Epidemiology, Pathophysiology, and Prevention of Heart Failure in People with HIV

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Abstract

Heart failure (HF) has been a known complication of HIV/AIDS for three decades. As the treatment of HIV has changed, so has the epidemiology and pathophysiology of HF in people with HIV (PWH). Initial manifestations of HF in uncontrolled HIV primarily included a rapidly evolving cardiomyopathy with pericardial involvement. With the widespread uptake of effective antiretroviral therapy (ART), HF in PWH has become a chronic disease reflective of the aging population and associated comorbidities, albeit with a contribution from HIV-associated chronic immune dysregulation and inflammation. Despite viral suppression, PWH remain at elevated risk for both HF with reduced ejection fraction and HF with preserved ejection fraction. In this review, we discuss the changing epidemiology and mechanisms of HF in PWH and how that may inform HF prevention in this vulnerable population.

Keywords

Heart Failure; HIV; Immune Dysfunction

Introduction

Prior to widespread antiretroviral therapy (ART) uptake, several case reports and series noted a high incidence of heart failure (HF) in people with HIV/AIDS (PWH), marked by aggressive cardiomyopathy secondary to opportunistic infections, idiopathic lymphocytic myocarditis, and noninflammatory myocardial necrosis.[1,2] Early control of HIV with ART reduced the risk of AIDS-associated cardiomyopathy but potential cardiotoxic effects of these therapies began to emerge. Initial reports demonstrated zidovudine-induced

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myocarditis characterized by CD8 T-cell infiltration on endomyocardial biopsy.[3] Subsequently, the development of highly effective and less toxic ART over the years has allowed for early initiation and continuous uninterrupted treatment, with associated significant reductions in morbidity and mortality among PWH.[4,5]

Thus, leading causes of mortality for treated PWH have shifted from AIDS-related deaths to diseases of aging, including cardiovascular diseases (CVD), such as HF.[6] However, it is becoming clear that not only is the prevalence of HF rising in PWH, but the risk of HF for PWH is higher than the general population.[7–9] This increased risk is not fully explained by: (1) increasing prevalence of traditional CVD risk factors or high-risk behaviors, (2) disparities in treatment of CVD risk factors, or (3) potential harmful effects of current generation ART. Instead, there is mounting evidence that persistent immune dysregulation, even in those started on early suppressive ART, plays an important role in the development of myocardial dysfunction (either directly or through enhancing the effects of traditional CVD risk factors) and incident HF. In this review, we will discuss the changing epidemiology of HF in PWH and attempt to understand the underlying mechanisms that may contribute to HF risk and propose strategies to prevent HF in this vulnerable population.

Epidemiology of HIV-Associated HF

The global epidemiology of HF in PWH varies greatly with geographical location depending on access to, and uptake of, effective ART. Specifically, in resource-limited settings where access to ART is limited, AIDS-associated cardiomyopathy along with pericardial disease remains a common subtype of HF. The prevalence of AIDS-associated cardiomyopathy ranges from 9% to 57% depending on the study population, with one prospective study reporting an incidence of nearly 17% over 18 months.[10] AIDS-associated cardiomyopathy is strongly associated with advanced immunosuppression, specifically CD4 count $<100/mm^3$, and has a dismal prognosis.[10] Prior to ART, the prevalence of AIDS-associated cardiomyopathy was likewise 30%–40% even in high income countries.[11] Additionally, HIV accounted for up to 4% of all unexplained cardiomyopathies in the US during the 1980s and 1990s.[12] These data from low-and-middle income countries as well as high-income countries pre-ART clearly suggest that untreated, advanced HIV leads to direct myocardial injury.

While AIDS-associated cardiomyopathy is less of a concern in settings with high rates of continuous ART use, PWH on ART continue to be at increased risk of HF with reduced ejection fraction (EF; HFrEF) and HF with preserved EF (HFpEF) compared to the general population. Analysis of HIV-infected and uninfected veterans enrolled in the Veterans Aging Cohort Study (VACS) from 2000 to 2007 demonstrated a nearly 2-fold increased risk of HF in HIV-infected veterans.[13] This association persisted in those with and without coronary artery disease (CAD). In subgroup analysis, the association strengthened in those with elevated viral load at baseline while those with sustained suppression of viral load did not have an increased risk of HF. Increased risk was also seen in those with CD4 count below or above $200/mm^3$ and regardless of ART. In a subsequent analysis from VACS, HF was further categorized into HFrEF (EF<40%), HFpEF (EF 50%), and borderline HFpEF (EF 40–49%).[9] This analysis used administrative codes to define HF (with echocardiographic data to

sub-categorize HF types) and included predominantly men enrolled after 2003 and followed up through 2012. There were roughly equal numbers of HFpEF and HFrEF cases in PWH. PWH had an increased risk of all three subtypes of HF, but the association with HFrEF was strongest (hazard ratio 1.61) and persisted after adjustment for incident myocardial infarction (MI) during the follow-up period. The increased risk of overall HF remained in sensitivity analyses that excluded those with hypertension (HTN), alcohol or cocaine abuse, and ever smokers. In those with baseline suppressed viral load, the risk of HFrEF attenuated while the risk of HFpEF and borderline HFpEF remained elevated. In contrast, lower CD4 count, especially <200/mm^3 was associated with all three subtypes of HF. The risk attenuated with a rising CD4 count for all three HF subtypes with no increased risk of HFpEF was found in those with CD4 count >500/mm^3.

Additional cohorts have further corroborated these findings. In an electronic health records-derived database of patients receiving care for HIV at a large urban medical center in Chicago from 2000 to 2016, a rigorous, systematic approach was taken to adjudicate HF endpoints with the goal of enhancing diagnostic accuracy and HF sub-phenotyping.[14] Similar to prior studies of administrative records, PWH had a 2-fold higher risk of adjudicated HF compared to controls.[15] Higher viral load was associated with increased HF risk while higher CD4 count was associated with lower HF risk. Another study from a Taiwanese nationwide cohort using data from 2003 to 2014 also showed an increased risk of incident HF in PWH using a competing risk model.[16] In addition, those receiving ART had significantly higher risk of incident HF than those not receiving ART. However, no specific class of ART was associated with a higher risk of HF, and the risk of HF decreased as ART duration increased. Despite a small number of women in the Taiwanese cohort, in subgroup analyses, the HIV-associated risk of HF appeared to be stronger in women (HR 2.5) than in men (HR 1.44). Finally, in an analysis of a large healthcare database that used administrative codes to define HF, risks for HF among PWH were likewise elevated, with an adjusted relative risk of 1.66 for PWH vs. HIV-uninfected persons.[7] An analysis of women in VACS from 2003 to 2009 showed that women with HIV had a significantly higher risk of CVD than HIV-uninfected women (HR 2.8).[17] After excluding atherosclerotic CVD, the risk of HF remained higher in women with HIV (HR 2.5). The median age of CVD onset was lower in women with HIV. Among those with HF, women with HIV have higher rates of HF hospitalization, longer HF hospital stays, and higher rates of CVD mortality compared to uninfected women.[18]

These studies done in the era of modern ART have helped establish HIV as an independent risk factor for incident HF even in the absence of the classic AIDS-associated cardiomyopathy. However, few studies distinguished between HFpEF and HFrEF and none comprehensively phenotyped HF etiologies (e.g. ischemic vs. non-ischemic) – a clear area of need. Several studies have evaluated phenotypes of subclinical myocardial dysfunction. One meta-analysis evaluated the prevalence and type of cardiac dysfunction in HIV.[19] This analysis included 18 studies from North America, 15 from Europe, 11 from Africa, and 10 from Asia. The pooled relative risk of HF was 1.7, similar to the studies described above. The pooled prevalence of left ventricular (LV) systolic dysfunction and any diastolic dysfunction were 12.3% and 29.3%, respectively. The prevalence of advanced diastolic dysfunction was 11.7%. The prevalence of LV systolic dysfunction was higher in studies

with greater proportion of participants with AIDS and was lower among more recent studies and those with higher proportion of participants on ART. These results, along with the findings from the cohort studies discussed above, suggest that systolic dysfunction and HFrEF are strongly linked to burden of HIV viremia. It is important to note that the 2014 HIV treatment guidelines were the first to recommend ART regardless of CD4 count and only the most recent 2018 guidelines stress the importance of very early ART initiation, including immediately after diagnosis.[20,21] These recommendations have led to an increase in the proportion of PWH on ART and a significant decrease in the median time from HIV diagnosis to ART initiation (418 days to 77 days) during this decade.[22] Thus, it stands to reason that with the evolution of early to immediate ART initiation, HFpEF may become the dominant subtype of HF in PWH living in the developed world (Figure 1). Future studies more heavily weighted toward the modern ART era are needed to better characterize this changing epidemiology.

Pathophysiology of HIV-Associated Heart Failure

Given the changing epidemiology of HF as well as treatment of HIV in this population, the exact mechanisms underlying the increased risk of HF have not been fully elucidated. However, there are many potential pathways that may be implicated in HIV-associated HF pathogenesis based on emerging data (Figure 2).

AIDS-Associated Cardiomyopathy and Systolic Dysfunction – Relevance After Immune Recovery

Early studies evaluating AIDS-associated severe, dilated cardiomyopathy described the pathophysiology as related to opportunistic infections, autoimmune myocarditis, and direct HIV-induced myocardial damage. In autopsy studies of PWH, many different organisms including fungi, protozoa, bacteria, and viruses were identified in the myocardium.[23] Mechanisms for increased risk of autoimmune myocarditis have also been identified. These include a greater presence of cardiac-specific autoantibodies in PWH, potentially resulting in increased cardiac expression of HLA antigens and subsequent cardiac injury.[24,25] An initial landmark study showed that HIV nucleic acid sequences could be detected in the myocytes of patients with AIDS-associated cardiomyopathy but, importantly, this manuscript was later retracted due to concerns for falsification of data.[26] Subsequent studies have demonstrated that the site of cardiac infection is more likely to be the macrophages, dendritic cells, and endothelial cells, rather than cardiomyocytes which lack the HIV-1 receptor protein.[27] The HIV protein *Tat* has also been shown to cause dilated cardiomyopathy through mitochondrial damage in a transgenic mouse model.[28]

In the current era of early and uninterrupted ART, it is also important to understand whether there are any mechanisms that lead to cardiac injury during the acute phase of the infection that can contribute to downstream incident HF. Acute HIV infection is characterized by uncontrolled viral replication and results in a cytokine cascade involving tumor necrosis factor (TNF) α, interferon α, interferon γ, interleukin (IL) 6, IL 8, and IL 15.[29] While one purpose of this cytokine release is to activate the immune system to help control viral replication, it may also contribute to early cardiac pathology. In a study of 49 patients with

no underlying CVD, levels of N-terminal prohormone of brain natriuretic peptide (NT-proBNP) and troponin T during acute HIV infection were significantly elevated compared to levels after achieving viremic control.[30] Both biomarkers had a strong correlation with viral load. Thus, cardiac injury appears to begin early after HIV infection. More studies are needed to understand whether this early cardiac injury may create vulnerability to "second-hit" HF-inducing comorbidities, even after considerable immune recovery following uninterrupted ART.

Traditional Heart Failure Risk Factors

The predictors of HFpEF and HFrEF in the general population primarily consist of traditional cardiovascular risk factors such as age, HTN, diabetes mellitus (DM), smoking, along with underlying atherosclerotic CVD.[31] Therefore, measuring the prevalence of these risk factors in PWH is necessary to determine if they help explain the increased risk of HF. However, these risk factors are also deeply intertwined with HIV-associated immune dysfunction and ART, thus making it difficult to determine whether they are confounders or mediators of the HIV effect.

A meta-analysis of studies with data collected during 1996–2014 from 63,554 participants across the world showed an overall estimated prevalence of 25.2% for HTN. The prevalence was 34.7% for the ART-experienced group and 12.7% for the ART-naïve group.[32] The lower prevalence of HTN in the ART-naïve group has been shown in other studies as well and may be accounted for by factors associated with advanced HIV such as younger age, lower body mass index (BMI), and perhaps increased vasodilation in the setting of opportunistic infections.[33] While the prevalence of HTN in PWH on ART might be greater than that of the uninfected population, it is not clear whether HIV increases the risk of developing HTN compared to the general population[34–36] or whether this is merely an epidemiological artifact.

The rising rates of obesity and DM have contributed significantly to the increase in prevalence of HF, especially HFpEF, in the general population. These same risk factors are also affecting the HIV population.[37] Therefore, it is crucial to understand whether underlying HIV pathophysiology and associated factors, such as ART potentiate this relationship between metabolic dysfunction and HF in PWH. HIV infection was initially a wasting syndrome, although some studies in the pre-ART era showed significantly increased triglyceride levels in patients with AIDS compared to controls.[38] Lipodystrophy began to occur as a consequence of initial ART regimens, characterized by peripheral lipoatrophy and excess visceral adiposity eventually leading to dyslipidemia, insulin resistance, and DM. These toxicities were primarily attributed to PIs and mitochondrial toxicity from thymidine-based NRTIs.[39–41] While the currently recommended therapies are significantly less toxic, they continue to have some metabolic effects. There has been some concern regarding the association of abacavir with MI based on some cohort studies, although other analyses have not found an association.[42–44] Integrase strand inhibitors (INSTIs) are well-tolerated and have minimal effect on the lipid profile; however, some studies suggest increased risk of insulin resistance and there have been case reports of DM.[45] Both INSTIs and the current

generation of PIs, which are considered second line, still lead to increase in peripheral and central fat depots after initiation.[46]

While the current generation of ART may contribute to metabolic dysfunction, their potential effects are modest; thus, other HIV-related factors are likely implicated in the increased risk of metabolic disease such as DM. A recent survey from a nationally representative US sample of PWH showed a higher prevalence of DM than in uninfected adults, potentially at younger ages and lower BMI.[47] Potential mechanisms involve accessory proteins produced by HIV that are present in the blood even in the absence of viremia and contribute to adipocyte dysfunction. These proteins have been shown to inhibit pre-adipocyte differentiation as well as peroxisome proliferator-activated receptor gamma (PPAR-γ) in hepatocytes, while stimulating glucocorticoid receptors in adipocytes leading to hyperglycemia, dyslipidemia, and hepatic steatosis.[48] They may also regulate gene transcription by inhibiting Dicer, an RNAse that plays a role in maintaining the functionality of subcutaneous adipose tissue. Immune dysfunction in adipose tissue is thought to play a role as well. T-cells within the white adipose tissue of lean PWH are enriched for CD8+ T-cells, which is characteristic of obesity. These CD8+ T cells lead to increased adipocyte inflammation which promotes insulin resistance and DM through dysregulation of adipokines.[48] Furthermore, a study among PWH in Uganda demonstrated that pericardial fat was associated with subclinical myocardial dysfunction, suggesting that metabolic abnormalities in PWH may directly affect the heart.[49]

Cigarette smoking is another important risk factor for HF that disproportionately affects the HIV population. Rates of current smoking in PWH are 2- to 3-fold higher than in the general population. Prior data have shown that the risk of MI associated with being a previous or current smoker compared with a never smoker was significantly higher in PWH than in uninfected controls.[50] Similarly, exposure to smoking is associated with a population attributable fraction of 72% in PWH compared to 24% in uninfected controls.[50] This augmented effect of smoking on CVD in HIV may be explained, in part, by the increased levels of immune activation seen in smokers with HIV.[51]

The risk of HF is not only affected by a direct effect of risk factors discussed above on the myocardium but also through pathways involving coronary artery disease (CAD). While studies investigating risk of HF in PWH excluded baseline CVD and adjusted for interval MI in their analyses, CAD remains the most common cause of HF and thus is integral for HF prevention. The association between HIV and increased risk of MI has been demonstrated in several cohorts. In a large healthcare system-based cohort of PWH followed between 1996 and 2004, PWH had 1.75-fold higher adjusted relative risk for MI compared with HIV-uninfected persons.[52] Similarly, in a subsequent analysis of VACS data, PWH were at increased risk of MI compared with HIV-uninfected controls across 3 decades, from ages 40–70.[53] This increased risk of nearly 50% persisted despite adjusting for traditional CVD risk factors including cigarette smoking and substance use. Additional analyses with physician adjudication and phenotyping of MI in the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort showed approximately half of all MIs in PWH were type 2 MIs caused by clinical conditions such as infection and illicit drug use.[54] While a type 2 MI does not reflect an atherothrombotic event, it usually occurs in the setting of

underlying CAD and leads to myocardial injury. In the general population, incident type 2 MI has been shown to predict CVD death as well as HF.[55] Whether it also increases the risk of HF in PWH is not known, although a recent analysis demonstrated very high rates of mortality after type 2 MI for PWH.[56]

Myocardial Dysfunction from Persistent Immune Dysregulation

While traditional risk factors are certain to play a big role in the development of HF, chronic immune dysfunction in PWH likely contributes to myocardial dysfunction directly and perhaps by enhancing the effects of those risk factors on the myocardium. We have only recently started to appreciate the role of the immune system in cardiac homeostasis and disease in the general population. The response of immune cells to different cardiac insults including MI, infections, and CVD risk factors, such as HTN and DM, is important in understanding the subsequent development of HFpEF or HFrEF. Therefore, chronic immune dysfunction in HIV should be viewed as a key enhancing risk factor for HF in this population.

Persistent immune dysfunction in HIV primarily results from maintenance of viral reservoirs. HIV-1 preferentially infects activated memory CD4+ T-cells, most of which die, but a small proportion become part of a latent reservoir.[57] All antiretroviral medications work by preventing the virus from replicating but they do not target HIV-1 genomic material that is already integrated into the host cell DNA and they cannot eliminate the cells which harbor the integrated DNA. Interestingly, these memory CD4+ T cells and HIV-1 help promote each other. HIV-1 genes are often integrated with host genes associated with cell growth, thus promoting expansion of these T cells. At the same time, T cell activation creates chronic inflammation which stimulates immunoregulatory responses and down regulates effector cells that could help decrease HIV replication.[57] While memory CD4+ T cells are the primary reservoir cell for HIV-1 and predominantly reside in secondary lymph nodes, spleen, and gut mucosa, there is evidence that other T cell subsets and macrophages may also serve as an important reservoir.[58] Given that recruited monocytes from the periphery contribute to cardiac fibrosis and dysfunction in the general population, this could be a potential mechanism through which chronic HIV infection contributes to myocardial damage.[59] A study using the simian immunodeficiency virus model of AIDS in Rhesus macaques illustrated that blocking monocyte/macrophage trafficking to the heart decreases cardiac fibrosis and dysfunction.[60] There is also evidence in humans that there is persistent monocyte/macrophage activation despite suppressive ART.[61]

Cardiovascular imaging studies have allowed us to better quantify the relationship between myocardial dysfunction and persistent immune dysregulation in PWH. In a cross-sectional study, treated PWH without underlying CVD had increased levels of intramyocardial lipid and fibrosis compared to matched uninfected controls on cardiac magnetic resonance imaging (CMR). These findings strongly correlated with increased levels of markers associated with inflammation and monocyte activation.[62] Similarly, women with HIV on ART had increased myocardial fibrosis and diastolic dysfunction compared to matched uninfected controls. Both myocardial fibrosis and diastolic dysfunction significantly correlated with markers of monocyte activation.[63] Markers of monocyte and macrophage

activation are also significantly associated with increased levels of arterial wall inflammation in the aorta of PWH.[64] As aortic stiffness is known to contribute to HFpEF pathophysiology in the general population, these findings might represent another mechanism through which risk of HFpEF is increased in this population.[65]

Other studies have not evaluated myocardial dysfunction in the context of immune dysfunction in HIV. However, they have illustrated that subclinical myocardial dysfunction is significantly increased in PWH without other comorbidities, suggesting pathways that bypass traditional cardiovascular risk factors. In a study comparing normotensive PWH on ART with normotensive uninfected controls with similar fasting glucose and cholesterol levels, PWH had increased LV mass and worse diastolic function.[66] In fact their LV mass and diastolic function was similar to hypertensive uninfected controls. In a study of nonsmokers without history of CVD or DM and no difference between groups with respect to blood pressure or anthropometric measures, PWH on ART had higher myocardial lipid levels and myocardial fibrosis, along with a lower LV systolic longitudinal strain compared to uninfected controls.[67] Additional CMR studies have confirmed these findings of increased myocardial mass, myocardial lipid, diastolic dysfunction, localized scar, and diffuse myocardial fibrosis in PWH on ART without prior CVD.[62,68–70] While these studies have focused on PWH without prior CVD, there is evidence that HIV-infected adults develop more extensive myocardial scar than uninfected persons in the post-MI setting.[71]

In totality, these results lend credence to the hypothesis that immune dysfunction contributes significantly to the increased risk of incident HF in PWH. However, there is a strong need for further delineating the pathways that lead from immune dysregulation to myocardial dysfunction. This will need a combination of additional studies using both animal models such as SIV-infected macaques and well-curated cohorts of PWH on current generation ART with linked biorepositories, myocardial imaging, and adjudicated HF events.

Heart Failure Prevention

The first step in preventing incident HF in this population is to effectively treat the underlying traditional cardiovascular risk factors. The rates of appropriate guideline-recommended cardiovascular care are lower in PWH compared to the general population.[72] PWH are also at high risk for mental health disorders such as depression, which is associated with an increased risk of incident HF.[73] This disparity is further compounded by factors such as sex and race. Compared to whites, blacks are less likely to receive ART, experience viral control, HTN control, DM control or lipid monitoring.[74] Further, recent data suggest that racial disparities in appropriate statin prescription may be exacerbated for PWH compared with HIV-uninfected persons.[75] Removing these barriers to primary prevention through public policy and promoting awareness of the increased risk of CVD in this population are key initial steps. Furthermore, comprehensive scientific statements reviewing the best available data and determining practices most likely to prevent CVD among PWH are essential; the recent American Heart Association scientific statement on HIV and CVD provides general guidance regarding CVD prevention for PWH,[76] albeit in the context of still-limited data.

Risk prediction is another important tool in prevention. Yet, unlike atherosclerotic CVD, there is no well-accepted HF risk prediction tool for the general population. Nonetheless, a risk prediction score can aid in risk stratification and provide physicians the impetus to intensify available therapies; however, quantification of HF risk attributable to HIV is not exact. As described earlier, studies have demonstrated a 1.5–2 fold greater risk for HF in PWH, especially in those who had a delay in ART initiation and were exposed to a prolonged period of viremia with evidence of immune dysfunction (current low CD4 count, low CD4/CD8 ratio, or low nadir CD4). In the AHA scientific statement discussed above, the writing group offers a general guide to assessing CVD risk for PWH.[76]

Early identification of subclinical myocardial damage through serum and imaging-based markers may also be important in preventing incident HF for PWH. This will be especially important as the epidemiology shifts to HFpEF, which can be more difficult to diagnose. Markers such as NT-proBNP have been associated with CVD events, including HF, and mortality in the HIV population.[77,78] However, using NT-proBNP as a screening tool in PWH to reduce incident HF has not been evaluated. Other biomarkers expressed by cardiac tissue in the setting of stress, such as soluble ST2 and growth differentiation factor-15, have also been associated with adverse cardiac mechanics and overall mortality in PWH.[79,80] Routine use of speckle tracking to quantify left ventricular longitudinal strain might also help identify early myocardial dysfunction in PWH. Decrease in left ventricular global longitudinal strain has been associated with immune dysfunction as measured by nadir CD4 <250 cells/mm^3 or current CD4 <500 cells/mm^3.[81]

In PWH with risk factors such as DM and HTN, data are sparse with respect to which treatment options might be most effective in decreasing long-term CVD risk. Small studies with Telmisartan, which acts as both an angiotensin receptor blocker and a PPAR-γ agonist, have illustrated dramatic effects on blood pressure as well improvement in lipid metabolism, renal function, and a potential endothelial protective effect in PWH.[82] Given that HIV-1 promotes production of renin by CD4 T cells and, in return, renin is important for HIV replication within T cells, inhibition of RAAS is appealing as the first line therapy for HTN.[83]

Similarly, there are no HIV-specific guidelines for first-line therapy for DM. The rising prevalence of metabolic dysfunction, obesity, and DM should make sodium-glucose cotransporter 2 (SGLT2) inhibitors an attractive agent in PWH as a HF prevention therapy. The cardio-protective effects of SGLT2 inhibitors work through mechanisms that are enhanced in HIV. These effects include amelioration of cardiac fibrosis, reduction in sympathetic activity and epicardial fat, improved metabolism leading to weight loss and decreased insulin resistance, and potential improvement in systemic inflammation and endothelial dysfunction.[84] However, the potential benefits of metformin in HIV are worth considering as well. Metformin appears to improve metabolic indices and even reduce atherosclerosis progression in PWH.[85] However, it might have unique benefits in PWH by reducing the HIV reservoir through immunomodulatory effects, as metformin may actually help improve CD4+ T cell counts in diabetic PWH.[86] The effects of metformin in PWH could be due to multiple pathways including overcoming the inhibition of adenosine monophosphate-activated protein kinase (energy sensor for cells including T cells) from

HIV Tat protein, anti-inflammatory effect on the gut by suppressing nuclear factor κB activation, reduction of anti-inflammatory cytokines such as TNF-α, and changing the gut microbiota composition.[87] The hypothesis that metformin can reduce HIV reservoir in the gut and decrease immune activation is currently being evaluated in the Lilac study.[87]

Statins have also been shown to have immunomodulatory and anti-inflammatory effects. Therefore, statin therapy could play a role in HF prevention in PWH beyond effects related to prevention of MI. Studies have shown a decrease in markers of fibrosis in PWH with statin therapy, an effect that correlates closely with decrease in immune activation.[88] Pitavastatin has also been shown to significantly reduce markers of immune activation and arterial inflammation.[89] The effects of Pitavastatin on CVD in PWH will be comprehensively evaluated in the ongoing REPRIEVE trial.[90]

While these therapies have been translated from work done in the general population, it will be important to develop therapies that address HIV-specific pathophysiology, such as the underlying immune dysfunction. These therapies have been broadly focused on eradicating latent reservoirs of HIV. One strategy has been to induce latently infected cells to produce virus and reverse latency with subsequent interventions to augment the ability of the host to clear these cells.[91] These interventions could include vaccines, neutralizing monoclonal antibodies, and immune checkpoint blockade. Both vaccines and immune checkpoint inhibitors allow for a more robust HIV-1 specific CD8+ T cell response, which has also been observed in elite controllers (individuals who can control viral replication without ART). Development of targeted therapies that eradicate the latent reservoirs and restore immune function may help treat chronic diseases such as HF in PWH.

Conclusions

There are numerous pathways that require further investigation using methods spanning the translational spectrum to lower the elevated risk of incident HF in PWH. This involves improving systems of care to allow for more equitable delivery of healthcare and more trials in the HIV population, as findings in the general population may not always apply. Developing tools and drugs that selectively reverse immune dysfunction may help prevent and treat HF in this population. In the meantime, it will be important for clinicians taking care of PWH to identify individuals at the highest risk (presence of immune dysfunction and CVD risk factors) and consider early screening for further risk stratification (sample pathway for HF prevention in PWH provided Figure 3). For those at highest risk, clinicians should consider aggressive risk factor modification with RAAS inhibition, statin therapy, and perhaps SGLT2 inhibitor or metformin when applicable.

As the HIV population ages, the morbidity and mortality attributable to HF will continue to rise. The focus of HIV treatment has switched from preventing opportunistic infections to preventing chronic diseases such as HF. While important advances have been made in identifying the increased risk of HF in HIV, many gaps remain in our understanding. These include the changing epidemiology of HF in the setting of current ART guidelines, underlying immune mechanisms that contribute to myocardial dysfunction and exacerbate the myocardial effects of traditional CVD risk factors, and optimal methods for HF risk

assessment and prevention. These gaps need to be filled to address the growing burden of HF in this population.

Acknowledgments

Abbreviations:

ART	antiretroviral therapy
BMI	body mass index
BP	blood pressure
CAD	coronary artery disease
CMR	cardiac magnetic resonance imaging
CNICS	Centers for AIDS Research Network of Integrated Clinical Systems
CVD	cardiovascular disease
DM	diabetes mellitus
EF	ejection fraction
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HR	hazard ratio
HTN	hypertension
IL	interleukin
INI	integrase inhibitors
LV	left ventricular
MI	myocardial infarction
NNRTI	non-nucleoside reverse transcriptase inhibitors
NRTI	nucleoside reverse transcriptase inhibitor
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
PWH	people living with HIV

PI	protease inhibitors
PPAR-γ	peroxisome proliferator-activated receptor gamma
RAAS	renin-angiotensin-aldosterone system
SGLT2	sodium-glucose cotransporter 2
SIV	simian immunodeficiency virus
TNF	tumor necrosis factor
VACS	Veterans Aging Cohort Study

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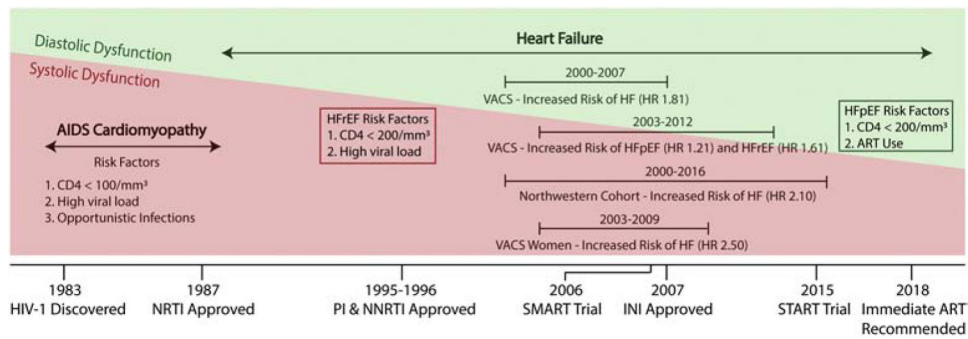
Figure 1.
Evolving epidemiology of heart failure and cardiac dysfunction. The pre-ART era was characterized by AIDS-cardiomyopathy. The post-ART era is characterized by less systolic dysfunction and rising diastolic dysfunction. Major cohort studies have demonstrated an increased risk of heart failure in people with HIV. Both HFpEF and HFrEF are associated with immune dysfunction as characterized by nadir CD4+ T cell count. HFrEF is also associated with viral load while HFpEF is associated with certain ART regimens.
HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; VACS, Veterans Aging Cohort Study; ART, antiretroviral therapy; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; INI, integrase inhibitor; SMART Trial[4], continuous ART superior to episodic ART guided by CD4+ T cell count; START Trial[5], early ART initiation at CD4+ T cell count >500/mm³ was beneficial.
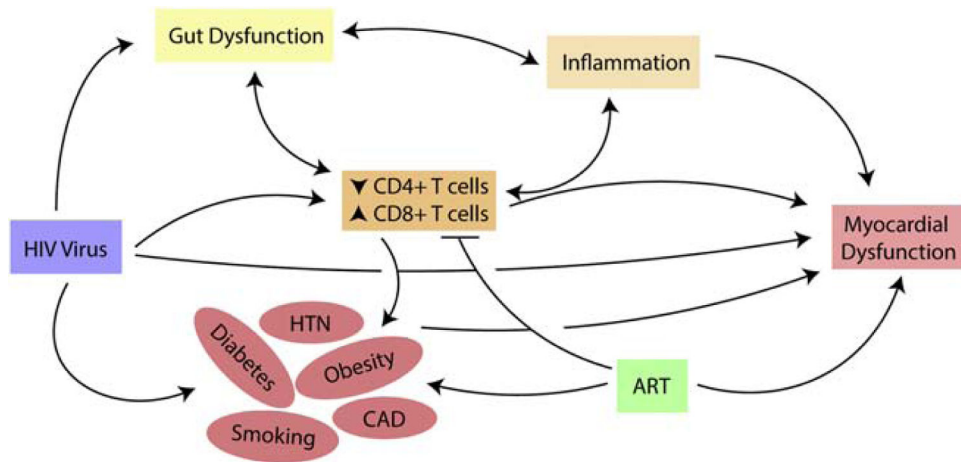
Figure 2.
Pathways leading to myocardial dysfunction and development of heart failure in people with HIV.

CAD, coronary artery disease; HTN, hypertension; ART, antiretroviral therapy.
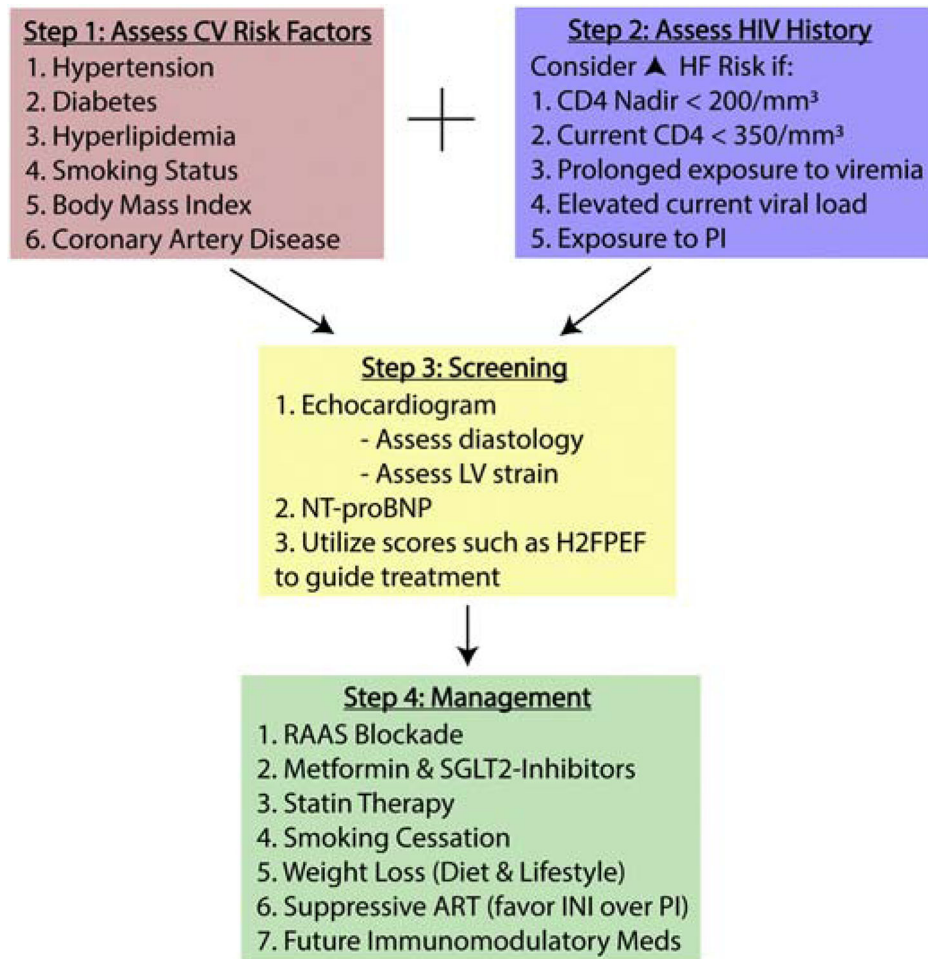
Step 1: Assess CV Risk Factors
1. Hypertension
2. Diabetes
3. Hyperlipidemia
4. Smoking Status
5. Body Mass Index
6. Coronary Artery Disease

Step 2: Assess HIV History
Consider ▲ HF Risk if:
1. CD4 Nadir < 200/mm³
2. Current CD4 < 350/mm³
3. Prolonged exposure to viremia
4. Elevated current viral load
5. Exposure to PI

Step 3: Screening
1. Echocardiogram
    - Assess diastology
    - Assess LV strain
2. NT-proBNP
3. Utilize scores such as H2FPEF
to guide treatment

Step 4: Management
1. RAAS Blockade
2. Metformin & SGLT2-Inhibitors
3. Statin Therapy
4. Smoking Cessation
5. Weight Loss (Diet & Lifestyle)
6. Suppressive ART (favor INI over PI)
7. Future Immunomodulatory Meds

Figure 3.
Proposed algorithm to prevent heart failure in people with HIV.
CV, cardiovascular; HF, heart failure; LV, left ventricular; NT-proBNP, N-terminal-pro B-type Natriuretic Peptide; H2FPEF, echocardiogram and clinical characteristics score to determine risk of heart failure with preserved ejection fraction[92]; RAAS, renin-angiotensin-aldosterone system; SGLT2, sodium-glucose cotransporter 2; ART, antiretroviral therapy; PI, protease inhibitor; INSTI, integrase strand transfer inhibitor.