as leptin shows promising results, but more research needs to be performed to look at other cytokines such as adiponectin and visfatin. Drugs such as metformin, glitazones, statins, GH and its secretagogues as well as uridine do provide some benefit in HIV LD, though their use has some undesirable effects. Metformin could be associated with further limb fat loss, which is unacceptable. The same applies to GH use, which shows that it may improve lean body mass and visceral adiposity, but with the possibility of further limb fat loss. GHRH analogues offer benefits without the typical side effects associated with GH. Both GH and GHRH analogues are costly and need to be given parenterally, which may not be tolerable. Regarding PPAR-γ agonists, serious issues of increased cardiovascular events with rosiglitazone preclude the use of this drug, though pioglitazone may be of some benefit. Uridine treatment is beneficial in lipatrophy and might be of use to prevent lactic acidosis, which is a serious and life-threatening side effect of NRTIs.

On the whole, larger research studies need to be carried out to look into appropriate patient selection, optimal doses, long-term effects and effects of combinations of the drugs discussed to see if meaningful benefits can be achieved in patients with HIV LD.

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Transparency declarations

None to declare.

References


