The Impact of Cumulative Depression along the HIV Care Continuum in Women Living with HIV during the Era of Universal Antiretroviral Treatment

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Abstract

Background: Data are limited on cumulative impacts of depression on engagement in care and HIV outcomes in women living with HIV (WLWH) during the era of universal antiretroviral therapy (ART). Understanding the relationship of accumulated depression with HIV disease management may help identify benefits of interventions to reduce severity and duration of depressive episodes.

Setting: A cohort of WLWH (N=1,491) from the Women's Interagency HIV Study (WIHS) at nine sites across the US.

Methods: This longitudinal observational cohort study (2013-2017) followed WLWH for a maximum of nine semi-annual visits. Depression was quantified as a time-updated measure of percent of days depressed (PDD) created from repeated assessments using the Center for Epidemiologic Studies Depression (CES-D) scale. Marginal structural Poisson regression models were used to estimate the effects of PDD on the risks of missing an HIV care appointment, <95% ART adherence, and virological failure (200 copies/mL).

Results: The risk of missing an HIV care appointment [risk ratio (RR)=1.16, 95% confidence interval (CI)=0.93 to 1.45; risk difference (RD)=0.01, −0.01 to 0.03], being <95% ART adherent (RR=1.27, 1.06 to 1.52; RD=0.04, −0.01 to 0.07), and virological failure (RR=1.09, 1.01 to 1.18; RD=0.01, −0.01 to 0.03) increased monotonically with increasing PDD (comparing those with 25 to those with 0 PDD). The total effect of PDD on virological failure was fully (%100) mediated by being <95% ART adherent.

Conclusions: Time spent depressed increases the risk of virological failure through ART adherence, even in the era of universal ART regimes forgiving of imperfect adherence.

Keywords

HIV; Mental Illness; Cumulative Depression; HIV Care Continuum

INTRODUCTION

Approximately 20%-40% of people living with HIV (PLWH) experience clinical depression with even higher prevalence (30–60%) among women living with HIV (WLWH).[1-3] In addition to being extremely common, depression complicates management of HIV disease throughout the HIV care continuum. Depression has been linked to missed HIV care

appointments,[4-6] reduced adherence to antiretroviral therapy (ART),[7-9] and increased levels of HIV viremia. [4,9-11]

The vast majority of past literature examining the impacts of depression on HIV care outcomes has used standardized binary thresholds to define depression at a single point in time. This approach does not fully capture the chronic and cyclical nature of depression and thus may not account for the condition's potential cumulative impacts on health behaviors and clinical outcomes. More recently, two studies published results that used the cumulative burden of depression approach to explore the relationships between depression and HIV care continuum outcomes.[12,13] These studies found that relatively modest increases in time spent depressed led to increases in the risks of missing HIV care appointments, having a detectable HIV viral load, and mortality. However, both studies include data that pre-date the recommendation for treatment of all people with HIV infection regardless of CD4 cell count known as universal ART[14,15] and the availability ART regimens more forgiving of moderate nonadherence,[16,17] and may not fully reflect how depression is currently impacting health behaviors and HIV care outcomes.

The purpose of this paper is to expand upon prior research using a cumulative burden of depression approach by using data from a national cohort of WLWH during the period following recommendations for universal ART (2013).[15,18,19] We use data from the period of universal ART to estimate the effects of cumulative depression on the risks of missing an HIV care appointment, reporting <95% ART adherence, and virological failure. Using the cumulative approach in conjunction with recent data ensure the results of this study are reflective of and informative to the current landscape of managing HIV disease.

METHODS

Study Design and Population

We used data from the Women's Interagency HIV Study (WIHS), a longitudinal cohort of US women with or at risk for HIV. [20-22] The WIHS collects sociodemographic, clinical, healthcare utilization, and health behavior data at semiannual visits. For the present analysis, women from all four enrollment waves (1994–1995, 2001–2002, 2011–2012, 2013-present) recruited at nine sites (Bronx, NY; Brooklyn, NY; Washington, DC; Chicago, IL; San Francisco, CA; Atlanta, GA; Chapel Hill, NC; Miami, FL; Birmingham AL/Jackson MS) were eligible to participate. We limited our analysis to visits between 2013 and 2017 in order to generate results reflective of the current era of universal ART. Follow-up continued from the analysis baseline until the earliest of the following events: a maximum of nine visits (the last available visit in WIHS at time of this analysis), death, or loss to follow-up (defined as two consecutive missed visits).

At the time of this analysis, there were 3,704 women with HIV infection (prevalent at enrollment or seroconverted during follow-up) enrolled in WIHS. Of these women, 1,946 were excluded because they died prior to 2013 (n=1,114) or due to non-participation during the analysis period (n=832). Of the remaining 1,758 women, we excluded 14 women who had missing data on important potential confounders at their analysis baseline visit. Among the 1,744 women with complete data at their analysis baseline visit, 92 women were

immediately lost to follow-up (meaning they missed their next two consecutive visits) and therefore were excluded from the analysis. Finally, we excluded 161 women who reported not receiving regular HIV care at the analysis baseline visit. These criteria left a total of 1,491 women for analysis. Supplemental Materials Table S4 compares participants excluded to those included in the analysis on selected baseline characteristics. All participants provided written informed consent and local institutional review boards reviewed and approved all study protocols.

Exposure measure: Percent of days depressed

We defined percent of days depressed (PDD) as the estimated time-updated proportion of days a participant experienced symptoms consistent with clinical depression over the follow-up period. The method used to calculate PDD is based on previous studies employing the cumulative burden of depression approach and is described in detail elsewhere.[12,13] Briefly, PDD was calculated using serial participant CES-D scores (range: 0–60) observed at semi-annual WIHS visits. The CES-D is a previously validated instrument for measuring depressive symptoms.[23,24] Based on prior research, we converted consecutive CES-D scores into depression values ranging from 0 to 1. A score of 0 was assigned to CES-D values 9 indicating no depression symptoms, while a score of 1 was assigned to CES-D values 33 indicating fully symptomatic depression [12,25]. CES-D scores falling between 10 and 32 were assigned a prorated value between 0 and 1 indicating partial depressive symptoms. [12,26] After conversion, each pair of consecutive depression values was averaged and multiplied by the number of days between the two visits. This produced an estimated number of days with depression experienced in each interval. We then calculated a time-updated days with depression value representing the running sum of days with depression experienced from analysis baseline through the end of each interval. Finally, we calculated time-updated PDD as the quotient of the running total of days with depression and total days observed from analysis baseline to the end of each interval.

Outcome measures

We considered three repeated measure outcomes in our analysis that reflect important steps along the HIV continuum of care:[27], missed HIV care appointments, <95% ART adherence, and virological failure. We defined missed HIV care appointments as a binary outcome indicating whether or not the participant reported missing any scheduled regular HIV care appointments in the past six months without rescheduling.[28] ART adherence was measured via participant self-report of how often she took ART as prescribed since her last visit. As a binary variable, a self-report of taking ART as prescribed <95% of the time was given a value of 1, while a response indicating 95% was assigned a value of 0. Follow-up visits where the participant indicated they were no longer taking ART (9%, n=766) were assigned a value of 1. We defined virological failure as a binary outcome indicating whether or not the participant had an HIV-1 RNA viral load measure of 200 copies/mL.[29] For all three outcomes, the observed value was related to the time updated exposure (PDD) as of the most recent prior visit (approximately six month gap).

risk scale by comparing linear, quadratic, and restricted cubic spline specifications using Akaike's information criterion (AIC) and visual plots. For the missed HIV care appointment and <95% ART adherence models, evidence supported a non-linear relationship with PDD, and the best fitting model in both cases was a restricted cubic spline using three knots.[33] For the virological failure models, a simple linear relationship with PDD was supported. To facilitate interpretation, for all models we produced graphs depicting weighted predicted RRs and RDs and associated 95% confidence interval (CI) estimates for all observed values of PDD relative to 0 PDD. Additionally, we estimated RRs and RDs for 25 and 100 PDD relative to 0 PDD. All analyses were completed in Stata Version 15.1 (StataCorp, College Station, Texas) and SAS version 9.4 (SAS Institute, Cary, North Carolina).

Exploratory mediation analysis

We conducted an exploratory analysis to test the hypothesis that the total effect of PDD on the risk of virological failure would be partially or fully mediated by missing any HIV care appointment and/or being <95% ART adherent. To test the hypothesis, we compared the point estimate in our primary model assessing the total effect of PDD on virological failure to the point estimate after adding the hypothesized mediators to the outcome model. If our hypothesis is correct, we would expect to observe partial or complete attenuation of the coefficient for PDD after adding the mediators.[13,34]

Secondary Analysis

In a secondary analysis, we fit three covariate--adjusted models for each outcome in order to assess the impact of additional factors relative to depression. The covariate adjustment set mirrored the variables used to derive each outcome's IPEWs.

RESULTS

The baseline and follow-up characteristics of the study sample are provided in Table 1. At baseline, the median age of the 1,491 women was 48 years [interquartile range (IQR]), 42 to 54], 21% indicated <95% ART adherence and 17% had an HIV-1 RNA viral load 200 copies/mL. We observed a total of 4,303 person-years (8,624 visits) during which 53 women died and 23 were lost to follow-up. The median length of follow-up was 3.3 years (IQR, 2.4 to 3.5). Over follow-up, participants reported missing an HIV care appointment, <95% adherence to ART, and had an HIV-1 RNA viral load 200 copies/mL for 11%, 20% and 17% of the observed visits, respectively. At 41% of the observed visits, participants reported receiving mental health treatment. Among the visits where the participant reported receiving mental health treatment, 46% of the women scored 16 on the CES-D, a traditional cutoff point indicative of depressive symptoms.[23] At the last observed visit, the median PDD was 10 (IQR, 0 to 36). WIHS participants included in this study were less likely to be <95% ART adherent and have a HIV-1 RNA viral load 200 copies/mL compared to those excluded from the analysis due to non-participation, missing data and immediate loss to follow-up (See Supplemental Materials Table S4).

Missing an HIV care appointment

The risk of missing an HIV care appointment increased monotonically, if slightly nonlinearly, with increasing PDD (Figures 1.A. and 2.A.). For example, women who spent 25% of their observed time depressed (25 PDD) had a 16% [RR=1.16, 95% CI (0.93 to 1.45); RD=0.01, 95% CI (−0.01 to 0.03)] greater risk of missing an HIV care appointment compared to those with 0 PDD (Table 2). Women who spent 100% of their observed time depressed had an 82% greater risk of missing an HIV care appointment compared to those with 0 PDD [RR=1.82 (1.35 to 1.96); RD=0.07 (0.03 to 0.11)].

Less than 95% ART Adherent

Similarly, the risk of being <95% ART adherent also increased monotonically with increasing PDD (Figures 1.B. and 2.B.). For example, women who spent 25% of their observed time depressed had a 27% greater risk of reporting <95% ART adherence [RR=1.27 (1.06 to 1.52); RD=0.04 (0.01 to 0.07)] compared to those with 0 PDD (Table 2). Additionally, compared to women who reported 0 PDD, women who experienced depression 100% of the time had a 54% increase in the risk of reporting <95% ART adherence [(RR=1.54 (1.21 to 1.97); RD=0.08 (0.03 to 0.13)].

Virological Failure

Figures 1.C. and 2.C. present the weighted predicted RR and risks and associated 95% CIs for virological failure for each observed PDD value. This figure shows that the risk of virological failure increases in a linear fashion with time spent depressed. For example, women experience an 8% increase in the risk of virological failure for each additional 25 PDD [RR=1.09 (1.01 to 1.18); RD=0.01 (−0.01 to 0.03).

Exploratory mediation analysis

The additions of missed HIV care appointments and <95% ART adherence, both individually and in combination, caused the estimate for PDD to be attenuated towards the null, suggesting that these two variables explain part or all of the relationship between PDD and virological failure (Table 3).

Secondary Analysis

In covariate-adjusted models, PDD remained one of the strongest predictors of each outcome relative to other factors included as control variables (Supplemental Materials Tables S1, S2 and S3).

DISCUSSION

In this multi-site longitudinal cohort study of WLWH, we used a cumulative burden of depression approach to estimate the impacts of percent of days depressed (PDD) on three important outcomes along the HIV care continuum: HIV care appointment attendance, <95% ART adherence and virological failure. We found that a greater proportion of time spent depressed increased the risk of missing an HIV care appointment, being <95% ART adherent and virological failure in a dose-response fashion. In addition, our results suggest

that the relationship between PDD and virological failure is largely mediated by being <95% ART adherent. Our findings are consistent with past literature examining the relationships between depression and HIV care appointment attendance[5,13], ART adherence[7-9] and viral load.[4,9-11,13] Additionally, the present study's findings on HIV care appointment attendance and viral load are consistent with a recent publication using the cumulative depression approach in a national clinical cohort of PLWH in the United States.[13]

These findings have several important implications. First, our data suggest that even modest amounts of time spent depressed (25 PDD, equating to 1 in 4 days of full depression or persistent mild-moderate levels of depressive symptoms) can have a negative impact on treatment engagement, which in turn leads to an increased risk of virological failure. Secondly, our findings suggest that even in the modern era of universal ART with regimens that are more forgiving of moderate nonadherence[35-37], greater than 95% adherence to ART remains important for maintaining viral suppression. Third, our descriptive data revealed a potential gap in mental health care for depression among this study population. The existence of unmet depression treatment needs in conjunction with the negative consequences found to be associated with cumulative depression highlight the necessity for and potential clinical benefits of implementing and evaluating enhanced depression care models[38,39] that incorporate an HIV treatment engagement support component [39] into routine HIV clinical care settings. Finally, because PDD incorporates the cumulative history of depression, our data indicate that past exposure to depression, in addition to current symptomology, is an important predictor of negative health outcomes for WLWH. Thus, clinicians should consider a patient's entire history of exposure to depressive symptoms when evaluating present-day risks to HIV treatment success.

There are several limitations that must be considered when interpreting our results. Given that this is an observational study, lack of randomized assignment to depression status threatens effect estimates' internal validity. To address this threat, we used marginal structural models to approximate randomization on several important covariates. However, marginal structural models do not account for unmeasured confounders. Of particular concern in this study is co-occurring post-traumatic stress disorder, anxiety disorder, bipolar disorder, and schizophrenia. These conditions often present in conjunction with depression among PLWH[40] and have been shown to affect the outcomes of interest in this study.[41-44] Thus the estimates we report here may reflect the impact not just of depression alone, but potentially of depression in conjunction with other co-occurring psychiatric disorders on HIV care outcomes, suggesting the importance of coordinated responses to co-occurring mental health conditions among PLWH. This study's results were also subject to bias from participant exclusions due to missing data, immediate loss to follow-up and non-participation. However, excluded WIHS participants experienced greater depressive symptoms along with higher likelihoods of poor engagement in care and virological failure (See Supplemental Materials Table S4). As such, our findings are likely conservative estimates of the impact depression has on this study's outcomes.

An additional limitation is potential measurement error stemming from unobserved fluctuations in depressive symptoms that occurred between visits. Specifically, CES-D scores are collected every six months in the WIHS; therefore, 22 weeks of depressive

symptoms were not directly observed within each visit interval. In a recent study, Kinyanda and colleagues (2018) found that 67% of the major depressive disorder cases resolved in less than six months among a cohort of people with HIV (PWH) from Uganda.[45] In such cases, assessments every six months may not fully capture average depression experience. However, in contrast to the Uganda study, two recent investigations of large cohorts of PWH in the US reported stable depressive symptoms over time for a vast majority of participants.[46,47] In fact, Kelso-Chichetto and colleagues (2017) used data from the WIHS and observed stable depressive symptom patterns over a 10-year follow-up period for 93% of WLWH. This finding suggests semiannual assessments should provide a relatively accurate reflection of our study sample's average depression experience. Moreover, the method used to calculate PDD is built upon the metric depression-free days[26,48] which has been shown to perform just as effectively with semiannual assessments compared to more frequent measurements.[26] Additional limitations includes social desirability and error recall bias in self-reported outcomes along with limited generalizability to the general population of WLWH, many of whom do not have access to study related resources.

Despite these limitations, this study makes important contributions to the literature investigating factors that impede progress along the HIV care continuum. First, the present study expands upon past research that has employed the cumulative burden approach to quantifying depression by assessing this measure's impact on a range of important outcomes along the HIV care continuum. One specific contribution is the inclusion of ART adherence as an outcome measure, which had previously not been explored in relationship to cumulative depression. We also provide additional support for the conceptual framework that ART adherence remains an important pathway through which depression impacts HIV disease management. Specifically, we show that time spent depressed increases the risk for virological failure, even in the era of universal ART regimens thought to be forgiving of less than perfect adherence. Finally, we were able to employ sophisticated quantitative causal inference methods to produce robust effect estimates that accounted for important time-fixed and time-varying confounders.

CONCLUSIONS

To the best of our knowledge, this is the first study to employ the cumulative burden of depression approach to analyze the impacts of time spent depressed on engagement in HIV care and virological failure, with a focus on the era of universal ART. Even in the era of universal ART, with potent and durable antiretroviral regimens, our evidence indicates that time spent depressed poses a significant threat to viral suppression, largely through the mediating effect of ART adherence. Therefore, comprehensive approaches that simultaneously reduce severity and time spent depressed and barriers to treatment engagement are in need of evaluation to guide treatment decisions in the context of routine HIV clinical care. This line of work will be important to uncovering the most effective approaches for addressing the negative effects of time spent depressed on treatment engagement and viral suppression in WLWH.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS:

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A: Missed HIV Care Appointments
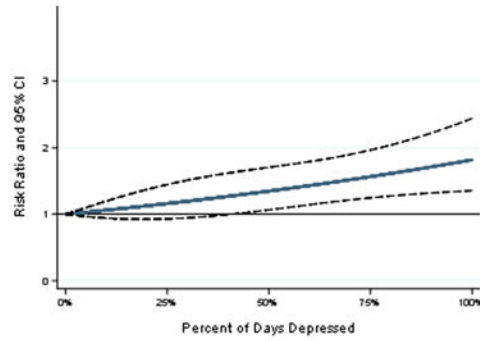
B: Less than 95% ART Adherence
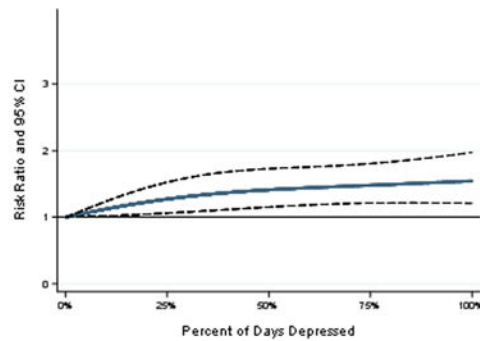
C: Virological Failure (HIV-1 RNA viral load ≥200)
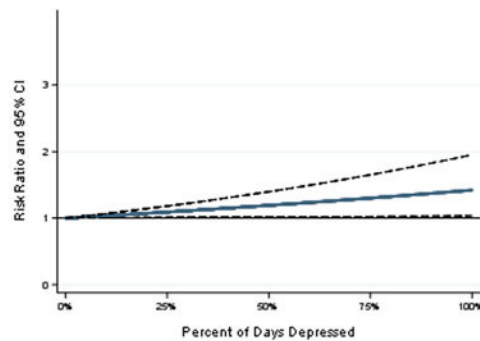
FIGURE 1.
Weighted predicted risk ratios and 95% confidence intervals (CI) for each observed value of percent of days depressed with 0 percent of days depressed serving as the reference point for A) Missed HIV Care Appointments, B) Being <95% ART Adherent and C) Virological Failure.

A: Missed HIV Care Appointments
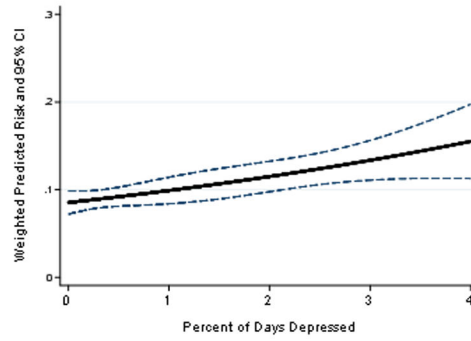
B: Less than 95% ART Adherence
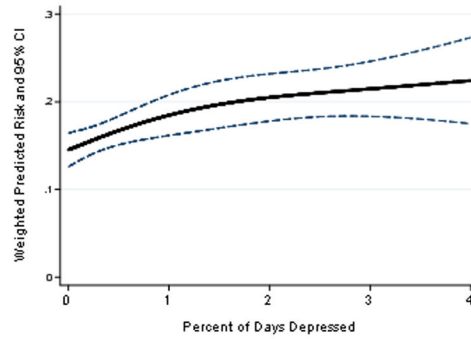
C: Virological Failure (HIV-1 RNA viral load ≥200)
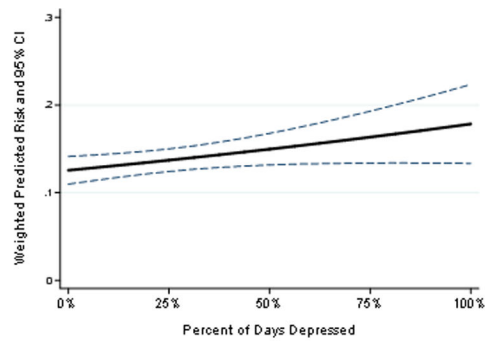
FIGURE 2.
Weighted predicted risk and 95% confidence intervals (CI) for each observed value of percent of days depressed with 0 percent of days depressed serving as the reference point for A) Missed HIV Care Appointments, B) Being <95% ART Adherent and C) Virological Failure.

TABLE 1.

Characteristics of Study Participants in The Women's Interagency HIV Study from 2013-2017 (N=1,491)

Characteristic	Baseline (N = 1,491), N (%)	Follow-up Visits[*] (N=8,624), N (%)
Outcomes of interest		
Missed HIV care appointment	184 (12)	928 (11)
<95% ART adherent (ART nonadherence)	312 (21)	1,735 (20)
Virological failure (200 copies/mL)	250 (17)	1,468 (17)
Depression		
CES-D score, median (IQR)	8 (3 to 18)	8 (3 to 18)
Cumulative PDD, median (IQR)	---	10 (0 to 36)
Covariates		
Site		
San Francisco, CA	187 (13)	---
Southern[**]	526 (35)	---
Bronx, NY	211 (14)	---
Brooklyn, NY	216 (14)	---
Wsshington DC	177 (12)	---
Chicago, IL	174 (12)	---
Age, median (IQR)	48 (42 to 54)	50 (44 to 56)
Race		
White non-Hispanic	147 (10)	---
Black non-Hispanic	1,080 (72)	---
Other non-Hispanic	45 (3)	---
Hispanic	219 (15)	---
Education		
Less than 12 years	500 (34)	---
12 years	473 (32)	---
More than 12 years	518 (35)	---
Employed at visit	490 (33)	2,989 (35)
Stable housing since last visit	1,310 (88)	7,763 (90)
Health insurance at visit	1,290 (87)	7,754 (90)
WIHS enrollment wave		
1: 1994-1995	470 (32)	---
2: 2001-2002	315 (21)	---
3: 2011-2012	188 (13)	---
4: 2013-present	518 (35)	---
CD4 T-cell count, median (IQR), cells/mm^3	594 (391 to 792)	638 (435 to 859)
Diabetes[a]	310 (21)	1,978 (23)
Hypertension[b]	1,065 (71)	6,548 (76)
Substance use[c]	395 (26)	2,211 (26)

Characteristic	Baseline (N = 1,491), N (%)	Follow-up Visits[*] (N=8,624), N (%)
ART Regimen		
HAART[d]	1,322 (89)	7,753 (90)
Integrase Inhibitor	370 (25)	3,416 (40)
Entry Inhibitor	5 (0)	32 (0)
Boosted protease Inhibitor	415 (28)	1,626 (19)
Unboosted protease Inhibitor	41 (3)	274 (3)
NNRTI and/or NRTI	491 (33)	2,405
Mono or dual therapy[e]	19 (1)	104 (1)
Unknown or Not on ART[f]		
Received mental health treatment[g]	564 (42)	3,254 (41)
Received mental health treatment and CES-D ≥ 16[h]	262 (46)	1,487 (46)

Abbreviations: HIV, human immunodeficiency virus; ART, antiretroviral therapy; IQR, interquartile range; CES-D, Center for Epidemiologic Studies-Depression; PDD, Percent of days depressed; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor.

[*]
4,303 person-years; median follow-up: 3.3 years (IQR, 2.4-3.5); maximum follow-up: 3.9 years; women lost due to missed visits: 23 (2% of participants); women died: 53 (4% of participants).

[**]
Includes Atlanta, GA; Chapel Hill, NC; Miami, FL; Birmingham AL/Jackson MS

[a]
Diabetes defined as, when nonpregnant, self-reported antidiabetic medication, 2 fasting glucose measurements ≥ 126 mg/dL, or concurrent measurements of hemoglobin A1c ≥ 6.5% and fasting glucose ≥ 126 mg/dL.

[b]
Hypertension defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, self-reported hypertension, or use of antihypertensive medications.

[c]
Defined as self-reported alcohol consumption that met the definition of at-risk drinking (>7 drinks per week) and/or self-reported drug illicit drug use, injected or otherwise.

[d]
HAART is defined as the reported use of three or more antiretroviral medications, one of which has to be a PI, an NNRTI, one of the NRTIs abacavir or tenofovir, an integrase inhibitor (e.g., raltegravir), or an entry inhibitor (e.g., Maraviroc or enfuvirtide). Subcategories defined by the ART class that anchors the regimen which has met the WIHS definition of HAART.

[e]
Regimens not meeting the definition of HAART including reported use of only one or two ART medications.

[f]
Self-reported receiving regular HIV care at baseline but either indicated not taking ART medication or did not provide ART medication information.

[g]
Defined as self-reported receipt of antidepressant medication or care from a psychiatrist, counselor or other mental health professional since the last visit; missing 132 at baseline and 765 during follow-up

[h]
Percentage out of the number of participants receiving mental health treatment (baseline: n=564; follow-up: n=3,254)

TABLE 2.

Results of Marginal Structural Poisson Regression Models (N=1,491) [*]

Outcome	25% of days depressed compared to never depressed				100% of days depressed compared to never depressed			
	RR	95% CI	RD	95% CI	RR	95% CI	RD	95% CI
Missed HIV care appointment [**]	1.16	0.93 to 1.45	0.01	−0.01 to 0.03	1.82	1.35 to 1.96	0.07	0.03 to 0.11
<95% ART adherence [**]	1.27	1.06 to 1.52	0.04	0.01 to 0.07	1.54	1.21 to 1.97	0.08	0.03 to 0.13
Virological failure (≥200 copies/mL)	1.09	1.01 to 1.18	0.01	−0.01 to 0.03	1.42	1.03 to 1.95	0.05	0.01 to 0.10

Abbreviations: ART, antiretroviral therapy; RR, risk ratio; CI, confidence interval; RD, risk difference.

[*]
Marginal structural Poisson regression models weighted for time-fixed (baseline) values of race, education, stable housing, employment status, health insurance status, WIHS site, WIHS enrollment wave, age, ART regimen type, virological failure and CD4 count, and time-varying CD4 count, days observed, diabetes, hypertension, stable housing, employment status, health insurance status, and substance use. Time-varying virological failure was included in the weight models in the ART adherence and missed appointment analyses.

[**]
Percent of days depressed specified as restricted cubic spline with 3 knots.

TABLE 3.

Results of Marginal Structural Poisson Regression Models Exploratory Mediation Analysis (N=1,491) [*]

Variable	Total effect of PDD on risk of virological failure		Direct effect of PDD on risk of virological failure controlling for mediator: missed HIV care appointment			Direct effect of PDD on risk of virological failure controlling for mediator: <95% ART adherence			Direct effect of PDD on risk of virological failure controlling for both mediators: Missed HIV care appointment and <95% ART adherence		
	RR	95 % CI	RR	95% CI	% Change in RR Point Estimate [***]	RR	95% CI	% Change in RR Point Estimate [***]	RR	95% CI	% Change in RR Point Estimate [***]
25 PDD [**]	1.09	1.01 to 1.18	1.07	0.99 to 1.16	−21%	1.00	0.93 to 1.07	−100%	1.00	0.93 to 1.07	−100%
Mediators											
Missed HIV care appointment	---	---	1.90	1.62 to 2.23	---	---	---	---	1.37	1.19 to 1.60	---
<95% ART adherent	---	---	---	---	---	4.32	3.60 to 5.18	---	4.12	3.42 to 4.96	---

Abbreviations: PDD, Percent of days depressed; ART, antiretroviral therapy; RR, risk ratio; CI, confidence interval.

[*]
Marginal structural Poisson regression models weighted for time-fixed (baseline) values of race, education, stable housing, employment status, health insurance status, WIHS site, WIHS enrollment wave, age, ART regimen type, virological failure and CD4 count, and time-varying CD4 count, days observed, diabetes, hypertension, stable housing, employment status, health insurance status, and substance use.

[**]
25% of days depressed compared to never depressed, or 25 PDD represents a 1 unit change

[***]
% change in RR on the log scale for the direct effect of PDD on risk of having a virological failure compared to the effect without controlling for mediators.