Therapeutic approaches to combating lipoatrophy: do they work?

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Therapeutic strategies for combating HIV-associated lipodystrophy, and lipoatrophy in particular, have been a major focus of HIV clinical research. The initial impetus focused on protease inhibitor withdrawal strategies, which resulted in improved lipid profiles and insulin resistance but no change in subcutaneous or visceral adipose tissue. Nucleoside reverse transcriptase inhibitor withdrawal strategies, specifically withdrawal of thymidine analogues, have achieved greater success in the reversal of lipoatrophy. In particular, the MITOX extension study demonstrated a 35% improvement in limb fat over a 2 year period after a switch from a thymidine analogue to abacavir. However, recovery from lipoatrophy is a slow process, and limited access to and potential toxicities introduced by alternative therapies can limit switch strategies. The use of thiazolidinediones as agents to reverse lipoatrophy has, unfortunately, been shown to be ineffective, as have alternative therapeutic approaches with agents such as metformin, lipid-lowering agents and growth hormones. Although prevention of lipodystrophy may be the only definitive approach to combat this syndrome, the role of intermittent highly active antiretroviral therapy as a means of reducing the incidence, or slowing the development, of lipodystrophy is currently under evaluation.

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Lipodystrophy

For the past 6 years, clinical research has focused on trying to understand, control, reverse and/or prevent lipodystrophy. The prevalence of HIV-associated lipodystrophy is as high as 50% in cross-sectional cohorts of HIV-infected adults treated with highly active antiretroviral therapy (HAART). The clinical implications of lipodystrophy are numerous. Features of lipodystrophy such as increased visceral abdominal fat and hyperlipidaemia are associated with an increased risk of cardiovascular disease, whereas subcutaneous adipose tissue loss, especially around the face, can be stigmatizing for some and lead to reduced adherence to treatment. Lipodystrophy is a heterogeneous condition of multifactorial aetiology, involving protease inhibitor (PI)-induced alterations in lipid metabolism and nucleoside analogue-induced mitochondrial toxicity. To date, no effective therapy for lipodystrophy has been identified. In particular, reversal of subcutaneous fat loss (lipoatrophy) has proven particularly difficult. Although several therapeutic strategies have been investigated, it is unclear whether there is an irreversible component to lipodystrophy in general, and lipoatrophy in particular.

Protease inhibitors

In patients who receive a PI-containing antiretroviral regimen, the prevalence of hyperlipidaemia has been shown to range from 28 to 80%. PIs may contribute to hyperlipidaemia by inhibiting the proteosomal breakdown of sterol regulatory element binding protein-1 (SREBP1) in the liver, or by reducing peroxisome-proliferator-activated receptor γ (PPAR-γ) activity in peripheral fat, resulting in dysfunction and diminished proliferation of peripheral adipocytes eventually leading to lipodystrophy. Loss of this subcutaneous adipose tissue depot removes an important buffer to dietary fats, which may contribute to or exacerbate hypercholesterolaemia. Although PI withdrawal can result in improvements in hypercholesterolaemia and insulin resistance, this strategy has little effect on subcutaneous or visceral adipose tissue depots, neither of which have been shown to return to normal.

Nucleoside reverse transcriptase inhibitors

With several studies demonstrating that stopping or switching PIs had little or no effect on body composition, research has concentrated on the role of nucleoside reverse transcriptase inhibitors (NRTIs), especially the thymidine NRTIs (tNRTIs) zidovudine and stavudine, in the pathogenesis of lipoatrophy. In a small cross-sectional study, patients on stavudine experienced greater subcutaneous fat loss and visceral fat gain than antiretroviral-naïve or stavudine-treated HIV-infected patients. This finding was confirmed in a larger cohort where use of stavudine increased the risk of fat wasting by 265% per year compared
with zidovudine. In a prospective study of antiretroviral-naive patients starting HAART, subjects lost a median 13.6% limb fat per year of therapy, with use of stavudine being the only independent factor associated with rate of limb fat loss.

In vitro, NRTIs inhibit mitochondrial DNA polymerase-α, an important enzyme involved in replication of mitochondrial DNA (mtDNA), leading to mtDNA depletion. As mitochondria are abundant in subcutaneous adipose tissue, it has been proposed that this mechanism leads to depletion of mtDNA in subcutaneous fat, resulting in cellular dysfunction and increased apoptosis. Several studies have demonstrated reduced mtDNA in subcutaneous adipose tissue of subjects treated with tNRTIs, particularly stavudine. In one study, in addition to mtDNA depletion, subjects treated with stavudine also showed significantly lower expression of PPAR-γ compared with controls.

Where reversibility in body fat has been described, the most compelling data comes from tNRTI withdrawal studies, particularly the MITOX study. The MITOX study was a large, prospective, randomized controlled trial, examining the strategy of switching from a tNRTI to abacavir, with the primary endpoint being change in limb fat. Participants were randomized to switch from zidovudine or stavudine to abacavir or continue their current thymidine-containing HAART regimen. At the end of the initial 24 week phase, limb fat improved by 11% (or 0.4 kg) in the switch group; a benefit which, although statistically significant \((P = 0.02)\), was not noticeable clinically. For the extension phase (2 years) participants initially randomized to continue their tNRTI were allowed to switch to abacavir, giving rise to three groups; those who commenced abacavir at baseline, those that switched at week 24 and those that remained on stavudine or zidovudine. At 104 weeks, those who switched at baseline experienced a 35% increase in limb fat (or 1.3 kg; \(P = 0.001)\), an effect that was clinically noticeable. Those switching at week 24 increased limb fat by 15% (0.6 kg; not clinically noticeable). In contrast, those remaining on stavudine or zidovudine only gained 0.2 kg of limb fat over the 2 year period. Multivariate analysis indicated that improvement in limb fat was significantly associated with reduced usage of stavudine on-study. These and other switch studies demonstrate the central role of thymidine analogues in the pathogenesis of lipoatrophy. However, the potential benefits of switching need to be weighed against the potential to introduce new toxicities from alternative antiretrovirals, together with the increased risk of virological failure. For example, in the MITOX study, 10% of those who initially switched to abacavir experienced a hypersensitivity reaction.

In addition to switch strategies, studies have investigated initial antiretroviral regimens that avoid the use of tNRTIs. In one substudy of 96 subjects randomized to an NRTI backbone of stavudine/didanosine \((n = 46)\) or the tNRTI-sparing backbone of abacavir/lamivudine \((n = 50)\), those on the tNRTI-sparing regimen experienced slower rates of change in body composition as measured using anthropometry. In a larger, randomized study of stavudine/lamivudine versus the tNRTI-sparing regimen of tenofovir/lamivudine in 262 antiretroviral-naive subjects, subjects randomized to the tNRTI-sparing arm had 2.9 and 4.1 kg more limb fat after 96 and 144 weeks of therapy, respectively (both \(P < 0.01)\). Such strategies may delay the onset of lipoatrophy in populations of antiretroviral-naive subjects, but may be difficult to implement outside developed countries owing to limitations of cost and availability of drugs.

### Thiazolidinediones

The thiazolidinedione (TDZ) class of drugs act as PPAR-γ ligands and are used for the treatment of diabetes. It was hoped that use of TDZs like rosiglitazone would help reverse lipodystrophy, as use of this drug in diabetes and non-HIV lipodystrophy has been associated with an increase in peripheral fat, decreased visceral fat and improved glycaemic parameters. Although a small study reported a benefit of rosiglitazone on limb fat, a larger, randomized, placebo-controlled 48 week study failed to show any significant differences in limb fat in subjects with HIV lipodystrophy treated with rosiglitazone compared with placebo, possibly owing to the persistent effects of continued HAART, particularly tNRTIs. This underscores the multifactorial aetiology of lipoatrophy and highlights the difficulties faced in the search for a single effective therapeutic agent.

### Surgical correction of facial lipoatrophy

Both autologous fat transplantation and implantation of synthetic bulking agents have been used for the cosmetic correction of facial lipodystrophy. In a small study of 15 subjects with facial lipodystrophy, the Coleman technique of harvesting abdominal fat and injecting it into the face resulted in increases in facial fat thickness lasting for up to 24 weeks, with a majority of patients (13/15) being happy with the result. This technique is not without its complications. In several cases where fat was harvested from HIV-infected patients with buffalo hump, the transplanted fat hypertrophied in the cheeks, causing a disfiguring ‘hamster’ appearance requiring significant corrective surgical intervention in some cases. Of the synthetic agents, intradermal injections of polyylactic acid (New-Fill) have been shown to result in a durable increase in total cutaneous thickness (TCT) persisting to 48 weeks, with 61% of the 50 subjects studied having TCT > 10 mm at week 48, with associated improvements in quality of life. Although this approach offers patients benefits from both cosmetic and psychological aspects, problems with respect to cost and access limit its widespread use.

### Alternative therapeutic approaches

Other areas of HIV-associated lipodystrophy research have included the use of metformin, lipid-lowering agents, growth hormones and, more recently, intermittent HAART. Metformin has been shown to reduce intra-abdominal fat accumulation and insulin resistance, but worsen peripheral lipodystrophy. Neither gemfibrozil (used in the treatment of hypertriglyceridaemia) nor pravastatin (a lipid-lowering agent) improve lipoatrophy, and have only modest effects on triglycerides and cholesterol. Although use of growth hormone can be effective in reducing central abdominal fat in this population, its use has been associated with side effects such as increased insulin resistance, consistent with excess insulin-like growth factor 1, and worsening lipodystrophy. In contrast, in a 12 week, 31 subject study, growth hormone-releasing hormone was shown to improve lipoatrophy and reduce visceral fat without unwanted glycaemic effects; however, larger studies need to be conducted to confirm this finding. We have yet to see the findings from studies on intermittent HAART therapy.
Conclusions

Reversal of lipoatrophy appears to be a slow and most likely an incomplete process, so that avoidance of lipoatrophy would be more prudent than attempting to reverse the pathological process once it is established. Research into the long-term effects of HAART regimens thought to be lipotoxic are required to determine whether avoidance of lipoatrophy is a realistic option. Utilizing different HAART regimens that avoid those drugs implicated in causing lipodystrophy is an attractive option, although this strategy may be limited by development of resistance to various drug classes and the availability of a broad spectrum of antiretroviral medications in resource-limited settings.

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