Current perspectives

Metabolic disorders and cardiovascular risk in HIV-infected patients treated with antiretroviral agents

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The clinical management of HIV-infected individuals is based on highly active antiretroviral combination therapy, which provides significant clinical benefit in most patients, but causes in a high proportion of them a metabolic syndrome that includes body fat redistribution, hypercholesterolemia, hypertriglyceridemia, and insulin resistance. These effects are particularly evident in patients treated with protease inhibitors. It is likely that the metabolic disorders related to anti-HIV treatment will eventually translate into an increased cardiovascular risk in patients submitted to such regimens.

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The introduction in recent years of new potent drugs against HIV infection, in particular protease inhibitors (PIs), has resulted in an improved clinical outcome and survival[1-3] but their use requires a knowledge of the limitations imposed by the toxicity of single drugs and of the interactions between drugs used in combination[4]. In particular, concern has been raised about several class-specific metabolic side effects that may have a potentially deleterious effect on the cardiovascular system. These newly recognized side effects include increased insulin resistance, abnormalities in lipid metabolism, and a fat redistribution syndrome[5-9]. In the pre-PI era several disorders considered as risk factors for coronary artery disease were described in HIV-infected patients, including endothelial dysfunction[10,11], hypercoagulability[12], hypertriglyceridemia[13] and abnormal coronary artery pathology[14,15]. However, despite the above associations, coronary heart disease was not commonly documented in HIV-infected patients in the pre-PI era, perhaps because of premature death. Now that the prolonged survival of patients allows much longer observation periods, cardiac involvement directly or indirectly caused by HIV infection may well become clinically relevant.

Antiretroviral therapy

The development of new drugs against HIV infection has evolved at a rapid pace. The first agent for the treatment of HIV, zidovudine, was approved in 1987 and in the following 11 years fifteen new antiretroviral agents have been introduced. The understanding of HIV replication and drug resistance mechanisms led to the use of combination drug therapies. The new potent regimens are commonly defined as highly active antiretroviral therapy (HAART). Currently, three classes of drugs are employed (Table I). Nucleoside reverse transcriptase inhibitors (NRTIs) act as nucleoside analogues and interfere with the DNA polymerase function of the viral reverse transcriptase[16]. The non-nucleoside reverse transcriptase inhibitors (NNRTIs) include molecules with different chemical structures. They determine allosteric inhibition of enzyme function by binding at sites different from the nucleoside-binding site[16]. PIs are able to block the cleavage of polyproteins necessary to transform them in mature proteins causing the production of immature, defective viral particles[17,18].

The recommended treatment regimens for individuals in whom either no or very limited anti-HIV therapies had been previously employed include the use of a PI or

Table I. Approved nucleoside reverse transcriptase inhibitors (NRTIs).

NRTIs	Non-NRTIs	Protease inhibitors
Zidovudine	Nevirapine	Indinavir
Didanosine	Delavirdine	Ritonavir
Zalcitabine	Efavirenz	Nelfinavir
Stavudine		Saquinavir
Lamivudine		Amprenavir
Abacavir		Lopinavir + ritonavir

an NNRTI in combination with two NRTIs or the use of reduced doses of two PIs in combination with two NRTIs[18].

Highly active antiretroviral therapy-related metabolic disorders

Dyslipidemia. Significant increases in triglyceride and cholesterol levels have been associated with the use of all PIs[19-22], occurring in up to 60% of patients. The average increases in total serum cholesterol and triglyceride levels reported in these studies are respectively of 28 and 96%. It was observed that hyperlipidemia occurs early after the initiation of PIs and may be proportional to the duration of treatment[20,23-25]. The use of PIs has no effect on the level of high-density lipoprotein (HDL) levels (generally reported to be low during HIV infection) causing an elevated ratio of total cholesterol to HDL, a recognized risk factor for atherosclerotic disease[26]. Other alterations in lipid metabolism include an increase in the serum levels of apolipoproteins B, E and lipoprotein(a)[27-29]. The mechanism of these side effects is multifactorial. According to Carr et al.[30], the metabolic and somatic alterations in PI-treated subjects could be ascribed to the homology of the catalytic region of the HIV protease, the molecular target of PIs, to regions of two human proteins that regulate lipid metabolism: cytoplasmic retinoic-acid binding protein type 1 (CRABP-1) and low-density lipoprotein-receptor-related protein (LRP). The hypothesis is that PIs inhibit the CRABP-1-modified and CYP3A-mediated synthesis of cis-9-retinoic acid and of the peroxisome proliferator activated receptor type gamma heterodimer. This results in an increased apoptosis of adipocytes and in a reduced differentiation of pre-adipocytes to adipocytes, and consequently in reduced triglyceride storage and increased lipid release. PI binding to LRP would impair hepatic chylomicron uptake resulting in hyperlipidemia and insulin resistance. As reported above, even patients treated with NRTIs who never used PIs can experience hyperlipidemia and lipodystrophy, suggesting alternative or additional pathogenetic mechanisms[31], perhaps related to the inhibition of mitochondrial DNA polymerase gamma.

As recently reported[32], genetic factors could also be implicated in the individual susceptibility to HAART-related hyperlipidemia.

Insulin resistance. Insulin resistance is associated with abnormalities in endothelial function, impaired nitric oxide production, and decreased vasodilation thus contributing to atherosclerotic disease[30]. Since 1997 investigators have observed that impaired glucose tolerance, insulin resistance and new-onset diabetes mellitus can occur in patients on PI therapy[33]. Recent studies report a 25-62% prevalence of insulin resistance among PI-treated patients[7,9,30].

Besides, even healthy HIV-seronegative volunteers developed insulin resistance after 4 weeks of treatment with the PI indinavir[34].

The pathogenesis of PI-associated insulin resistance, impaired glucose tolerance and diabetes mellitus is not clear, although it is possible that a significant interaction between PIs and NRTIs contributes to the various aspects of the HAART-related syndrome, including insulin resistance[35]. In a recent study on a small group of patients receiving HAART, evidence of a reduced glucose uptake and impaired intracellular glucose phosphorylation in skeletal muscle was provided. It was thus concluded that this may have been the primary site of insulin resistance in this group of patients[36].

The fat redistribution syndrome. Antiretroviral therapy is associated with somatic changes attributable to a redistribution of body fat (lipodystrophy). The clinical presentation is highly variable. Observed clinical features include an increase in the waist-to-hip ratio, an increase in abdominal visceral fat, breast tissue hypertrophy, the presence of a cervical fat pad or "buffalo hump", wasting of the extremities, and loss of facial fat[37,38]. Recent data indicate that the combination of NRTIs and PIs is associated with a higher risk of lipodystrophy[39]. Additional risk factors for fat redistribution include age, the duration of HIV infection, the duration of antiretroviral therapy, and the magnitude of HIV suppression[40]. Other recent studies report a wide range of prevalence of lipodystrophy (18-83%)[22,38,41,42] possibly due to a lack of specific diagnostic criteria for this new clinical manifestation. The pathogenesis of the fat redistribution is not clear and investigators formulated many hypotheses including HIV suppression[43], immune reconstitution, abnormal local cortisol metabolism[44], hyperinsulinemia[45], and mitochondrial toxicity[46].

The fat redistribution syndrome may represent a significant risk factor for cardiovascular disease. In a study in which the metabolic and clinical features of 71 HIV-infected patients with lipodystrophy were evaluated and compared to those of 213 healthy control subjects from the Framingham Offspring Study, it was found that the former had significantly higher fasting

insulin levels, a higher incidence of diabetes and of hypertriglyceridemia and reduced levels of HDL cholesterol[25]. HAART-related lipodystrophy resembles a syndrome described in the 1980s that is termed metabolic syndrome X or visceral syndrome[47,48]. The association between syndrome X, type 2 diabetes mellitus and accelerated atherosclerosis is well documented and raises concerns on the long-term consequences of lipodystrophy as a risk factor of coronary disease in HIV-infected patients treated with HAART[49].

Highly active antiretroviral therapy and cardiovascular risk

Recent reports of myocardial infarctions in young patients receiving PIs have induced physicians to examine the associations between HIV infection, HAART and coronary artery disease. Cardiovascular events closely associated with PI therapy were anecdotally described[50-52]. In a study from the French Hospital Data Base on HIV it was found that patients treated with PIs for more than 30 months had a 3.1-fold increased risk of myocardial infarction when compared with untreated patients[53]. The study however was limited by the small number of events. An American retrospective case-control study examined 15 HIV-infected individuals with a recent cardiovascular event and compared them with matched controls. In this study HAART did not appear to be a risk factor in a multivariate analysis[54]. Even the issue of peripheral atherosclerosis has been addressed. A recently published study reported a high prevalence of atherosclerotic plaques within the femoral or carotid arteries in a population of 168 HIV-infected patients, but their presence was not associated with the use of PIs[55]. Different results were reported in another study, in which a higher than expected prevalence of premature carotid lesions in PI-treated patients when compared to PI-naive patients was observed[56].

Many prospective trials are presently addressing the important issue of HAART and cardiovascular risk[57,58]. A large multinational joint venture with the participation of 11 national HIV cohorts is now ongoing. Approximately 22 000 subjects are followed at 180 sites across Europe, Australia and the United States. The data at present available indicate that older treated subjects with preserved immunity, better viral suppression and lipodystrophy and a higher age are at risk for cardiovascular disease. This risk estimate is based on the lipid profile. To what extent this will lead to accelerated atherosclerosis is presently unknown, but data on the incidence of cardiovascular events will be available in 2003[59]. Data from a prospective cohort of HIV-infected persons that indicate an increased incidence of myocardial infarction in patients taking PIs versus patients who did not take PIs (13/3013 vs 2/2663, adjusted odds ratio 4.92, $p = 0.04$) have recently been presented[60]. Because of the relatively short observation period and of the small number of cardiovascular events, epidemiological evidence of an increased risk of coronary artery disease in HIV-infected patients treated with HAART is presently not strong enough. However, it is likely that more data will be shortly accumulated thus allowing us to quantify this risk. The rapid development of atherosclerosis has not yet been demonstrated in PI treated individuals. This is due to the relatively short observation period since the widespread use of HAART. This possibility is worrisome since rapidly forming plaques can be unstable and more prone to rupture thus increasing the likelihood of acute coronary events. As clinical experience with HAART continues to grow, the observation that drug-induced changes in lipid levels have resulted in an increased cardiovascular risk in other diseases[61-63] is yet another reason for concern in HIV-infected patients. In some HIV-infected groups, such as i.v. drug users, heavy cigarette smoking is highly prevalent, adding a well-known risk factor for ischemic heart disease. Moreover, the role of non-traditional risk factors for coronary artery disease that may possibly be more prevalent in HIV-infected populations, e.g. the use of cocaine and of anabolic steroids, must be taken into account.

Management of metabolic disorders and cardiovascular risk

Preliminary guidelines for the evaluation and management of dyslipidemia in HIV-infected patients receiving HAART have recently been published[64].

The main points of these recommendations are the routine screening of HIV-infected patients for coronary risk factors, a comprehensive analysis of the fasting lipid profile before starting antiretroviral therapy and the treatment of selected cases. In case of hypercholesterolemia, except for those patients with very high serum levels of cholesterol (> 400 mg/dl), a first therapeutic attempt should include dietary interventions and a reduction or abolishment of correctable risk factors for coronary disease, such as cigarette smoking, physical inactivity, diabetes mellitus, and hypertension. If deemed necessary, the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, or statins, can be prescribed. Since many of these compounds are cytochrome P 450 substrates, the concomitant use with PIs could retard their metabolism and thus increase their toxicity. With regard to this, the safest drug has proved to be pravastatin[65]. Even hypertriglyceridemia should be initially treated with a non-pharmacological approach and an adequate diet, exercise and smoking cessation are to be recommended. Marked increases in triglyceride serum levels are a risk factor not only for coronary disease, but also for pancreatitis and should be treated with lipid-lowering agents. Fibrates are the

most effective drugs used for the treatment of hypertriglyceridemia and have been proposed as possible first-line drugs for patients with both hypercholesterolemia and hypertriglyceridemia[64]. Gemfibrozil was initially used in dyslipidemic HIV-infected patients receiving PIs[66,67]. In spite of some encouraging preliminary results obtained with lipid-lowering agents in patients with HAART-related hyperlipidemia, more recent and complete data did not confirm these initial observations[68].

PI-sparing therapy is another approach which may be employed in an attempt to control metabolic side-effects. The switch from a PI-containing regimen to a regimen containing efavirenz[69] appears to have favorable effects on metabolic disorders. In one study the improvements in the triglyceride serum levels and in the fasting insulin resistance index were respectively reported in 31 and 28% of patients who were switched from PI- to efavirenz-containing regimens. Interestingly, patients who are started on a nevirapine-containing regimen show a favorable lipoprotein profile, as revealed by a sustained rise in HDL cholesterol (46% increase in HDL cholesterol from baseline in the nevirapine-treated patients)[70]. Recent studies reported that the replacement of PIs by efavirenz[71] or abacavir[72] is associated with a slower evolution in body fat changes and with an improved metabolic profile.

Conclusions

Although cardiac involvement and abnormalities of lipid metabolism in HIV-infected patients have been described even in the pre-HAART era, now that the prolonged survival of HIV-infected patients is well established, the risk of premature cardiovascular events attributable to coronary artery disease in HAART-treated patients is likely to become a key issue. Clinical trials comparing PI-containing regimens to PI-sparing regimens and large epidemiological studies are needed to determine the incidence of coronary artery disease and the related risk factors in HAART-treated patients.

Until definitive data are available, it is reasonable to evaluate all HIV-infected patients even for the presence of traditional coronary disease risk factors, including lipid metabolism[73]. The first-line treatment of dyslipidemia should include dietary interventions and a reduction or abolishment of correctable risk factors for coronary disease. In selected cases the pharmacological treatment of dyslipidemia should also be considered and its interaction with antiretroviral drugs borne in mind.

The dramatically increased survival and quality of life of HIV patients have undoubtedly confirmed the success of HAART, but the efficaciousness of these regimens may be hampered by the risks related to the as yet undefined cardiovascular toxicity.

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