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Clinical characteristics of HIV-infected patients with adjudicated heart failure

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Abstract

Aims—HIV-infected persons may have elevated risks for heart failure, but factors associated with heart failure in the modern era of HIV therapy are insufficiently understood. Despite substantial disagreement between physician-adjudicated heart failure and heart failure diagnosis codes, few studies of HIV cohorts have evaluated adjudicated heart failure. We evaluated associations of HIV viremia, immunosuppression, and cardiovascular risk factors with physician-adjudicated heart failure.

Methods and results—We analyzed clinical characteristics associated with heart failure in a cohort of 5041 HIV-infected patients receiving care at an urban hospital system between 2000 and 2016. We also evaluated characteristics of HIV-infected patients who screened negative for heart failure, screened positive for possible heart failure but did not have heart failure after adjudication, and had adjudicated heart failure. HIV-infected patients with heart failure ($N = 216$) were older and more likely to be black, hypertensive, and have diabetes than HIV-infected patients without heart failure; heart failure with reduced ejection fraction was more common than heart failure with preserved ejection fraction. In our primary analyses restricted to HIV-infected patients whose heart failure diagnoses did not precede their HIV diagnoses ($N = 149$), peak HIV viral load $\geq 100,000$ copies/mL (odds ratio (OR) 2.12, 1.28–3.52) and nadir CD4 T-cell count < 200 cells/mm³ (OR 2.35, 1.04–5.31) were associated with significantly elevated odds of heart failure. Overall, 30.6% of patients with any diagnosis code of heart failure had adjudicated heart failure.

Conclusion—Higher peak HIV viremia and lower CD4 cell nadir are associated with significantly elevated odds of heart failure for HIV-infected persons. Physician adjudication of heart failure may be helpful in HIV cohorts.

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Author contribution

ABS and MJF contributed to the conception and design of the work and drafted the manuscript. ABS, MJF, AEP, DS, PN, and JMS contributed to the data analysis and statistical analysis. CJA, SJS, and DML-J contributed to the design of the work. All authors contributed to the critical revision of the manuscript, gave final approval, and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of conflicting interests

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Keywords

Heart failure; HIV; adjudication; electronic cohort

Introduction

There are an estimated 1.2 million people living with HIV and 50,000 new HIV diagnoses each year in the United States.¹ With the development of and broader access to effective antiretroviral therapy (ART), persons with HIV are living longer and increasingly at risk for chronic diseases, particularly cardiovascular diseases (CVDs).²⁻⁴ Compared with uninfected individuals, risks for various manifestations of CVD – including myocardial infarction, pulmonary hypertension, arrhythmias, and heart failure (HF) – are significantly elevated among HIV-infected persons even after accounting for demographics and traditional CVD risk factors.^{3,5-11}

Whereas HIV/AIDS-related cardiomyopathy was responsible for the bulk of HIV-associated HF in the pre-ART era,¹²⁻¹⁴ a growing burden of traditional CVD risk factors and myocardial infarction among persons with well-controlled chronic HIV infection may be driving HIV-associated HF.^{15,16} However, the relative extent to which traditional (e.g. hypertensive or ischemic heart disease) and HIV-related factors drive the association between HIV and HF is poorly characterized, and no previous analyses in diverse HIV cohorts have adjudicated HF events. Several observational cohort studies have found an elevated risk of HF for HIV-infected patients using diagnosis codes alone.^{5,17,18} However, cross-sectional studies of smaller HIV cohorts with sufficiently rich clinical data to evaluate myocardial dysfunction in HIV have generally not had adequate size or follow-up to assess clinical outcomes such as HF; the sole exception is a recent small study that adjudicated 34 heart failure events among HIV-infected women in an all-female cohort.¹⁹⁻²² Adjudication of HF is challenging because it requires comprehensive clinical data, including non-standardized clinical notes, laboratory/biomarker evaluations, and cardiac imaging data. While large HIV cohorts have not evaluated adjudicated HF, this is potentially important given the substantial disagreement (30% or greater disagreement rate) between HF diagnosis codes and physician-adjudicated HF in the general population.^{23,24}

To understand better the potential links of cardiovascular and HIV-related risk factors with HF, there is a need for HIV cohorts with extensive clinical and imaging data that are large enough and have long enough follow-up to evaluate clinical outcomes. In this study, we sought to understand better HIV-related and general clinical characteristics associated with HF in HIV. Our central hypotheses were: (a) HIV-related risk factors including nadir CD4 cell count and peak HIV viral load have a significant association with HF even after adjustment for hypertension and diabetes; and (b) HIV-infected patients with adjudicated HF have a significantly higher burden of CVD comorbidities than HIV-infected patients who screen positive for HF using electronic health record (EHR)-based criteria but are determined not to have HF.

Methods

Study population

We used the Northwestern Medicine Enterprise Data Warehouse (NMEDW), which stores over 40 billion data points on 6.4 million patients receiving care at a large urban medical system, to create an EHR-based cohort of HIV-infected persons and matched uninfected controls: the HIV Electronic Comprehensive Cohort of CVD Complications (HIVE-4CVD). We identified HIV-infected adults aged 18 years and older during the period of observation from 1 January 2000 to 12 July 2016 using a previously validated method for electronic health data in which HIV is defined as follows: (a) positive HIV-1 antibody or serology; (b) positive (>0) HIV viral load; or (c) at least three orders of HIV viral load and a CD4 T-cell count ordered on the same date.²⁵ The first date on which any of the above three criteria were met was considered baseline. The HIVE-4CVD cohort creation and research protocol was approved by the institutional review board at Northwestern University (Chicago, IL, USA).

Demographic and clinical covariates

Age, sex, and race were determined based on administrative data at the date of the first occurring of the following: (a) death; (b) HF diagnosis date; or (c) most recent date of data extraction in the cohort (12 July 2016). Hepatitis B virus infection was defined as a positive result for hepatitis B surface antigen or detectable viremia. Hepatitis C virus infection was defined as a positive result for hepatitis C antibody or detectable viremia.²⁶ Diabetes diagnosis was defined as possible if an individual had an International Classification of Disease (ICD)-9 or ICD-10 code (see Supplementary material), and positive if an individual had a ICD-9 or ICD-10 code and (a) a hemoglobin A1C >6.5% or (b) was prescribed any diabetic medication.²⁷ Hypertension was defined by ICD-9 (401–405) or ICD-10 (I10–I15) codes given the heterogeneity of inpatient and outpatient visits in this cohort (e.g. some patients not having outpatient encounters and potential systematic differences between inpatient and outpatient blood pressure measurements) as well as potential inaccuracy and inconsistency of routine outpatient blood pressure measurements.^{5,28–31} Stroke was defined by ICD-9 (433–436) or ICD-10 (I60–I63) codes given the previously demonstrated high positive predictive value (of approximately 90%).^{32–34} Diagnoses of myocardial infarction and coronary heart disease were based on validated ICD-9 or ICD-10 codes that have demonstrated generally high levels of agreement with expert chart review (ICD-9-CM 410–412, ICD-10-CM 121–123 and ICD-9-CM 410–414, ICD-10-CM 121–125, respectively).^{30,35,36} Diagnoses of atrial fibrillation and atrial flutter were screened for by ICD-9 and ICD-10 codes (427.3; I48; CPT codes 93653, 93655, 93656, 93657) and subsequently confirmed or rejected following physician review of electrocardiography and physician notes. Laboratory analyses and cardiovascular imaging study data were collected for each patient from 1 January 2000 to 12 July 2016. For HIV-infected patients, we collected data on CD4 lymphocyte counts, HIV-1 RNA levels, and the use of ART. We confirmed deaths using the Northwestern Medicine electronic health record and the linked social security administration death master file.

HF screening and adjudication

HF was the primary outcome of interest in this study. Persons with possible HF events were initially identified using NMEDW data as those with any of the following:³⁷ (a) HF diagnosis in the EHR by any previously validated inpatient or outpatient ICD-9 (398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425, 428, 429) or ICD-10 (I42, I43, I50) diagnosis code;^{38,39} (b) B-type natriuretic peptide (BNP) >100 pg/mL;⁴⁰ or (c) the use of intravenous diuretics. Records of all HIV-infected patients in HIVE-4CVD underwent screening using these criteria to identify possible HF events.

Possible events identified during screening were then adjudicated using a protocol adapted from the Multi-Ethnic Study of Atherosclerosis (MESA).^{41,42} Diagnoses of probable HF required symptoms, diagnosis by a physician and HF medication use. Symptoms were defined as the presence of shortness of breath or lower extremity swelling. In situations in which signs such as elevated jugular venous pressure or lower extremity edema were noted on exam and criteria for physician diagnosis and medication use were met, this was considered a qualifying synonym. Physician diagnosis was defined as the presence of a diagnosis of HF or acceptable synonym such as ‘volume or fluid overload’ in the setting of objective criteria demonstrating a cardiac etiology of the symptoms or a superseding diagnosis such as ‘severe valvulopathy or cardiomyopathy’. Medication use was defined as the prescription of a beta-blocker, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, aldosterone antagonist, or diuretic.

A diagnosis of definite HF required objective data in addition to the criteria described above for probable HF (symptoms, physician diagnosis, and medication use). Objective data included: (a) chest radiography with pulmonary edema or signs of volume overload; (b) echocardiography with at least one of the following: left ventricular ejection fraction less than 50%, left ventricular chamber dilation (left ventricular end diastolic volume index >97mL/m²), diastolic dysfunction (suggested by left ventricular end-diastolic pressure > 16mmHg, pulmonary capillary wedge pressure > 12mmHg, E/E' >15, and/or left atrial volume index >34mL/m²),^{43,44} evidence of right ventricular failure (‘depressed systolic function’, ‘dilation’, ‘evidence of volume/pressure overload’ noted in the report), other reported etiologies of cardiomyopathy (severe valvular abnormalities or obstruction (i.e. hypertrophic obstructive cardiomyopathy)), or regional wall motion abnormalities; or (c) other cardiac studies including radionuclide ventriculogram/multigated acquisition, or other contrast ventriculography with any of the above abnormalities noted. Two physician reviewers performed adjudication independently and cases with disagreement were discussed jointly to reach agreement based on the above protocol. Records of 886 HIV-infected patients in HIVE-4CVD underwent physician adjudication.

Statistical analyses

Demographic and clinical characteristics were compared across HF adjudication groups (screened negative (S–), screened positive/adjudicated negative (S+A–), and screened positive/adjudicated positive (S+A+)) for HIV-infected patients using one-way analysis of variance (ANOVA) or the non-parametric equivalent where appropriate for continuous variables and Pearson’s chi-squared for categorical variables. After comparing overall HF

adjudication groups, persons whose first screen positive for HF date preceded their date of HIV diagnosis by more than 7 days were excluded from subsequent multivariable analyses. The purpose of this was to make it less likely that the outcome (HF) clearly preceded the central exposure (HIV).

HF characteristics and echocardiographic measures were compared across nadir CD4 cell count and peak HIV viral load strata for HIV-infected patients with adjudicated HF, using one-way ANOVA or the non-parametric equivalent where appropriate for continuous variables and Pearson's chi-squared for categorical variables. We created interaction terms of HIV diagnosis and treatment era (early ART era (prior to 2006) versus modern ART era (2006 and after)) and exposures (nadir CD4 cell count and peak HIV viral load) to evaluate whether there were any significant interactions with these terms and HF.

Logistic regression analyses were then performed to evaluate odds ratios (ORs) of HF across clinically relevant levels of HIV-related factors for persons with complete covariate data. Nadir CD4 cell count groups were compared with the nadir CD4 cell count 500 or greater group as the referent and peak HIV viral load groups were compared with the peak HIV viral load less than 1000 group as the referent, in separate analyses. Regression models were unadjusted (model 1); adjusted for age, sex, race (model 2); adjusted for model 2 covariates plus hypertension, diabetes, baseline body mass index, high-density lipoprotein-cholesterol, total cholesterol, and smoking history (model 3); and adjusted for model 3 covariates plus ART use and protease inhibitor use (model 4). Sensitivity analyses included all persons found to have adjudicated HF (even if the screen positive date preceded the HIV diagnosis date) in the multivariable logistic regression analyses.

Results

Screening and adjudication

As shown in Figure 1, records of all HIV-infected patients in HIVE-4CVD ($n = 5041$) underwent screening for HF using our electronic criteria; 4155 screened negative and 886 screened positive for possible HF. Of the patients that screened positive for possible HF, 216 were found to have adjudicated HF (S+A+) and the remaining 670 were found not to have HF (S+A-). The most common reason for misclassification of S+A- patients was ICD-9 or ICD-10 codes; only 216 of 705 (30.6%) patients with diagnosis codes of HF were determined to have HF by physician adjudication. Among the 670 S+A- patients, HF diagnosis codes were present in 489 patients, whereas only 189 (28.2%) had a BNP level greater than 100 pg/ml and 237 (35.4%) were given intravenous diuretics. There was a greater than 96% agreement rate between the two independent physicians adjudicating HF diagnoses (Kappa statistic 0.91, Cronbach's alpha 0.96).

Comparisons of demographic and clinical characteristics across HF screening and adjudication groups, as well as information regarding missingness of variables, are shown in Table 1. Of all HIV-infected patients in HIVE-4CVD, 216 were found to have adjudicated HF (4.3%). A far greater proportion of S+A+ patients were black (53.6% compared to 29.7% of S- patients). In general, S+A+ and S+A- patients had more advanced HIV and comorbid disease. As expected, S+A+ patients had a substantially greater burden of

traditional CVD risk factors, including hypertension, diabetes and comorbid CVD diagnoses (adjudicated atrial fibrillation and myocardial infarction). Among S+A+ patients, a comparison of the 149 HIV-infected patients whose HF diagnoses did not precede HIV diagnoses and the 67 HIV-infected patients whose HF diagnoses preceded HIV diagnoses is shown in Table 2; the only notable difference between these groups was that patients whose HF diagnoses preceded their HIV diagnoses were more likely to have had a myocardial infarction and more likely to have been prescribed a statin. For subsequent analyses of the association between HIV-related exposures and HF, we excluded the 67 HIV-infected patients whose HF diagnoses preceded their HIV diagnoses.

HF by CD4 T-cell count and HIV viral load

The proportion of HIV-infected patients with a nadir CD4 cell count less than 200 cells/mm³ who had HF (4.9%) was nearly threefold greater than for HIV-infected patients with a nadir CD4 cell count of 200 cells/mm³ or greater ($P<0.001$; Figure 2). A significantly higher proportion of patients with a peak HIV viral load of 100,000 copies/mL or greater had HF (4.5%) compared with patients with a lower peak HIV viral load ($P=0.005$; Figure 2). These patterns persisted when results were stratified by HIV diagnosis date (before 1 January 2006 vs. on or after; Figure 2). Of these 149 patients, 143 had complete CD4 cell count data and 147 had complete HIV viral load data and therefore were included in the analyses of HF characteristics by HIV status shown in Table 3. Exploratory analyses comparing rates of HF medication use, hospitalization, nadir left ventricular ejection fraction, peak left ventricular size, and left atrial size across different levels of nadir CD4 cell count and peak HIV viral load yielded no substantial or consistent differences across groups.

In logistic regression analyses (restricted to patients with complete covariates), the odds of adjudicated HF were substantially higher for patients with a nadir CD4 cell count less than 200 cells/mm³ than patients with a nadir CD4 cell count of 500 cells/mm³ or greater in unadjusted analyses and after adjustment for age, sex, and race, traditional CVD risk factors and HIV-related medications (OR 2.35, 95% confidence interval (CI) 1.04–5.61) (Figure 3; Supplementary Table 1). Likewise, patients with peak HIV viral load of 100,000 copies/mL or greater were significantly more likely to have adjudicated HF than patients with peak HIV viral load less than 1000 copies/mL in unadjusted analyses and after adjustment for age, sex, race, CVD risk factors, and HIV-related medications (OR 2.12, 95% CI 1.28–3.52) (Figure 3; Supplementary Table 2).

In sensitivity analyses in which nadir CD4 cell count and peak HIV were treated as continuous variables, lower nadir CD4 cell count and higher (log-transformed) peak HIV viral load both remained significantly associated with elevated odds of HF after multivariable adjustment (model 4, which includes adjustment for demographic, clinical, and HIV-related covariates as discussed above). The odds of HF by CD4 cell count in the multivariable-adjusted model were 0.9985 (0.9976, 0.9995), which translates to 15% lower odds of HF for every 100 cells/mm³ greater CD4 cell count. Similarly, the odds of HF by log-transformed HIV viral load in the multivariable-adjusted model were 1.06 (1.01, 1.11), which translates to a 6% greater odds of HF for every 10-fold elevation in HIV viral load. In

another sensitivity analysis in which we matched the 149 HIV-infected persons with HF that did not precede HIV diagnosis with 149 HIV-infected persons without HF on age (year), sex, race, diabetes, and hypertension status, the findings were similar: mean values for nadir CD4 cell count and peak HIV viral load for HIV-infected persons with HF were 171.4 (± 181.0) cells/mm³ and 10.24 (± 3.12) copies/mL, compared with 275.3 (± 199.5) and 9.24 (± 3.22) for matched HIV-infected persons without HF ($P < 0.001$ and $P = 0.015$, respectively).

Discussion

In this study, we had the unique opportunity to evaluate associations of traditional cardiovascular risk factors and HIV-related factors with adjudicated HF for HIV-infected patients in a large electronic clinical cohort. We found that lower nadir CD4 cell count and higher HIV viremia was associated with significantly greater odds of adjudicated HF even after adjustment for demographics, CVD risk factors, and HIV-related medication use. These results support a potential role of HIV-associated immunodeficiency and viremia in HIV-associated HF pathogenesis.^{22,45}

We also found significant differences between HIV-infected persons with adjudicated HF (S +A+) and those who screened positive for possible HF but did not have adjudicated HF (S +A-); this underscores the importance of adjudicating HF diagnoses in EHR-based analyses of HIV-infected patients. Whereas traditional CVD risk factors were highly prevalent among patients with adjudicated HF, there are likely several mechanisms by which HIV infection drives the development of clinical HF, including direct effects of HIV virus, immune activation and autoimmune damage to the myocardium, and toxic inflammation induced by the virus.^{15,46} Another possibility is that certain ARTs have long-term metabolic effects and/or direct deleterious effects leading to myocardial damage and dysfunction, although most modern ARTs appear to be far less toxic than earlier ART regimens.^{47,48}

In the pre-ART and early ART eras, HIV-associated HF had been driven primarily by HIV/AIDS cardiomyopathy, characterized by decreased left ventricular systolic function and a dilated left ventricle. However, HF phenotypes are evolving as HIV has become a treatable chronic disease marked by chronic inflammation and immune activation rather than the overt uncontrolled viremia implicated in HIV/AIDS cardiomyopathy.^{15,16} These diverse phenotypes are reflected in the high prevalence of diastolic dysfunction in HIV,^{19,49} left ventricular systolic dysfunction,^{19,50,51} as well as elevated HIV-associated risks for myocardial infarction, which can lead to myocardial damage and resultant HF.^{6,52} Further distinction of HIV-associated HF phenotypes, as well as how these phenotypes compare with general population HF phenotypes, is needed in future studies.

Of note, the methods we used to screen independently for and adjudicate HF yielded a greater than 96% agreement rate between adjudicators, which suggests this approach may be reproducible in other EHR-based cohorts. Given the high rates of HF diagnosis codes in the EHR among those who screened positively but did not adjudicate to have HF, adjudication is appropriate in this population. Our screening process was designed to be highly sensitive, and as was expected, those patients who screened positively but were not adjudicated to have

HF had more severe HIV-related disease and CVD than those who screened negative. An area of further investigation and risk stratification may be whether those patients who screened positively are at increased risk of developing HF in the future.

Limitations

This study should be interpreted in the context of its limitations. Although HF screening criteria were intentionally highly sensitive to capture all possible events, it is certainly possible that HF events were missed for patients receiving out-of-network care. As with any EHR-based analysis, data quality is subject in part to the quality of physician documentation, which may vary substantially between physicians and specialties. The adjudication process was conducted by two physicians, although they were not fully blinded to HIV status given the nature of EHR review. In addition, the first approximately 100 cases were discussed jointly during the adjudication process to adapt the protocol to an EHR-based cohort. Such limitations were largely unavoidable given the EHR-based nature of our study. Another limitation of our analyses relates to the heterogeneity in timing and ascertainment of HIV and HF diagnoses, which theoretically could have differed systematically across exposure groups and created substantial bias in time-to-event analyses. For instance, if person A and person B both have mild HF but person A has worse HIV viral and immunological control and is thus hospitalized more often for non-HF-related reasons, it is likely that person A's HF would be ascertained first due to more frequent inpatient encounters. We were not able to assess HIV duration or precise time from HIV diagnosis to HF accurately because our electronic cohort uses data collected in the clinical care of patients within a large hospital system beginning 1 January 2000. Therefore, for patients whose HIV diagnoses predate 1 January 2000 and patients whose initial HIV diagnoses and care were out of network, their true HIV durations would be longer than what we were able to assess. Considering such potential sources of bias, we did not perform time-to-event analyses. We were also unable to assess substance use or abuse reliably, which may contribute to HF among HIV-infected persons to a greater extent than uninfected persons; however, a previous analysis in a cohort of HIV-infected and uninfected veterans suggested that the association between HIV and HF is independent of alcohol abuse or dependence.⁵

Given the single-center nature of this cohort and the modest number of adjudicated HF diagnoses, our findings may not be generalizable to the broader HIV-infected population in the United States. Because the cohort is composed of data collected in routine clinical care at this center, we were not able to account for differential loss-to-follow up, which may have impacted the findings. It is conceivable that HIV-infected persons with poor viral and immunological control (as evidenced by higher peak HIV viral load and lower nadir CD4 cell count) may be less likely to access care and follow up in-network, and therefore less likely to have HF diagnoses ascertained in-network. This would bias our results towards the null, however, and therefore would suggest that the effect size we found of greater HF odds among HIV-infected persons with poor viral and immunological control may actually underestimate the true effect size. In light of the limitations discussed here, it is most accurate to describe our results as hypothesis generating; accordingly, this study's results should be confirmed in longer term follow-up of inception cohorts of HIV-infected persons.

Furthermore, despite these limitations, this analysis represents the largest size sample of HIV-infected persons with adjudicated HF to date.

Conclusions

We found that lower nadir CD4 cell count and higher HIV viremia were associated with significantly greater odds of HF even after adjustment for demographics, CVD risk factors, and HIV-related medication use. These findings require confirmation in future analyses of HIV inception cohorts with standardized enrollment and follow-up. These analyses, as well as future analyses comparing HF incidence and characteristics for HIV-infected persons and uninfected controls, may help inform prevention and treatment strategies related to HF among HIV-infected persons.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Heart failure ascertainment.

Figure 2.
Heart failure prevalence by nadir CD4 cell count and peak HIV viral load.

Figure 3.

Forest plot of adjusted odds ratios of heart failure by HIV-related risk factors.

Table 1

Baseline characteristics of HIV-infected cohort undergoing heart failure screening and adjudication.

Characteristic	Screened negative; S- (n = 4155)	Screened positive, adjudicated no heart failure; S+A- (n = 670)	Adjudicated heart failure; S+A+ (n = 216)	P value
Race and ethnicity, N(%)				<0.001 *
White, non-Hispanic	1406 (35.2%)	218 (33.3%)	56 (26.8%)	
Black, non-Hispanic	1185 (29.7%)	275 (42.0%)	112 (53.6%)	
Hispanic	136 (3.4%)	27 (4.1%)	9 (4.3%)	
Other	1263 (31.6%)	134 (20.5%)	32 (15.3%)	
Sex, N(%)				0.97
Male	3430 (82.6%)	557 (83.1%)	179 (82.9%)	
Female	723 (17.4%)	113 (16.9%)	37 (17.1%)	
Age (years)	47 (11)	54 (11)	55 (12)	<0.0001
Baseline body mass index (kg/m ²)				0.26
<18.5	105 (2.8%)	38 (5.8%)	8 (3.7%)	
18.5–24.9	1682 (44.0%)	269 (41.0%)	100 (46.5%)	
25.0–29.9	1353 (35.4%)	216 (32.9%)	59 (27.4%)	
30.0	683 (17.9%)	134 (20.4%)	48 (22.3%)	
(Number with complete body mass index data)	N=3823	N= 657	N= 215	
Baseline HDL-cholesterol (mg/dl)	40.5 (14.2)	37.1 (15.9)	34.8 (15.9)	<0.0001
(Number with complete HDL data)	N=3005	N= 528	N= 190	
Baseline triglycerides	155.1 (147.3)	189.5 (356.2)	175.0 (143.5)	0.0001
(Number with complete triglycerides data)	N= 3016	N= 544	N= 191	
Baseline total cholesterol (mg/dl)	173.3 (42.0)	169.6 (55.1)	156.0 (46.0)	<0.0001 *
(Number with complete total cholesterol data)	N= 3009	N= 531	N= 191	
Baseline CD4 cell count (cells/mm ³)	410.0 (271.6)	335.6 (288.0)	350.4 (322.5)	0.0001
Nadir CD4 cell count (cells/mm ³)	296.6 (207.7)	181.8 (189.8)	185.1 (203.8)	0.0001
(Number with complete CD4 cell count data)	N= 3994	N= 650	N= 210	
Nadir CD4 cell count, groups (cells/mm ³), N (%)				<0.001
CD4 cell count <200	1444 (36.1%)	412 (63.4%)	141 (67.1%)	
CD4 cell count 200 to <500	1927 (48.3%)	191 (29.4%)	52 (24.8%)	
CD4 cell count 500	623 (15.6%)	47 (7.2%)	17 (8.1%)	
Baseline HIV viral load (copies/mL)	108,618.2 (1,240,297)	109,057.9 (576,352.8)	145,469.8 (722,207.4)	0.04
Peak HIV viral load (copies/mL)	144,005.6 (547,534.5)	234,178.7 (815,450.9)	306,124.8 (1,001,517)	0.01
(Number with complete HIV viral load data)	N= 4062	N= 662	N= 213	
Peak HIV viral load, groups (copies/mL), N (%)				0.001
<1000	1513 (37.2%)	242 (36.6%)	65 (30.5%)	

Characteristic	Screened negative; S- (<i>n</i> = 4155)	Screened positive, adjudicated no heart failure; S+A- (<i>n</i> = 670)	Adjudicated heart failure; S+A+ (<i>n</i> = 216)	<i>P</i> value
	Mean (SD)	Mean (SD)	Mean (SD)	
1000–<10,000	481 (11.8%)	82 (12.4%)	24 (11.3%)	
10,000–<100,000	1119 (27.6%)	148 (22.4%)	53 (24.9%)	
100,000	949 (23.4%)	190 (28.7%)	71 (33.3%)	
Antiretroviral use, <i>N</i> (%)	3441 (82.8%)	613 (91.5%)	197 (91.2%)	<0.001
Protease inhibitor use, <i>N</i> (%)	1807 (43.5%)	420 (62.7%)	136 (63.0%)	<0.001
Hypertension, <i>N</i> (%)	1086 (26.2%)	400 (59.7%)	188 (87.0%)	<0.001 *
Diabetes, <i>N</i> (%)	273 (6.6%)	129 (19.2%)	61 (28.2%)	<0.001 *
HCV, <i>N</i> (%)	301 (7.2%)	95 (14.2%)	29 (13.4%)	<0.001
HBV, <i>N</i> (%)	209 (5.0%)	59 (8.8%)	17 (7.9%)	<0.001
Atrial fibrillation or atrial flutter, adjudicated, <i>N</i> (%)	20 (0.5%)	40 (6.0%)	39 (18.0%)	<0.001 *
Myocardial infarction, <i>N</i> (%)	0 (0.0%)	52 (7.9%)	55 (25.5%)	<0.001 *
Statin use, <i>N</i> (%)	705 (17.0%)	244 (36.4%)	123 (56.9%)	<0.001 *
Antihypertensive use <i>N</i> , (%)	1170 (28.1)	533 (79.6%)	216 (100.0%)	<0.001 *
Smoking history, <i>N</i> (%)	2108 (59.8%)	424 (64.4%)	151 (70.2%)	<0.001 *
Peak BNP (pg/mL)	32.1 (23.9)	322.7 (523.9)	1446.1 (1425.1)	0.0001 *
(Number with BNP data)	<i>N</i> = 235	<i>N</i> = 299	<i>N</i> = 184	
BNP > 100 (pg/mL), <i>N</i> (%)	0	189 (28.2%)	162 (75.0%)	<0.001
IV diuretic use, <i>N</i> (%)	0	237 (35.4%)	145 (67.1%)	<0.001
HF diagnosis code, <i>N</i> (%)	0	489 (73.0%)	209 (96.8%)	<0.001

* *P* < 0.05 between those patients who S+A- and S+A+.

BNP: B-type natriuretic peptide; HDL: high-density lipoprotein; HCV: hepatitis C virus; HBV: hepatitis B virus; IV: intravenous; HF: heart failure.

Table 2

Baseline characteristics of HIV-infected cohort with adjudicated heart failure comparing non-preceding diagnosis to pre-existing diagnoses of heart failure.

Characteristic	Adjudicated HF not preceding HIV diagnosis (<i>n</i> = 149) Mean (SD)	Adjudicated HF preceding HIV diagnosis (<i>n</i> = 67) Mean (SD)	<i>P</i> value
Race and ethnicity, <i>N</i> (%)			0.13
White, non-Hispanic	34 (23.6%)	22 (33.8%)	
Black, non-Hispanic	76 (52.8%)	36 (55.4%)	
Hispanic	7 (4.9%)	2 (3.1%)	
Other	27 (18.7%)	5 (7.7%)	
Sex, <i>N</i> (%)			0.33
Male	121 (81.2%)	58 (86.6%)	
Female	28 (18.8%)	9 (13.4%)	
Age (years)	53 (12)	58 (11)	0.003
Baseline body mass index (kg/m ²)			0.66
<18.5	6 (4.0%)	2 (3.0%)	
18.5–24.9	67 (45.3%)	33 (49.2%)	
25.0–29.9	44 (29.7%)	15 (22.4%)	
30.0	31 (20.9%)	17 (25.4%)	
(Number with complete body mass index data)	<i>N</i> = 148	<i>N</i> = 67	
Baseline HDL-cholesterol (mg/dl)	34.9 (17.3)	34.5 (12.5)	0.86
(Number with complete HDL-cholesterol data)	<i>N</i> = 130	<i>N</i> = 60	
Baseline triglycerides	166.0 (120.8)	194.6 (183.1)	0.40
(Number with complete triglycerides data)	<i>N</i> = 131	<i>N</i> = 60	
Baseline total cholesterol (mg/dl)	154.6 (46.5)	159.0 (45.2)	0.54
(Number with complete total cholesterol data)	<i>N</i> = 131	<i>N</i> = 60	
Baseline CD4 cell count (cells/mm ³)	331.4 (308.4)	392.9 (350.8)	0.37
Nadir CD4 cell count (cells/mm ³)	173.0 (181.3)	210.8 (244.5)	0.46
(Number with complete CD4 cell count data)	<i>N</i> = 143	<i>N</i> = 67	
Nadir CD4 cell count, groups (cells/mm ³), <i>N</i> (%)			0.66
CD4 cell count <200	98 (68.5%)	43 (64.2%)	
CD4 cell count 200 to <500	35 (24.5%)	17 (25.4%)	
CD4 cell count ≥ 500	10 (7.0%)	7 (10.5%)	
Baseline HIV viral load (copies/mL)	126,309 (566,902)	188,802 (991,817)	0.43
Peak HIV viral load (copies/mL)	342,408 (1,010,086)	225,311 (984,957)	0.11
(Number with complete HIV viral load data)	<i>N</i> = 147	<i>N</i> = 66	
Peak HIV viral load, groups (copies/mL), <i>N</i> (%)			0.47
<1000	42 (28.6%)	23 (34.8%)	
1000–<10,000	16 (10.9%)	8 (12.1%)	
10,000–<100,000	35 (23.8%)	18 (27.3%)	
100,000	54 (36.7%)	17 (25.8%)	

Characteristic	Adjudicated HF not preceding HIV diagnosis (<i>n</i> = 149)	Adjudicated HF preceding HIV diagnosis (<i>n</i> = 67)	<i>P</i> value
	Mean (SD)	Mean (SD)	
Antiretroviral use, <i>N</i> (%)	135 (90.6%)	62 (92.5%)	0.64
Protease inhibitor use, <i>N</i> (%)	90 (63.0%)	46 (68.7%)	0.24
Hypertension, <i>N</i> (%)	128 (85.9%)	60 (89.5%)	0.46
Diabetes, <i>N</i> (%)	35 (23.5%)	26 (38.8%)	0.02
HCV, <i>N</i> (%)	20 (13.4%)	9 (13.4%)	0.99
HBV, <i>N</i> (%)	11(7.8%)	6 (9.0%)	0.69
Atrial fibrillation or atrial flutter, adjudicated, <i>N</i> (%)	23 (15.4%)	16 (23.9%)	0.14
Myocardial infarction, <i>N</i> (%)	27 (18.1%)	28 (41.8%)	<0.001
Statin use, <i>N</i> (%)	77 (51.7%)	46 (68.7%)	<0.02
Antihypertensive use, <i>N</i> (%)	149 (100%)	67 (100%)	
Smoking history, <i>N</i> (%)	104 (70.3%)	47 (70.1%)	0.99
Peak BNP (pg/mL)	1419 (1354)	1501 (1571)	0.91
(Number with BNP data)	<i>N</i> = 124	<i>N</i> = 60	
BNP > 100 (pg/mL), <i>N</i> (%)	108 (72.5%)	54 (80.6%)	0.20
IV diuretic use, <i>N</i> (%)	96 (64.4%)	49 (73.1%)	0.21
HF diagnosis code, <i>N</i> (%)	142 (95.3%)	67 (100%)	0.07

BNP: B-type natriuretic peptide; HDL: high-density lipoprotein; HCV: hepatitis C virus; HBV: hepatitis B virus; IV: intravenous; HF: heart failure.

Table 3

Heart failure characteristics by nadir CD4 cell count and peak HIV viral load.

	Nadir CD4 T cell count (cells/mm ³)			Peak HIV viral load (copies/mL)			
	Nadir CD4 cell count <200	Nadir CD4 cell count 200 to <500	Nadir CD4 cell count 500	P value	Peak HIV viral load <1000	Peak HIV viral load 1000–<100,000	Peak HIV viral load 100,000
Medication use, N (%)							P value
Diuretic	96 (98.0%)	33 (94.3%)	10 (100%)	0.45	41 (97.6%)	16 (100%)	34 (97.1%)
Beta-blocker	88 (89.8%)	32 (91.4%)	10 (100%)	0.56	40 (95.2%)	14 (87.5%)	32 (91.4%)
ACE inhibitor	72 (73.5%)	24 (68.6%)	9 (90.0%)	0.40	29 (69.0%)	10 (62.5%)	30 (85.7%)
Angiotensin receptor blocker	13 (13.3%)	6 (17.1%)	1 (10.0%)	0.79	7 (16.7%)	2 (12.5%)	9 (25.7%)
Aldosterone antagonist	21 (21.4%)	11 (31.4%)	6 (60.0%)	0.02	10 (23.8%)	11 (68.7%)	10 (28.6%)
HF hospitalization, N (%)	93 (94.9%)	27 (77.1%)	8 (80.0%)	0.008	36 (85.7%)	15 (93.8%)	31 (88.6%)
Lowest EF <50%, N (%)	64 (65.3%)	21 (60.0%)	3 (30.0%)	0.09	22 (52.4%)	10 (62.5%)	22 (62.9%)
N with complete EF and CD4 cell count data = 137 (95.8%)					N with complete EF and HIV viral load data = 143 (97.3%)		
Ischemic HF etiology, N (%)	16 (16.3%)	7 (20.0%)	2 (20.0%)	0.87	8 (19.0%)	2 (12.5%)	7 (20.0%)
Highest LVEDD (mm)	5.4 (0.8)	5.2 (1.0)	5.1 (0.9)	0.50	5.1 (0.9)	5.7 (1.2)	5.8 (0.9)
N with complete LVEDD and CD4 cell count data = 135 (94.4%)					N with complete LVEDD and HIV viral load data = 139 (94.6%)		
Highest LA diameter (mm)	4.2 (0.7)	4.2 (0.7)	3.9 (1.0)	0.80	4.1 (0.7)	4.4 (0.9)	4.4 (0.8)
N with complete LA diameter and CD4 cell count data = 134 (93.7%)					N with complete LA diameter and HIV viral load data = 138 (93.9%)		

(N = 143 with complete CD4 cell count data; N = 149 with complete HIV viral load data).

HF: heart failure; ACE: angiotensin-converting enzyme; EF: ejection fraction; LVEDD: left ventricular end-diastolic dimension; LA: left atrial.