UCLA
UCLA Previously Published Works

Title

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.

Permalink

https://escholarship.org/uc/item/6h34q4nq

Journal

JAMA cardiology, 2(5)

ISSN

2380-6583

Authors

Freiberg, Matthew S
Chang, Chung-Chou H
Skanderson, Melissa
et al.

Publication Date

2017-05-01

DOI

10.1001/jamacardio.2017.0264

Peer reviewed

eScholarship.org Powered by the California Digital Library
University of California

HIV infection and the risk of HFrEF and HFpEF in the Antiretroviral Therapy Era: Results from the Veterans Aging Cohort Study

Matthew S. Freiberg, MD, MSc, Cardiovascular Medicine Division, Vanderbilt University School of Medicine and Veterans Affairs Tennessee Valley Healthcare System, Nashville, Tennessee

Chung-Chou H. Chang, PhD, Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

Melissa Skanderson, MSW, Veterans Affairs (VA) Connecticut Health Care System, West Haven Veterans Administration Medical Center, West Haven, Connecticut

Olga V. Patterson, PhD, Veterans Affairs (VA) Salt Lake City Health Care System and University of Utah School of Medicine, Salt Lake City, Utah

Scott L. Duvall, PhD, Veterans Affairs (VA) Salt Lake City Health Care System and University of Utah School of Medicine, Salt Lake City, Utah

Cynthia A. Brandt, MD, MPH, VA Connecticut Healthcare System and Department of Emergency Medicine, Yale University School of Medicine, New Haven, Connecticut

Kaku A. So-Armah, PhD, Division of General Internal Medicine, Boston University, Boston, Massachusetts

Ramachandran S. Vasan, MD, National Heart, Lung, & Blood Institute's Framingham Heart Study, Framingham, Massachusetts, and Preventive Medicine and Cardiology, Department of Medicine, Boston University School of Medicine, Boston, Massachusetts

Kris Ann Oursler, MD, ScM, University of Maryland School of Medicine and the Baltimore VA Health Care System, Baltimore, Maryland

John Gottdiener, MD, University of Maryland School of Medicine, Baltimore, Maryland

Stephen Gottlieb, MD, University of Maryland School of Medicine and the Baltimore VAMC, Baltimore, Maryland

David Leaf, MD, MPH, David Geffen School of Medicine, UCLA (University of California, Los Angeles), Los Angeles, California

Maria Rodriguez-Barradas, MD, Baylor College of Medicine and Michael E. DeBakey VA Medical Center, Houston, Texas

Russell P. Tracy, PhD, University of Vermont College of Medicine, Burlington, Vermont

Cynthia L. Gibert, MD, MS, George Washington University School of Medicine and the Washington, DC, VA Medical Center Washington, DC

David Rimland, MD, Emory University School of Medicine and Atlanta VA Medical Center, Atlanta, Georgia

Roger J. Bedimo, MD, MS, Department of Medicine, VA North Texas Health Care System, Dallas, Texas

Sheldon T. Brown, MD, James J. Peters Veterans Affairs Medical Center, Department of Medicine, Bronx and Department of Medicine, Icahn School of Medicine at Mt. Sinai, New York, New York

Matthew Bidwell Goetz, MD, David Geffen School of Medicine, UCLA (University of California, Los Angeles) and the VA Greater Los Angeles Health Care System, Los Angeles, California

Alberta Warner, MD, David Geffen School of Medicine, UCLA (University of California, Los Angeles) and the VA Greater Los Angeles Health Care System, Los Angeles, California

Kristina Crothers, MD, University of Washington School of Medicine, Seattle, Washington

Hilary A. Tindle, Department of Medicine, Vanderbilt University School of Medicine and Nashville Veterans Affairs Medical Center, Nashville, Tennessee

Charles Alcorn, MA, Graduate School of Public Health, Department of Biostatistics, University of Pittsburgh, Pennsylvania

Justin M. Bachmann, MD, MPH, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee

Amy C. Justice, MD, PhD, Veterans Affairs (VA) Connecticut Health Care System, West Haven Veterans Administration Medical Center, West Haven, Connecticut

Adeel A. Butt, MD, MS, VA Pittsburgh Healthcare System, Pittsburgh, Pennsylvania; Weill Cornell Medical College, Doha, Qatar and New York, New York; Hamad Medical Corporation, Doha, Qatar

Word Count: 3000

Corresponding Author

Matthew S Freiberg MD, MSC

Associate Professor of Medicine

Division of Cardiovascular Medicine

Vanderbilt University Medical Center

2525 West End Avenue

Suite 300-A

Nashville, TN 37203

615 875 9729

Matthew.s.freiberg@vanderbilt.edu

Key Points

Question: Does HIV infection increase the risk of reduced ejection fraction heart failure, preserved ejection fraction heart failure or both in the antiretroviral therapy era and do these risks vary by age, race, HIV specific biomarkers and antiretroviral therapy?

Findings: In this observational cohort study that included 98,015 veterans, HIV infected veterans have a 61% increased risk of reduced ejection fraction heart failure (EF<40%); a 21% increased risk of preserved ejection fraction heart failure (EF>=50%); and a 37% increased risk of borderline preserved ejection fraction heart failure (EF 40-49%) as compared to 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, HIV specific biomarkers and receipt of antiretroviral therapy.

Meaning: There needs to be a strategy that encompasses HIV treatment, heart failure risk factor prevention and management, and the development of heart failure risk stratification tools for this high risk population.

Importance: With improved survival, heart failure (HF) has become a major complication for HIV infected (HIV+) people it is unclear if this risk extends to different types of HF in the ART era. Determining whether HIV infection is associated with reduced ejection fraction HF (HFrEF), preserved ejection fraction HF (HFpEF) or both is critical because HF types differ with respect to underlying mechanism, treatment, and prognosis.

Objectives: To determine whether HIV infection increases the risk of future HFrEF and HFpEF and if this risk varies by sociodemographic and HIV-specific factors.

Design, Setting, and Participants: We evaluated 98,105 participants without baseline cardiovascular disease from the Veterans Aging Cohort Study, an observational cohort of HIV+ and age, sex, race/ethnicity, and clinical site matched uninfected veterans, enrolled after 4/1/2003 and followed through 9/30/2012.

Exposures: HIV infection

Main Outcomes and Measures: HFrEF (EF<40), HFpEF (EF ≥50), borderline HFPEF (EF=40-49), unknown type HF (EF missing)

Results: During a median follow-up of 7.1 years, there were 2,636 HF events (37.1% were HFrEF, 34.6% were HFpEF, 15.5% were borderline HFPEF, and 12.8% were unknown type). As compared to uninfected veterans, HIV+ veterans had an increased risk of HFrEF (hazard ratio [HR]=1.61, 95% CI=1.40-1.86), HFpEF (HR=1.21, 95% CI=1.03-1.41) and borderline HFpEF (HR=1.37, 95%CI=1.09-1.72). This risk of HFrEF was pronounced in the young (age<40 years at baseline, HR=3.59, 95% CI=1.95-6.58). Among HIV+ veterans, baseline ART regimens compared to no ART were associated with an increased risk of HFpEF, time-updated HIV viral load>500 copies/ml as compared to <500 copies/ml was associated with an increased risk HFREF, and time-updated CD4 cell counts<200 cells/mm^3 as compared to CD4 cell counts>500 cells/mm^3 was associated with increased risk of HFpEF and HrREF ($p<0.05$ for all).

Conclusions: HIV+ people have an increased risk of HFrEF, HFpEF, and borderline HFpEF compared to uninfected people. These risks vary by HIV-specific biomarkers and ART. The increased risk of HFrEF can present decades earlier than would be expected in a typical uninfected population. Future research should focus on prevention, risk stratification, and identifying the mechanisms for HFREF and HFPEF in the HIV+ population.

Over 36 million people are HIV infected(HIV+) worldwide.[1] Nearly 17 million are on antiretroviral therapy (ART).[1] With the improved life expectancy due to ART,[2] cardiovascular diseases (CVD) is now a major health complications facing HIV+ people.[3] Acute myocardial infarction (AMI) has been studied and the increased risk of AMI among HIV+ people compared to uninfected people well documented. [4-7] Similarly, an excess risk of HF is also present for HIV+ compared to uninfected people, however, it is not known what types of HF are associated with this risk and whether the risk of different types of HF vary by age, race, HIV-specific biomarkers and ART.[8,9]

Recent studies show HIV infection increases the risk of HF independent of AMI[9,10] and that the increased risk is higher among older people, blacks, those with obesity, hypertension, diabetes, current smoking, alcohol abuse and dependence, elevated HIV viral loads, and those with an history of AMI.[8,9] The presence of these risk factors in combination with the success of ART and improvements in cardiovascular care have translated into increased survival for those with HIV and those with AMI, respectively.[2,11] Consequently many HIV+ people will survive with a damaged heart and their healthcare providers will have the challenge of preventing and managing HF in this high risk population.

To reduce the risk of HF in the HIV population, there is a need to understand the epidemiology surrounding HIV and the risk of HF in the ART era. Among uninfected people, differentiating between reduced ejection fraction HF (HFrEF) and preserved ejection fraction HF (HFpEF) is critical because these types of HF differ with respect to underlying mechanism, treatment, and prognosis.[12] In the HIV 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 both HFrEF and HFpEF.[13-20] There are no large studies that show HIV+ people have a significantly increased risk of HrREF and HFpEF events compared to demographically and behaviorally similar uninfected people in the ART era. Similarly, data describing the association between HIV infection and

type of HF across age groups, by race, and by HIV-specific biomarkers and ART regimens are also lacking. Yet HIV infection is common among younger adults,[21] minority populations,[22] and is increasingly common among older adults.[21] As such, health care providers do not have the information needed to advise and risk stratify HIV+ patients who may be at risk for HF.

We therefore investigated whether HIV infection is associated with an increased risk of HFpEF and HFrEF in a national cohort of HIV+ and uninfected veterans in care. We evaluated whether this risk varied by age groups, race, HIV biomarkers, and ART regimens.

Methods

The Veterans Aging Cohort Study (VACS) is an observational, longitudinal cohort of HIV+ and age, sex, race/ethnicity, and clinical site matched uninfected veterans enrolled in the same calendar year that has been described previously. [23] Subjects have been continuously enrolled each year since 1998 using a validated existing algorithm from United States Department of Veterans Affairs (VA) national electronic medical record system.[23] Data for this cohort are extracted from VA central data warehouse. The Vanderbilt University and the West Haven VAMC institutional review boards approved this study.

Study population

For this analysis, we included all VACS participants who were alive and enrolled in VACS on or after 4/1/2003. Baseline date was a participant's first clinical encounter on or after 4/1/2003. All participants were followed from their baseline date to either a HF event, death, or the last follow-up date (9/30/2012). We excluded participants with prevalent CVD based upon 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% were HIV+.

Independent Variable

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

Dependent Variables

We used the presence of 1 or more inpatient (discharge diagnosis) and/or 2 or more 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, 428.9). This definition was based on prior validation work within and outside the VA.[24] Ejection fraction (EF) measurements were used only to classify HF into HFpEF, HFrEF, borderline HFpEF 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 mentions 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.[26] When the application used for this study was tested across multiple data sources, the application achieved on average positive predictive value of 0.968-1.0 and sensitivity of 0.801-0.899 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. HFpEF was HF with documentation of an EF≥50%, or when no numeric value was recorded the left ventricular (LV) function was described as normal; borderline HFpEF was an EF between 40-49%, HFrEF was HF with an EF<40% or

when no numeric 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, lipids, renal disease, body mass index (BMI, and anemia using clinical outpatient and laboratory data collected closest to the baseline date. HMG-CoA 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 (JNC) VIII criteria.[28] Our blood pressure measurement was the average of the three routine outpatient clinical measurements closest to the baseline date. Diabetes was diagnosed using a validated metric that considers glucose measurements, antidiabetic agent use, and ≥ 1 inpatient and/or ≥2 outpatient ICD-9 codes for this diagnosis.[29] Current HMG-CoA reductase inhibitor use was defined a prescription filled within 180 days of the baseline date. Smoking status was categorized into current, past, and never while BMI was dichotomized as BMI ≥ or< 30 kg/m^2. Hepatitis C (HCV) infection was defined as a positive HCV antibody test or ≥ 1 inpatient and/or ≥2 outpatient ICD-9 codes for this diagnosis.[29,30] History of cocaine and alcohol abuse or dependence, and atrial fibrillation were defined using ICD-9 codes. [31] We collected data (i.e., CD4+ lymphocyte counts (CD4+ cell counts) and HIV-1 RNA) at baseline (i.e., within 180 days of our enrollment date) through 9/30/12. Baseline ART was categorized by regimen of ART within 180 days of baseline: protease inhibitors (PI) plus nucleoside reverse transcriptase inhibitors (NRTI); non-nucleoside reverse transcriptase inhibitors (NNRTI) plus NRTI, other (i.e., use of PI, NRTI, or NNRTI medications but not in combination as described in other two categories), and no ART use (referent group). All ART medications that were on VA formulary during the study period were included. We have

previously demonstrated in a nested sample that 98% of HIV+ veterans obtain their ART medications from the VA.[23]

Analysis

Descriptive statistics for all variables by HIV status were assessed using t-tests or its nonparametric counterpart for continuous variables, and chi-square test or Fisher's exact test for categorical variables. We calculated incident total HF, HFpEF, borderline HFpEF, HFrEF, and unknown type of HF rates per 1,000 person-years and incidence rate ratios stratified by age group and HIV status. We constructed Cox proportional hazards models to estimate the hazard ratio (HR) and 95% confidence intervals (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 the VA (i.e., HF diagnosed using Medicare and VA fee for service HF ICD-9 codes). For these analyses, we linked those non-VA 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 status using the log-log 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 status and types of HF in important subgroups (e.g., those<40 years of age). Among HIV+ veterans, we examined the association between time-updated HIV-1 RNA, CD4+ cell count and HF type while also adjusting for potential confounders including baseline ART. Missing covariate data were included in the analyses using multiple imputation techniques that generated five data sets with complete covariate values to increase the robustness of the Cox models.

Results

In this analysis, there were 98,105 veterans (32% HIV+) who were free of baseline CVD. CVD risk factors and substance use measures varied by HIV 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+ veterans had a higher prevalence of non-traditional CVD risk factors (e.g., hepatitis C infection, **Table 1**). For HIV+ veterans, the median baseline HIV viral load was 1,300 copies/mL, baseline CD4+ cell count was 381 cells/mm^3, the majority were on ART (~74%) consisting of PIs (~58% of those on ART) and NRTIs (74%; **Table 1**).

During a median follow-up of 7.1 years, there were 2,636 total HF events. Of these events, 36% occurred in HIV+ veterans; 37.1% were HFrEF, 34.6% were HFpEF, 15.5% were borderline HFpEF, and 12.8% were unknown type. Compared to uninfected veterans, HIV+ veterans had higher rates of total HF, HFrEF, but not HFpEF and borderline HFpEF (**Table 2**). Similar results were observed when rates were stratified by HIV status and age group categories except among those ≥70 years of age (**Table 2**).

Compared to uninfected veterans, HIV+ veterans had a significantly increased risk of total HF, HFrEF, HFpEF, and borderline HFpEF after adjusting for possible confounders(**Table 3**). In sensitivity analyses involving non Veteran Affairs HF events and Veteran Affairs EF data, the association between HIV and total HF, HFrEF, HFpEF, and borderline HFpEF remained essentially unchanged **(Supplementary Table 1**). Similarly the association between HIV and HF remained when we restricted the sample to those without hypertension (HR=1.32, 95% CI=1.08-1.61); those without alcohol or cocaine abuse or dependence (HR=1.43, 9%% CI=1.25-1.65), and never smokers (HR=1.33, 95% CI=1.05-1.70). This 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 (under age 40 years at baseline), whites, and blacks, HIV infection was significantly associated with an increase in total HF, HFrEF but not HFpEF or borderline HFpEF (**Table 3**). When we compared uninfected veterans to HIV+ veterans stratified by HIV specific biomarkers, the risk of HFrEF persisted even among HIV+ veterans with a baseline HIV viral load<500 copies/ml as compared to uninfected veterans (HR=1.41, 95% CI=1.17-1.70, **Table 4**).

When we restricted the sample to only HIV+ veterans, and adjusted for covariates including baseline HIV 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) as compared to no ART were associated with an increased risk of HFpEF but not HFrEF. In time-updated analyses, CD4+ cell count<200 cells/mm^3 was associated with an increased risk of total HF, HFrEF, HFpEF, and borderline HFpEF (Table 5) whereas time-updated HIV viral load >500 copies/ml was only associated with HFrEF (**Table 5**).

Discussion:

In the VACS, HIV+ veterans have an increased risk of HFrEF, HFpEF and borderline HFpEF. The association between HIV and HFrEF remained significant even when the sample size was reduced for subgroup analyses involving whites, blacks, and the young, and after adjustment for AMI in the follow up period. Among HIV+ veterans, time-updated HIV viral load ≥500 copies/ml as compared to <500 copies/ml was associated with an increased risk HFrEF, whereas time-updated CD4 cell counts<200 cells/mm^3 as compared to CD4 cell counts>500 cells/mm^3 was associated with increased risk of HF, HFrEF, HFpEF, and borderline HFpEF

This is the first large study to report that HIV+ people have a significantly increased risk of HFrEF, HFpEF, and borderline HFpEF events compared to demographically and behaviorally similar uninfected people in

the ART era. These findings are consistent with and extend earlier echocardiographic reports linking HIV infection to both reduced LV systolic function and diastolic dysfunction,[13-20] as well our earlier work reporting an association between HIV infection and total HF.[8] More specifically, we show that the risk of HFrEF extends beyond AMI, is present across multiple decade age groups, occurs among blacks, whites, those without decades long exposure to HF risk factors, and those with high HIV viral load and low CD4 counts over time. In fact, HFrEF among HIV+ people in the ART era can present at a young age, decades earlier than might be expected among uninfected people.[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 play important roles. HIV+ people with low CD4 cell counts have increased levels of immune activation and inflammation,[34] which are themselves associated with increased HF risk.[35] In murine models T regulatory cell depletion leads to increased myocardial fibrosis—a factor consistent with both HFrEF and HFpEF phenotypes.[36] Importantly, our data also suggest that even HIV+ people with high CD4 cell counts are likely still at risk for HF as compared to uninfected people in part because HIV+ people 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 viral load was only significantly associated with HFrEF. These findings are consistent with pre-ART era reports where 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 that ART plays in the development of HF is less clear. Cardiac mitochondrial toxicity in the HAART era is well documented.[42] In this 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 viral load and higher CD4 cell count reduces the risk of HFpEF and HFrEF. As prior studies have shown, ART can simultaneously lower AMI risk through viral suppression[43] and increase AMI risk likely through medication side effects.[44] Thus, determining if newer ART medications play a role in the development of HF should be explored as many HIV+ people will be on ART medications for decades.

Our findings have important implications for HIV+ people and their health care providers. In the United States, 25% of all new cases of HIV are among those aged 13 to 24 years, 25% of HIV+ people are older than 55 years,[21] and 44% of new HIV infections occur in African Americans,[22] who are at high risk for HF.[45] Globally, HF is common in low and middle income countries where the burden of HIV is high and availability of ART can be limited.[46] Given these facts, providers should focus on guideline recommended HIV treatment, HF risk factor prevention including diabetes, hypertension, renal disease, smoking, alcohol abuse and dependence, and obesity; (2) and screening for HIV with new onset heart failure where appropriate.[25] Developing tools designed to risk stratify HIV+ people for HF will also be required.

Our investigation has limitations that warrant discussion. First as HF was determined using ICD-9 codes, it is possible some misclassification occurred (i.e., some true HF events were not captured by ICD-9 codes). However this finding would have biased our results to the null. Second, as EF data were extracted using a natural language processing application, it is possible that some misclassification 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 (i.e., positive predictive value= 0.99-1.00). Therefore, we expect the corresponding misclassification to be small. Third, as our study population was comprised of 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. Lastly, our

analysis focused on HF events occurring in the VA because EF data outside 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.

In summary, HIV+ people have an increased risk of HFrEF, HFpEF and borderline HFpEF. For HIV+ people, CD4 cell counts<200 cells/ mm^3 compared to CD4 cell counts>500 cells/mm^3 are risk factors for HFrEF, HFpEF and borderine HFpEF whereas HIV viral load ≥500 copies/ml as compared to <500 copies/ml is a risk factor for HFrEF. Importantly, the risk of HFrEF in HIV+ people can present decades earlier than would be expected among uninfected people. To prevent HF, a strategy focusing on guideline recommended HIV treatment, prevention and management of HF risk factors, and screening for HIV infection when appropriate for new onset HF, as well as the development of HF risk stratification tools will be needed. Lastly, there is a need for basic and translational science research focusing on elucidating the underlying mechanism(s) causing this excess risk of HFREF and HFPEF in HIV+ populations.

Funding Sources

This work was supported by grants HL095136, HL125032, from the National Heart, Lung, and Blood Institute and grants AA020790, and AA020794 from the National Institutes of Health on Alcohol Abuse and Alcoholism at the NIH.

Disclaimer

The views expressed in this article are those of the authors and do not necessarily reflect the position or policies of the Department of Veterans Affairs.

References

1. AIDS.gov. Global HIV/AIDS overview. 2016; https://www.aids.gov/federal-resources/around-the-world/global-aids-overview/. Accessed 10/24/2016, 2016.
2. Palella FJ, Jr., Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *The New England journal of medicine.* 1998;338(13):853-860.
3. Greene M, Justice AC, Lampiris HW, Valcour V. Management of human immunodeficiency virus infection in advanced age. *Jama.* 2013;309(13):1397-1405.
4. Freiberg MS, Chang CC, Kuller LH, et al. HIV infection and the risk of acute myocardial infarction. *JAMA Intern Med.* 2013;173(8):614-622.
5. Triant VA, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. *The Journal of clinical endocrinology and metabolism.* 2007;92(7):2506-2512.
6. Currier JS, Taylor A, Boyd F, et al. Coronary heart disease in HIV-infected individuals. *J Acquir Immune Defic Syndr.* 2003;33(4):506-512.
7. Silverberg MJ, Leyden WA, Xu L, et al. Immunodeficiency and risk of myocardial infarction among HIV-positive individuals with access to care. *J Acquir Immune Defic Syndr.* 2014;65(2):160-166.
8. Butt AA, Chang CC, Kuller L, et al. Risk of heart failure with human immunodeficiency virus in the absence of prior diagnosis of coronary heart disease. *Arch Intern Med.* 2011;171(8):737-743.
9. Suttisintong K, White JD. Synthesis of two subunits of the macrolide domain of the immunosuppressive agent sanglifehrin a and assembly of a macrolactone precursor. application of masamune anti-aldol condensation. *J Org Chem.* 2015;80(4):2249-2262.
10. Al-Kindi SG, ElAmm C, Ginwalla M, et al. Heart failure in patients with human immunodeficiency virus infection: Epidemiology and management disparities. *Int J Cardiol.* 2016;218:43-46.
11. Velagaleti RS, Pencina MJ, Murabito JM, et al. Long-term trends in the incidence of heart failure after myocardial infarction. *Circulation.* 2008;118(20):2057-2062.
12. Borlaug BA, Redfield MM. Diastolic and systolic heart failure are distinct phenotypes within the heart failure spectrum. *Circulation.* 2011;123(18):2006-2013; discussion 2014.
13. Fontes-Carvalho R, Mancio J, Marcos A, et al. HIV patients have impaired diastolic function that is not aggravated by anti-retroviral treatment. *Cardiovasc Drugs Ther.* 2015;29(1):31-39.
14. Luo L, Zeng Y, Li T, et al. Prospective echocardiographic assessment of cardiac structure and function in Chinese persons living with HIV. *Clin Infect Dis.* 2014;58(10):1459-1466.
15. Cerrato E, D'Ascenzo F, Biondi-Zoccai G, et al. Cardiac dysfunction in pauci symptomatic human immunodeficiency virus patients: a meta-analysis in the highly active antiretroviral therapy era. *Eur Heart J.* 2013;34(19):1432-1436.
16. Reinsch N, Neuhaus K, Esser S, et al. Prevalence of cardiac diastolic dysfunction in HIV-infected patients: results of the HIV-HEART study. *HIV Clin Trials.* 2010;11(3):156-162.
17. Malebranche R, Tabou Moyo C, Morisset PH, Raphael NA, Wilentz JR. Clinical and echocardiographic characteristics and outcomes in congestive heart failure at the Hospital of The State University of Haiti. *Am Heart J.* 2016;178:151-160.
18. Hsue PY, Hunt PW, Ho JE, et al. Impact of HIV infection on diastolic function and left ventricular mass. *Circ Heart Fail.* 2010;3(1):132-139.
19. Reinsch N, Kahlert P, Esser S, et al. Echocardiographic findings and abnormalities in HIV-infected patients: results from a large, prospective, multicenter HIV-heart study. *Am J Cardiovasc Dis.* 2011;1(2):176-184.

20. Mondy KE, Gottdiener J, Overton ET, et al. High Prevalence of Echocardiographic Abnormalities among HIV-infected Persons in the Era of Highly Active Antiretroviral Therapy. *Clin Infect Dis.* 2011;52(3):378-386.
21. Prevention CfDCa. HIV/AIDS Risk by Age Group. 2016; http://www.cdc.gov/hiv/group/age/index.html. Accessed June 14th, 2016.
22. Prevention CfDCa. HIV/AIDS Risk by Racial/Ethnic Groups. 2016; http://www.cdc.gov/hiv/group/racialethnic/index.html. Accessed June 14th, 2016.
23. Fultz SL, Skanderson M, Mole LA, et al. Development and verification of a "virtual" cohort using the National VA Health Information System. *Med Care.* 2006;44(8 Suppl 2):S25-30.
24. Saczynski JS, Andrade SE, Harrold LR, et al. A systematic review of validated methods for identifying heart failure using administrative data. *Pharmacoepidemiol Drug Saf.* 2012;21 Suppl 1:129-140.
25. Writing Committee M, Yancy CW, Jessup M, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation.* 2013;128(16):e240-327.
26. Garvin JH, Duvall SL, South BR, et al. Automated extraction of ejection fraction for quality measurement using regular expressions in Unstructured Information Management Architecture (UIMA) for heart failure. *Journal of the American Medical Informatics Association : JAMIA.* 2012.
27. McGinnis KA, Brandt CA, Skanderson M, et al. Validating smoking data from the Veteran's Affairs Health Factors dataset, an electronic data source. *Nicotine Tob Res.* 2011;13(12):1233-1239.
28. Lenfant C, Chobanian AV, Jones DW, Roccella EJ. Seventh report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7): resetting the hypertension sails. *Hypertension.* 2003;41(6):1178-1179.
29. Butt AA, McGinnis K, Rodriguez-Barradas MC, et al. HIV infection and the risk of diabetes mellitus. *AIDS.* 2009;23(10):1227-1234.
30. Goulet JL, Fultz SL, McGinnis KA, Justice AC. Relative prevalence of comorbidities and treatment contraindications in HIV-mono-infected and HIV/HCV-co-infected veterans. *Aids.* 2005;19 Suppl 3:S99-105.
31. Kraemer KL, McGinnis KA, Skanderson M, et al. Alcohol problems and health care services use in human immunodeficiency virus (HIV)-infected and HIV-uninfected veterans. *Med Care.* 2006;44(8 Suppl 2):S44-51.
32. Klein J, Moeschberger M. *Survival Analysis: Techniques for Censored and Truncated Data.* Second ed. New York, New York: Springer; 2003.
33. Levy D, Kenchaiah S, Larson MG, et al. Long-term trends in the incidence of and survival with heart failure. *The New England journal of medicine.* 2002;347(18):1397-1402.
34. Deeks SG, Tracy R, Douek DC. Systemic effects of inflammation on health during chronic HIV infection. *Immunity.* 2013;39(4):633-645.
35. Lee DS, Vasan RS. Novel markers for heart failure diagnosis and prognosis. *Curr Opin Cardiol.* 2005;20(3):201-210.
36. Meng X, Yang J, Dong M, et al. Regulatory T cells in cardiovascular diseases. *Nat Rev Cardiol.* 2016;13(3):167-179.
37. Freiberg MS, Bebu I, Tracy R, et al. D-Dimer Levels before HIV Seroconversion Remain Elevated Even after Viral Suppression and Are Associated with an Increased Risk of Non-AIDS Events. *PLoS One.* 2016;11(4):e0152588.
38. Fiala M, Popik W, Qiao JH, et al. HIV-1 induces cardiomyopathyby cardiomyocyte invasion and gp120, Tat, and cytokine apoptotic signaling. *Cardiovasc Toxicol.* 2004;4(2):97-107.

39. Lopes de Campos WR, Chirwa N, London G, et al. HIV-1 subtype C unproductively infects human cardiomyocytes in vitro and induces apoptosis mitigated by an anti-Gp120 aptamer. *PLoS One*. 2014;9(10):e110930.
40. Currie PF, Goldman JH, Caforio AL, et al. Cardiac autoimmunity in HIV related heart muscle disease. *Heart*. 1998;79(6):599-604.
41. Barbaro G. Pathogenesis of HIV-associated heart disease. *AIDS*. 2003;17 Suppl 1:S12-20.
42. Barbaro G. Metabolic and cardiovascular complications of highly active antiretroviral therapy for HIV infection. *Curr HIV Res*. 2006;4(1):79-85.
43. El-Sadr WM, Lundgren JD, Neaton JD, et al. CD4+ count-guided interruption of antiretroviral treatment. *The New England journal of medicine*. 2006;355(22):2283-2296.
44. Lundgren JD. Combination Antiretroviral Therapy and the Risk of Myocardial Infarction: The Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group. *New England Journal of Medicine*. 2003;349(21):1993-2003.
45. Bibbins-Domingo K, Pletcher MJ, Lin F, et al. Racial differences in incident heart failure among young adults. *The New England journal of medicine*. 2009;360(12):1179-1190.
46. Bloomfield GS, Alenezi F, Barasa FA, Lumsden R, Mayosi BM, Velazquez EJ. Human Immunodeficiency Virus and Heart Failure in Low- and Middle-Income Countries. *JACC Heart Fail*. 2015;3(8):579-590.

Table 1. Characteristics of VACS participants*

Variable		All participants		P value
		Uninfected (n=66,492	HIV Infected (n=31,523)	
Age, y				<0.001
	Mean (SD)	48.4 (9.7)	47.9 (9.9)	
	Median	49	48	
Male sex, %		96.9	97.1	0.02
Race/ethnicity, %				<0.001
	African American	48.2	48.4	
	White	38.2	38.9	
	Hispanic	8.0	7.2	
	Other	5.6	5.6	
Hypertension				<0.001
	None	34.7	47.9	
	Controlled	31.5	27.3	
	Uncontrolled	29.4	23.6	
	Missing	4.4	1.3	
Diabetes mellitus		14.0	9.6	<0.001
Lipids, mg/dL				
				<0.001
	LDL cholesterol <100	24.4	37.3	
	LDL cholesterol 100-129	25.7	23.8	
	LDL cholesterol 130-159	17.3	13.0	
	LDL cholesterol >=160	9.1	6.0	
	Missing	23.5	19.8	<0.001
	HDL cholesterol ?60	11.5	9.1	
	HDL cholesterol 40-59	36.9	30.8	
	HDL cholesterol <40	29.0	41.4	
	Missing	22.6	18.6	
	Triglycerides <150	48.5	45.2	
	Triglycerides >=150	29.0	37.7	<0.001
	Missing	22.5	17.2	
Smoking, %				<0.001
	Current	34.4	37.9	
	Past	11.5	10.3	
	Never	22.1	19.4	
	Missing	32.0	32.3	
Other risk factors, %				

	Current HMG-CoA reductase-inhibitor use	22.9	13.6	<0.001
	HCV infection	12.6	29.1	<0.001
Renal disease, mL/min/1.73m^2				<0.001
	eGFR >=60	84.8	89.5	
	eGFR 30-59	3.3	4.3	
	eGFR <30	0.4	0.9	
	Missing	11.6	5.3	

Table 1. Characteristics of VACS participants* (continued)

Variable		All participants Uninfected (n=66,492	HIV Infected (n=31,523)	P value
BMI <30, %		57.0	82.7	<0.001
BMI >=30, %		36.2	15.0	
Missing		6.1	2.3	
Anemia, g/dL				<0.001
	Hemoglobin >=14	64.4	53.6	
	Hemoglobin 12-13.9	20.1	30.6	
	Hemoglobin 10-11.9	2.9	9.0	
	Hemoglobin <10	0.4	2.4	
	Missing	12.6	4.5	
History of substance use, %				
	Alcohol abuse and dependence	26.7	25.0	<0.001
	Cocaine abuse and dependence	15.3	18.8	<0.001
Atrial fibrillation, %		0.63	0.55	0.12
Major depression, %		15.0	15.8	<0.001
HIV-specific biomarkers				
CD4 at baseline				
	CD4 cell count, mm^3			
	Mean (SD)		425.2 (297.3)	
	Median		382	
	Missing CD4 cell count (%)		17.1	
	HIV-1 RNA, copies/mL			
	Mean (SD)		73,571.7 (958843.6)	
	Median		1357	
	Missing HIV-1 RNA (%)		15.0	
ART regimen, %				
	NRTI plus PI		23.7	
	NRTI plus NNRTI		47.3	
	Other		2.9	
	No ART		26.1	

ART class, %		
	PI	58.4
	NRTI	73.6
	NNRTI	47.4

Table 2. HIV and the incidence of total HF, HFPEF, HFREF, and HF with missing EF by HIV status

		Age Group, years				
Status		<40	40-49	50-59	60-69	70
Total HF	HIV-					
No. of participants		10,896	25,180	23,227	5,957	1,232
No. of HF events		55	506	830	209	95
HF rates per 1,000 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		5,888	11,707	10,487	2,845	596
No. of HF events		62	296	422	116	45
HF rates per 1,000 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 EF≥50	HIV-					
No. of participants		10,896	25,180	23,227	5,957	1,232
No. of HF events, EF≥50		18	172	328	75	36
HF rates per 1,000 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		5,888	11,707	10,487	2,845	596
No. of HF events, EF≥50		12	81	133	35	23
HF rates per 1,000 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)
HF EF 40-49	HIV-					
No. of participants		10,896	25,180	23,227	5,957	1,232
No. of HF events, EF 40-49		7	78	135	29	18
HF rates per 1,000 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		5,888	11,707	10,487	2,845	596
No. of HF events, EF 40-49		7	45	66	18	6
HF rates per 1,000 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)

Table 2. HIV and the incidence of total HF, HFPEF, HFREF, and HF with missing EF by HIV status (continued)

		Age Group, years				
Status		<40	40-49	50-59	60-69	³70
HFREF	HIV-					
No. of participants		10,896	25,180	23,227	5,957	1,232
No. of HF events, EF <40		21	200	278	75	23
HF rates per 1,000 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		5,888	11,707	10,487	2,845	596
No. of HF events, EF <40		34	128	168	42	8
HF rates per 1,000 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, 1.84)	1.33 (0.89, 1.97)	0.84 (0.33, 1.95)
EF Missing	HIV-					
No. of participants		10,896	25,180	23,227	5,957	1,232
No. of HF events, EF missing		9	56	89	30	18
HF rates per 1,000 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		5,888	11,707	10,487	2,845	596
No. of HF events, EF missing		9	42	55	21	8
HF rates per 1,000 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)

Table 3. HIV and the risk of HF by type of HF in important subgroups

			Total HF		HFPEF ≥ 50		HF EF 40-50		HFREF		EF missing	
Group		N	No. of events	HR* 95% CI	No. of events	HR* 95% CI	No. of events	HR* 95% CI	No. of events	HR* 95% CI	No. of events	HR 95% CI
Total*	HIV-	66,492	1695	1.00 (ref)	629	1.00 (ref)	267	1.00 (ref)	597	1.00 (ref)	202	1.00 (ref)
	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	1.43 (1.12-1.82)
white†	HIV-	25,382	583	1.00 (ref)	227	1.00 (ref)	93	1.00 (ref)	173	1.00 (ref)	90	1.00 (ref)
	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	1.15 (0.79-1.67)
black‡	HIV-	32,067	982	1.00 (ref)	368	1.00 (ref)	148	1.00 (ref)	377	1.00 (ref)	89	1.00 (ref)
	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	1.76 (1.23-2.52)
<40 years§	HIV-	10,896	55	1.00 (ref)	18	1.00 (ref)	7	1.00 (ref)	21	1.00 (ref)	9	1.00 (ref)
	HIV+	5,888	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	1.84 (0.65-5.22)

*Model adjusted for age, race/ethnicity, sex, hypertension, lipids, smoking, LDL and HDL cholesterol, triglycerides, smoking, HMG Co-A reductase-inhibitor use, HCV infection, renal disease, BMI, substance use, atrial fibrillation, and major depression

†Model adjusted for age, sex, hypertension, lipids, smoking, LDL and HDL cholesterol, triglycerides, smoking, HMG Co-A reductase-inhibitor use, HCV infection, renal disease, BMI, substance use, atrial fibrillation, and major depression among only white participants

‡Model adjusted for age, sex, hypertension, lipids, smoking, LDL and HDL cholesterol, triglycerides, smoking, HMG Co-A reductase-inhibitor use, HCV infection, renal disease, BMI, substance use, atrial fibrillation, and major depression among only black participants

§Model adjusted for age, race/ethnicity, sex, hypertension, lipids, smoking, LDL and HDL cholesterol, triglycerides, smoking, HMG Co-A reductase-inhibitor use, HCV infection, renal disease, BMI, substance use, atrial fibrillation, and major depression among participants <40 years of age at baseline

Table 4. HIV infection and the risk of total HF and type of HF by HIV viral load and CD4 cell count status

		Total HF	HFPEF≥50	HF EF 49-50	HFREF	EF missing
		HR* 95% CI	HR* 95% CI	HR* 95% CI	HR* 95% CI	HR* 95% CI
VL model*	HIV-	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	HIV+, VL<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+, VL>=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 model*	HIV-	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	HIV+, 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+, 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+, 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 value	VL<500 vs. VL>=500	0.04	0.88	0.70	0.02	0.29
	CD4 200-499 vs. >=500	0.15	0.13	0.91	0.92	0.045
	CD4 <200 vs. >=500	0.001	0.08	0.38	0.048	0.01
	CD4 200-499 vs. <200	0.02	0.67	0.31	0.03	0.47

*All models are adjusted for age, race/ethnicity, hypertension, lipids, smoking, LDL and HDL cholesterol, triglycerides, smoking, HMG Co-A reductase-inhibitor use, HCV infection, renal disease, BMI, substance use, atrial fibrillation, and major depression

Table 5. HIV viral load, CD4 Cell count, and ART Regimen and the risk of HF among HIV+ Veterans*

HIV biomarker category	Total HF	HFPEF≥50	HF EF 40-49	HFREF	HF Missing
CD4 cell count >=500 per mm^3	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
CD4 cell count 200-499 per mm^3	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)
CD4<200 cell count per mm^3	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 viral load <500 copies per mm^3	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
HIV viral load >=500 copies per mm^3	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)

*Models are simultaneously adjusted for HIV viral load, CD4 cell count ART regimen, age, race/ethnicity, hypertension, lipids, smoking, LDL and HDL cholesterol, triglycerides, smoking, HMG Co-A reductase-inhibitor use, HCV infection, renal disease, BMI, substance use, atrial fibrillation, major depression, and baseline ART regimen.