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OBSERVATION

Heart and HAART: Two sides of the coin for HIV-associated cardiology issues

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Abstract

The introduction of highly active antiretroviral therapy (HAART) has generated a contrast in the cardiac manifestations of acquired immunodeficiency syndrome. In developed countries, we have observed an approximately 30% reduction in the prevalence of human immunodeficiency virus (HIV)-associated cardiomyopathy, possibly related to a reduction of opportunistic infections and myocarditis. In developing countries, however, where the availablity of HAART is limited and the pathogenic impact of nutritional factors is significant, we have observed an approximately 32% increase in the prevalence of HIV-associated cardiomyopathy and a related high mortality rate from congestive heart failure. Also, some HAART regimens in developed countries, especially those including protease inhibitors, have been shown to cause, in a high proportion of HIV-infected patients, an iatrogenic metabolic syndrome (HIV-lipodystrophy syndrome) that is associated with an increased risk of cardiovascular events related to a process of accelerated atherosclerosis, even in young HIV-infected people. 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. A close collaboration between cardiologists and infectious disease specialists is needed for decisions regarding the use of antiretrovirals, for a careful stratification of cardiovascular risk factors, and for cardiovascular monitoring of HIV-infected patients receiving HAART, according the most recent clinical guidelines.

Key words: Human immunodeficiency virus; Acquired immunodeficiency syndrome; Cardiovascular disease; Lipodystrophy syndrome; Highly active antiretroviral therapy

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INTRODUCTION

The introduction of highly active antiretroviral therapy (HAART) has significantly improved the clinical evolution of human immunodeficiency virus (HIV) disease, with increased survival of HIV-infected patients. How-

ever, this generated contrasting and intriguing issues in HIV-associated cardiovascular complications.

HIV-ASSOCIATED CARDIOLOGY ISSUES

HIV infection is recognized as an important cause of dilated cardiomyopathy. In developed countries, we have observed a reduction of 30% in the prevalence of HIV-associated cardiomyopathy, possibly related to the reduction of the incidence of opportunistic infections and myocarditis. On the other hand, in developing countries, with somewhat limited availability of HAART, and with a significant impact of nutritional factors, we have observed an increase in the prevalence of HIV-associated cardiomyopathy (about 32%)[1], with a related high mortality rate for congestive heart failure. A similar trend has been observed for pericardial effusion, the prevalence of which was reduced by 30%-35% after the introduction of HAART in developed countries[2], whereas in developing countries, the prevalence of pericardial effusion is increased by 35%-40%, mostly related to *Mycobacteria* infections[3,4].

The prevalence of infective endocarditis does not vary in HIV-infected patients who use intravenous drugs after the introduction of HAART, even in developed countries[5]. Estimates of infective endocarditis prevalence vary from 6.3% to 34% of HIV-infected patients who use intravenous drugs independently of HAART[6]. 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*[6]. Patients with HIV infection generally have similar presentations and survival (85% *vs* 93%) from infective endocarditis as those without HIV. However, patients with late-stage HIV disease have about 30% higher mortality with endocarditis than asymptomatic HIV-infected patients, which may be related to the degree of immunodeficiency[7]. Nonbacterial thrombotic endocarditis, also known as marantic endocarditis, had a prevalence of 3%-5% in acquired immunodeficiency syndrome (AIDS) patients, mostly in those with HIV-wasting syndrome, before the introduction of HAART[6]. Marantic endocarditis is now more frequently observed in developing countries with a high incidence (10%-15%) and mortality for systemic embolization[3,4].

The incidence of HIV-associated pulmonary hypertension increased after the introduction of HAART. It has has been estimated at 1/200, which is much higher than 1/200 000 found in the general population[8]. In this condition, a key pathogenetic role is played by pulmonary dendritic cells, which are not sensitive to HAART and may hold HIV-1 on their surfaces for extended time periods[8]. The infection of these cells by HIV-1 cause chronic release of cytotoxic cytokines (e.g. endothelin-1, interleukin-6, interleukin-1β and tumor necrosis factor-α), which contribute to vascular plexogenic lesions and progressive tissue damage, independently of opportunistic infections, stage of HIV disease and HAART regimens[8]. Positive results have been reported with the use of bosentan, an endothelin-1 receptor antagonist, even in association with HAART, especially in the early stages of the disease[9,10]. The efficacy of phosphodiesterase-5 inhibitors (e.g. sildenafil) is still debated because of their interaction with antiretroviral drugs, especially protease inhibitors (PIs).

The prevalence of cardiac Kaposi's sarcoma in AIDS patients ranges from 12% to 28% in retrospective autopsy studies performed before the introduction of HAART[6]. Non-Hodgkin's lymphoma involving the heart is infrequent in AIDS[6,11]. The introduction of HAART led to a reduction by about 50% in the overall incidence of cardiac involvement by Kaposi's sarcoma and non-Hodgkin's lymphoma, possibly related to an improved immunological state of the patients and to reduced prevalence of opportunistic infections (human herpes virus 8 and Epstein-Barr virus), which are known to play an etiological role in these neoplasms. On the contrary, an increased prevalence of cardiac involvement of AIDS-associated tumors may be observed in developing countries in relation to the scant availability of HAART[3,5].

A wide range of inflammatory vascular diseases including polyarteritis nodosa, lupus-like syndrome, Henoch-Schonlein purpura, and drug-induced hypersensitivity vasculitis may develop in HIV-infected individuals. Kawasaki-like syndrome[12-14] and Takayasu's arteritis[15] have also been described. Drug-induced hypersensitivity vasculitis is common in HIV-infected patients who receive HAART[13]. The vasculitis associated with drug reactions typically involves small vessels and has a lymphocytic or leukocytoclastic histopathology[13]. 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 etiology for a vasculitic syndrome in an HIV-infected patient[13].

HIV-associated lipodystrophy or lipoatrophy, which were not reported before the introduction of HAART, was first described in 1998[16]. It is characterized by the presence of a dorsocervical 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% in otherwise healthy HIV-infected patients who are receiving HAART, although reported rates range from 18% to 83%[17,18]. The pathogenesis of HAART-associated lipodystrophy is complex and a number of factors are involved, including direct effects of HAART on lipid metabolism, endothelial and adipocyte cell function, and mitochondrial dysfunction[19]. As in genetic lipodystrophy syndromes, fat redistribution may precede the development of metabolic complications in HIV-infected patients who are receiving HAART. Among HIV-infected patients with lipodystro-

phy, increased serum total and low-density lipoprotein cholesterol and triglyceride levels have been observed in about 70%, whereas insulin resistance (elevated C-peptide and insulin) and type 2 diabetes mellitus have been observed in 8%-10%[17-19].

The increased cardiovascular risk associated with lipodystrophy syndrome may be related to a specific action of antiretroviral drugs and to individual risk factors (e.g. smoking habit, and inheritated metabolic disease). Some HAART regimens, such as those that include zidovudine, some non-nucleoside reverse transcriptase inhibitors (e.g. efavirenz), and PIs disrupt endothelial cell junctions and cytoskeletal actin of the endothelial cells, which leads to endothelial dysfunction and damage[20-22]. PIs may also reduce endothelial nitric oxide synthase expression and increase the levels of superoxide anion as expression of increased endothelial oxidative stress[23].

According to most clinical studies, HAART should be considered a strong, independent predictor for the development of subclinical atherosclerosis in HIV-infected patients, as demonstrated by measurement of carotid intima-media thickness (cIMT), regardless of known major cardiovascular risk factors and atherogenic metabolic abnormalities induced by this therapy[24-27]. The increased use of lipid-lowering agents and PI-free HAART regimens, and the reduction of smoking may decrease cIMT in HIV-infected patients over time[28]. Markers of subclinical atherosclerosis should be carefully assessed in HIV-infected patients who are receiving HAART, especially in those with lipodystrophy syndrome.

HIV-associated endothelial dysfunction and injury, autoimmune reaction to viral infection (vasculitis), and renal disease have been hypothesized to play a role in the pathogenesis of HIV-associated hypertension. HIV-associated renal impairment 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[29]. Arterial hypertension, even in agreement with the Adult Treatment Panel-Ⅲ guidelines[30], is currently considered part of HAART-associated metabolic syndrome[31]. It appears to be related to PI-induced lipodystrophy[32] and metabolic disorders, especially to elevated fasting triglyceride and insulin resistance[31,33].

Besides inherited disorders, HIV-infected patients who are 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 S[34,35]. For instance, protein S deficiency has been reported in up to 73% of HIV-infected men[34,35]. These abnormalities are associated with thromboses involving veins and arteries and seem to be related to HAART regimens that include PIs[36]. Thrombocytosis has been reported in 9% of patients who are receiving HAART, with cardiovascular complications in up to 25% of cases[37].

A debated issue concerns coronary artery disease. The association between viral infection (cytomegalovirus or HIV-1) 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 infarction[38]. Conflicting data still exist on the relationship between HAART and the incidence of acute coronary syndromes, such as unstable angina or myocardial infarction, among HIV-infected patients who are receiving PI-containing HAART[39-43]. Differences in the study design, selection of patients, definition of the cardiovascular events and study endpoints, and statistical analyses might explain this disparity. However, longer exposure to HAART and/or PIs 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 was associated with a 26% relative risk increase in the rate of myocardial infarction per year of HAART exposure[44]. 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 risk[45]. 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 provide[45].

For patients on HAART, it may be important to evaluate the traditional vascular risk factors and try to intervene in those that can be modified. Existing guidelines for the management of dyslipidemia in the general population, such as those of the National Cholesterol Education Program[30], currently represent the basis for therapeutic recommendations in HIV-infected individuals, such as those reported by the HIV Medicine Association of the Infectious Disease Society of America and Adult AIDS Clinical Trial Groups and by the Pavia Consensus Statement[46,47]. In the absence of specific trial data, HIV patients who present with acute coronary syndromes should be treated according to the international guidelines. Diet and exercise should not be overlooked, because both can be effective in managing these complications without causing further side effects. Fibric-acid derivatives and statins can lower HIV-associated cholesterol and triglyceride levels, although further data are needed on interactions between statins and PIs. Most statins are metabolized through the CYP3A4 pathway, which raises concern over potential interactions with PIs. The inhibition of CYP3A4 by PIs could potentially increase by several-fold the concentration of statins, thus increasing the risk of skeletal muscle or hepatic toxicity. Pravastatin, fluvastatin and rosuvastatin appear to be the safest agents at this time, since they are least influenced by the CYP3A4 metabolic pathway[48]. Although further controlled clinical trials are needed, promising results have been reported with the administration of ezetimibe and omega-3 fatty acids[48]. They do not interact with PIs and may be safely administrered in combination with

low-dose statins. In treating hypertension in HIV-infected patients with metabolic syndrome, it may be important to remember that beta-blockers and diuretics may worsen the metabolic profile in these patients. Calcium channel blockers should be used with caution since they may interact with PIs. ACE inhibitors and angiotensin II receptor blockers may be recommended, but controlled clinical trials are still lacking in this subset of patients[47]. Hypoglycemic agents may have some role in managing glucose abnormalities. Glitazones can be administered in combination with metformin. However, glitazones may interact with PIs and cannot be recommended for fat abnormalities alone, and metformin may cause lactic acidosis[47].

New insights in defining the cardiometabolic risk in patients with HAART-associated metabolic syndrome have been recently provided by the echocardiographic measurement of the epicardial adipose tissue. Epicardial adipose tissue is the true visceral fat of the heart and is significantly correlated with both epicardial fat and abdominal visceral fat measured by magnetic resonance imaging[49]. In patients with HIV-lipodystrophy syndrome, echocardiographic epicardial fat correlates with intra-abdominal visceral fat, cIMT, and clinical parameters of the metabolic syndrome (especially waist circumference, blood pressure, high-density lipoprotein cholesterol, fasting glucose and insulin), with adiponectin and with markers of fatty liver disease[49-51]. 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-lipodystrophy syndrome[49,50].

CONCLUSION

The introduction of HAART has revealed two sides of the coin for HIV-associated cardiology issues. It has significantly reduced in developed countries the prevalence of HIV-associated cardiomyopathy, 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, HAART-associated lipodystrophy syndrome and related cardiovascular risks 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 most recent clinical guidelines, with a close collaboration between cardiologists and infectious disease specialists.

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