Metabolic Abnormalities, Antiretroviral Therapy and Cardiovascular Disease in Elderly Patients with HIV

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Summary

One of the most recent phenomena related to the acquired immunodeficiency syndrome (AIDS) is the emergence of a new vulnerable population: the elderly. One of the factors that account for this increase is the development of combination antiretroviral therapy (ART), which has provided better quality of life and life expectancy for HIV-positive patients. However, ART is associated with adverse effects such as dyslipidemia, diabetes mellitus and insulin resistance, which are risk factors for cardiovascular disease. Due to the impact of ART on lipid and glucose metabolism, many studies were published involving HIV infection and cardiovascular disease, as well as their risk factors and the use of ART, but few of them reported on the cardiotoxicity of this therapy in the elderly. The objective of this study is to review the main metabolic changes caused by the use of antiretroviral therapy and its impact on an increased risk of cardiovascular disease in elderly people with HIV.

Introduction

The Human Immunodeficiency Syndrome (AIDS), resulting of infection by the Human Immunodeficiency Virus (HIV), was identified in the early 80’s, and for some years it was considered a specific condition of homosexual males, sex workers and drug users. One of the most recent phenomena of the syndrome is the emergence of a new vulnerable population: the elderly (the United Nations [UN] define as elderly those individuals aged over 60 years in developing countries and 65 years in developed countries).

According to the Brazilian Ministry of Health, the first reported case of AIDS in subjects over 60 years occurred in the year 1984, and among the 474,273 cases of AIDS that were notified up to June 2007, 11,110 were elderly. Of these, 7,408 cases occurred in males and 3702 in females. In the state of Rio Grande do Sul, a total of 883 cases were notified in this age group up to January 2008.

In the 80s, the main mode of HIV transmission in this age group was through blood transfusion, however, currently, the most common mode of infection is through sexual contact, mainly by heterosexual transmission. This change in the mode of transmission of viruses occurred due to advancements in medicine and in the pharmaceutical industry, which extended the active sex life of the elderly.

An aggravating factor for the diagnosis of HIV in the elderly is the similarity between the opportunist diseases that often affect individuals with HIV and the diseases that affect the elderly and which, therefore, have lower rates of HIV testing than those for young adults. El-Sadr, Gettler investigated the prevalence of non-diagnosed HIV infection among patients aged over 60 years who died in the study institution and who had no history of HIV infection. Of the 257 samples analyzed, 5% (13) contained antibodies to HIV, although these thirteen patients had not died of HIV infection.

Perez, More evaluated mortality rates among 253 patients with HIV aged ≥ 50 years and among 535 young subjects who were also HIV carriers. The elderly who did not receive antiretroviral therapy had an odds ratio for death two times higher (HR = 2.4, CI (95%): 1.4-3.9) than that found in the young age group. After the introduction of the antiretroviral therapy, elderly patients with HIV had a 72% reduction in mortality (adjusted for confounding variables). And after three months, there were no statistically or clinically significant differences in survival rates between young and elderly patients.

The development of combination antiretroviral therapy (ART) (table 1), in 1996, improved the prognosis, the quality of life and the life expectancy for subjects with HIV; however, factors such as the possibility of developing viral resistance to drugs, the potential toxicity of drugs in the medium and long term and the need for adherence to ART, remain as major obstacles to success. The prescription should be personalized, using criteria such as effectiveness, durability and tolerability.

Although associated with improved quality of life for subjects with HIV, ART resulted in changes in cardiovascular events, because an increasing number of cases of coronary syndromes and peripheral vascular events have been associated with both the increased survival of patients and the toxicity of the therapy. ART and especially the use of
protease inhibitors have been associated with dyslipidemia, insulin resistance and diabetes mellitus, which are considered risk factors for cardiovascular disease22-23, and, according to some authors, the use of this class of drugs accounts for over 60% of the above mentioned metabolic changes24-27.

Due to the impact of ART on lipid and glucose metabolism, there were many studies involving HIV infection and cardiovascular disease, as well as their risk factors and the use of ART, but few of them reported on the cardiotoxicity of this therapy in the elderly. The elderly have a slower immunologic response to ART and an increased risk of developing cardiovascular disease by the association of aging, HIV infection and ART28. The objective of this study is to review the main metabolic changes caused by the use of antiretroviral therapy and its impact on an increased risk of cardiovascular disease in elderly people with HIV.

**Metabolic abnormalities in individuals with HIV**

**Changes in lipid metabolism**

ART-associated dyslipidemia is characterized by increased levels of VLDL (major carrier of triglycerides), LDL, and lipoprotein (a), and reduced levels of HDL29. In HIV carriers, the accumulation of these substances in plasma has been associated with the development of atherosclerosis and its complications, such as myocardial infarction and peripheral vascular disease30-32.

The mechanism by which dyslipidemia occurs in patients with HIV is not yet fully elucidated. It has not yet been established if the dyslipidemia occurs by a direct effect of ART or by the interaction of several factors, such as the antiretroviral treatment, genetic predisposition, environmental factors including diet and exercise, or other factors such as host response to HIV infection33.

Carr et al.34 proposed a theory based on the homology between the HIV protease catalytic site (within which protease inhibitors are bound) and the proteins involved in lipid metabolism: CRABP-1 (Cellular Retinoic Acid-Binding Protein Type 1) and LRP (Low Density Lipoprotein Receptor-Related Protein). Therefore, protease inhibitors inhibit key steps of human metabolism, as they inhibit the action of CRBP-1 and bind to LRP, which result in hyperlipidemia. Due to the occupation of the CRBP-1 site, protease inhibitors interrupt retinoic acid metabolism and reduce PPAR-γ activity (Peroxisome-Proliferator-Activated Receptor Gamma). This is important for the occurrence of adipocyte differentiation and apoptosis in these cells, and it also improves peripheral sensitivity to insulin. These phenomena lead to hyperlipidemia by reducing the peripheral storage and increasing the release of lipids in the blood35-37.

Inhibition of LRP results in lower uptake of triglycerides by the liver and reduced cleavage of fatty acids and glycerol, which should occur through LRP-LPL complex activity (lipoprotein lipase)38. Hypertriglyceridermia accounts for the increased insulin resistance, which can lead to diabetes mellitus type II39-40.

The prevalence of dyslipidemia varies according to the type of drug used by the patients. Calzà et al.41 followed, from 1998 to 2000, 212 HIV patients who initiated treatment with protease inhibitors, to assess the incidence of hyperlipidemia and its clinical adverse events. After one-year follow up, the treatment with protease inhibitors caused a statistically significant increase in triglyceride (p <0.005) and LDL cholesterol (p<0.05) levels, and the incidence of hypertriglyceridermia and hypercholesterolemia were 38.2% and 25%, respectively. The incidence of increased triglyceride levels was significantly higher in patients treated with ritonavir (66.6%) or lopinavir/ritonavir (60.7%) when compared to other protease inhibitors (p <0.04), and there was no clinical event adversely related to hyperlipidemia.

### Table 1 – Drugs currently used in combined antiretroviral therapy (ART) with their mechanism of action and main side effects

<table>
<thead>
<tr>
<th>Class</th>
<th>Generic name</th>
<th>Mechanism of action</th>
<th>Adverse effects</th>
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<tbody>
<tr>
<td>Nucleoside Analogue Reverse Transcriptase Inhibitors (NRTIs)</td>
<td>Abacavir (ABC), Didanosine (ddI), Stavudine (d4T), Lamivudine(3TC), Zidovudine (AZT) Tenofovir (TDF)*</td>
<td>Prevent acute infection of cells, therefore act on reverse transcriptase, preventing the viral RNA from being transformed into complementary DNA</td>
<td>mitochondrial toxicity, liver toxicity, lipodystrophy, anemia, myopathy, peripheral neuropathy, pancreatitis</td>
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<tr>
<td>Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)</td>
<td>Efavirenz (EFZ), Nevirapine (NVP), Delavirdine</td>
<td>Prevent protease cleavage of the viral polypeptide precursor and virus maturation.</td>
<td>Metabolic toxicity, lipodystrophy, dyslipidemia, hyperglycemia, insulin resistance, diabetes, gastrointestinal intolerance, liver toxicity</td>
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<tr>
<td>Protease Inhibitors (PI)</td>
<td>Fosamprenavir (FAPV), Atazanavir (ATV), Darunavir (DRV), Indinavir (IDV), Lopinavir (LPV), Nelfinavir (NFV), Ritonavir (RTV), Saquinavir (SQV)</td>
<td>Prevents the entry of viral genetic material into the cell due to its action on the same HIV entry site in cells that express CD4 receptor</td>
<td>Hypersensitivity reactions, mainly local, or more rarely systemic</td>
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<tr>
<td>HIV entry inhibitor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fusion inhibitor</td>
<td>Enfuvirtide (T-20)</td>
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* nucleotide analogue.
Changes in glycolytic metabolic

The prevalence of insulin resistance, glucose intolerance and diabetes has increased significantly since the introduction of ART. The clinical picture of type 2 diabetes mellitus and insulin resistance has been reported in 8-10% of cases\(^1\) and hyperglycemia with or without diabetes mellitus occurs in 3 to 17% of patients receiving ART\(^2\). The elucidation of the factors involved in these changes in glucose homeostasis, particularly insulin resistance, is still a major challenge that hinders efforts to improve patients’ quality of life.

Among users of protease inhibitors an increased occurrence of insulin resistance has been observed without the development of diabetes mellitus\(^3\). Treatment with indinavir (protease inhibitor) for four weeks, of individuals not infected with HIV promoted an increase in the levels of glucose and a 20% reduction in insulin sensitivity\(^4\). Schwarz et al.\(^5\) also showed a 17% decrease in insulin sensitivity, associated with an increase in the production of glucose and glycogenolysis, indicating that indinavir induces peripheral insulin resistance and increases the production of endogenous glucose. It is noteworthy that this condition may be associated with HIV infection, probably by direct action of the virus on pancreatic β-cell function or in the mechanism of action of insulin\(^6\).

Behrens et al.\(^7\) compared 38 HIV-positive patients on therapy with protease inhibitors, and 17 patients who were beginning therapy with the same drugs, using the oral glucose tolerance test. Eighteen (46%) patients on treatment had impaired glucose tolerance and five (13%) had diabetes, whereas in the group which was initiating therapy only 4 (24%) had glucose intolerance and none had diabetes. In the same study, fasting insulin, proinsulin and C-peptide concentrations and the concentrations of these substances after oral ingestion of glucose were increased in the treatment group, suggesting a dysfunction of the pancreatic beta cells and peripheral insulin resistance.

The mechanism involved in the induction of insulin resistance by protease inhibitors may be explained by three non-exclusive assumptions: inhibition of the activity of glucose transporters (GLUT1 and GLUT4) in the plasma membrane, inhibition of preadipocyte/adipocyte differentiation, and induction of apoptosis in mature adipocytes\(^8\). Hiruz et al.\(^9\) and Murata et al.\(^10\) suggested that one of the main mechanisms responsible for the induction of insulin resistance by protease inhibitors is the inhibition of the glucose transporter GLUT4. Protease inhibitors selectively and potentially decrease the activity of the glucose transporter GLUT4, without affecting insulin signaling events or GLUT4 translocation\(^11\). Since the transport of glucose is one of the limiting steps in the elimination of glucose, the inhibitory effect of protease inhibitors on GLUT4 causes insulin resistance in HIV positive individuals that use this class of drugs. Some of these patients may develop diabetes due to the failure of pancreatic β-cells in compensating for this resistance.

The mechanisms that possibly account for the induction of insulin resistance in HIV-positive patients treated with protease inhibitors are described in Figure 1.

Cardiovascular events and antiretroviral therapy

The use of ART provided the patients with greater life expectancy and a reduction in the incidence of opportunistic infections. However, due to the prevalence of diabetes mellitus, dyslipidemia and lipodystrophy increased, premature cardiovascular and cerebrovascular diseases have been described. The predisposition to atherosclerosis results from HIV infection, from metabolic changes resulting from the use of antiretroviral therapy or from both\(^12\).

The DAD study (Data Collection on Adverse Events of Anti-HIV Drugs Study), a multi-cohort study which investigated the incidence of cardiovascular and cerebrovascular accidents in patients with HIV infection and the association of risk factors for cardiovascular disease and ART\(^13\), included the participation of more than 20,000 patients. An article published by this study group, in 2007, confirmed the existence of an association between duration of antiretroviral therapy and increased risk of AMI, with an adjusted relative risk of 1.16 per year of exposure to therapy (95% CI: 1.09-1.23). The incidence of AMI was 1.53/1,000 person-years in those who were not exposed to protease inhibitors, and 6.01/1,000 person-years in those who were exposed to protease inhibitors\(^14\).

Rickerts et al.\(^15\) conducted a retrospective study with 4,993 HIV-positive subjects, from 1983 to 1998, to investigate if the use of ART was associated with an increased incidence of myocardial infarction. Although the absolute number was low (only 29 cases of myocardial infarction), the incidence of myocardial infarction per 1000 patient-years increased, after the introduction of therapy, from 0.86 (1983-1986) to 3.41 (1995-1998) (p = 0.002). Klein et al.\(^16\) also evaluated retrospectively, for a period of 5.5 years, a total of 4,159 men infected with HIV. During this period, there were 72 cardiovascular events, and 47 were of myocardial infarction\(^17\). Exposure to antiretroviral therapy did not alter the incidence of cardiovascular events. However, the incidence in patients infected with HIV was higher (4.86 per 1,000 person-years) than in patients of the control group (3.69 per 1,000 person-years, n=39,877 non-infected men).

Mary-Krause et al.\(^18\) studied the impact of protease inhibitors on the risk of myocardial infarction in HIV-infected male patients included in the French Hospital Database on HIV. From 1996 to 1999, myocardial infarction was diagnosed in 60 men among 88,029 person-years, including 49 cases in men who were receiving protease inhibitors (PI). The results showed a relationship between the use of protease inhibitors and myocardial infarction, with a high incidence among men exposed to PI for more than 18 months.

In their study, Obel et al.\(^19\) determined the hospitalization rate for ischemic heart disease in 3953 patients with HIV from 1995 to 2004, and compared it with the hospitalization rate of a control group that included 373,856 people. The data were obtained from the Danish National Hospital (Danish National Hospital), and the authors concluded that patients receiving antiretroviral therapy had an increased risk of developing ischemic heart disease, but the relative risk may remain stable for 8 years after the beginning of the treatment\(^20\).

Barbaro et al.\(^21\) conducted a study to assess the incidence...
of coronary artery disease according to the treatment used: a group received 2 nucleoside analogue reverse transcriptase inhibitors associated with 1 protease inhibitor, and the other group received 1 non-analogue reverse transcriptase inhibitor and 2 analogue reverse transcriptase inhibitors (with no protease inhibitors). A total of 1551 patients were followed for approximately 36 months and the annual cumulative incidence of events related to coronary artery disease was 9.8 per 1000 in the group with protease inhibitors, and 0.8/1000 in the group without protease inhibitors (p < 0.001), and the annual incidence of myocardial infarction was 5.1/1000 and 0.4/1000, respectively (p <0.001). Of all the patients who developed coronary artery disease and who received protease inhibitor (n=23), 73.9% had lipodystrophy and hypertriglyceridemia, and all of them presented hypercholesterolemia.\(^{61}\)

Bergersen et al.\(^{62}\) compared the risk of cardiovascular disease, by the Framingham score, in HIV-positive with or without ART with the risk in a control group (non-carriers of HIV). The study included 721 people: 219 individuals with HIV receiving antiretroviral therapy, 64 without antiretroviral therapy and 438 non-carriers of HIV. The prevalence of coronary risk > 20% in 10 years was twice as high in patients receiving ART (p = 0.25) and the control group (p = 0.76), with a prevalence of 6.3% for coronary risk > 20%. The HIV-positive group had higher prevalence of smoking habit and dyslipidemia.

The objective of the Italian study SIMONE (Metabolic Syndrome ONE) was to identify and characterize HIV patients at high risk of cardiovascular disease.\(^{63}\) In the study, individuals who had a Framingham score > 10% and/or metabolic syndrome were considered at high risk. Of the total of 1230 people analyzed, 6.3% (77) were aged above 60 years. The odds ratio was estimated for the group with high cardiovascular risk, using as reference the < 40 year age group, and for individuals > 60 years the odds ratio was 53.5 (CI [95%]: 23.4-122.4), for the 50-59 year age group it was 11.2 (CI [95%]: 7.3-17.2), and for the 40-49 year age group it was 3.0 (CI [95%]: 2.2-4.1).

From 1996 to 2004, Triánta et al.\(^{64}\) conducted a cohort study with 3851 HIV-infected patients and 1,044,589 non-infected patients to determine acute myocardial infarction rates and cardiovascular risk factors. According to the study, a cohort of individuals with HIV had proportions of hypertension (21.2 vs. 15.9%), diabetes (11.5 vs. 6.6%) and dyslipidemia (23.3 vs. 17.6 %) higher than the cohort of non-carriers (p <0.0001 for each comparison). The rate of acute myocardial infarction per 1000 person-years was 11.13 in patients with HIV (CI [95%]: 9.58-12.68), and 6.98 for those without HIV receiving ART (p = 0.25) and the control group (p = 0.76), with a prevalence of 6.3% for coronary risk > 20%. The HIV-positive group had higher prevalence of smoking habit and dyslipidemia.
Biochemical tests was higher in the elderly than in controls were included. The percentage of patients with abnormal markers of endothelial dysfunction (PAI-1 and tPA), which is vital due to the potentiation of the nephrotoxic effects, visceral fat and insulin resistance, and also reduces serum hepatotoxicity and myotoxicity of these drugs. If metabolic changes persist, pharmacotherapy should be initiated, although with extreme caution.

Pharmacological management of metabolic changes in HIV carriers

The pathophysiologic mechanism of the metabolic changes observed in patients with HIV is not yet fully elucidated and, therefore, specific guidelines for their treatment are not yet available. After a comprehensive analysis of risk factors for cardiovascular disease, the same treatment recommendations for the general population should be followed. Non-pharmacological treatment should be the first option, i.e., changes in lifestyle, including diet and exercise. If metabolic changes persist, pharmacotherapy should be initiated, although with extreme caution.

The treatment of ART-associated dyslipidemia includes three categories of assistance: change of antiretroviral scheme, changes in lifestyle, and prescription of a hypolipemiant agent. All HIV-infected patients require an annual assessment of their lipid profile before the beginning of antiretroviral therapy and at every three months after the initiation of the treatment or after any change in their therapeutic regimen. The pharmacological treatment of dyslipidemia in patients with HIV follows the same criteria of the National Cholesterol Education Program (NCEP) for the general population: statins, fibrates and niacine.

With the exception of pravastatin and rosuvastatin, most statins are metabolized by cytochrome P-450 isofrom 3A4, which is inhibited by PIs. If statins are administered concomitantly with antiretroviral therapy, a strict monitoring of renal function, liver enzymes and creatine kinase (CPK) is vital due to the potentiation of the nephrotoxic effects, hepatotoxicity and myotoxicity of these drugs.

As to the treatment of diabetes in HIV-infected patients, it is suggested that metformin reduces fasting plasma glucose, visceral fat and insulin resistance, and also reduces serum markers of endothelial dysfunction (PAI-1 and tPA), which may be increased in this group of patients. It is important to emphasize that the concomitant use of metformin and antiretroviral drugs of the class of the nucleoside analogues of reverse transcriptase inhibitors (NRTIs) may increase the risk of lactic acidosis (adverse event of this class of antiretroviral therapy); therefore, they must be strictly monitored and used with caution.
Conclusion

The use of antiretroviral therapy is critical for improving AIDS patients’ quality of life, but its use is associated with the development of dyslipidemia, diabetes and insulin resistance, which are risk factors for cardiovascular disease. There are evidences that the dyslipidemia associated with antiretroviral therapy accelerates the development of atherosclerosis and promotes a higher incidence of cardiovascular events, which is possibly related to the duration of the treatment. The pathophysiologic mechanism of the metabolic changes is not yet fully elucidated, and therefore specific guidelines for their treatment are not yet available. The pharmacological management used at the moment for HIV-infected patients follows the same recommendations for the general population: it should begin with non-pharmacological measures, such as following a diet and exercise. If metabolic changes persist, pharmacotherapy should be initiated, but with extreme caution.

As shown in this article, there are few studies reporting on the cardiotoxicity of antiretroviral therapy in the elderly. The recommendations for the use of therapy targeted particularly adolescents and adults, demonstrating the need for clinical trials with older people to better define the interaction between age and HIV infection both in the progression of the syndrome and the effectiveness of antiretroviral treatment, pharmacokinetics and short-term and long-term ART. In addition, further studies comparing elderly HIV-positive individuals with same age subjects without HIV infection are needed to evaluate issues such as age, HIV infection and antiretroviral therapy.

Potential Conflict of Interest

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