Heart failure and adverse heart failure outcomes among persons living with HIV in a US tertiary medical center

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Background Persons living with HIV (PLHIV) have an increased risk of heart failure (HF). However, little is known about outcomes among PLHIV with HF. The study aim was to compare HF outcomes among PLHIV with HF versus individuals without HIV with HF.

Methods Our cohort included 2,308 individuals admitted with decompensated HF. We compared baseline characteristics, 30-day HF readmission, and cardiovascular (CV) and all-cause mortality. Within PLHIV, we assessed outcomes stratified between CD4 count and viral load (VL), and tested the association between traditional and HIV-specific parameters with 30-day HF readmission.

Results There were 374 (16%) PLHIV with HF. Among PLHIV, 92% were on antiretroviral therapy and 63% had a VL <200 copies/mL. Groups were similar with respect to age, sex, race/ethnicity, and CV risk factors. In follow-up, PLHIV had increased 30-day HF readmission (49% vs 32%) and CV (26% vs 13.5%) and all-cause mortality rates (38% vs 22%). Among PLHIV, cocaine use, HIV-specific parameters (CD4, VL), and coronary artery disease were predictors of 30-day HF readmission. Specifically, among PLHIV, those with detectable VL had higher 30-day HF readmission and CV mortality, whereas PLHIV with undetectable VL had a similar 30-day HF readmission rate and CV mortality to uninfected controls with HF. Similar outcomes were observed across strata of left ventricular ejection fraction and by CD4.

Conclusions PLHIV with a low CD4 count or detectable VL have an increased 30-day HF readmission rate as well as increased CV and all-cause mortality. In contrast, PLHIV with a higher CD4 count and undetectable VL have similar HF outcomes to uninfected controls. (Am Heart J 2019;210:39-48.)

Access to combined antiretroviral therapy (ART) has dramatically increased survival among people living with HIV (PLHIV), transforming HIV into a chronic illness.[1,2] Moreover, the proportion of PLHIV >50 years old is rising across all regions—particularly in high-resource regions.[3] Individuals aging with HIV, however, face a heightened risk of cardiovascular (CV) comorbidities, including both heart failure with a preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF).[4,5] Few studies have examined ways in which HIV status influences HF outcomes. We previously reported in a small study that women with HIV and HF have increased HF hospitalization rates, longer HF hospitalizations, and increased CV and all-cause mortality as compared with non–HIV-infected women with HF.[6] In this prior study, the predominant type of HF was HFpEF, and men were not represented. The present investigation is the first to examine in a large, mixed-sex, contemporary US-based cohort whether outcomes differ among individuals with and without HIV hospitalized with HFrEF as well as HFpEF.

Methods

Study design and patient population

After obtaining Institutional Review Board approval, we created a registry of all 2,578 patients admitted to a single academic center in 2011 with decompensated HF (Bronx-

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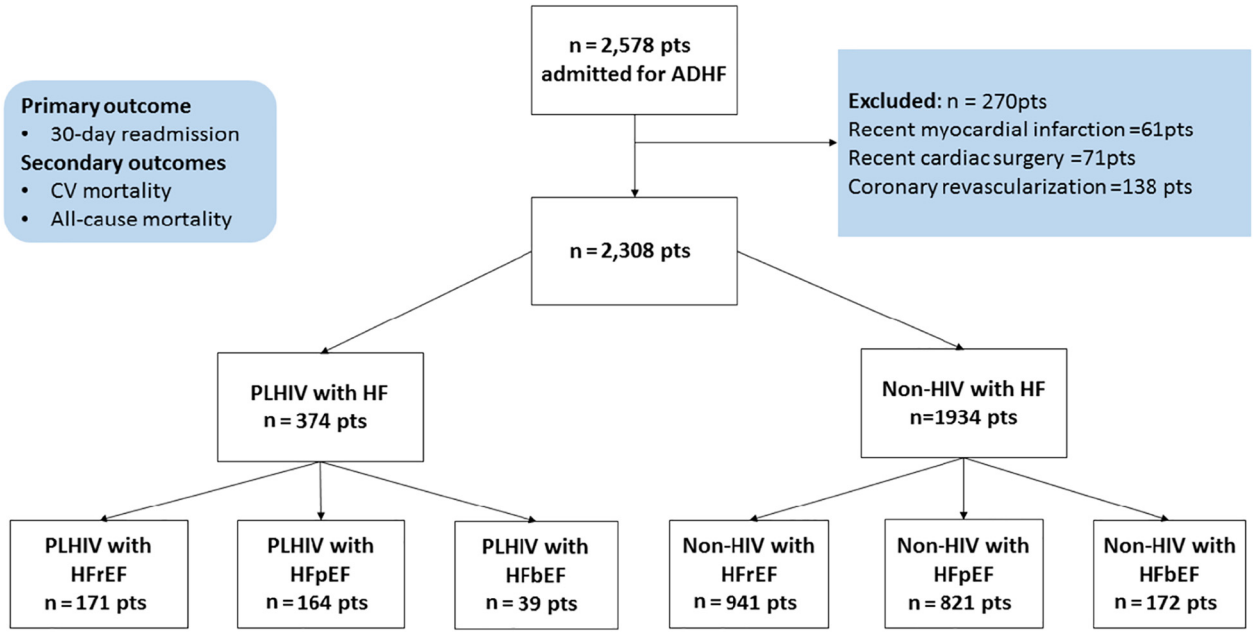
Figure 1



Consort diagram for the study. *ADHF*, acute decompensated heart failure; *Pts*, patients.

Lebanon Hospital Center of Icahn School of Medicine at Mount Sinai, Bronx, NY). The primary aim of the registry was to compare outcomes and predictors of HF outcomes among PLHIV and controls. An acute decompensated HF admission was identified by HF *International Classification of Diseases, Ninth Revision* (ICD-9) codes (428.21, 428.31, 428.23, 428.33, 428.41, and 428.43), and after individual electronic health record (EHR) review, a final confirmed diagnosis was given to patients who fell into the consensus criteria based on previously published literature[7] (Supplemental Table XI). For this study, we used the same cohort as previously described by our group.[8] We excluded those individuals with a recent (≤3 months) history of myocardial infarction (n = 61), cardiac surgery (n = 71), and coronary revascularization (n = 138). The remaining 2,308 patients were divided into 2 groups: PLHIV (n = 374) and persons without HIV (non–HIV-infected, n = 1934). Myocardial infarction, cardiac surgery, and coronary revascularization were identified with both ICD codes and confirmed with extensive medical record review of these patients. The patients among the control population had not undergone HIV testing and were presumed to be HIV negative. The cohort was further stratified by HFrEF (left ventricular ejection fraction [LVEF] <40%), HF with borderline LVEF (HFbEF, LVEF 40%-49%), and HFpEF (LVEF ≥50%) (Figure 1). The individual EHRs of all 2,308 patients were reviewed, and HIV diagnoses were ascertained.

Outcomes

Our primary outcome was 30-day HF readmission rate defined according to European Society of Cardiology consensus criteria.[9] The follow-up period began on the date of discharge from the first 2011 HF hospitalization until the last follow-up within 2 years of the date of death. As per the hospital protocol, most of the patients with a primary diagnosis of HF on admission received a postdischarge follow-up within 10 days of the discharge date in the heart failure or cardiology clinic. Both (PLHIV and non-HIV controls) groups were followed over 2 years with median follow-up period of 19 months among both groups. Our secondary outcomes included rates of CV mortality and all-cause mortality. *CV death* was defined as death due to HF, sudden cardiac death, arrhythmias, and acute ischemic events.[10] Death was determined through Social Security death index. All outcomes were confirmed by physician-adjudicated individual EHR review. If the documentation of the cause of death was not available, the case was listed in all-cause mortality but not in CV mortality. If the information on a patient's follow up, readmission or death was not available, an assumption was made that the patient did not die or readmitted during the follow-up period. Outcomes were adjudicated by physicians blinded to HIV status.

Covariates

Through EHR review, data on traditional CV disease risk factors including hypertension (HTN), dyslipidemia,

diabetes mellitus, coronary artery disease (CAD), sleep apnea, body mass index, any prior or active cigarette smoking, and any prior or active cocaine use were collected, as previously defined.[6,11,12] The values for LVEF (estimated via biplane method) and pulmonary artery systolic pressure (PASP) (measured from tricuspid regurgitation jet velocity and right atrial pressure) were obtained from echocardiogram[13] performed during index HF hospitalization. For patients who had >1 echocardiogram during hospitalization, the measurements were obtained from the first available upon hospitalization. Through EHR review, data were also collected on medication use at discharge from the index HF hospitalization. Details on HIV-specific parameters (current ART, duration of ART, CD4, viral load [VL]) were recorded from those available closest to the time of discharge from the index HF hospitalization (91% were within 1 month of hospitalization).

Statistical analysis

Continuous variables were presented as mean and SD or median (interquartile range [IQR]), as appropriate, based on normality, and categorical variables were presented as percentages. For the primary assessments, 2 groups were defined as follows: PLHIV with HF and non–HIV-infected individuals with HF. Continuous data were compared with the use of unpaired Student *t* tests or Wilcoxon rank-sum tests, as appropriate. Categorical data were compared using the χ^2 or the Fisher exact test. Survival curves were plotted using Kaplan-Meier curves. To facilitate subgroup analyses, the group of PLHIV with HF was further stratified based on either CD4 count at the time of index HF hospitalization (≥ or <200 cells/mm^3) (≥ or <500 cells/mm^3) or VL at the time of index HF hospitalization (≥ or <200 copies/mL). Univariate and multivariate regression analyses were performed to determine the association between baseline covariates (including HIV status) and 30-day HF readmission rate. Multivariate Cox proportional hazard regression analyses for 30-day HF readmission rate were constructed using $P < .01$ on the univariate analysis for entry. Both VL and CD4 count were not included in the multivariate model because of the overlap between those individuals with a low CD4 count and a high VL. Otherwise, statistical significance was defined using a 2-tailed P value ≤ .05. Statistical analyses were performed using SPSS (Chicago, IL) software version 23.

Results

Demographics and baseline characteristics

Among 2,308 individuals with HF at a single US tertiary care hospital in 2011, 374 were known to have HIV (PLHIV), whereas 1,934 were not. Among PLHIV, 92% (343/374) were on ART at the time of discharge, and the median duration of ART use was 9 years (IQR 4-16 years). The mean CD4 count was 368 cells/mm^3, and 53% (199/374) had a CD4 count of ≥200 cell/mm^3. Out of 374 PLHIV, 63% (235/374) had a VL <200 copies/mL. As per Table I, those with and without HIV did not differ with respect to age, sex, race/ethnicity, or the prevalence of traditional CV risk factors including diabetes, hypertension, dyslipidemia, and cigarette smoking. The admission heart rate, systolic blood pressure, diastolic blood pressure, and LVEF during admission were also similar between groups. However, among PLHIV with HF, PASP was higher (45 ± 9.5 vs 40 ± 9.0 mm Hg, $P < .001$), as was cocaine use (36% vs 19%, $P < .001$) and hepatitis C virus infection (13% vs 7%, $P < .001$) (Table I).

Groups were also separated according to the LVEF; there were 1,112 individuals with HFrEF (171 PLHIV, 941 non-HIV), 985 with HFpEF (164 PLHIV, 821, non-HIV), and 211 individuals with HFbEF (39 PLHIV, 172 non-HIV) (Figure 1).

Outcomes

The median follow-up duration was 19 months (IQR 3-24). Among the entire cohort, 35% were readmitted with decompensated HF within 30 days of discharge from the incident HF hospitalization.

Primary outcome: 30-day readmission due to HF

The 30-day HF hospital readmission rate was higher among PLHIV versus non–HIV-infected individuals (49% vs 32%, $P < .001$) (Figure 2, *A* and *B*). Among PLHIV, those with a CD4 count of <200 cells/mm^3 had a higher 30-day HF readmission rate as compared to those with a CD4 count ≥200 cells/mm^3 (64% vs 36%, $P < .001$) (Figure 2, *A*). Similarly, among PLHIV, those with detectable VL (≥200 copies/mL) had a higher 30-day readmission rate as compared with those with suppressed VL (68% vs 37%, $P < .001$) (Figure 2, *B*). The 30-day readmission rate among PLHIV with HF with a CD4 count ≥200 cells/mm^3 did not differ significantly from the rate among non–HIV-infected individuals with HF (36% vs 32%, $P = .24$) (Figure 2, *A*). Similarly, the 30-day readmission rate among PLHIV with HF with an undetectable VL did not differ significantly from the rate among non–HIV-infected individuals with HF (37% vs 32%, $P = .10$) (Figure 2, *B*).

However, when a CD4 count of ≥500 cells/mm^3 was used as a threshold, there was no significant difference in 30-day HF readmission rate between PLHIV with a CD4 of ≥500 cells/mm^3 and non–HIV-infected individuals (34% vs 32%, $P > .05$).

Among PLHIV, factors associated 30-day readmission due to HF on univariate analysis included traditional CV risk factors (such as diabetes, history of CAD, smoking, cocaine use, elevated PASP) and HIV parameters (such as low CD4 count and high VL) (Supplemental Table I). In a multivariable model, after adjusting for age, gender, cardiac risk factors, HF medications, and HIV parameters, the following parameters remained independently associated with 30-day readmission rate: smoking, history of

Table I. Baseline characteristics PLHIV vs non-HIV

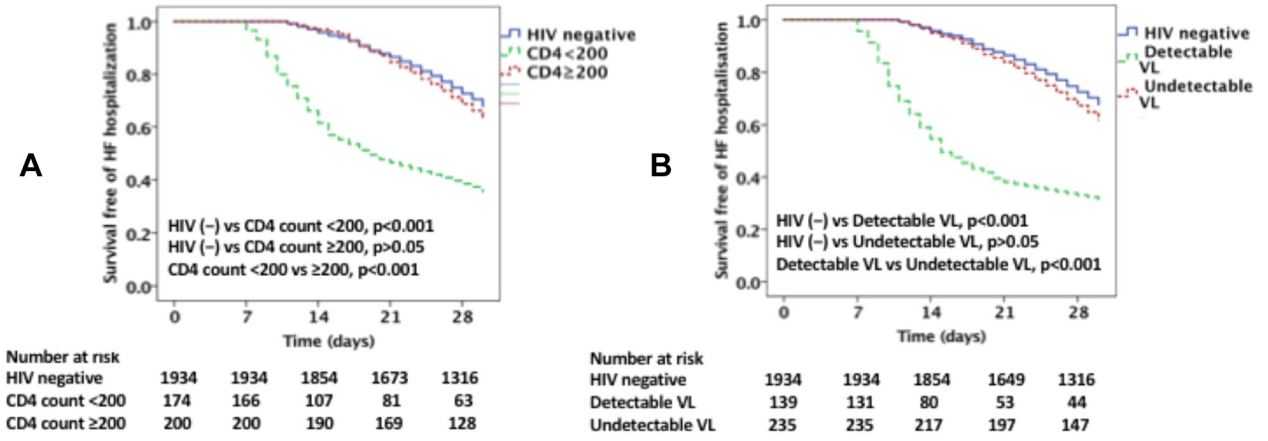
	PLHIV (n = 374)	Non-HIV (n = 1934)	*P* value
Female	176 (47%)	882 (45%)	.605
Age (y, mean ± SD)	60 ± 9.5	60 ± 9.4	.981
Race			.102
Hispanic	142 (38%)	812 (42%)	
African American	153 (41%)	677 (35%)	
Others	79 (21%)	445 (23%)	
CV risk factors			
Diabetes	138 (36%)	669 (34%)	.392
Hypertension	240 (64%)	1194 (62%)	.383
Hyperlipidemia	166 (44%)	778 (40%)	.134
Smoking	181 (48%)	939 (49%)	.956
Systolic blood pressure (mm Hg, mean ± SD)	143 ± 27.7	141 ± 28.6	.214
Diastolic blood pressure (mm Hg, mean ± SD)	77 ± 18.2	75 ± 18.6	.340
Heart rate (beat/min, mean ± SD)	84 ± 21.4	83 ± 21.2	.559
LVEF (%, mean ± SD)	47 ± 12.0	48 ± 12.3	.741
PASP (mm Hg, mean ± SD)	45 ± 9.5	40 ± 9.0	<.001*
BMI (kg/m^2, mean ± SD)	27. ± 5.7	34 ± 5.9	<.001
Serum creatinine (mg/dL)	1.37 ± 1.0	1.31 ± 1.1	.327
CKD	59 (16%)	251 (13%)	.146
Sleep apnea	110 (29%)	515 (27%)	.268
CAD	157 (42%)	693 (36%)	.024*
Cocaine use	136 (36%)	376 (19%)	<.001*
HCV	49 (13%)	135 (7%)	<.001*
HBV	31(8%)	116 (6%)	.096
HF subtypes			.469
HFrEF	171 (46%)	941 (48%)	
HFbEF	39 (10%)	172 (8.8%)	
HFpEF	164 (44%)	821 (42%)	
Ischemic HF	157 (42%)	693 (36%)	.024*
ICD parameters			
Single-chamber ICD	27 (7%)	119 (6%)	
Dual-chamber ICD	23 6%)	113 (5.8%)	.856
CRT-D	9 (2.4%)	35 (1.8%)	
Primary prevention	46 (12%)	189 (10%)	.308
Secondary prevention	13 (3.5%)	78 (4%)	
HIV parameters			
CD4 count cells/mm^3 (mean ± SD)	368 ± 245		
VL< 200 copies/mL	235 (63%)		
ART therapy	343 (92%)		
Duration of therapy (y), median (IQR)	9 (4–16)		
Duration of HIV (y), median (IQR)	9 (4–16)		
Medications			
β-Blocker	322 (86%)	1718 (88%)	.131
ACE-I/ARB	320 (86%)	1706 (88%)	.152
Spironolactone	38 (10%)	222 (11%)	.460
Furosemide	289 (77%)	1545 (80%)	.252

BMI, body mass index; *CKD*, chronic kidney disease (estimated glomerular filtration rate <60); *HCV*, hepatitis C virus infection; *HBV*, hepatitis B virus infection, *ICD*, implantable cardioverter defibrillator, *ACE-I*, angiotensin-converting enzyme inhibitor; *ARB*, angiotensin receptor blocker. β-Blocker, Beta Blocker; CRT-D, Cardiac resynchronization therapy defibrillator.
* Represents a statistically significant *P*-value (<0.05).

CAD, cocaine use, elevated PASP, and low CD4 count (or high VL) (Table II, Supplemental Table II).

PLHIV with HFrEF. The 30-day hospital readmission rate was higher among PLHIV with HFrEF versus non–HIV-infected individuals with HF (52% vs 31%, $P < .001$). Among PLHIV with HFrEF, those with a CD4 count of <200 cells/mm^3 had a higher 30-day HF readmission rate as compared to those with a CD4 count ≥200 cells/mm^3 (69% vs 40%, $P < .001$). Similarly, among PLHIV, those with detectable VL (≥200 copies/mL) had a higher 30-day readmission rate as compared with those with suppressed VL (70% vs 37%, $P < .001$). The 30-day readmission rate among PLHIV with HFrEF with a CD4 count ≥200 cells/mm^3 did not differ significantly from the rate among non–HIV-infected individuals with HFrEF (40% vs 31%, $P = .19$). Similarly, the 30-day readmission rate among PLHIV with HFrEF with an undetectable VL did not differ significantly from the rate among non–HIV-

Figure 2



Kaplan-Meier survival curves comparing 30-day readmission among (**A**) PLHIV with CD4 count <200 cells /mm^3 and ≥200 cells /mm^3 with uninfected controls, and (**B**) PLHIV with detectable and undetectable VL with uninfected controls.

Table II. Multivariate analysis PLHIV with HF (30-day readmission outcome)

Covariates	Hazard ratio	95% CI		*P* value
		Lower	Upper	
H/o CAD	1.714	1.332	2.473	<.001
Cocaine	1.433	1.202	2.313	.002
ICD firing	1.523	1.071	2.221	.004
History of CVA	1.248	0.976	2.764	.134
Chronic kidney disease	1.343	1.021	2.621	.021
PASP	1.141	1.125	1.457	<.001
CD4 count	0.992	0.987	0.999	<.001

Cox proportional hazard regression for multivariate analysis after adjusting for age, gender cardiac risk factors, HF medications and HIV parameters. Both VL and CD4 count were not included in the multivariate model together due to the overlap between those individuals with a low CD4 count and a high VL. VL was included in the multivariate model (Supplemental Table I).
H/o CAD, History of coronary artery disease; ICD, Implantable cardioverter defibrillator.

infected individuals with HFrEF (37% vs 31%, P = .21). Factors associated with rehospitalization among PLHIV with HFrEF were similar to the entire cohort and are in Supplemental Tables III and IV.

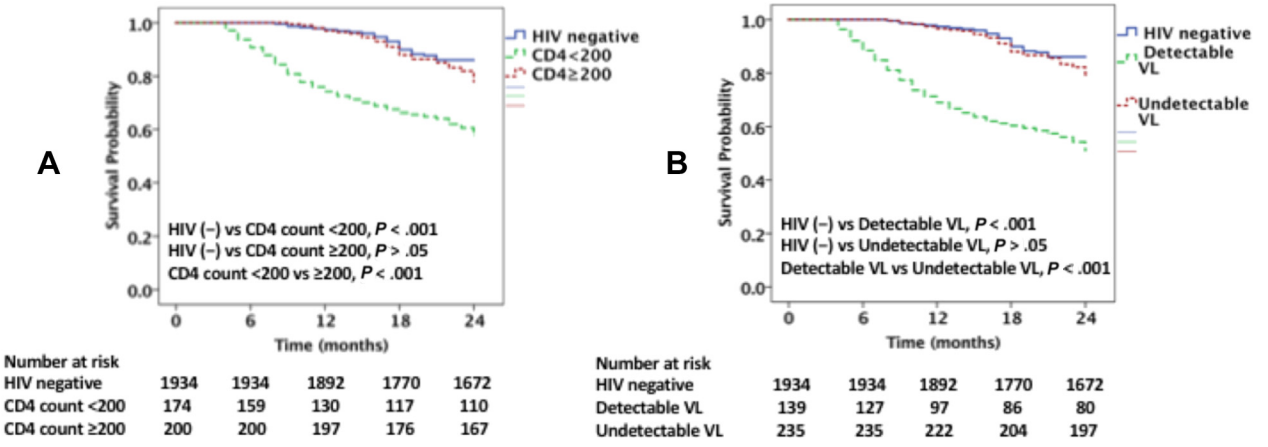
PLHIV with HFpEF. Parallel findings were noted among HFpEF. Specifically, the 30-day hospital readmission rate was higher among PLHIV with HFpEF versus non–HIV-infected individuals with HF (44% vs 33%, P = .006). Among PLHIV, those with a CD4 count of <200 cells/mm^3 had a higher 30-day HF readmission rate as compared to those with a CD4 count ≥200 cells/mm^3 (56% vs 34%, P = .005). Similarly, among PLHIV, those with detectable VL (≥200 copies/mL) had a higher 30-day readmission rate as compared with those with suppressed VL (62% vs 35%, P < .001). However, the 30-day readmission rate among PLHIV with HFpEF with a CD4 count ≥200 cells/mm^3 did not differ significantly from the rate among non–HIV-infected individuals with HFpEF (34% vs 33%, P = .80). Similarly, the 30-day readmission rate among PLHIV with HFrEF with an undetectable VL did not differ significantly from the rate among non–HIV-infected individuals with HFpEF (35% vs 33%, P = .64). Factors associated with rehospitalization among PLHIV with HFpEF were similar to the entire cohort and are in Supplemental Tables V and VI.

PLHIV with HFbEF. Identical findings were observed among the PLHIV with HFbEF. The 30-day hospital readmission rate was higher among PLHIV with HFbEF versus non–HIV-infected individuals with HF (53% vs 33%, P = .01), with a similar effect of CD4 count and VL (data not shown). Factors associated with rehospitalization among PLHIV with HFbEF were similar to the entire cohort (Supplemental Tables VII and VIII).

Secondary outcomes: CV and all-cause mortality

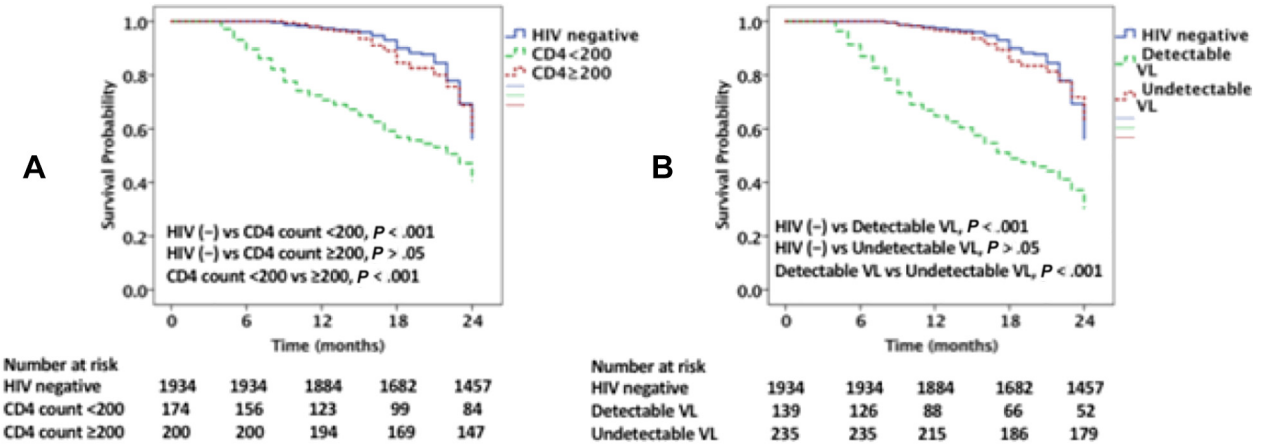
Among the PLHIV admitted for decompensated HF (374 patients), there were 97 (26%) CV deaths and 143 (38%) all-cause deaths over 2 years of follow-up. There were 11 (3%) deaths with an unknown cause. The CV and all-cause mortality rates were significantly higher among PLHIV with HF versus non–HIV-infected individuals with

Figure 3



Kaplan-Meier survival curves comparing CV mortality among (**A**) PLHIV with CD4 count <200 cells /mm^3 and ≥200 cells/mm^3 with uninfected controls, and (**B**) PLHIV with detectable and undetectable VL with uninfected controls.

Figure 4



Kaplan-Meier survival curves comparing all-cause mortality among (**A**) PLHIV with CD4 count <200 cells /mm^3 and ≥200 cells/mm^3 with uninfected controls, and (**B**) PLHIV with detectable and undetectable VL with uninfected controls.

HF (CV mortality: 26% vs 13.5%, all-cause mortality: 38% vs 22%, $P < .001$ for both) (Figures 3, *A* and *B* and 4, *A* and *B*). Among PLHIV, those with a CD4 count of <200 cells/mm^3 had a higher CV and all-cause mortality rates as compared to those with a CD4 count ≥200 cells/mm^3 (CV mortality: 37% vs 16.5%, all-cause mortality: 52% vs 27%, $P < .001$ for both) (Figures 3, *A* and 4, *A*). Similarly, among PLHIV, those with detectable VL had higher CV and all-cause mortality rates as compared with those with suppressed VL (CV mortality: 48% vs 17%, all-cause mortality: 64% vs 26%, $P < .001$ for both) (Figures 3, *B* and 4, *B*). However, the CV mortality and all-cause mortality rates among PLHIV with HF with a CD4 count ≥200 cells/mm^3 did not differ significantly from the rates among non–HIV-infected individuals with HF (CV mortality: 16.5% vs 13.5%, $P = .249$; all-cause mortality: 27% vs 22%, $P = .14$) (Figures 3, *A* and 4, *A*). Similarly, the CV mortality and all-cause mortality rates among PLHIV with HF with an undetectable VL did not differ significantly from the rate among non–HIV-infected individuals with HF (CV mortality: 17% vs 13%, $P = .15$; all-cause mortality: 26% vs 22%, $P = .66$) (Figures 3, *B* and 4, *B*).

However, there was no significant difference in CV mortality as well as all-cause mortality between PLHIV with HFrEF with a CD4 count ≥500 cells/mm^3 versus non–HIV-infected individuals with HF (CV mortality: 14.5% vs 13.5%; all-cause mortality: 24% vs 22%, $P > .05$ for both).

PLHIV with HFrEF. Among the patients admitted for HFrEF (n = 1,112), the CV and all-cause mortality rates were significantly higher among PLHIV with HFrEF versus non–HIV-infected individuals with HF (CV mortality: 28% vs 15%; all-cause mortality: 41% vs 26%, $P < .001$ for both). Among PLHIV, those with a CD4 count of <200 cells/mm^3 had a higher CV and all-cause mortality rates as compared to those with a CD4 count ≥200 cells/mm^3 (CV mortality: 38% vs 19%, $P = .006$; all-cause mortality: 54% vs 26%, $P < .001$). Similarly, among PLHIV, those with detectable VL had higher CV and all-cause mortality rates as compared with those with suppressed VL (CV mortality: 47% vs 16%, $P = .02$; all-cause mortality: 65% vs 29%, $P < .001$). However, the CV mortality and all-cause mortality rates among PLHIV with HFrEF with a CD4 count ≥200 cells/mm^3 did not differ significantly from the rates among non–HIV-infected individuals with HF (CV mortality: 19% vs 15%, $P = .33$; all-cause mortality: 29% vs 26%, $P = .56$). Similarly, the CV mortality and all-cause mortality rates among PLHIV with HF with an undetectable VL did not differ significantly from the rate among non–HIV-infected individuals with HF (CV mortality: 16% vs 15%, $P = .86$; all-cause mortality: 29% vs 26%, $P = .52$).

PLHIV with HFpEF. Among the patients admitted for HFpEF (n = 985), the CV and all-cause mortality rates were significantly higher among PLHIV with HF versus non–HIV-infected individuals with HF (CV mortality: 24% vs 12%; all-cause mortality: 36% vs 18%, $P < .001$ for both). Among PLHIV, those with a CD4 count of <200 cells/mm^3 had a higher CV and all-cause mortality rates as compared to those with a CD4 count ≥200 cells/mm^3 (CV mortality: 33% vs 17%, $P = .01$; all-cause mortality: 48% vs 26%, $P = .004$). Similarly, among PLHIV, those with detectable VL had higher CV and all-cause mortality rates as compared with those with suppressed VL (CV mortality: 42% vs 14%, $P < .001$; all-cause mortality: 58% vs 24%, $P < .001$). However, the CV mortality and all-cause mortality rates among PLHIV with HF with a CD4 count ≥200 cells/mm^3 did not differ significantly from the rates among non–HIV-infected individuals with HF (CV mortality: 17% vs 12%, $P = .56$; all-cause mortality: 26% vs 18%, $P = 0{\cdot}08$). Similarly, the CV mortality and all-cause mortality rates among PLHIV with HF with an undetectable VL did not differ significantly from the rate among non–HIV-infected individuals with HF (CV mortality: 18% vs 12%, $P = .17$; all-cause mortality: 24% vs 18%, $P = .14$).

PLHIV with HFbEF. Among the patients admitted for HFbEF (n = 221), the CV and all-cause mortality rate was significantly higher among PLHIV with HF versus non–HIV-infected individuals with HF (CV mortality: 24% vs 12%; all-cause mortality: 36% vs 18%, $P < .001$ for both) with a similar effect of CD4 count and VL (data not shown).

Discussion

The present analysis reveals that PLHIV with HF at a US urban tertiary care medical center have a markedly increased 30-day HF readmission rate and increased rates of CV and all-cause mortality as compared with individuals without HIV with HF. Among PLHIV, those with a detectable VL (preserved CD4) had a higher HF readmission and higher CV mortality; PLHIV with an undetectable VL had a similar 30-day HF readmission rate and CV mortality to uninfected controls with HF and as with uninfected HF patients. Additionally, among PLHIV, smoking, cocaine use, and HIV-specific parameters were predictors of HF readmission. Similar outcomes were observed regardless of the type of HF.

The present study reveals that the 30-day readmission as well as CV and all-cause mortality risks are increased among PLHIV compared to the ones without HIV. These findings with respect to increased CV and all-cause mortality rates among PLHIV with HF (including preserved as well as reduced ejection fraction) expand upon previous findings by Freiberg et al based out of the US Veterans Aging Cohort Study–Virtual Cohort (~97% male) suggesting that individuals with HIV and HF face increased mortality as compared with non–HIV-infected individuals with HF,[4] especially those with a detectable VL/lower CD4 count. HIV is associated with increased CV mortality because of traditional CV risk factors, residual virally mediated inflammation despite HIV treatment, and adverse effects of ART.[8,14-17] In the same cohort, we have previously shown that PLHIV who are prescribed protease inhibitors are associated with significantly increased CV mortality compared to the PLHIV who were prescribed a non–protease inhibitor ART regimen.[8] In another study, our group has also demonstrated that PLHIV with an ICD have a higher rate of ICD firing and subsequently an increased risk of CV mortality compared to the non-HIV individuals.[14] Therefore, from the previous results, it may be plausible that the poor HF outcomes among PLHIV are multifactorial, contributed by different elements.

In our cohort of PLHIV with HF, CD4 count and VL were risk factors for adverse outcomes among patients with all types of HF. Specifically, PLHIV with HF with a CD4 count <200 cells/mm^3 had worse outcomes (30-day HF readmission, CV mortality, and all-cause mortality) as compared with those with CD4 count ≥200 cells/mm^3; a low CD4 count/high VL independently related to poor outcome (increased 30-day HF readmission rate) even after controlling for major traditional and nontraditional HF risk factors. We found similar results when stratifying the PLHIV as ≥ or <500 cells/mm^3. Furthermore, the adverse outcomes were further decreased with CD4 count ≥500 cells/mm^3. Several studies suggest that less well-controlled HIV is associated with an increased CV risk. Observationally, immune suppression and detectable viremia have been associated with incident myocardial infarction[18] and other vascular events among PLHIV.[19] In the seminal SMART study, individuals with HIV randomized to intermittent ART had a trend toward increased rates of CV events compared to individuals with HIV randomized to continuous ART.[20] In the SMART study, CV events included nonfatal myocardial

infarction, nonfatal stroke, CAD requiring percutaneous coronary intervention or coronary artery bypass graft surgery, and death from cardiovascular disease (CVD) but did not include HF. Our study provides complementary observational support for a protective effect of immune recovery and viral suppression against HF and HF outcomes. Specifically, this study suggests that effective ART (with immunologic rebound and suppressed viremia) may partially protect PLHIV against adverse outcomes associated with HF. The mechanism involved in the increased rates of adverse HF in HIV and the protective effect of a suppressed VL and higher CD4 count are incompletely understood but may be explained by activation of immune system and persistent inflammation associated with HIV, which have been associated with an elevated HF risk.[17] Moreover, these findings are also consistent with studies in the pre-ART phase in which HIV viremia perhaps via direct infection of cardiomyocytes or cardiac autoantibodies resulted in a cardiomyopathy.[21-23]

In our study, among those individuals with HF, the group with HIV had a higher prevalence of cocaine use and a higher PASP as compared with the non–HIV-infected group. By contrast, the 2 groups did not differ significantly with respect to age, sex, race, ethnicity, and prevalence of numerous traditional HF risk factors including diabetes, hypertension, dyslipidemia, and cigarette smoking. Both cocaine use and higher PASP/pulmonary HTN predicted adverse outcomes. Cocaine use is known to be increased among PLHIV in the United States.[24] In the general population, cocaine use is a known cause of pulmonary HTN,[25] which may be expected to contribute to the development and progression of HF.[26-28] Among individuals with HIV, cocaine use has been associated with CAD (eg, calcified plaque)[29] and with structural heart disease (eg, myocardial fibrosis).[30] Previous studies have also shown an increased prevalence of pulmonary HTN among individuals with versus without HIV[27] and have shown an association between even borderline elevations in PASP and hospitalization/mortality.[26] Future studies are needed to assess whether measures to reduce cocaine use may represent yet another avenue for preventing adverse outcomes among PLHIV with HF.

The present investigation examines in a contemporary US-based population whether outcomes differ among individuals with and without known HIV with HF. There are some data from other studies to support these findings. Specifically, results from prognostic models involving more than 1,000 patients enrolled in the THESUS-HF, a prospective registry of patients admitted with HF in 9 sub-Saharan African countries, revealed an association between the presence of HIV with 180-day all-cause mortality.[31] We extended these findings and extracted from the medical records detailed phenotypic data on traditional CVD risk factors, nontraditional CVD risk factors, CV parameters (LVEF, PASP), and HIV-specific parameters. Those with and without HIV were similarly distributed in terms of age, sex, race, and prevalence of traditional CV risk factors. This helps us to isolate the potential contribution of HIV to risk of adverse outcomes, and indeed, our analyses suggest that *uncontrolled* HIV infection is particularly relevant. Our modeling for factors related to 30-day HF readmission rate also highlights potential avenues for clinical interventions (linkage to HIV care, substance abuse recovery programs) and highlights that factors important to HIV care may also impact HF outcomes.

Potential limitations of our study are as follows: First, this is a retrospective cohort study based out of a single US urban tertiary care center, and data may not be widely generalizable to PLHIV with HF in other regions. There are no data characterizing 30-day HF readmission among PLHIV; however, there are data on the 30-day HF readmission rates among presumed HIV-uninfected patients with HF.[32] In a large contemporary study involving 1,430,030 patients with HF, Krumholz et al found that the 30-day HF readmission rate ranged from 16% to 35%.[33] This 30-day readmission rate in broad populations is similar to the rate of 30% in our cohort without HIV. An additional important point is that a relatively large proportion of our cohort had CD4 count <200 cells/mm^3 (47%) or VL >200 copies/mL (37%) despite an ART prescription rate of >90%. Therefore, a potential explanation for the worse outcomes among PLHIV is poor adherence to treatment for either HIV or HF, as both, and in combination, are associated with a significant pill burden. In this retrospective study, adherence could not be assessed. However, we did test whether other surrogates of adherence were different between cases and controls. In patients with HF who do not take HF medications, both heart rate and blood pressure are increased. In our study cohort, there was no difference between the blood pressure and heart rate between the PLHIV and non-HIV controls, suggesting that adherence with HF medications may be similar between groups. Advances in therapies for HIV, such as the use of integrase inhibitors as well as fixed-dose combination pills, may be associated with better medication adherence as well as more favorable metabolic effects and ultimately better outcomes. Additionally, prospective studies are needed in populations with HIV and HF where factors such as cocaine use are less common. In this study, the group without known HIV did not have confirmatory HIV testing. However, the potential inclusion of some individuals with HIV in the "non–HIV-infected" analytic group would have been expected to *decrease* the magnitude/significance of our primary findings. An additional limitation is that the readmission and CV mortality data from other institutions as well as the duration of hospitalization were not available. However, in our previously published data, we found that women living with HIV admitted for HF had a higher length of hospitalization compared to the non-HIV women with HF.[6] Data were obtained from EHR; therefore, an important limitation is our dependency on documentation as well as unavailability of some data. For example, the

mode of cocaine use was not available, and the prevalence of cocaine use may have been significantly underestimated.

In conclusion, our work is the first to examine in a contemporary US-based population whether outcomes differ among individuals with and without known HIV with HF. Furthermore, we carefully explored the potential effects of traditional HF risk factors, nontraditional HF risk factors, and HIV-specific parameters on adverse outcomes among PLHIV with HF, identifying an important potential contribution of HIV disease parameters as novel HF risk factors. Understanding how HIV status and HIV disease stage influence the development of HF and its outcomes is of critical public health importance to the population aging with HIV worldwide. Previous studies have shown that risks of HFpEF and HFrEF are increased in HIV. This study advances our understanding of HF progression in HIV, illustrating that critical outcomes (rates of 30-day HF readmission, CV mortality, and all-cause mortality) are worse among individuals with a low CD4 count or nonsuppressed VL.

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Conflict of interest statement

The authors do not have any commercial or other association that might pose a conflict of interest.

Appendix. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2019.01.002.

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