

METABOLIC COMPLICATIONS OF ANTIRETROVIRAL THERAPY

Access to antiretroviral therapy has improved outcomes of people living with HIV, but is not without its complications.

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Access to highly active antiretroviral therapy (HAART) in South Africa has dramatically improved the lives of those able to access these drugs. However, as with all drugs, antiretroviral use is associated with side-effects and toxicities. It is reported that up to 25% of patients on HAART discontinue their original regimen owing to treatment failure, non-compliance or toxic effects.

In the public sector the nucleoside reverse transcriptase inhibitors (NRTIs) form the backbone of the antiretroviral cocktail. This class includes zidovudine (AZT), lamivudine (3TC), stavudine (d4T), didanosine (ddI), tenofovir and abacavir. Two NRTIs are often used in combination with one drug from one of the remaining classes, the non-nucleoside reverse transcriptase inhibitors (NNRTIs) or the protease inhibitors (PIs). The NNRTI class comprises nevirapine, efavirenz and delavirdine. Adverse effects of drugs used as part of the rollout programme are given in Table I. This article reviews the adverse effects of HIV therapy, with specific attention to the metabolic abnormalities associated with their use.

METABOLIC COMPLICATIONS

The use of HAART is associated with adverse effects that occur shortly after starting therapy, such as nausea, rashes and immune reconstitution syndrome, and toxicities that occur after prolonged usage, which include the redistribution of body fat, lipid abnormalities and insulin resistance. The term 'lipodystrophic syndrome' has been used to refer to these physical and metabolic abnormalities, although there is no general consensus on the definition of the syndrome. Prevalence rates vary widely in cross-sectional studies, from 11% to 83%. This wide range reflects the lack of a consensus case definition, compounded by a lack of control of the effects of variations in HAART regimens. Effects of ethnicity and genetic predisposition to insulin resistance and obesity also need to be considered.

Body fat abnormalities

Patients may have subcutaneous lipoatrophy and/or accumulation of central adiposity. Body fat abnormalities usually take one of three forms:

Table I. Commonly used antiretroviral drugs and their adverse effects

| Drug | Most common adverse effects | Other |
|------------------|--|---------------------|
| Zidovudine (AZT) | Nausea, headache, rash, anaemia, leukopenia, increased liver enzymes and creatine kinase, hyperlactataemia/lactic acidosis | Do not use with d4T |
| Lamivudine (3TC) | Neutropenia (rare) | |
| Didanosine (ddI) | GI intolerance, pancreatitis, peripheral neuropathy, hyperlactataemia/lactic acidosis | Do not use with d4T |
| Nevirapine | Rash, elevated liver enzymes | |
| Efavirenz | Central nervous system toxicity, rash, lipodystrophy | |

- Localised lipotrophy most noticeable on the face, limbs and buttocks.
- Fat accumulation (lipohypertrophy), which is characterised by abnormal amounts of fat involving the abdomen, breasts or dorsocervical spine.
- A mixed pattern with both lipotrophy and lipohypertrophy.

These fat redistribution changes are associated with metabolic abnormalities, such as insulin resistance, dyslipidaemia and possibly atherosclerosis.

The type and duration of use of antiretroviral therapy are strongly associated with the severity of lipodystrophy. The use of 2 NRTIs plus a PI appears to increase the risk for the development of severe lipotrophy. The NRTI most strongly linked to lipotrophy is stavudine. Other risk factors for lipotrophy are given below:

- stavudine therapy
- older age
- lower body weight before commencement of therapy
- lower nadir CD4 count before commencement of therapy
- diagnosis of AIDS before commencement of therapy
- long duration of therapy.

The pathogenesis of lipodystrophy is poorly understood and is likely to be multifactorial. It is thought that NRTIs may contribute to lipodystrophy by inhibiting mitochondrial polymerase γ within adipocytes. Other possible mechanisms are the inhibition of transcription factors involved in adipocyte differentiation and lipogenesis as demonstrated by *in vitro* studies with PIs.

Lipid abnormalities

Longitudinal assessment of patients with HIV seroconversion suggests that patients initially show a decrease in total cholesterol, HDL cholesterol and LDL cholesterol. With the initiation of HAART, total and LDL cholesterol as well as triglyceride levels increase. All groups of drugs have been implicated

as causes for dyslipidaemia; however, this effect varies among the individual drugs in each class.

In patients who receive a PI-containing antiretroviral regimen, the prevalence of hyperlipidaemia ranges from 30% to 80%. It includes hypertriglyceridaemia in the majority of cases, followed by hypercholesterolaemia. Among the PIs, ritonavir carries the highest risk for hypertriglyceridaemia. Longer exposure to the drugs exacerbates the hyperlipidaemia. Additional factors contributing to the hyperlipidaemia are the presence of clinically apparent lipodystrophy and older age. The effect of the individual NNRTIs on lipids and insulin sensitivity is variable. In a study of the lipid profiles of patients receiving nevirapine compared with those of patients receiving efavirenz over a period of 48 weeks, nevirapine-containing regimens appear to produce a more favourable lipid profile, with these patients developing a greater increase in HDL cholesterol than those on efavirenz.

Pathogenesis

The mechanisms by which these drugs cause increases in triglyceride levels remain under investigation. It is clear that there is interpatient variability in the lipid effects of the various drugs. This suggests genetic predisposition. For example, some patients on ritonavir show marked increases in triglyceride levels, while others show no change whatsoever. A handful of studies have suggested that HIV-positive patients who are heterozygous or homozygous for the apolipoprotein E-2 genotype are more likely to experience elevated cholesterol and triglyceride levels on starting therapy with a PI. Other possible mechanisms are the effects of viral infection, cytokine effects and inhibition of adipogenesis by the drugs.

Insulin resistance and glucose abnormalities

Insulin resistance defines a condition characterised by decreased tissue sensitivity to the action of insulin.


This resistance is relative, since supernormal levels of circulating insulin from the pancreas may normalise the plasma glucose. Prior to the common use of HAART, insulin sensitivity in patients with HIV infection was noted to be increased. However, in the post-HAART era an increased prevalence of insulin resistance and impaired glucose tolerance among patients on treatment has been observed. Diabetes mellitus is found in up to 5% of patients receiving HAART.

Risk factors for diabetes and insulin resistance in HIV-infected adults include the use of some PIs and NRTIs, increasing age, visceral adiposity, dorsocervical fat accumulation and lipotrophy. An association between insulin resistance and lipotrophy is not surprising, since insulin resistance and dyslipidaemia are characteristic of congenital lipotrophy. The incidence rate has been highest among patients receiving PI-based regimens and higher still among HIV/HCV-co-infected patients receiving at least one PI. In addition, NRTIs that induce lipotrophy, particularly stavudine, also induce insulin resistance.

Pathogenesis


The mechanism by which insulin resistance occurs in HIV-positive patients receiving HAART has not been established. PIs have been shown to induce insulin resistance by reducing

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Up to 25% of patients on HAART discontinue their original regimen owing to treatment failure, non-compliance or toxic effects.

The term 'lipodystrophic syndrome' has been used to refer to these physical and metabolic abnormalities, although there is no general consensus on the definition of the syndrome.

The risk of cardiovascular disease is unlikely to outweigh the major benefits of HAART, particularly in those with advanced HIV disease.

glucose transport mediated by glucose transporter 4. A number of studies have indicated that fat redistribution changes, including increases in visceral adipose tissue and decreased subcutaneous adipose tissue, are indirect causes of insulin resistance.

Cardiovascular risk

The metabolic abnormalities, as discussed above, that are known to occur with the use of antiretroviral therapy, are associated with an increased risk of cardiovascular abnormalities. Studies in HIV-negative patients have consistently demonstrated that insulin resistance has effects on thrombosis, lipid metabolism, blood pressure regulation, and vascular function. There have also been data concluding that the risk of cardiovascular disease is similar in patients with type 2 diabetes and no prior myocardial infarction (MI) to that in non-diabetic patients with a prior MI. It is therefore likely that insulin resistance or diabetes in HIV-positive patients on treatment carries a similar risk.

Retrospective analyses designed to estimate the risk of cardiovascular disease in relation to antiretroviral therapy have yielded variable results.

The findings suggest, however, that the risk of cardiovascular disease may be greater in younger than in older patients.

The largest prospective study of cardiovascular risk with HAART is the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study. Of 23 468 participants, 0.5% developed their first MI during follow-up, an incidence of 3.5 per 1 000 person years. Of these events, 28% were fatal, representing 7% of all deaths in the study. The incidence of MI or of any ischaemic vascular event increased directly with longer exposure to antiretroviral therapy (relative risk 1.17 per year of exposure; $p < 0.0001$). Too few ischaemic events occurred to determine the relative risk associated with a specific antiretroviral drug class or with individual drugs. Hypercholesterolaemia, older age, smoking, diabetes mellitus, male sex and a prior history of cardiovascular disease were also associated with increased risk of MI.

Although the DAD Study group found that the relative risk of cardiovascular disease increased as the duration of antiretroviral therapy increased, the absolute risk of cardiovascular disease will remain low for most patients, except for those with multiple other cardiovascular risk factors.

Assessment of metabolic parameters

All potential cardiovascular risk factors should be assessed before initiation of HAART, annually during stable therapy, and within 1 - 3 months after any regimen change (Table II). The combination of these factors is likely to predict overall cardiovascular risk.

Risk factor modification and treatment options

The risk of cardiovascular disease is unlikely to outweigh the major benefits of HAART, particularly in those with advanced HIV disease. In HIV-negative individuals, effective strategies to reduce cardiovascular risk include smoking cessation, treatment of hypertension, diabetes and dyslipidaemia, weight reduction, and exercise.

Table II. Suggested cardiovascular assessment

Metabolic assessment (fasting)

- Lipogram – total, LDL and HDL cholesterol and triglycerides
- Glucose
- Oral glucose tolerance test

Others

- Age
- Sex
- Smoking status
- Blood pressure and use of antihypertensive agents
- Family history of cardiovascular disease
- Weight
- Waist and hip circumference

Cigarette smoking is the most important modifiable cardiovascular risk factor for HIV-infected patients. In the DAD Study, about 50% of participants were current or former smokers, and smoking conferred a greater than two-fold increased risk of MI.

Metabolic interventions

Lipid-lowering drugs

A lipid-lowering diet, as recommended by the National Cholesterol Education Program (NCEP) guidelines, has been shown to reduce LDL cholesterol and triglyceride levels in HIV-infected adults by 11% and 21% respectively. As in adults not infected with HIV, dietary interventions alone often fail to normalise lipid levels, suggesting that additional interventions will be required. The NCEP guidelines should be used when lipid-lowering therapy is initiated in HIV-infected patients. Drug interactions, especially between PIs and statins, should be considered. In general, a statin should be used to treat hypercholesterolaemia and a fibrate should be used to treat isolated hypertriglyceridaemia. Combined statin-fibrate therapy can be considered when the response is incomplete. The statins least likely to interact with antiretroviral therapy are pravastatin, fluvastatin and rosuvastatin, followed by atorvastatin. Simvastatin and lovastatin should be avoided in a patient receiving a regimen containing a PI, because statin levels can be greatly increased

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when co-administered with these agents, leading to an excess risk of hepatitis or rhabdomyolysis.

Insulin-sensitising drugs

Metformin has been shown to improve insulin sensitivity and decrease visceral adiposity in HIV-infected individuals with central adiposity and hyperinsulinaemia. To avoid lactic acidosis metformin should not be used in patients with raised serum creatinine, aminotransferase or lactate levels.

Three randomised studies have investigated the effects of thiazolidinediones in HIV-infected adults. Results of these studies suggest that the thiazolidinediones and rosiglitazone improved insulin

resistance, but had no beneficial effect on fat distribution and resulted in an increase in total cholesterol and LDL cholesterol levels.

Changes in antiretroviral therapy

Cessation of therapy with a thymidine NRTI, mainly stavudine or zidovudine, and substitution with either abacavir or tenofovir, leads to a slow but significant improvement in limb fat mass.

CONCLUSIONS

Metabolic and body fat abnormalities are common among HIV-infected individuals receiving NRTIs and PI therapy. Preliminary evidence suggests that these patients are at increased risk of cardiovascular disease. It seems appropriate to first initiate dietary and lifestyle alterations, including interventions for smoking and hypertension. However, the majority of patients will require additional

interventions such as lipid-lowering medications for hyperlipidaemia and insulin-sensitising agents for diabetes. The relative risks and benefits of switching HAART v. initiating lipid-lowering or insulin-sensitising therapy still remain to be determined.

Further reading

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IN A NUTSHELL

Well-described metabolic complications of HAART, i.e. hypercholesterolaemia, hypertriglyceridaemia, low HDL cholesterol, insulin resistance, and type 2 diabetes, have all been linked to an increased risk of cardiovascular disease.

The incidence of MI correlates with longer exposure to HAART, hypercholesterolaemia, older age, smoking, prior history of cardiovascular disease and male sex.

The absolute risk of cardiovascular disease remains low for most HIV-infected patients on treatment, except for those with other cardiovascular risk factors.

Risk factors for dyslipidaemia in HIV-infected adults include the use of PIs, lipodystrophy, particularly with stavudine, increasing age, visceral adiposity and the use of efavirenz.

PIs and NRTIs that induce lipodystrophy induce insulin resistance in HIV-infected individuals. Other risk factors for insulin resistance and diabetes include increasing age and visceral and central fat accumulation.


All potential cardiovascular risk factors, including dyslipidaemia, diabetes, hypertension, smoking and family history, should be assessed before initiation of HAART, and then annually and within 1 - 3 months of any regimen change.

Cardiovascular risk should not influence the timing of the initiation of antiretroviral therapy.

A statin should be considered for isolated hypercholesterolaemia and a fibrate for isolated hypertriglyceridaemia.

Simvastatin and lovastatin are contraindicated in patients receiving a regimen containing a PI.

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