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

Veterans Aging Cohort Study

Jessica R. White, Dr PH; Chung-Chou H. Chang, PhD; Kaku A. So-Armah, PhD; Jesse C. Stewart, PhD; Samir K. 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 A. Tindle, MD, MPH; Amy C. Justice, MD, MSCE, PhD; Matthew S. Freiberg, MD, MSc

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=81 427: 26 908 HIV+, 54 519 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;132:1630-1638. DOI: 10.1161/CIRCULATIONAHA.114.014443.)**

Key Words: depression ■ epidemiology ■ heart failure ■ HIV

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]

Editorial see p 1602
Clinical Perspective on p 1638

Received December 3, 2014; accepted August 3, 2015.

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.); Hamad Healthcare Quality Institute, Doha, Qatar (A.A.B.); Hamad Medical Corporation, 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, TN (M.S.F.).

The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.114.014443/-/DC1.

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

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 mm Hg and no antihypertensive medication use), controlled (blood pressure <140/90 mm Hg and antihypertensive medication use), and uncontrolled (blood pressure ≥140/90 mm Hg).[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 (mL·min^{-1}·1.73 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 ≥30 kg/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	…	…	36.4	28.8
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 ($P>0.05$).

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-years (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.

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

	HR (95% CI)		
Characteristic	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

	Whites*		Blacks*	
HIV / MDD Group	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

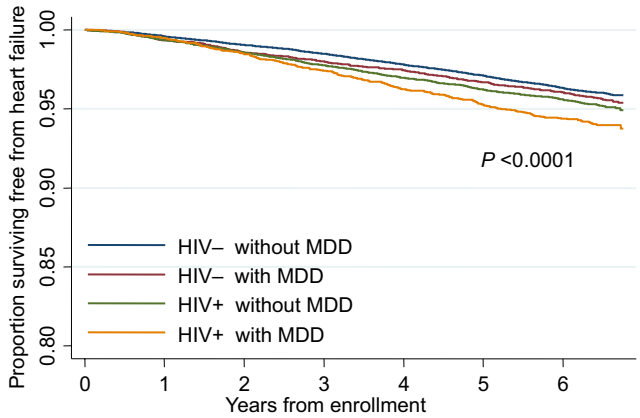
CI indicates confidence interval; HF, heart failure; HR, adjusted hazard ratio; and MDD, major depressive disorder.

*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



Number at risk

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

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

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 an 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.

Sources of Funding

This work was supported by grants HL095136 and HL126557, and T32 Cardiovascular Epidemiology Training Program HL083825 from the National Heart, Lung, and Blood Institute, and grants AA013566, AA020790, and AA020794 from the National Institutes of Health on Alcohol Abuse and Alcoholism.

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.

References

1. Samji H, Cescon A, Hogg RS, Modur SP, Althoff KN, Buchacz K, Burchell AN, Cohen M, Gebo KA, Gill MJ, Justice A, Kirk G, Klein MB, Korthuis PT, Martin J, Napravnik S, Rourke SB, Sterling TR, Silverberg MJ, Deeks S, Jacobson LP, Bosch RJ, Kitahata MM, Goedert JJ, Moore R, Gange SJ; North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) of IeDEA. Closing the gap: increases in life expectancy among treated HIV-positive individuals in the United States and Canada. *PLoS One*. 2013;8:e81355. doi: 10.1371/journal.pone.0081355.
2. Bhaskaran K, Hamouda O, Sannes M, Boufassa F, Johnson AM, Lambert PC, Porter K; CASCADE Collaboration. Changes in the risk of death after HIV seroconversion compared with mortality in the general population. *JAMA*. 2008;300:51–59. doi: 10.1001/jama.300.1.51.
3. Deeks SG, Lewin SR, Havlir DV. The end of AIDS: HIV infection as a chronic disease. *Lancet*. 2013;382:1525–1533. doi: 10.1016/S0140-6736(13)61809-7.
4. Butt AA, Chang CC, Kuller L, Goetz MB, Leaf D, Rimland D, Gibert CL, Oursler KK, Rodriguez-Barradas MC, Lim J, Kazis LE, Gottlieb S, Justice AC, Freiberg MS. Risk of heart failure with human immunodeficiency virus in the absence of prior diagnosis of coronary heart disease. *Arch Intern Med*. 2011;171:737–743. doi: 10.1001/archinternmed.2011.151.
5. Ng B, MacPherson P, Haddad T, Dwivedi G. Heart failure in HIV infection: focus on the role of atherosclerosis. *Curr Opin Cardiol*. 2014;29:174–179. doi: 10.1097/HCO.0000000000000041.
6. Freiberg M, Chang J, Oursler KA, Gottdiener J, Gottlieb S, Warner A, Leaf D, Rodriguez-Barradas M, Felter S, Butt AA. The risk of and survival with preserved vs. reduced ejection fraction heart failure by HIV status. Paper presented at: Conference on Retroviruses and Opportunistic Infections; March 3–6, 2013; Boston, MA.
7. Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, Rush AJ, Walters EE, Wang PS; National Comorbidity Survey Replication. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA*. 2003;289:3095–3105. doi: 10.1001/jama.289.23.3095.
8. Rabkin JG. HIV and depression: 2008 review and update. *Curr HIV/AIDS Rep*. 2008;5:163–171.
9. Ciesla JA, Roberts JE. Meta-analysis of the relationship between HIV infection and risk for depressive disorders. *Am J Psychiatry*. 2001;158:725–730.
10. Whooley MA, Browner WS. Association between depressive symptoms and mortality in older women: Study of Osteoporotic Fractures Research Group. *Arch Intern Med*. 1998;158:2129–2135.
11. Abramson J, Berger A, Krumholz HM, Vaccarino V. Depression and risk of heart failure among older persons with isolated systolic hypertension. *Arch Intern Med*. 2001;161:1725–1730.
12. Williams SA, Kasl SV, Heiat A, Abramson JL, Krumholz HM, Vaccarino V. Depression and risk of heart failure among the elderly: a prospective community-based study. *Psychosom Med*. 2002;64:6–12.
13. Rutledge T, Reis VA, Linke SE, Greenberg BH, Mills PJ. Depression in heart failure a meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. *J Am Coll Cardiol*. 2006;48:1527–1537. doi: 10.1016/j.jacc.2006.06.055.
14. Carney RM, Freedland KE, Veith RC. Depression, the autonomic nervous system, and coronary heart disease. *Psychosom Med*. 2005;67(suppl 1):S29–S33. doi: 10.1097/01.psy.0000162254.61556.d5.

15. Kop WJ, Gottdiener JS. The role of immune system parameters in the relationship between depression and coronary artery disease. *Psychosom Med*. 2005;67(suppl 1):S37–S41. doi: 10.1097/01.psy.0000162256.18710.4a.
16. Bruce EC, Musselman DL. Depression, alterations in platelet function, and ischemic heart disease. *Psychosom Med*. 2005;67(suppl 1):S34–S36. doi: 10.1097/01.psy.0000164227.63647.d9.
17. Fultz SL, Skanderson M, Mole LA, Gandhi N, Bryant K, Crystal S, Justice AC. Development and verification of a "virtual" cohort using the National VA Health Information System. *Med Care*. 2006;44(suppl 2):S25–S30. doi: 10.1097/01.mlr.0000223670.00890.74.
18. van Weel-Baumgarten EM, van den Bosch WJ, van den Hoogen HJ, Zitman FG. The validity of the diagnosis of depression in general practice: is using criteria for diagnosis as a routine the answer? *Br J Gen Pract*. 2000;50:284–287.
19. Trinh NH, Youn SJ, Sousa J, Regan S, Bedoya CA, Chang TE, Fava M, Yeung A. Using electronic medical records to determine the diagnosis of clinical depression. *Int J Med Inform*. 2011;80:533–540. doi: 10.1016/j.ijmedinf.2011.03.014.
20. Lee DS, Donovan L, Austin PC, Gong Y, Liu PP, Rouleau JL, Tu JV. Comparison of coding of heart failure and comorbidities in administrative and clinical data for use in outcomes research. *Med Care*. 2005;43:182–188.
21. Wang TJ, Gona P, Larson MG, Tofler GH, Levy D, Newton-Cheh C, Jacques PF, Rifai N, Selhub J, Robins SJ, Benjamin EJ, D'Agostino RB, Vasan RS. Multiple biomarkers for the prediction of first major cardiovascular events and death. *N Engl J Med*. 2006;355:2631–2639. doi: 10.1056/NEJMoa055373.
22. Lee DS, Gona P, Vasan RS, Larson MG, Benjamin EJ, Wang TJ, Tu JV, Levy D. Relation of disease pathogenesis and risk factors to heart failure with preserved or reduced ejection fraction: insights from the Framingham Heart Study of the National Heart, Lung, and Blood Institute. *Circulation*. 2009;119:3070–3077. doi: 10.1161/CIRCULATIONAHA.108.815944.
23. Kottgen A, Russell SD, Loehr LR, Crainiceanu CM, Rosamond WD, Chang PP, Chambless LE, Coresh J. Reduced kidney function as a risk factor for incident heart failure: the Atherosclerosis Risk in Communities (ARIC) study. *J Am Soc Nephrol*. 2007;18:1307–1315. doi: 10.1681/ASN.2006101159.
24. Kenchaiah S, Evans JC, Levy D, Wilson PW, Benjamin EJ, Larson MG, Kannel WB, Vasan RS. Obesity and the risk of heart failure. *N Engl J Med*. 2002;347:305–313. doi: 10.1056/NEJMoa020245.
25. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ; Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 2003;42:1206–1252. doi: 10.1161/01.HYP.0000107251.49515.c2.
26. Butt AA, Fultz SL, Kwoh CK, Kelley D, Skanderson M, Justice AC. Risk of diabetes in HIV infected veterans pre- and post-HAART and the role of HCV coinfection. *Hepatology*. 2004;40:115–119. doi: 10.1002/hep.20289.
27. Kraemer KL, McGinnis KA, Skanderson M, Cook R, Gordon A, Conigliaro J, Shen Y, Fiellin DA, Justice AC. Alcohol problems and health care services use in human immunodeficiency virus (HIV)-infected and HIV-uninfected veterans. *Med Care*. 2006;44(suppl 2):S44–S51. doi: 10.1097/01.mlr.0000223703.91275.78.
28. 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.
29. McGinnis KA, Brandt CA, Skanderson M, Justice AC, Shahrir S, Butt AA, Brown ST, Freiberg MS, Gibert CL, Goetz MB, Kim JW, Pisani MA, Rimland D, Rodriguez-Barradas MC, Sico JJ, Tindle HA, Crothers K. Validating smoking data from the Veteran's Affairs Health Factors dataset, an electronic data source. *Nicotine Tob Res*. 2011;13:1233–1239. doi: 10.1093/ntr/ntr206.
30. Freiberg MS, Chang CC, Kuller LH, Skanderson M, Lowy E, Kraemer KL, Butt AA, Bidwell Goetz M, Leaf D, Oursler KA, Rimland D, Rodriguez Barradas M, Brown S, Gibert C, McGinnis K, Crothers K, Sico J, Crane H, Warner A, Gottlieb S, Gottdiener J, Tracy RP, Budoff M, Watson C, Armah KA, Doebler D, Bryant K, Justice AC. HIV infection and the risk of acute myocardial infarction. *JAMA Intern Med*. 2013;173:614–622. doi: 10.1001/jamainternmed.2013.3728.
31. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Franco S, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Huffman MD, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Magid D, Marcus GM, Marelli A, Matchar DB, McGuire DK, Mohler ER, Moy CS, Mussolino ME, Nichol G, Paynter NP, Schreiner PJ, Sorlie PD, Stein J, Turan TN, Virani SS, Wong ND, Woo D, Turner MB; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2013 update: a report from the American Heart Association. *Circulation*. 2013;127:e6–e245. doi: 10.1161/CIR.0b013e31828124ad.
32. Bui AL, Horwich TB, Fonarow GC. Epidemiology and risk profile of heart failure. *Nat Rev Cardiol*. 2011;8:30–41. doi: 10.1038/nrcardio.2010.165.
33. Grinspoon SK. Metabolic syndrome and cardiovascular disease in patients with human immunodeficiency virus. *Am J Med*. 2005;118(suppl 2):23S–28S.
34. Riddler SA, Smit E, Cole SR, Li R, Chmiel JS, Dobs A, Palella F, Visscher B, Evans R, Kingsley LA. Impact of HIV infection and HAART on serum lipids in men. *JAMA*. 2003;289:2978–2982. doi: 10.1001/jama.289.22.2978.
35. So-Armah KA, Chang J, Alcorn C, Lo Re V, Baker JV, Tracy R, Butt AA, Agan BK, Rimland D, Gibert CL, Goetz MB, Oursler KK, Rodriguez-Barradas MC, Kuller LH, Brown ST, Stein JH, Skanderson M, Justice AC, Freiberg MS. HIV infection, antiretroviral therapy initiation and longitudinal changes in biomarkers of organ function. *Curr HIV Res*. 2014;12:50–59.
36. Grippo AJ, Johnson AK. Biological mechanisms in the relationship between depression and heart disease. *Neurosci Biobehav Rev*. 2002;26:941–962.
37. Joynt KE, Whellan DJ, O'Connor CM. Depression and cardiovascular disease: mechanisms of interaction. *Biol Psychiatry*. 2003;54:248–261.
38. Sher Y, Lolak S, Maldonado JR. The impact of depression in heart disease. *Curr Psychiatry Rep*. 2010;12:255–264. doi: 10.1007/s11920-010-0116-8.
39. Brion JM, Rose CD, Nicholas PK, Sloane R, Corless IB, Lindgren TG, Wantland DJ, Kemppainen JK, Sefcik EF, Nokes KM, Kirksey KM, Eller L, Hamilton MJ, Holzemer WL, Portillo CJ, Mendez MR, Robinson LM, Moezzi S, Rosa M, Human S, Maryland M, Arudo J, Ros AV, Nicholas TP, Cuca Y, Huang E, Bain C, Tyer-Viola L, Zang SM, Shannon M, Peters-Lewis A, Willard S. Unhealthy substance-use behaviors as symptom-related self-care in persons with HIV/AIDS. *Nurs Health Sci*. 2011;13:16–26. doi: 10.1111/j.1442-2018.2010.00572.x.
40. Aberg JA, Gallant JE, Anderson J, Oleske JM, Libman H, Currier JS, Stone VE, Kaplan JE; HIV Medicine Association of the Infectious Diseases Society of America. Primary care guidelines for the management of persons infected with human immunodeficiency virus: recommendations of the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis*. 2004;39:609–629. doi: 10.1086/423390.
41. Lang UE, Borgwardt S. Molecular mechanisms of depression: perspectives on new treatment strategies. *Cell Physiol Biochem*. 2013;31:761–777. doi: 10.1159/000350094.
42. Stewart JC, Perkins AJ, Callahan CM. Effect of collaborative care for depression on risk of cardiovascular events: data from the IMPACT randomized controlled trial. *Psychosom Med*. 2014;76:29–37. doi: 10.1097/PSY.0000000000000022.
43. Matthews KA, Chang YF, Sutton-Tyrrell K, Edmundowicz D, Bromberger JT. Recurrent major depression predicts progression of coronary calcification in healthy women: Study of Women's Health Across the Nation. *Psychosom Med*. 2010;72:742–747. doi: 10.1097/PSY.0b013e3181eeeb17.
44. Association AP. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: American Psychiatric Association; 2000.
45. Burcusa SL, Iacono WG. Risk for recurrence in depression. *Clin Psychol Rev*. 2007;27:959–985. doi: 10.1016/j.cpr.2007.02.005.

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 increased 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.

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

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

Circulation. 2015;132:1630-1638; originally published online September 10, 2015;
doi: 10.1161/CIRCULATIONAHA.114.014443
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

SUPPLEMENTAL MATERIAL

Supplemental Table 1. List of antidepressants included in study by class*

Class	Generic Name	Brand Name
Selective Serotonin Reuptake Inhibitors (SSRI)	Citalopram	Celexa
	Escitalopram	Lexapro, Cipralex
	Fluoxetine	Prozac, Sarafem
	Fluvoxamine	Luvox
	Paroxetine	Paxil
	Sertraline	Zoloft
Tricyclic Antidepressants (TCA)	Amitriptyline	Elavil, Endep, Levate
	Clomipramine	Anafranil
	Desipramine	Norpramin, Pertofrane
	Dosulepin	Dothiepin, Prothiaden
	Doxepin	Adapin, Sinequan
	Imipramine	Tofranil
	Lofepramine	Feprapax, Gamanil
	Nortriptyline	Pamelor
	Protriptyline	Vivactil
	Trimipramine	Surmontil
Tetracyclic Antidepressant (TeCA)	Amoxapine	Asendin
	Maprotiline	Deprilept, Ludiomil, Psymion
	Mianserin	Bolvidon, Norval, Tolvan
	Mirtazapine	Remeron
Monoamine Oxidase Inhibitors	Isocarboxazid	Marplan

(MAOI)	Moclobemide	Manerix
	Phenelzine	Nardil
	Selegiline	L-Deprenyl, Eldepryl, Zelapar, Emsam
	Tranylcypromine	Parnate
	Pirlindole	Pirazidol
Serotonin-Norepinephrine Reuptake Inhibitor (SNRI)	Desvenlafaxine	Pristiq
	Duloxetine	Cymbalta
	Milnacipran	Savella
	Venlafaxine	Effexor, Effexor XR
Serotonin Antagonist and Reuptake Inhibitor (SARI)	Etoperidone	Axiomin, Etonin
	Lubazodone	YM-992, YM-35,995
	Nefazodone	Serzone, Nefadar
	Trazodone	Desyrel, Apo-Trazodone
Norepinephrine Reuptake Inhibitor (NRI)	Reboxetine	Edronax , Vestra
	Viloxazine	Vivalan
Norepinephrine-Dopamine Reuptake Inhibitor (NDRI)	Bupropion	Wellbutrin, Wellbutrin SR, Wellbutrin XL, Zyban
	Dexmethylphenidate	Focalin
	Methylphenidate	Ritalin, Concerta
Miscellaneous	Tianeptine	Stablon
	Viloxazine	Vivalan
	Tandospirone	Sediel

	Ago melatine	Valdoxan

*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

Supplemental Table 2. The association between HIV, depression and HF and the corresponding percent variance explained for unadjusted, demographic adjusted and fully adjusted models.

Model	R-square (95% bootstrap CI)
HIV/MDD only	0.0104 (0.0050, 0.0164)
HIV/MDD + demographics (age, sex, race)	0.2710 (0.2432, 0.2940)
Full model (in Table 3)	0.4922 (0.4710, 0.5315)

SUPPLEMENTAL MATERIAL

Supplemental Table 1. List of antidepressants included in study by class*

Class	Generic Name	Brand Name
Selective Serotonin Reuptake Inhibitors (SSRI)	Citalopram	Celexa
	Escitalopram	Lexapro, Cipralex
	Fluoxetine	Prozac, Sarafem
	Fluvoxamine	Luvox
	Paroxetine	Paxil
	Sertraline	Zoloft
Tricyclic Antidepressants (TCA)	Amitriptyline	Elavil, Endep, Levate
	Clomipramine	Anafranil
	Desipramine	Norpramin, Pertofrane
	Dosulepin	Dothiepin, Prothiaden
	Doxepin	Adapin, Sinequan
	Imipramine	Tofranil
	Lofepramine	Feprapax, Gamanil
	Nortriptyline	Pamelor
	Protriptyline	Vivactil
	Trimipramine	Surmontil
Tetracyclic Antidepressant (TeCA)	Amoxapine	Asendin
	Maprotiline	Deprilept, Ludiomil, Psymion
	Mianserin	Bolvidon, Norval, Tolvan
	Mirtazapine	Remeron
Monoamine Oxidase Inhibitors	Isocarboxazid	Marplan

(MAOI)	Moclobemide	Manerix
	Phenelzine	Nardil
	Selegiline	L-Deprenyl, Eldepryl, Zelapar, Emsam
	Tranylcypromine	Parnate
	Pirlindole	Pirazidol
Serotonin-Norepinephrine Reuptake Inhibitor (SNRI)	Desvenlafaxine	Pristiq
	Duloxetine	Cymbalta
	Milnacipran	Savella
	Venlafaxine	Effexor, Effexor XR
Serotonin Antagonist and Reuptake Inhibitor (SARI)	Etoperidone	Axiomin, Etonin
	Lubazodone	YM-992, YM-35,995
	Nefazodone	Serzone, Nefadar
	Trazodone	Desyrel, Apo-Trazodone
Norepinephrine Reuptake Inhibitor (NRI)	Reboxetine	Edronax , Vestra
	Viloxazine	Vivalan
Norepinephrine-Dopamine Reuptake Inhibitor (NDRI)	Bupropion	Wellbutrin, Wellbutrin SR, Wellbutrin XL, Zyban
	Dexmethylphenidate	Focalin
	Methylphenidate	Ritalin, Concerta
Miscellaneous	Tianeptine	Stablon
	Viloxazine	Vivalan
	Tandospirone	Sediel

	Ago melatine	Valdoxan

*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

Supplemental Table 2. The association between HIV, depression and HF and the corresponding percent variance explained for unadjusted, demographic adjusted and fully adjusted models.

Model	R-square (95% bootstrap CI)
HIV/MDD only	0.0104 (0.0050, 0.0164)
HIV/MDD + demographics (age, sex, race)	0.2710 (0.2432, 0.2940)
Full model (in Table 3)	0.4922 (0.4710, 0.5315)