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Depression and All-Cause Mortality Risk in HIV-infected and HIV-uninfected U.S. Veterans: A cohort study

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Abstract

Objective: The contribution of depression to mortality in adults with and without HIV is unclear. We hypothesized that depression increases mortality risk and this association is stronger among those with HIV.

Methods: Veterans Aging Cohort Study (VACS) data were analyzed from the first clinic visit on/after 4/1/2003 (baseline) to 9/30/2015. Depression definitions: 1) major depressive disorder by ICD-9 codes; 2) depressive symptoms by Patient Health Questionnaire (PHQ)-9 scores ≥ 10. Outcome: all-cause mortality. Covariates: demographics, comorbid conditions, health behaviors.

Results: Among 129,140 eligible participants, 30% had HIV, 16% had major depressive disorder diagnosis, and 24% died over a median follow-up of 11 years. The death rate (95% confidence interval [CI]) was 25.3 [25.0–25.6] deaths per 1000 person-years. Major depressive disorder was associated with mortality: hazard ratio (HR) [95% CI] = 1.04 [1.01, 1.07]. This association was modified by HIV status (interaction p-value=0.02). In HIV-stratified analyses, depression was significantly associated with mortality among HIV uninfected veterans but not among those with HIV. Among those with PHQ-9 data (N=7372), 50% had HIV, 22% had PHQ-9 scores ≥ 10, and 28% died over a median follow-up of 12 years. The death rate was 27.3 (26.1–28.5) per 1000 person-years. Depressive symptoms were associated with mortality (1.16 [1.04, 1.28]). This association was modified by HIV status (interaction p-value=0.05). In HIV-stratified analyses, depressive symptoms were significantly associated with mortality among veterans with HIV but not among those without HIV.

Conclusion: Depression was associated with all-cause mortality. This association was modified by HIV status and method of depression ascertainment.

Keywords

HIV; depression; mortality

Introduction

Depression is the most frequently reported mental health condition in people living with HIV in the United States (U.S.), with prevalence ranging from 20–40%.(1–5) Depressive disorders have been associated with increased mortality in persons with chronic diseases, including heart disease, end stage renal disease, and diabetes.(6–8) Several studies have described similar associations in the context of HIV infection, although conflicting data exist. Limitations in prior work include absence of a comparator group without HIV that would inform conclusions about whether HIV infection modifies the association between depression and mortality. If HIV infection strengthens the association between depression and mortality, this would suggest that among people with HIV, greater emphasis on depression screening, better synchronization of HIV and depression treatment, and more research into the mechanisms underlying the interaction of HIV and depression on mortality risk are warranted. Thus, it is important to understand the interplay among HIV infection, depression and all-cause mortality (Figure 1). Our objectives were to assess the independent association of depression and mortality and to determine whether and how HIV modifies this association.

Methods

Study design and participants

We used the Veterans Aging Cohort Study (VACS) to assess the relationships between depression, HIV infection, and all-cause mortality. The VACS is a prospective, multisite, longitudinal cohort of HIV-infected and age, race/ethnicity, and geographic region matched uninfected adults in the U.S. Department of Veterans Affairs (VA) system.(9) In the VACS each HIV-infected veteran is matched to two uninfected veterans also in clinical care. The

baseline date of participation was defined as the date of a participant's first clinic visit on or after April 1, 2003.

A subset of VACS participants completed comprehensive annual health and behavior surveys. These surveys included the PHQ-9, a validated screening tool for major depressive disorder as defined by the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM-IV) criteria.(10) For this subset of participants (PHQ-9 subset), an additional baseline was defined as the date on which they completed their baseline survey. This was to enable analyses using two different definitions for depression status i.e. diagnostic codes and formal depression screening.

All participants were followed from their baseline date until date of death, the last follow-up date, or the censoring date of February 11, 2016.

The University of Pittsburgh, Yale University, and West Haven VA Medical Center institutional review boards approved this study.

Outcome variable

The primary outcome variable was all-cause mortality, which was determined from the VA vital status file, the Social Security Administration death master file, the Beneficiary Identification and Records Locator Subsystem, and the Veterans Health Administration Medical Statistical Analysis Systems inpatient data sets.

Exposure variables

The primary exposure variable was depression. We defined depression at baseline as having at least one inpatient or two outpatient International Classification of Diseases, Ninth Revision [ICD-9] codes for major depressive disorder (296.2 or 296.3).(11, 12) Among those with PHQ-9 data available at baseline (PHQ-9 subset), we also defined clinically significant depressive symptoms as a PHQ-9 score ≥ 10.(13) PHQ-9 scores ≥ 10 indicate the presence of depressive symptoms with strong reliability and validity for diagnosing major depressive disorder.(14)

Effect modifier and covariates

HIV status was the primary effect modifier. HIV infection was defined as at least one inpatient or two outpatient ICD-9 codes for HIV in the VA Immunology Case Registry as previously described.(15)

HIV-specific data included in these analyses were CD4 cell count, HIV-1 RNA level, and antiretroviral therapy (ART) regimen obtained as part of clinical care at baseline (defined as 180 days prior to through 7 days after the baseline enrollment date). Baseline CD4 cell counts were categorized as ≥500/mm^3, 200–499/mm^3, or <200/mm^3 and HIV-1 RNA levels as <500 or ≥500 copies/mL. Being on any ART regimen (yes/no) and the use of efavirenz (which was specifically included due to its potential neuropsychiatric effects and higher risk of suicidality(16)), were obtained through pharmacy data.

Covariates were obtained closest to baseline date as previously described.(17, 18) Sociodemographic variables of age, self-reported sex, and self-reported race/ethnicity were determined through administrative data. History of cardiovascular disease, chronic obstructive pulmonary disease, and cancer (either AIDS-defining or non-AIDS-defining) were assessed by ICD-9 codes as previously defined.(19–24) History of an AIDS-defining illness was also defined by ICD-9 codes (Supplementary Table 1). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were defined by averaging the three routine outpatient systolic and diastolic blood pressure measurements performed closest to the baseline date. Hypertension was categorized as no hypertension (blood pressure <140/90mmHg and no antihypertensive medication), controlled hypertension (<140/90 mmHg with antihypertensive medication), or uncontrolled hypertension (≥140/90 mmHg). GFR was estimated using the CKD-EPI equation(25) and was categorized as <60 or ≥60 mL/min/1.73m^2. Hemoglobin levels were categorized as either <12g/dL or ≥12g/dL. Diabetes was identified using a previously validated metric that incorporates glucose measurements, antidiabetic agent use, and/or at least one inpatient or two outpatient ICD-9 codes for diabetes.(26) Hepatitis C virus seropositivity was defined as a positive hepatitis C virus antibody test result or at least one inpatient or two outpatient ICD-9 codes for this diagnosis.(27)

Smoking and body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) were assessed using the VA electronic medical record health factor data collected through standardized clinical reminders to VA clinicians.(28) Smoking was categorized as never, current, or past, and BMI was dichotomously categorized (<30 or ≥30 kg/m^2). History of alcohol abuse or dependence and history of cocaine use were defined using ICD-9 codes.(29)

For analyses restricted to the PHQ-9 subset, smoking data were from self-report, BMI data were from laboratory results, alcohol use data were from both Alcohol Use Disorders Identification Test (AUDIT-C) and ICD-9 codes (28, 30). For analysis using AUDIT-C data, alcohol use was categorized as not current, not hazardous, hazardous, at-risk or heavy episodic, or alcohol abuse or dependence.

Baseline antidepressant use was assessed using VA pharmacy records documenting a filled prescription for the following selective serotonin reuptake inhibitors: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline; and tricyclic antidepressants: amitriptyline, amitriptyline/perphenazine, clomipramine, desipramine, doxepin, imipramine, and nortriptyline. ICD-9 codes were used to define schizophrenia, bipolar disorder, and post-traumatic stress disorder (PTSD) (Supplementary Table 1).

Statistical Analysis

Baseline characteristics were stratified by depression status and presented as median (interquartile range) for continuous variables and frequencies with percentages for categorical variables.

Cox proportional hazards models were used to estimate the association of depression status with all-cause mortality. We applied restricted cubic splines on continuous predictors in

order to allow a nonlinear relationship between the covariate and outcome. Interactions between depression and HIV status were assessed in each model. 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. We also constructed Kaplan-Meier curves showing survival distributions over follow-up time.

We constructed three Cox models to estimate the association of depressive disorder diagnoses or depression symptoms, defined using either ICD-9 codes or PHQ-9 scores respectively, and mortality. Model 1 was adjusted for HIV status. Model 2 adjusted for demographics (age, sex, race/ethnicity) and HIV status. Model 3 built upon Model 2 and additionally adjusted for co-morbid conditions that could confound the association between depression and mortality including prevalent cardiovascular disease, AIDS-defining illnesses, chronic obstructive pulmonary disease, cancer, diabetes, hypertension, hypercholesterolemia, renal disease, anemia and hepatitis C seropositivity. Model 3 was our primary model. Model 3B included an interaction term for depression and HIV status. Interactions were considered statistically significant at the $p<0.10$ threshold and HIV-stratified analyses were performed. HIV-stratified analyses were further adjusted for HIV-1 RNA, CD4+ T-cell count and antiretroviral therapy prescription among those with HIV.

We then performed several exploratory analyses to assess the effects of other potential confounding or mediating influences on the relationships between depression and all-cause mortality. First, we added behavioral factors including baseline body mass index (a surrogate of diet and physical activity), smoking status, alcohol use, and cocaine use to Model 3. Then, we adjusted Model 3 for other mental health diagnoses present at baseline, i.e., schizophrenia, bipolar disorder, and post-traumatic stress disorder. Lastly, we examined the role of antidepressant medication use by adjusting Model 3 for use of selective serotonin reuptake inhibitor or tricyclic antidepressant medications prescribed at baseline.

Missing data methods are described in the Online Supplement.

Results

Characteristics of the VACS participants

There were 129,140 VACS participants included in this study with a mean age of 50 years, >90% men, 50% black or African American, and median (IQR) duration of follow-up was 10.7 (6.3–12.7) years (Table 1). Of these participants, 16% had a diagnosis of major depressive disorder at baseline. Among those with major depressive disorder, 32% had HIV compared to an HIV prevalence of 30% among those without major depressive disorder. Those with major depressive disorder had a higher prevalence of cardiovascular disease, chronic obstructive pulmonary disease, hepatitis C, current smoking, alcohol or cocaine abuse/dependence diagnoses, and history of schizophrenia, bipolar disorder, or post-traumatic stress disorder (Table 1). These characteristics were similar in the PHQ-9 subset (median (IQR) follow-up time 12.2 (7.4–13.0) years) with the exception of prevalent cardiovascular disease, which had similar prevalence among those with PHQ-9< 10 compared to those with PHQ-9≥10.

Unadjusted mortality rates

At the end of follow-up, almost 24% of the VACS cohort had died, giving a mortality rate of 25 deaths per 1000 person years. Among HIV uninfected people, mortality rates (95% confidence interval) were 20.2 (19.9–20.5) among those without major depressive disorder and 22.7 (21.0–23.5) among those with major depressive disorder. Among those with HIV, these rates were 36.9 (36.2–37.7) and 39.4 (37.8–41.0), respectively (Table 2). In the PHQ-9 subset, mortality rates were similar among uninfected people with PHQ-9 score <10 compared to their counterparts with PHQ-9 score ≥10. However, mortality rates were higher among those with HIV with PHQ-9≥10 (43.2 [38.6–48.1]) versus PHQ-9<10 (33.7 [31.6–36.0]) (Table 2).

Associations between depression and mortality

A diagnosis of major depressive disorder was associated with a 9% increased risk of mortality adjusting for HIV status only (Table 3a). This association persisted after further adjustment for demographics and comorbid conditions that could confound the association between major depressive disorder and mortality (Table 3a). The hazard ratio (95% confidence interval) for major depressive disorder in the primary model (Model 3a) was 1.04 (1.01–1.07). We detected a significant interaction between major depressive disorder and HIV status (p=0.02). Thus, we stratified our analyses by HIV status and detected modestly increased mortality risk associated with major depressive disorder that reached statistical significance among HIV uninfected people (1.06 [1.02–1.11]) but not among people with HIV (1.04 [0.99–1.09]; Table 3b). Exploratory analyses adjusting for behavioral factors, mental health diagnoses, and depression treatment completely attenuated the modest associations observed in the primary analyses regardless of HIV status (Table 4a).

In the PHQ-9 subset, compared to those with PHQ-9<10, veterans with PHQ-9≥10 had a 17% increased risk of mortality adjusting for HIV status only (Table 4a). This association persisted in fully adjusted models (Table 4a). The hazard ratio (95% confidence interval) PHQ-9≥10 in the primary model was 1.16 (1.04–1.28). We detected a significant interaction between depressive symptoms and HIV status (p=0.05). Thus, we stratified our analyses by HIV status and detected no increased mortality risk associated with PHQ-9≥10 among HIV uninfected people (1.00 [0.83–1.20]) but significantly increased mortality risk associated with PHQ-9≥10 among people with HIV (1.24 [1.09–1.42]; Table 4b). Exploratory analyses adjusting for behavioral factors, mental health diagnoses, and depression treatment had little impact on the associations observed in the primary analyses (Table 4b).

Discussion

To our knowledge, this is the largest cohort study to date investigating the relationships among depressive disorders or symptoms, HIV status, and all-cause mortality. We report a moderate association of depressive symptoms and a modest association of depression diagnoses with mortality, which appear to differ by HIV status. Among people with HIV, there was a 24% increased mortality risk associated with elevated depressive symptoms ascertained by PHQ-9 but no significant increase in risk for depressive disorders ascertained by ICD-9 codes. For HIV uninfected people, there was a 6% increased mortlity risk

associated with depressive disorders ascertained by ICD-9 codes and a non-significant 4% increased mortality risk for elevated depressive symptoms ascertained by PHQ-9.

Prior studies investigating depression and mortality among people with HIV have reported increased mortality risk among those with depression diagnoses or questionnaire-based depressive symptoms (2, 31–37) with exceptions.(1, 38) Some studies have focused on multiple mental health and/or substance use disorders (39), while others investigated joint effects of depression and antiretroviral therapy adherance on mortality.(40, 41) None of these studies included a group of people without HIV to determine whether HIV status modifies the effect of depression on mortality. The current study therefore extends the existing literature with the finding of an associaiton of depressive symptoms with mortality among people with HIV but not among HIV uninfected people.

The discrepancy in our findings between depression diagnoses (ICD-9) and depressive symptoms (PHQ-9) may have multiple explanations. First, it may reflect a positive effect of depression treatment on mortality risk. If people with a clinical diagnosis are more likely to receive treatment for – and thus improvement in – their depression than people with depressive symptoms without a clinical diagnosis, this would explain why depressive symptoms but not depression diagnoses were associated with mortality among people with HIV. Second, it may reflect lower risk of depression missclassification in the PHQ-9 subset versus the full VACS cohort. This is because the PHQ-9 was administered to everyone in the PHQ-9 subset (i.e., systematic assessment), reducing the likelihood of depression misclassification compared to ICD-9 codes recorded as part of routine clinical care (i.e. non-systematic assessment). Additionally, most of the above-referenced HIV studies used questionnaires to measure depressive symptoms and reported associations of depressive symptoms and mortality consistent with our findings among those with HIV. The two studies investigating major depressive disorder diagnoses (ICD-9 codes) and mortality among people with HIV reported conflicting results. The first (also from the VA) found no association of depressive disorders with mortality (1) while the second (from Kaiser Permanente Northern California) found psychiatric diagnoses (including major depressive disorder) were associated with increased mortality risk.(39) Our results are consistent with the other VA study and difficult to compare to the Kaiser Permanente study, which did not specifically report associations for major depressive disorders alone.

Analyses in most of the prior HIV studies had limited adjustment for potential confounders beyond demographics, HIV, HIV treatment and immune function characteristics. Our primary analysis included demographics, cardiovascular and pulmonary diseases, cancer, diabetes, and hepatitis C. These comorbidities are known to be associated with both depression and mortality,(42–47) and, as such, need to be adjusted for as potential confounders. Although several previous meta-analyses(48–50) in the general population have reported a positive association between depression and mortality, few of the included studies accounted for potential confounders beyond demographics and calendar time. For example, in a 2015 meta-analysis of 203 studies of mortality in mental disorders in the general population, seven adjusted for smoking and two adjusted for diabetes.(50) Thus, our results extend the literature by providing effect sizes that may be more reflective of the independent effect of depression on mortality among HIV uninfected people.

Although our study was not designed to assess the mechanisms by which HIV infection modifies the association between depressive symptoms and mortality, we offer potential explanations for this result. It is possible that AIDS-related mortality drives a substantial proportion of the association between depression and mortality among those with HIV. This idea is supported by prior work supporting a positive associations between depression and AIDS-related mortality and no association between depressive symptoms and mortality among people initiating antiretroviral therapy who were adherent to this therapy.(1, 34, 36, 37, 40, 41) Second, HIV infection is associated with other detrimental behaviors (e.g., substance misuse, polypharmcy leading to reduced treatment adherence, social isolation), (51–53) which could feedback to depression symptom recurrence or exacerbation and amplify the association of depression with mortality (Figure 1). A third potential explanation involves the association of both HIV infection and depression with increased chronic systemic inflammation, (17, 54, 55) an immunologic phenomenon associated with increased mortality risk.(56–58) In this case, we speculate that combined effect of chronic systemic inflammation from both HIV and depression on mortality is greater than would have been expected from their individual effects.(59).

If HIV infection increases the risk of death associated with depressive symptoms, this has important clinical and research implications. As people with HIV are living longer, their risk for diseases of aging (e.g., cancer, cardiovascular disease) increases, and this risk is accentuated (higher risk at all ages) among people with HIV compared to those without HIV infection.(60) These diseases of aging are associated with depression and may, combined with HIV, further increase mortality risk in this population (i.e., three-way interaction between HIV, depression and diseases of aging). Despite clinical guidelines recommending routine screening for depressive symptoms, there is varying success in implementation and there is underdiagnosis of depression in HIV.(61–63) This needs to be improved; better understanding of barriers and facilitators to effective depression screening and integrating depression treatment into HIV primary care is needed. Even with effective screening, depression treatment is challenging,(64) particularly in the context of HIV infection. Many people with HIV in the combination antiretroviral therapy era are on at least five medications.(65) Adding depression therapy to this background increases risk of harm from polypharmacy including drug drug interactions and decreased treatment adherence. To reduce mortality risk associated with depression among people with HIV, future studies compare watchful waiting, pharmacotherapy, psychotherapy and their appropriate combination paying close attention to the adverse effects of polypharmacy.

There were limitations to this analysis. First, we did not perform time-updated analyses. This may have led to an underestimation of effects depression on mortality because new onset depression was not captured. Second, these results may not be generalizable to women. Third, we cannot exclude the possibility that even with our extensive adjustments, unmeasured confounding due to other variables differing between the HIV and depressed subgroups led to discordant results.

In conclusion, we found that depressive symptoms were moderately associated with all-cause mortality among U.S. veterans with HIV but not among their counterparts without HIV infection. Depression diagnoses were modestly associated with mortality among those

without HIV but not among those with HIV infection. To reduce mortality risk, these findings reinforce the need to assess and treat depressive symptoms and major depressive disorder in patients with and without HIV infection; a strategy supported by a recently published trial showing depression treatment is associated with long-term cardiac outcomes (including mortality) among people with recent acute coronary syndrome.(66) Particularly among people with HIV, there is a need to compare the effectiveness of different depression treatment modalities (e.g., watchful waiting, pharmacotherpy, psychotherapy) accounting for health consequences of polypharmacy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key points:

Depressive symptoms were associated with all-cause mortality among those with HIV but not among their counterparts without HIV infection. Depression diagnoses were modestly associated with mortality among those without HIV but not among those with HIV infection.

Research in context

Evidence before this study:

Depressive disorders have been associated with increased mortality in persons with chronic diseases, including heart disease, end stage renal disease, and diabetes. Several studies have described similar associations in the context of HIV infection, although conflicting data exist. Limitations in prior work include absence of a comparator group without HIV that would inform conclusions about whether HIV infection modifies the association between depression and mortality.

Added value of this study:

This is the largest cohort study to date investigating the relationships among depressive disorders or symptoms, HIV status (including HIV uninfected comparators), and all-cause mortality.

Implications of available evidence:

To reduce mortality risk, our findings reinforce the need to assess and treat depressive symptoms and major depressive disorder in patients with and without HIV infection.

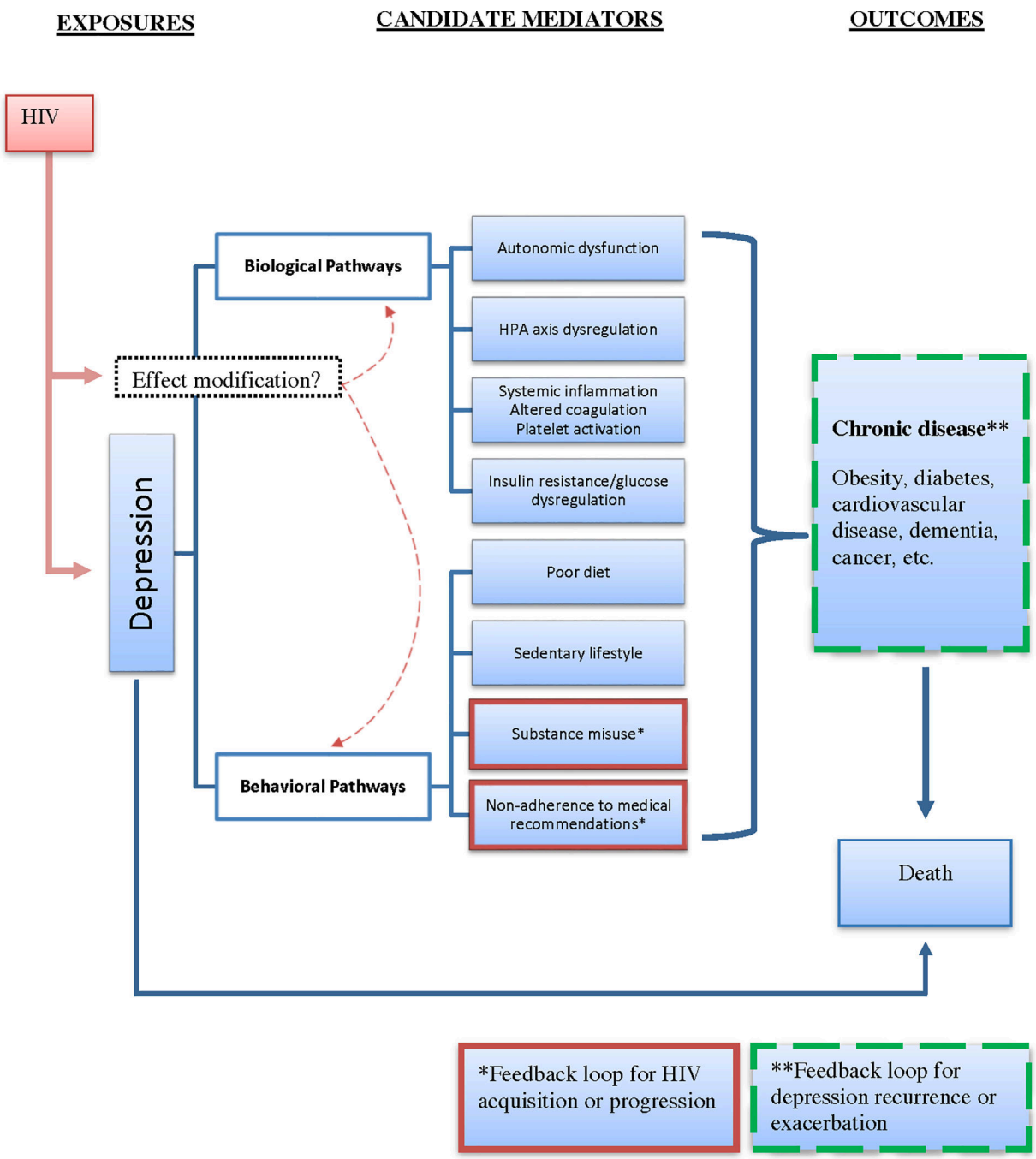

Figure 1.

Conceptual model linking depression and mortality and highlighting a potential role for HIV as an effect modifier.

Table 1.

Baseline Characteristics of the Veterans Aging Cohort Study (VACS)

	VACS (n=129140)				PHQ-9 Subset (n=7372)			
	Non-depressed (n=108136)		Depressed (n=21004)		No depressive symptoms (n=5779)		Depressive symptoms (n=1593)	
	HIV-negative (n=75646)	HIV-positive (n=32490)	HIV-negative (n=14280)	HIV-positive (n=6724)	HIV-negative (n=2932)	HIV-positive (n=2847)	HIV-negative (n=765)	HIV-positive (n=828)
Baseline year								
2003–2006	56523 (74.7)	23456 (72.2)	11600 (81.2)	5501 (81.8)	2530 (86.3)	2470 (86.8)	642 (83.9)	700 (84.5)
2007–2012	19123 (25.3)	9034 (27.8)	2680 (18.8)	1223 (18.2)	402 (13.7)	377 (13.2)	123 (16.1)	128 (15.5)
Age, y	50.6 (44.2–56.9)	50.0 (43.3–56.4)	50.22 (44.9–55.2)	49.1 (43.6–54.6)	51.1 (44.9–57.0)	49.8 (44.1–55.4)	49.9 (44.9–54.4)	49.0 (44.1–54.2)
Male sex	73805 (97.6)	31742 (97.7)	13659 (95.7)	6419 (95.5)	2718 (92.7)	2772 (97.4)	700 (91.5)	805 (97.2)
Race/ethnicity								
White	29292 (38.7)	12409 (38.2)	5903 (41.3)	2886 (42.9)	664 (22.6)	530 (18.6)	195 (25.5)	186 (22.5)
Black or African-American	36051 (47.7)	15986 (49.2)	6764 (47.4)	3157 (47.0)	1887 (64.4)	1966 (69.1)	445 (58.2)	497 (60.0)
Hispanic	5695 (7.5)	2185 (6.7)	1307 (9.2)	524 (7.8)	290 (9.9)	244 (8.6)	88 (11.5)	103 (12.4)
Other	4608 (6.1)	1910 (5.9)	306 (2.1)	157 (2.3)	91 (3.1)	107 (3.8)	37 (4.8)	42 (5.1)
History of CVD	12470 (16.5)	3923 (12.1)	2990 (20.9)	1141 (17.0)	503 (17.2)	377 (13.2)	152 (19.9)	127 (15.3)
History of AIDS		5976 (18.4)		1648 (24.5)		767 (26.9)		281 (33.9)
History of cancer	1785 (2.4)	1070 (3.3)	349 (2.4)	285 (4.3)	103 (3.4)	133 (4.7)	25 (3.3)	29 (3.5)
History of diabetes	13510 (17.9)	3918 (12.1)	3061 (21.4)	1013 (15.1)	632 (21.6)	435 (15.3)	190 (24.8)	144 (17.4)
History of COPD	7867 (10.4)	3136 (9.7)	2557 (17.9)	1215 (18.1)	292 (10.0)	294 (10.3)	102 (13.3)	137 (16.5)
SBP, mm Hg	132.0 (123.0–142.0)	128.7 (119.0–138.7)	131.0 (121.7–141.3)	128.3 (119.3–138.3)	131.3 (121.3–141.7)	128.0 (118.3–138.0)	130.3 (120.7–140.7)	127.3 (118.0–136.7)
DBP, mm Hg	79.0 (73.0–85.7)	77.7 (71.3–84.3)	79.3 (73.0–85.7)	78.0 (72.0–84.3)	78.7 (72.7–85.0)	77.7 (71.7–84.3)	78.3 (72.3–84.0)	77.7 (72.3–84.0)
Total cholesterol ≥200 mg/dL	23383 (38.0)	8226 (29.7)	4811 (38.8)	1801 (29.9)	915 (33.6)	770 (28.3)	233 (33.1)	181 (23.2)
eGFR <60 mL/min/1.73 m^2	5455 (8.2)	2736 (9.0)	853 (6.4)	459 (7.1)	213 (7.5)	213 (7.5)	42 (5.6)	47 (5.7)
Seropositive for Hepatitis C	8309 (11.0)	9243 (28.4)	3009 (21.1)	2701 (40.2)	628 (21.4)	1236 (43.4)	263 (34.4)	435 (52.5)
Hemoglobin <12 g/dL	3043 (4.6)	4274 (13.9)	654 (4.9)	795 (12.1)	154 (5.5)	374 (13.2)	47 (6.3)	130 (15.8)
BMI ≥30 kg/m^2	28616 (40.6)	4914 (15.6)	5769 (41.3)	1209 (18.2)	1181 (40.6)	404 (14.2)	338 (44.3)	132 (16.0)
Smoking								
Current	24367 (48.0)	11839 (54.5)	6484 (59.4)	3216 (64.3)	1242 (43.0)	1417 (50.0)	438 (58.5)	531 (64.3)

	VACS (n=129140)				PHQ-9 Subset (n=7372)			
	Non-depressed (n=108136)		Depressed (n=21004)		No depressive symptoms (n=5779)		Depressive symptoms (n=1593)	
	HIV-negative (n=75646)	HIV-positive (n=32490)	HIV-negative (n=14280)	HIV-positive (n=6724)	HIV-negative (n=2932)	HIV-positive (n=2847)	HIV-negative (n=765)	HIV-positive (n=828)
Former	9663 (19.0)	3573 (16.4)	1807 (16.6)	730 (14.6)	821 (28.4)	723 (25.5)	151 (20.2)	147 (17.8)
Never	16731 (33.0)	6321 (29.1)	2625 (24.0)	1059 (21.2)	828 (28.6)	693 (24.5)	160 (21.4)	148 (17.9)
Alcohol								
Not current	N/A	N/A	N/A	N/A	1053 (36.0)	1032 (36.4)	306 (40.1)	294 (35.6)
Not hazardous	N/A	N/A	N/A	N/A	727 (24.8)	767 (27.0)	121 (15.8)	161 (19.5)
Hazardous	N/A	N/A	N/A	N/A	86 (2.9)	60 (2.1)	9 (1.2)	11 (1.3)
At-risk or heavy episodic	N/A	N/A	N/A	N/A	444 (15.2)	431 (15.2)	91 (11.9)	106 (12.8)
Abuse/dependence	16470 (21.8)	6958 (21.4)	7483 (52.4)	3522 (52.4)	616 (21.1)	547 (19.3)	237 (31.0)	255 (30.8)
Cocaine use	8691 (11.5)	5116 (15.7)	4689 (32.8)	2731 (40.6)	733 (25.0)	761 (26.7)	315 (41.2)	330 (39.9)
History of schizophrenia	5170 (6.8)	1210 (3.7)	2830 (19.8)	986 (14.7)	202 (6.9)	176 (6.2)	113 (14.8)	89 (10.7)
History of bipolar disorder	3121 (4.1)	1163 (3.6)	2974 (20.8)	1182 (17.6)	154 (5.3)	150 (5.3)	116 (15.2)	106 (12.8)
History of post-traumatic stress disorder	8093 (10.7)	2058 (6.3)	6019 (42.1)	1949 (29.0)	378 (12.9)	273 (9.6)	283 (37.0)	183 (22.1)
Antidepressant medication use								
SSRI use	15953 (21.1)	7144 (22.0)	10912 (76.4)	5094 (75.8)	729 (24.9)	770 (27.0)	470 (61.4)	497 (60.0)
TCA use	8877 (11.7)	4316 (13.3)	3852 (27.0)	1952 (29.0)	367 (12.5)	527 (18.5)	193 (25.2)	238 (28.7)
HIV-1 RNA ≥500 copies/mL	N/A	14822 (54.8)	N/A	3239 (57.1)	N/A	1287 (45.3)	N/A	449 (54.4)
CD4 cell count/mm^3	N/A		N/A		N/A		N/A	
<200	N/A	6473 (24.7)	N/A	1194 (21.6)	N/A	596 (21.0)	N/A	214 (26.0)
211–499	N/A	11059 (42.1)	N/A	2295 (41.6)	N/A	1327 (46.8)	N/A	370 (45.0)
≥500	N/A	8724 (33.2)	N/A	2031 (36.8)	N/A	911 (32.1)	N/A	238 (29.0)
Receiving ART regimen	N/A	14308 (44.0)	N/A	3345 (49.7)	N/A	2304 (80.9)	N/A	648 (78.3)
Receiving efavirenz	N/A	5871 (18.1)	N/A	1116 (16.6)	N/A	699 (27.3)	N/A	189 (25.1)

Abbreviations: CVD, cardiovascular disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; COPD, chronic obstructive pulmonary disease; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; N/A, not applicable or not available.

Notes: All data presented as n (%) or median (IQR). In the VACS, the following characteristics include fewer than 129140 patients because of missing baseline data (n, %): BMI (6556, 5.1%), SBP (4698, 3.6%), DBP (4698, 3.6%), total cholesterol (21392, 16.6%), hypertension (4698, 3.6%), smoking status (40725, 31.5%), eGFR (11994, 9.3%), hemoglobin (12542, 9.7%), HIV-1 RNA (6496, 16.6% of HIV-positive), CD4 cell count (7438, 19.0% of HIV-positive), receiving efavirenz (11663, 29.4% of HIV-positive). In the PHQ-9 subset, the following characteristics include fewer than 7372 patients because of missing baseline data (n, %): BMI (36, 0.5%), SBP (12, 0.2%), DBP (12, 0.2%), total cholesterol (443, 6%), hypertension (12, 0.2%), smoking status (73, 1%), eGFR (107, 1.5%), hemoglobin (158, 2.1%), alcohol use (18, 0.2%), HIV-1 RNA (10, 0.3% of HIV-positive), CD4 (19, 0.5% of HIV-positive), receiving efavirenz (366, 9.9% of HIV-positive).

Table 2.

All-cause Mortality Rates of the Veterans Aging Cohort Study (VACS) and PHQ-9 subset

Characteristic	VACS (major depressive disorder defined by ICD-9 code)				PHQ-9 subset (depressive symptoms defined by PHQ-9)			
HIV and depression status at baseline	**Number at baseline**	**All-cause mortality over follow-up, n (%)**	**Total person-years of follow-up**	**Mortality rate/ 1000 person-years (95% CI)**	**Number at baseline**	**All-cause mortality over follow-up, n (%)**	**Total person-years of follow-up**	**Mortality rate/ 1000 person-years (95% CI)**
HIV-negative without depression	75646	14617 (19.3)	723508	20.2 (19.9–20.5)	2932	622 (21.2)	31423	19.8 (18.3–21.4)
HIV-negative with depression	14280	3211 (22.5)	141288	22.7 (21.0–23.5)	765	159 (20.8)	8001	19.9 (17.0–23.2)
HIV-positive without depression	32490	10145 (31.2)	274695	36.9 (36.2–37.7)	2847	932 (32.7)	27625	33.7 (31.6–36.0)
HIV-positive with depression	6724	2359 (35.1)	59907	39.4 (37.8–41.0)	828	320 (38.6)	7412	43.2 (38.6–48.1)
Total	129140	30332 (23.5)	1199398	25.3 (25.0–25.6)	7372	2033 (27.6)	74461	27.3 (26.1–28.5)

Table 3a:

Mortality risk by diagnosis of major depressive disorder (defined by ICD-9 code) in the Veterans Aging Cohort Study (VACS)

	Model 1		Model 2		Model 3*	
	Hazard ratio [95% CI]	**p-value**	**Hazard ratio [95% CI]**	**p-value**	**Hazard ratio [95% CI]**	**p-value**
No major depressive disorder	1 (ref)	<0.01	1 (ref)	<0.01	1 (ref)	0.02
Major depressive disorder	1.09 [1.06, 1.13]		1.23 [1.20, 1.27]		1.04 [1.01, 1.07]	

*Model 3B includes an interaction term for major depressive disorder diagnosis and HIV status. The p-value for this interaction term was 0.02

Model 1 is adjusted for HIV status only. Model 2 additionally adjusted Model 1 for age, sex, and race. Model 3 additionally adjusted Model 2 for baseline cardiovascular disease, chronic obstructive pulmonary disease, cancer, diabetes, systolic blood pressure, diastolic blood pressure, total cholesterol, estimated glomerular filtration rate, hemoglobin, and hepatitis C seropositivity.

Table 3b:

HIV-stratified mortality risk by diagnosis of major depressive disorder (defined by ICD-9 code) in the Veterans Aging Cohort Study (VACS)

		Hazard ratio [95% CI]	
		HIV uninfected	**HIV infected**
Model 3	No major depressive disorder	1 (ref)	1 (ref)
	Major depressive disorder	1.06 (1.02, 1.11)	1.04 (0.99, 1.09)
Model 4	No major depressive disorder	1 (ref)	1 (ref)
	Major depressive disorder	0.98 (0.94, 1.02)	0.99 (0.95, 1.04)
Model 5	No major depressive disorder	1 (ref)	1 (ref)
	Major depressive disorder	1.02 (0.98, 1.07)	1.01 (0.96, 1.06)
Model 6	No major depressive disorder	1 (ref)	1 (ref)
	Major depressive disorder	1.01 (0.96, 1.05)	0.97 (0.92, 1.02)

Model 3 adjusted age, sex, race, prevalent cardiovascular disease, chronic obstructive pulmonary disease, cancer, diabetes, systolic blood pressure, diastolic blood pressure, total cholesterol, estimated glomerular filtration rate, hemoglobin, and hepatitis C seropositivity. Model 4 adjusted for 3 for body mass index, smoking status, alcohol use, cocaine use. Model 5 adjusted Model 3 for baseline diagnosis of schizophrenia, bipolar disorder, and post-traumatic stress disorder. Model 6 adjusted Model 3 for baseline prescription of selective serotonin reuptake inhibitors and tricyclic antidepressant medications. All Models for the HIV-infected participants were then further adjusted for baseline use of antiretroviral therapy, CD4 cell count, and HIV-1 RNA level

Table 4a:

Mortality risk by depressive symptoms (defined by PHQ-9) in the PHQ-9 subset

	Model 1		Model 2		Model 3*	
	Hazard ratio [95% CI]	**p-value**	**Hazard ratio [95% CI]**	**p-value**	**Hazard ratio [95% CI]**	**p-value**
No depressive symptoms (PHQ-9)	1 (ref)	<0.01	1 (ref)	<0.01	1 (ref)	<0.01
Depressive symptoms present (PHQ-9)	1.17 [1.06, 1.30]		1.34 [1.21, 1.49]		1.16 [1.04, 1.28]	

*Model 3B includes an interaction term for depressive symptoms and HIV status. The p-value for this interaction term was 0.05

Model 1 is adjusted for HIV status only. Model 2 additionally adjusted Model 1 for age, sex, and race. Model 3 additionally adjusted Model 2 for baseline cardiovascular disease, chronic obstructive pulmonary disease, cancer, diabetes, systolic blood pressure, diastolic blood pressure, total cholesterol, estimated glomerular filtration rate, hemoglobin, and hepatitis C seropositivity.

Table 4b:

HIV-stratified mortality risk by depressive symptoms (defined by PHQ-9) in the PHQ-9 subset

		Hazard ratio [95% CI]	
		HIV uninfected	**HIV infected**
Model 3	No moderate/severe depression by PHQ-9	1 (ref)	1 (ref)
	Moderate or severe depression by PHQ-9	1.00 (0.83, 1.20)	1.23 (1.08, 1.41)
Model 4	No moderate/severe depression by PHQ-9	1 (ref)	1 (ref)
	Moderate or severe depression by PHQ-9	0.89 (0.74, 1.07)	1.17 (1.02, 1.33)
Model 5	No moderate/severe depression by PHQ-9	1 (ref)	1 (ref)
	Moderate or severe depression by PHQ-9	0.98 (0.81, 1.18)	1.22 (1.07, 1.39)
Model 6	No moderate/severe depression by PHQ-9	1 (ref)	1 (ref)
	Moderate or severe depression by PHQ-9	0.96 (0.80, 1.16)	1.22 (1.07, 1.40)

Model 3 adjusted age, sex, race, prevalent cardiovascular disease, chronic obstructive pulmonary disease, cancer, diabetes, systolic blood pressure, diastolic blood pressure, total cholesterol, estimated glomerular filtration rate, hemoglobin, and hepatitis C seropositivity. Model 4 adjusted for 3 for body mass index, smoking status, alcohol use, cocaine use. Model 5 adjusted Model 3 for baseline diagnosis of schizophrenia, bipolar disorder, and post-traumatic stress disorder. Model 6 adjusted Model 3 for baseline prescription of selective serotonin reuptake inhibitors and tricyclic antidepressant medications. All Models for the HIV-infected participants were then further adjusted for baseline use of antiretroviral therapy, CD4 cell count, and HIV-1 RNA level.