Atherosclerotic cardiovascular disease and HIV infection: an update


ABSTRACT

Before high-power antiretroviral therapy was introduced, cardiovascular complications in the HIV-infected population were mainly related to immunosuppression. However, after the advent of combined use antiretroviral drugs the morbimortality of these patients decreased considerably. It seems, however, that metabolic complications such as insulin resistance and dyslipidemia have become more frequent, suggesting an increased risk of atherosclerotic disease. The purpose of this article is to review the literature and describe the cardiovascular complications related to HIV infection, with an emphasis on the period after combined antiretroviral therapy was introduced. The review was conducted to highlight the cardiovascular risk factors, mainly of atherosclerotic heart disease and its peculiarities among the HIV-infected population.

Key words: Cardiovascular Diseases; Atherosclerosis; HIV; Metabolic Diseases; Lipodystrophy.

INTRODUCTION

Despite the intense effort to stop the spread of the human immunodeficiency virus (HIV) epidemic around the world, epidemiological data remain alarming. In 2009, according to a publication by the World Health Organization, there were almost 33 million people living with HIV throughout the world.1 We must be alert to the increasing prevalence among women and adolescents.2
Atherosclerotic cardiovascular disease and HIV infection: an update

During the first years of the epidemic, most infected patients progressed to a state of almost complete immunosuppression. The introduction of highly active antiretroviral therapy (HAART) in 1997 caused a dramatic change in the natural history of the infection by HIV, resulting in a decrease of defining events of acquired immunodeficiency syndrome (AIDS) and HIV-related mortality.\(^5\) \(^6\)

Thus, there were significant changes in the spectrum of diseases reported by patients and the drugs’ adverse effects take on an important role in disease management. The success of HAART is associated with problems such as dyslipidemia, insulin resistance, increased intra-abdominal fat and loss of peripheral fat.\(^7\) \(^8\) The pattern of these metabolic abnormalities in patients using antiretroviral (ARV) drugs is similar to that found in metabolic syndrome, which is known to increase the risk of atherosclerotic cardiovascular disease. It is not the aim of this review discuss the controversy surrounding the existence of metabolic syndrome as a nosologic entity.\(^9\) \(^10\) Thus, whenever we refer to the syndrome, the risk factors comprising it are implicit. Regarding the combined therapy with antiretroviral drugs, is not yet well established how and after how long after exposure to HAART these clinically detectable abnormalities can occur. Several long-term prospective studies are in progress to evaluate the incidence of cardiovascular events in this population since we find that, in the current scenario, ARV drugs are introduced increasingly early and for longer periods.\(^11\) \(^12\)

Atherosclerotic disease in HIV-infected patients is still not very well understood and the findings of various studies remain contradictory. More recent studies have suggested that this population presents higher cardiovascular risk. But would this increase be due to infection per se, to its treatment, or to both? Is it necessary to calculate the cardiovascular risk for all infected patients? Should we consider HIV-positive individuals to have high cardiovascular risk as are diabetic patients? Should we consider the stratification of risk to define the onset of HAART? Which ARV therapy scheme should be introduced for patients with high cardiovascular risk?

On account of the countless questions related to management of these patients, their increased survival, increased incidence, and great morbidity and mortality of atherosclerotic disease, it is imperative that professionals involved be more familiar with this disease so as to identify patients with high risk of cardiovascular disease and find the best therapeutic approach for them Table 1 contains a summary of the main ARV drugs available and their respective classes.

**HIV INFECTION AND ATHEROSCLEROTIC CARDIOVASCULAR DISEASE**

**Pre-HAART phase**

The cardiovascular manifestations of HIV infection underwent significant changes after the introduction of HAART, especially in Brazil, where these drugs are provided free of charge by the public health system, granting all patients access to treatment, regardless of their social class.

Studies have revealed that almost 7% of HIV-infected individuals already had cardiovascular manifestations before HAART; with the great majority incurring in myocardium, endocardium, and/or of the pericardium involvements. These abnormalities were often caused by the HIV infection, opportunistic infections, neoplasms, complications from the ARV (for example, zidovudine), complications in the treatment of opportunistic infections, nutritional deficiencies (vitamin B12), among others.\(^13\)

Only recently have the subclinical inflammatory changes occurring on arterial walls triggered by cardiovascular risk factors been implicated in the pathogenesis of atherosclerotic disease.\(^14\) Besides immunosuppression and resulting from the decrease in systemic inflammatory response caused by HIV, the infection causes profound changes in endothelial function, similar to those found in the subclinical inflammatory reaction of diffuse atherosclerotic disease. High levels of Von Willebrand factor are found in these two situations, correlating with levels of proinflammatory cytokines. The hypercoagulable state is directly proportional to viremia. We should highlight that expression of protein S is also decreased and production of prothrombotic antiphospholipid autoantibodies increased in these patients.\(^15\)

**Post-HAART phase**

In addition to the classic cardiovascular risk factors associated with use of HAART, HIV-infected patients seem to have endothelial dysfunctions, impaired fibrinolysis and a proinflammatory state that contributes to the progression of diffuse atherosclerotic disease.
Atherosclerotic cardiovascular disease and HIV infection: an update

Risk factors for atherosclerotic cardiovascular disease

Well established factors: advanced age, family history (FH), male sex, smoking, sedentary lifestyle, obesity, hypertension, diabetes mellitus, insulin resistance and dyslipidemia, with high levels of LDL cholesterol (LDL-c) and reduced levels of HDL cholesterol (HDL-c). Non-modifiable risk factors: sex, age, and FH. Control of modifiable risk factors, such as smoking and dyslipidemia, should be considered a priority in the management of HIV-positive patients.20

Dyslipidemia

Before the use of HAART, HIV-infected patients underwent changes in lipid metabolism characterized by increased levels of triglycerides (TG) and reduction of total cholesterol, LDL and HDL.21 Reduction in the level of this fraction of cholesterol in HIV-positive patients is due to stimulation of endothelial lipase and phospholipase A2 by the inflammatory process, as well as by preventing release of HDL-c by HIV-infections.
fected macrophages. Additionally, the HDL molecule is full of TG during hypertriglyceridemia and, for this reason, it is a substrate for hepatic lipase. This reduction contributes to the atherosclerotic process due to its antioxidizing and anti-inflammatory functions. Finally, the nutritional status of patients with weight loss and protein depletion can also contribute to reduction of total cholesterol and its fractions.

Dyslipidemia associated with HIV is similar to that found in other chronic viral infections. High levels of interferon-α (IFN-α) in advanced stages of the disease are correlated with increased TG dosage due to a decrease in the “clearance” of rich lipoproteins in this nutrient. Similarly, high levels of tumor necrosis factor α (TNF-α), mainly when an opportunistic infection occurs, interfere with the metabolism of fatty acids in lipid oxidation and with the inhibition of insulin-mediated suppression of lipolysis, thereby causing hypertriglyceridemia.

Dyslipidemia tends to worsen after ARVs are introduced. It is characterized by hypertriglyceridemia and reduction of HDL-c levels and increase of total cholesterol, with or without increase of LDL-c levels. This pattern is related to insulin resistance and changes in body fat distribution, although it can occur without obvious lipoatrophy or insulin resistance. Dyslipidemia associated with use of protease inhibitors (PI) includes hypercholesterolemia with increase of VLDL, IDL, and LDL 20 It is important to emphasize that some systematic comparisons exist between the various drugs in this class regarding their effect on lipid profile. Abnormalities appear to be more pronounced with ritonavir or lopinavir-ritonavir. Amprenavir and nelfinavir appear to have an intermediate effect, while darunavir and atazanavir have minimal effects on lipid profile. 20

As regards nucleoside analog reverse-transcriptase inhibitors (NARTIs), stavudine seems to lead to a larger increase of total cholesterol, LDL, and TG. Tenofovir interferes less with plasma lipids when compared to other drugs and there is evidence that it can reduce them through an independent mechanism of virus suppression. 20

The non-nucleoside analog reverse-transcriptase inhibitors (NNRTI) are considered good anti-HIV medicines as regards lipid profile. They are associated with a slight increase in TG and LDL-c and with an increase in HDL-c levels. Patients receiving nevirapine seem to progress with a greater increase in HDL-c when compared to efavirenz. Etiravirine is a new drug in the NNRTI class and preliminary studies have shown better lipid profile with this drug when compared to efavirenz and nevirapine. 21

New classes of ARVs, such as the integrase inhibitors (raltegravir) and fusion inhibitors, which are indicated when there is resistance to usual ARV schemes, were not associated with any significant changes in lipid profile. 24

For the time being, there are no prospective, double-blind, randomized trials providing reduction of cardiovascular risk in HIV-positive patients whose dyslipidemia is treated aggressively. However, even without incontrovertible evidence, it is reasonable to consider that the reduction of plasma lipids in these patients would provide the same benefit found in HIV-negative patients with high cardiovascular risk.

According to the current recommendations, lipid profiles should be requested regularly, especially before the start of HAART and approximately three months after the start of medication. 20

Patients new to ARV treatment and with preexisting dyslipidemia should receive an ARV therapy scheme that contributes to a favorable lipid profile. Changing the ARV therapy scheme due to metabolic changes should only be the case if, even after optimizing the lipid-lowering treatment, the patient’s lipid profile remains at unacceptable levels. However, it is important to note that changing drugs to prevent complications should be considered a secondary objective since the initial objective is to achieve immunovirologic control and prevent viral resistance.

HMG-CoA reductase inhibitors (statins) are the drugs indicated for patients with increased LDL. However, simvastatin and lovastatin should not be used in patients using PI since the plasma levels of these statins may rise, increasing the risk of rhabdomyolysis. Atorvastatin and rosuvastatin should be used with caution. Pravastatin is considered the drug of choice, when associated with PI, because it is not metabolized by cytochrome P-450; however, its hypolipidemic power is much lower. 21

Ezetimibe is a hypolipidemic agent that is effective in reducing LDL-c, safe for patients using ARVs, and is useful when added to statins in refractory patients because it acts in synergism (it is possible to reduce the doses). However, it is important to emphasize that there are no studies suggesting that ezetimibe can effectively lower this outcome. On the other hand, use of exchange enzymes such as cholestyramine is contraindicated as they can increase TG levels and even compromise absorption of other drugs. 25
When TG levels are above 500 mg/dL use of fibrates must be started first. In this case, fenofibrate is the medication with the least risk of drug interaction. Other drugs that can also be used to reduce triglyceridemia are omega-3 and slow release niacin.  

**Insulin Resistance, impaired glucose tolerance and diabetes mellitus (DM)**

Patients with diabetes have similar risk of cardiovascular events than non-diabetic patients who survived a previous AMI. It is also well known that these patients have a higher chance for other coexisting risk factors.  

With regard to glucose metabolism disorders, we can highlight metabolic syndrome and its association with high cardiovascular risk. This nosological picture includes insulin resistance, accumulation of central fat, dyslipidemia (increase of TG and a reduction in HDL-c) and systemic arterial hypertension. These changes predispose prothrombotic, release of inflammatory cytokines, endothelial dysfunction, and intimal vascular hyperplasia.  

The abnormalities of glucose homeostasis are common among patients under ART. These individuals present mainly fasting hyperinsulinemia and post-overload hyperglycemia. Fasting hyperglycemia is less common. Mechanisms of insulin resistance in these patients seem to be related to the increase of free fatty acids, change in body composition and direct effect of ARVs.  

The prevalence of DM is increased among HIV-infected patients making use of ARVs. Brown et al., in a study with 1,278 men, 710 non-infected and 568 infected, found prevalence of 5% and 14%, respectively. Exposure to PI, stavudine, and efavirenz were independent factors associated with development of DM. This effect does not appear to be class-specific since more recent PIs such as atazanavir seem to have less effect on glucose metabolism. Several mechanisms have already been suggested to explain this pathogenesis of this process, such as: effect on carrier-mediated glucose transporter (GLUT-4), pancreatic islet cell dysfunction, alterations in hepatic glucose production, and inhibited transformation of pro-insulin into insulin. Given that multiple criteria and techniques can be used, the prevalence of insulin resistance among patients in ART is not well established. It is, however, believed to be quite high, reaching 60%.  

NRTI drugs also alter glucose homeostasis, whether indirectly from changes in body fat distribution, or directly through the effect of the drugs themselves. Mitochondrial toxicity can reduce tissue sensitivity to insulin and administration of stavudine may lead to changes in lipolysis, resulting in increase of fatty acids and insulin resistance.  

Periodical measurement of fasting blood glucose levels and assessment of the need for oral glucose tolerance tests are recommended to HIV-infected patients and especially for patients using ARVs. There are medications currently recommended for patients with insulin resistance and no changes in their glycemic profile. Those with a diagnosis of DM should receive insulin-sensitizing drugs, in particular metformin.  

**Changes in body composition**

HIV-infected individuals using ARVs commonly present changes in body fat distribution, characterized by loss of peripheral fat and accumulation of central body fat as well increased waist-to-hip ratio. It is known that excess of visceral fat increases the content of free fatty acids in the portal system, promotes insulin resistance, changes fibrinolysis, and generates endothelial dysfunctions. Patients with increased waist-to-hip ratio display more significant changes in lipid profile. In the general population, advanced age, male gender, and ethnic group are related to increase in visceral fat and cardiovascular risk. These factors appear to contribute similarly among HIV-infected patients.  

**Other cardiovascular risk factors**

Some studies show that smoking rates among HIV-infected patients are very high and, thus, its interruption should be intensively encouraged. As with the general population, smoking and advanced age also represent risk factors for cardiovascular disease in HIV-infected patients.
Atherosclerotic cardiovascular disease and HIV infection: an update

Predictive factors of cardiovascular risk

Biochemical markers (circulating inflammatory molecules)

High sensitivity C-reactive protein (CRP) is a known marker of subclinical inflammatory activity and hence can be used as a predictor of complications related to atherosclerotic disease. However, despite being highly available in out setting, its use remains undefined for this specific purpose.37

There are few studies that assess this marker in HIV-positive patients. In 2003, Feldman et al.38 showed that an increase in CRP levels in HIV-infected women can predict risk of cardiovascular-related death among these patients. Dolan et al.39 found that the CRP levels in HIV-infected patients with increased central fat were high.

Masià et al.40 found that patients in HAART had higher CRP levels when compared to non-users. The same was found by Guimaraes et al.41, who showed significant increase in ultra-sensitive CRP among HAART patients. Independent factors associated with levels of this marker were use of NNRTIs, PI, and existence of metabolic syndrome.9

Infection by HIV can be considered a process of pro-inflammatory activation, as well as a pro-thrombotic situation. HIV-infected patients treated with combined ARV therapy display increase in homocysteine, tissue plasminogen activator (tPA) and antifibrinolytic factor PAI-1.41-43 It has been well established that this hypercoagulable state predisposes seronegative patients to cardiovascular events.44,45

Another biochemical marker studied in the HIV-infected population is adiponectin, whose levels are inversely related to body fat. Adipokine has anti-inflammatory properties, and probably suppresses infiltration of the vessels’ intimal space by inflammatory cells, and its deficiency increases adhesion of endothelial molecules.46,47 A low dosage of this adipokine is found in various states of insulin resistance, such as obesity and DM.46 Kosinski et al.47 compared adiponectin levels in HIV-infected individuals and in a group of HIV-negative and found that although HIV-positive patients have a smaller amount of adipose tissue, they did not display higher increase in adiponectin. This low dosage might be associated with peripheral lipoatrophy since the production of this marker is probably more pronounced in subcutaneous adipocytes in comparison with visceral adipocytes.49

Prediction models of cardiovascular risk

The main objective of equations for cardiovascular risk prediction is to identify patients at high risk of event in order to define preventive measures. The Framingham score has been validated as a predictive model and is the most widely used in the general population.50 However, data on HIV-positive individuals are scarce. Egger et al.51 used this score to assess the cardiovascular risk in patients on HAART. Age, gender, and smoking were the main determinants of risk, which increased considerably with use of ARV.51

Hadigan et al.33 also used the Framingham equation to assess cardiovascular risk in patients with lipodystrophy. They detected that 30% had elevated risk of a cardiovascular event in 10 years, versus 13% among seronegative individuals. However, when the groups were matched according to the waist-to-hip ratio, no difference was observed in risk.33

Bergersen et al.52 studied HIV-negative and positive patients and noticed that the latter have increased risk of events over 10 years, two times higher than controls. In 2008, Adeyemi et al.53 evaluated metabolic syndrome and cardiovascular risk using the Framingham score in HIV-infected individuals above 50 years. Among the 121 patients evaluated, 34% met criteria for metabolic syndrome and 49% presented moderate to high cardiovascular risk.53

The Prospective Cardiovascular Munster (PROCAM) study and the Systematic Coronary Risk Evaluation (SCORE) are alternative models also developed to predict cardiovascular risk. The first, developed for a northern European male population was assessed by the PROCAM study and uses Framingham risk factors as well as TG levels, family and individual history for cardiovascular disease. The second is based on a series of cohort studies proposed by major European societies. It is a function used for calculating the risk of death from cardiovascular events that is pable to predict any type of fatal cardiovascular event over 10 years.54,55

There are few studies in HIV-infected patients using the last two models. Knobel et al.56 studied this population using all three models and showed that the concordance between methodologies is only moderate, with the Framingham equation identifying a greater number of patients at moderate risk.56 In 2010,
Atherosclerotic cardiovascular disease and HIV infection: an update

Assess HIV-positive individuals and the clinical implications of their findings are still unclear. Stein et al. found more FDM impairment among infected individuals, mainly those using PI, while Nolan et al. found no correlation between FDM and lipids, insulin, or body mass index, with no difference in FDM between the group of patients using or not using PI. Torriani et al. showed improved endothelial function with three ARV schemes (PI, NRTI and NNRTI) in a population assessed before and after these therapies were introduced. The findings are justified by an improvement in inflammatory status after HAART onset.

Most of the work with HIV-infected patients shows greater impairment of the arteries, such as flow changes or increase in the number of plaques and/or calcifications. However, there is still disagreement regarding the involvement of ARVs in this process.

**Cardiovascular outcome in HIV-infected patients**

After HAART was introduced, several reports have suggested greater early cardiovascular morbidity in HIV-infected patients. Law et al. compared the number of AMIs in the population in a prospective longitudinal study entitled Data Collection on Adverse Events of Anti-HIV Drugs (DAD) with the amount of events predicted by Framingham score. The number of IMs in patients using ARV exceeded the prediction, while among non-users of this therapy this number was lower than expected. It was shown, therefore, that length of exposure to drugs significantly increases the number of events seen and predicted, which corroborates the suspicion that preventive interventions in patients with multiple risk factors should be indicated, especially among those using ARV.

In spite of several predictive models of cardiovascular risk, there is still little data available in the literature regarding the best approach for HIV-positive individuals. Only after the actual incidence of cardiovascular events in this population is defined will it be possible to establish the most appropriate methodology.

**Surrogate Markers of cardiovascular risk: endothelial dysfunction and vascular disease**

Vascular image studies, because of they are non-invasive, are a good way to assess subclinical cardiovascular impairment in HIV-infected patients. However, the cost of this approach is quite high.

High-resolution ultrasound is used to evaluate peripheral arteries to quantify blood vessel thickness and presence of atherosclerotic plaques in the carotid and femoral arteries.

A ultrasonographic study comparing seronegative and HIV-positive individuals identified in the latter a considerable number of atherosclerotic plaques or greater thickening of the intima-media complex carotid.

Ultrasound of the brachial artery for measuring flow-mediated dilation (FDM) is another technique recently introduced into the assessment of endothelial dysfunction and, consequently, cardiovascular risk. This technique allows us to measure flow in arteries with several levels of occlusion, as well as response to vasodilators. There are few studies that use it to assess HIV-positive individuals and the clinical implications of their findings are still unclear. Stein et al. found more FDM impairment among infected individuals, mainly those using PI, while Nolan et al. found no correlation between FDM and lipids, insulin, or body mass index, with no difference in FDM between the group of patients using or not using PI. Torriani et al. showed improved endothelial function with three ARV schemes (PI, NRTI and NNRTI) in a population assessed before and after these therapies were introduced. The findings are justified by an improvement in inflammatory status after HAART onset.

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PLs was 1.16. For NNRTI, it was 1.05. After adjusting for lipid levels, there was a reduction in the effect of exposure to ARVs to 1.10 (95% CI, 1.04-1.18) and 1.00 (95% CI, 0.93-1.09), respectively. This study shows that longer exposure to PLs increases the risk of AMI, which may also be partly explained by dyslipidemia.77

In a recent DAD analysis of distinct ARVs, a significant increase in RR for AMI for each year of use of the PLs indinavir and lopinavir was highlighted. No increase was detected with use of NNRTIs nevirapine or efavirenz. Conversely, NRTIs didanosine and abacavir were associated with increase in RR. Abacavir was credited for a significant increase for each year of exposure.78

Once the association between ARVs, especially PI, and the adverse effects on cardiovascular risks was established, it was suggested that the temporary interruption of therapy while the virus was supressed and immunological control was achieved could minimize the adverse effects in this population. However, according to a segment of the study Strategies for Management of AntiRetroviral Therapy (SMART), intermittent treatment poses more risks of cardiovascular events in comparison with continuous treatment.79

**FINAL CONSIDERATIONS**

So far, we can notice that HIV infection and use of ARVs may contribute to increased cardiovascular risk for three main reasons: a) higher prevalence of smoking and poorer diet; b) triggering or intensification of traditional risk factors, such as dyslipidemia and insulin resistance, by infection and/or the treatment; c) direct action of the HIV and ARVs in the pathogenesis of atherosclerosis, causing subclinical inflammation and endothelial dysfunction.

More studies are needed to clarify the real contribution of the HIV, drug toxicity, and the metabolic changes that take place in the course of infection in the development of cardiovascular diseases. It is important to stress that the risk will probably rise as the HIV-positive population ages and is exposed to drugs and metabolic abnormalities for longer.

Finally, it can be said that HIV-infected patients are at a high risk of cardiovascular events, especially those whose viremia and traditional cardiovascular risk factors are poorly controlled. These complications should be treated aggressively, with priority being given to controlling viremia, immune function, and traditional modifiable risk factors.

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Atherosclerotic cardiovascular disease and HIV infection: an update


Atherosclerotic cardiovascular disease and HIV infection: an update