Cardiovascular Manifestations in Patients Infected with the Human Immunodeficiency Virus

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Today, it is estimated that the infection caused by the human immunodeficiency virus affects 42 million people worldwide. In Brazil, 1,200,000 individuals are infected, and 257,780 of them have the Acquired Immuno-deficiency Syndrome (AIDS). AIDS currently accounts for 1.41% of reported deaths in Brazil, a number that is decreasing owing to the national antiretroviral treatment distribution policy, which provides HIV-infected individuals universal access to available therapy.

The year 1996 is a landmark in the history of HIV infection and separates it into two eras: pre- and post-1996. Before 1996 but after detection of the infection in 1981, early diagnosis and treatment of opportunistic diseases were sought. After 1996, with the advent of combined antiretroviral therapy (HAART - Highly Active Antiretroviral Therapy), significant improvements in fighting the infection were achieved, with an increase in survival and an improvement in the quality of life of infected individuals.

The use of combined antiretroviral therapy to increase patients’ life span, together with a reduction in opportunistic infections, resulted in the emergence of chronic diseases and conditions related to common risk factors in the general population in this group, especially cardiovascular changes associated with the infection caused by the human immunodeficiency virus and those related to adverse heart effects of antiretroviral agents, which became more significant in recent years.

Heart involvement due to the HIV infection was first described in 1983 by Autran et al who described a myocardial case of Kaposi’s sarcoma in a patient with AIDS. Since then, during the pre-HAART era, prevalences ranging from 28% to 73% of heart involvement affecting the pericardium, endocardium, myocardium and vessels were observed in HIV-infected patients—mainly in autopsies. There are several cardiovascular manifestations due to the HIV infection itself, autoimmunity, immunological reaction to other viral infections, chronic inflammation, neoplasias, delayed immunosupression, malnutrition and drug cardiotoxicity.

Multiple therapy has introduced qualitative changes in cardiovascular manifestations. There has been a decrease in heart conditions caused by opportunistic agents, malnutrition and long-term immunosupression. However, there has been an increase in the number of cases of coronary syndromes and peripheral vascular events related both to the increased survival of HIV-infected individuals and to drug toxicity.

Our objective is to discuss the various cardiac manifestations in HIV-infected patients, with a comprehensive literature review emphasizing practical topics related to clinical assessment and our experience treating patients at the Casa da Aids, at the Instituto do Coração, in São Paulo.

PERICARDIAL DISEASES

Pericardial effusion was the most common heart manifestation in the pre-HAART era, with prevalence ranging from 21% to 30% in HIV-positive patients and an annual incidence of 11%. These data indicate that the investigation of pericardial effusion today should include serum HIV detection exams because current studies have detected positive serum when assessing pericardial effusion in 72% of cases in Africa, 33% of cases in Europe and in 7% to 28% of cases in the USA. The presence of pericardial effusion in HIV infection is a marker of the advanced stage of the disease and implies a poorer prognosis, regardless of CD4 cell counts and serum albumin level. Pericardial effusion is associated with shortening survival to an average of six months.
There are many causes of pericardial effusion. In most investigational studies the etiological agent is not found. Cases in which an agent was identified show that the most frequent causes are infections caused by microbacteria followed by bacterium infection and neoplasias. Effusions caused by opportunistic virus (HIV, herpes simplex, adenovirus, coxsackie, cytomegalovirus, Epstein Barr) related to systemic diseases (heart failure, cirrhosis, acute myocarditis, infection, uremia, myocardiitis) and associated with a chronic inflammatory condition (increased permeability) and malnutrition have been also described. Chart I shows the causes of pericardial effusion in HIV-infected patients.

The clinical picture of pericardium involvement is extensive, ranging from total absence of symptoms to the occurrence of shock and cardiopulmonary arrest. Fever, chest pain and coughing may be present. Pericardial involvement includes pericarditis, effusion with or without tamponade, constrictive pericarditis and neoplastic infiltration. Most effusions are mild, without any hemodynamic change, with an annual incidence of 9% of tamponade. Studies assessing pericardial effusion in HIV-infected patients do not show any relationship between the infection status and the severity of the effusion. In 42% of the cases, pericardial effusion is self-limited, with spontaneous resolution, which does not exclude poor prognosis associated with its detection. In the study conducted by Gowda et al, most patients died during hospitalization or soon after, indicating that pericardial effusion is a marker of the advanced stage of the disease.

Diseases of the Endocardium

The frequency of endocarditis in patients with HIV infection is similar to the frequency observed in patients of other risk groups, such as intravenous drug users. HIV infection does not increase the frequency nor the severity of endocarditis. The incidence of endocarditis in HIV-infected patients and toxic intravenous drug users ranges from 6% to 34% and their survival rate is similar to that of HIV-negative patients with endocarditis (85% x 93%). Mortality rate caused by endocarditis is 30% higher in patients in the advanced stage of the infection.

Endocarditis in toxic intravenous drug users usually affects the valves on the right side - the tricuspid in 90% and the pulmonary in 10% of cases. Twenty percent of the patients have simultaneous commitment of the mitral or aortic valve, which results in a poor prognosis. The clinical picture varies: fever, poor general condition, weight loss, sudoresis, clinical manifestations of pulmonary or systemic embolization, and in some cases, association with meningitis and pneumonia. Due to a higher rate of tricuspid valve endocarditis, pulmonary embolizations with subsequent infarctions are frequent, present in up to 56% of cases. Immunological mediated manifestations are also found in HIV- positive patients, such as glomerulonephritis.
hemophilus bacteria such as mean survival time of 101 days in patients with ventricular due to heart failure is 5.86) 4. Lipshultz et al MYOCARDIAL DISEASES nonbacterial thrombotic endocarditis 23,24. In autopsy during the pre-HAART era was marantic endocarditis or endocarditis and therapeutic failure. failure, sepsis, systemic embolization, fungus-caused same criteria for surgical management: unresponsive heart failure, sepsis, systemic embolization, fungus-caused endocarditis and therapeutic failure.

Another type of endocarditis found in patients with AIDS during the pre-HAART era was marantic endocarditis or nonbacterial thrombotic endocarditis23,24. In autopsy samples, it was found in 3% to 5% of patients. It affects the four valves—mainly the mitral and the aortic valves. It is marked by the presence of friable vegetation, rich in platelets over a fibrin network, with little inflammation and high rates of systemic embolization. There are no reports of this type of endocarditis in the post-HAART era.

**MYOCARDIAL DISEASES**

Dilated cardiomyopathy secondary to HIV infection accounts for 3% to 6% of cases of dilated heart conditions4,11. Compared to patients with idiopathic dilated cardiomyopathy, HIV-infected patients have a significantly shorter survival time (the relative risk of death due to heart failure is 5.86) 4. Lipshtultz et al observed a mean survival time of 101 days in patients with ventricular dysfunction and of 472 days in patients with normal heart status in the same stage of the HIV infection27.

Clinical pathological studies from the pre-HAART era show a 30% prevalence of cardiomyopathy in patients with AIDS28. In a five-year prospective study with asymptomatic HIV patients, the incidence of dilated cardiomyopathy was 15.9/1,00029. Echocardiographic studies showed early diastolic dysfunction in up to 15% of patients with HIV infection30,31. As cardiomyopathy advances, diffuse hypokinesia, overall dilation of the chambers and systolic dysfunction are observed32. Reduced ejection fraction and thicker ventricular walls have been associated with increased mortality, which was found in a multicentric study conducted with children infected by their HIV-positive mothers33. Etiopathogenesis of dilated cardiomyopathy associated with HIV is multifactorial. HIV itself, other viral infections, myocarditis, autoimmunity, chronic inflammation, long-term immunosuppression, endothelial dysfunction, arteritis, HIV-related encephalopathy, autonomic dysfunction, nutritional and trace element deficiencies and drug-induced cardiotoxicity are involved.

Experimental studies that examined the infection caused by the simian immunodeficiency virus (SIV) in rhesus monkeys aimed to examine the pathogenesis of the myocardial injury related to retroviral infection. SIV-chronic infection results in reduced ventricular systolic function and extensive coronary arteriopathy suggesting an injury mediated by immune cell response34. Approximately two-thirds of the primates infected that died because of the viral infection had cardiomyopathy. Lymphocytic myocarditis and coronary vasculopathy were found in nine of the fifteen animals in necropsy studies. In some primates, areas of coronary occlusion and reperfusion related to areas of myocardial necrosis were observed, in addition to a case ventricular mural thrombus 25.

HIV infection and the myocardial inflammatory process (myocarditis) related to it are the most studied causes of cardiomyopathy in HIV-infected patients. HIV-1 virions seem to irregularly infect the myocardial cells, without any direct association between the qualitative presence of the virus and myocyte dysfunction29. Necrosis of the myocardial fibers is usually minimal, with associated lymphocytic infiltrates. It is unclear how HIV-1 enters the myocytes since they do not have CD4 receptors25. Possibly, other cells such as the dendritic cells play a role not only as a reservoir, but also as antigen-presenting cells in the context of the major histocompatibility complex and activities of progressive tissue injury mediated by cytokines such as Interleukins 1 and 6 (IL-1 and IL-6) and the tumor necrosis factor alpha(TNF-a)41.

However, there is growing evidence to support autoimmunity as the main mechanism causing cardiomyopathy in HIV-infected patients41,42. Compared to patients with idiopathic dilated cardiomyopathy whose

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Staphylococcus aureus (75%)
Streptococcus viridans (20%)
Staphylococcus epidermidis
Streptococcus pneumoniae
Haemophilus influenzae
The HACEK group
MRSA
Salmonella sp
Mycobacterium avium-intracellulare
Candida sp
Cryptococcus neoformans
Aspergillus fumigatus
Pseudallescheria boydii
inflammatory infiltrates indicate a preponderance of CD4 (+) T cells and B lymphocytes. HIV-infected patients with echocardiographic diagnosis of dilated cardiomyopathy and histopathology compatible with myocarditis present more CD3 (+) and CD8 (+) T cells. The existence of an active immune process within the myocardium was suggested by findings of viral hybridization and increased expression of class I major histocompatibility complex molecules (CPH-I). As for humoral immunity, myocardial-specific anti-alpha-myosin antibodies were found in 15% of HIV-positive patients, compared to a prevalence of 3.5% in control groups. In HIV-infected patients who present left ventricular dysfunction these antibodies are found in up to 43% of cases and can be a marker of ventricular dysfunction with prognostic implications. Another finding that supports the theoretical role played by autoimmunity in cardiomyopathy associated with HIV is the therapeutic response of patients with heart failure to immunoglobulins, which act by inhibiting cardiac antibodies, competing with Fc receptors and reducing the secretion and action of inflammatory cytokines.

As myocardial dysfunction is global and not segmented when there are foci of viral infection in the myocytes, this suggests that circulating factors or cytokines play a role as co-factors in the pathogenesis of cardiomyopathy. Local production of cytokines in the myocardium increases, especially IL-1 and TNF-a. Viral infection as a stimulator of cytokines such as IL-1 and TNF-a is more likely to cause myocarditis and myocardium damage than isolated viral damage. TNF-a has a negative inotropic effect by changing the hemostasis of intracellular calcium and probably by inducing the synthesis of nitric oxide, which also reduces myocardial contractility. Myocardial biopsies of patients with cardiomyopathy related to HIV have shown a higher intensity of markers of TNF-a and inducible nitric oxide synthase when compared to individuals with idiopathic cardiomyopathy. Dysfunction and activation of the vascular endothelium have been described in HIV infection. Circulating markers of endothelial activation such as blood procoagulants and cell adhesion molecules are found less often in these patients. These findings occur because of the secretion of cytokines as a response to the activation of mononuclear cells or to a viral infection in the tunica adventitia or a response to the effects of the viral proteins gp 120 and Tat in the endothelium. Endothelial cells that have been injured and activated can cause tissue damage, inflammation and remodeling, accelerating the development of cardiovascular disease. The same mechanism of endothelial dysfunction, changes in leukocyte adhesion and arteritis can stimulate atherogenesis and eventually ischemia and myocardial injury.

Several studies reveal that HIV-infected patients with encephalopathy have a greater probability of dying from heart failure than patients without encephalopathy. HIV may remain in the reservoir cells in the myocardium and in the cerebral cortex even after antiretroviral treatment. These cells hold HIV on their surfaces for extended periods of time and may chronically release cytokines (TNF-a, IL-6 and endothelin-1), contributing to chronic and progressive tissue damage in both systems, regardless of HAART.

HIV infection can be associated with changes in the autonomous nervous system, especially in the advanced stages of the disease. 5% to 77% of patients suffered changes in cardiovascular autonomic reflexes according to the definition of the complication. This can cause orthostatic hypotension, syncope and cardiopulmonary arrest during invasive procedures. The cause is unclear, although it is known that HIV is neurotropic and that it has been isolated in the peripheral neural tissue. Actually, one of the mechanisms suspected in relation to ventricular dysfunction is reduction of myocardial sensitivity to beta-adrenergic stimulus.

Nutritional deficiencies are commonly observed in HIV infection, especially in more advanced stages of the disease. They make ventricular dysfunction more probable. Malabsorption and diarrhea promote fluid and electrolyte disorders and nutritional deficiencies. Trace element deficiencies have been directly or indirectly related to cardiomyopathy. Selenium deficiency has been shown to exacerbate the virulence of agents that induce myocarditis. Deficiencies of thyroid hormones, vitamin B12, carnitine and growth hormones have been described in infected patients, related to left ventricular dysfunction.

Drug-induced cardiotoxicity in HIV-infected patients has been a highly controversial issue, especially due to the association between zidovudine and dilated cardiomyopathy. There is evidence that zidovudine is related to diffuse destruction of ultrastructures and inhibition of mitochondrial DNA replication, resulting in lactic acidosis that contributes to myocardial dysfunction. However, no direct clinical relationship has been proved connecting exposure to reverse transcriptase inhibitors and induction of ventricular dysfunction. Other cardiotoxic drugs that have been used for a long time to treat this population are doxorubicin (to treat Kaposi’s sarcoma and lymphoma), interferon-alpha, phospharnet, cotrimoxazole, pentamidine and ganciclovir. Toxic agents with a high prevalence of use in this population, such as alcohol and cocaine, are aggressive agents with respect to the myocardium and are believed to aggravate ventricular dysfunction in these patients.

Dilated cardiomyopathy is a late event in HIV infection, usually associated with reduced CD-4 levels. It is related to prognosis because it is associated with high mortality rates. Pathological findings show endocardial fibrosis and mural thrombus, especially at the apex, histological evidence of myocardial hypertrophy and degeneration with...
increased interstitial and endocardial fibrillar collagen. These findings are probably related to evidence of myocarditis. In a prospective study with 952 asymptomatic, HIV-infected patients, echocardiographic diagnosis of dilated cardiopathy was observed in 76 (8%) of patients, with an annual incidence of 15.9/1,000. All patients with echocardiographic confirmation were submitted to myocardial biopsy, and myocarditis was present in 63 (83%) of the patients. Thirty-six individuals (57%) presented positive hybridization signals for HIV. In some cases, coinfection with another virus – coxsackie, cytomegalovirus and Epstein-Barr was observed.

Dilated cardiomyopathy associated with HIV infection is a clinical and echocardiographic finding. Clinically, patients are similar to non-infected individuals and in some cases the echocardiographic examination can detect the infection while the patient is still in the asymptomatic phase, usually with isolated diastolic dysfunction. Recommendation of the echocardiogram as a routine and screening measure in HIV-positive patients is unclear. The benefits of early diagnosis, at the initial stages of the disease, are indisputable; however, the cost-effectiveness of the procedure has not been well established. In general, as shown by studies, dilated cardiomyopathy affects patients during the advanced stage of the HIV infection. Thus the echocardiogram is well indicated for patients in which there is clinical suspicion of HIV infection or when the CD4 count is below 200.

Endomyocardial biopsy is another method to diagnose dilated cardiomyopathy whose objective is to establish the etiology and the prognosis, but its low sensitivity and risks related to the procedure limits its use to highly experienced centers and in the protocols of clinical trials. The Italian group, similar to the Instituto do Coração, recommend endomyocardial biopsy in every systolic dysfunction case associated with HIV infection, which has produced varied findings of viral myocarditis, reactivation of Chagas’ disease, cardiac fungal infections and toxoplasmosis, many times with a satisfactory response to specific therapies.

Management of dilated cardiomyopathy related to HIV is similar to that provided to manage the idiopathic form of the disease. Because of the small number of prospective studies specifically directed to this population, management is based on results obtained in HIV-negative patients, observing some particular characteristics. In spite of the recommendation to use converting enzyme inhibitors and betablockers, there may be adverse effects in some cases in patients with reduced systemic vascular resistance because of dehydration, diarrhea or infection. Patients with myocarditis are more sensitive to digoxin and should be monitored. The use of immunosuppressors is controversial in this population and promising positive results were observed in children with immunoglobulins given intravenously.

PULMONARY HYPERTENSION

Pulmonary hypertension was found in HIV-positive patients. Its prevalence is 1/200 cases, compared with 1/200,000 cases in the general population. Its detection is often associated with pulmonary infections, use of intravenous drugs, transfusion of factor VIII to hemophilic patients, venous thromboembolism, heart failure and the presence of HLA-DR6 and HLA-DR5. It affects approximately 0.5% of hospitalized patients with AIDS. Some studies revealed precapillary muscular pulmonary artery, arteriole medial hypertrophy, fibroelastosis, and eccentric intimal fibrosis without direct viral infection of pulmonary artery cells. These findings suggest release of mediators from infected cells and probably cytokine-mediated injury.
Little is known regarding the pathogenesis of primary pulmonary hypertension, but it seems to be multifactorial. However, in some HIV-positive patients, primary pulmonary hypertension is described without the presence of any predisposing factors. It is suggested that HIV itself causes endothelial injury and release of vasoconstrictive mediators such as endothelin-1, interleukin-6 (IL-6), and the tumor necrosis factor alpha in the pulmonary arteries. HIV is often identified in the alveolar macrophages in histological tests. These macrophages release TNF-α, free radicals and proteolytic enzymes in response to the infection. Lymphokines also seem to contribute to the endothelial proliferation observed in pulmonary hypertension since they promote leukocyte adhesion in the endothelium. Activation of α1-adrenergic receptors and genetic factors (increased frequency of HLA-DR 6 and DR 52) have also been observed in pulmonary hypertension since they promote endothelial proliferation.

The symptoms and prognosis of patients with right ventricular dysfunction due to pulmonary hypertension are related to the severity of the hypertension. The picture can vary from the absence of symptoms to advanced heart failure and cor pulmonale. According to the Swiss HIV Cohort study, HIV-positive patients with pulmonary hypertension have their survival shortened when compared to non-infected patients (1.3 years vs. 2.6 years).

Management with anticoagulant and vasodilating agents should consider possible drug interactions, especially with anticoagulants. There is no data to justify the wide use of vasodilating agents. Epoprostenol is used only in the most severe patients due to its high cost, need for venous infusion and increased risk of infection. To date, the effects of HAART on the incidence and clinical outcome of pulmonary hypertension and its treatment is unknown.

**HIV infection and atherosclerosis**

Morbidity and mortality monitoring of HIV-infected patients naturally exposes them to degenerative-chronic processes such as atherosclerosis that were not manifest in the past given the early mortality of the disease. Furthermore, predisposition to atherosclerosis is also a consequence of cumulative exposure to the virus itself and important metabolic changes secondary to the antiretroviral treatment. Given this, an alarming incidence of cardiovascular and cerebrovascular events would not be surprising. Thus, this topic is still subject for further discussion.

**Metabolic changes**

Although the main focus on the relationship between AIDS and metabolic changes is on the side effects of antiretroviral treatment, studies from the pre-HAART era established that the HIV infection itself causes a more unfavorable lipid profile, mainly hypertriglyceridemia and low HDL-cholesterol levels. Constans et al even observed prognostic implications of these changes: the lower the CD4 lymphocyte count the higher the level of triglycerides and the lower the HDL-cholesterol levels.

The pathophysiology of this association is not clear, although the pathways by which antiretroviral treatment, especially protease inhibitors, enhances this lipid disorder and affects other related to it, such as increased insulin resistance, diabetes mellitus, lipodystrophy and centripetal obesity are better understood.

Carr et al proposed a theory based on the structural homology finding between the catalytic site of HIV protease and important human proteins in lipid metabolism (CRABP-1: cytoplasmic retinoic acid binding protein I and the LRP: LDL receptor related protein) in such a way that protease inhibitors would also inhibit important steps of human metabolism. Eventually, protease inhibitors would determine interruption of retinoic acid metabolization and reduced PPAR-y (peroxisome-proliferator-activated receptor type gamma) activity. PPAR-y plays a key role in the differentiation of adipocytes and apoptosis of these cells, in addition to improving peripheral sensitivity to insulin. The final results of these effects are increased release of lipids in the blood flow and hypertriglyceridemia.

LRP inhibition, in turn, results in lower uptake of triglycerides by the liver and also less cleavage of triglycerides to fatty acids and glycerol that should occur because of the activity of the endothelial LRP-LPL (lipoproteic lipase) complex. Hypertriglyceridemia would be responsible for increased insulin resistance, which in susceptible individuals can promote the development of type II diabetes mellitus. Inhibition of the of cytochrome P450 3A enzyme, a step shared with protease inhibitors and retinoic acid metabolism, would also contribute to this metabolic dyscrasia.

**Epidemiology of cardiovascular events and risk factors for atherosclerosis**

Initially, the association between HIV infection and cardiovascular disease was inferred based on case reports of young HIV-positive patients that suffered an acute myocardial infarction, and mainly pathological findings in necropsy studies, with evidence of obstructive disease in the coronary arteries of patients without the usual risk factors for atherosclerosis. Immuno-histochemical studies provided objective documentation of the presence of HIV in coronary arteries impaired by inflammation and atherosclerotic obstruction. A direct association between HIV infection and the presence of coronary arteritis has been suggested, without ruling out classical atherosclerotic pathophysiology regardless of the low prevalence of risk factors in the patients studied.
With the increasing emergence and use of aggressive antiretroviral treatment and its indisputable impact on lipid and glucose metabolism, studies with growing number of cases seek to correlate HIV infection with cardiovascular disease, and cardiovascular disease with antiretroviral treatment and cardiovascular risk factors. In 2000, Rickerts et al retrospectively studied the incidence of infarction in 4,993 patients with HIV. Although the absolute number was small, a significant increase in the infarction rate after exposure to HAART was observed (table I). After two years, Holmberg et al confirmed the same findings among a population of 5,672 HIV-positive patients between 1993 and 2002, showing evidence of a significant increase of the incidence of infarction after 1996, the year HAART was introduced. However, the authors already emphasized the participation of risk factors such as smoking and dyslipidemia.

It was also in 2002 that Klein et al retrospectively examined 4,159 HIV-positive men. During 5.5 years of observation 72 cardiovascular events were described, 47 of them of myocardial infarction. The authors did not observe the impact of exposure to antiretroviral therapy in the incidence of cardiovascular events, but their incidence in HIV-infected patients was greater than that observed among the 39,877 non-infected men in the control group (4.86 x 3.69 per 1,000 persons-year; p = 0.003). As for risk factors, a higher prevalence of dyslipidemia and smoking was observed among HIV-positive patients, but with a lower prevalence of diabetes and hypertension compared to the control group.

David et al studied the risk profile of sixteen HIV-infected patients (1.7% of the total 951 infected patients) with confirmed diagnosis of coronary artery disease. Their findings showed that 81% of them were smokers, 63% had hypertension, 50% had dyslipidemia and 31% had family history of cardiovascular diseases. The authors compared the characteristics of these patients with the characteristics of 32 HIV-positive individuals without evidence of coronary artery disease (CAD). They showed that the prevalence of risk factors was significantly higher in those with evidence of CAD with no association between exposure to protease inhibitors and increased risk.

The largest number of cases was published in 2003. Bozzette et al retrospectively studied 36,766 HIV-infected patients undergoing treatment between 1993 and 2001 for general mortality, specific mortality due to cardiovascular and cerebrovascular events and their hospitalization rates. The only expressive changes observed during this period were an important reduction in general mortality rate and a significant increase in antiretroviral therapy, especially after 1995 and 1996. There was no increase in the incidence of cardiovascular or cerebrovascular events concomitant to improved survival rates. Although the authors did not specify the profile of classical risk factors for atherosclerosis in this population, they relate that 23.9% of patients had already been previously treated for diabetes, hypertension or smoking, and 6.6% of them already had been diagnosed for vascular disease. The authors also observed the interesting growth in the use of lipid-lowering drugs from 140 patients making use of some medication available to control dyslipidemia in 1995 to 2,417 patients in 2001.

Currier et al conducted a study, also retrospective, including 28,513 patients with HIV and 3,054,696 non-infected patients, with the objective of determining the specific incidence of coronary artery disease by age groups of HIV-positive men and women compared to non-infected individuals. Mean observation time was 2.5 years for HIV-positive patients and 2.64 years for HIV-negative patients. HIV-infected patients had 1,360 cardiovascular events, whereas the control group had 234,521. When these events were studied according to gender and age group, HIV infection proved to be an important risk marker for men younger than 34 and for women younger than 44. This association was not very strong in older age groups for both genders, but there was a curious finding in some of these lower risk brackets among HIV-positive patients: a relative risk of CAD in men between 55 and 64 years (infected vs. non-infected) of 0.60 (0.51 – 0.71; p < 0.0001). The use of antiretroviral therapy was associated with increased risk of coronary disease (relative risk of 2.06; p < 0.001) for patients younger than 33. The authors observed a profile with higher risk among HIV-infected patients with a progressive increase in prevalence of cardiovascular risk factors in older age groups.

In November, 2003 data from the DAD (Data Collection on Adverse Events of Anti-HIV Drugs) were published with evidence of positive correlation between the duration of exposure to antiretroviral therapy and the risk of myocardial infarction. A prospective study examined 23,468 patients with HIV, with mean follow-up of less than 2 years and 126 recorded cases of myocardial infarction. Only 55% of the 126 cases met the definitive criteria for this condition according to the requirements of the MONICA project. The absolute rate of events was low, corresponding to 3.5 events per thousand persons-year. However, each year of exposure to combined antiretroviral therapy determined a 26% increase in the relative risk of myocardial infarction during the first four to six years of exposure. In the same cohort of patients, the prevalence of traditional risk factors for coronary disease was high: smoking: 56.2%; dyslipidemia: 45.9%; hypertension: 7.2%; diabetes: 2.8%. Old age, a history of smoking, male gender and early diagnosis of cardiovascular disease are independent predictive factors of myocardial infarction.

Varriale et al conducted a 3-year prospective study with 690 hospitalized HIV-infected patients. There were 29 cases of myocardial infarction during the study, with
an incidence of 1/100 patients-year of observation, similar to what is found in the general North-American population. The cardiovascular risk profile of these patients showed that 55% smoked, 21% had dyslipidemia, 14% had hypertension, 14% had family history of early CAD onset and 21% did not present any risk factor. The mean age of infarcted patients was 46 years (±10 y.), 66% received a protease inhibitor, and although 79% of them had at least a risk factor for atherosclerosis, the association between them was low in most cases.

Matetzky et al conducted a prospective study with 24 patients with AIDS hospitalized with a diagnosis of myocardial infarction between 1998 and 2000. Mean follow-up was fifteen months. Comparing the HIV-positive patients to 48 infarcted HIV-negative patients in the control-group, the authors did not observe significant differences between the prevalences of diabetes, hypertension, smoking, dyslipidemia or family history of CAD, which suggested the direct impact of retroviral infection in the disease. However, the non-inferiority of the risk profile reinforces the importance of traditional factors in the etiopathogenicity of coronary disease in HIV-infected patients. In this group, 58% of the patients smoked; 58% had dyslipidemia; 50% had a family history of early CAD; 29% had hypertension and 12% had diabetes. Furthermore, the authors conducted a comparative study regarding morbidity and mortality in the short and in the medium terms, showing that HIV-positive patients had a benign nosocomial outcome, but that morbidity was higher after discharge: a larger rate of reinfarction (20% vs. 4%; p = 0.07) and a higher recurrence of symptoms (45% vs.11%; p = 0.007), but without an increase in mortality rate (0 vs. 4%; p > 0.99). No difference was observed in the angiographic characteristics regarding damage to the coronary arteries.

Finally, Hsue et al retrospectively assessed the risk factors and the clinical outcome of 68 HIV-infected patients hospitalized between 1993 and 2003 due to unstable angina or myocardial infarction. They compared their characteristics to a control group made up of 68 HIV-negative individuals with a diagnosis of acute CAD.

Prevalence of smoking (46% vs. 28%; p = 0.003) and low HDL-cholesterol (35 ± 12 vs. 41 ± 9; p = 0.005) was higher in patients with AIDS and they were younger as well (50 ± 8 vs. 61 ± 11 years; p < 0.001). However, prevalence of diabetes and dyslipidemia was higher in the control-group. The general risk score was assessed by the TIMI score. It was higher in the control-group, whose angiograms showed a larger area of coronary artery damage. However, the rate of restenosis with clinical manifestations was higher in HIV-infected patients than in control subjects that had been submitted to angioplasty with a stent (50% vs. 18%; p = 0.078). Overall, 29 angioplasties were performed in HIV-positive patients, with the use of stents in 22 of these procedures. In the control group, eleven angioplasties with stents were performed and ten used only a balloon-tip catheter.

A recent study sought to objectively establish the risk relationship between cardiovascular disease and the use of antiretroviral therapy. The sample consisted of 721 subjects divided into three paired groups based on age and gender; 219 patients were HIV-positive and used HAART, 64 HIV-positive patients who did not receive HAART and 438 control subjects (HIV-negative). Cardiovascular risk was estimated using the Framingham risk score. This study showed that the prevalence of coronary risk estimated at greater than 20% in ten years was twice as high in HAART-treated patients than in the control-group (11.9% vs. 5.3%; p = 0.004). HIV-positive patients that had not received HAART treatment had an estimated risk greater than 20% in ten years of 6.3%, without a significant difference when compared to the HIV-positive patients receiving HAART (p=0.25) or to the control group (p = 0.76). Among the risk factors observed, the prevalence of smoking was higher in HIV-positive patients than in the control group (54.5% vs. 30.1%), along with higher levels of total cholesterol and lower levels of HDL-cholesterol.

In general, primary and secondary prevention of cardiovascular disease initially considers only the exposure to risk factors, but the need of a more precise definition

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<td>Rickerts/2000</td>
<td>Retrospective</td>
<td>4,993 HIV+</td>
<td>1983-1998</td>
<td>Increased incidence of MI after HAART (0.86/1,000 vs. 3.41/1,000 persons-year)</td>
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<td>Holmberg/2002</td>
<td>Retrospective</td>
<td>5,672 HIV+</td>
<td>1993-2002</td>
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<td>Klein/2002</td>
<td>Retrospective</td>
<td>4,159 HIV+39,877 HIV-</td>
<td>1996-2001</td>
<td>Increased hospitalization rate because of CAD (4.86 vs. 3.69/1,000 persons-year; p=0.003) Non-related to HAART</td>
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<td>Bozette/2003</td>
<td>Retrospective</td>
<td>36,766 HIV+</td>
<td>1993-2001</td>
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<td>Currie/2003</td>
<td>Retrospective</td>
<td>28,513 HIV+3,054,696 HIV-</td>
<td>1994-2000</td>
<td>Increased risk for CAD Men &lt; 34 years and women &lt; 44 years</td>
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<td>DAD/2003</td>
<td>Prospective/Observational</td>
<td>23,468 HIV+</td>
<td>1999-2002</td>
<td>Low incidence of MI (3.5/1,000 patients-year) Related to the length of use of HAART therapy</td>
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of populations at risk led to the implementation of tracking exams to identify atherosclerosis before its clinical manifestations known as subclinical atherosclerosis which has been proven to be related to a higher incidence of future events. Among the exams performed, an ultrasound of the carotid and femoral arteries to detect thickening of the intima-media complex in these arteries, endothelial function tests and, more recently, detection of calcium in the coronaries should be highlighted. In the specific context of HIV infection, an increased prevalence of endothelial function, mainly among patients that receive protease inhibitors, as well as an increased prevalence of the thickening of the intima/media layers of the carotids have already been shown\(^7\). Recently, in addition to increased thickening of the media/intima layers of the carotids of the patient when compared to the control group, faster progression of this thickening was observed within one year\(^7\).

### Dyslipidemia management in patients HIV-positive

The Framingham study showed that control of dyslipidemia reduces the risk of cardiovascular diseases both as primary and secondary prevention. There are no conclusive epidemiological studies on this issue specifically among HIV-positive individuals. However, increased survival of these patients is related to the adoption of measures to reduce real cardiovascular risk. The Brazilian Society of Cardiology (SBC) was the first to include a specific topic regarding management of HIV-positive patients in the Brazilian Guidelines for Dyslipidemias and Atherosclerosis Prevention in 2001. The SBC recommends measuring the lipid profile at the beginning of follow-up: if results are normal and if protease inhibitors are not given the test should be repeated one month later and then every three months. Treatment of dyslipidemic HIV-infected patients should follow the guidelines established for the general population after overall assessment of other risk factors. Drug-based treatment should be introduced with caution and only if dyslipidemia persists after non-pharmacological management\(^7\).

However, the prescription of lipid-lowering agents can add complications to complex antiretroviral combinations\(^7\). Some options for the pharmacological management of dyslipidemia have been suggested, such as changing the regimen of antiretroviral treatment by replacing the current protease inhibitor with a different one or with a non-nucleoside reverse transcriptase inhibitor. But these theoretically favorable changes have not produced considerable benefits in clinical trials. Furthermore, there is the possibility that they may change the characteristics of the chronic viral infectious process such as resistance and serotyping\(^7\).

The drugs most commonly used to treat HIV-positive patients with dyslipidemia are the same used to treat the general population: statins, fibrates and niacin. Recommendations from AIDS study groups use the NCEP Panel III to manage dyslipidemia\(^7\). Guidelines are based on the patient’s overall risk analysis and on the LDL-cholesterol fasting levels.

**Statins**: Except for pravastatin and rosuvastatin, most statins are metabolized by the cytochrome P450 3A4 isoenzyme that is inhibited by current protease inhibitors. Therefore, administration of statins with protease inhibitors can increase blood statin to dangerous levels, possibly causing musculoskeletal toxicity and other adverse effects\(^7\). Statins must be given initially in low doses with frequent monitoring due to potential interactions. In clinical practice, some authors used atorvastatin safely in this population, a fact confirmed in our experience\(^7\). Consequently, in theory, the safest statins for use with protease inhibitors are pravastatin, atorvastatin and rosuvastatin. They are the drugs of choice to treat subjects with hypercholesterolemia, in addition to being effective for treating hypertriglyceridemia, especially atorvastatin and rosuvastatin.

**Fibrates**: Fibrates are the first choice to manage combined dyslipidemia in HIV-infected patients, the most commonly observed change in this population\(^7\). The long-term effects of the combination of fibrates with protease inhibitors are unknown. Gemfibrozil is well tolerated by HIV-positive patients and its interaction profile shows that it can be used. A study showed a 30% reduction in total cholesterol and a 60% reduction in tryglyceride levels when atorvastatin and gemfibrozil were given to patients with HIV\(^7\). Recommendations favor the use of gemfibrozil or fenofibrate in this population\(^7\).

**Niacin**: Niacin reduces LDL-cholesterol and triglycerides and increases HDL-cholesterol. However, side effects such as flushing, itching, high glucose level and especially liver toxicity do not recommend it as first choice agent to treat HIV-positive subjects.

**Other agents**: Cholestyramine and colestipol are not recommended because they interfere with the bioavailability of protease inhibitors and because they increase triglyceride levels\(^7\). Glitazones, PPAR-\(\gamma\) receptor activators, did not prove to be useful for managing dyslipidemia in these patients. Metformin proved to be effective in reducing tryglcerides, but may increase the risk of lactic acidosis, especially in the presence of continuous use of reverse transcriptase inhibitors\(^7\). Omega-3 fatty acids are useful for treating hypertriglycerideremia in HIV-positive patients, but they have not been assessed in patients that had been given protease inhibitors\(^7\). Another frontier to be explored is the pursuit of protease inhibitors with a lower atherogenic profile and fewer interactions with lipid lowering drugs. Atazanavir a powerful and effective protease inhibitor has been recently approved. It is been suggested that it has a lower incidence of metabolic side effects in patients treated for 108 weeks\(^7\).
In patients that switched from nelfinavir to atazanavir, lipid levels returned to those found before treatment with nelfinavir. However, a careful analysis reveals that these studies have similar methodological deficiencies, including inadequate sample size, absence of fasting or alcohol abstinence before collecting blood for lipid profile analysis and non-correction of potential misleading factors such as diabetes or diet. In our opinion, no preferred antiretroviral regimen with the objective of lower cardiovascular risk has been satisfactorily defined taking into account the major importance of other risk factors related to dyslipidemia in this specific population combined with the limitations of the studies available.

To conclude, given the characteristics of the cardiovascular risk profile of this population, non-pharmacological interventions seem to have the most important effect in preventive treatment of HIV-infected patients. These patients should be counseled to control the risk factors related to lifestyle issues such as stop smoking, follow a diet, be active, and control high blood pressure and diabetes.

**AIDS IN CHILDREN**

**Epidemiology**

In spite of all efforts to prevent maternal-fetal transmission of the HIV virus in Brazil, it is still common. In addition, advances in controlling the disease and its complications have resulted in progressive reduction of its lethality during childhood. This results in a significant increase of infected children that need to control possible long-term complications (graphic 1).

International data have shown a significant decline in child mortality due to AIDS and an overall increase in survival of these children. But although there is a reduction of infection-related deaths, there is a secular trend of discreet, but progressive, increase of proportional mortality due to cardiac causes in children affected by AIDS.

When the impact of cardiovascular complications on mortality rate in children with AIDS is studied, they are seen to indicate a poor prognosis. Studies conducted with children that died showed that cardiomegaly, pericardial effusions and systolic or diastolic ventricular dysfunctions were frequently present. However, clinical manifestations of congestive heart failure, increased heart rate or systemic arterial hypertension seem to be independent predictive factors of mortality.

Cardiovascular complications of AIDS in children are highly common. These complications have been shown to affect 25% of ten-year old children and there is direct relationship between the prevalence of these complications and the length of the disease.

Clinical signs in children with heart complications due to AIDS are not always present, but there are some correlations between clinical picture and heart conditions. Rapidly progressive forms of AIDS in children are usually associated with increased heart and respiratory rates and fractional shortening of the left ventricle. There is evidence of a negative association between nutritional status and left ventricular mass, suggesting increased sympathetic tone in the more severely affected patients. The presence of encephalopathy, in turn, seems to be associated with progressive fractional shortening of the left ventricle.

Pulmonary hypertension also seems to be a frequent complication in the chronic situation of children with AIDS. It seems to be related to recurrent bronchopulmonary infection and the hystopathological injury most commonly found is plexogenic pulmonary arteriopathy.

**Graphic 1 - Number of new AIDS cases and deaths provoked by it in Brazilian children and adolescents, from 1981 to 2003. Source: Datasus**
There is a negative relation between CD4+ T lymphocyte levels and systolic function of the left ventricle in the initial stages of the disease. As it advances, this association becomes weaker33. HIV-positive patients with normal levels of serum IgG or undergoing replacement treatment usually have normal ventricular function and structure, suggesting immunological mediation in left ventricle remodeling29. When the presence and level of dilation of the left ventricle are studied, there is a positive association between the viral and negative load with CD4+ T lymphocytes34.

In addition to direct injury of the myocardium caused by HIV, immunosuppression can result it a higher risk of myocarditis caused by other infectious agents. The genome of several viruses in the myocardium of children with advanced stage of AIDS was found. These children usually had dilated cardiomyopathy and congestive heart failure95.

There is still no consensus as to whether or not there is cardiac protection when new antiretroviral agents are used to treat children with AIDS82,96-98. However, signs of mitochondrial injury in myocytes associated with the use of these agents were found, regardless of the direct action of the infection99.

**AIDS in children, vascular injury and atherogenesis**

Some studies in children have shown a positive relation between HIV infection and vascular injury. Laboratory evidence shows an increase in von Willebrand and tissue plasminogen activator factors, two markers of endothelial dysfunction. It seems that their levels are directly related to the viral load, cytokines and advanced stage of the disease100. The pathophysiological mechanism has not been fully explained, but it seems to be mediated by the synergism between HIV-1 Tat protein (released by infected cells) and TNF-α101. The dilation of the aortic root observed in HIV-infected children may also represent a manifestation of vascular lesion, perhaps caused by lymphoproliferative inflammation due to the virus94.

There is increasing concern with respect to diagnosis of endothelial dysfunction in childhood or adolescence because this is the first sign of the progression of atherosclerosis. Bonnet, studying a series of cases of 49 HIV-positive children, found significantly higher changes of artery distensibility in infected children than in the control group. This was not seen when differences related to the thickness of the intima and media layers of the carotid were studied102.

The effects of antiretroviral agents and the progress of atherosclerosis have been extensively studied. This is important for infected children and adolescents who have been theoretically exposed to these effects for a longer period of time. However, if on the one hand the blood-lipid increasing effect of these agents are described as occurring at any age, on the other hand there is evidence that they can reduce the serum expression of vascular activation markers such as the soluble vascular cell adhesion molecule (sVCAM1), von Willebrand factor and the D-dimer104.

**The Experience at InCor**

In a pioneer study, we examined the changes in the lipid profile of thirty HIV-positive patients before and after providing protease inhibitors. Patients were monitored at the Outpatient unit Casa da Aids-SP and by the team of the Interdisciplinary Medical Unit at InCor. A mean increase of 31% was found in the total circulating cholesterol level (p < 0.0006) and of 146% in the triglyceride level (p < 0.0001). In the same study, thirteen patients with persistent hypertriglyceridemia after dietary therapy received fenofibrate. A 6.6% reduction in total cholesterol level was observed (p = 0.07), as well as a significant reduction of 45.7% in the triglyceride level (p = 0.0002), with no adverse effects104. More recently, we analyzed the role played by bezafibrate in treating dyslipidemia related to the use of antiretroviral therapy. We evaluated the behavior of the lipid profile before and after treatment with bezafibrate in 84 patients whose high triglyceride levels persisted after dietary therapy. A significant decrease in blood triglyceride, total cholesterol and fasting glucose levels was observed with good tolerability (graphic II).

**Conclusions and perspectives**

Throughout its twenty-year history, the human immunodeficiency virus infection epidemic has provided multiple learning lessons for science. These lessons became necessary to understand this disease and others. The difficult initial search for its etiological agent was soon replaced by perspectives related to its treatment and reduction of morbidity and mortality rates, which were attained. However, during this period, with widespread use of antiretroviral agents in powerful combinations, we were able to learn the natural history of HIV infection, the different aspects of the disease in the 1980’s and the beginning of the 1990’s. Due to virological control and better preservation of the immune system, opportunistic infections were replaced by clinical manifestations of the disease caused by the virus itself, thus allowing us to detect the autoimmune, inflammatory and cardiovascular diseases related to it. In this context, the adverse effects of antiretroviral agents emerged. They have contributed to an expressive morbidity, especially from the metabolic point of view.

Since patients live longer, the cardiovascular system has increased in importance and is no longer a mere observer of the patient succumbing to opportunistic infections. Furthermore, there is a series of cardiovascular risks and metabolic complications that affect them. The
The heart is affected in different ways by the disease. Involvement of the pericardium, endocardium and myocardium is recognized, ranging from asymptomatic disease to death. Studies show an increased mortality rate for patients with cardiovascular impairment, which triggers the need for intervention. Some aspects attract our attention. First, the high prevalence of smoking and the inadequate lifestyle and diet followed by these patients, which contribute to increased cardiovascular risk. The pleiotropic effect of the virus should be emphasized, from myocardial infection to metabolic disorders resulting from its presence in the body. No less important is the contribution of the adverse effects of antiretroviral agents, which negatively affect patients' metabolism, in addition to promoting significant drug interactions whenever other agents are used.

The assessment of patients with HIV with respect to cardiovascular disease demands a high level of clinical suspicion since the clinical picture is very frequently frustrating or confused with the other most commonly found diseases. Knowledge of cardiovascular manifestations in HIV infection leads to the need to implement effective measures in order to reduce the occurrence of cardiovascular diseases in this population, which can be attained by strict control of risk factors, early diagnosis of cardiopathy, adequate therapy, and, finally, the constant pursuit of antiretroviral treatment that offers less adverse effects without affecting efficacy.

The cardiologist, together with the infectious disease specialist, should contribute to reducing cardiovascular risks in HIV-positive patients, giving overall consideration to the various risk factors and strengthening recommendations regarding diet and lifestyle and, in special situations, cautiously provide combined pharmacological agents.

Graphic 2 - Behavior of lipid profile and fasting glucose levels in HIV-positive patients monitored at InCor before and after treatment with bezafibrate (BZF)

<table>
<thead>
<tr>
<th></th>
<th>Pre-BZF</th>
<th>Post-BZF</th>
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</thead>
<tbody>
<tr>
<td>Triglycerides</td>
<td>640.48</td>
<td>372.31</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>252.96</td>
<td>227.78</td>
</tr>
<tr>
<td>Fasting glycemia</td>
<td>106.6</td>
<td>97.48</td>
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