

Review Article

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Human immunodeficiency virus & cardiovascular risk

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Highly active antiretroviral therapy (HAART) significantly changed the prevalence of the cardiovascular manifestations of human immunodeficiency virus (HIV)/AIDS. In developed countries, a 30 per cent reduction in the prevalence of cardiomyopathy and pericardial effusion was observed, possibly related to a reduction of opportunistic infections and myocarditis. In developing countries, however, where the availability of HAART is limited, and the pathogenic impact of nutritional factors is significant, a 32 per cent increase was seen in the prevalence of cardiomyopathy and related high mortality rate from congestive heart failure. Also, some HAART regimens in developed countries, especially those including protease inhibitors, may cause, in a high proportion of HIV-infected patients, a lipodystrophy syndrome that is associated with an increased risk of cardiovascular events related to a process of accelerated atherosclerosis. Careful cardiac screening is warranted for patients who are being evaluated for, or who are receiving HAART regimens, particularly for those with known underlying cardiovascular risk factors, according to the most recent clinical guidelines.

Key words Acquired immunodeficiency syndrome - cardiovascular disease - highly active antiretroviral therapy - human immunodeficiency virus - lipodystrophy syndrome

Introduction

The introduction of highly active antiretroviral therapy (HAART) has significantly improved the clinical evolution of human immunodeficiency virus (HIV)/AIDS disease, with an increased survival of infected patients. However, the introduction of HAART has generated contrasting aspects in the clinical manifestation of cardiovascular complications. In developed countries, a reduction has been observed in the prevalence of HIV-associated cardiomyopathy, possibly related to the reduction in the incidence of opportunistic infections and myocarditis. On the other

hand, in developing countries, where HAART is not widely available, an increase has been noted in the prevalence of cardiomyopathy and pericardial effusion, with a related high mortality rate for congestive heart failure¹. In the context of these new clinical findings, it has been observed in developed countries that some HAART regimens, especially those including protease inhibitors, may cause a iatrogenic metabolic syndrome (HIV-associated lipodystrophy syndrome) that is associated with an increased risk for cardiovascular events (myocardial infarction and stroke) because of a process of accelerated atherosclerosis.

HIV-associated cardiology issues: pre-HAART vs post-HAART period

Cardiomyopathy and pericardial effusion: HIV/AIDS is recognized as an important cause of dilated cardiomyopathy, with an estimated annual incidence of 15.9/1,000 before the introduction of HAART¹. This incidence is mainly related to that of myocarditis, which is still the best-studied cause of dilated cardiomyopathy in HIV/AIDS. Myocarditis has been documented at autopsy in 40-52 per cent of patients who died of AIDS before the introduction of HAART². Another important cause of cardiomyopathy in HIV/AIDS is drug cardiotoxicity. Zidovudine is associated with diffuse destruction of cardiac mitochondrial ultrastructure and inhibition of mitochondrial DNA replication that may contribute to myocardial cell dysfunction³. Doxorubicin (adriamycin), which is used to treat AIDS-associated Kaposi's sarcoma and non-Hodgkin's lymphoma, has a dose-related effect on dilated cardiomyopathy⁴, as does foscarnet sodium when used to treat cytomegalovirus oesophagitis⁵.

The introduction of HAART regimens, by preventing opportunistic infections and reducing the incidence of myocarditis, has reduced the prevalence of HIV-associated cardiomyopathy by about 30 per cent in developed countries⁶. However, the median prevalence of HIV-associated cardiomyopathy is increasing in developing countries (about 32%), where the availability of HAART is scanty and greater is the pathogenetic impact of nutritional factors⁷. Nutritional deficiencies, in fact, are common in HIV-infected subjects living in developing countries and may contribute to ventricular dysfunction independently of HAART⁷. Selenium, as a component of glutathione peroxidase, is involved in the antioxidant response in cells and tissues and is associated with congestive cardiomyopathy and skeletal-muscle disorders. Low levels of selenium have been described in African HIV-infected patients with cardiomyopathy and recognized as an independent factor associated with cardiomyopathy in multivariate analysis⁷. The selenium depletion in these patients may be responsible for the cardiotoxic effects of coxsackievirus B3 and for the ability of these viruses to enhance the toxic effects of zidovudine on skeletal and myocardial muscle⁸. HIV infection may also be associated with altered levels of vitamin B12, carnitine, growth hormone, and thyroid hormone, all of which have been associated with left ventricular dysfunction⁹. A trend similar

to that observed for cardiomyopathy has also been observed for pericardial effusion, the prevalence of which is reduced by 30-35 per cent after the introduction of HAART in developed countries, whereas in the developing countries, the prevalence of pericardial effusion is increased by 35-40 per cent, mostly related to *Mycobacterium* infections^{10,11}.

Endocarditis: The prevalence of infective endocarditis did not vary in HIV-infected patients who use intravenous drugs after the introduction of HAART even in the developed countries, being similar to that observed in HIV-uninfected intravenous drug addicts¹. Among intravenous drug addicts, the tricuspid valve is most frequently affected and the most frequent agents are *Staphylococcus aureus* (>75% of cases), *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Candida albicans*, *Aspergillus fumigatus* and *Cryptococcus neoformans*². A virulent bacteria, as the HACEK group (*Haemophilus* species, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens* and *Kingella kingae*), which are often part of the endogenous flora of the mouth, can cause endocarditis in HIV-infected patients¹². A prevalence of 3-5 per cent of nonbacterial thrombotic endocarditis, also known as marantic endocarditis was seen in AIDS patients, mostly with HIV-wasting syndrome, before the introduction of HAART². Marantic endocarditis is now more frequently observed in developing countries with a high incidence (about 10-15%) and mortality for systemic embolization^{10,11}.

Pulmonary hypertension: The incidence of HIV-associated pulmonary hypertension is increased in HIV-infected patients after the introduction of HAART. It has been estimated in 1/200, much higher than 1/200,000 found in the general population¹³. A key pathogenetic role in this condition is played by pulmonary dendritic cells which are not sensitive to HAART and may hold HIV-1 on their surfaces for extended time periods. The infection of these cells by HIV-1 causes a chronic release of cytotoxic cytokines (e.g., endothelin-1, interleukin-6, interleukin-1 beta and TNF-alpha) contributing to vascular plexogenic lesions and progressive tissue damage and congestive heart failure, independently of opportunistic infections, stage of HIV disease and HAART regimens¹³. Endothelin-1 receptor antagonists, such as bosentan, may be useful, even in combination with HAART in the early stages of the disease^{14,15}. The use of phosphodiesterase-5 inhibitors (e.g., sildenafil), although promising, is still debated because of their interaction with protease inhibitors.

AIDS-associated neoplasms: The introduction of HAART reduced significantly the prevalence of cardiac involvement in AIDS-associated neoplasms. The prevalence of cardiac Kaposi's sarcoma in AIDS patients ranged from 12 to 28 per cent in retrospective autopsy studies performed in the pre-HAART era, with a lower prevalence for non-Hodgkin lymphoma². The introduction of HAART led to a reduction by about 50 per cent in the overall incidence of cardiac involvement by Kaposi's sarcoma and non-Hodgkin lymphomas. The fall may be attributable to the improved immunologic state of the patients and the prevention of opportunistic infections (human herpes virus-8 and Epstein-Barr virus) known to play an aetiological role in these neoplasms. On the contrary, an increased prevalence of cardiac involvement of AIDS-associated tumours has been observed in developing countries in relation to the scanty availability of HAART¹⁰.

Vasculitis: A wide range of inflammatory vascular diseases including polyarteritis nodosa, Henoch-Schonlein purpura, and drug-induced hypersensitivity vasculitis may develop in HIV-infected individuals. Kawasaki-like syndrome^{16,17} and Takayasu's arteritis¹⁸ have also been described. Some HIV-infected patients have a clinical presentation resembling systemic lupus erythematosus with arthralgias, myalgias, and autoimmune phenomena with a low titre positive antinuclear antibody, coagulopathy with lupus anticoagulant, haemolytic anaemia, and thrombocytopenic purpura¹⁹. Drug-induced hypersensitivity vasculitis is common in HIV-infected patients receiving HAART¹⁹. The vasculitis associated with drug reactions typically involves small vessels and has a lymphocytic or leukocytoclastic histopathology. Medical practitioners need to be especially aware of abacavir hypersensitivity reactions because of the potential for fatal outcomes. Hypersensitivity reactions of this type should always be considered as a possible aetiology for a vasculitic syndrome in an HIV-infected patient¹⁹.

Viral infection and coronary artery disease: The association between viral infection (cytomegalovirus or HIV-1 itself) and coronary artery lesions is not clear. HIV-1 sequences have been detected by *in situ* hybridization in the coronary vessels of an HIV-infected patient who died from acute myocardial infarction²⁰. Potential mechanisms through which HIV-1 may damage coronary arteries include activation of cytokines and cell-adhesion molecules and alteration of major-histocompatibility-complex (MHC) class I

molecules on the surface of smooth-muscle cells²⁰. It is possible also that HIV-1-associated protein gp 120 may induce smooth-muscle cell apoptosis through a mitochondrion-controlled pathway by activation of inflammatory cytokines²¹.

HIV-associated lipodystrophy syndrome and cardiovascular risk

HIV-associated lipodystrophy or lipoatrophy, first described in 1998²², after the introduction of HAART in 1996, is characterized by the presence of a dorso-cervical fat pad (also known as *buffalo hump*), increased abdominal girth and breast size, lipoatrophy of subcutaneous fat of the face, buttocks and limbs, and prominence of veins on the limbs. The overall prevalence of at least one physical abnormality is thought to be about 50 per cent in otherwise healthy HIV-infected patients receiving HAART, although reported rates range from 18 to 83 per cent^{23,24}. Among HIV-infected patients with lipodystrophy, increased serum total and low density lipoprotein cholesterol and triglyceride levels have been observed in about 70 per cent, whereas insulin resistance (elevated C-peptide and insulin) and type 2 diabetes mellitus have been observed in 8 to 10 per cent^{23,24}. The increased risk for cardiovascular events associated with lipodystrophy syndrome may be related both to a specific action of antiretroviral drugs, especially protease inhibitors, and to individual risk factors (*e.g.* smoking habit, and inherited metabolic disease).

Coagulation disorders: HIV-infected patients receiving HAART, especially those with fat redistribution and insulin resistance, might develop coagulation abnormalities, including increased levels of fibrinogen, D-dimer, plasminogen activator inhibitor-1, and tissue-type plasminogen activator antigen, or deficiency of protein S²⁵. For instance, protein S deficiency has been reported in up to 73 per cent of HIV-infected men²⁵. These abnormalities have been associated with thromboses involving veins and arteries and seem to be related to HAART regimens that include protease inhibitors^{26,27}. Thrombocytosis has been reported in 9 per cent of patients receiving HAART, with cardiovascular complications in up to 25 per cent of cases²⁸.

Systemic arterial hypertension and renal disease: The prevalence of systemic arterial hypertension in HIV infected individuals had been estimated to be about 20-25 per cent before the introduction of HAART²⁹. Arterial hypertension, even in agreement with the Adult

Treatment Panel-III guidelines³⁰, is currently considered part of HIV-associated lipodystrophy syndrome³¹. It appears to be related to protease inhibitors-induced lipodystrophy³² and metabolic disorders, especially to elevated fasting triglyceride and insulin resistance^{31,33}. HIV-associated endothelial dysfunction and injury, autoimmune reaction to viral infection (vasculitis), and renal disease have been also hypothesized in the aetiopathogenesis of HIV-associated hypertension. HIV-associated renal impairment can present as acute or chronic kidney disease³⁴. It can be caused directly or indirectly by HIV-1 and/or by drug-related effects that are directly nephrotoxic or lead to changes in renal function by inducing metabolic vasculopathy and renal damage. Antiretroviral agents such as indinavir and tenofovir have been found to be associated with nephrotoxic effects that were reversible in most cases³⁴.

Peripheral vascular disease: The risk for peripheral vascular disease in HIV-infected patients receiving HAART has been evaluated by surrogate markers of atherosclerosis, such as the measurement of carotid intima-media thickness (cIMT)³⁵⁻³⁸. There is a unanimous consensus on the increased prevalence of subclinical atherosclerosis in HIV-infected patients compared to the general population. Presumably, both HIV infection and HAART may promote atherosclerosis through mechanisms involving endothelial cells, either directly or indirectly via metabolic disorders. However, HAART should be considered as a strong, independent predictor for the development of subclinical atherosclerosis in HIV-infected patients, regardless of known major cardiovascular risk factors and atherogenic metabolic abnormalities induced by this therapy³⁵⁻³⁸. The increased use of lipid-lowering agents, protease inhibitors-free HAART regimens, and the reduction of smoking may decrease cIMT in HIV-infected patients over time³⁹. Markers of subclinical atherosclerosis should be carefully assessed in HIV-infected patients receiving HAART, especially in those with lipodystrophy.

Coronary artery disease: Prevalence of coronary artery disease in HIV-infected patients receiving HAART is widely debated⁴⁰⁻⁴⁵. Differences in the study design, in the selection of the patients and in the statistical analyses of data, might explain this disparity. However, longer exposure to HAART and/or protease inhibitors seems to increase the risk of myocardial infarction. The results of the Data Collection on Adverse Events of Anti-HIV Drugs study showed that HAART therapy is associated with a 26 per cent relative risk increase in the rate of

myocardial infarction per year of HAART exposure⁴³. A recent analysis of the risk for myocardial infarction in relation to the exposure to specific antiretroviral drugs has shown that indinavir, lopinavir-ritonavir, didanosine and abacavir are associated with a more significant risk⁴⁵. However, as with any observational study, these findings must be interpreted with caution (given the potential for confounding) and in the context of the benefits that these drugs provide⁴⁵.

Cardiovascular risk stratification in HIV-infected patients on HAART

For patients on HAART, it may be important to evaluate the traditional vascular risk factors and to try to intervene on those that can be modified. Existing guidelines for the management of dyslipidaemias in the general population, such as those of the National Cholesterol Education Program³⁰, currently represent the basis for therapeutic recommendations in HIV-infected individuals as well, such as those reported by the HIV Medicine Association of the Infectious Disease Society of America and Adult AIDS Clinical Trial Groups⁴⁶ and by the Pavia Consensus Statement⁴⁷. New insights in defining the cardiometabolic risk in patients with HAART-associated metabolic syndrome have been provided recently by the echocardiographic measurement of the epicardial adipose tissue⁴⁸. Epicardial adipose tissue is the true visceral fat of the heart and is significantly correlated with abdominal visceral fat measured by magnetic resonance imaging. Given its potential as an easy and reliable marker of visceral fat, epicardial fat has been recently evaluated in patients with HIV-associated lipodystrophy syndrome. In these patients, echocardiographic epicardial fat correlated with intra-abdominal visceral fat, cIMT, and clinical parameters of the metabolic syndrome (especially, waist circumference, blood pressure, fasting glucose, fasting insulin, and markers of fatty liver disease)⁴⁹⁻⁵¹. Taken together, these findings suggest that echocardiographic assessment of epicardial fat may have the potential to be a simple and reliable marker of visceral adiposity and increased cardiovascular risk in patients with HIV-associated lipodystrophy syndrome.

Conclusions

The introduction of HAART in the developed countries has significantly reduced the prevalence of cardiomyopathy and pericardial effusion, which heavily influenced the prognosis of HIV-infected patients living in these countries in the pre-HAART period, and still influences the prognosis of HIV-infected patients living

in developing countries. However, HIV-associated lipodystrophy syndrome and related cardiovascular risk in developed countries is an increasingly recognized clinical entity. The multifactorial pathogenesis of HIV-associated lipodystrophy syndrome represents an intriguing field of future basic and clinical research. Careful cardiac screening for patients who are being evaluated for, or who are receiving HAART regimens, is warranted according to the current clinical guidelines, with a close collaboration between cardiologists and infectious disease specialists.

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