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Heart failure in patients with human immunodeficiency virus: a review of the literature

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Coronary artery disease represents the leading cause of death for HIV patients treated with highly active antiretroviral treatment. Besides this, an extensive amount of data related to the risk of overt heart failure and consequently of atrial fibrillation and sudden cardiac death (SCD) in this population has been reported. It seems that persistent deregulation of immunity in HIV-infected patients is a common pathway related to both of these adverse clinical outcomes. Despite the fact that atrial fibrillation and heart failure are relatively common in HIV, few data are reported about screening, diagnosis, and potential treatment of these conditions.

Introduction

Highly active antiretroviral treatment (HAART) represented the turning point for patients with HIV, reaching life expectancies similar to patients without the infection.¹ HIV-positive patients are consequently exposed to both the detrimental effects of lifelong HAART and the negative effect of the virus itself. Recent data indicate that deregulation of immunity is one factor leading to premature aging in this population.²

The first critical and deeply investigated cardiac complication in HIV-infected patients, although not yet clarified, is represented by the presence of diffuse and severe coronary artery disease (CAD), with a high rate of recurrent thrombotic events.^{3,4} Additionally, an extensive amount of data cast light on other potentially life-threatening cardiovascular complications, such as symptomatic cardiomyopathy (overt heart failure) potentially leading to atrial fibrillation.⁵⁻⁷

In the present review the following points are analyzed¹: Pathophysiology of heart failure in HIV patients;² how common is heart failure, atrial fibrillation, and SCD in HIV patients?;³ what will be the impact of heart failure on prognosis?; and⁴ how can general physicians, cardiologists, and specialists in infectious disease prevent and treat heart failure?

Viral load and highly active antiretroviral treatment: an inextricable relationship

The first case of symptomatic dilated cardiomyopathy was reported in 1986 in patients with HIV infection: in the 1980s and 1990s, presence of heart failure was mainly related to myocarditis because of HIV itself or opportunistic pathogens, autoimmune processes, nutritional deficiencies, and prolonged immunosuppression.⁸⁻¹⁰

The introduction of HAART in the first years of 21st century has deeply reduced opportunistic infections and improved control of viral load, consequently resolving the most common causes of heart failure in these patients. On the other side, very few data have been reported, before and after HAART introduction, about incidence and management of atrial fibrillation, despite the fact that HIV patients are at a higher risk of stroke not only related to atherosclerotic carotid disease.¹¹

Despite the introduction of HAART, two recent reports from the Veterans Aging Cohort Study,^{5,6} describe an approximate two-fold increase in heart failure between infected and un-infected patients, even in the absence of CAD, and a higher incidence of atrial fibrillation. From a pathophysiological point of view higher viral load (quantified as HIV-RNA) is a risk factor for both atrial fibrillation and heart failure, independent of other traditional risk factors^{5,6} (see Fig. 1 Fig. 1).¹¹

On the one hand, HIV infection could promote atherosclerosis through mechanisms related to immune activation, chronic inflammation, coagulation disorders, and/or lipid disturbances.¹² Direct HIV infection could also stimulate proliferation of human vascular smooth muscle cells and therefore promote atherosclerosis.¹² HIV alone, independent of HAART, is associated with known atherogenic dyslipidemia associated with increased concentrations of triglycerides (impaired lipase activity) and decreased concentrations of high-density lipoprotein cholesterol correlated with a higher concentration of cytokines.¹² All these mechanisms can lead to heart failure.

On the other hand, the relationship between inflammation and the development of cardiomyopathy leading to heart failure has always been challenging. In this subset, ongoing replication of the virions appears to be directly related to development of heart failure and of atrial fibrillation. Indeed, viral proteases have been demonstrated to directly cleave the dystrophin–sarcoglycans complex, causing cardiac dilatation,¹³ and activate innate immunity for systemic clearance of the virus, with potential consequences on alterations of inflammation.¹⁴ Moreover, alterations of auto-immunity, with infections of the virus leading to myocardial damage and to exposure of auto-antigens (HIV-infected patients are more likely to have cardiac-specific autoantibodies) and of high rate of cytokines,¹⁰ may cause an auto-immune response and secondary myocardial damage.^{14,15} Finally, HCV co-infections¹⁶ enhance the risk of cardiomyopathy, probably because of inflammation and apoptosis playing a crucial role in this progressive process. Similarly, an increased inflammation pattern has also been involved in the pathogenesis of atrial fibrillation⁶ (even if it is not clear if this represents an effect of common risk factors such as hypertension or diabetes mellitus itself).

The role of HAART for HIV patients remains difficult to assess and questionable: there is no evidence from published prospective studies about HAART benefit on HIV-associated cardiomyopathy. From one side, HAART reduces viral load, improves the immunologic state of the patients, and gives a better control of opportunistic infection, thus limiting potential direct and indirect damage of the virions to the heart.¹⁰ On the other side, however, zidovudine and phosphorylated azidothymidine (AZT) have been most commonly implicated in the development of cardiomyopathy because they inhibit the function of mitochondria,¹³ but these findings have not been confirmed in other studies¹⁴ and besides the fact that AZT is nowadays seldom used in clinical practice. For the new classes of antiretroviral drugs, there is a suggestion of a prevailing protective role for HAART to prevent the development of heart failure.

On the contrary, viral load may explain a large amount of SCDs in HIV patients, but certainly not all. In the recent article of Tseng *et al.*⁷ patients who died suddenly did not report a high viral load/low CD4 cell count when compared with those who survived. The authors concluded that although acute coronary thrombotic events may partly explain SCD, other potential mechanisms may be involved, for example long **QT interval at ECG**, due both to HAART and to the virus itself.^{17,18}

Role of traditional risk factors

Traditional risk factors for heart failure should not be forgotten, being reported as independent predictive factor for development of both heart failure and atrial fibrillation; moreover, patients with heart failure are exposed to a higher risk of atrial fibrillation.^{5,6}

The data on the prevalence of traditional risk factors in HIV patients reported in the examined studies are described in [Table 1](#) [Table 1](#).

The data about hypertension in HIV are conflicting,^{19–23} showing a relationship with dyslipidemia and initial kidney disease,²⁴ but an unclear causal association with HAART; on the contrary, high rates of smoking²⁵ and uncontrolled lipid levels^{26–30} have often been reported, the latter being related to exposure to antiretroviral medications. The same critical interactions between chronic immune-activation and HIV medications play a crucial role in the development of diabetes mellitus.^{31,32} Although all these factors, along with HIV uncontrolled replication and instability of atherosclerotic plaque, concurred to development of CAD, potentially leading to heart failure, it remains noteworthy that the risk of heart failure is independent of CAD in these patients.⁵

Another peculiar cause of heart failure in patients with HIV is related to the development of arterial pulmonary hypertension that occurs in 0.5% of the HIV patients.³³ A direct infection of HIV on pulmonary vascular endothelial cells has never been reported,^{35–37} but the presence of viral antigens in pulmonary endothelium directly stimulates abnormal apoptosis, growth, and proliferation. Owing to the mechanistic role of infection, HIV viral load has been shown to be linked to poor survival in a recent cohort.³⁸ In this setting, differential diagnosis performed usually through right heart catheterization, between primary pulmonary hypertension and secondary one due to left ventricle dysfunction, is crucial to identify in the first scenario target therapy.³²

Incidence and prognosis of heart failure in HIV patients

A recent meta-analysis of 2242 HIV patients treated with HAART³⁹ demonstrated a prevalence for left ventricular dysfunction of 8.33% (left ventricle ejection fraction \leq 35%) and 11% for second and third degree diastolic dysfunction for pauci-symptomatic patients (NHYA class I or II). Similarly a recent article by Butt *et al.* has demonstrated an incidence of heart failure of 7.12 per 1000 person-years for HIV-infected patients **versus** 4.82 per 1000 person-years any un-infected patient, with a risk for overt heart failure of 0.5% per year for a 48-year-old male HIV patient treated with HAART. This is a 10% risk to develop heart failure before 70 years old, which is more than double the risk compared with a 48-year-old patient with similar risk factors but without HIV (4%).⁴⁰ Interestingly, similar risk was demonstrated for patients with comparable age and risk factors to develop atrial fibrillation (0.4% for year), stressing the concept of common pathophysiology, mutual interplay, and development.^{40,41}

The incidence of atrial fibrillation in HIV-infected patients is about 3.6 events per 1000 person-years⁶ but its impact on prognosis in this specific subset of patients remains to be determined, especially because of young age at clinical presentation. The larger cohorts exploited to derive a clinical risk model usually enrolled patients older than 60,^{41–43} consequently limiting translation of the prognostic impact of heart failure and atrial fibrillation in HIV patients.

Moreover, the risk of SCD was relevant in these patients, with a 0.3%/year for a young patient to die suddenly (more than four times than an uninfected one).⁷

Risk stratification: how to screen the HIV population?

As reported in international guidelines all HIV patients should be subjected to complete cardiovascular risk stratification, and to a periodically cardiovascular monitoring because cardiovascular complications are important contributors to morbidity and mortality in HIV-infected patients. These complications can usually be detected at subclinical levels with monitoring, which can help guide targeted interventions.⁴⁴

Presence of dyspnea, angina, or palpitations should be weighted with an elevated concern given the higher risk of both CAD,^{3,4} heart failure, and atrial fibrillation in this population.

A different approach should be reserved to asymptomatic HIV patients because of the previously described interaction between viral load and HAART; traditional risk scores (like Framingham⁴⁵ or Progetto Cuore⁴⁶ for the Italian population) failed to achieve enough accuracy in this subset of patients.⁴⁵

A recent dedicated score (DAD: data collection on adverse effects of anti-HIV drugs study) was developed and externally validated on an HIV HAART-treated population⁴⁵ and included traditional risk factors but also use and length of HAART therapy and the exposure to certain drugs (indinavir, lopinavir, abacavir): it was associated with better performance to predict myocardial infarction and coronary heart disease even if the Framingham score effectiveness was highlighted. Consequently, DAD score represents probably the most accurate one; nevertheless, no study has so far compared the performance of these risk calculators to predict events after 5 years.

As outlined before, probably one of the most evident limits of this model is represented by absence of information on viral activity. Thus, because of the relevant systolic or diastolic dysfunction reported in our meta-analysis,³⁹ we propose to consider at risk and evaluate for cardiac disease asymptomatic HIV patients treated with HAART, with a DAD risk score over 5 year more than 5%⁴⁵ or with CD4s less than 200/mm³ (Fig. 2 Fig. 2).

First¹ a close monitoring of blood levels of cholesterol and of diabetes should be performed, along with plasma B-natriuretic peptide.⁴⁷⁻⁵¹

Electrocardiogram² should be performed in these patients in order to assess presence of sinus rhythm, and of presence of Q waves and of ST segment variations suggestive of ischemic heart disease and of hypertension. Moreover, also assessment of the QT interval, which may be prolonged because of both HAART and the HIV virus itself,^{37,38} remains important to be assessed. In this setting, although less evidence has been provided, also Holter ECG may be useful to detect supraventricular and ventricular arrhythmias.⁵²

Echocardiography may guide noninvasive differential diagnosis³ for alterations suggestive of ischemia, and from a structural point of view, it may be useful to detect left and right ventricle function and volumes, alterations of segmental kinesis, diastolic function, and presence of valvular disease; moreover, recent evidences suggest to use echocardiography to evaluate the presence and the entity of pericardial fat to better stratify the cardiovascular risk of HIV patients.⁴⁸⁻⁵⁰ Moreover, these patients should be evaluated to accurately appraise their functional capacity with a 6-min walking test. Although it is only mildly effective to predicting prognosis for heart failure,⁵³ pulmonary hypertension,⁵⁴ and stable angina,⁵⁵ it could be useful to detect subtle and subclinical reduction of performance, especially during follow-up.

Cardiac magnetic resonance (CMR) represents an intriguing diagnostic choice for HIV patients.⁵⁶ For everyday clinical practice it may be useful for differential diagnosis in patients with a reduced ejection fraction without CAD, whereas it allows researchers to perform a more accurate diagnosis of subclinical myocardial disease. Actually CMR may give much more details than other instrumental techniques. For example, in the recent study of Holloway *et al.*,⁵⁶ up to 45% of HIV asymptomatic patients reported higher median myocardial lipid levels and up to 76% myocardial fibrosis when compared with 13% non HIV asymptomatic patients with similar cardiovascular risk factors. Shifting from micro to macro alterations, the article of Lai *et al.*,⁵⁷ also in patients without diagnosed symptoms, demonstrated that HIV infection is associated with subclinical regional left ventricular systolic alterations. Similarly Kjaer *et al.*⁵⁸ showed that half of asymptomatic HIV patients reported reduction of right ventricle function, although with preserved volumes. Given the limited sample size of this study, a prospective project has been recently started⁵⁸ with the aim to perform CMR in patients with elevated pro BNP levels, and will provide interesting insights on this topic.

Detection of cardiac disease in asymptomatic HIV patients: risk of over or undertreatment?

Detection of cardiac alterations at previous cited exams should be weighted according to clinical experience and practice, ranging from ergometric stress testing,⁶⁰ cardiac scintigraphy,⁶¹ coronary computed tomography⁶² or left heart catheterization with coronary angiography³ for alterations suggestive of ischemia, right heart catheterization for suspected pulmonary hypertension,⁶³ or implantation of a loop recorder if high suspicion of atrial fibrillation is present.⁶⁴ Moreover, in patients with unclear diagnosis and ventricle dysfunction, CMR⁴⁷ may be useful to perform differential analysis.

It remains interesting to note that despite a wide bulk of literature about heart failure and ventricle dysfunction in HIV patients, no study has reported on the consequences, or at least the diagnostic findings for them. From a treatment point of view, these patients should probably take benefits from current standard pharmacological options,²¹ although few studies have been prospectively performed on them. Two important challenges exist pertaining to treatment in these patients. First, there is a high prevalence of drug–drug interactions (DDIs) reported in this population. Most of the HAART drugs have an impact on drug-metabolizing enzymes such as cytochrome P450 isoforms (CYP3A4, CYP2B6) and drug transporters (such as p-glycoprotein and OATP1B1) and therefore the risk of DDIs is very high.⁶⁵ The most complete database on this subject is the one developed and managed by the University of Liverpool.⁶⁶ In general, **Protease Inhibitors** (with the exception of tipranavir) are potent CYP and OATP1B1 inhibitors and should not be used with simvastatin, but few data about safety and efficacy of the new antiplatelet, new and old anticoagulants and antiarrhythmic drugs have been reported, so according to the data collected in the database of the University of Liverpool these drugs should not be coadministered with HAART, or may require close monitoring, alteration of drug dosage, or timing of administration. As regard drugs indicated in heart failure, β -blockers, calcium channel blockers, digoxin, and isosorbide dinitrate should be administered with careful attention to possible DDIs,⁶⁶ whereas furosemide, spironolactone, **Angiotensin Receptor Blockers (ARBs)**, and **Angiotensin Converting Enzyme Inhibitor (ACE-I)** may be administered without any clinically significant interaction expected.⁶⁶

Second, with the increasing life expectancy and prevalence of comorbidities these patients are treated with several drugs and this could impact their compliance to medications.⁶⁵

Despite the therapeutic strategy of HIV patients with heart disease is not easily definable, thanks to HAART, we will be increasingly faced with the questions about what to do when heart failure becomes so severe as to consider the option of heart transplantation. HIV patients have traditionally been excluded from organ transplantation, but nowadays have been reported some cases of successful heart transplantation⁶⁶ and even cases of VAD implantation.⁶⁸

Is prevention the next big thing? Role of the 'cardiologist-specialist' in infectious disease

A recent randomized controlled trial of patients with hematological malignancies undergoing high doses of anthracyclines demonstrated a benefit on limiting the reduction of ejection fraction with the use of enalapril or carvedilol.⁶⁹ When compared with HIV patients, the latter may be different, being exposed to these drugs for a short period of time; however, it may be possible to hypothesize a role for prevention in high-risk patients, that is, those with reduced CD4 cell counts exposed for long term to HAART.

In support of a prevention strategy in high-risk patients, a recent study²¹ has demonstrated the efficacy of telmisartan in the control of hypertension and microalbuminuria in HIV-infected patients. It investigates the possible endothelial protective effect of telmisartan in HIV patients, where the endothelial dysfunction is related to infection and chronic inflammation.

The growing interest and increase in evidence stress that HIV-positive patients should be managed jointly by cardiologists and an infectious disease specialist, in order to accurately stratify their cardiovascular risk, and to avoid undertreatment of potentially fatal cardiac complications. We advocate the need for long-term management in centers with dedicated specialists (such as Heart Infectious Disease team), as suggested by guidelines.⁴⁴ If not possible, however, a close collaboration both from a clinical and a researcher point of view may be useful. Another crucial point would be ascertaining the extent and impact of ACS in limited-resource countries; although the burden of cardiovascular disease is still limited,^{70,71} the ongoing rapid urbanization and 'westernization' of many African societies may rapidly change this scenario and the prevalence of traditional risk factors.

Conclusion

CAD represents the most frequent cardiac complication in HIV patients treated with HAART. However, the development of heart failure and atrial fibrillation in these patients is frequent, deserving both clinical care in diagnosis, prevention, and treatment, and further experimental researches. Further studies are needed to understand the efficacy and safety of both prevention and treatment of heart failure and atrial fibrillation in these patients.

Uncited reference

[34,59,67].

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Fig 1 Viral load, traditional risk factors, and HAART: an inextricable relationship. gr1

Fig. 2 . gr2

Table 1 CV risk factors in HIV patients

Study	Years of the study	Number of HIV patients	Patients on HAART	Prevalence of CV risk factor	Prevalence of CV risk factor in patients on HAART	Prevalence of CV risk factor in patients no on HAART
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[0,1-7]Hypertension

Jerico C, AJH 2005 [15]	2003	710 (802 controls)	88.2%	13.1% HIV patients (13.5% in controls)	in 14%	5.9%
Saeberg EC, AIDS 2005 [16]	1984–2003	5578	37%	Systolic hypertensio n: 7.3%	Systolic hypertensio n: 12%	Systolic hypertensio n: 5.4%
				Diastolic hypertensio n: 8%	Diastolic hypertensio n: 9.2%	Diastolic hypertensio n: 12%
Crane HM, AIDS 2006 [17]	1998–2005	444	100%		Hypertensio n developed in 21% of patients	
[0,1-7]Hyperlipidemia						
Anastos K, J Acquir Immune Defic Syndr 2007 [21]	1994–1995 and 2001– 2002	2794 (976 controls)	59%	Total C > 200 mg/dl	Total C > 200 mg/dl	Total C > 200 mg/dl
		All women		HIV patients: 27%	33%	16%
				Controls: 24%		
				LDL C > 130 mg/dl	LDL C > 130 mg/dl	LDL C > 130 mg/dl
				HIV patients: 18%	15%	20%
				Controls: 22%		
				HDL C < 40 m g/dl	HDL C < 40 m g/dl	HDL C < 40 m g/dl

				HIV patients: 34%	27%	45%	
				Controls: 16%			
				TG > 150 mg/dl	TG > 150 mg/dl	TG > 150 mg/d	
				HIV patients: 33%	38%	24%	
				Controls: 16%			
Aszalos BF, 2005 Atherosclerosis 2006 [22]	48 (96 controls with and 96 controls without CAD)	100% (comparing data pre and post HAART)	Total C (mg/dl)	Total C	Total C	Total C	
(no available prevalence, but cholesterol and triglycerides levels)			HIV - CAD -: 198 ± 39	Post HAART: 195 ± 47	Pre HAART: 166 ± 43		
			HIV - CAD +: 193 ± 35				
			LDL C (mg/dl)	LDL C	LDL C	LDL C	
			HIV - CAD -: 126 ± 35	Post HAART: 110 ± 36	Pre HAART: 97 ± 33		
			HIV - CAD +: 119 ± 30				
			HDL C	HDL C	HDL C	HDL C	

				(mg/dl)		
				HIV – CAD	Post	Pre
				–: 49 ± 13	HAART:	HAART:
					37 ± 13	36 ± 11
				HIV – CAD		
				+: 41 ± 13		
				TG (mg/dl)	TG	TG
				HIV – CAD	Post	Pre
				–:	HAART:	HAART:
				115 ± 69	242 ± 254	164 ± 106
				HIV – CAD		
				+:		
				172 ± 119		
[0,1-7]Diabetes						
Brown TT, JAMA 2005 [25]	1984–1991	568 (710 controls)	72%	HIV patients 11.9%	14%	7%
		All men		(controls 5%)		
Justman JE, J Acquir Immune Defic Syndr 2003[26]	1994–1998	1435 (350 controls)	43%	HIV patients 4%	6.1%	2.2%
		All women		(controls 3.7%)		

CV, cardiovascular; HAART, highly active antiretroviral treatment.