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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

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Abstract

IMPORTANCE—With improved survival, heart failure (HF) has become a major complication for individuals with human immunodeficiency virus (HIV) infection. It is unclear if this risk extends to different types of HF in the antiretroviral therapy (ART) era. Determining whether HIV infection is associated with HF with reduced ejection fraction (HFrEF), HF with preserved ejection fraction (HFpEF), or both is critical because HF types differ with respect to underlying mechanism, treatment, and prognosis.

OBJECTIVES—To investigate whether HIV infection increases the risk of future HFrEF and HFpEF and to assess if this risk varies by sociodemographic and HIV-specific factors.

DESIGN, SETTING, AND PARTICIPANTS—This study evaluated 98 015 participants without baseline cardiovascular disease from the Veterans Aging Cohort Study, an observational cohort of

HIV-infected veterans and uninfected veterans matched by age, sex, race/ethnicity, and clinical site, enrolled on or after April 1, 2003, and followed up through September 30, 2012. The dates of the analysis were October 2015 to November 2016.

EXPOSURE—Human immunodeficiency virus infection.

MAIN OUTCOMES AND MEASURES—Outcomes included HFpEF (EF ≥50%), borderline HFpEF (EF 40%–49%), HFrEF (EF <40%), and HF of unknown type (EF missing).

RESULTS—Among 98 015 participants, the mean (SD) age at enrollment in the study was 48.3 (9.8) years, 97.0% were male, and 32.2% had HIV infection. During a median follow-up of 7.1 years, there were 2636 total HF events (34.6% were HFpEF, 15.5% were borderline HFpEF, 37.1% were HFrEF, and 12.8% were HF of unknown type). Compared with uninfected veterans, HIV-infected veterans had an increased risk of HFpEF (hazard ratio [HR], 1.21; 95% CI, 1.03–1.41), borderline HFpEF (HR, 1.37; 95% CI, 1.09–1.72), and HFrEF (HR, 1.61; 95% CI, 1.40–1.86). The risk of HFrEF was pronounced in veterans younger than 40 years at baseline (HR, 3.59; 95% CI, 1.95–6.58). Among HIV-infected veterans, time-updated HIV-1 RNA viral load of at least 500 copies/mL compared with less than 500 copies/mL was associated with an increased risk of HFrEF, and time-updated CD4 cell count less than 200 cells/mm³ compared with at least 500 cells/mm³ was associated with an increased risk of HFrEF and HFpEF.

CONCLUSIONS AND RELEVANCE—Individuals who are infected with HIV have an increased risk of HFpEF, borderline HFpEF, and HFrEF compared with uninfected individuals. The increased risk of HFrEF can manifest decades earlier than would be expected in a typical uninfected population. Future research should focus on prevention, risk stratification, and identification of the mechanisms for HFrEF and HFpEF in the HIV-infected population.

More than 36 million people are infected with human immunodeficiency virus (HIV) worldwide.¹ Almost 17 million are receiving antiretroviral therapy (ART).¹ With the improved life expectancy because of ART,² cardiovascular disease (CVD) is now a major health complication among HIV-infected individuals.³ Acute myocardial infarction (AMI) has been studied, and the increased risk of AMI among HIV-infected individuals compared with uninfected individuals is well documented.^{4–7} Similarly, an excess risk of heart failure (HF) is also present for HIV-infected individuals compared with uninfected individuals; however, it is not known what types of HF are associated with this risk and whether the risk of different types of HF varies by age, race/ethnicity, HIV-specific biomarkers, and receipt of ART.^{8,9}

Studies have shown that HIV infection increases the risk of HF independent of AMI^{9,10} and that the increased risk is higher among older people, individuals of black race/ethnicity, and those with obesity, hypertension, diabetes, current smoking, alcohol abuse or dependence, elevated HIV-1 RNA viral loads, or a history of AMI.^{8,9} The success of ART has increased life expectancy for patients with HIV, and treatment of modifiable HF risk factors, in combination with improvements in CVD care, has increased survival for patients with AMI.^{2,11} Consequently, many HIV-infected individuals will survive with a damaged heart, and their health care professionals will have the challenge of preventing and managing HF in this high-risk population.

To reduce the risk of HF in the HIV-infected population, there is a need to understand the epidemiological patterns surrounding HIV and the risk of HF in the ART era. Among uninfected people, differentiating between HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF) is critical because these types of HF differ with respect to underlying mechanism, treatment, and prognosis.¹² In the HIV-infected population, our present knowledge on HIV and type of HF in the ART era is limited to case reports, cross-sectional data, and longitudinal data linking HIV infection to echocardiographic changes consistent with HFrEF and HFpEF.^{13–20} To our knowledge, there are no large studies showing that HIV-infected individuals have a significantly increased risk of HFrEF and HFpEF events compared with demographically and behaviorally similar uninfected individuals in the ART era. Similarly, data describing the association between HIV infection and type of HF across age groups, by race/ethnicity, by HIV-specific biomarkers, and by receipt of ART regimens are also lacking. Yet, HIV infection is common among younger adults²¹ and minority populations²² and is increasingly diagnosed among older adults.²¹ Health care professionals do not have the information needed to advise and risk stratify HIV-infected patients who may be at risk for HF.

Therefore, we investigated whether HIV infection is associated with an increased risk of future HFrEF and HFpEF in a national cohort of HIV-infected and uninfected veterans. We evaluated whether this risk varied by age group, race/ethnicity, HIV-specific biomarkers, and receipt of ART regimens.

Methods

The Veterans Aging Cohort Study (VACS) is an observational, longitudinal cohort of HIV-infected veterans and uninfected veterans matched by age, sex, race/ethnicity, and clinical site who were enrolled in the same calendar year that has been described previously.²³ Study participants are known to have been continuously enrolled each year since 1998 using a validated existing algorithm from the US Department of Veterans Affairs (VA) national electronic medical record system.²³ Data for this cohort are extracted from the VA Central Data Warehouse. The Vanderbilt University and West Haven Veterans Affairs Medical Center institutional review boards approved this study. The VACS has a waiver of informed consent.

Study Population

For this analysis, we included all VACS participants who were alive and enrolled in the VACS on or after April 1, 2003. The baseline date was a participant's first clinical encounter on or after April 1, 2003. All participants were followed up from their baseline date to an HF event, death, or the last follow-up date (September 30, 2012). The dates of the analysis were October 2015 to November 2016. We excluded participants with prevalent CVD based on *International Classification of Diseases, Ninth Revision (ICD-9)* codes for AMI, unstable angina, other coronary heart disease, stroke or transient ischemic attack, or HF on or before their baseline date. After these exclusions (n = 35 003), our final sample included 98 015 veterans, of whom 32.2% were infected with HIV.

Independent Variable and Dependent Variables

Using a previously validated algorithm, HIV was defined as the presence of at least 1 inpatient or at least 2 outpatient *ICD-9* codes for HIV and inclusion in the VA Immunology Case Registry.²³

For the dependent variables, we used the presence of at least 1 inpatient (discharge diagnosis) or at least 2 outpatient VA *ICD-9* codes to identify HF events (*ICD-9* codes 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.0, 428.1, 428.20, 428.21, 428.22, 428.23, 428.30, 428.31, 428.32, 428.33, 428.40, 428.41, 428.42, 428.43, and 428.9). This definition was based on prior validation work within and outside of the VA.²⁴ Ejection fraction (EF) measurements were used only to classify HF into HFpEF, borderline HFpEF, HFrEF, or HF of unknown type as per guidelines.²⁵ All EF data were obtained using an automated information extraction application that was developed and validated within the VA health care system to identify, among other variables, the mention of EF in clinical notes and corresponding quantitative or qualitative values. This application was informed in part based on an earlier application that extracted EF data from the VA electronic medical record system.²⁶ When the application used for this study was tested across multiple data sources, the application achieved, on average, positive predictive values of 0.968 to 1.000 and sensitivities of 0.801 to 0.899 for EF measurements across different document types. Using values extracted from clinical notes, we selected the EF data closest to the date on or after the incident HF event. The presence of HFpEF was defined as HF with documentation of an EF of at least 50%; when no numerical value was recorded, the left ventricular (LV) function was described as normal. Borderline HFpEF was defined as an EF between 40% and 49%. The presence of HFrEF was defined as HF with an EF less than 40%; when no numerical value was present, the LV dysfunction was described as moderate or severe. When no EF documentation was present, the HF was classified as unknown type.

Covariates

We used administrative data to determine age, sex, and race/ethnicity. We assessed hypertension, diabetes, lipid levels, renal disease, body mass index (BMI), and anemia using clinical outpatient and laboratory data collected closest to the baseline date. Hydroxymethylglutaryl coenzyme A reductase inhibitor use and ART were based on pharmacy data, and smoking was measured from health factors data that are collected in a standardized form within the VA.²⁷ Hypertension was categorized based on Joint National Committee 7 criteria.²⁸ Our blood pressure measurement was the mean of the 3 routine outpatient clinical measurements closest to the baseline date. Diabetes was diagnosed using a validated metric that considers glucose measurements, antidiabetic agent use, and at least 1 inpatient or at least 2 outpatient *ICD-9* codes for this diagnosis.²⁹ Current hydroxymethylglutaryl coenzyme A reductase inhibitor use was defined as a prescription filled within 180 days of the baseline date. Smoking status was categorized as current, past, or never, while BMI (calculated as weight in kilograms divided by height in meters squared) was dichotomized as BMI of at least 30 or less than 30. Hepatitis C virus (HCV) infection was defined as a positive HCV antibody test result or at least 1 inpatient or at least 2 outpatient *ICD-9* codes for this diagnosis.^{29,30} History of alcohol and cocaine abuse or dependence was defined using *ICD-9* codes, as was a history of atrial fibrillation.³¹ We

collected data (eg, on CD4 lymphocyte counts [CD4 cell counts] and HIV-1 RNA) at baseline (ie, within 180 days of our enrollment date) through September 30, 2012. Baseline ART was categorized by regimen of ART within 180 days of baseline, including a nucleoside reverse transcriptase inhibitor (NRTI) plus a protease inhibitor (PI), an NRTI plus a non-NRTI (NNRTI), other (ie, use of PI, NRTI, or NNRTI medications but not in combination as described in the other 2 categories), and no ART (reference group). All ART medications that were on VA formulary during the study period were included. Our group has previously demonstrated in a nested sample that 98% of HIV-infected veterans obtain their ART medications from the VA.²³

Statistical Analysis

Descriptive statistics for all variables by HIV infection status were assessed using *t* test or its nonparametric counterpart for continuous variables and using χ^2 test or Fisher exact test for categorical variables. We calculated incident total HF, HFpEF, borderline HFpEF, HFrEF, and HF of unknown type rates per 1000 person-years and incidence rate ratios stratified by age group and HIV infection status. We constructed Cox proportional hazards regression models to estimate the hazard ratio (HR) and 95% CI for the association between HIV and the risk of each type of HF after adjusting for other covariates. We also performed sensitivity analyses that included HF events outside of the VA (ie, HF diagnosed using Medicare and VA fee-for-service HF *ICD-9* codes). For these analyses, we linked those non-VA HF events to EF data within the VA after the non-VA HF event date. Proportional hazards assumption was not violated for the main predictor (HIV infection status) using the loglog survival plot.³² In secondary analyses, we adjusted our final HFrEF model for incident AMI during the follow-up period. In separate, similar analyses, we also examined the association between HIV infection status and types of HF in important subgroups (eg, those younger than 40 years). Among HIV-infected veterans, we examined the association between time-updated HIV-1 RNA, CD4 cell count, and HF type while also adjusting for potential confounders, including base-line ART. Missing covariate data were included in the analyses using multiple imputation techniques that generated 5 data sets with complete covariate values to increase the robustness of the Cox proportional hazards regression models.

Results

In this analysis, there were 98 015 veterans (32.2% infected with HIV) who were free of baseline CVD. Their mean (SD) age at enrollment in the study was 48.3 (9.8) years, and 97.0% were male. The CVD risk factors and substance use measures varied by HIV infection status (Table 1), in part because of the large sample size. In general, uninfected veterans had a higher prevalence of traditional cardiovascular risk factors except smoking, whereas HIV-infected veterans had a higher prevalence of nontraditional CVD risk factors (eg, HCV infection). For HIV-infected veterans, the median baseline HIV-1 RNA viral load was 1357 copies/mL, the median baseline CD4 cell count was 382 cells/mm³, and 73.9% were receiving ART consisting of PIs (58.4% of those receiving ART) and NRTIs (73.6% of those receiving ART).

During a median follow-up of 7.1 years, there were 2636 total HF events. Of these events, 35.7% occurred in HIV-infected veterans (34.6% were HFpEF, 15.5% were borderline HFpEF, 37.1% were HFrEF, and 12.8% were HF of unknown type). Compared with uninfected veterans, HIV-infected veterans had higher rates of total HF and HFrEF but not HFpEF and borderline HFpEF (Table 2). Similar results were observed when rates were stratified by HIV infection status and age group categories except among those 70 years or older.

Compared with uninfected veterans, HIV-infected veterans had a significantly increased risk of total HF, HFpEF, borderline HFpEF, and HFrEF after adjusting for possible confounders (Table 3). In sensitivity analyses that included non-VA HF events and VA EF data, the association between HIV and total HF, HFpEF, borderline HFpEF, and HFrEF remained essentially unchanged (eTable in the Supplement). Similarly, the association between HIV and HF held when we restricted the sample to those without hypertension (HR, 1.32; 95% CI, 1.08–1.61), individuals without alcohol or cocaine abuse or dependence (HR, 1.43; 95% CI, 1.25–1.65), and never smokers (HR, 1.33; 95% CI, 1.05–1.70). The association between HIV infection and HFrEF persisted after further adjustment for incident AMI during the follow-up period (HR, 1.58; 95% CI, 1.37–1.82).

Among the younger veterans (<40 years at baseline) and individuals of white or black race/ethnicity, HIV infection was significantly associated with an increase in total HF and HFrEF but not HFpEF or borderline HFpEF (Table 3). When we compared uninfected veterans with HIV-infected veterans stratified by HIV-specific biomarkers, the risk of HFrEF persisted even among HIV-infected veterans with a baseline HIV-1 RNA viral load less than 500 copies/mL compared with uninfected veterans (HR, 1.41; 95% CI, 1.17–1.70) (Table 4).

When we restricted the sample to only HIV-infected veterans and adjusted for covariates, including baseline HIV-1 RNA viral load and CD4 cell count, baseline NRTI plus PI (HR, 1.80; 95% CI, 1.19–2.71), NRTI plus NNRTI (HR, 1.48; 95% CI, 1.01–2.15), and other (HR, 3.46; 95% CI, 1.79–6.72) compared with no ART were associated with an increased risk of HFpEF but not HFrEF. In time-updated analyses, CD4 cell count less than 200 cells/mm³ was associated with an increased risk of total HF, HFpEF, borderline HFpEF, and HFrEF (Table 5), whereas time-updated HIV-1 RNA viral load of at least 500 copies/mL was only associated with HFrEF.

Discussion

In the VACS, HIV-infected veterans had an increased risk of HFpEF, borderline HFpEF, and HFrEF. The association between HIV and HFrEF remained significant even when the sample size was reduced for subgroup analyses that included individuals of white or black race/ethnicity and the younger veterans, as well as after adjustment for AMI in the follow-up period. Among HIV-infected veterans, time-updated HIV-1 RNA viral load of at least 500 copies/mL compared with less than 500 copies/mL was associated with an increased risk of HFrEF, whereas time-updated CD4 cell count less than 200 cells/mm³ compared with at least 500 cells/mm³ was associated with an increased risk of total HF, HFpEF, borderline HFpEF, and HFrEF.

To our knowledge, this investigation is the first large study to report that HIV-infected individuals have a significantly increased risk of HFpEF, borderline HFpEF, and HFrEF events compared with demographically and behaviorally similar uninfected individuals in the ART era. These findings are consistent with and extend earlier echocardiographic reports linking HIV infection to reduced LV systolic function and diastolic dysfunction,^{13–20} as well as our group's earlier work reporting an association between HIV infection and total HF.⁸ More specifically, we show herein that the risk of HFrEF extends beyond AMI, is present across multiple decades of age groups, and occurs among individuals of black or white race/ethnicity, those without decades-long exposure to HF risk factors, and those with high HIV-1 RNA viral load and low CD4 cell count over time. In fact, HFrEF among HIV-infected individuals in the ART era can manifest at a young age, decades earlier than might be expected among uninfected individuals.³³

While the exact mechanisms underlying the association between HIV and types of HF remain unclear, the fact that time-updated low CD4 cell count was associated with HFrEF and HFpEF suggests that duration of HIV infection and, by extension, chronic inflammation, T-cell activation, and loss of adaptive immunity likely all have important roles. Individuals who are infected with HIV with low CD4 cell counts have increased levels of immune activation and inflammation,³⁴ which are associated with an increased HF risk.³⁵ In murine models, depletion of T-regulatory cells leads to increased myocardial fibrosis, a factor consistent with HFrEF and HFpEF phenotypes.³⁶ Most important, our data also suggest that even HIV-infected individuals with high CD4 cell counts are likely still at risk for HF compared with uninfected individuals, in part because HIV-infected individuals with high CD4 cell counts who are rapidly diagnosed, treated, and virally suppressed do not return to their pre-HIV levels of inflammation.³⁷ Moreover, this residual inflammation is associated with an increased risk of future non-AIDS diseases.³⁷ In contrast, time-updated elevated HIV-1 RNA viral load was only significantly associated with HFrEF. These findings are consistent with reports before the ART era in which unsuppressed HIV viremia, perhaps through direct infection of cardiac myocytes^{38,39} or cardiac autoantibodies,⁴⁰ results in a cardiomyopathy consistent with HFrEF.⁴¹

The role of ART in the development of HF is less clear. Cardiac mitochondrial toxic effects in the highly active ART era is well documented.⁴² In the present study, baseline ART use was associated with an increased HFpEF risk, whereas our time-updated data suggested that successful ART as measured by lower HIV-1 RNA viral load and higher CD4 cell count reduces the risk of HFrEF and HFpEF. As prior studies have shown, ART can simultaneously lower AMI risk through viral suppression⁴³ and increase AMI risk likely through medication adverse effects.⁴⁴ Therefore, determining if newer ART medications have a role in the development of HF should be explored because many HIV-infected individuals will be receiving ART medications for decades.

Our findings have important implications for HIV-infected individuals and their health care professionals. In the United States, 25% of all new cases of HIV are among those aged 13 to 24 years, and 25% of HIV-infected individuals are older than 55 years,²¹ while 44% of new HIV infections occur in persons of black race/ethnicity,²² who are at high risk for HF.⁴⁵ Globally, HF is common in low-income and middle-income countries, where the burden of

HIV is high and availability of ART can be limited.⁴⁶ Given these facts, health care professionals should focus on guideline-recommended HIV treatment and HF risk factor prevention (including diabetes, hypertension, renal disease, smoking, alcohol abuse and dependence, and obesity), as well as screening for HIV in individuals with new-onset HF where appropriate.²⁵ Developing tools designed to risk stratify HIV-infected individuals for HF will also be required.

Limitations

Our investigation has limitations that warrant discussion. First, because HF was determined using *ICD-9* codes, it is possible that some misclassification occurred (ie, some true HF events were not captured by *ICD-9* codes). However, this finding would have biased our results to the null. Second, because EF data were extracted using a natural language processing application, misclassification may have occurred. However, the application was developed to capture EF data internally within the VA health care system, and its validation against manual data extraction demonstrated high accuracy (positive predictive value, 0.99–1.00). Therefore, we expect the corresponding misclassification to be small. Third, because our study population comprised mostly men, we cannot generalize our findings to women. Fourth, our ART analyses do not include ART duration, nor did we examine specific ART medications. Fifth, our analysis focused on HF events occurring in the VA because EF data outside of the VA were not available. However, when we analyzed non-VA HF event data and linked those events to EF data within the VA after the non-VA HF event date, the associations between HIV infection and types of HF remained essentially unchanged.

Conclusions

In summary, HIV-infected individuals have an increased risk of HFrEF, HFpEF, and borderline HFpEF. For people who are infected with HIV, CD4 cell count less than 200 cells/mm³ compared with at least 500 cells/mm³ is a risk factor for HFpEF, borderline HFpEF, and HFrEF, whereas HIV-1 RNA viral load of at least 500 copies/mL compared with less than 500 copies/mL is a risk factor for HFrEF. Most important, the risk of HFrEF in HIV-infected individuals can manifest decades earlier than would be expected among uninfected individuals. To prevent HF, a strategy focusing on guideline-recommended HIV treatment, prevention, and management of HF risk factors will be required, with screening for HIV infection where appropriate for individuals with new-onset HF, in addition to the development of HF risk stratification tools. Finally, there is a need for basic and translational science research focusing on elucidating the underlying mechanisms causing the excess risk of HFrEF and HFpEF in HIV-infected populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points

Question

Does HIV infection increase the risk of heart failure with reduced ejection fraction, heart failure with preserved ejection fraction, or both, and do these risks vary by age, race/ethnicity, HIV-specific biomarkers, and receipt of antiretroviral therapy?

Findings

In this cohort study of 98 015 veterans, individuals with HIV infection had a 61% increased risk of heart failure with reduced ejection fraction (ejection fraction <40%), a 21% increased risk of heart failure with preserved ejection fraction (ejection fraction 50%), and a 37% increased risk of borderline heart failure with preserved ejection fraction (ejection fraction 40%–49%) compared with uninfected veterans. These risks are significant, even after adjusting for possible confounders, and the association between HIV infection and types of heart failure varies by age, race/ethnicity, HIV-specific biomarkers, and receipt of antiretroviral therapy.

Meaning

A strategy that encompasses HIV infection treatment, heart failure risk factor prevention and management, and the development of heart failure risk stratification tools would be beneficial for this high-risk population.

Table 1Baseline Characteristics of Participants in the Veterans Aging Cohort Study^a

Variable	Uninfected (n = 66 492)	HIV Infected (n = 31523)	P Value
Age, y			
Mean (SD)	48.4 (9.7)	47.9 (9.9)	<.001
Median	49	48	NA
Male, %	96.9	97.1	.02
Race/ethnicity, %			
Black	48.2	48.4	<.001
White	38.2	38.9	
Hispanic	8.0	7.2	
Other	5.6	5.6	
Hypertension, %			
None	34.7	47.9	<.001
Controlled	31.5	27.3	
Uncontrolled	29.4	23.6	
Missing	4.4	1.3	
Diabetes, %	14.0	9.6	<.001
LDL cholesterol level, mg/dL, %			
<100	24.4	37.3	<.001
100–129	25.7	23.8	
130–159	17.3	13.0	
160	9.1	6.0	
Missing	23.5	19.8	
HDL cholesterol level, mg/dL, %			
60	11.5	9.1	<.001
40–59	36.9	30.8	
<40	29.0	41.4	
Missing	22.6	18.6	
Triglyceride level, mg/dL, %			
<150	48.5	45.2	<.001
150	29.0	37.7	
Missing	22.5	17.2	
Smoking status, %			
Current	34.4	37.9	<.001
Past	11.5	10.3	
Never	22.1	19.4	
Missing	32.0	32.3	
Other risk factors, %			

Variable	Uninfected (n = 66 492)	HIV Infected (n = 31523)	P Value
Current HMG-CoA reductase inhibitor use	22.9	13.6	<.001
Hepatitis C virus infection	12.6	29.1	<.001
Estimated glomerular filtration rate, mL·min ⁻¹ ·1.73·m ⁻² , %			
60	84.8	89.5	<.001
30–59	3.3	4.3	
<30	0.4	0.9	
Missing	11.6	5.3	
BMI, %			
<30	57.0	82.7	<.001
30	36.2	15.0	
Missing	6.1	2.3	
Hemoglobin level, g/dL, %			
14	64.4	53.6	<.001
12–13.9	20.1	30.6	
10–11.9	2.9	9.0	
<10	0.4	2.4	
Missing	12.6	4.5	
History of substance use, %			
Alcohol abuse or dependence	26.7	25.0	<.001
Cocaine abuse or dependence	15.3	18.8	<.001
Atrial fibrillation, %	0.63	0.55	.12
Major depression, %	15.0	15.8	<.001
CD4 cells/mm ³			
Mean (SD)	NA	425.2 (297.3)	NA
Median	NA	382	NA
Missing, %	NA	17.1	NA
HIV-1 RNA viral load copies/mL			
Mean (SD)	NA	73 571.7 (958 843.6)	NA
Median	NA	1357	NA
Missing, %	NA	15.0	NA
Antiretroviral therapy regimen, %			
NRTI plus PI	NA	23.7	NA
NRTI plus NNRTI	NA	47.3	NA
Other	NA	2.9	NA
No antiretroviral therapy	NA	26.1	NA
Antiretroviral therapy class, %			
PI	NA	58.4	NA
NRTI	NA	73.6	NA
NNRTI	NA	47.4	NA

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HDL, high-density lipoprotein; HIV, human immunodeficiency virus; HMG-CoA, hydroxymethylglutaryl coenzyme A; LDL, low-density lipoprotein; NA, not applicable; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

SI conversion factors: To convert cholesterol level to millimoles per liter, multiply by 0.0259; hemoglobin level to grams per liter, multiply by 10.0; and triglycerides level to millimoles per liter, multiply by 0.0113.

^aSome categories do not sum to 100% because of rounding to the nearest 10th percent.

Table 2

Human Immunodeficiency Virus (HIV) Infection and the Incidence of Total Heart Failure (HF), HFpEF, HFrrEF, and HF With Missing Ejection Fraction (EF) by Age Group and HIV Infection Status

Variable	Age Group, y				
	<40	40–49	50–59	60–69	70
Total HF					
HIV–					
No. of participants	10 896	25 180	23 227	5957	1232
No. of HF events	55	506	830	209	95
HF rate per 1000 PY (95% CI)	0.88 (0.68–1.15)	3.01 (2.76–3.28)	5.58 (5.22–5.98)	6.77 (5.91–7.75)	14.0 (11.41–17.07)
HIV+					
No. of participants	5888	11707	10 487	2845	596
No. of HF events	62	296	422	116	45
HF rate per 1000 PY (95% CI)	1.78 (1.39–2.29)	4.04 (3.61–4.53)	7.10 (6.45–7.81)	8.93 (7.44–10.71)	16.02 (11.96–21.46)
Incidence rate ratio (95% CI)	2.02 (1.38–2.95)	1.35 (1.16–1.56)	1.27 (1.13–1.43)	1.32 (1.04–1.66)	1.15 (0.79–1.65)
HFpEF 50%					
HIV–					
No. of participants	10 896	25 180	23 227	5957	1232
No. of HF events, EF 50%	18	172	328	75	36
HF rate per 1000 PY (95% CI)	0.29 (0.18–0.46)	1.02 (0.88–1.19)	2.21 (1.98–2.46)	2.43 (1.94–3.05)	5.29 (3.82–7.33)
HIV+					
No. of participants	5888	11707	10 487	2845	596
No. of HF events, EF 50%	12	81	133	35	23
HF rate per 1000 PY (95% CI)	0.35 (0.20–0.61)	1.11 (0.89–1.38)	2.24 (1.89–2.65)	2.69 (1.93–3.75)	8.19 (5.44–12.32)
Incidence rate ratio (95% CI)	1.19 (0.52–2.62)	1.08 (0.82–1.42)	1.01 (0.82–1.24)	1.11 (0.72–1.68)	1.55 (0.88–2.69)
Borderline HFpEF 40%–49%					
HIV–					
No. of participants	10 896	25 180	23 227	5957	1232
No. of HF events, EF 40%–49%	7	78	135	29	18

Variable	Age Group, y				
	<40	40–49	50–59	60–69	70
HF rate per 1000 PY (95% CI)	0.11 (0.05–0.24)	0.46 (0.37–0.58)	0.91 (0.77–1.07)	0.94 (0.65–1.35)	2.64 (1.67–4.20)
HIV⁺					
No. of participants	5888	11707	10487	2845	596
No. of HF events, EF 40%–49%	7	45	66	18	6
HF rate per 1000 PY (95% CI)	0.20 (0.10–0.42)	0.61 (0.46–0.82)	1.11 (0.87–1.41)	1.39 (0.87–2.20)	2.14 (0.96–4.76)
Incidence rate ratio (95% CI)	1.79 (0.54–5.98)	1.33 (0.90–1.94)	1.22 (0.90–1.65)	1.47 (0.77–2.75)	0.81 (0.26–2.12)
HF+EF<40%					
HIV⁻					
No. of participants	10896	25180	23227	5957	1232
No. of HF events, EF<40%	21	200	278	75	23
HF rate per 1000 PY (95% CI)	0.34 (0.22–0.52)	1.19 (1.03–1.36)	1.87 (1.66–2.10)	2.43 (1.94–3.05)	3.38 (2.25–5.08)
HIV⁺					
No. of participants	5888	11707	10487	2845	596
No. of HF events, EF<40%	34	128	168	42	8
HF rate per 1000 PY (95% CI)	0.98 (0.70–1.37)	1.75 (1.47–2.08)	2.83 (2.43–3.29)	3.23 (2.39–4.37)	2.85 (1.42–5.70)
Incidence rate ratio (95% CI)	2.90 (1.63–5.25)	1.47 (1.17–1.85)	1.51 (1.24 to 1.84)	1.33 (0.89–1.97)	0.84 (0.33–1.95)
EF Missing					
HIV⁻					
No. of participants	10896	25180	23227	5957	1232
No. of HF events, EF missing	9	56	89	30	18
HF rate per 1000 PY (95% CI)	0.14 (0.08–0.28)	0.33 (0.26–0.43)	0.60 (0.49–0.74)	0.97 (0.68–1.39)	2.64 (1.67–4.20)
HIV⁺					
No. of participants	5888	11707	10487	2845	596
No. of HF events, EF missing	9	42	55	21	8
HF rate per 1000 PY (95% CI)	0.26 (0.13–0.50)	0.57 (0.42–0.78)	0.93 (0.71–1.21)	1.62 (1.05–2.48)	2.85 (1.42–5.70)
Incidence rate ratio (95% CI)	1.79 (0.63–5.09)	1.72 (1.13–2.62)	1.55 (1.08–2.19)	1.66 (0.91–3.00)	1.08 (0.41–2.60)

Abbreviations: HFpEF, heart failure with preserved ejection fraction; HF+EF, heart failure with reduced ejection fraction; HIV⁺, HIV positive; HIV⁻, HIV negative; PY, person-years.

Human Immunodeficiency Virus (HIV) Infection and the Risk of Total Heart Failure (HF) and HF Type by Subgroup

Table 3

Variable	Total HF		HFpEF 50%		Borderline HFpEF 40%–49%		HFrEF		EF Missing	
	No.	No. of Events	HR (95% CI) ^a	No. of Events	HR (95% CI) ^a	No. of Events	HR (95% CI) ^a	No. of Events	HR (95% CI) ^a	No. of Events
Total ^a										
HIV [−]	66 492	1695	1 [Reference]	629	1 [Reference]	267	1 [Reference]	597	1 [Reference]	202
HIV ⁺	31 523	941	1.41 (1.29–1.54)	284	1.21 (1.03–1.41)	142	1.37 (1.09–1.72)	380	1.61 (1.40–1.86)	135
White race/ethnicity ^b										
HIV [−]	25 382	583	1 [Reference]	227	1 [Reference]	93	1 [Reference]	173	1 [Reference]	90
HIV ⁺	12 254	303	1.31 (1.12–1.52)	94	1.13 (0.86–1.47)	52	1.44 (0.99–2.11)	104	1.54 (1.18–2.02)	53
Black race/ethnicity ^c										
HIV [−]	32 067	982	1 [Reference]	368	1 [Reference]	148	1 [Reference]	377	1 [Reference]	89
HIV ⁺	15 246	549	1.41 (1.26–1.59)	161	1.16 (0.94–1.42)	77	1.31 (0.96–1.79)	243	1.61 (1.35–1.93)	68
Age <40 y ^d										
HIV [−]	10 896	55	1 [Reference]	18	1 [Reference]	7	1 [Reference]	21	1 [Reference]	9
HIV ⁺	5888	62	2.41 (1.60–3.63)	12	1.16 (0.48–2.83)	7	2.12 (0.64–7.04)	34	3.59 (1.95–6.58)	9

Abbreviations: EF, ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HIV⁺, HIV positive; HIV[−], HIV negative; HR, hazard ratio.

^aModel is adjusted for age, race/ethnicity, sex, hypertension, lipid levels, low-density lipoprotein and high-density lipoprotein cholesterol levels, triglyceride levels, smoking status, hydroxymethylglutaryl coenzyme A reductase inhibitor use, hepatitis C virus infection, renal disease, body mass index, substance use, atrial fibrillation, and major depression.

^bModel is adjusted for age, sex, hypertension, lipid levels, low-density lipoprotein and high-density lipoprotein cholesterol levels, triglyceride levels, smoking status, hydroxymethylglutaryl coenzyme A reductase inhibitor use, hepatitis C virus infection, renal disease, body mass index, substance use, atrial fibrillation, and major depression among participants of white race/ethnicity.

^cModel is adjusted for age, sex, hypertension, lipid levels, low-density lipoprotein and high-density lipoprotein cholesterol levels, triglyceride levels, smoking status, hydroxymethylglutaryl coenzyme A reductase inhibitor use, hepatitis C virus infection, renal disease, body mass index, substance use, atrial fibrillation, and major depression among participants of black race/ethnicity.

^dModel is adjusted for age, race/ethnicity, sex, hypertension, lipid levels, low-density lipoprotein and high-density lipoprotein cholesterol levels, triglyceride levels, smoking status, hydroxymethylglutaryl coenzyme A reductase inhibitor use, hepatitis C virus infection, renal disease, body mass index, substance use, atrial fibrillation, and major depression among participants younger than 40 years at baseline.

Table 4

Human Immunodeficiency Virus (HIV) Infection and the Risk of Total Heart Failure (HF) and HF Type by HIV-1 RNA Viral Load and CD4 Cell Count

Variable	HR (95% CI) ^a				
	Total HF	HFpEF 50%	Borderline HFpEF 40%–49%	HFrEF	EF Missing
HIV-1 RNA viral load model ^a					
HIV ⁻	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
HIV ⁺ and RNA <500	1.30 (1.16–1.46)	1.20 (0.98–1.46)	1.32 (0.98–1.79)	1.41 (1.17–1.70)	1.27 (0.91–1.78)
HIV ⁺ and RNA 500	1.52 (1.36–1.70)	1.22 (0.99–1.50)	1.42 (1.06–1.91)	1.82 (1.54–2.16)	1.60 (1.17–2.19)
CD4 cell count model ^a					
HIV ⁻	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
HIV ⁺ and CD4 500	1.25 (1.08–1.43)	1.03 (0.82–1.31)	1.32 (0.93–1.86)	1.53 (1.24–1.88)	0.98 (0.64–1.49)
HIV ⁺ and CD4 200–499	1.41 (1.25–1.59)	1.29 (1.05–1.59)	1.28 (0.92–1.80)	1.51 (1.24–1.83)	1.61 (1.18–2.20)
HIV ⁺ and CD4 < 200	1.72 (1.49–1.99)	1.38 (1.05–1.81)	1.66 (1.10–2.49)	2.03 (1.61–2.55)	1.88 (1.28–2.77)
P values					
RNA <500 vs 500	.04	.88	.70	.02	.29
CD4 200–499 vs 500	.15	.13	.91	.92	.045
CD4 < 200 vs 500	.001	.08	.38	.048	.01
CD4 200–499 vs <200	.02	.67	.31	.03	.47

Abbreviations: CD4, CD4 cell count (in cells per cubic millimeter); EF, ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HIV⁺, HIV positive; HIV⁻, HIV negative; HR, hazard ratio; RNA, HIV-1 RNA viral load (in copies per milliliter).

^aModels are adjusted for age, race/ethnicity, hypertension, lipid levels, low-density lipoprotein and high-density lipoprotein cholesterol levels, triglyceride levels, smoking status, hydroxymethylglutaryl coenzyme A reductase inhibitor use, hepatitis C virus infection, renal disease, body mass index, substance use, atrial fibrillation, and major depression.

Table 5

Time-Updated HIV-1 RNA Viral Load, CD4 Cell Count, and the Risk of Heart Failure (HF) Type Among Human Immunodeficiency Virus (HIV)–Infected Veterans^a

Variable	Total HF	HFpEF	50%	Borderline HFpEF	40%–49%	HFrEF	EF Missing
CD4 cells/mm ³							
500	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
200–499	1.26 (1.07–1.49)	1.28 (0.97–1.72)	0.67 (0.17–2.63)	1.23 (0.95–1.60)	1.98 (1.22–3.20)		
<200	2.09 (1.71–2.55)	1.87 (1.28–2.73)	2.10 (1.30–3.39)	1.87 (1.36–2.57)	3.37 (1.95–5.84)		
HIV-1 RNA viral load copies/mL							
<500	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
500	1.31 (1.12–1.53)	1.07 (0.80–1.43)	1.26 (0.84–1.89)	1.63 (1.28–2.08)	1.18 (0.79–1.75)		

Abbreviations: EF, ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

^aModels are simultaneously adjusted for HIV-1 RNA viral load, CD4 cell count, age, race/ethnicity, hypertension, lipid levels, low-density lipoprotein and high-density lipoprotein cholesterol levels, triglyceride levels, smoking status, hydroxymethylglutaryl coenzyme A reductase inhibitor use, hepatitis C virus infection, renal disease, body mass index, substance use, atrial fibrillation, major depression, and baseline antiretroviral therapy regimen.