The lipodystrophy syndrome

Lipodystrophy is a common adverse effect of HAART, which comprises morphological and metabolic changes.

The underlying mechanisms for lipodystrophy are thought to be due to mitochondrial toxicity and insulin resistance.

Several management strategies for combating this syndrome are available, but they all have limitations.

There is therefore a need to explore alternative therapeutic options.

Some new approaches including glitazones, growth, metformin and statins (used alone or in combination) merit further investigation.

We hereby present a summary of a good review published on *Expert Opin Pharmacother* 2008,9(1):39-52, by Behrens GM.

1. The syndrome

HIV-associated lipodystrophy includes both clinical as well as metabolic alterations.

The most prominent clinical sign is a loss of subcutaneous fat (lipoatrophy) in the face (periorbital, temporal), limbs and buttocks.

Peripheral fat loss can be accompanied by an accumulation of visceral fat.

Truncal fat increases initially after therapy and then remains stable resulting in relative central adiposity. Fat accumulation may also be found as dorsocervical fat pads (‘buffalo hump’) within muscles and the liver.

There is now accumulating evidence that the major clinical components - lipoatrophy, central adiposity and the combination of both - result from different pathogenetic developmental processes.

Complex metabolic alterations can be associated with HIV therapy: these include peripheral and hepatic insulin resistance, impaired glucose tolerance, Type 2 diabetes, hypertriglyceridemia, hypercholesterinemia, increased free fatty acids and decreased high-density lipoprotein (HDL).
2. Lipoatrophy

Studies on AZT and d4T cessation

Uridine, glitazones, and Sculptra

**Uridine** is a biologic compound essential for the synthesis of DNA and RNA. As thymidine analogs have been proposed to deplete mitochondrial DNA and to reduce the endogenous pool of pyrimidines leading to loss of adipose tissue; substitution with uridine could potentially restore these side effects. In a small, randomized, placebo-controlled, double-blind trial, the impact of uridine to improve lipoatrophy was evaluated over 3 months. Unfortunately, intra-abdominal fat increased to some extend and there were no significant changes in subjective assessment of lipoatrophy.

**Glitazones**

Thiazolidinediones are novel insulin-sensitizing antidiabetic agents for the treatment of Type 2 diabetes. Given that rosiglitazone has been shown to increase subcutaneous fat and to improve insulin sensitivity in diabetic patients, it was expected that rosiglitazone could lead to desirable effects in HIV patients with lipodatrophy but a recently published meta-analysis of 42 trials about the
use of rosiglitazone in diabetic patients showed that, as compared with placebo or with other antidiabetic drugs, treatment with rosiglitazone was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that was of borderline significance. Although these data were based on relatively small number of events and limited access to trial results, these worrisome findings will most likely have a negative impact on further usage of glitazones in HIV patients with either lipodystrophy or Type 2 diabetes.

Many products used in plastic surgery for esthetic purposes have been used for the reconstruction of facial fat loss, between these Sculptra™, poly-L-lactic acid, is an effective compound for resolving facial lipoatrophy in HAART-treated patients, with lasting effects of up to 6 - 24 months. Sculptra is presently the only FDA-approved substance for correction of facial lipoatrophy, but its use has been limited by its expense.

3. Lipohypertrophy

Metformin and Serostim

Metformin has been shown in several studies to be associated with some reduction in visceral adipose tissue, independent of insulin resistance. In addition, metformin promotes general weight loss and patients may lose both lean body mass as well as subcutaneous fat.

Recombinant human growth hormone (e.g., Serostim™) is structurally identical to human pituary growth hormone. At supraphysiologic doses, somatropin has lipolytic activity that reduces visceral fat, as well as anabolic and anticitabolic properties. In some studies compared with the placebo group, growth-hormone therapy led to a significantly greater reduction from baseline in visceral adipose tissue. The most frequently observed side effects included peripheral edema (46 versus 5%), arthralgia (39 versus 17%), pain in the extremity (19 versus 4%) and headache (16 versus 4%).
Lifestyle changes

Participation in regular moderate- to high intensity exercise may prove to be an effective first-line treatment strategy for HIV metabolic abnormalities. Clinical and epidemiologic research suggests that increased physical activity is associated with improved lipid levels, glucose tolerance and insulin sensitivity, along with decreased adiposity.

Dietary interventions are commonly accepted as the first therapeutic option for hyperlipidemia, especially hypertriglyceridemia.

Whenever possible, dietary restriction of the total fat intake to 25 - 35% of the total caloric intake should be a part of the treatment in conjunction with lipid-lowering drugs.

Patients with excessive hypertriglyceridemia (> 1000 mg/dl) may benefit from a very low-fat diet and alcohol abstinence to reduce the risk of pancreatitis, especially if there is a positive family history or concurrent medications that may harbor a risk of developing pancreatitis.

Regular exercise may have beneficial effects, not only on triglycerides and insulin resistance, but probably also on fat redistribution (reduction in truncal fat and intramyocellular fat) and should be considered in all HIV infected patients.

Have a look at this randomized study reported on the right.
Therapy switch

The lipodystrophy syndrome

Therapy switch

Given the extensive indications that PIs are the culprits substantially contributing to the metabolic side effects, numerous attempts have tried to substitute the PI component of a regimen with nevirapine, efavirenz or abacavir. Indeed, many of these ‘switch studies’ have demonstrated substantial improvement, although not normalization, of serum lipids (total and LDL cholesterol, triglycerides) and/or insulin resistance in many patients.

Similarly, substitution of PI with ritonavir-boosted atazanavir has led to improved lipid profiles, especially total triglyceride in patients with previous hyperlipidemia.

Switching from stavudine to tenofovir has resulted in improvement in lipid profiles.
Statins and fibrates

Statins
Based on limited pharmacokinetic and clinical studies, atorvastatin (Sortis™), fluvastatin and pravastatin, carefully administered at increasing doses, are the preferred agents for a carefully monitored therapy in HIV-infected patients on HAART. Lovastatin and simvastatin should be avoided due to their potential interaction with PIs. Although the effect of lipid-lowering therapy appears to be more effective than replacement of PIs, the clinical benefit of lipid-lowering or insulinsensitizing therapy in HIV patients with lipodystrophy remains to be demonstrated.

Fibrates
Fibric-acid analogs such as gemfibrozil or fenofibrate are particularly effective in reducing the triglyceride levels by 50% and should be considered in patients with severe hypertriglyceridemia (> 1000 mg/dl).

Despite their potentially synergistic effect, coadministration of fibric-acid analogs and statins in patients on HAART should only be used carefully in selected patients, as both can cause rhabdomyolysis.
3. Conclusions

The lipodystrophy syndrome is a clinically relevant side effect of antiretroviral therapy with a complex pathophysiologic background and limited treatment options.

Where changes of antiretroviral therapy are a virologically and immunologically safe option these may be first considered for improving lipoatrophy and lipid disturbances.

Cosmetic interventions for facial lipoatrophy are effective, but costly.

Avoiding thymidine analogs has been proven best in preventing lipoatrophy.

Patients with accumulating cardiovascular risk factors may benefit from changes in modifiable risk factors and lipid-lowering therapy.

In particular, HIV patients with frank diabetes or coronary heart disease need intensified care to optimize glucose homeostasis, blood lipids and blood pressure.
Reference