Current HIV/AIDS Reports (2019) 16:371–380
https://doi.org/10.1007/s11904-019-00458-1

COMPLICATIONS OF HIV AND ANTIRETROVIRAL THERAPY (GA MCCOMSEY, SECTION EDITOR)

Heart Failure among People with HIV: Evolving Risks, Mechanisms, and Preventive Considerations

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Published online: 3 September 2019

Abstract

Purpose People with HIV (PHIV) with access to modern antiretroviral therapy (ART) face a two-fold increased risk of heart failure as compared with non-HIV-infected individuals. The purpose of this review is to consider evolving risks, mechanisms, and preventive considerations pertaining to heart failure among PHIV.

Recent Findings While unchecked HIV/AIDS has been documented to precipitate heart failure characterized by overtly reduced cardiac contractile function, ART-treated HIV may be associated with either heart failure with reduced ejection fraction (HFrEF) or with heart failure with preserved ejection fraction (HFpEF). In HFpEF, a "stiff" left ventricle cannot adequately relax in diastole—a condition known as diastolic dysfunction. Diastolic dysfunction, in turn, may result from processes including myocardial fibrosis (triggered by hypertension and/or immune activation/inflammation) and/or myocardial steatosis (triggered by metabolic dysregulation). Notably, hypertension, systemic immune activation, and metabolic dysregulation are all common conditions among even those PHIV who are well-treated with ART. Of clinical consequence, HFpEF is uniquely intransigent to conventional medical therapies and portends high morbidity and mortality. However, diastolic dysfunction is reversible—as are contributing processes of myocardial fibrosis and myocardial steatosis.

Summary Our challenges in preserving myocardial health among PHIV are two-fold. First, we must continue working to realize UNAIDS 90-90-90 goals. This achievement will reduce AIDS-related mortality, including cardiovascular deaths from AIDS-associated heart failure. Second, we must work to elucidate the detailed mechanisms continuing to predispose ART-treated PHIV to heart failure and particularly HFpEF. Such efforts will enable the development and implementation of targeted preventive strategies.

Keywords HIV · Heart failure

Introduction

Early in the course of the HIV epidemic, front-line physician-scientists noted diverse presentations of profound myocardial and pericardial disease among patients with AIDS [1]. In this pre-antiretroviral therapy (ART) era, AIDS-associated heart failure was typically characterized by overt reductions in cardiac contractile function, with or without ventricular chamber dilation [1]. Several factors were noted to underlie such heart failure presentations: first, direct myocardial infiltration by HIV [2]—with or without concomitant infiltration by opportunistic viruses, parasites, and/or bacteria [1]; second, a robust autoimmune reaction in the myocardial structural space, likely triggered by infection [3]; third, pericardial disease, particularly among those patients also battling tuberculosis, Kaposi's sarcoma, or lymphoma [1]. With the introduction of early ART, including the nucleoside reverse transcriptase inhibitor (NRTI) zidovudine (AZT), the contributions of co-infections to heart failure risk abated. At once, it became apparent that select antiretroviral therapeutics exerted cardiotoxic effects [4].

Today, PHIV with access to modern ART continue to face significant health threats from heart failure. Heart failure is a

This article is part of the Topical Collection on *Complications of HIV and Antiretroviral Therapy*

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disease of aging, whereby the general-population prevalence increases steadily across successive age deciles [5]. Adjusting for age, PHIV with access to ART confront an approximately two-fold increased risk of heart failure [6, 7•, 8, 9•, 10•]. Thus, as the global population of PHIV ages [11–13], heart failure prevalence in this group of 37 million individuals may be anticipated to spike. Of further concern, heart failure outcomes in the general population are poor [14] and worse still among PHIV: indeed, the 5-year mortality rate among PHIV diagnosed with heart failure approaches 50% [15].

Our challenges in preserving myocardial health among PHIV are thus two-fold. First, we must continue work to realize UNAIDS 90-90-90 goals. This achievement will reduce AIDS-related mortality, including cardiovascular deaths from dilated cardiomyopathy. Second, we must remain cognizant of the ongoing threat heart failure continues to pose to aging ART-treated PHIV. Our attention should center on elucidating mechanisms fueling heart failure risk among ART-treated PHIV, including persistent systemic immune activation and metabolic dysregulation. Enhanced understanding of factors contributing to increased heart failure risk and associated adverse outcomes in the aging HIV population will enable the development and implementation of targeted preventive strategies. Given the poor prognosis of heart failure among PHIV, primacy is on prevention. In this context, the present review focuses on heart failure risks, mechanisms, and preventive considerations relevant to ART-treated PHIV.

Heart Failure Risks Among Contemporary Cohorts of PHIV

A systematic review and meta-analysis of cardiac dysfunction among PHIV—inclusive of studies across time and place—highlights the manner in which population-specific heart failure risks are evolving [16••]: Erqou et al. selected 54 studies conducted in diverse regions (Africa, Asia, Europe, and North America) and published anywhere between 1988 and 2017 [16••]. Analyzing data from 125,382 PHIV (82% men), Erqou et al. determined a pooled heart failure prevalence of 6.5% (4.4%, 9.6%). This observed heart failure prevalence among PHIV was surprisingly high, given the relatively low average age of the cohort (47 years). Of note, among those PHIV studied, only 77% were on ART and a significant proportion had untreated, uncontrolled HIV/AIDS [16••].

Importantly, key North American studies analyzing incident heart failure by HIV status in contemporary cohorts consistently suggest an increased relative risk of heart failure among PHIV with access to ART [6, 7•, 8, 9•]. Butt et al. examined data from an all-male cohort of US Veterans without prior cardiovascular disease (CVD), including 2391 PHIV and 6095 controls followed from 2000 through 2007 [6]. Median age in both groups was 48 years. Age- and race-adjusted heart failure incidence per 1000 person-years (based on diagnosis codes) was 7.21 among PHIV (95% confidence interval, CI, 6.90–7.34) and 4.82 (95% CI 4.72–4.91) among controls. Overall, the hazard ratio for heart failure among individuals with vs. without HIV was 1.81 (95% CI 1.39–2.36), after adjustment for traditional heart failure risk factors [6]. Of note, this hazard ratio was not adjusted for history of depression, renal dysfunction, or liver dysfunction—all parameters subsequently associated with incident heart failure in this cohort [17–19]. Feinstein et al. explored data from a predominantly male US cohort including 4640 PHIV (83% men) and 4250 matched control subjects (80% men)—all without prior heart failure—followed from 2000 to 2016 [7•]. In this study, the hazard ratio for incident physician-adjudicated heart failure among PHIV vs. controls was 2.10 (95% CI 1.38–3.21) after adjustment for traditional heart failure risk factors. Compared with the VA Cohort, this cohort was slightly younger (average age 40–41 years) [7•]. Notably, in both cohorts, only approximately half of PHIV evidenced viral loads < 500 copies/ml [6, 7•]. In the study by Butt et al., the increased risk of heart failure among PHIV was *only* significant among those with uncontrolled viremia. By contrast, in the study by Feinstein et al., higher viral load (and lower $CD4^+$ T cell count) tracked with heart failure risk among PHIV, but even those PHIV with suppressed viremia saw increased heart failure risk as compared with controls [6, 7•]. Finally, the US Partners Healthcare Database heart failure study—focused on 1388 women with HIV (WHIV) and 13,781 matched control subjects without prior heart failure—demonstrated a nearly four-fold increased incidence of physician-adjudicated heart failure among WHIV [9•]. In this study, led by Janjua et al., the average age of both cohorts was 59 years. Among the WHIV, 92% were on ART, though again, only approximately 50% had achieved viral suppression [9•].

Most recently, Yen et al. published a large study analyzing nationally representative data on heart failure among PHIV from the Taiwan Centers for Disease Control and Prevention HIV Surveillance System, coupled with data on heart failure among age- and sex-matched controls without HIV from the Taiwan National Health Insurance Research Database [10•]. Overall 24,153 PHIV (94% men; 72% on ART) and 96,612 control subjects (94% men) without known heart failure were followed from 2003 to 2014. In this cohort, the average age was only 33 years. Nevertheless, PHIV demonstrated a 1.5-fold increased incidence of heart failure (non-adjudicated). The hazard ratio for heart failure among individuals with vs. without HIV was 1.52 (95% CI 1.27 to 1.82) after adjustment for traditional heart failure risk factors. Moreover, the time to incident heart failure was significantly shorter among PHIV vs. controls ($P < 0.001$) [10•].

Taken together, studies from North America and Asia reveal an approximately 2-fold increased risk of heart failure

among contemporary cohorts of PHIV with access to ART. Within these cohorts, even when ART has been prescribed, suboptimal viral control is common and appears to be associated with augmented risk.

Outcomes Among Contemporary Cohorts of PHIV with Heart Failure

Soberingly, multiple studies across regions suggest heart failure outcomes are worse among PHIV vs. non-HIV-infected individuals. In the general population, a diagnosis of heart failure is associated with recurrent hospitalization, decreased quality of life, and high rates of mortality within 5 years [14]. Analysis of data from the predominantly male US Veterans Cohort suggests that among PHIV with heart failure, 5-year mortality rates approached 50% [15]. Analogously, Janjua et al. showed through the US Partners Healthcare Database heart failure study that among women with heart failure, HIV positivity conferred an increased risk of all-cause mortality, cardiovascular mortality, and heart failure hospitalization [9•]. Indeed, the hazard ratio for recurrent heart failure hospitalization among WHIV vs. non-HIV-infected women was 2.58 (95% CI 1.55–4.29) after adjustment for traditional heart failure risk factors [9•]. Finally, through the sub-Saharan Africa Survey of Heart Failure (THESUS HF) study, Sliwa et al. analogously confirmed worse outcomes among PHIV with heart failure [20, 21]. This prospective multi-center study recruited 1006 patients with acute heart failure (51% women) from 9 countries in sub-Saharan Africa between 2007 and 2010 and followed these patients for 6 months. Within this cohort, hypertension prevalence was a striking 56% while HIV prevalence was 7%. Analyses by Sliwa et al. illustrated that in this group, HIV status conferred an increased risk of all-cause mortality and 60-day hospital readmission [20, 21].

A recent mixed-sex study of heart failure outcomes among US PHIV vs. controls suggested worse outcomes only among those PHIV with unchecked viremia [22]. In this study, Alvi et al. studied all individuals admitted with heart failure to an urban academic medical center (Montefiore) in 2011 and followed for 2 years [22]. The recruited cohort included 374 PHIV (53% men) and 1934 non-HIV infected individuals (55% men). Groups were similar with respect to demographics (average age 60 years) and traditional CV risk factors. In follow-up, the broad group of PHIV demonstrated increased rates of all-cause mortality, CV mortality, and heart-failure re-admission. Among this group, 92% were on ART, but a smaller percentage evidenced suppressed viral load. In sub-analyses, the aforementioned trends held up only for the subgroup with unchecked viremia (viral load > 500 copies/ml) or markedly reduced immune function ($CD4^+$ T cell count < 200 cell/mm^3). Of potential clinical relevance, additional analyses performed within the cohort of PHIV showed that use of ritonavir-boosted protease inhibitors (PIs) was associated with a 2-fold increased risk of cardiovascular mortality and 30-day heart failure readmission [23]. This finding ran in contrast to early work implicating older NRTIs in mitochondrial injury and attendant cardiotoxicity [24–26].

What Clinicians Caring for PHIV Need to Know About Heart Failure Subtypes

Heart failure is subclassified based on left ventricular ejection fraction (EF), which is the percentage of blood leaving the left ventricle each time it contracts [27]. Patients with clinical heart failure may thus have heart failure with reduced ejection fraction (HFrEF; EF < 40%), heart failure with preserved ejection fraction (HFpEF; EF ≥ 50%), or heart failure with borderline ejection fraction (EF 40–49%). Several experts believe HFrEF and HFpEF constitute distinct disease processes, whereby HFpEF may not represent a stage *en* route to HFrEF [27]. Indeed, differences abound in HFrEF vs. HFpEF etiology, triggering risk factors, and ensuing pathophysiology.

HFrEF tends to be caused by disorders which affect myocardial contractile function and/or afterload (the pressure against which the heart pumps to circulate blood) [28]. Examples include acute myocardial infarction leading to focal myocardial fibrosis, infectious/autoimmune myocarditis, toxin-induced cardiomyopathy, and valvulopathy. Thus, parameters predisposing to HFrEF include traditional metabolic risk factors (hypertension, dyslipidemia, dysglycemia, cigarette smoking) as well as infectious risk factors and toxic exposures [28, 29]. With the aforementioned etiologies, myocyte loss and associated cardiac remodeling may ensue, possibly leading to chamber dilation. From a pathophysiologic perspective, by affecting contractile function and/or afterload, etiopathologic causes of HFrEF reduce the stroke volume (blood volume pumped from ventricle with each cardiac cycle) and, in turn, the cardiac output (a product of stroke volume and heart rate). Thus, HFrEF patients experience reduced forward flow of blood during systole and a secondary back-up of high pressures [28].

HFpEF, by contrast, is typically caused by processes which incite the myocardium to stiffen, resulting in inadequate relaxation during diastole (or "diastolic dysfunction") [30]. Examples include diffuse myocardial fibrosis and myocardial steatosis. Risk factors for HFpEF include select traditional metabolic risk factors such as hypertension and dysglycemia, as well as female sex and advanced chronological age [29, 30]. Myocyte loss and ensuing chamber dilation are less common, but increased wall thickness is characteristic. By affecting relaxation during diastole, etiopathologic causes of HFpEF result in unacceptably highly filling pressures required to achieve adequate preload and maintain cardiac output.

Increased left ventricular filling pressures, in turn, lead to a back-up of high pressures. Moreover, while patients with HFpEF appear to have grossly normal systolic function at rest, these patients often cannot adequately augment cardiac output in response to exercise [30].

Differences notwithstanding, HFrEF and HFpEF have select features in common [27]. For example, a shared *clinical* presentation of heart failure characterized by a combination of exertional dyspnea (related to reduced forward flow), pulmonary edema (related to left-sided pressure back-up), and possibly hepatic congestion/peripheral edema (related to right-sided pressure back-up). Though systolic dysfunction defines HFrEF and diastolic dysfunction remains a hallmark of HFpEF, subtle forms of both types of dysfunction may co-exist in patients with either of these diseases. Moreover, both diseases are characterized by chronotropic incompetence (inability to adequately augment heart rate) and vascular dysfunction (e.g., impaired endothelial vasorelaxation, leading to vascular stiffness). Finally, both forms of heart failure may trigger analogous compensatory responses including activation of the sympathetic nervous system and renin-angiotensin-aldosterone system (RAAS) and release of natriuretic peptides. In the short term, these compensatory processes may help maintain cardiac output, but in the long run, these responses exacerbate ventricular remodeling and worsening symptomatology [27].

As HFrEF and HFpEF may differ with respect to underlying etiology and pathophysiology, it is plausible that these two diseases may respond differently to medical therapies. Among patients with HFrEF, several pharmacologic interventions significantly reduce the hazard ratio for heart failure hospitalization or death [27]. Thus, there is a standard paradigm for treating patients with HFrEF: RAAS blockade, beta blockade, and possibly symptomatic treatment with diuresis or afterload reduction [31]. In contrast, among patients with HFpEF, analogous interventions have not been shown to reduce the hazard ratio for heart failure hospitalization or death [30]. Thus, the astute clinician must try to identify early HFpEF phenotypes and intervene on relevant risk factors in the hopes of forestalling the transition to overt HFpEF—a morbid condition intransigent to medical therapy.

Clinical and Pre-clinical Heart Failure Phenotypes Among PHIV: Evolving Patterns

Erqou's meta-analysis of cardiac dysfunction as assessed through multiple studies across time and place highlights ways in which heart failure risk is evolving among PHIV [16••]. In this meta-analysis, a shift toward a lower prevalence of systolic dysfunction among PHIV was noted in more recent studies and studies conducted in regions characterized by widespread ART access. Overall, the pooled prevalence of left ventricular systolic dysfunction (EF < 50% or fractional shortening < 26%) was 12.3% (95% CI 6.4%–19.7%). Consonant with these observations are juxtaposed findings on clinical heart failure phenotypes among PHIV gleaned from the South African Heart of Soweto Study and from three US studies. Through the Heart of Soweto study, Sliwa et al. characterized the presentation of 518 PHIV (62% women, average age 39 years, 54% on ART) presenting to a major urban hospital between 2006 and 2008 with acute CVD [32•]. Among all CVD presentations, a significant proportion were caused by dilated cardiomyopathy (38%) or pericarditis (25%). No cases of HFpEF were noted [32•]. By contrast, studies of predominantly male cohorts of US PHIV with heart failure (US Veterans Cohort; US Montefiore Cohort) suggest a near-even split of HFrEF vs. HFpEF [22, 33•]. Moreover, in Janjua's analysis of US WHIV with heart failure (Partners Healthcare Cohort), a striking shift toward HFpEF was noted (71% HFpEF vs. 29% HFrEF) [9•]. Notably, the average age in the US cohorts was significantly higher than that in the South African cohort and ART uptake was higher [9•, 22, 33•]. By inference, it appears that among PHIV, ART access, chronologic age, and women's sex may represent risk factors for HFpEF. Thus, as ART access expands and the global population of PHIV ages, we may expect to see a surge in HFpEF cases—particularly in Sub-Saharan Africa. In Sub-Saharan Africa, where the majority of all adults with HIV reside [34], approximately 50% of PHIV are women [34] and among both WHIV and MHIV, hypertension is highly prevalent [35–37].

Among PHIV, while the prevalence of overt systolic dysfunction appears to be declining over time, rates of diastolic dysfunction—a pre-clinical phenotype, which progresses at a rate of 2%/year to symptomatic heart failure [38]—may be on the rise; Erqou's meta-analysis incorporating studies old and new suggested the population prevalence of diastolic dysfunction (grades 1–3) among PHIV was 29.3% (22.6 to 36.5%) [16••]. By contrast, general-population studies suggest the prevalence of diastolic dysfunction runs closer to 10% [39]. Perhaps not surprisingly, then, in Erqou's meta-analysis, the relative risk of all grades of diastolic dysfunction among studied PHIV vs. controls was 3 (95% CI 1.8–5.1) [16••]. Notably, a meta-analysis of cardiac dysfunction among PHIV by Cerrato et al. including 11 studies (1 from North Africa, 1 from Asia, 6 from Europe, and 3 from North America) all published between 2004 and 2011 suggested an even higher prevalence of diastolic dysfunction among PHIV [40]. In this study, among 2242 PHIV (%men not reported, median age 42 years, 98% ART, 74% undetectable viral load), the prevalence of diastolic dysfunction was 43.38% (95% CI 31.73–55.03). By contrast, the prevalence of overt systolic dysfunction (impaired LVEF) was 8.33% (95% CI 2.20–14.25). In multivariable analysis, factors

associated with diastolic dysfunction included older age (OR = 2.50 per 10 years increase; 95% CI 1.70–3.60) and hypertension (OR = 2.30; 95% CI 1.20–4.50). By contrast, factors associated with systolic dysfunction included history of myocardial infarction 15.90 (95% CI 1.94–329.00) and active cigarette smoking 1.70 (95% CI 1.03–2.77) [40].

Two Processes Which May Be Expected to Contribute to Diastolic Dysfunction Among ART-Treated PHIV Are Myocardial Fibrosis and Myocardial Steatosis

Myocardial fibrosis and myocardial steatosis are two pathologic processes which may be expected to contribute to diastolic dysfunction among contemporary cohorts of ART-treated PHIV. In a healthy state, cardiomyocytes occupy most of the myocardial structural space. The remaining myocardial structural space is filled by the cardiac interstitium, including collagen produced by myofibroblasts [41, 42]. Further, in a health state, cardiomyocytes contain miniscule amounts of triglyceride—on the order of 0.4–0.6% [43]. Myocardial fibrosis is a pathologic process in which the myocardial tissue collagen volume fraction is increased [42]. The distribution of myocardial fibrosis may be diffuse (reactive interstitial fibrosis) or focal (replacement fibrosis or scarring). Major drivers of diffuse myocardial fibrosis include aging, hypertension, systemic/myocardial inflammation/immune activation, and micro-ischemia caused by suboptimal stress-induced augmentation of myocardial blood flow. Focal myocardial fibrosis, by contrast, is most frequently caused by acute myocardial infarction [42]. Myocardial steatosis is a pathologic process characterized by increased deposition of lipids (predominantly triglycerides) within cardiomyocytes—increased intramyocardial triglyceride content. Major drivers of myocardial steatosis include age, obesity, abnormal lipid metabolism, dysglycemia, and endothelial dysfunction [43]. Both fibrosis and steatosis contribute to myocardial stiffness—impairing relaxation and resulting in diastolic dysfunction [42, 43]. Over the past decade, general-population studies have revealed that fibrosis relates closely to diastolic dysfunction, HFpEF, and cardiovascular mortality [44–46]. Moreover, studies in populations with diabetes suggest a close inverse relationship between steatosis and diastolic function [47, 48]. Importantly, among populations without HIV, both myocardial fibrosis and myocardial steatosis have been shown to be modifiable with therapy tailored to the pathophysiologic driver—e.g., antihypertensive therapy geared toward reducing fibrosis or therapy with peroxisome proliferator-activated receptor gamma (PPAR-γ) agonism aimed toward mitigating steatosis [49–52].

Among ART-treated PHIV, systemic immune activation may drive myocardial fibrosis while ongoing metabolic dysregulation may predispose to myocardial steatosis. Systemic immune activation persists even among those individuals with HIV whose virus is completely suppressed by combined antiretroviral therapy [53–55]. ART, even when administered early in the course of the disease, dampens select indices of systemic immune activation, but many indices of systemic immune activation remain elevated [56]. In this regard, low-level viral replication, viral coinfection, and enhanced microbial translocation may be culprits [57]. Further, a significant proportion of ART-treated PHIV experience metabolic dysregulation, which may be driven by HIV infection itself, HIV-associated immune activation, HIV-associated hormonal perturbations including relative growth hormone deficiency [58] and RAAS activation [59], and/or off-target effects of select antiretroviral therapeutics [24–26]. Forms of metabolic dysregulation demonstrated by PHIV are varied. While select early ART regimens tended to evoke overt lipodystrophy (peripheral lipoatrophy with or without central lipohypertrophy) [60], many modern regimens are better-tolerated. Nevertheless, ART initiation continues to be associated with weight gain [61], accumulation of excess adiposity [62], and ectopic fat deposition [63, 64]—all processes associated with development of traditional cardiometabolic risk factors.

Of interest, theoretically, systemic immune activation may predispose to myocardial fibrosis either by prompting inflammation in the myocardial structural space (inflammatory mechanism) or by contributing to arterial inflammation [65, 66] and downstream coronary microvascular dysfunction [67] (inflammatory-ischemic mechanism). Meanwhile, myocardial steatosis may trigger inflammation in the myocardial structural space, feeding into in situ fibrosis (metabolic-inflammatory mechanism). General-population studies have also highlighted relationships between coronary microvascular dysfunction and myocardial steatosis [68], but cause/effect determinations remain elusive. In at least one cardiac MRI/MRS study among PHIV, myocardial fibrosis has been shown to correlate with myocardial steatosis [69•], and in two such studies, myocardial steatosis has been shown to correlate with diastolic dysfunction [70, 71]. Notably, no cardiac MRI/MRS study among PHIV has identified a relationship between myocardial fibrosis and diastolic dysfunction, although such a relationship has been convincingly demonstrated in general-population studies [44]. Moreover, general-population studies have linked myocardial fibrosis with ensuing heart failure and cardiovascular death [45, 46]. Additional work is needed to examine whether the increased burden of diffuse myocardial fibrosis among asymptomatic PHIV with access to ART may help to explain heightened risks of diastolic dysfunction [40], heart failure [6, 7•, 8, 9•, 10•, 33•], pulmonary hypertension [72], and cardiac dysrhythmia/sudden cardiac death [73].

Insights on the Development of Pre-heart Failure Phenotypes Among Contemporary Cohorts of PHIV—Comparative Analysis of Population-Specific Physiology Studies Employing Cardiac Magnetic Resonance Imaging and/or Spectroscopy

Cardiac magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) technologies enable simultaneous, detailed characterization of myocardial structure and function [74–79]. A series of cardiac MRI/MRS studies in contemporary cohorts of asymptomatic individuals with vs. without HIV have contributed to elucidating pathophysiologic mechanisms underlying HIV-associated myocardial fibrosis/steatosis and diastolic dysfunction.

Two European studies employing cardiac MRI/MRS to study a predominantly male cohort revealed PHIV (vs. controls) have an increased prevalence of patchy focal fibrosis, suggestive of prior myocarditis, as well as diffuse fibrosis and steatosis [80•, 81, 82]. Further, these studies showed evidence of diastolic dysfunction among PHIV [80•, 81, 82]. Specifically, Holloway et al. enrolled 90 PHIV on ART (76% men) and 39 controls (67% men) without prior CVD from the UK between 2011 and 2012 [80•]. Groups were well-matched on age (mid 40s) and BMI (24–25 kg/m^2), although PHIV tended to have higher levels of circulating triglycerides and fasting glucose. Among PHIV, the authors noted an increased prevalence of focal patchy myocardial fibrosis (MRI: late gadolinium enhancement), an increased burden of diffuse myocardial fibrosis (MRI: T1 mapping), and apparent myocardial steatosis (MRS: intramyocardial triglyceride content 0.53 vs. 0.36%, $P = 0.003$). Further, PHIV evidenced signs of diastolic function (MRI: circumferential diastolic strain rate) as well as subtle systolic dysfunction (MRI: circumferential systolic strain rate). In multivariable modeling, HIV status remained an independent predictor of myocardial steatosis as well as both diastolic dysfunction and subtle systolic dysfunction [80•]. Through follow-up of the same cohort (augmented by the addition of ART-naïve PHIV), Ntusi et al. observed among PHIV frequent pericardial effusions and suggestive evidence of increased myocardial edema/inflammation [81]. Separately, a German study by Luetkens et al. centering on 28 asymptomatic ART-treated PHIV (79% men) vs. controls (68% men) similarly suggested among PHIV possible myocardial edema/inflammation, as well as reduced arterial distensibility [82].

Building on these findings, two North American studies elucidated important functional consequences of myocardial steatosis among PHIV. Nelson et al. enrolled from the US 27 asymptomatic ART-treated men with HIV (MHIV) and 22 controls between 2012 and 2013 [70]. The authors demonstrated among PHIV marked myocardial steatosis (MRS: intramyocardial triglyceride content) and reduced diastolic function. Among PHIV, myocardial steatosis related directly to triglyceride levels and ART exposure and inversely to diastolic function [70]. Thiara et al. enrolled from the US 95 asymptomatic PHIV (75% men; 93% on ART) and 30 matched controls (73% men) between 2010 and 2013. In this cohort, PHIV were slightly older than controls (49 years vs. 46 years), and both groups were borderline overweight (BMI 28–30 kg/m^2) [69•]. While PHIV exhibited increased rates of smoking, diabetes, and lipid-lowering medication use, Framingham risk scores (FRS) were comparable between groups. Among PHIV, myocardial steatosis was noted (MRS: intramyocardial triglyceride content 1.14 vs. 0.58%, $P = 0.04$), as was an increased burden of diffuse myocardial fibrosis (MRI: extracellular volume). Further, in this group, a positive correlation was discerned between the degree of steatosis and fibrosis. In multivariable modeling, women's sex and visceral adiposity independently predicted steatosis among PHIV while women's sex, hypertension, and HIV status predicted fibrosis among the whole group. Of note, among PHIV, neither HIV-specific parameters (viral load, CD4$^+$ T cell count) nor measured indices of systemic immune activation related to fibrosis or steatosis. By contrast, relationships between levels of systemic immune marker monocyte chemoattractant protein-1 (MCP-1) and measures of subclinical systolic dysfunction were identified [69•].

Most recently, a North American study focused on WHIV (vs. non-HIV-infected women) revealed diffuse myocardial fibrosis in relation to heightened systemic immune activation [83•] as well as myocardial steatosis in relation to metabolic dysregulation [71]. In this study, 20 asymptomatic ART-treated women with HIV (WHIV) and 14 control subjects were recruited from the USA between 2016 and 2017 [83•]. Groups were well-matched on age (52–53 years) and BMI (32 kg/m^2). As compared with non-HIV-infected women, WHIV evidenced increased myocardial fibrosis (MRI: extracellular volume) and decreased diastolic function (MRI: circumferential diastolic strain rate). Additionally, novel systemic immune indices relevant to HIV-associated myocardial fibrosis and/or diastolic dysfunction were identified. Specifically, among WHIV, increased levels of the monocyte activation marker sCD163 related to myocardial fibrosis, while heightened expression of the cell-surface receptor CCR2 on inflammatory monocytes (CD14$^+$CD16$^+$) related both to myocardial fibrosis and diastolic dysfunction [83•]. Of interest, the monocyte-expressed honing receptor, CCR2, is known to promote cell-specific transmigration into target tissues among PHIV [84]. It remains possible, then, that among WHIV, primed CD14$^+$CD16$^+$ monocytes more robustly hone to the myocardial structural space, where they may transform into inflammatory macrophages and engender a local fibrotic response. Within the same US cohort, Toribio et al. demonstrated that WHIV (vs. non-HIV-infected women) exhibited marked myocardial steatosis reflected in a three-fold

increase in intramyocardial triglyceride content [71]. Moreover, among women, myocardial steatosis was noted to relate to metabolic and hormonal perturbations [71].

Additional insights are anticipated from three ongoing cardiac MRI ± MRS studies being conducted among diverse cohorts of PHIV. Underway and fully enrolled, the NHLBI-funded CHART study (Characterizing HIV-related Diastolic Dysfunction) is assessing myocardial structure and function among ~200 asymptomatic US PHIV through application of cardiac MRI and dynamic ECHO [85]. Detailed immunophenotyping as well as proteomic/metabolomic assessments will permit for sophisticated correlational analyses. Meanwhile, Baker, Ntsekhe et al. are applying cardiac MRI to assess subclinical myocardial pathology among asymptomatic PHIV from South Africa, as well as region-specific parameters fueling this pathology. Finally, Neilan, Zanni et al. are leading a study applying cardiac MRI/MRS to determine whether statin therapy (vs. placebo) forestalls the progression of myocardial fibrosis and myocardial steatosis among 129 asymptomatic PHIV recruited from the USA and South Africa.

Preventive Considerations—Including Knowledge Gaps and Future Directions

How can we apply what we know about mechanisms underlying heart failure risk among ART-treated PHIV to conceptualize and critique possible preventive strategies? The first strategy to consider is immediate ART. Ample evidence supports the notion that unchecked HIV/AIDS and associated conditions adversely affect the heart muscle [1]. Further, the START study confirmed that immediate ART upon HIV diagnosis reduces all-cause mortality [86]. Thus, immediate ART, as recommended by the WHO, may help protect myocardial health among PHIV. However, we must augment our understanding as to which antiretroviral therapeutic regimens exert fewest cardiotoxic effects and work to expand access to these. Second, we must identify and target region-specific risk factors for myocardial damage. Such risk factors may include co-infections (e.g., tuberculosis), nutritional deficiencies, and/or toxic exposures [87–90]. Third, we must target behavioral and traditional metabolic risk factors for myocardial disease including sedentary lifestyle, cigarette smoking, excess alcohol use, cocaine use, obesity, hypertension, dyslipidemia, and dysglycemia. Behavioral and traditional metabolic risk factors feed into several general myocardial injury mechanisms which are not specific to PHIV (ischemic heart disease, coronary microvascular disease, myocardial toxicity, valvular disease, and arrhythmia) [91] but which may be synergistically activated by HIV-specific mechanisms. Fourth, we must determine the specific mechanisms by which systemic immune activation and metabolic dysregulation predispose to myocardial fibrosis and steatosis among PHIV and identify safe, targeted strategies to forestall these processes. Future research in the field will need to be attentive to the influence of underlying genetics, as well as sex, gender identity, race/ethnicity, and region-specific risk factors. Finally, educational outreach emphasizing heart failure risks among ART-treated PHIV will facilitate early detection of pre-heart failure phenotypes (e.g., exercise-induced dyspnea) and obviate diagnostic overshadowing (i.e., false attribution of heart-failure suggestive symptomatology to HIV itself or secondary infection). Though heart failure portends a poor prognosis, particularly among PHIV, general-population studies highlight the promise of efforts geared toward heart failure prevention [92].

Financial Information This work was supported in part by the following grants/awards: mentored research award 5KL2TR001100-05 to Dr. Toribio, project grant 1R01HL137562 to Drs. Neilan and Zanni, Pilot and Feasibility Award from the P30 AI060354 Harvard University Center for AIDS Research to Drs. Neilan and Zanni, and Pilot Grant from the P30DK040561 Nutrition and Obesity Research Center at Harvard to Dr. Zanni.

Compliance with Ethical Standards

Conflict of Interest Dr. Toribio has no conflicts of interest. Dr. Neilan has participated in a Scientific Advisory Board Meeting for BMS and has served as a consultant for Aprea Therapeutics, Parexel, and Intrinsic Imaging. Dr. Zanni received investigator-initiated research grant support from Gilead Sciences to her institution (Massachusetts General Hospital).

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Acierno LJ. Cardiac complications in acquired immunodeficiency syndrome (AIDS): a review. J Am Coll Cardiol. 1989;13(5):1144–54.
2. Calabrese LH, Proffitt MR, Yen-Lieberman B, Hobbs RE, Ratliff NB. Congestive cardiomyopathy and illness related to the acquired immunodeficiency syndrome (AIDS) associated with isolation of retrovirus from myocardium. Ann Intern Med. Nov 1987;107(5):691–2.
3. Currie PF, Goldman JH, Caforio AL, et al. Cardiac autoimmunity in HIV related heart muscle disease. Heart. 1998;79(6):599–604.
4. Herskowitz A, Willoughby SB, Baughman KL, Schulman SP, Bartlett JD. Cardiomyopathy associated with antiretroviral therapy in patients with HIV infection: a report of six cases. Ann Intern Med. 1992;116(4):311–3.

5. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. Aug 22 2015;386(9995):743–800.
6. Butt AA, Chang CC, Kuller L, et al. Risk of heart failure with human immunodeficiency virus in the absence of prior diagnosis of coronary heart disease. Arch Intern Med. Apr 25 2011;171(8):737–743.
7.• Feinstein MJ, Steverson AB, Ning H, et al. Adjudicated heart failure in HIV-infected and uninfected men and women. J Am Heart Assoc. 2018;7(21):e009985. **This study explored the risk of heart failure among a contemporary cohort of asymptomatic US PHIV, employing physician-adjudication of heart failure diagnoses**.
8. Womack JA, Chang CC, So-Armah KA, et al. HIV infection and cardiovascular disease in women. J Am Heart Assoc. 2014;3(5):e001035.
9.• Janjua SA, Triant VA, Addison D, et al. HIV infection and heart failure outcomes in women. J Am Coll Cardiol. 2017;69(1):107–8. **This study highlighted heart failure risks, subtype presentations, and outcomes among a contemporary cohort of US women with HIV**.
10.• Yen YF, Ko MC, Yen MY, et al. Human immunodeficiency virus increases the risk of incident heart failure. J Acquir Immune Defic Syndr. 2019;80(3):255–63. **This study explored parameters associated with heart failure risk among a contemporary cohort of asymptomatic PHIV in China**.
11. Nakagawa F, Lodwick RK, Smith CJ, et al. Projected life expectancy of people with HIV according to timing of diagnosis. AIDS. 2012;26(3):335–43.
12. Lohse N, Obel N. Update of Survival for Persons With HIV Infection in Denmark. Ann Intern Med. 2016;165(10):749–50.
13. Johnson LF, Mossong J, Dorrington RE, Schomaker M, Hoffmann CJ, Keiser O, et al. Life expectancies of South African adults starting antiretroviral treatment: collaborative analysis of cohort studies. PLoS Med. 2013;10(4):e1001418.
14. Ziaeian B, Fonarow GC. Epidemiology and aetiology of heart failure. Nat Rev Cardiol. Jun 2016;13(6):368–78.
15. Freiberg MS CC, Oursler KK, Gottdiener J, Gottlieb S, Warner A, Leaf D, Rodriguez-Barradas MC, Felter S, Butt AA. The risk of and survival with preserved vs reduced ejection fraction heart failure by HIV status. CROI 2013.
16.•• Erqou S, Lodebo BT, Masri A, et al. Cardiac dysfunction among people living with HIV: a systematic review and meta-analysis. JACC Heart Fail. 2019;7(2):98–108. **This meta-analysis synthesized information on multiple forms of cardiac dysfunction among PHIV gleaned from studies spanning place and time and noted important trends pertaining to evolving population-specific risks**.
17. White JR, Chang CC, So-Armah KA, et al. Depression and human immunodeficiency virus infection are risk factors for incident heart failure among veterans: Veterans Aging Cohort Study. Circulation. 2015;132(17):1630–8.
18. Choi AI, Li Y, Deeks SG, Grunfeld C, Volberding PA, Shlipak MG. Association between kidney function and albuminuria with cardiovascular events in HIV-infected persons. Circulation. 2010;121(5):651–8.
19. So-Armah KA, Lim JK, Lo Re V, Tate JP, Chang CCH, Butt AA, et al. FIB-4 stage of liver fibrosis predicts incident heart failure among HIV-infected and uninfected patients. Hepatology. Oct 2017;66(4):1286–95.
20. Damasceno A, Mayosi BM, Sani M, et al. The causes, treatment, and outcome of acute heart failure in 1006 Africans from 9 countries. Arch Intern Med. 2012;172(18):1386–94.
21. Sliwa K, Davison BA, Mayosi BM, Damasceno A, Sani M, Ogah OS, et al. Readmission and death after an acute heart failure event: predictors and outcomes in sub-Saharan Africa: results from the THESUS-HF registry. Eur Heart J. Oct 2013;34(40):3151–9.
22. Alvi RM, Afshar M, Neilan AM, Tariq N, Hassan M, Gerber J, et al. Heart failure and adverse heart failure outcomes among persons living with HIV in a US tertiary medical center. Am Heart J. 2019;210:39–48.
23. Alvi RM, Neilan AM, Tariq N, et al. Protease inhibitors and cardiovascular outcomes in patients with HIV and heart failure. J Am Coll Cardiol. 2018;72(5):518–30.
24. Maagaard A, Kvale D. Mitochondrial toxicity in HIV-infected patients both off and on antiretroviral treatment: a continuum or distinct underlying mechanisms? J Antimicrob Chemother. Nov 2009;64(5):901–9.
25. Lewis W, Kohler JJ, Hosseini SH, et al. Antiretroviral nucleosides, deoxynucleotide carrier and mitochondrial DNA: evidence supporting the DNA pol gamma hypothesis. AIDS. 2006;20(5):675–84.
26. Feeney ER, Mallon PW. Impact of mitochondrial toxicity of HIV-1 antiretroviral drugs on lipodystrophy and metabolic dysregulation. Curr Pharm Des. Oct 2010;16(30):3339–51.
27. Borlaug BA, Redfield MM. Diastolic and systolic heart failure are distinct phenotypes within the heart failure spectrum. Circulation. May 10 2011;123(18):2006–2013; discussion 2014.
28. Bloom MW, Greenberg B, Jaarsma T, et al. Heart failure with reduced ejection fraction. Nat Rev Dis Primers. 2017;3:17058.
29. Ho JE, Enserro D, Brouwers FP, et al. Predicting heart failure with preserved and reduced ejection fraction: the international collaboration on heart failure subtypes. Circ Heart Fail. 2016;9(6).
30. Borlaug BA. The pathophysiology of heart failure with preserved ejection fraction. Nat Rev Cardiol. Sep 2014;11(9):507–15.
31. Yancy CW, Jessup M, Bozkurt B, et al. ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Am Coll Cardiol. 2017;70(6):776–803.
32.• Sliwa K, Carrington MJ, Becker A, Thienemann F, Ntsekhe M, Stewart S. Contribution of the human immunodeficiency virus/acquired immunodeficiency syndrome epidemic to de novo presentations of heart disease in the Heart of Soweto Study cohort. Eur Heart J. 2012;33(7):866–74. **This study described the influence of HIV infection to presentations of cardiovascular disease among a contemporary cohort of individuals seeking cardiovascular care in South Africa**.
33.• Freiberg MS, Chang CH, Skanderson M, et al. Association between HIV infection and the risk of heart failure with reduced ejection fraction and preserved ejection fraction in the antiretroviral therapy era: results from the veterans aging cohort study. JAMA Cardiol. 2017;2(5):536–46. **This study highlighted risks for heart failure subtypes among a contemporary cohort of asymptomatic US PHIV**.
34. UNAIDS. Report on the Global AIDS Epidemic. https://www.unaids.org/en/resources/documents/2013/20130923_UNAIDS_Global_Report_2013. Accessed 3 July 2019.
35. Gomez-Olive FX, Ali SA, Made F, et al. Regional and sex differences in the prevalence and awareness of hypertension: an H3Africa AWI-gen study across 6 sites in sub-Saharan Africa. Glob Heart. Jun 2017;12(2):81–90.
36. Irazola VE, Gutierrez L, Bloomfield G, Carrillo-Larco RM, Prabhakaran D, Gaziano T, et al. Hypertension prevalence, awareness, treatment, and control in selected LMIC communities: results from the NHLBI/UHG Network of Centers of Excellence for Chronic Diseases. Glob Heart. Mar 2016;11(1):47–59.

37. Nulu S, Aronow WS, Frishman WH. Hypertension in sub-Saharan Africa: a contextual view of patterns of disease, best management, and systems issues. Cardiol Rev. Jan-Feb 2016;24(1):30–40.
38. Kane GC, Karon BL, Mahoney DW, et al. Progression of left ventricular diastolic dysfunction and risk of heart failure. JAMA. 2011;306(8):856–63.
39. Fischer M, Baessler A, Hense HW, Hengstenberg C, Muscholl M, Holmer S, et al. Prevalence of left ventricular diastolic dysfunction in the community. Results from a Doppler echocardiographic-based survey of a population sample. Eur Heart J. Feb 2003;24(4):320–8.
40. Cerrato E, D'Ascenzo F, Biondi-Zoccai G, Calcagno A, Frea S, Grosso Marra W, et al. Cardiac dysfunction in pauci symptomatic human immunodeficiency virus patients: a meta-analysis in the highly active antiretroviral therapy era. Eur Heart J. May 2013;34(19):1432–6.
41. Frangogiannis NG. The extracellular matrix in myocardial injury, repair, and remodeling. J Clin Invest. 2017;127(5):1600–12.
42. Gonzalez A, Schelbert EB, Diez J, Butler J. Myocardial interstitial fibrosis in heart failure: biological and translational perspectives. J Am Coll Cardiol. 2018;71(15):1696–706.
43. Iozzo P. Myocardial, perivascular, and epicardial fat. Diabetes Care. May 2011;34(Suppl 2):S371–9.
44. Martos R, Baugh J, Ledwidge M, et al. Diastolic heart failure: evidence of increased myocardial collagen turnover linked to diastolic dysfunction. Circulation. 2007;115(7):888–95.
45. Su MY, Lin LY, Tseng YH, Chang CC, Wu CK, Lin JL, et al. CMR-verified diffuse myocardial fibrosis is associated with diastolic dysfunction in HFpEF. JACC Cardiovasc Imaging. Oct 2014;7(10):991–7.
46. Neilan TG, Farhad H, Mayrhofer T, Shah RV, Dodson JA, Abbasi SA, et al. Late gadolinium enhancement among survivors of sudden cardiac arrest. JACC Cardiovasc Imaging. Apr 2015;8(4):414–23.
47. Rijzewijk LJ, van der Meer RW, Smit JW, et al. Myocardial steatosis is an independent predictor of diastolic dysfunction in type 2 diabetes mellitus. J Am Coll Cardiol. 2008;52(22):1793–9.
48. Ng AC, Delgado V, Bertini M, et al. Myocardial steatosis and biventricular strain and strain rate imaging in patients with type 2 diabetes mellitus. Circulation. 2010;122(24):2538–44.
49. Brilla CG, Matsubara LS, Weber KT. Antifibrotic effects of spironolactone in preventing myocardial fibrosis in systemic arterial hypertension. Am J Cardiol. 1993;71(3):12A–6A.
50. Brilla CG, Funck RC, Rupp H. Lisinopril-mediated regression of myocardial fibrosis in patients with hypertensive heart disease. Circulation. 2000;102(12):1388–93.
51. Diez J, Querejeta R, Lopez B, Gonzalez A, Larman M, Martinez Ubago JL. Losartan-dependent regression of myocardial fibrosis is associated with reduction of left ventricular chamber stiffness in hypertensive patients. Circulation. 2002;105(21):2512–7.
52. Zib I, Jacob AN, Lingvay I, Salinas K, McGavock JM, Raskin P, et al. Effect of pioglitazone therapy on myocardial and hepatic steatosis in insulin-treated patients with type 2 diabetes. J Investig Med. Jul 2007;55(5):230–6.
53. Wada NI, Jacobson LP, Margolick JB, et al. The effect of HAART-induced HIV suppression on circulating markers of inflammation and immune activation. AIDS. 2015;29(4):463–71.
54. Kaplan RC, Landay AL, Hodis HN, et al. Potential cardiovascular disease risk markers among HIV-infected women initiating antiretroviral treatment. J Acquir Immune Defic Syndr. 2012;60(4):359–68.
55. Kroeze S, Wit FW, Rossouw TM, et al. Plasma biomarkers of HIV-related systemic inflammation and immune activation in sub-Saharan Africa before and during suppressive antiretroviral therapy. J Infect Dis. May 14 2019.
56. Sereti I, Krebs SJ, Phanuphak N, et al. Persistent, albeit reduced, chronic inflammation in persons starting antiretroviral therapy in acute HIV infection. Clin Infect Dis. 2017;64(2):124–31.
57. Hunt PW. Very early ART and persistent inflammation in treated hiv. Clin Infect Dis. 2017;64(2):132–3.
58. Stanley TL, Grinspoon SK. GH/GHRH axis in HIV lipodystrophy. Pituitary. 2009;12(2):143–52.
59. Lo J, Abbara S, Rocha-Filho JA, Shturman L, Wei J, Grinspoon SK. Increased epicardial adipose tissue volume in HIV-infected men and relationships to body composition and metabolic parameters. AIDS. 2010;24(13):2127–30.
60. Brown TT, Glesby MJ. Management of the metabolic effects of HIV and HIV drugs. Nat Rev Endocrinol. Jan 2012;8(1):11–21.
61. Mave V, Erlandson KM, Gupte N, et al. Inflammation and change in body weight with antiretroviral therapy initiation in a multinational cohort of HIV-infected adults. J Infect Dis. 2016;214(1):65–72.
62. Nduka CU, Uthman OA, Kimani PK, Stranges S. Body fat changes in people living with HIV on antiretroviral therapy. AIDS Rev. 2016;18(4):198–211.
63. Godfrey C, Bremer A, Alba D, et al. Obesity and fat metabolism in HIV-infected individuals: immunopathogenic mechanisms and clinical implications. J Infect Dis. Mar 20 2019.
64. Lake JE. The fat of the matter: obesity and visceral adiposity in treated HIV infection. Curr HIV/AIDS Rep. 2017;14(6):211–9.
65. Subramanian S, Tawakol A, Burdo TH, et al. Arterial inflammation in patients with HIV. JAMA. 2012;308(4):379–86.
66. Zanni MV, Toribio M, Wilks MQ, et al. Application of a novel CD206+ macrophage-specific arterial imaging strategy in HIV-infected individuals. J Infect Dis. 2017;215(8):1264–1269.
67. Knudsen A, Thorsteinsson K, Christensen TE, et al. Cardiac microvascular dysfunction in women living with HIV is associated with cytomegalovirus immunoglobulin G. Open Forum Infect Dis. 2018;5(9):ofy205.
68. Wei J, Nelson MD, Szczepaniak EW, et al. Myocardial steatosis as a possible mechanistic link between diastolic dysfunction and coronary microvascular dysfunction in women. Am J Physiol Heart Circ Physiol. 2016;310(1):H14–9.
69.• Thiara DK, Liu CY, Raman F, et al. Abnormal myocardial function is related to myocardial steatosis and diffuse myocardial fibrosis in HIV-infected adults. J Infect Dis. 2015;212(10):1544–51. **This cardiac MRI/MRS-based study explored associations between immune/metabolic parameters and subclinical cardiac pathology among a contemporary cohort of asymptomatic US PHIV**.
70. Nelson MD, Szczepaniak LS, LaBounty TM, Szczepaniak E, Li D, Tighiouart M, et al. Cardiac steatosis and left ventricular dysfunction in HIV-infected patients treated with highly active antiretroviral therapy. JACC Cardiovasc Imaging. 2014;7(11):1175–7.
71. Toribio M, Neilan TG, Awadalla M, et al. Intramyocardial Triglycerides among Women with vs. without HIV: Hormonal Correlates and Functional Consequences. J Clin Endocrinol Metab. Aug 8 2019.
72. Hsue PY, Deeks SG, Farah HH, et al. Role of HIV and human herpesvirus-8 infection in pulmonary arterial hypertension. *AIDS*. 2008;22(7):825–33.
73. Tseng ZH, Secemsky EA, Dowdy D, et al. Sudden cardiac death in patients with human immunodeficiency virus infection. J Am Coll Cardiol. 2012;59(21):1891–6.
74. Pennell DJ. Cardiovascular magnetic resonance. Circulation. 2010;121(5):692–705.
75. Hudsmith LE, Neubauer S. Magnetic resonance spectroscopy in myocardial disease. JACC Cardiovasc Imaging. Jan 2009;2(1):87–96.
76. Neilan TG, Coelho-Filho OR, Shah RV, Abbasi SA, Heydari B, Watanabe E, et al. Myocardial extracellular volume fraction from T1 measurements in healthy volunteers and mice: relationship to aging and cardiac dimensions. JACC Cardiovasc Imaging. Jun 2013;6(6):672–83.

77. Iles LM, Ellims AH, Llewellyn H, Hare JL, Kaye DM, McLean CA, et al. Histological validation of cardiac magnetic resonance analysis of regional and diffuse interstitial myocardial fibrosis. Eur Heart J Cardiovasc Imaging. Jan 2015;16(1):14–22.
78. de Meester de Ravenstein C, Bouzin C, Lazam S, et al. Histological validation of measurement of diffuse interstitial myocardial fibrosis by myocardial extravascular volume fraction from Modified Look-Locker imaging (MOLLI) T1 mapping at 3 T. J Cardiovasc Magn Reson. 2015;17:–48.
79. Reingold JS, McGavock JM, Kaka S, Tillery T, Victor RG, Szczepaniak LS. Determination of triglyceride in the human myocardium by magnetic resonance spectroscopy: reproducibility and sensitivity of the method. Am J Physiol Endocrinol Metab. Nov 2005;289(5):E935–9.
80.• Holloway CJ, Ntusi N, Suttie J, et al. Comprehensive cardiac magnetic resonance imaging and spectroscopy reveal a high burden of myocardial disease in HIV patients. Circulation. 2013;128(8):814–22. **This cardiac MRI/MRS-based physiology study conducted in the UK was one of the first to characterize myocardial structural disease (fibrosis, steatosis) and cardiac dysfunction among a contemporary cohort of asymptomtic PHIV**.
81. Ntusi N, O'Dwyer E, Dorrell L, Wainwright E, Piechnik S, Clutton G, et al. HIV-1-related cardiovascular disease is associated with chronic inflammation, frequent pericardial effusions, and probable myocardial edema. Circ Cardiovasc Imaging. Mar 2016;9(3):e004430.
82. Luetkens JA, Doerner J, Schwarze-Zander C, Wasmuth JC, Boesecke C, Sprinkart AM, et al. Cardiac magnetic resonance reveals signs of subclinical myocardial inflammation in asymptomatic HIV-infected patients. Circ Cardiovasc Imaging. Mar 2016;9(3):e004091.
83.• Zanni MV, Awadalla M, Toribio M, et al. Immune correlates of diffuse myocardial fibrosis and diastolic dysfunction among aging women with human immunodeficiency virus. J Infect Dis. May 17 2019. **This cardiac MRI-based physiology study identified novel immune correlates of myocardial fibrosis and diastolic dysfunction among a contemporary cohort of asymptomatic US women with HIV**.
84. Williams DW, Byrd D, Rubin LH, Anastos K, Morgello S, Berman JW. CCR2 on CD14(+)CD16(+) monocytes is a biomarker of HIV-associated neurocognitive disorders. Neurol Neuroimmunol Neuroinflamm. 2014;1(3):e36.
85. Butler J, Kalogeropoulos AP, Anstrom KJ, Hsue PY, Kim RJ, Scherzer R, et al. Diastolic dysfunction in individuals with human immunodeficiency virus infection: literature review, rationale and Design of the Characterizing Heart Function on Antiretroviral Therapy (CHART) study. J Card Fail. Apr 2018;24(4):255–65.
86. Lundgren JD, Babiker AG, Gordin F, et al. Initiation of antiretroviral therapy in early asymptomatic HIV infection. N Engl J Med. 2015;373(9):795–807.
87. Bloomfield GS, Alenezi F, Barasa FA, Lumsden R, Mayosi BM, Velazquez EJ. Human immunodeficiency virus and heart failure in low- and middle-income countries. JACC Heart Fail. Aug 2015;3(8):579–90.
88. Ntusi NAB, Ntsekhe M. Human immunodeficiency virus-associated heart failure in sub-Saharan Africa: evolution in the epidemiology, pathophysiology, and clinical manifestations in the antiretroviral era. ESC Heart Fail. Sep 2016;3(3):158–67.
89. Kavanaugh-McHugh AL, Ruff A, Perlman E, Hutton N, Modlin J, Rowe S. Selenium deficiency and cardiomyopathy in acquired immunodeficiency syndrome. JPEN J Parenter Enteral Nutr. May-Jun 1991;15(3):347–9.
90. Bloomfield GS, Kirwa K, Agarwal A, Eliot MN, Alenezi F, Carter EJ, et al. Effects of a cookstove intervention on cardiac structure, cardiac function, and blood pressure in Western Kenya. J Am Soc Echocardiogr. Mar 2019;32(3):427–30.
91. Feinstein MJ, Hsue PY, Benjamin LA, et al. Characteristics, prevention, and management of cardiovascular disease in people living with HIV: a scientific statement from the American Heart Association. Circulation. Jun 3 2019:CIR0000000000000695.
92. Ledwidge M, Gallagher J, Conlon C, et al. Natriuretic peptide-based screening and collaborative care for heart failure: the STOP-HF randomized trial. JAMA. 2013;310(1):66–74.