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Review

Cardiomyopathy and Heart Failure in Patients With HIV Infection

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ABSTRACT

With the advent and widespread use of antiretroviral therapy (ART), the epidemiology of cardiomyopathy and heart failure (HF) associated with HIV infection is changing. Near-normal life expectancy in contemporary HIV-infected populations has been associated with prolonged exposure to increased cardiometabolic burden and chronic immune activation and systemic inflammation. Therefore, the pre-ART phenotype of HIV-associated cardiomyopathy with overt left ventricular systolic dysfunction and poor prognosis has been replaced over time by cardiomyopathy with a more insidious course, more frequent ischemic background, and highly prevalent left ventricular diastolic dysfunction. Patients with HIV are more prone to development of coronary artery disease and development of HF after myocardial infarction. The role of ongoing immune activation and systemic inflammation, despite highly active ART (HAART), appears to be central in this process. The role of HAART toxicity is controversial, as HAART itself appears to be protective for the development of HF, but recent data suggest that protease inhibitors might adversely affect the course of HIV-associated HF. Because of these unique features, the optimal therapeutic approach for HIV-associated cardiomyopathy remains unknown. The current

RÉSUMÉ

Avec la mise au point et l'utilisation généralisée du traitement antirétroviral (TAR), les caractéristiques épidémiologiques de la cardiomyopathie et de l'insuffisance cardiaque (IC) associées à l'infection par le VIH sont en train de changer. L'espérance de vie quasi normale des populations contemporaines infectées par le VIH a été associée à une exposition prolongée à une augmentation du fardeau métabolique, à une activation immunitaire chronique et à une inflammation généralisée. Par conséquent, le phénotype pré-TAR de la cardiomyopathie associée au VIH, une dysfonction systolique ventriculaire gauche manifeste de pronostic défavorable, a été remplacé au fil du temps par une cardiomyopathie caractérisée par une évolution plus insidieuse, un contexte ischémique plus fréquent et une dysfonction diastolique ventriculaire gauche extrêmement prévalente. Chez les patients vivant avec le VIH, la probabilité de survenue d'une coronaropathie et d'une IC après un infarctus du myocarde est plus élevée. L'activation immunitaire chronique et l'inflammation généralisée, malgré un TAR hautement actif (TARHA), semblent jouer un rôle central dans ce processus. L'effet de la toxicité du TARHA est une question controversée, car alors que le TARHA semble protéger

The global prevalence of HIV infection in 2017 was estimated at approximately 36.9 million people with an annual incidence of 1.8 million cases.[1] In 2017, 21.7 million people were estimated to receive long-term antiretroviral therapy (ART), an increase of 2.3 million since 2016 and up from 8 million in 2010.[1] Improved access to ART along with developments in ART have transformed HIV infection into a treatable chronic disease. In high-income countries, this progress has translated into near-normal life expectancy for these patients.[2] With decreasing morbidity from infections, most deaths in people with HIV are now due to non-communicable illnesses.[3] In particular, HIV-infected individuals are at higher risk for cardiovascular disease (CVD)[3] and heart failure (HF).[4] By 2030, it is anticipated that 73% of HIV-infected patients will be age 50 years or older and 78% will have CVD.[5]

In the past 3 decades, the epidemiology of left ventricular (LV) dysfunction in HIV-infected patients has shifted from a predominantly LV systolic dysfunction phenotype, with a prevalence of 2%-20%, to a predominantly LV diastolic dysfunction phenotype, with strikingly high rates of 26%-50%.[6-21] In the 1980s and 1990s, the leading causes of HIV-related HF were primary or secondary myocarditis,

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therapeutic approaches are an extrapolation from noninfected populations. Importantly, the significance of the highly prevalent diastolic abnormalities among HIV-infected patients is not known. Therefore, further research is needed to identify its prognostic implications. Considering the prevalence of structural and functional cardiac abnormalities in HIV-infected persons and the lack of evidence on how to best screen and treat these patients, systematic research on this topic is a public health priority.

contre l'apparition de l'IC, des données récentes laissent croire que les inhibiteurs de la protéase pourraient avoir un effet défavorable sur l'évolution de l'IC associée au VIH. En raison de ces caractéristiques uniques, l'approche thérapeutique optimale de la cardiomyopathie liée au VIH demeure incertaine. Les schémas thérapeutiques actuels ont été élaborés par extrapolation des résultats obtenus dans des populations non infectées. Fait important, on ignore quelle est la portée des anomalies diastoliques hautement prévalentes chez les patients infectés par le VIH. Par conséquent, il est important de poursuivre les recherches afin de déterminer les conséquences pronostiques d'une telle situation. Compte tenu de la prévalence des anomalies cardiaques structurelles et fonctionnelles chez les personnes infectées par le VIH et l'absence de données probantes sur les méthodes les plus appropriées de dépistage et de traitement de ces patients, la recherche continue sur cette question est une priorité de santé publique.

direct viral effects, opportunistic infections, cell and humoral immunity dysregulation, nutritional deficiencies, or severe immunosuppression.[4,14,22,23] Those cases were characterized by LV systolic dysfunction and dilation, which portended a poor prognosis. With wider access to highly active ART (HAART) and concomitant improvement in life expectancy, cardiac involvement in HIV patients has shifted toward diastolic dysfunction and HF with preserved ejection fraction (HFpEF) with a concomitant decrease in the incidence of HF with reduced ejection fraction (HFrEF). In addition, chronic exposure to metabolic disturbances, accelerated atherosclerosis, and increasing rates of coronary artery disease have shifted the etiology of myocardial involvement.

Epidemiology of HF and Cardiomyopathy in HIV-Infected Patients

Clinically manifest (stage C) HF

High-quality data on the prevalence of clinically manifest (stage C) HF in contemporary HIV-infected populations are limited. In a study in the United States from a large administrative database, among 36,400 adults with HIV and > 12 million controls, HF was present in 7.2% of HIV-infected patients and 4.4% of controls (relative risk, 1.66; 95% confidence interval [CI], 1.60-1.72], $P < 0.0001$).[24] Although the absolute HF prevalence was higher in older patients with HIV, the relative risk was highest in young people and in women. The prevalence of HF was lower among patients receiving ART (6.4% vs 7.7%; $P < 0.0001$).[24] In a prospective cohort of 803 HIV-infected subjects in Germany (mean age, 44 years; 16.6% female), the prevalence of self-reported HF was 3.1%, with higher prevalence among patients 45 years old or older (5.2% vs 1.5%).[20] Two-thirds of HF cases were of ischemic etiology.

Contemporary data on HF incidence in HIV-infected patients are limited. In the **V**eterans **A**ging **C**ohort **S**tudy (VACS), among > 98,000 veterans (97.0% male) without evidence of CVD at baseline, 32.2% of whom were affected by HIV, the incidence of HF over a median of 7.1 years ranged from 1.78 to 16.0 cases per 1000 patient-years depending on age (Fig. 1).[25] HIV-infected veterans were at increased risk of HF in general, and HFrEF, HFpEF, and HF with borderline ejection fraction specifically, after adjusting for confounders. The increased risk associated with HIV infection in the VACS was more pronounced in younger patients. Inadequate viral suppression (time-updated HIV-1 RNA viral load $\geq$ 500 vs < 500 copies per millilitre) was associated with increased risk of HFrEF, and time-updated CD4 cell count < 200 compared with $\geq$ 500 cells/mm^3 was associated with an increased risk of HFrEF and HFpEF.[25] These data suggest that viral and immune system mechanisms play a role in the development of HF in HIV-infected patients.

Subclinical (stage B) HF

In a meta-analysis including 11 studies from Europe and the United States with 2242 HIV-infected patients receiving HAART, the prevalence of systolic dysfunction was 8.3% whereas the prevalence of diastolic dysfunction was 43.4%.[16] However, in the Heart of Soweto Study, South Africa, where access to and use of HAART is substantially lower, systolic dysfunction in patients with concomitant HIV infection was 29%, underlying the significant regional disparities.[17] More sensitive modalities can detect early changes in myocardial function in a substantial proportion of HIV-infected patients. In a study of 28 young HIV-infected patients (age 7-29 years) and 28 controls, HIV-1 infected patients had impaired radial strain and longitudinal and circumferential strain and strain rate despite the absence of gross systolic dysfunction.[26]

The prevalence of LV systolic dysfunction appears to be declining in patients with HIV receiving HAART.[4] However, rising rates of diastolic dysfunction have been reported compared with age-matched controls (Table 1).[19,27-29] Also, patients with HIV seem to develop diastolic dysfunction at a significantly younger age.[16] The reasons for this shift are still unclear. Although certain HAART agents have been implicated in early studies, recent work suggests minimal effect of HAART on diastolic dysfunction.[29] Despite the higher rates of diastolic dysfunction in HAART-treated HIV-infected patients, there are limited data on its natural history and pathogenesis. In the VACS study, risk for HFpEF among HIV-infected veterans was increased compared with noninfected veterans,[25] indicating that diastolic dysfunction in

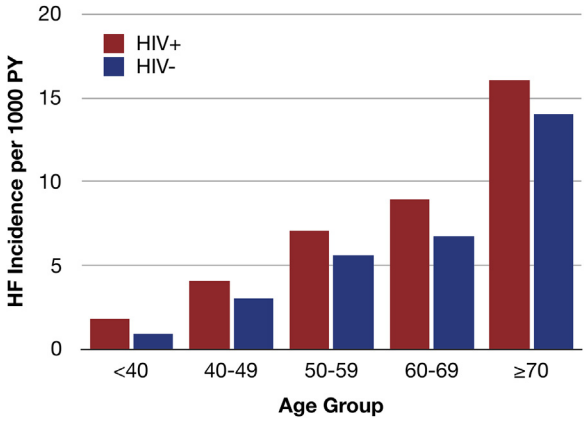

Figure 1. Incidence of heart failure (HF) in the Veterans Aging Cohort Study according to HIV status. PY, person-years. Data from Freiberg et al.[25]

HIV patients can lead to clinical HF. The recently completed **C**haracterizing **H**eart Function on **A**ntiretroviral **T**herapy (CHART) Study will provide further insights into this topic.[30]

Pathophysiology

In the pre-ART era, HIV-associated cardiomyopathy most commonly manifested as severe, dilated cardiomyopathy, which was believed to be the result of opportunistic infections or myocarditis. In contemporary populations with HIV, however, the pathophysiology of HIV-associated cardiomyopathy has become more multifactorial, with proposed causes including direct HIV infection with or without myocarditis, coinfection with other viruses, HAART toxicity, autoimmune mechanisms, opportunistic infections, and nutritional disorders (Fig. 2).

Direct HIV-induced myocardial damage

Viral infection of the heart has been considered to play a major role in the development of systolic dysfunction in HIV infection.[31] *In situ* hybridization studies with myocardial samples from humans with AIDS[32] and primates infected with Simian immunodeficiency virus[33] suggest that macrophages and other immune system cells rather than the myocytes are the primary site of cardiac infection. This is consistent with evidence suggesting that cardiomyocytes lack HIV-1 receptor proteins (gp120 or gp24). Furthermore, it has been shown that cardiac interstitial cells (dendritic cells or endothelial cells) can serve as viral reservoirs and antigen-presenting cells mediating inflammation.[34] Studies have suggested that HIV gene products might contribute and HIV-related proteins expressed in response to infection lead to cardiomyopathy.[35,36] Transgenically expressed HIV-1 Tat protein in the mouse causes systolic dysfunction, which can be relieved by antioxidants.[37,38]

Immune mechanisms and systemic inflammation

Cardiotropic viruses alter surface antigens and can therefore lead to autoimmune reaction to endogenous epitopes.[22]

Table 1. Diastolic dysfunction among HIV-infected persons receiving antiretroviral therapy in comparative studies

Reference	Population	Findings
Schuster et al.[27]	30 HIV-infected men (age 42.1± 4.7 years; duration of HIV infection 10.4 ± 4.7 years; duration of ART 5.3 ± 2.1 years) and 26 age-matched HIV-negative controls	HIV-infected patients had similar height-indexed LV mass vs controls (40.6 ± 9.5 vs 37.5 ± 9.3 g/m; $P > 0.05$), but higher prevalence of DD (abnormal relaxation or pseudonormal filling): 64% vs 12% ($P < 0.001$). LV systolic function indexes were lower and pulmonary artery pressure was higher in HIV-positive patients compared with controls
Hsue et al.[19]	196 HIV-infected adults (median age, 47 years; 85% male; median duration of HIV infection, 15 years; 82% receiving ART) and 52 controls	Median BSA-indexed LV mass was higher in HIV-infected vs HIV-negative (77.2 vs 66.5 g/m^2; $P < 0.001$). LV ejection fraction was similar. Among HIV-infected, 50% had mild DD vs 29% in HIV-negative participants ($P = 0.008$). HIV-infected patients had an adjusted odds ratio of 2.4 for DD compared with controls ($P = 0.019$)
Grandi et al.[58]	60 HIV-infected patients (30 hypertensive and 30 normotensive), all receiving ART and 60 HIV-not infected persons (30 hypertensive and 30 normotensive)	HIV-infected patients had a higher prevalence of DD vs controls (30% vs 10%; $P = 0.012$). The prevalence was greater in hypertensive HIV-infected patients compared with HIV-infected normotensive patients and hypertensive HIV-not infected patients (43.3% vs 16.6% vs 20%, respectively)
Luo et al.[28]	325 HIV-infected initially ART-naive patients, repeat evaluation after 48 weeks of ART, 97 age-matched HIV-negative controls	HIV-infected patients had a higher prevalence of DD vs controls (16.5% vs 7.2%; $P = 0.027$) and LV systolic dysfunction (7.3% vs 2.1%; $P = 0.056$). DD increased from baseline to week 48 (23.3%; $P = 0.056$ vs baseline) in HIV-infected patients
Fontes-Carvalho et al.[29]	206 HIV-infected persons (88 ART-naive and 116 receiving ART, 41.7 ± 9.4 years, 70.4% male) and 30 controls	Prevalence of DD in HIV-infected patients was 23% vs 3.3% in controls ($P = 0.01$), but not different between ART-naive (19%) and those receiving ART (23%) HIV-infected patients. No differences in systolic function
Secemsky et al.[18]	332 HIV-infected patients (51 ART-naive, 20 had received ART in the past, 261 were receiving ART) and 50 age- and sex-matched controls	Prevalence of DD in HIV-infected patients 45% vs 28% in controls ($P = 0.02$). Prevalence of systolic dysfunction in HIV-infected patients 5% vs 0% in controls ($P = 0.23$)

ART, antiretroviral therapy; BSA, body surface area; DD, diastolic dysfunction; LV, left ventricular.

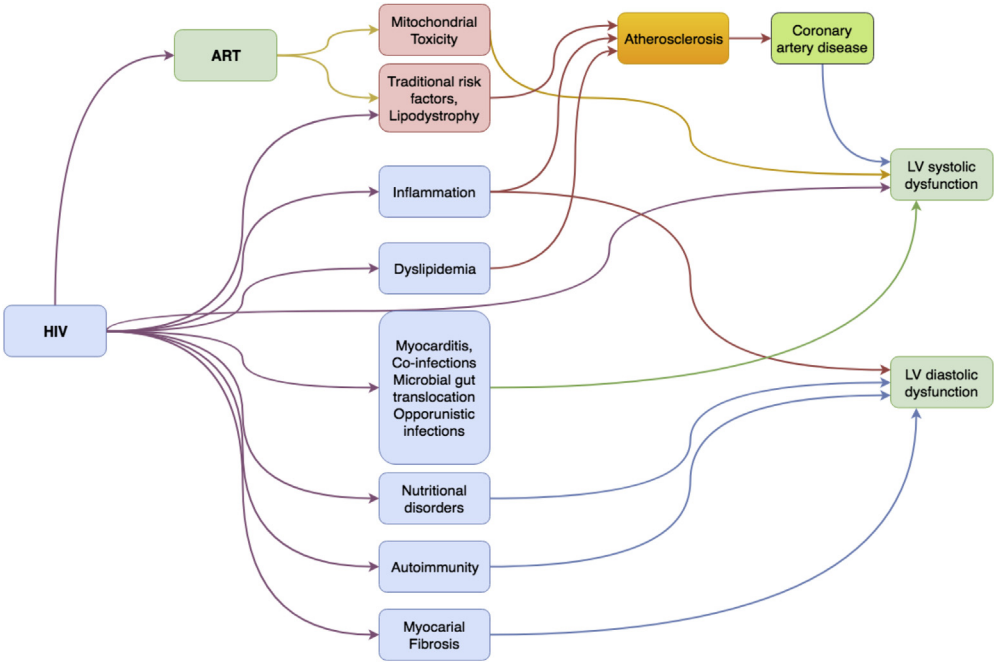

Figure 2. Proposed mechanisms of systolic and diastolic cardiac dysfunction in HIV-infected persons. ART, antiretroviral therapy; LV, left ventricular.

In addition, cardiac-specific autoantibodies are more common among HIV-infected individuals, especially those with evidence of myocardial disease.[39] Increased myocardial expression of human leukocyte antigen class I antigens is commonly seen in patients with HIV and symptomatic systolic dysfunction.[40] Interestingly, blocking some of these proteins might be cardioprotective,[36,39,41,42] and monthly intravenous immunoglobulin(s) in HIV-1 infected children has been shown to ameliorate LV dysfunction and improve other markers of myocardial injury.[43,44]

Despite beneficial effects of HAART,[45,46] there is ongoing T-cell activation[47] and inflammation[48,49] in HIV-infected persons. This is thought to be the result of residual viral replication,[50] gut mucosal injury and microbial translocation,[51] coinfections,[52] and impaired homeostatic drive.[53] Elevated levels of inflammatory and prothrombotic biomarkers predict CVD risk in HIV-infected patients.[54] Proinflammatory cytokines, particularly interleukin-1 and tumour necrosis factor (TNF), have been shown to exert negative inotropic effects.[55,56] Overexpression of inducible nitric oxide synthase and TNF has been shown in HIV-associated cardiomyopathy,[34] and presence of TNF in apoptotic cardiomyocytes suggest that TNF is a potent inducer of apoptosis.[57]

The role of direct HIV effects on diastolic dysfunction is poorly understood, but LV hypertrophy is more common in HIV-infected patients than in controls, regardless of hypertensive status.[58] In an echocardiographic study, average LV mass index was 8 g/m^2 higher in HIV-infected participants vs controls ($P = 0.001$), and this effect was associated with a lower nadir CD4 T-cell count, suggesting that immunodeficiency might play a role.[19] In HIV-infected patients, T-cell activation has been linked to arterial stiffness,[59] which in turn is associated with diastolic dysfunction in the general population.[60] In a cardiac magnetic resonance (CMR) study of 28 adequately treated patients with HIV, native T1 relaxation times, relative T2 signal intensity, and early gadolinium enhancement, were all elevated compared with controls, indicating myocardial inflammation.[26] In another CMR study, subclinical myocardial edema and fibrosis, increased LV mass, lower systolic function, and pericardial effusions were reported in 103 persons receiving HAART, pointing to chronic inflammation involving the myocardium and pericardium.[61]

Myocardial inflammation and fibrosis

In a number of CMR studies, a higher prevalence of myocardial inflammation and interstitial fibrosis, focal and diffuse, has been reported in patients with HIV.[26,61-63] Also, HIV-infected patients have increased myocardial lipid content.[63,64] These findings correlate with impaired myocardial function in these patients.[63] Of note, myocardial deformation (strain) parameters suggest that HIV-infected patients have impaired LV systolic function despite normal LV ejection fraction in CMR studies.[26,61-63]

Accelerated myocardial fibrosis appears to play a major role in HIV-induced systolic and diastolic dysfunction. Soluble ST2, a marker of cardiac fibrosis that is linked to diastolic dysfunction[65] and mortality in HFpEF,[66] is associated with cardiac dysfunction and mortality in HIV-infected patients. Galectin-3, another marker of fibrosis that has been linked to incident HF and mortality,[67] is overexpressed in HIV-infected patients.[68] Growth differentiation factor 15, which is produced by myocytes and endothelial cells and correlates with cardiac mass and fibrosis,[69] predicts all-cause mortality in

HIV-infected patients.[18] Imbalances between matrix metalloproteinases and their tissue inhibitors have been reported in HIV-infected patients.[70] These alterations have been linked to LV hypertrophy and HF.[71] Despite these lines of evidence, the exact mechanisms that lead to focal and diffuse fibrosis in HIV-infected patients are still unclear.

Coronary artery disease

Patients with HIV are at higher risk for coronary artery disease, which is a major contributor to HF. In a recent meta-analysis encompassing approximately 800,000 persons with HIV, the relative risk of myocardial infarction associated with HIV infection was 1.79 (95% CI, 1.54-2.08).[3] Viral suppression does not completely eliminate this risk. In the VACS, HIV-positive veterans had 48% higher risk of myocardial infarction compared with uninfected veterans (95% CI, 27%-72%) after adjusting for known risk factors, comorbidities, and substance use.[72] The excess risk persisted among patients maintaining an HIV-1 RNA level < 500 copies per millilitre in time-updated analyses (hazard ratio, 1.39; 95% CI, 1.17-1.66).[72] Importantly, HIV-infected patients appear to be more vulnerable to development of HF after a myocardial infarction. In a French hospital-based registry, hospitalization for HF by 1 year after myocardial infarction was more frequent in HIV-infected than in uninfected patients (3.3% vs 1.4%, respectively; $P = 0.020$), and HIV infection was an independent predictor of incident HF.[73]

The prevalence of coronary artery disease among HIV-infected patients with HF has not been well studied. In a retrospective cohort of 394 HIV-infected patients with HF receiving HAART, coronary artery disease was present in 40% of patients.[74]

Cardiometabolic risk factors

Cardiometabolic risk factors, including glucose and lipid metabolism alterations, are known to induce a proinflammatory milieu and promote atherosclerosis and diastolic dysfunction in the general population. These factors are at least equally prevalent in HIV-infected patients.[75] Also, traditional coronary risk factors are more common in HIV patients, particularly those receiving HAART, than in noninfected persons.[76] Dyslipidemia, metabolic syndrome, hypertension, and cigarette smoking are all more prevalent in HIV patients, leading to higher 10-year Framingham Risk Scores in this group than in noninfected controls.[77] In a meta-analysis of 65 studies with 55,000 HIV-infected patients across 5 continents, the prevalence of metabolic syndrome was 16.7%-31.3% depending on definition, and was comparable with that in noninfected populations.[75] The presence of metabolic syndrome is a predictor for CVD and death in HIV patients.[78]

Body fat abnormalities have been reported in up to 50% of ambulatory HIV-infected patients and the proportion is greater among those receiving combination HAART.[76] Lipodystrophy, which describes a redistribution of the fat of the body with areas of lipoatrophy (loss of subcutaneous fat from the upper and lower extremities as well as from the face) and areas of lipohypertrophy (increased fat accumulation in the neck, anteriorly and posteriorly, and trunk and intra-abdominal region) develops in 20%-35% of patients after initiation of HAART. Those receiving protease inhibitors and the nucleoside reverse-transcriptase inhibitors stavudine and didanosine appear to be particularly prone to lipodystrophy.[79] Lipodystrophy shares features of the metabolic syndrome, including insulin resistance, impaired glucose tolerance, elevated triglycerides, low high-density lipoprotein cholesterol levels, and hypertension. Progression to metabolic syndrome is common in the first 3 years after initiation of HAART that includes stavudine or lopinavir/ritonavir but is less common with newer medications. Of note, lipodystrophy is not directly related to myocardial lipid infiltrates but represents a predisposing factor for metabolic alterations. To date, no study has directly addressed the association between HAART, lipodystrophy, and myocardial lipid infiltrates.

Treatment of lipid abnormalities among HIV-infected patients is challenging. Coadministration of statins with protease inhibitors, a cornerstone of antiretroviral treatment, is not free of adverse effects, especially liver toxicity. However, low-dose statins are safe. Pravastatin has proven to be safe in regular doses, low-dose atorvastatin can be relatively safely coadministered with certain protease inhibitors, fluvastatin is considered safe, and rosuvastatin can be used at low doses.[80,81] Furthermore, an ongoing trial will shed light on the usefulness of pitavastatin in HIV-infected persons.[82] An ongoing systematic review and network meta-analysis will compare the effects of various statins in HIV-infected persons.[83]

HIV medications

Although HAART overall seems to benefit the cardiomyopathic process in HIV by ameliorating viral effects on the myocardium, some antiretroviral medications might have adverse myocardial effects in the long term, including mitochondrial toxicity. Also, HAART might have indirect effects on the myocardium by unfavourably modifying cardiovascular risk factors, including lipid profile.

Children exposed to HAART provide valuable insights, because the cardiovascular system is still developing. Echocardiographic data from the Adolescent Master Protocol of the Multicenter Pediatric HIV/AIDS Cohort Study showed that LV structure and function were relatively preserved in the long-term HAART-exposed group compared with the relatively HAART-unexposed Vertically Transmitted HIV Infection cohort but still were not normal.[84] Children exposed perinatally to multidrug ART or HAART had below-normal LV mass, LV dimension, and septal wall thickness. In a larger cohort of HIV-exposed uninfected perinatally HAART-exposed children, 16% of them had at least 1 abnormal echocardiographic measure.[85] Also, in HIV-exposed uninfected children, serum cardiac biomarker measurements suggested that perinatal exposure to HAART agents might result in subclinical myocardial inflammation.[86] Of note, HAART appears to have a protective effect on cardiac structure after perinatal infection, as well as a deterrent effect on the development of HF.[87] Although initially there is a protective role of HAART early in life with better measurements of cardiac function, this effect might decline on long-term follow-up.[88] Mitochondrial toxicity is an acknowledged side effect of certain antiretroviral agents.[89] Defects in mitochondrial DNA replication and energetics have been reported by zidovudine[90,91] and other nucleoside reverse transcriptase inhibitors,

including clevudine and lodenosine.[92,93] In all, the data on the effects of HAART in the adult heart are limited and additional work is required to elucidate the effects of individual classes. In a recent retrospective study of 394 patients with treated HIV infection and HF, patients receiving protease inhibitors had increased cardiovascular mortality and 30-day readmission rates.[74]

Nutritional deficiencies

HIV-infected persons often experience nutritional deficiencies as a result of malabsorption and diarrheic syndromes. Nutritional deficiencies have a more central role in the development of HIV-associated cardiomyopathy in developing countries. Selenium deficiency, probably the most studied nutritional deficiency in HIV-infected persons, has been frequently reported in HIV-infected patients and is associated with a form of cardiomyopathy most frequently encountered in China, known as Keshan disease.[94,95] However, because nutritional deficiencies are closely related to socioeconomic status, the role of nutritional deficiencies in the development of cardiomyopathy is difficult to disentangle. For example, in a prospective study in sub-Saharan Africa, selenium deficiency was associated with twice the risk for cardiomyopathy.[96] However, selenium deficiency correlates also with low socioeconomic status and CD4 count.[96] Selenium supplementation has several beneficial effects for patients with HIV.[97] However, the effects of supplementary selenium on the incidence and course of HIV cardiomyopathy are unknown.

Treatment

Medical therapy

The optimal therapy for HIV-associated HF and the response of HIV-infected patients to common HF medications is unknown because no randomized trials of HF medications have been performed in this patient population. Of note, data on HIV status are not regularly collected in clinical trials and registries. Therapy is thus driven by consensus and data are derived from retrospective analyses and case series or from extrapolation from non-HIV-infected patients. General recommendations include standard, guideline-driven therapy,[98] but no prospective studies have assessed the benefits of these strategies specifically in HIV-infected patients.

However, some information regarding differential response to therapy may be glimpsed from HF studies in regions with a high prevalence of HIV. In Botswana, among 193 patients with acute HF,[99] the prevalence of HIV infection was 33.9%. The 6-month mortality was 30.9% without any difference according to HIV status at index hospitalization. In Uganda, the prevalence of HIV among 215 patients hospitalized for HF was 18.6%.[100] Despite that most patients had chronic HF, use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and β-blockers before admission was very low and mortality at 6 months was a striking 43%, with no difference according to HIV status. These data suggest that response to therapy is similar in HIV-infected vs noninfected patients and that other factors, including access to care and medications, are the determinants of prognosis in this context.

Implantable devices

The effects of device therapy in patients with HIV cardiomyopathy have not been studied. It has been suggested that HIV-infected patients are less likely to receive an implantable defibrillator or cardiac resynchronization therapy device, potentially because of a misbelief that patients with HIV have limited life expectancy or because of perceived of infectious complications.[101] Of note, the latter concern is not unfounded, because a recent study reported higher rates of bacteremia despite HAART in infected patients compared with the general population.[102]

Transplantation and circulatory support devices

HIV infection has been generally considered a contraindication for cardiac transplantation because of historically poor survival and concerns over progression to AIDS with immunosuppression.[103] However, limited data are available on the prognosis of HIV-infected patients undergoing heart transplantation in the HAART era.[104] Early reports of cardiac transplantation in patients with HIV showed poor outcomes.[105] In more recent series from the United States and Europe, no increase in rejection or worsening of HIV status with immunosuppression have been reported.[106,107] In all, in the era of HAART, recipients with HIV infection seem to achieve satisfactory outcomes without developing HIV-related events. Consequently, selected HIV patients are reasonable candidates for heart transplantation.[104] In fact, evidence suggests that immunosuppressant medications can actually increase the efficacy of HAART in treating HIV infection.[108]

Data on long-term mechanical circulatory support devices in HIV-infected patients are limited. However, case series indicate reasonable outcomes in HIV-infected LV assist device recipients and no significant adverse events attributed to HIV infection.[109] Although more robust data are needed, these reports support the notion that advanced therapies can be considered for HIV-associated cardiomyopathy.

HAART and immune therapy

The effect of HAART on the myocardium is multifaceted. Poorly controlled HIV infection has been associated with more pronounced systolic dysfunction. However, HAART has been also associated with higher incidence of coronary disease, which is a risk factor for development of HF. Some case reports have suggested regression and normalization of cardiomyopathy with HAART in adults[110] and children.[111] However, in a recent retrospective study, protease inhibitors specifically have been associated with worse outcomes among HIV-infected patients hospitalized with HF.[74] Whether HAART can reverse HIV cardiomyopathy has not been answered and warrants further investigation.[112,113]

The role of immune therapy in HIV-associated HF is unclear. In a retrospective review of intravenous immunoglobulin therapy in 49 children with HIV infection, significant improvements in LV wall thickness and decreases in peak wall stress have been reported.[114] Favourable trends were also noted in fractional shortening and contractility. The

therapeutic benefit of intravenous immunoglobulin might result from its ability to inhibit TNF and interleukin production. However, data on immune-modulating therapies in adults with HIV-associated HF are lacking.

Prognosis of HF in HIV-Infected Patients

HIV-associated cardiomyopathy in the pre-ART era carried a grim prognosis. In one study, the median survival time in patients with AIDS and cardiomyopathy was 101 days, compared with 472 days in patients with AIDS alone,[115] whereas another study showed an adjusted hazard for death of 5.86 (95% CI, 3.92-8.77) compared with patients with idiopathic cardiomyopathy.[116] However, with widespread use of HAART, prognosis has improved. In a study of HIV-infected patients with systolic dysfunction (mean ejection fraction 28 $\pm$ 11%) undergoing dobutamine stress echocardiography, there were 11 cardiac deaths after 2.1 $\pm$ 1.8 years (event rate 7.6% per year) because of worsening HF and arrhythmias.[117] Inotropic contractile reserve was associated with significantly better prognosis, because patients without contractile reserve had a 7-times higher event rate (24% per year vs 3.4% per year; $P < 0.001$). Furthermore, patients with contractile reserve were more likely to have improvement in ejection fraction over time (80% vs 33%; $P = 0.003$) despite no difference in the use of antiremodelling medications between groups.[117]

ART appears to affect the course of cardiomyopathy. In a recent retrospective single-centre study of 394 HIV-infected patients who were hospitalized with HF, patients who were receiving protease inhibitors had higher rates of hyperlipidemia, diabetes mellitus, and coronary artery disease; higher pulmonary artery systolic pressure; and lower LV ejection fraction compared with those receiving nonprotease inhibitors.[74] Protease inhibitor use was independently associated with increased cardiovascular mortality over 2 years (35% vs 17%; $P < 0.001$) and 30-day readmission for HF (68% vs 34%; $P < 0.001$).[74]

Patients with HIV-associated cardiomyopathy are at increased risk for cardiac death. Currently cardiac diseases account for a quarter of deaths compared with less than 10% in the pre-ART era. Symptoms of HF or echocardiographic evidence of cardiomyopathy are associated with 6.5 and 4.0 times higher risk for death, respectively.[118] In a retrospective study, sudden cardiac death occurred at a 4.5 times higher rate than expected among HIV-infected patients.[119] In a subset of patients with available echocardiograms, a high prevalence of structural and functional abnormalities was observed.[119] At this time, however, there is insufficient evidence to support a role for imaging modalities in the screening and prognostic assessment of HIV-infected persons.

Conclusion

Our understanding of HIV-associated cardiomyopathy has evolved, but it is still inadequate. The widespread use of HAART has changed the disease from a severe, dilated form of cardiomyopathy to one of less severe LV systolic dysfunction and varying degrees of diastolic dysfunction. The prevalence of systolic dysfunction has decreased in developed countries. However, in parts of the world where HIV is most prevalent, use of HAART is not widespread and thus HIV cardiomyopathy frequently presents as severe systolic impairment with poor prognosis. The exact significance of diastolic abnormalities among these patients is not known, necessitating further research to determine their prognosis and how best to prevent its development. Several lines of evidence support a role of immune mechanisms and chronic immune activation and inflammation in the cardiomyopathic process. In addition, the protective role of HAART on the myocardium early in life might be blunted in the long-term as a result of adverse effects on myocardial energetics and cardiovascular risk factors; these effects might vary according to antiretroviral agent class. Because of these unique features, the optimal therapeutic approach for patients with HIV-associated cardiomyopathy remains unknown. The current therapeutic approaches are an extrapolation from noninfected populations. Considering the prevalence of structural and functional cardiac abnormalities among HIV-infected individuals and the lack of evidence on how to best screen and treat these patients, further research on this topic is a public health priority.

Disclosures

The authors have no conflicts of interest to disclose.

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