

Cumulative Burden of Depression and All-Cause Mortality in Women Living With Human Immunodeficiency Virus

Jon C. Mills,¹ Brian W. Pence,² Jonathan V. Todd,¹ Angela M. Bengtson,² Tiffany L. Breger,² Andrew Edmonds,² Robert L. Cook,³ Adebola Adedimeji,⁴ Rebecca M. Schwartz,⁵ Seble Kassaye,⁶ Joel Milam,⁷ Jennifer Cocohoba,⁸ Mardge Cohen,⁹ Elizabeth Golub,¹⁰ Gretchen Neigh,¹¹ Margaret Fischl,¹² Mirjam-Colette Kempf,¹³ and Adaora A. Adimora¹

¹Institute for Global Health and Infectious Diseases, University of North Carolina at Chapel Hill, and ²Department of Epidemiology, University of North Carolina at Chapel Hill, Gillings School of Global Public Health; ³Departments of Epidemiology and Medicine, University of Florida, Gainesville; ⁴Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, and ⁵Department of Occupational Medicine, Epidemiology and Prevention, Hofstra Northwell School of Medicine, Great Neck, New York; ⁶Department of Infectious Diseases, Georgetown University, Georgetown University Medical Center, Washington, D.C.; ⁷Institute for Health Promotion and Disease Prevention Research, University of Southern California, Keck School of Medicine, Los Angeles, and ⁸Department of Clinical Pharmacy, University of California San Francisco, School of Pharmacy; ⁹Department of Medicine, John H. Stroger, Jr. Hospital of Cook County, Chicago, Illinois; ¹⁰Department of Epidemiology, Johns Hopkins University, Bloomberg School of Public Health, Baltimore, Maryland; ¹¹Department of Anatomy and Neurobiology, Virginia Commonwealth University, School of Medicine, Richmond; ¹²Department of Medicine/Infectious Diseases, Miami Center for AIDS Research, University of Miami, Miller School of Medicine, Florida; ¹³Schools of Nursing, Public Health and Medicine, University of Alabama at Birmingham

Background. Research linking depression to mortality among people living with human immunodeficiency virus (PLWH) has largely focused on binary “always vs never” characterizations of depression. However, depression is chronic and is likely to have cumulative effects on mortality over time. Quantifying depression as a cumulative exposure may provide a better indication of the clinical benefit of enhanced depression treatment protocols delivered in HIV care settings.

Methods. Women living with HIV (WLWH), naive to antiretroviral therapy, from the Women’s Interagency HIV Study were followed from their first visit in or after 1998 for up to 10 semiannual visits (5 years). Depressive symptoms were assessed using the Center for Epidemiologic Studies Depression (CES-D) scale. An area-under-the-curve approach was used to translate CES-D scores into a time-updated measure of cumulative days with depression (CDWD). We estimated the effect of CDWD on all-cause mortality using marginal structural Cox proportional hazards models.

Results. Overall, 818 women contributed 3292 woman-years over a median of 4.8 years of follow-up, during which the median (interquartile range) CDWD was 366 (97–853). Ninety-four women died during follow-up (2.9 deaths/100 woman-years). A dose-response relationship was observed between CDWD and mortality. Each additional 365 days spent with depression increased mortality risk by 72% (hazard ratio, 1.72; 95% confidence interval, 1.34–2.20).

Conclusions. In this sample of WLWH, increased CDWD elevated mortality rates in a dose-response fashion. More frequent monitoring and enhanced depression treatment protocols designed to reduce CDWD may interrupt the accumulation of mortality risk among WLWH.

Keywords. HIV/AIDS; mental illness; cumulative burden of depression; mortality.

Depression is the most common psychiatric comorbidity among people living with human immunodeficiency virus (PLWH) [1]. Depression affects an estimated 20%–40% of PLWH [1, 2], with higher estimates for women (30%–60%) than men [3]. Unfortunately, there is a strong association between depression and mortality in PLWH [3–14], particularly in women [3, 5, 6, 12–14]. For example, Todd et al [14] found that among women living with HIV (WLWH), depression more than tripled the rate of all-cause mortality; this effect was comparable

among both women who started antiretroviral therapy (ART) and women who remained ART naive. Similarly, Cook et al [5] found that women with chronic depressive symptoms had a 70% greater risk of AIDS-related mortality over 7.5 years compared to those with no depressive symptoms. While not yet fully understood, evidence suggests that depression may lead to an increased risk of mortality among PLWH through several behavioral (eg, completed suicide, poor engagement care) and direct biological (eg, compromised immunity) pathways [15–18].

Most prior studies examining the relationship between depression and mortality have used a binary (yes/no) or categorical (eg, chronic, intermittent) measure to characterize depression as an exposure. However, depression is a chronic and cyclical condition [19, 20] whose effect on mortality is unlikely to be captured realistically by a dichotomous representation. As effective ART has dramatically increased life spans, this time-varying nature of depression may have an important

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Correspondence: J. C. Mills, Department of Epidemiology, The University of North Carolina at Chapel Hill, Gillings School of Global Public Health, McGavran-Greenberg Hall 2103B, Chapel Hill, NC 27599 (jon_mills@med.unc.edu).

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cumulative effect on long-term survival. Capturing the cumulative nature of depression may result in more accurate estimates of the relationship between depression and mortality. Furthermore, a cumulative measure is likely to enable better estimates of the potential benefit of depression interventions that would be likely to shorten but not completely eliminate the occurrence of depressive episodes in WLWH.

Here, we used repeated depressive symptom measures in a cohort of WLWH to calculate a time-updated, cumulative measure of depression burden. We used causal inference methods to estimate the total effect of increased depression burden on all-cause mortality and compared the prognostic value for estimating the risk of mortality of the cumulative depression burden measure to traditional binary representations of depression.

METHODS

Study Design and Participants

We used data from the Women's Interagency HIV Study (WIHS), a longitudinal cohort of WLWH and women at risk for HIV infection recruited from 6 sites (Bronx, New York; Brooklyn, New York; Washington, DC; Chicago, Illinois; San Francisco, California; and Los Angeles, California) [21, 22]. Participants in WIHS complete interviews at semiannual visits to assess a range of sociodemographic and clinical characteristics, medication utilization history, self-reported disease symptom severity, and health behaviors.

We limited our analysis to women from the first 3 enrollment phases (1994–1995, 2001–2011, 2011–2012) who were infected with HIV at the start of their participation in WIHS. Of women from the third enrollment wave (2011–2012), only those who completed at least 2 visits during 2011 were included in the analysis due to administrative censoring on 31 December 2011. The 31 December 2011 date was selected to correspond with the most recent available mortality data in WIHS.

At the time of this analysis, there were 3232 women with HIV upon enrollment in the WIHS. In order to focus our analysis on the era of effective treatment for HIV, analysis began with the participant's first visit in or after 1998 and continued for a maximum of 10 visits (approximately 5 years) or until the earliest of the following dates: death, loss to follow-up (2 consecutive missed visits), or administrative censoring on 31 December 2011. The study time frame restriction (1998–2011) resulted in the exclusion of 583 women who had no visits after 1998 either due to death ($n = 338$) or nonparticipation ($n = 245$). We excluded an additional 1761 women who were prevalent users of ART at their first visit in order to mitigate survivor bias [23]. Furthermore, an additional 46 women were excluded due to missing baseline data for covariates that we included in our analysis as potential confounders. Last, women were required to have at a minimum 2 consecutive visits (from analysis baseline) with a Center for Epidemiologic Studies Depression (CES-D) [24] score in order to calculate the exposure variable of interest,

cumulative days with depression, which resulted in an additional 24 women being excluded. After all exclusion criteria were applied, 818 women remained for analysis. All participants provided written informed consent, and all study protocols were reviewed and approved by local institutional review boards.

Exposure Measure: Cumulative Days With Depression

The exposure of interest was cumulative days with depression (CDWD). CDWD is the running sum of accumulated days with depression, experienced consecutively or over intermittent episodes, by a participant during follow-up. CDWD is the converse of depression-free days (DFD), a measure commonly used in depression treatment trials to quantify the relative benefit of an intervention in shortening the duration of depressive illness [25–27]. CDWD is similar to other cumulative exposure measures such as HIV viremia copy-years [28].

We calculated CDWD using participants' semiannual CES-D scores (range, 0–60), a validated instrument for assessing depressive symptoms [24, 29]. CES-D scores were first assigned thresholds for no symptoms, mild to moderate symptoms, and symptoms consistent with clinical depression using a crosswalk developed by Choi et al [30]. Then, we followed established DFD methodology [27] to convert these thresholds into a depression value that ranged from 0 to 1 at each time point. Specifically, a CES-D score ≤ 9 was set to a depression value of 0, indicating no depression. A CES-D score ≥ 33 was set to a depression value of 1, indicating symptoms consistent with clinical depression. For CES-D scores between 10 and 32, we used linear interpolation to assign depression values between 0 and 1, indicating a partial level of depression corresponding to the mild-to-moderate range [27].

Continuing to follow DFD methodology, the consecutive depression values were combined to estimate the number of days depressed in each interval between visits. The number of days depressed in each interval was calculated as the average of the starting and ending depression levels multiplied by the number of days in the interval [27]. Finally, time-updated CDWD was calculated as the running sum of the days with depression for all intervals occurring prior to and including the current visit. Given the unit of analysis is 1 day of depression, which is likely to have a minimal effect size, we rescaled CDWD so that a 1-unit change corresponded to 91, 182, or 365 days in order to generate 3 separate regression model coefficients with meaningful interpretations.

Traditional Depression Measures

We considered 2 alternative measures of depression for comparability to prior studies: baseline depression and depression status at the most recent visit. For both measures, CES-D scores were dichotomized based on a previously established threshold of ≥ 16 [24, 29]. Scores ≥ 16 indicated high depressive symptoms, and scores < 16 indicated no depressive symptoms.

Mortality Measure

We defined the outcome of interest as all-cause mortality. As soon as WIHS staff are made aware of a participant's death, this event is confirmed by review of death certificate and medical records. Further, National Death Index Plus searches are performed annually for all WIHS participants who were known to have died or were lost to follow-up.

Other Covariates

Several time-fixed and time-varying covariates were used to control for confounding. Time-fixed baseline covariates included age, race (white, black, other), CD4 count, HIV RNA viral load (\log_{10} scale), self-reported substance use (any illicit drug use or alcohol use of >7 drinks/week), and WIHS site. We also controlled for 4 comorbidities: hypertension, diabetes, cancer, and cardiovascular disease. Time-varying age, time the participant was under observation updated at each visit (measured in years), self-reported receipt of ART at each visit (yes/no), CD4 count, HIV RNA viral load (\log_{10} scale), and self-reported substance use were also included in the analysis. A last-observation-carried-forward approach was used to address missing values for all time-varying variables.

Statistical Analyses

Weighted Kaplan-Meier curves were used to visualize differences in the survival function between different categories of CDWD. Marginal structural Cox proportional hazards models were used to estimate time to all-cause mortality as a function of CDWD. We compared linear, quadratic, and restricted cubic spline specifications of the continuous CDWD measure using likelihood ratio tests and concluded that the linear specification was appropriate. We assessed the proportional hazards assumption using Schoenfeld residuals and concluded the assumption held. We fit 3 separate models, including 1 for CDWD, baseline depression, and most recent depression. Then, we fit a fourth model that included all 3 variables (CDWD, baseline depression, most recent measure of depression) in 1 model. Finally, we compared "variable importance" in terms of prognostic value for estimating the relationship between depression and mortality using a previously established methodology by Cole et al [31]. Specifically, we calculated and compared weighted Akaike's information criterion (AIC) values from all 4 models, with higher weighted AIC values indicating greater importance. All analyses were completed using Stata version 14.2 [32].

We adjusted for confounders with inverse-probability-of-exposure weights generated with the covariates described above. Since CDWD is a continuous variable, we used a "quantile binning approach" previously tested and recommended to create inverse probability weights for continuous exposures [33]. As such, we first binned CDWD into deciles. We then fitted a pooled ordinal logistic regression model using the deciles of exposure as the dependent variable. The weights were calculated

for all participants' visits as the inverse of the predicted probability of the exposure decile experienced. We also created inverse-probability-of-censoring weights to account for bias from informative censoring due to loss to follow-up. Given loss to follow-up is a binary event, weights were the inverse of the predicted probability of censoring using pooled logistic regression for binary outcomes. Finally, a stabilized unified weight was calculated as the product of the inverse-probability-of-exposure weight and the inverse-probability-of-censoring weight [34].

In an exploratory analysis, we examined whether ART moderated the relationship between depression and all-cause mortality. We did this by including an interaction term in all 4 models between the depression variable and time-updated self-reported receipt of ART.

RESULTS

Participant Characteristics

At analysis baseline, the median age of the 818 women participants was 38 years (interquartile range [IQR], 33–44; Table 1). The median CD4 count was 438 cells/ μL^3 (IQR, 262–644), and the median HIV RNA viral load was 3.5 \log_{10} copies/mL (IQR, 2.7–4.3). A total of 3292 woman-years were observed during which 171 women were lost to follow-up and 553 were administratively censored. The median length of follow-up was 4.8 years. There were 94 deaths, equating to an all-cause mortality rate of 2.9 deaths/100 women-years. At the last observed visit, the median CDWD was 366 (IQR, 97–853). Among participants who died, the median CDWD was 435 (IQR, 149–870), while participants lost to follow-up or administratively censored had a median CDWD of 355 (IQR, 91–848).

Cox Proportional Hazards Models

Weighted Kaplan-Meier estimates of all-cause mortality stratified according to categories of CDWD were compared (Figure 1). The probability of survival began to decrease at a faster rate for the highest CDWD category (>365 CDWD) compared to the lower categories at approximately 1 year of follow-up (log-rank test, $P < .001$).

In a weighted Cox proportional hazards marginal structural model (Table 2), each additional 365 CDWD led to a 72% increase in the hazard of all-cause mortality (hazard ratio [HR], 1.72; 95% confidence interval [CI], 1.34–2.20). In separate models, both baseline depressive severity (HR, 1.96; 95% CI, 1.18–3.28) and most recent depressive severity (HR, 1.70; 95% CI, 1.03–2.80) led to increases in the hazard for all-cause mortality. When the 3 measures of depression were combined in a single model, the effect estimate for 365 CDWD was attenuated by 19% on the log scale, whereas the estimate for baseline and most recent depressive symptoms was attenuated by 93% and 57%, respectively. CDWD had the highest variable importance with a weighted AIC value of 99 compared to 40 and 42 for baseline and most recent depressive symptoms, respectively.

Table 1. Participant Characteristics, Women's Interagency Human Immunodeficiency Virus Study: 1998–2011

Characteristic	At Study Entry	Over Follow-up
	n = 818 Participants	3292 Women-Years ^a
	Number (%)	Number (%)
Age, median (IQR)	38 (33–44)	40 (35–46)
Race		
White	156 (19)	...
Black	542 (66)	...
Other	120 (15)	...
Education ^b		
Less than high school	312 (38)	...
High school	256 (31)	...
More than high school	248 (30)	...
Receiving antiretroviral therapy at visit ^c	0 (0)	958 (30)
CD4 count, median (IQR), cells/ μ L ³	438 (262–644)	428 (271–618)
Human immunodeficiency virus RNA viral load, median (IQR), log ₁₀ copies/mL	3.5 (2.7–4.3)	3.3 (2.3–4.2)
Diabetes ^d	38 (5)	280 (9)
Hypertension ^d	356 (44)	2005 (61)
Cancer ^d	14 (2)	78 (2)
Cardiovascular disease ^e	8 (1)	105 (3)
Substance use ^f	322 (39)	1257 (38)
CES-D score, median (IQR) ^g	16 (7–27)	14 (6–25)
High depressive symptoms (CES-D \geq 16) ^g	424 (52)	1753 (53)
Cumulative days with depression ^h		
All women, median (IQR)	...	366 (97–853)
Those censored, median (IQR)	...	355 (91–846)
Those who died, median (IQR)	...	435 (149–871)

Abbreviations: CES-D, Center for Epidemiologic Studies Depression; IQR, interquartile range.

^aMedian follow-up, 4.8 years; maximum follow-up, 6.2 years; lost to follow-up, 171; administratively censored, 553; 94 deaths, incidence rate, 2.9 deaths/woman-years.

^bTwo participants missing baseline education data.

^cSelf report by Women's Interagency HIV Study participant of receiving antiretroviral therapy at the current visit.

^dDiabetes defined as, when nonpregnant, self-reported antidiabetic medication, 2 fasting glucose measurements \geq 126 mg/dL, or concurrent measurements of hemoglobin A1c \geq 6.5% and fasting glucose \geq 126 mg/dL. Hypertension defined as systolic blood pressure \geq 140 mm Hg, diastolic blood pressure \geq 90 mm Hg, self-reported hypertension, or use of antihypertensive medications. Cancers include only confirmed and adjudicated cases.

^eCardiovascular disease defined as myocardial infarction, hospitalization for congestive heart failure or chest pain, cerebral vascular accident, transient ischemic attack, or surgery on heart vessels.

^fDefined as self-reported drinking since the last visit that met the definition of at-risk drinking (>7 drinks per week) and/or self-reported drug illicit drug use, injected or otherwise, since the last visit.

^gRange 0–60; threshold for depression \geq 16.

^hThe median number of days of depression accumulated since baseline for this analysis at time of death, loss to follow-up, or administrative censoring.

Finally, in our exploratory analysis, we observed no evidence that time-updated receipt of ART moderates the relationship between depression and all-cause mortality.

DISCUSSION

In the present study, we estimated the total effect of CDWD on all-cause mortality in a large cohort of WLWH. We found that more time spent depressed, experienced consecutively or intermittently, increased the hazard of mortality in a dose-response fashion. Moreover, our models revealed that CDWD continued to be associated with mortality, even after adjusting for depressive symptoms observed at the most recent visit. This result demonstrates that depression accumulated over time may have a lasting impact on the risk of mortality independent of current depression status (see Table 2 “Single model including all 3 depression measures”). Finally, using weighted

AICs, we demonstrated that a cumulative measure of depression was more prognostic of mortality than binary measures of depression.

Our results highlighting the significance of the durational component of depression have important clinical implications for current practices used in HIV primary care settings. At present, HIV treatment guidelines recommend monitoring patients with stable viral loads every 6 months [35]. However, we found that CDWD for less than 182 days (Table 2) increases the risk of mortality. As such, more frequent monitoring of patients with depression in conjunction with integrated depression care protocols designed to shorten the course of depressive episodes could potentially offset further accumulation of mortality risk. In addition to clinical ramifications, our study also has important methodological implications. Specifically, the performance of the CDWD variable compared to binary measures suggests

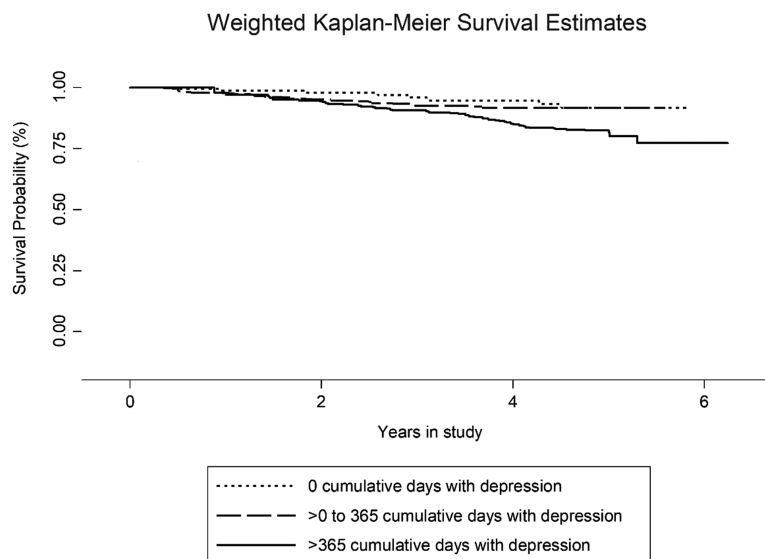


Figure 1. Women’s Interagency HIV Study, 1998–2011. Weighted Kaplan-Meier approximately 5-year (10-visit) survival estimates stratified by categories of cumulative days with depression. Log-rank test for equality of survivor curves: $P < .001$.

that a cumulative approach may provide a more accurate understanding of the impacts of depression on PLWH in future research.

There are several limitations that must be considered when interpreting our results. First, given that we were unable to determine the initial onset of depression symptoms, there was unobserved time spent depressed prior to WIHS enrollment. However, since depression in this population is typically a chronic condition [19, 20], the trend in the accumulation of

depression during the study is likely to be highly correlated with the time spent depressed prior to entry. Second, CES-D scores are only collected every 6 months; therefore, fluctuations in depressive symptoms between visits may have been missed. However, past research has demonstrated that measuring symptoms more frequently than semiannually has little impact on estimation of DFD [27]. Third, informative censoring is a known source of bias in observational studies. Women in our study with more severe depression or chronic illnesses (eg, hypertension,

Table 2. Women’s Interagency Human Immunodeficiency Virus Study, 1998–2011: Marginal Structural Cox Proportional Hazards Models for All-Cause Mortality by Measures of Depression Among 818 HIV Positive Women Representing 3292 Women-Years of Follow-up

Variables	Hazard Ratio (95% Confidence Interval)	P Value
Separate model for each depression variable ^a		
Cumulative days with depression		
365 CDWD = 1 unit change ^b	1.72 (1.34–2.20)	<.0001
182 CDWD = 1 unit change ^b	1.31 (1.16–1.48)	<.0001
91 CDWD = 1 unit change ^b	1.14 (1.08–1.22)	<.0001
Baseline high depressive symptoms (yes/no) ^c	1.77 (1.08–2.88)	.023
Most recent visit high depressive symptoms (yes/no) ^c	2.17 (1.37–3.44)	.001
Single model including all 3 depression measures ^d		
Cumulative days with depression (365 days)		
365 CDWD = 1 unit change ^b	1.55 (1.15–2.09)	.005
182 CDWD = 1 unit change ^b	1.24 (1.07–1.44)	.005
91 CDWD = 1 unit change ^b	1.11 (1.03–1.20)	.005
Baseline high depressive symptoms (yes/no) ^c	1.04 (0.59–1.83)	.892
Most recent visit high depressive symptoms (yes/no) ^c	1.39 (0.83–2.33)	.207

Weighted for age, race, viral load, CD4 count, antiretroviral therapy, substance use, and physical comorbidities (cancer, cardiovascular disease, diabetes, and hypertension).

Abbreviation: CDWD, cumulative days with depression.

^aEach row represents the estimated effect for a model with the corresponding depression measure as the only explanatory variable.

^bHazard ratio produced with Stata lincom command to produce post-estimation effects for rescaled versions of the original model using the raw CDWD variable.

^cCenter for Epidemiologic Studies Depression score range, 0–60; threshold for high depressive symptoms ≥ 16 .

^dThe estimates are results for 1 model that included all 3 depression measures. For example, the hazard ratio (1.55) for “365 CDWD = 1 unit change” is the estimate after controlling for baseline and most recent visit high depressive symptoms.

diabetes) may have had a higher probability of being lost to follow-up. We addressed this potential for informative censoring by modeling inverse-probability-of-censoring weights with CDWD and the available diagnosis data. However, the effectiveness of this approach rests upon the assumption (no misspecification) that all factors associated with informative censoring are included in the weight model. While we were able to account for what we considered the most important health-related factors, the assumption of no misspecification is empirically untestable. Therefore, we cannot rule out the existence of remaining bias stemming from loss to follow-up. Fourth, the validity of our effect estimates depend on several additional assumptions, including positivity, treatment-variation irrelevance, no interference, correct specification of the weight models, and no unmeasured confounding (conditional exchangeability) [36]. Of most concern in this study is unmeasured confounding. In our exposure weight model we accounted for many important confounders of the depression–mortality relationship, but uncontrolled confounding always remains a possibility. An additional limitation of this study is due to the use of data that predates current treatment guidelines of universal ART [37]. Universal ART has resulted in significant improvements in survival [38]. Given only 30% of the women-years are receiving ART in this study, it is possible that our data generated overestimates of the impact of depression on mortality. On the other hand, since depression is known to be a barrier to continuous receipt of ART (eg, linkage to, initiation of, and retention in care) [15–18], the relationship we observed is likely generalizable to the current era of HIV treatment. Moreover, our exploratory analysis did not produce evidence that receipt of ART moderates the relationship between depression and mortality, which is consistent with past research using WIHS data [14]. Finally, findings in this study have limited generalizability to males living with HIV, given that WLWH have previously been shown to report higher depressive symptoms than their male counterparts [3].

These limitations should be balanced against several key strengths of this study. Our results come from a large multisite national cohort of WLWH with long-term follow-up; systematic mortality ascertainment; and standardized, semiannual depression symptom assessments. We adapted established methodology to generate a clinically relevant measure of CDWD that demonstrated that potential benefits may exist from enhanced monitoring and timely interventions for reducing the duration of depressive episodes. Our CDWD measure can be adapted in other settings where depression is an outcome of interest and represents a refinement of less realistic, dichotomous specifications. Finally, we applied sophisticated weighting methods to address both informative censoring and confounding by measured covariates, generating an estimate of the total effect on mortality we would expect to observe, under certain assumptions, if depression was randomly assigned and no one was lost to follow-up.

Several potential lines of research logically flow from this study. First, randomized clinic-level trials are needed to evaluate the feasibility and effectiveness of enhanced monitoring and depression care models integrated into routine HIV care settings. Additionally, researchers should consider using the CDWD measure to assess the impact of depression on proximal outcomes such as HIV care engagement and viral suppression. Finally, future studies should seek to demonstrate the generalizability of our findings to males with HIV.

In conclusion, we calculated a cumulative exposure measure of depression using data from a cohort of WLWH. We identified a dose–response relationship between time spent depressed and an increased hazard of all-cause mortality. These findings highlight the clinical importance of enhanced treatment protocols designed to reduce the duration and frequency of depressive episodes among WLWH. Finally, we demonstrated the additional value of specifying depression as a cumulative exposure when investigating the impact of depression on all-cause mortality.

Notes

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