

# HIV & Metabolism:

## What Are the Complications?



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Altered fat distribution (lipodystrophy), dyslipidemia and insulin-resistance are common in adults infected with the human immunodeficiency virus (HIV) who are receiving highly active antiretroviral therapy. This heterogeneous metabolic syndrome has been associated with an increased risk of coronary heart disease (CHD).

### Discussing lipodystrophy in HIV-infected adults...

The fat redistribution appears in one of three prevalent forms:

- generalized or localized lipodystrophy involving buttocks and the extremities,
- central lipohypertrophy with increased visceral fat deposition in the abdominal region (buffalo hump),

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...associated lipodystrophy. The prevalence of lipodystrophy is 100% sensitivity and 80% specificity. Variables included in this

- gender,
- duration of HIV infection,
- clinical stage of HIV,
- anion gap,
- high-density lipoprotein (HDL) cholesterol, as well as various anthropometric measurements, such as the ratio of waist to hip circumference, the ratio of trunk to limb fat, leg fat percentage (assessed with whole-body dual energy X-ray absorptiometry) and
- intra-abdominal to extra-abdominal fat ratio (assessed with abdominal computed tomography scan at L4).<sup>1</sup>

Most HIV-infected patients who develop lipodystrophy are receiving highly active antiretroviral therapy. A recent study revealed that lipodystrophy develops in approximately 40% of patients who are treated with a protease inhibitor for more than one year.<sup>2</sup>

The mechanisms by which protease inhibitors cause lipodystrophy are not fully understood, though it is hypothesized that protease inhibitors would impair the differentiation of adipocytes.<sup>3</sup>

### *Dyslipidemia and insulin resistance...*

Many clinical studies conducted in both pre- and post-antiretroviral drug eras have shown that dyslipidemia and insulin-resistance are typical features of chronic HIV infection.

The dyslipidemia associated with HIV infection is predominantly characterized by marked hypertriglyceridemia, elevated plasma low-density lipoprotein (LDL) cholesterol and apolipoprotein (apo) B levels, as well as decreased HDL-cholesterol and apo A-I levels.

The severity of dyslipidemia has been correlated with a number of clinical features, including the duration of exposure to antiretroviral drugs, older age, higher CD4 counts, associated lipodystrophy and lower plasma HIV RNA levels. Furthermore, antiretroviral drugs have been suggested to play a causative role in the pathogenesis of insulin resistance in HIV-infected patients.

A recent study reported that the adjusted rate of incident diabetes mellitus was 4.1-fold higher in HIV-infected subjects receiving antiretroviral agents compared with HIV-seronegative participants.<sup>4</sup> It has been proposed that the increased peripheral lipolysis found in HIV-infected subjects receiving antiretroviral drugs would give rise to fatty acid accumulation in skeletal muscle cells that have been associated with insulin resistance and impaired glucose disposal.

### *Inflammation and HIV-associated metabolic complications...*

There is some evidence that inflammation and adipocytokines play a central role in the progression of atherosclerosis in these patients. Studies of dyslipidemic HIV-infected patients have found elevated plasma levels of pro-inflammatory cytokines that appear permissive in the development of dyslipidemia and insulin-resistance. Therefore, abnormalities in adipocytokine homeostasis may be crucial in promoting the inflammatory changes found in HIV-associated metabolic complications.

*Lipodystrophy develops in approximately 40% of patients treated with a protease inhibitor for more than one year.*



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### **Examining the increased risk of cardiovascular disease...**

The elevated plasma levels of LDL-cholesterol, apo B, triglycerides and reduced HDL-cholesterol and hyperinsulinemia found in HIV-infected patients appear to play major roles in the acceleration of atherosclerosis.

A recent study found that combination antiretroviral therapy is associated with a 26% increase in the relative risk of myocardial infarction (MI) per year of exposure during the first four to six years of use.<sup>5</sup> The association between combination antiretroviral therapy and the incidence of MI remained highly significant after adjustment for total cholesterol, triglycerides, diabetes and hypertension, suggesting that nontraditional risk factors could play an important role in modulating coronary heart disease (CHD) risk of HIV-infected patients receiving highly active antiretroviral agents.

Finally, a recent report showed 76% of HIV-infected patients with acute MI were younger than age 55 and more than 50% of these patients had one or no major risk factor for CHD.<sup>6</sup>

#### References

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### **Taking a therapeutic approach...**

Cardiovascular risk factors, including dyslipidemia, smoking, arterial hypertension, family history of premature coronary heart disease and sedentary lifestyle, should be assessed carefully.

Only a few studies have investigated the effect of dietary modification as a potential treatment for human immunodeficiency virus (HIV)-associated metabolic complications. For that reason, there is no specific dietary recommendation for the management of metabolic complications in HIV-infected patients. The current recommendations are based on Canada's Food Guide, promoting a diet low in saturated fat and high in dietary fibre.

#### Also...

- Cigarette smoking is the most important modifiable risk factor in HIV-infected patients and cessation of smoking should be strongly encouraged.
- Exercise has been shown to reduce abdominal obesity in HIV subjects with elevated waist circumference.
- 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) should be used with the objective to reduce the number of atherogenic apo B-containing lipoproteins (mainly low-density lipoprotein [LDL] and very low density lipoprotein particles).
- A fibrate should be considered to treat severe hypertriglyceridemia (> 8 mmol/L) associated with an increased risk of pancreatitis. However, in hypertriglyceridemic patients receiving a fibrate in monotherapy, a paradoxical elevation of plasma LDL-cholesterol and apo B levels is often noted.
- It should be emphasized that the use of lipid-lowering drugs in HIV-infected patients is of concern given the potential interactions with antiretroviral agents.
- Insulin-sensitizing drugs, such as metformin and thiazolidinediones, should be considered to improve insulin-resistance.

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