Cardiovascular Disease Prevention and Treatment in Patients with Human Immunodeficiency Virus

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Abstract

Highly active antiretroviral therapy has dramatically improved the quality of life and life expectancy of patients with human immunodeficiency virus. However, the prolonged use of HAART leads to severe metabolic adverse events. Both HIV infection and HAART can cause changes in lipid and glucose metabolism as well as elevation of blood pressure, promoting the development of atherosclerosis. Cardiovascular diseases have become a major cause of mortality among HIV-infected subjects who respond well to antiretroviral therapy. Nevertheless, a proper lifestyle and pharmacologic intervention can improve cardiovascular risk factors in the HIV-treated population and significantly reduce healthcare investments in the treatment of future cardiovascular complications in this population. In this review we summarize the current knowledge of CVD prevention and treatment in HIV patients.

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Highly active antiretroviral therapy has dramatically improved the life expectancy of patients with human immunodeficiency virus [1]. In the present HAART era, many HIV-infected patients are experiencing the health problems that accompany the ageing process, mainly the risk of cardiovascular disease. Therefore, the question to be addressed is the extent to which HIV and/or its specific treatment (HAART) accelerates the risk for the development of CVD. Recently, cross-sectional data from the D:A:D cohorts (Data Collection of Adverse Events of Anti-HIV Drugs) were evaluated for the underlying cardiovascular risk factors in over 17,000 HIV-infected patients [2]. The results showed that over 50% of the patients were smokers, 33% had increased triglyceride levels, 22% had elevated levels of total cholesterol, and about 2.5% of HIV patients had diabetes. Furthermore, about 11% had a family history of coronary heart disease, 1.5% had a prior coronary heart disease and 8% had hypertension [2]. It is important to point out that the time interval from the earliest events in atherogenesis, namely endothelial dysfunction, to the development of atherosclerotic plaque and overt vascular events such as myocardial infarction or stroke is quite long. HAART has been available for approximately 7 years, thus the full impact of its metabolic complications on the development of CVD cannot yet be precisely estimated. Nevertheless, one should consider the metabolic disturbances associated with HAART in HIV-treated patients as significant surrogate markers for evaluation of future cardiovascular morbidity and mortality.

Hyperlipidemia

HIV infection by itself, without HAART, can cause changes in lipid metabolism. Accordingly, before the availability of HAART, increases in serum triglyceride levels and decreases in cholesterol – including total cholesterol, low density lipoprotein-cholesterol and high density lipoprotein-cholesterol levels – were observed in HIV patients [3].

The MACS study (Multicenter AIDS Cohort) examined recent seroconverters before and after starting HAART [4]. HIV seroconversion was found to be associated with a mean decrease in total cholesterol levels of about 15%, including reductions in the levels of both LDL-cholesterol and HDL-cholesterol. The MACS study also showed that within 3–6 months of treatment HAART increased the total cholesterol to the levels observed before the seroconversion. Moreover, the levels of the total cholesterol were further increased (above the normal or pre-seroconversion levels) with the continuation of HAART [4]. In contrast, the decrease in HDL-cholesterol associated with HIV infection was not reversed by the antiviral treatment [4]. In the D:A:D study [2], all three antiretroviral drug classes (nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors) were shown to cause hyperlipidemia when compared to naïve (untreated) HIV patients. The HAART-associated hyperlipidemia can occur as early as 2–3 weeks following the initiation of treatment [5]. The hyperlipidemia is usually mild to moderate, but high lipid levels complicated by the development of pancreatitis were also reported [6]. Although elevations in the levels of both triglycerides and cholesterol were reported in patients receiving PI-sparing regimens, the later drugs (PI) were shown to be responsible for the

Highly active antiretroviral therapy improves both quality and length of life in HIV patients

HAART = highly active antiretroviral therapy
HIV = human immunodeficiency virus
CVD = cardiovascular disease
LDL = low density lipoprotein
HDL = high density lipoprotein
PI = protease inhibitors

development of hyperlipidemia in most cases [2]. The exact mechanism(s) by which the PI drugs cause hyperlipidemia are not known. It was suggested that the later drugs could, *in vivo*, bind and disturb the activity of specific regulatory lipid-binding proteins [5]. Various studies demonstrated differences in both the rate and the magnitude of the hyperlipidemia following treatment with different PI agents [7]. Ritonavir, saquinavir, and lopinavir were shown to cause hyperlipidemia, whereas atazanavir appears to be the least likely to cause lipid abnormalities [7,8]. Moreover, in the BMS AI424-044 study, patients who were switched from nelfinavir to atazanavir demonstrated significant decreases in cholesterol and triglyceride levels [9]. The most significant elevations of blood lipids have been observed with lopinavir/ritonavir treatment (also known as LPV/r) [10,11].

Other HAART drugs, in addition to PIs, can also influence lipid levels. Among the NNRTIs, both nevirapine and efavirenz have been associated with an increase in total and LDL-cholesterol, but in contrast to the PIs the later drugs increase rather than decrease the levels of HDL-cholesterol [12]. Nevirapine is associated with a better total cholesterol:HDL-cholesterol ratio in comparison to efavirenz [12]. Among the NRTI drugs, stavudine significantly increased total cholesterol and triglyceride levels [13].

Impaired glucose tolerance and diabetes mellitus

Abnormalities in glucose metabolism (insulin resistance, hyperglycemia, diabetes mellitus) are of concern, since persistently high blood glucose levels are associated with an increased risk for cardiovascular disease. The prevalence of insulin resistance in patients receiving PI therapy is estimated to be 25–62% [14]. Abnormalities related to impaired glucose tolerance can occur as early as 2 weeks after the initiation of the therapy and have been related mainly to the use of PI medications. The mechanism for HIV-associated diabetes involved both pancreatic B cell dysfunction and peripheral insulin resistance [15]. However, it appears that peripheral insulin resistance has a major role in the development of diabetes in HIV patients [15]. In addition, PIs were shown to affect the conversion of pro-insulin to insulin [14,15]. Moreover, recent studies demonstrated that PI medications interfere with glucose uptake receptors (GLUT 4, located on adipocytes and myocytes; GLUT 2, located on pancreatic islet cells) [16]. Unlike other PIs, atazanavir does not impair glucose tolerance and does not induce insulin resistance. In a randomized, double-blind, placebo-controlled, two-period crossover study, atazanavir had no effect on insulin sensitivity, insulin-mediated glucose disposal rates or the mean glycolic storage rate, whereas lopinavir/ritonavir treatment demonstrated significant impairment in glucose tolerance [17].

Insulin sensitizers, such as metformin [18], rosiglitazone [19] and pioglitazone [20], were shown to decrease insulin resistance in HIV patients treated with PIs, although the above metabolic disturbances did not return to normal. Moreover, treatment with rosiglitazone was associated with worsening of hypertriglyceridemia [21].

Arterial hypertension

Elevated blood pressure has been observed in HIV patients treated with HAART and may coexist with other metabolic disturbances, such as diabetes mellitus, hyperlipidemia and lipodystrophy [22]. It was recently shown that hypertension in HIV patients on HAART is linked to insulin resistance as part of the metabolic syndrome X [23].

Accelerated atherosclerosis, cardiovascular and cerebrovascular diseases

Lipid abnormalities, insulin resistance and arterial hypertension are all risk factors for the development of premature atherosclerosis in HIV patients. In addition, the chronic inflammation process associated with HIV infection, particularly the increased levels of C-reactive protein and pro-inflammatory cytokines [24], may also play a role in atherogenesis. Recently, Dressman et al. [25] demonstrated that PIs promote atherosclerosis lesions independent of dyslipidemia by increasing the CD36 gene expression on macrophages.

HAART is independently associated with a relative increased risk of 26% for myocardial infarction per year of exposure during the first 4–6 years of treatment [26]. Mary-Krause and colleagues [27] updated a prior report of hospitalizations for myocardial infarction among HIV-infected patients and found an increased risk of myocardial infarction in their HIV-infected cohort after 18 months of PI therapy. Using equations based on the Framingham cohort data, Gandy and co-workers [28] demonstrated an increased rate of myocardial infarction among HIV patients receiving PIs, that was associated with the duration of therapy.

Prolonged use of HAART may cause severe metabolic adverse effects, mainly hyperlipidemia, hyperglycemia, and the development of atherosclerosis and cardiovascular diseases

Taken together, HIV patients – especially those treated with PI-based HAART medications – are at increased risk for the early development of cardiovascular disease, including coronary heart [29] and cerebrovascular [30] diseases. Thus, all known risk factors should be carefully controlled in HIV patients by both primary and secondary prevention [31,32].

Cardiovascular disease prevention and treatment in HIV patients

To reduce cardiovascular risk in HIV patients, both non-pharmacologic and pharmacologic interventions should be used. Non-pharmacologic interventions include measures such as smoking cessation, diet modification and increased exercise. The Cardio-

NNRTI = non-nucleoside reverse transcriptase inhibitors
NRTI = nucleoside reverse transcriptase inhibitors

vascular Disease Focus Group of the ACTG (AIDS Clinical Trials Group) published recommendations for the management of lipid abnormalities in HIV-associated dyslipidemia [33]. The ACTG Cardiovascular Subcommittee recommended a three-step guideline to gauge heart disease risk in patients with HIV infection:

1. Count the number of cardiovascular disease risk factors that modify the National Cholesterol Education Program (NCEP) LDL goals. The risk factors are: a) cigarette smoking, b) systolic blood pressure of 140 mmHg or higher, or treatment with antihypertensives, c) HDL below 40 mg/dl, d) coronary heart disease in a first-degree male relative under 55 years old or a first-degree female relative under 65 years old, and e) age over 45 years for men and over 55 years for women.
2. Test fasting lipids before starting any antiretrovirals and then monitor lipid levels for 3 to 6 months.
3. If a person has two or more risk factors, estimate their 10 year risk for heart attack or cardiac death with an online risk assessment tool: http://hin.nhlbi.nih.gov/atpiii/calculator.asp.

After determining the risk category, identify the LDL-C goals as demonstrated in Table 1.

Other potential factors that can contribute to the development of hyperlipidemia, such as hypogonadism, hypothyroidism, liver or kidney disease, and alcohol abuse, should also be evaluated and addressed. The potential lipid-modifying effects of other drugs, including glucocortioids, beta-blockers, thiazide diuretics, thyroid preparations and hormonal agents such as androgens, progestins and estrogens, should also be considered.

The ACTG Cardiovascular Subcommittee then proposes a general approach to controlling lipid disorders in HIV patients:

1. Address modifiable risk factors such as diet, exercise and smoking.
2. If lipids remain above the threshold levels [Table 1] despite vigorous lifestyle interventions, consider altering antiretroviral therapy or lipid-lowering drugs.
3. If lipid-lowering drugs are indicated, consider treatment with statins. Statins other than pravastatin (Lipidal®) or atorvastatin (Lipitor®) should be avoided due to unfavorable pharmacologic interactions with antiretroviral agents.
4. If lipid-lowering drugs are necessary, and if triglycerides levels are above 500 mg/dl, consider treatment with bezafibrate (Bezalip®) or fenofibrate (Tricor®).

It is clear that the best way to limit the need for additional interventions and/or medications is to choose a HAART that durably suppresses HIV but also has the lowest risk of triggering metabolic disturbances. Once established, the metabolic syndrome may be a vicious, self-perpetuating cycle with limited treatment options [34]. At this stage, removing the trigger for the metabolic disturbances – i.e., PI drugs – may not lead to its reversal. Thus, it is critical to avoid development of the metabolic syndrome. Since the new-generation antiretroviral medications have an equal (or near equal) potency in HIV suppression, cardiovascular risk factors should be a priority in constructing and choosing the HAART medications.

Several studies have investigated and compared the impact of various boosted and unboosted PIs on lipid levels. LPV/r-based HAART increased both total cholesterol and triglyceride levels to a significantly greater degree than other PI medications such as nelfinavir [10] or unboosted fosamprenavir [35], whereas fosamprenavir boosted with ritonavir leads to similar lipid abnormalities as did LPV/r in HIV-treated patients [8]. Recently, several studies demonstrated that the new PI drug atazanavir, unboosted or boosted with ritonavir, has a much safer metabolic profile (in terms of lipid levels and glucose intolerance) as compared to LPV/r [36,37] or even to the NNRTI efavirenz [38].

Table 1. Recommendations for treatment of hypercholesterolemia in HIV patients

	LDL-C level (mg/dl)		
Risk category	Goal	Initiate therapeutic lifestyle change	Consider drug therapy
Coronary heart disease or risk equivalent	<100	⩾100	⩾130*
2 or more risk factors and 10 year risk of 10–20%	<130	⩾130	⩾130
2 or more risk factors and 10 year risk less than 10%	<130	⩾130	⩾160
0 to 1 risk factors	<160	⩾160	⩾190**

* For LDL-C of 100–129 mg/dl, drug therapy is optional; consider treating HDL-C and triglyceride disorders.

** For an LDL-C of 160–189 mg/dl, drug therapy is optional.

Protease inhibitors are the main cause of metabolic syndrome

Summary

Heart disease and stroke are the first and third leading causes of death in developed countries, respectively, accounting for nearly 40% of all deaths in the general population. Cardiovascular disease has become a major cause of mortality among HIV-infected subjects who respond well to antiretroviral therapy. The most frequent underlying causes of death in these patients are non-AIDS defining malignancies (19%), cardiovascular diseases (16%), liver failure (16%), AIDS-related illnesses (15%, mainly non-Hodgkin lymphoma), and suicide (11%) [39]. Among these causes of death, cardiovascular disease is the most easily preventable. Choosing the most metabolically favorable medications is the basis for this prevention. The main issues to consider at the time of initiation of HAART as first-line antiretroviral therapy are the potency and durability of HIV suppression and the tolerability of the regimen, both in terms of its simplicity or convenience and the likelihood of long-term toxicities. Metabolic disturbances and cardiovascular disease are one of the major and significant long-term and significant toxicities that should be considered before initiating HAART. Table 2 summarizes the metabolic and cardiovascular

Table 2. Influence of antiretroviral drugs on the cardiovascular system

	Atherosclerosis	Hyperlipidemia	Glucose intolerance/ diabetes mellitus	Arterial hypertension
PI	PI > than NNRTI or NRTI	↑↑ Triglycerides ↑ LDL ↓ HDL	↓ Glucose metabolism ↑ Insulin levels ↑ Insulin resistance ↓ Glucose metabolism	↑Blood pressure
NNRT		↑ Triglycerides ↑ LDL may increase HDL level (nevirapine)		
NRTI		↑ Triglycerides (stavudine)		

effects of different antiretroviral drugs. Primary and secondary prevention, including lifestyle interventions and pharmacologic treatments, can improve cardiovascular risk factors, thereby reducing morbidity, mortality and healthcare investments in HIV patients.

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