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Authors

White, Jessica R
Chang, Chung-Chou H
So-Armah, Kaku A
et al.

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Original Article

Depression and Human Immunodeficiency Virus Infection Are Risk Factors for Incident Heart Failure Among Veterans Veterans Aging Cohort Study

Jessica R. White, MS; Chung-Chou H. Chang, PhD; Kaku A. So-Armah, PhD;
 Jesse C. Stewart, PhD; Samir Kumar Gupta, MD; Adeel A. Butt, MD, MS;
 Cynthia L. Gibert, MD, MS; David Rimland, MD; Maria C. Rodriguez-Barradas, MD;
 David A. Leaf, MD; Roger J. Bedimo, MD, MS; John S. Gottdiener, MD;
 Willem J. Kop, PhD; Stephen S. Gottlieb, MD; Matthew J. Budoff, MD;
 Tasneem Khambaty, MS; Hilary Tindle, MD, MPH; Amy C. Justice, MD, MSCE, PhD;
 Matthew S. Freiberg, MD, MPH

AQ2

Background—Both HIV and depression are associated with increased heart failure (HF) risk. Depression, a common comorbidity, may further increase the risk of HF among adults with HIV infection (HIV+). We assessed the association between HIV, depression, and incident HF.

Methods and Results—Veterans Aging Cohort Study (VACS) participants free from cardiovascular disease at baseline (n=81427: 26908 HIV+, 54519 without HIV [HIV−]) were categorized into 4 groups: HIV− without major depressive disorder (MDD) [reference], HIV− with MDD, HIV+ without MDD, and HIV+ with MDD. *International Classification of Diseases, Ninth Revision* codes from medical records were used to determine MDD and the primary outcome, HF. After 5.8 years of follow-up, HF rates per 1000 person-years were highest among HIV+ participants with MDD (9.32; 95% confidence interval [CI], 8.20–10.6). In Cox proportional hazards models, HIV+ participants with MDD had a significantly higher risk of HF (adjusted hazard ratio, 1.68; 95% CI, 1.45–1.95) compared with HIV− participants without MDD. MDD was associated with HF in separate fully adjusted models for HIV− and HIV+ participants (adjusted hazard ratio, 1.21; 95% CI, 1.06–1.37; and adjusted hazard ratio, 1.29; 95% CI, 1.11–1.51, respectively). Among those with MDD, baseline antidepressant use was associated with lower risk of incident HF events (adjusted hazard ratio, 0.76; 95% CI, 0.58–0.99).

Conclusions—Our study is the first to suggest that MDD is an independent risk factor for HF in HIV+ adults. These results reinforce the importance of identifying and managing MDD among HIV+ patients. Future studies must clarify mechanisms linking HIV, MDD, antidepressants, and HF and identify interventions to reduce HF morbidity and mortality in those with both HIV and MDD. (*Circulation*. 2015;132:00-00. DOI: 10.1161/CIRCULATIONAHA.114.014443.)

Key Words: depression ■ epidemiology ■ heart failure ■ HIV

AQ4

Antiretroviral therapy (ART) and effective clinical management have resulted in improved life expectancy for adults with HIV infection (HIV+).^{1,2} However, the risk for cardiovascular disease (CVD) is higher for HIV+ adults compared with those without HIV (HIV−).³ The risk of

heart failure (HF) is significantly higher in HIV+ adults compared with HIV− adults who are similar in age, sex, and race/ethnicity.⁴⁻⁶

Clinical Perspective on p XXX

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From Department of Epidemiology, University of Pittsburgh Graduate School of Public Health, PA (J.R.W.); Department of Medicine, University of Pittsburgh School of Medicine, PA (C.-C.H.C.); Department of Medicine, Boston University, MA (K.A.S.-A.); Department of Psychology, Indiana University-Purdue University Indianapolis (J.C.S., T.K.); Department of Medicine, Indiana University School of Medicine, Indianapolis (S.K.G.); Department of Medicine, Hamad Medical Corp, Doha, Qatar (A.A.B.); VA Medical Center, Washington, DC (C.L.G.); Division of Infectious Diseases, Emory University School of Medicine, Atlanta, GA (D.R.); Atlanta VA Medical Center, Decatur, GA (D.R.); Infectious Diseases Section, Michael E. DeBakey VAMC and Department of Medicine, Baylor College of Medicine, Houston, TX (M.C.R.-B.); UCLA School of Medicine and Division of General Medicine, Greater Los Angeles VA Healthcare System, CA (D.A.L.); Department of Medicine, VA North Texas Health Care System, Dallas (R.J.B.); Division of Cardiology, University of Maryland Medical Center, Baltimore (J.S.G.); Department of Medical and Clinical Psychology, Tilburg University, The Netherlands (W.J.K.); Department of Medicine, University of Maryland School of Medicine, Baltimore (S.S.G.); Los Angeles Biomedical Research Institute, Torrance, CA (M.J.B.); Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN (H.T.); Yale University School of Medicine, New Haven, CT (A.C.J.); Veterans Affairs Connecticut Health Care System, West Haven Veterans Administration Medical Center, CT (A.C.J.); and Cardiovascular Medicine Division, Vanderbilt University School of Medicine and Tennessee Valley Healthcare System, Nashville (M.S.F.).

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Correspondence to Matthew S. Freiberg, MD, MPH, Cardiovascular Medicine Division, Vanderbilt University School of Medicine, 2525 W End, Ste 300-A, Nashville, TN 37203. E-mail matthew.s.freiberg@vanderbilt.edu

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Poor mental health is an additional concern for HIV+ adults. Depression is common in the United States, with the general population facing an estimated 6.6% 12-month risk of developing major depressive disorder (MDD).⁷ Estimates for 12-month MDD prevalence among HIV+ adults range from 5% to 10%.⁸ A meta-analysis reported that the frequency of MDD diagnoses among HIV+ participants was nearly 2 times higher than the frequency among HIV- participants.⁹ Like HIV infection, MDD may increase the risk for HF.¹⁰⁻¹³

Possible mechanisms for the association between HIV and HF include chronic inflammation and platelet activation.⁵ Similarly, depression is associated with autonomic nervous system dysregulation, inflammation, and platelet activation.¹⁴⁻¹⁶ It stands to reason that HIV+ adults with MDD may be at heightened risk for HF compared with the remaining population; however, to date, no studies have examined the risk of HF in individuals burdened with co-occurring HIV and MDD.

Therefore, our objectives were to determine the association among HIV, MDD, and incident HF in a subset of HIV+ and HIV- veterans from the Veterans Aging Cohort Study (VACS) and to explore the effects of antidepressant use, HIV severity, and ART use on this association.

Methods

Participants

Details of the prospective, longitudinal VACS have been published previously.¹⁷ Since 1998, the VACS has continually enrolled HIV+ and age-, sex-, race/ethnicity-, and geographic region-matched HIV- veterans in the same calendar year from the US Department of Veterans Affairs (VA) system. For this analysis, data from VACS participants alive and enrolled as of April 1, 2003, were extracted from the VA national electronic medical record system. The institutional review boards from the University of Pittsburgh, Yale University, and West Haven VA Medical Center approved this study.

Participants were included in this analysis if they were free of clinical CVD at baseline (April 1, 2003). Prevalent CVD at baseline was defined by the use of *International Classification of Diseases, Ninth Revision (ICD-9)* codes for HF, acute myocardial infarction, unstable angina, stroke or transient ischemic attack, peripheral vascular disease, or cardiovascular revascularization on or before the baseline date. The final sample included 81 427 veterans (26 908 HIV+, 54 519 HIV-).

Independent Variables

Participants were considered HIV+ if they had at least 1 inpatient or ≥ 2 outpatient *ICD-9* codes for HIV at baseline. The algorithm used to identify HIV+ veterans has high sensitivity (90%), specificity (99.9%), and positive predictive value (88%).¹⁷

Participants were considered to have MDD if at least 1 inpatient or 2 outpatient *ICD-9* codes for MDD (296.2x and 296.3x) were identified in their electronic medical record beginning in 1998 (the earliest time point of available *ICD-9* data in VACS) and up to the participant's enrollment date in the VACS. Since 2000, the VA has promoted a strong screening, diagnosis, and treatment program within the VA. Screening programs include the use of Patient Health Questionnaire-2 instruments, followed by clinical interviews in primary care or referrals to primary care mental health clinics or specialty care (eg, psychiatry) for confirmation of diagnosis and treatment. In a small study that compared MDD diagnoses made by general practitioners in primary care settings with *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria ranges for MDD, specificity was 89% and sensitivity was 79%.¹⁸ These findings were supported by a larger study that investigated the validity of billing diagnoses for clinical depression in electronic medical records.¹⁹

We categorized participants into 4 groups: HIV- without MDD (reference), HIV- with MDD, HIV+ without MDD, and HIV+ with MDD.

Dependent Variables

The primary outcome for this report, HF, was determined by the use of VA and Medicare *ICD-9* codes (428.xx, 429.3, 402.11, 402.91, 425.x), a method shown to have a positive predictive value of 94.3%.²⁰ The follow-up time for participants began from their first clinical encounter on or after April 1, 2003, and continued until a HF event, death, or the last date of follow-up (December 31, 2009).

Covariates

Our covariates were selected a priori on the basis of our prior work and studies from others examining risk factors for HF. The Framingham Heart Study and others have identified risk factors for HF, including age, hypertension, diabetes mellitus, smoking, cholesterol, body mass index, substance use, atrial fibrillation and flutter, and renal disease.^{4,21-24} Administrative data were used to obtain age, sex, and race/ethnicity. Outpatient and laboratory reports from baseline visits stored in the VA medical record provided data on hypertension, diabetes mellitus, lipid concentrations, hemoglobin concentrations, renal function, atrial fibrillation, atrial flutter, alcohol abuse or dependence, cocaine abuse or dependence, and hepatitis C virus (HCV) infection. Baseline body mass index (kg/m^2) and smoking status were acquired from health factor data collected by the VA and recorded in the VA medical record. Baseline antidepressant and statin data were obtained from VA pharmacy records.¹⁷

Three hypertension categories were used: none (blood pressure $<140/90$ mmHg and no antihypertensive medication use), controlled (blood pressure $<140/90$ mmHg and antihypertensive medication use), and uncontrolled (blood pressure $\geq 140/90$ mmHg).²⁵ Diabetes mellitus diagnosis was determined with the use of a combination of glucose levels, antidiabetes medication, and *ICD-9* codes, an algorithm previously validated in the VACS.²⁶ Dyslipidemia was assessed using levels of low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides (mg/dL). Statin use was determined within 6 months of enrollment. Anemia was based on hemoglobin concentrations (g/dL), and renal function was based on estimated glomerular filtration rate ($\text{mL}\cdot\text{min}^{-1}\cdot 1.73 \text{ m}^{-2}$). Alcohol abuse or dependence and cocaine abuse or dependence were determined on the basis of *ICD-9* codes.²⁷ HCV infection was defined by ≥ 1 inpatient or ≥ 2 outpatient *ICD-9* codes for a positive HCV antibody test result.²⁸ Body mass index and smoking status (current, past, and never) were included in the VA electronic medical health record after prompts to the clinicians during patient visits. Obesity was defined as body mass index $\geq 30 \text{ kg}/\text{m}^2$. The smoking status reported in this health factor data set has shown high agreement with self-reported smoking status on VACS-8 surveys.²⁹

Antidepressant use was defined as documentation of a filled prescription for selective serotonin reuptake inhibitor, tricyclic antidepressant, or other antidepressant use from the VA pharmacy records during the baseline period (1998-2003). Medications were classified as "other" if they were in the following classes: tetracyclic antidepressant, monoamine oxidase inhibitor, serotonin-norepinephrine reuptake inhibitor, serotonin antagonist and reuptake inhibitor, norepinephrine reuptake inhibitor, norepinephrine-dopamine reuptake inhibitor, and miscellaneous (Table I in the online-only Data Supplement). Generic and brand names for antidepressants were used to search outpatient pharmacy records.

We included HIV-specific variables (CD4+ T-cell [CD4] counts, HIV-1 RNA, and ART use) for HIV+ participants from 2 time periods: baseline and recent.³⁰ Baseline variables were obtained during participant visits within 180 days of the baseline enrollment date (April 1, 2003). Recent variables were obtained during the visit closest to HF, death, or the last follow-up date (December 31, 2009). Antiretroviral medications were based on pharmacy data and categorized by drug class (ie, nucleoside reverse-transcriptase inhibitors [NRTIs], non-nucleoside reverse-transcriptase inhibitors, or protease inhibitors).

Table 1. Baseline Participant Characteristics by MDD Diagnosis and HIV Status (n=81 427)*

Characteristic	HIV-Uninfected		HIV-Infected	
	No MDD (n=45 728)	MDD (n=8791)	No MDD (n=21 850)	MDD (n=5058)
Age, mean (SD), y	48.8 (9.5)	48.1 (7.4)	48.3 (9.7)	47.4 (7.9)
Male, %	97.5	95.6	97.7	95.3
Race/ethnicity, %				
White	37.0	41.6	37.0	42.5
Black	48.0	46.8	48.5	45.9
Hispanic	7.5	9.2	6.9	8.2
Other	7.4	2.4	7.7	3.4
Body mass index ≥ 30 kg/m ² , %	38.7	38.6	13.7	16.6
Hypertension, %				
None	58.3	60.8	67.3	68.6
Controlled	9.4	10.1	7.0	7.9
Uncontrolled	32.4	29.0	25.7	23.6
Diabetes mellitus, %	20.0	23.1	13.3	16.1
Lipids, %				
LDL cholesterol <100 mg/dL	31.2	33.5	46.2	46.5
LDL cholesterol 100–129 mg/dL	33.3	33.4	29.7	29.6
LDL cholesterol 130–159 mg/dL	23.2	21.1	15.9	15.7
LDL cholesterol ≥ 160 mg/dL	12.3	12.0	8.2	8.1
HDL cholesterol ≥ 60 mg/dL	15.0	13.4	11.1	10.2
HDL cholesterol 40–59 mg/dL	47.7	45.5	38.0	37.2
HDL cholesterol <40 mg/dL	37.3	41.1	50.9	52.6
Triglycerides ≥ 150 mg/dL	37.4	42.2	46.9	49.1
Statin use within 6 mo of enrollment, %	9.4	11.6	6.4	6.8
Hemoglobin, %				
≥ 14 g/dL	73.1	70.9	55.1	57.1
12–13.9 g/dL	22.9	24.9	31.9	32.0
10–11.9 g/dL	3.2	3.5	9.5	8.5
<10 g/dL	0.8	0.8	3.5	2.5
Renal function, %				
eGFR ≥ 60 mL·min ⁻¹ ·1.73 m ⁻²	95.3	95.9	93.6	94.6
eGFR 30–59 mL·min ⁻¹ ·1.73 m ⁻²	4.2	3.7	5.2	4.4
eGFR <30 mL·min ⁻¹ ·1.73 m ⁻²	0.5	0.3	1.2	1.1
Atrial fibrillation, %	1.0	0.8	0.8	0.7
Atrial flutter, %	0.3	0.4	0.3	0.2
Smoking, %				
Never	31.4	22.8	28.4	19.3
Past	16.5	13.4	13.7	11.0
Current	52.1	63.8	57.8	69.7
Alcohol abuse or dependence, %	10.5	27.5	10.8	28.1
Cocaine abuse or dependence, %	5.5	16.3	8.5	23.3
HCV infection, %	13.9	24.0	32.7	43.2
Antidepressant use, %†				
Any SSRI use	20.4	73.7	22.8	73.6
Any TCA use	11.3	25.3	14.7	29.2
Any other antidepressants use‡	20.6	70.4	22.2	68.2
SSRI only use	8.0	14.1	9.8	14.8
TCA only use	5.4	2.0	7.3	2.7

(Continued)

Table 1. Continued

Characteristic	HIV-Uninfected		HIV-Infected	
	No MDD (n=45 728)	MDD (n=8791)	No MDD (n=21 850)	MDD (n=5058)
Other antidepressants only use	8.4	10.9	9.2	10.6
No antidepressant medications	64.1	10.0	58.4	9.4
HIV-specific risk factors				
CD4 cell count, %				
≥500 mm ³ at baseline	31.4	34.6
200–499 mm ³ at baseline	40.0	40.5
200 mm ³ at baseline	28.6	24.9
≥500 mm ³ at recent visit	41.5	41.7
200–499 mm ³ at recent visit	39.2	38.4
<200 mm ³ at recent visit	19.3	20.0
HIV-1 RNA ≥500 copies/mL at baseline, %	55.1	56.5
HIV-1 RNA ≥500 copies/mL at recent visit, %	24.5	26.4
ART use, %				
NRTI at baseline	48.3	49.6
NNRTI at baseline	22.6	22.1
PI at baseline	25.3	27.1
NRTI at recent visit	73.7	68.1
NNRTI at recent visit
PI at recent visit	38.1	39.8
Regimen, %				
NRTI+PI at baseline	20.4	21.6
NRTI+NNRTI at baseline	22.1	21.6
Other at baseline	6.7	7.2
No ART at baseline	50.9	49.6
NRTI+PI at recent visit	32.4	34.1
NRTI+NNRTI at recent visit	35.9	28.6
Other at recent visit	8.3	8.6
No ART at recent visit	23.4	28.8

ART indicates antiretroviral therapy; eGFR, estimated glomerular filtration rate; HCV, hepatitis C virus; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MDD, major depressive disorder; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor; SSRI, selective serotonin reuptake inhibitors; and TCA, tricyclic antidepressant.

*All characteristics were significantly different between groups ($P<0.05$) except atrial flutter ($P=0.201$), recent CD4 cell counts ($P=0.492$), baseline HIV-1 RNA concentration ($P=0.104$), baseline NRTI use ($P=0.093$), baseline NNRTI use ($P=0.436$), and baseline ART regimens ($P=0.080$).

†Any antidepressant use refers to the proportion of veterans in a category who were taking a class of antidepressant, regardless of whether they were on multiple medications. “Only use” refers to the proportion of veterans who were taking only that 1 class of medication. “No medication” refers to the proportion of veterans who were not on any of the classes of antidepressant medication.

‡See Table I in the online-only Data Supplement for medications included in each antidepressant medication category.

Additionally, 4 types of ART regimens were defined: NRTI with protease inhibitors, NRTI with nonnucleoside reverse-transcriptase inhibitors, other regimen, and no ART use (reference). A previous study reported that 96% of HIV+ veterans obtain their ART medications through the VA system.¹⁷

Statistical Analysis

Baseline descriptive statistics were calculated for each HIV/MDD group. Student *t* tests (or nonparametric counterpart) and χ^2 tests were used to determine significant differences between the groups as appropriate. Incident HF diagnosis rates per 1000 person-years were calculated for each HIV/MDD group. Cox proportional hazards regression

was used to model the association between HIV/MDD group and incident HF. We constructed 3 models: unadjusted; adjusted for demographics; and adjusted for age, sex, race/ethnicity, body mass index, hypertension, diabetes mellitus, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, statin use, hemoglobin, renal function, atrial fibrillation, atrial flutter, smoking status, alcohol abuse or dependence, cocaine abuse or dependence, and HCV infection. The percent variance associated with each model is presented in Table II in the online-only Data Supplement. We tested assumptions for Cox proportional hazard models using Schoenfeld residual plots. These plots did not show deviation from proportionality for our main exposure variable. Additional analyses examined this association among whites and blacks separately. A Kaplan–Meier

curve was created to display time to incident HF by the 4 HIV/MDD groups. Among those with MDD, HF incidence rates per 1000 person-years and adjusted hazard ratios (aHRs) were calculated by HIV status and antidepressant use. In a second analysis, we used Cox regression to model the association of MDD and incident HF among the HIV+ participants. This analysis included additional adjustments for baseline and recent CD4 counts, HIV-1 RNA, and ART use. We included only participants with a diagnosis of MDD in our third analysis, which explored the association between antidepressant use and incident HF among HIV+ and HIV- participants.

Results

Within this cohort of 81 427 veterans, MDD prevalence was 17.0% overall and not significantly different between HIV+ and HIV- participants (18.8% versus 16.1%, respectively). The 4 HIV/MDD groups made up the following proportions of the total sample: HIV- without MDD, 56.2%; HIV- with MDD, 10.8%; HIV+ without MDD, 26.8%; and HIV+ with MDD, 6.2%.

Baseline characteristics differed between the 4 HIV/MDD groups (Table 1). Regardless of MDD diagnosis, HIV+ participants were more likely than HIV- participants to have low high-density lipoprotein cholesterol, high triglycerides, HCV infection, renal disease, anemia, and cocaine abuse or dependence and to be current smokers. However, HIV+ participants were less likely to have hypertension, diabetes mellitus, and high low-density lipoprotein cholesterol and to be obese. Regardless of HIV status, participants with MDD were more likely than participants without MDD to have diabetes mellitus, high triglycerides, HCV infection, cocaine abuse or dependence, and alcohol abuse or dependence; to be current smokers; and to use antidepressant medications (all $P < 0.05$).

During a median of 5.8 years (25th–75th percentile, 3.3–6.6 years) of follow-up, there were 2666 incident HF events. The HF rate per 1000 person-years was significantly higher among HIV+ participants with co-occurring MDD compared with rates in the other 3 groups, that is, HIV- without MDD, HIV- with MDD, and HIV+ without MDD (Table 2).

After adjustment for traditional CVD risk factors, HIV- participants with MDD, HIV+ participants without MDD, and HIV+ participants with MDD had higher risk of incident HF than HIV- participants without MDD (Table 3). Age, hypertension, diabetes mellitus, low hemoglobin, low estimated glomerular filtration rate, atrial fibrillation, current smoking, cocaine abuse or dependence, and HCV infection were independently associated with increased risk of incident HF. Hispanic race/ethnicity was associated with a lower risk of incident HF. When this model was additionally adjusted for selective serotonin

reuptake inhibitor, tricyclic antidepressant, and other antidepressant use, the risk of HF remained elevated among HIV- participants with MDD (aHR, 1.17; 95% confidence interval [CI], 1.02–1.34), HIV+ participants without MDD (aHR, 1.28; 95% CI, 1.16–1.41), and HIV+ participants with MDD (aHR, 1.64; 95% CI, 1.41–1.92) compared with the referent group. Importantly, this association was present for whites and blacks (Table 4). Moreover, when participants without MDD who were taking antidepressants were removed from the analysis, the HIV-infected and depressed veterans continued to have the highest risk of HF (HR, 1.73; 95% CI, 1.47–2.01). Participants with co-occurring HIV infection and MDD diagnosis had the poorest survival free of HF of all 4 groups (Figure). In separate analyses, we did not find a significant multiplicative interaction between HIV and MDD ($P > 0.05$).

We further explored incident HF risk in HIV- and HIV+ participants separately. MDD was associated with increased risk of HF in both groups (aHR, 1.21; 95% CI, 1.06–1.37; and aHR, 1.29; 95% CI, 1.11–1.51, respectively). Among HIV+ participants, MDD remained a significant risk factor for HF after further adjustment for baseline traditional CVD risk factors, CD4 count, baseline HIV-1 RNA concentration, and ART regimen documented at the baseline visit (aHR, 1.30; 95% CI, 1.11–1.51). We found similar results when the model included recent CD4 count, recent HIV-1 RNA concentration, and recent ART regimen or recent protease inhibitor, NRTI, and NRTI use.

The majority of participants with MDD (90.2%) had at least 1 antidepressant prescription during the baseline period. Among all participants in the sample with MDD, baseline antidepressant use was associated with fewer incident HF events after adjustment for HIV and CVD risk factors (aHR, 0.76; 95% CI, 0.58–0.99). In a model that stratified the MDD participants by both HIV status and antidepressant use, the rates of incident HF were highest among HIV+ participants who did not use antidepressants (Table 5).

Discussion

Our findings indicate that both depression and HIV are associated with an increased risk of HF in veterans, even after adjustment for traditional CVD risk factors, comorbidities, and substance use. Participants with co-occurring HIV and MDD had the highest rates and risk of HF relative to those with only 1 of the conditions or neither condition. Furthermore, among HIV+ veterans, depression was associated with an increased risk of HF after additional adjustment for CD4 cell count, HIV-1 RNA levels, and ART use.

Our findings are consistent with previous studies reporting associations between HIV and incident HF and between depression and incident HF in HIV- samples.^{4,5,13,31} However, this study is the first to simultaneously examine HIV status, MDD diagnosis, and antidepressant use as predictors of incident HF in a large national cohort of HIV-infected and -uninfected people. In addition, our results are the first to suggest that MDD is an independent risk factor for HF in HIV+ adults. This finding is important because rates of incident HF among the HIV+ participants with depression in this cohort (≈ 9 per 1000 person-years) were higher than in the US population (≈ 2 –5 per 1000 person-years).³²

Table 2. Unadjusted Rates of Incident HF by MDD Diagnosis and HIV status (n=81 427)

HIV Status/MDD Diagnosis	Participants, n	HF Events, n	Rates of HF/1000 person-y (95% CI)
HIV-/no MDD	45 728	1339	6.04 (5.73–6.38)
HIV-/MDD	8791	319	6.87 (6.16–7.67)
HIV+/no MDD	21 850	774	7.56 (7.05–8.11)
HIV+/MDD	5058	234	9.32 (8.20–10.60)

CI indicates confidence interval; HF, heart failure; and MDD, major depressive disorder.

Table 3. Cox Proportional Hazard Regression Models Examining the Association Between HIV/MDD Group and Incident HF

Characteristic	HR (95% CI)		
	Model 1	Model 2	Model 3
HIV/MDD group			
HIV-/no MDD	1 (Reference)	1 (Reference)	1 (Reference)
HIV-/MDD	1.13 (1.00–1.27)	1.30 (1.15–1.47)	1.19 (1.05–1.35)
HIV+/no MDD	1.25 (1.15–1.37)	1.32 (1.20–1.44)	1.28 (1.16–1.41)
HIV+/MDD	1.54 (1.34–1.77)	1.87 (1.62–2.15)	1.68 (1.45–1.95)
Age, 10-y intervals		2.04 (1.96–2.12)	1.78 (1.70–1.86)
Female sex		1.00 (0.77–1.31)	1.01 (0.77–1.33)
Race/ethnicity			
White		1 (Reference)	1 (Reference)
Black		1.34 (1.24–1.46)	1.05 (0.96–1.15)
Hispanic		0.80 (0.68–0.95)	0.77 (0.65–0.92)
Other		0.88 (0.73–1.07)	0.92 (0.76–1.11)
Body mass index ≥ 30 kg/m ²			1.25 (1.14–1.36)
Hypertension			
None			1 (Reference)
Controlled			1.78 (1.58–2.01)
Uncontrolled			1.94 (1.77–2.12)
Diabetes mellitus			1.75 (1.61–1.91)
Lipids, mg/dL			
LDL cholesterol <100			1 (Reference)
LDL cholesterol 100–129			0.88 (0.79–0.98)
LDL cholesterol 130–159			0.88 (0.78–1.00)
LDL cholesterol ≥ 160			0.93 (0.78–1.12)
HDL cholesterol ≥ 60			1 (Reference)
HDL cholesterol 40–59			1.04 (0.90–1.21)
HDL cholesterol <40			1.04 (0.89–1.21)
Triglycerides ≥ 150			1.00 (0.91–1.10)
Statin use within 6 mo			1.08 (0.97–1.21)
Hemoglobin, g/dL			
≥ 14			1 (Reference)
12–13.9			1.32 (1.20–1.45)
10–11.9			1.84 (1.58–2.14)
<10			2.23 (1.75–2.85)
Renal function, mL·min ⁻¹ ·1.73 m ⁻²			
eGFR ≥ 60			1 (Reference)
eGFR 30–59			2.01 (1.78–2.28)
eGFR <30			5.21 (4.31–6.30)
Atrial fibrillation			2.15 (1.63–2.84)
Atrial flutter			1.59 (0.91–2.78)
Smoking			
Never			1 (Reference)
Past			1.09 (0.96–1.23)
Current			1.42 (1.29–1.57)
Alcohol abuse or dependence			0.98 (0.86–1.12)
Cocaine abuse or dependence			1.27 (1.09–1.48)
HCV infection			1.30 (1.19–1.43)

CI indicates confidence interval; eGFR, estimated glomerular filtration rate; HCV, hepatitis C virus; HDL, high-density lipoprotein; HF, heart failure; HR, hazard ratio; LDL, low-density lipoprotein; and MDD, major depressive disorder. Model 1, HIV MDD only; model 2, model 1 plus age, sex, race/ethnicity; and model 3, model 2 plus all covariates.

Table 4. Cox Proportional Hazard Regression Models Examining the Association Between HIV/MDD Group and Incident Heart Failure in Whites and Blacks

HIV / MDD Group	Whites*		Blacks*	
	HR (95% CI)	P Value	HR (95% CI)	P Value
HIV-/no MDD	1.00		1.00	
HIV-/MDD	1.25 (1.02–1.53)	0.03	1.07 (0.90–1.27)	0.46
HIV+/no MDD	1.22 (1.04–1.44)	0.02	1.27 (1.11–1.45)	<0.001
HIV+/MDD	1.63 (1.28–2.09)	<0.001	1.71 (1.40–2.09)	<0.001

CI indicates confidence interval; HF, heart failure; HR, adjusted hazard ratio; and MDD, major depressive disorder

*All models for HF were adjusted for age, sex, body mass index, hypertension, diabetes mellitus, lipids, statin use, hemoglobin, renal function, atrial fibrillation, atrial flutter, smoking, alcohol abuse or dependence, cocaine abuse or dependence, and hepatitis C virus infection

The physiological mechanisms underlying the associations of HIV infection and depression with future HF have yet to be elucidated. With HIV infection, the risk of HF may be explained by vascular damage associated with the virus itself, chronic inflammation, lack of vascular repair owing to CD4 cell depletion, or dyslipidemia after HIV infection or ART-induced metabolic syndrome.^{4,30,33–35} With depression, possible mechanisms include alterations to the hypothalamic-pituitary-adrenal axis, dysregulation of the autonomic nervous system, chronic inflammation, and platelet activation.^{36,37} In addition to these physiological changes, both HIV infection and depression are associated with unhealthy behavioral changes such as substance use and decreased physical activity, which are risk factors for HF.^{38,39}

In this study, HIV+ participants with co-occurring MDD had the highest risk of HF. The Infectious Diseases Society of America has stressed the importance of recognizing depression in HIV+ patients.⁴⁰ Our findings bolster this recommendation by adding another reason for doing so: depression as a potential risk factor for HF. In Table 4, we report preliminary evidence that raises the possibility that antidepressant use may decrease the excess risk for HF in HIV+ and HIV- adults. However, a prospective, randomized, controlled trial is needed to determine whether depression is a causal risk factor for HF and whether depression interventions reduce the risk of HF in the HIV-infected and -uninfected populations.^{41,42}

There are limitations of this study that warrant discussion. First, because our participants were predominantly men, the findings might not generalize to women. Second, HF and depression were based on *ICD-9* codes. Therefore, some misclassification may have occurred (eg, patients with true MDD or HF that was not indicated in their medical record with an *ICD-9* code); however, such misclassification would have biased our results to the null. Third, baseline depressive disorder diagnosis was used as a predictor. Depressive symptom severity tends to fluctuate over time, and previous findings suggest that the mean of symptom severity assessed at multiple time points is a stronger predictor of subclinical CVD than depressive symptom severity assessed at a single time point.⁴³ However, because depressive episodes are likely to recur in those with a MDD diagnosis, a baseline measure of MDD diagnosis as we defined it should capture those at risk for long-term exposure to the unhealthy impact of depression.^{44,45} Moreover, we did not assess whether “current” MDD (ie, MDD within 6 months of and before baseline) was associated with HF because restricting the time window could lead to misclassification (ie, participants who had been diagnosed with MDD but were not seen in clinic within 6 months before the baseline enrollment date would be classified as non-MDD). Lastly, our findings that depression treatment is associated with a reduced risk of HF among HIV+ veterans with MDD, although novel and intriguing, should be interpreted

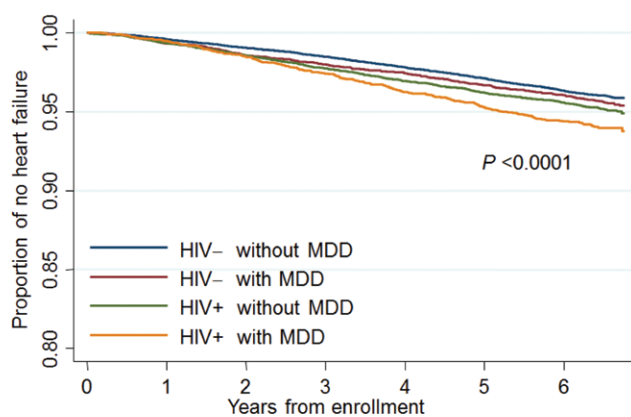


Figure. Kaplan–Meier survival curves for incident heart failure stratified by HIV and major depressive disorder (MDD) status.

AQ9

	Number at risk						
	0	1	2	3	4	5	6
HIV- without MDD	45728	43061	40028	36130	32010	27419	20409
HIV- with MDD	8791	8434	7990	7408	6827	6106	5069
HIV+ without MDD	21850	20299	18320	16247	14226	12204	9717
HIV+ with MDD	5058	4733	4327	3924	3541	3166	2668

Table 5. Rates and aHRs of Incident HF Among Those with Baseline MDD (n=13 849) Stratified by HIV and Baseline Antidepressant Use

HIV Status	Antidepressant Use	n	HF Events	HF Rates per 1000 person-y (95% CI)	P Value	aHR* (95% CI)	P Value
HIV-	Yes	7916	283	6.73 (5.99–7.56)	0.25†	1.00 (Reference)	0.28‡
HIV-	No	875	36	8.25 (5.95–11.44)		1.21 (0.85–1.71)	
HIV+	Yes	4582	206	8.97 (7.82–10.28)	0.055§	1.39 (1.14–1.68)	0.053
HIV+	No	476	28	13.20 (9.11–19.11)		2.07 (1.39–3.08)	

aHR indicates adjusted hazard ratio; CI, confidence interval; HF, heart failure; and MDD, major depressive disorder.

*All models for HF were adjusted for age, sex, race/ethnicity, body mass index, hypertension, diabetes mellitus, lipids, statin use, hemoglobin, renal function, atrial fibrillation, atrial flutter, smoking, alcohol abuse or dependence, cocaine abuse or dependence, and hepatitis C virus infection.

†P value for the comparison of HF rates: HIV- participants who did not use antidepressants at baseline compared with HIV- antidepressant users.

‡P value for the comparison of aHRs: HIV- participants who did not use antidepressants at baseline compared with HIV- antidepressant users.

§P value for the comparison of HF rates: HIV+ participants who did not use antidepressants at baseline compared with HIV+ antidepressant users.

||P value for the comparison of aHRs: HIV+ participants who did not use antidepressants at baseline compared with HIV+ antidepressant users.

with caution. Because this is an observational study and not a randomized, controlled trial, we cannot eliminate confounding resulting from indication associated with the treatment of depression. Moreover, improved HF outcomes may be attributed to more frequent visits with a provider and better management of CVD risk factors and other medical conditions, in addition to MDD treatment. Additionally, only 10% of participants with an MDD diagnosis did not have a prescription for an antidepressant during the baseline period. The high prevalence of treatment is likely a reflection of the fact that MDD in our study was determined by clinical diagnostic codes and not by a formal depression screening instrument administered to all participants. It is likely that some participants with unrecognized depression existed in our non-MDD group. This possible misclassification, however, would lead us to underestimate the strength of the MDD-HF relationship because veterans with unrecognized depression would be included in our referent group.

Conclusions

HIV and MDD are each associated with an increased risk of incident HF. HIV+ veterans with MDD had the highest rates of and risk for HF compared with veterans with HIV, depression, or neither condition. These results suggest that MDD is a possible independent risk factor for HF among HIV+ patients and thus reinforce the importance of screening for and effectively managing depression in this patient population. Future studies in both HIV-infected and -uninfected adults should aim to clarify the mechanisms underlying the depression-HF association and to determine whether evidence-based depression treatment may help to reduce HF morbidity and mortality in these populations.

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Disclosures

None. The views expressed in this article are those of the authors and do not necessarily reflect the position or policies of the VA.

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CLINICAL PERSPECTIVE

Both HIV and depression are associated with heart failure. Depression is a common comorbidity among those with HIV infection. Whether depression among those infected with HIV contributes to an increase risk of heart failure is not known. This study reports that depression is an independent risk factor for heart failure in HIV-infected people. Our findings reinforce the importance of identifying and managing depression among HIV-infected people. Identifying depression in the HIV population may be important for reducing future heart failure events.

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