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ORIGINAL RESEARCH

Depression as a Risk Factor for Incident Ischemic Stroke Among HIV-Positive Veterans in the Veterans Aging Cohort Study

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BACKGROUND: HIV infection and depression are each associated with increased ischemic stroke risk. Whether depression is a risk factor for stroke within the HIV population is unknown.

METHODS AND RESULTS: We analyzed data on 106 333 (33 528 HIV-positive; 72 805 HIV-negative) people who were free of baseline cardiovascular disease from an observational cohort of HIV-positive people and matched uninfected veterans in care from April 1, 2003 through December 31, 2014. *International Classification of Diseases, Ninth Revision* (*ICD-9*) codes from medical records were used to determine baseline depression and incident stroke. Depression occurred in 19.5% of HIV-positive people. After a median of 9.2 years of follow-up, stroke rates were highest among people with both HIV and depression and lowest among those with neither condition. In Cox proportional hazard models, depression was associated with an increased risk of stroke for HIV-positive people after adjusting for sociodemographic characteristics and cerebrovascular risk factors (hazard ratio [HR], 1.18; 95% CI: 1.03–1.34; 0.014). The depression-stroke relationship was attenuated by alcohol use disorders, cocaine use, and baseline antidepressant use, and unaffected by combined antiretroviral therapy use or individual antiretroviral agents. A numerically higher HR of depression on stroke was found among those younger than 60 years.

CONCLUSIONS: Depression is associated with an increased risk of stroke among HIV-positive people after adjusting for sociodemographic characteristics, traditional cerebrovascular risk factors, and HIV-specific factors. Alcohol use disorders, cocaine use, and baseline antidepressant use accounted for some of the observed stroke risk. Depression may be a novel, independent risk factor for ischemic stroke in HIV, particularly among younger people.

Key Words: combined antiretroviral therapy ■ depression ■ HIV ■ ischemic stroke ■ stroke risk

Given impressive improvement in life expectancy in the era of combined antiretroviral therapy (cART), HIV-positive people are living long enough to develop vascular risk factors associated with aging (eg, hypertension and atrial fibrillation).[1-5] This improved survival also comes with the increased risk of developing measures of subclinical cardiovascular disease (CVD), which tend to be more unfavorable compared with healthy comparators (eg, greater carotid intima-media thickness, greater coronary artery calcification, faster pulse-wave velocity, and poorer endothelial function),[6] and the potential sequelae of living longer with a chronic viral infection, including an HIV-associated chronic inflammatory state. Not surprisingly, being HIV-positive has been independently associated with incident CVD events, including acute myocardial infarction (AMI), congestive heart failure (CHF), peripheral arterial disease, and ischemic stroke.[7-13]

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CLINICAL PERSPECTIVE

What Is New?

- Depression is associated with an increased risk of incident ischemic stroke among veterans living with HIV.

What Are the Clinical Implications?

- Understanding the possible causes by which depression increases the risk of stroke among veterans may help identify opportunities to mitigate stroke risk.
- Whether the results are generalizable to other populations remains unknown.

Nonstandard Abbreviations and Acronyms

cART	combined antiretroviral therapy
VA	Veterans Affairs
VACS	Veterans Aging Cohort Study
VIReC	VA Information Resource Center

Many cerebrovascular risk factors are observed less frequently among HIV-positive versus HIV-negative people (eg, hypertension, diabetes mellitus), suggesting that other factors may increase stroke risk in this patient population.[11] Other potential mechanisms for elevated cerebrovascular risk among HIV-positive patients include direct damage to the arterial wall from HIV viral particles, arterial damage due to chronic inflammation, absence of repair due to loss of CD4+ cells, or secondary effects due to cART, including cART-induced metabolic syndrome[14] and dysfunctional endothelium and platelets.[13,15-17] One potentially modifiable stroke risk factor that has not previously been examined among HIV-positive people is depression.[18]

Depression, one of the most common comorbidities of HIV infection, is predictive of incident AMI and CHF among HIV-positive people.[12,13] Depression is accompanied by many vascular and systemic changes which are hypothesized to underlie the observed relationship between depression and vascular disease. Depression is associated with subclinical measures of vascular disease among HIV-positive people.[19] Moreover, systemic changes occurring in response to chronic stress are altered in depression, including growth factors, inflammatory markers, endocrine markers, and metabolic markers.[20] In addition to physiological changes, depression is associated with maladaptive behavioral changes, such as decreased treatment adherence, physical inactivity, poor dietary habits, and cigarette smoking, all of which can contribute to vascular risk.[18,19,21-23] Some cART regimens have been linked with depression.[24]

Data regarding the potential relationship between depression and stroke risk in HIV are nonexistent. Studies conducted in the general population have demonstrated an independent association between depression and future ischemic stroke.[18,21-23] The presence of stable high depressive symptoms was predictive of incident stroke among younger but not older people, suggesting a moderating effect of age on depression-stroke risk relationship in the general population.[18,23]

Although HIV and depression share physiological pathways that increase stroke risk and despite depression having been shown to increase AMI and CHF risk in HIV, current literature lacks observational studies examining whether depression similarly increases ischemic stroke risk in people living with HIV. To address this knowledge gap, we tested the prospective association between depression and incident ischemic stroke in HIV-positive people from the VACS (Veterans Aging Cohort Study), while exploring potential influences of age, antidepressant medication, and cART use on the depression-stroke risk relationship.

METHODS

Data Availability Statement

Due to Veterans Affairs (VA) regulations and our ethics agreements, the analytic data sets used for this study are not permitted to leave the VA firewall without a Data Use Agreement. This limitation is consistent with other studies based on VA data. However, VA data are made freely available to researchers with an approved VA study protocol. For more information, please visit https://www.virec.research.va.gov or contact the VA Information Resource Center at VIReC@va.gov.

Study Sample

The VACS virtual cohort is a prospective, multisite cohort of HIV-positive adults and age, race/ethnicity, and clinical site matched to 2 HIV-negative adults enrolled in the same calendar year in the US Department of VA system.[25] Participants in VACS have been continually selected for inclusion since 1998 by using an existing validated algorithm from the VA national electronic medical record system. Baseline was defined as the date of a participant's first clinic visit on or after April 1, 2003. The participants were followed up from their baseline date until an ischemic stroke event, death, the date of last follow-up, or censored on December 31, 2014. The University of Pittsburgh, Yale University, and West Haven VA Medical Center institutional review boards approved this study. Subject informed consent was waived.

For the current analysis, participants with prevalent CVD (ie, coronary heart disease, AMI, cardiovascular revascularization, heart failure, or stroke [ischemic/hemorrhagic]) at baseline (n=22 712) and those who seroconverted during the follow-up period (n=589) were excluded. The final analytic sample consisted of 106 333 veterans (33 528 HIV-positive; 72 805 HIV-negative).

Independent and Stratifying Variables

Depression at baseline was defined as a diagnosis of major depressive disorder (at least one inpatient or 2 outpatient *International Classification of Diseases, Ninth Revision* [*ICD-9*] codes 296.2 or 296.3) or dysthymic disorder (*ICD-9* code 300.4).[12,26] HIV was defined as at least one inpatient or 2 outpatient *ICD-9* codes for HIV in the VA Immunology Case Registry. Baseline HIV infection was defined as participants having ≥1 inpatient and/or ≥2 outpatient *ICD-9* codes for the diagnosis. The algorithm has a high sensitivity (90%), specificity (99.9%), and positive predictive value (88%) in identifying HIV-positive participants.[3] The HIV-specific factors of HIV-1 RNA level and CD4 cell count were obtained from the VA Corporate Data Warehouse, whereas cART use (yes/no) obtained through pharmacy data as part of clinical care within a window of 180 days before baseline through 7 days post baseline. Participants were categorized into 4 groups: HIV-positive with depression, HIV-positive without depression, HIV-negative with depression, and HIV-negative without depression (reference group).

Dependent Variable

The primary outcome of this study was incident ischemic stroke, which was defined as at least one inpatient or 2 outpatients *ICD-9* codes from medical records for any of the following conditions: occlusion and stenosis of precerebral arteries (433.x1), occlusion of cerebral arteries excluding thrombosis/embolism without infarction (434, excluding 434.x0), and acute but ill-defined cerebrovascular disease (436).[11]

Covariates

Covariates were obtained closest to the baseline date and have been previously described.[9,27] Briefly, sociodemographic variables of age, sex, and race/ethnicity were determined through administrative data. Hypertension was categorized as "no hypertension" (<140/90 mm Hg and no antihypertensive medication), "controlled hypertension" (<140/90 mm Hg with antihypertensive medication), or "uncontrolled hypertension" (≥140/90 mm Hg).[28] Blood pressure was defined by averaging 3 routine outpatient systolic blood pressure and diastolic blood pressure measurements. Low-density lipoprotein cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were obtained from laboratory data. Statin use was defined as a prescription receipt of a 3-hydroxy-3-methyl-glutaryl-coenzyme A reducatase inhibitor from pharmacy records from the participant's baseline enrollment date.[11] Diabetes mellitus (yes/no) was identified using a previously validated metric that incorporates glucose measurements, hemoglobin A1c, antidiabetic agent use, and/or at least one inpatient or 2 outpatient *ICD-9* codes for diabetes mellitus.[29] Body mass index, calculated as kg/m^2, was assessed using the VA Health Factor Dataset. Estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation based on outpatient and clinical laboratory data.[30] Hemoglobin levels were obtained from laboratory data. Histories of atrial fibrillation, alcohol use disorders (ie, alcohol abuse or dependence), and cocaine use were defined using *ICD-9* codes.[9,11] Smoking status was categorized as never, current, or past and obtained from the VA Health Factor Dataset.[31] Hepatitis C virus seropositivity (yes/no) was defined as a positive Hepatitus C virus antibody test result or at least one inpatient or 2 outpatient *ICD-9* codes. Baseline antidepressant use was defined as documentation of a filled prescription for a selective serotonin uptake inhibitor, a tricyclic antidepressant, or another antidepressant type from VA pharmacy records within 180 days of baseline enrollment date.

Statistical Analysis

Baseline characteristics are presented in groups defined by depression status and HIV status. We report means (SD) for continuous variables and frequencies (percentage) for categorical variables. We constructed Kaplan-Meier event-free survival curves, including the number of patients at risk and the number of censored patients, and performed log-rank tests to compare the various groups. We calculated incident rates per 1000 person-years stratified by age category. Separately, we constructed Cox proportional hazards regression models to estimate the adjusted hazard ratio (aHR) and 95% CIs for the association between depression and incident ischemic stroke. Cox PH modeling was not used to calculated incident rates. We constructed several models stratified by HIV status: (1) Model One: adjusting sociodemographic factors (ie, age, sex, and race/ethnicity); (2) Model Two: Model One plus CVD risk factors (ie, SBP, DBP, LDL cholesterol, HDL cholesterol, triglycerides, statin use, diabetes mellitus, body mass index, smoking status, estimated glomerular filtration rate, hemoglobin, and Hepatitis C virus); (3) Model Three: Model Two plus atrial fibrillation; (4) Model Four: Model Three plus HIV-specific factors (ie, HIV-1 RNA level, CD4 cell count, and cART use); (5) Model Five: Model Three plus alcohol use disorders;

(6) Model Six: Model Three plus cocaine use; (7) Model Seven: Model Three plus alcohol use disorders and cocaine use; (8) Model Eight: Model Three plus antidepressant medication use. Model Three served as the primary model for this analysis. Continuous predictors were modeled using restricted cubic splines with 3 knots to allow a nonlinear relationship between the variable and outcome. To investigate age as a potential moderator of the relationship between depression-incident stroke, we included a depression x age interaction term in Models One, Two, and Three. We report the *P* value of interactions and present the data graphically.

The proportional hazards assumption was tested by the Schoenfeld residuals and including the interaction term of the covariates by time as evaluated by the "cox.zph" function in R. To handle missing values, multiple imputations using chained equations with 5 separate imputed data sets were generated based on predictive mean matching using the "mice" library of R programming language. Multiple imputations were made for missing values. Participants without an ischemic stroke or death were censored at the end of the study (see Online data supplement). Cox survival models were fitted in each imputed data set and then combined to obtain pooled hazard ratios and standard errors. Variation inflation factors were calculated to assess for multicollinearity between depression and antidepressant use variables in Model Eight. All analyses were performed using R software (version 3.3.3; www.r-project.org).

RESULTS

The prevalence of depression at baseline in our cohort was 19.0% overall and was similar among HIV-positive and HIV-negative people (19.5% versus 18.8%, respectively). Percentages of people in the 4 groups were 6.2% for HIV-positive with depression, 25.4% for HIV-positive without depression, 12.9% for HIV-negative with depression, and 55.6% for HIV-negative without depression (Table 1).

During a median of 9.2 (25th–75th percentile, 5.2–11.5) follow-up years, there were 4355 incident stroke events and an overall stroke rate per 1000 person-years of 5.0 (4.9–5.2). Incident stroke rates were highest among HIV-positive participants with depression and lowest among HIV-negative participants without depression (Table 2). Kaplan-Meier event-free survival curves in Figure 1 depict time to first incident ischemic stroke, with HIV-positive people with depression having the poorest stroke-free survival of all 4 groups (*P* value of log-rank test: 0.001). It is worth noting that, while we detected statistically significant group differences, the absolute group differences in stroke-free survival were modest.

Cox models adjusted for sociodemographic factors demonstrated that HIV-positive people with depression, compared with HIV-positive people without depression, had a 22% higher risk of incident stroke (aHR, 1.22; 95% CI, 1.07–1.38; 0.003; Table 3, Model One). A similar statistically significant, though mildly attenuated, association persisted after further adjusting for cerebrovascular disease risk factors (aHR, 1.18; 95% CI, 1.03–1.34; 0.014, Model Three) and HIV-specific factors (aHR, 1.18; 95% CI, 1.03–1.35; 0.014, Model Four). The association between depression and incident ischemic stroke in HIV-positive people was modestly attenuated and fell short of statistical significance when alcohol use disorders and cocaine use were added to Model Three separately (Models Five and Six, respectively) and both within the same model (Model Seven). The association between depression and ischemic stroke risk in unadjusted and adjusted models showed similar effect sizes and degree of attenuation between HIV-positive and HIV-negative people.

In separate supplemental models, we also sought to explore the potential influences of age, antidepressant medication, and specific ARTs on the depression-incident stroke relationship. We explored whether age moderated the relationship between depression and incident stroke by testing for interaction terms and using a graphical approach. Among HIV-positive people, age was not a statistically significant moderator of the relationship between depression and stroke risk (Model One [*P*=0.190], Model Two [*P*=0.175], Model Three [*P*=0.145], Table 3, footnote[§]). However, when displayed graphically, a declining association between depression and incident stroke as age increases was evident. Moreover, the depression-stroke risk association was significant for people younger than 60 years but not older (Figure 2).

When baseline antidepressant use was added to Model Three, the previously statistically significant association between depression and incident stroke in HIV-positive people fell just short of significance (aHR, 1.16; 95% CI, 1.00–1.36; *P*=0.055; Model Eight, Table 3). Of note, there was no evidence of multicollinearity among the depression and antidepressant use variables in this model (see variation inflation factors in Table 3, footnote[‖]).

The addition of HIV specific factors to Model Three showed results similar to our primary model (aHR, 1.18; 95% CI, 1.04–1.35; *P*=0.011; Model Four, Table 3). To explore influence of specific ARTs having mechanisms that may confer increased cerebrovascular risk,[15-17,32] we reran Model Three and replaced all cART use with efavirenz and abacavir use. While the depression-incident stroke relationship remained significant in these models, there was no statistically significant association between specific cART agents and stroke risk (Table S1).

Table 1. Baseline Characteristics of VACS Virtual Cohort, N=106 333

Factor	HIV Positive (n=33 528)		HIV Negative* (n=72 805)	
	With Depression (n=6554)	Without Depression (n=26 974)	With Depression (n=13 713)	Without Depression (n=59 092)
Age, y, mean (SD)†	48.0 (8.5)	48.4 (10.2)	48.9 (7.9)	49.3 (10.1)
Sex, male	6246 (95.3)	26 323 (97.6)	13 079 (95.4)	57 463 (97.2)
Race/ethnicity				
White	2809 (42.8)	10 204 (37.8)	5612 (40.9)	22 086 (37.4)
Black§	3017 (46.1)	13 539 (50.2)	6552 (47.8)	29 394 (49.7)
Hispanic	603 (9.2)	2094 (7.8)	1308 (9.5)	5093 (8.6)
Other	125 (1.9)	1138 (4.2)	241 (1.8)	2529 (4.3)
Hypertension				
None	2717 (41.5)	13 097 (48.6)	4195 (30.6)	20 426 (34.6)
Controlled	2344 (35.8)	7185 (26.6)	5471 (39.9)	18 566 (31.4)
Uncontrolled	1442 (22.0)	6254 (23.2)	3777 (27.5)	16 958 (28.7)
SBP, mm Hg, median (Q1, Q3)†	128.0 [119.0, 137.7]	128.3 [119.0, 138.0]	130.7 [121.7, 140.3]	132.0 [123.0, 141.3]
DBP, mm Hg, median (Q1, Q3)	78.0 [72.0, 84.3]	78.0 [71.7, 84.3]	79.3 [73.3, 85.7]	79.3 [73.3, 85.7]
Hyperlipidemia				
LDL cholesterol, mg/dL				
<100	2537 (38.7)	9993 (37.0)	3655 (26.7)	14 278 (24.2)
100–129	1654 (25.2)	6317 (23.4)	3675 (26.8)	15 034 (25.4)
130–159	827 (12.6)	3511 (13.0)	2375 (17.3)	10 145 (17.2)
≥160	410 (6.3)	1636 (6.1)	1297 (9.5)	5307 (9.0)
HDL cholesterol, mg/dL				
<40	2863 (43.7)	11 024 (40.9)	4450 (32.5)	16 780 (28.4)
40–59	2031 (31.0)	8290 (30.7)	5182 (37.8)	21 633 (36.6)
≥60	626 (9.6)	2451 (9.1)	1515 (11.0)	6867 (11.6)
Triglyceride, mg/dL ≥150	2753 (42.0)	9938 (36.8)	4617 (33.7)	16 640 (28.2)
Statin use	994 (15.2)	3646 (13.5)	3474 (25.3)	13 746 (23.3)
Diabetes mellitus	721 (11.0)	2413 (8.9)	2253 (16.4)	8800 (14.9)
BMI, kg/m^{2}† ≥30	1112 (17.0)	3966 (14.7)	5231 (38.1)	21 739 (39.8)
Atrial fibrillation	68 (1.0)	234 (0.9)	145 (1.1)	557 (0.9)
Smoking‡				
Current	3146 (48.0)	9717 (36.0)	6322 (46.1)	19 071 (32.3)
Former	698 (10.6)	2797 (10.4)	1632 (11.9)	6965 (11.8)
Never	1058 (16.1)	5373 (19.9)	2544 (18.6)	13 479 (22.8)
Substance use				
Alcohol use disorder	3300 (50.4)	5299 (19.6)	7110 (51.8)	12 372 (20.9)
Cocaine use	2546 (38.8)	3887 (14.4)	4501 (32.8)	6562 (11.1)
eGFR mL/min per 1.73 m^2 <60	333 (5.1)	1591 (5.9)	510 (3.7)	2413 (4.1)
Anemia (hemoglobin <12 g/dL)‡	719 (11.0)	3198 (11.9)	482 (3.5)	1796 (3.0)
Hepatitis C	2557 (39.0)	7398 (27.4)	2840 (20.7)	6358 (10.8)
HIV specific factors				
HIV 1 RNA*, copies/mL ≥500	3133 (47.8)	12 335 (45.7)	…	…
CD4 cell count*, mm^3				
<200	1183 (18.1)	5525 (20.5)	…	…
211–499	2330 (35.6)	9457 (35.1)	…	…
≥500	2074 (50.2)	7635 (28.3)	…	…
cART*	3288 (50.2)	11 760 (43.6)	…	…

(*Continued*)

Table 1. Continued

Factor	HIV Positive (n=33 528)		HIV Negative* (n=72 805)	
	With Depression (n=6554)	Without Depression (n=26 974)	With Depression (n=13 713)	Without Depression (n=59 092)
Integrase inhibitor use*	42 (0.6)	334 (1.2)	…	…
Efavirenz*	900 (13.7)	4442 (16.5)	…	…
Abacavir*	1398 (21.3)	4707 (17.5)	…	…
Antidepressant medication use				
SSRI	4833 (73.7)	5299 (19.6)	10 136 (73.9)	10 789 (18.3)
TCA	1786 (27.3)	3243 (12.0)	3447 (25.1)	6201 (10.5)
Miscellaneous	4460 (68.1)	5102 (18.9)	9533 (69.5)	11 027 (18.7)

BMI indicates body mass index; cART, combined antiretroviral therapy; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; and VACS, Veterans Aging Cohort Study.

*Because HIV-uninfected veterans do not have HIV-specific biomarkers or antiretroviral therapy regimens, these cells contain a dashed line.

†Data represent mean (SD) for continuous variables and n (%) for categorical variables.

‡The following variables include fewer than 106 333 patients because of missing data (n missing): hypertension (3901, 3.7 %), SBP (3901, 3.7%), DBP (3901, 3.7%), LDL cholesterol (23 682, 22.3%), HDL cholesterol (22 621, 21.3%), triglycerides (22 164, 20.8%), BMI (6568, 6.2%), smoking (33 531, 31.5%), eGFR (10 315, 9.7%), hemoglobin (10 734, 10.1%), HIV-1 RNA (5299, 15.8% of HIV-positive people), and CD4 cell count (5324, 15.9% of HIV-positive people).

§Other includes Indian, Black, Asian, mixed race, Hawaiian, and missing.

DISCUSSION

In a large sample of veterans with 9 years of follow-up, the presence of a depressive disorder at baseline was associated with an 18% increased risk of ischemic stroke among HIV-positive people after adjusting for sociodemographic characteristics, cerebrovascular disease risk factors, and HIV-specific factors, with people living with both depression and HIV having the highest stroke risk compared with people with one or neither of these conditions. Adjustment for alcohol use disorders and cocaine use, both individually and in combination, attenuated the association between depression and stroke risk, suggesting that these factors account for some of the depression-incident stroke relationship. In considering supplemental models, while the interaction terms between age and depression were not statistically significant, graphical displays suggest a declining association between depression and incident stroke as age increases. In addition, the depression-stroke risk relationship was present in people younger than 60 years but not in those older than 60 years. Baseline antidepressant use slightly attenuated the relationship, whereas cART use did not alter the depression-stroke relationship. The association between depression and ischemic stroke showed similar effect sizes between those with and without HIV were similar. Altogether, our findings suggest that: (1) depression may be a novel independent risk factor for ischemic stroke in people living with HIV; (2) alcohol use disorders, cocaine use, and antidepressant use may serve as areas of future research to determine prospectively how addressing

Table 2. Number and Incident Rates of Ischemic Stroke

Age, y	Overall	HIV Positive		HIV Negative	
		With Depression	Without Depression	With Depression	Without Depression
Number of ischemic strokes					
20–40	186/17 521	21/1069	66/4973	33/1738	66/9732
40–50	1220/39 578	133/2795	283/9630	199/5721	605/21 432
50–60	1924/37 129	123/2271	470/9026	303/5377	1028/20 455
60–96	1025/12 114	36/419	264/3345	79/877	646/7473
Overall	4355/106 333	313/6554	1083/26 974	614/13 713	2345/59 092
Incident rate*					
20–40	1.3 (1.2–1.5)	2.3 (1.5–3.4)	1.7 (1.3–2.1)	2.1 (1.5–3.0)	0.9 (0.7–1.1)
40–50	3.6 (3.4–3.8)	5.5 (4.6–6.5)	3.6 (3.2–4.1)	3.8 (3.3–4.3)	3.2 (3.0–3.5)
50–60	6.4 (6.1–6.7)	7.0 (5.8–8.3)	7.1 (6.5–7.8)	6.5 (5.8–7.2)	6.0 (5.6–6.4)
60–96	12.1 (11.4–12.9)	13.4 (9.5–18.2)	12.4 (10.9–13.9)	12.8 (10–15.6)	11.9 (11–12.8)
Overall	5.0 (4.9–5.2)	5.8 (5.2–6.5)	5.3 (5–5.6)	5.1 (4.7–5.5)	4.8 (4.6–5.0)

*Incident rate is per 1000 person-years.

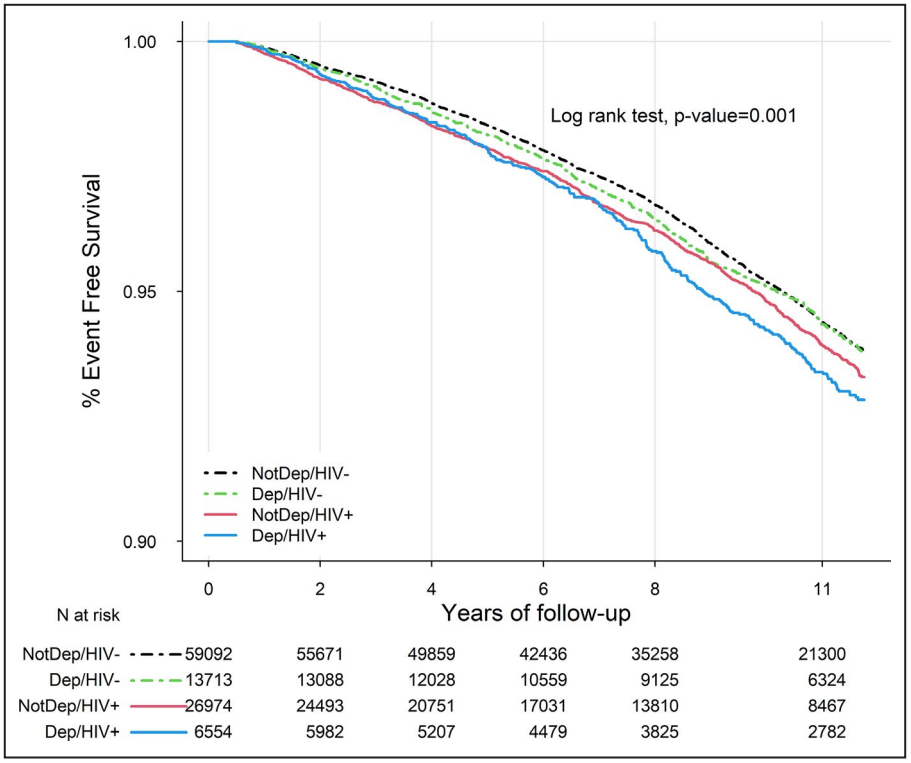

Figure 1. Unadjusted Kaplan-Meier survival curves of ischemic stroke by depression and HIV status.
Dep indicates depressed; and NotDep, not depressed.

substance use and treating depression and may mitigate stroke risk; (3) the depression-incident stroke relationship may be more important in younger people; (4) cART and specific cART agents that theoretically may increase stroke risk are not associated with increased stroke risk, and; (5) other HIV specific factors, including HIV status, CD4 count, and viral load may not strongly influence the depression-incident stroke association.

When considering the ke risk factors as hypertension, diabetese, there is pronounced need to effectively treat known risk factors and to identify novel and underappreciated contributors to stroke risk.[5,21] In the era of cART, HIV-positive people are living longer[2,3] and are at increased risk of developing clinically important vascular events (eg, AMI, CHF, peripheral arterial disease, ischemic stroke),[7,9-13,33] subclinical CVD (eg, endothelial dysfunction),[6] and conditions associated with increased cerebrovascular risk (eg, hypertension).[1,5] HIV has previously been independently associated with ischemic stroke in VA-based[3] and community cohorts.[10,34] Ours is the first study to examine the association between depression, incident ischemic stroke, and HIV status in a large, national, contemporary cohort, while adjusting for sociodemographic characteristics, known cerebrovascular risk factors, HIV-specific factors, alcohol and cocaine use, and antidepressant use.

Mechanisms underlying the association between depression and incident ischemic stroke among HIV-positive people have not been thoroughly investigated though likely are multifactorial. Chronic HIV infection has been associated with a chronic, systemic inflammatory state, coagulopathies, platelet dysfunction, CD4 cell depletion with resultant lack of vascular repair, cART associated dyslipidemia, and direct vascular damage by HIV.[8,9,11,14,35] While our results support the hypothesis that depression increases stroke risk among HIV-positive people, this association was attenuated by controlling for alcohol and cocaine use. The American Heart Association/American Stroke Association Primary Prevention of Ischemic Stroke Guidelines consider alcohol and illicit drugs, including cocaine, "less well documented or potentially modifiable risk factors," in part because of the complexities of their association with stroke risk and comorbidity with depression. Alcohol use disorders are associated with increased risk of developing such stroke risk factors as hypertension, diabetes mellitus, hyperlipidemia, cardiomyopathy, and atrial fibrillation and is known to modulate platelet aggregation, impair synthetic liver function, cause hyperhomocysteinemia, and predispose to thromboembolism.[36] A "J shape" association between alcohol consumption and ischemic stroke risk has been described in the HIV-negative population,

Table 3. Cox Proportional Hazard Models Predicting Incident Ischemic Stroke Stratified by HIV Status*,†

	HIV Positive‡		HIV Negative§	
	HR [95% CI]	*P* Value	HR [95% CI]	*P* Value
Model one: sociodemographic factors‖				
With depression	1.22 [1.07–1.38]	0.003	1.15 [1.05–1.26]	0.002
Without depression	1.0	…	1.0	…
Model two: model one+CVD risk factors¶				
With depression	1.19 [1.04–1.35]	0.010	1.11 [1.02–1.22]	0.023
Without depression	1.0	…	1.0	…
Model three: model two+atrial fibrillation#				
With depression	1.18 [1.03–1.34]	0.014	1.11 [1.01–1.22]	0.026
Without depression	1.0	…	1.0	…
Model four: model three+HIV-specific factors**				
With depression	1.18 [1.04–1.35]	0.011	…	…
Without depression	1.0	…	…	…
Model five: model three+alcohol use disorders††				
With depression	1.10 [0.96–1.25]	0.180	1.04 [0.95–1.15]	0.388
Without depression	1.0	…	1.0	…
Model six: model three+cocaine use‡‡				
With depression	1.13 [0.99–1.30]	0.066	1.08 [0.99–1.19]	0.093
Without depression	1.0	…	1.0	…
Model seven: model three+alcohol use disorders, and cocaine use§§				
With depression	1.10 [0.96–1.26]	0.162	1.04 [0.95–1.15]	0.367
Without depression	1.0	…	1.0	…
Model eight: model three+antidepressant medication use variables‖‖				
Depression	1.16 [1.00–1.35]	0.056	0.97 [0.87–1.08]	0.607
Without depression	1.0	…	1.0	…

CVD indicates cardiovascular disease; and HR, hazard ratio.

*All covariates were measured at baseline. In HIV-positive people, N=33 528 (ischemic stroke, n=1396). In HIV-negative people, N=72 805 (ischemic stroke, n=2959). For continuous predictors, restricted cubic splines with 3 knots were applied in order to allow a nonlinear relationship between the covariate and outcome. For variables with missing values multiple imputations with 5 imputed data sets were generated based on predictive mean matching method using "mice" library of R programming language.

†*P* values of interaction between HIV status and depression: 0.503 (Model One), 0.460 (Model Two), 0.445 (Model Three).

‡*P* values of interaction between age and depression among HIV-positive people: 0.190 (Model One), 0.175 (Model Two), and 0.145 (Model Three).

§*P* values of interaction between age and depression among HIV-negative people: 0.417 (Model One), 0.337 (Model Two), 0.333 (Model Three). As HIV-uninfected people do not have HIV-specific biomarkers or antiretroviral therapy regimens, these cells contain a dashed line.

‖Model one: adjusted for sociodemographic factors (ie, age, sex, and race/ethnicity).

¶Model two: adjusted for variables in Model One and CVD risk factors (ie, systolic blood pressure [SBP], diastolic blood pressure [DBP], low-density lipoprotein [LDL] cholesterol, high-density lipoprotein [HDL] cholesterol, triglycerides, statin use, diabetes mellitus, BMI, smoking status, estimated glomerular filtration rate [eGFR], hemoglobin, and hepatitis C infection).

#Model three: adjusted for variables in model two and atrial fibrillation.

**Model four: adjusted for variables in model three and HIV-specific factors (ie, viral load, CD4 count, and antiretroviral therapy).

††Model five: adjusted for variables in model three and alcohol use disorders.

‡‡Model six: adjusted for variables in model three and cocaine use.

§§Model seven: adjusted for variables in model three and alcohol use disorders, and cocaine use.

‖‖Model Eight: adjusted for variables in model three and the three antidepressant medication use variables (ie, selective serotonin uptake inhibitor [SSRI] use, tricyclic antidepressant [TCA] use, and miscellaneous antidepressant use). Variance inflation factors (VIF) were calculated to determine whether multicollinearity existed between the depression and antidepressant use variables. VIFs from Model 8: For HIV-positive: depression: 1.5; SSRI: 1.4; TCA: 1.1; miscellaneous antidepressant: 1.4. For HIV-negative: depression 1.4; SSRI: 1.5; TCA: 1.1; miscellaneous antidepressant: 1.5. As VIFs were <10, there was no evidence of multicollinearity.

with alcohol having a protective effect at low and moderate levels of consumption and a noxious effect at higher levels.[37] Cocaine use has also been linked to factors increasing stroke risk, including reversible vasospasm, hypertensive surges, drug-induced arteritis, cardiac arrhythmias, cardiomyopathy, increased platelet aggregation, and thromboembolism.[38] Higher rates of unhealthy alcohol and cocaine use have been described in both depressed[39,40] and HIV-positive populations.[9,12,13] Increased stroke risk among people with depression and HIV using alcohol and/or cocaine may also be explained by poorer medication adherence, less healthy behavior modification, toxic effects of alcohol on multiple aspects of physiology and vascular

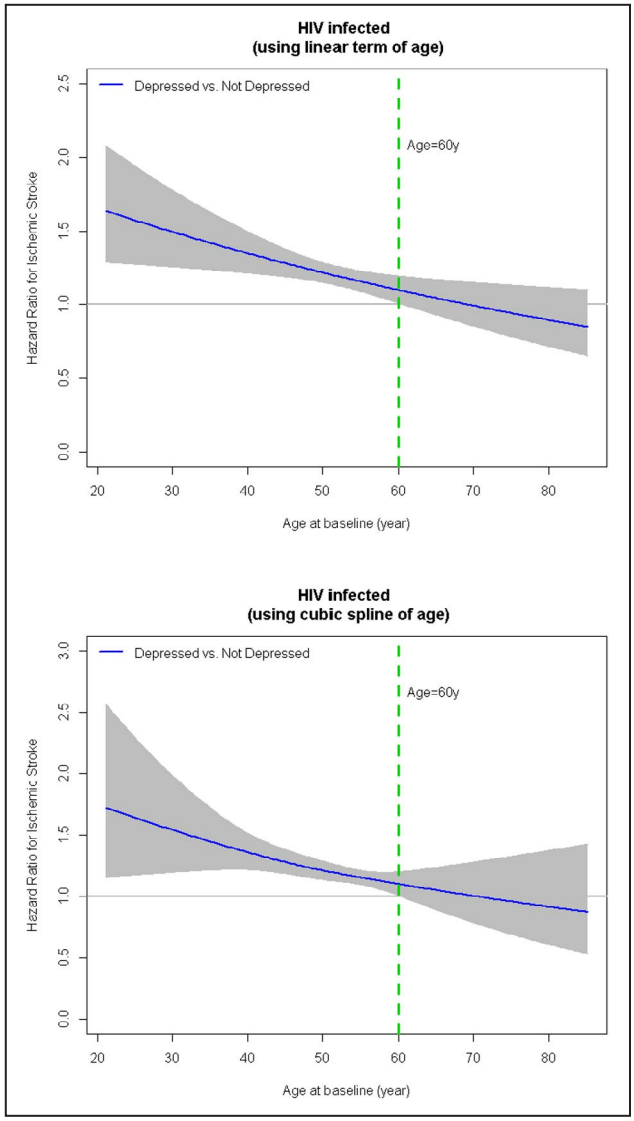

Figure 2. Effect of depression on stroke risk across age strata.
Graphic depiction of the effect of depression on stroke risk across age strata to explore age as a potential moderator of the depression-incidence stroke relationship.

health, and increased rates of other vascular risk conditions (eg, smoking).[41] Given that many of these vascular risk factors are not specific to HIV, cART was not associated with increased stroke risk, and the effect sizes from Cox models were similar between those with and without HIV, it appears that most of the association between depression and stroke risk is not driven by HIV or HIV-specific factors.

Depression has been associated with incident stroke in the general population. A meta-analysis of 17 prospective studies involving 206 641 participants and 6086 stroke cases demonstrated a positive association between depression and subsequent stroke risk (pooled relative risk, 1.34; 95% CI, 1.17–1.54) after adjustment for potential confounders.[21] Another meta-analysis and systematic review of 28 prospective studies involving 317 540 participants and 8478 reported stroke cases also demonstrated, among 6 studies focusing on ischemic stroke, a positive association between depression and ischemic stroke (pooled aHR ratio: 1.25; 95% CI, 1.11–1.40). Also like HIV-infection, depression has been associated chronic inflammation, platelet dysfunction, dysregulation of both the autonomic nervous system and hypothalamic-pituitary-adrenal axis, and the development of atherosclerosis, hypertension, diabetes mellitus, and arrhythmias.[21,42-46] Behavioral mechanisms seen with increasing frequency among people with depression may also contribute to increase stroke risk, including sedentary lifestyle, cigarette smoking, and poorer medication adherence.[5,21] In our current analysis, while some risk factors occurred more commonly among HIV-positive people with depression (eg, hypertension), others occurred similarly across groups (eg, atrial fibrillation). Combining these results with the findings that adjusting for cerebrovascular risk factors did not attenuate the observed depression-stroke risk association suggests that depression does not solely operate through increasing the prevalence of established vascular risk factors.

Age is a well-described, non-modifiable risk factor for incident ischemic stroke.[1,5] Outside of the HIV literature, people with stable high depressive symptoms aged 50 to 64 years have been reported to have the highest risk of incident stroke (aHR, 1.87; 95% CI, 1.10–3.16), whereas those ≥65 years with a similar degree of depression demonstrated no increased stroke risk (aHR, 1.32; 95% CI, 0.99–1.77).[22] Similarly, among a cohort of 3852 stroke-free people older than 55 years of age, baseline depression was associated with increased stroke risk (aHR, 2.84; 95% CI, 1.11–7.29) among people aged 55 to 64 years but not among people older than 65 years (aHR, 1.20; 95% CI, 0.80–1.79).[23] Conversely, a meta-analysis and systematic review of depression and stroke risk conducted across 28 prospective studies containing 317 540 people found positive associations between depression and stroke risk among those <65 years and those ≥65 years. Of note, the association was more pronounced among younger people.[18] We similarly report that depression may have a greater association with incident stroke among younger people living with HIV.

In HIV-positive people, we found that the association between depression and incident stroke was slightly attenuated after adjustment for baseline antidepressant use. Interestingly, a meta-analysis conducted on depression and stroke risk commented that, "it is expected that depression treatment would reduce the risk of development of stroke."[21] However, the literature does not completely support

this contention. One case-control study reported an increased risk of incident stroke among patients receiving pharmacological treatments for depression.[47] This relationship, however, may have been confounded by depression severity, given that patients with more severe depression are more likely to receive pharmacological treatment. In our analysis, we present information for baseline antidepressant medication use, rather than information related to longitudinal medication adherence or depression severity. Noting the limitations of the current data, while it would be premature for this observational study to claim that pharmacologic treatment of depression reduces stroke risk, it does suggest the need for randomized controlled trial data to address whether successful treatment of depression reduces stroke risk among HIV-positive people.

The strengths of our study include the larger sample size, the longer follow-up period, and ability to control for many potential confounders. Limitations of the current work should also be noted. First, given that this is an observational study, we cannot completely exclude unmeasured or residual confounding, and we can only comment on association rather than causation. Second, given the use of *ICD-9* codes to identify depression and stroke, misclassification could have occurred, although stroke *ICD-9* codes have been shown to be sensitive and specific within the Veteran population and have high agreement with formally adjudicated stroke outcomes.[11,48] Depression misclassification may have occurred; however, if we classified some patients as not having a depressive disorder when they did have one, this would have biased our results towards the null and may have attenuated the depression-incident stroke relationship.[13] Third, we did not review imaging data on all patients diagnosed with an ischemic stroke. As such, we do not know the cause of ischemic stroke or stroke subtype, as these are not routinely available in administrative data. Fourth, these data are applicable to incident stroke rather than recurrent ischemic stroke. Finally, as our cohort is comprised of predominantly male veterans, these results may less generalizable to other populations.

In conclusion, we used a large, contemporary database to conduct the first prospective cohort study to determine whether there is an independent association between depression and incident ischemic stroke in people with HIV. While depression has been associated with incident AMI and CHF among people with and without HIV, and though HIV has been associated with incident ischemic stroke, studies examining the association between depression and incident stroke within the HIV-positive population are lacking. Ischemic stroke is a leading cause of morbidity and mortality worldwide, with an increasing prevalence among HIV-positive people. Therefore, investigating novel cerebrovascular risk factors that are also potentially modifiable may have important treatment implications for HIV-positive people. In this study, not only was depression independently associated with incident stroke, we also report that incident stroke risk is partially accounted for, to varying degrees, by alcohol use disorders, cocaine use, and baseline antidepressant use. Furthermore, depression may be a more important contributor to stroke risk for HIV-positive people younger versus older than 60 years. Apart from understanding the underlying, and likely interconnected, mechanisms by which depression increases stroke risk among people with and without HIV, future work should explore the relationship between the pharmacologic and non-pharmacologic treatment of depression and cerebrovascular risk reduction. This would include examining specific types of therapies and classes of antidepressant medications, treatment adherence, and depression severity. Providers caring for HIV-positive people should be aware that depression may be an important comorbidity as it relates to future stroke risk and consider counseling their patients with HIV regarding the increased stroke risk among those with depression.

ARTICLE INFORMATION

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Supplementary Material

Table S1

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SUPPLEMENTAL MATERIAL

Table S1. Cox Proportional Hazard Models Predicting Incident Ischemic Stroke Restricted to Specific Combined Antiretroviral Agents [*,†,‡,§]

	HR [95% CI]	p-value
	Full Model from Primary Analysis [†]	
With Depression	1.18 [1.03, 1.34]	0.014
Without depression	1·0	—
	Full Model from Primary Analysis + HIV Specific Factors [‡]	
With Depression	1.18 [1.04, 1.35]	0.011
Without depression	1·0	—
	Supplemental Model One: Full Model from Primary Analysis restricted to Efavirenz and Abacavir Use [§]	
With Depression	1.17 [1.03, 1.33]	0.020
Without depression	1.0	—

[*] Abbreviations: hazard ratio (HR); confidence interval (CI), human immunodeficiency virus (HIV), cardiovascular disease (CVD). Full Model from Primary Analysis (i.e., Model Three from Primary Analysis) and full model from primary analysis + HIV specific factors (i.e., Model Four from Primary Analysis) included here for ease of reference.

[†] Full Model from Primary Analysis: Adjusted for variables in Model One and CVD risk factors (i.e., SBP, DBP, LDL cholesterol, HDL cholesterol, triglycerides, statin use, diabetes, BMI, smoking status, eGFR, hemoglobin, hepatitis C infection, and atrial fibrillation.

[‡] Full Model from Primary Analysis + HIV Specific Factors: Adjusted for variables in Full Model from Primary Analysis and HIV-specific factors (i.e., viral load, CD4 count, and antiretroviral therapy).

[§] Supplemental Model: Adjusted for variables in Full Model from Primary Analysis and HIV-specific factors (i.e., viral load, CD4 count) with cART analysis restricted only to efavirenz and abacavir use.