

Depressive Symptoms and Engagement in Human Immunodeficiency Virus Care Following Antiretroviral Therapy Initiation

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Background. The effect of depressive symptoms on progression through the human immunodeficiency virus (HIV) treatment cascade is poorly characterized.

Methods. We included participants from the Centers for AIDS Research Network of Integrated Clinic Systems cohort who were antiretroviral therapy (ART) naive, had at least 1 viral load and HIV appointment measure after ART initiation, and a depressive symptom measure within 6 months of ART initiation. Recent depressive symptoms were measured using the Patient Health Questionnaire-9 (PHQ-9) and categorized using a validated cut point (PHQ-9 ≥ 10). We followed participants from ART initiation through the first of the following events: loss to follow-up (>12 months with no HIV appointment), death, administrative censoring (2011–2014), or 5 years of follow-up. We used log binomial models with generalized estimating equations to estimate associations between recent depressive symptoms and having a detectable viral load (≥ 75 copies/mL) or missing an HIV visit over time.

Results. We included 1057 HIV-infected adults who contributed 2424 person-years. At ART initiation, 30% of participants reported depressive symptoms. In multivariable analysis, recent depressive symptoms increased the risk of having a detectable viral load (risk ratio [RR], 1.28; 95% confidence interval [CI], 1.07, 1.53) over time. The association between depressive symptoms and missing an HIV visit (RR, 1.20; 95% CI, 1.05, 1.36) moved to the null after adjustment for preexisting mental health conditions (RR, 1.00; 95% CI, 0.85, 1.18).

Conclusions. Recent depressive symptoms are a risk factor for unsuppressed viral load, while preexisting mental health conditions may influence HIV appointment adherence.

Keywords. HIV; depression; HIV treatment cascade; mental health; viral load.

Depression affects 20%–30% of adults living with human immunodeficiency virus (HIV), negatively influencing outcomes across the HIV treatment cascade [1, 2]. Depression has been associated with risk behaviors for sexual HIV transmission [3], reduced antiretroviral therapy (ART) adherence [4, 5], unsuppressed viral load [6–8], and increased mortality [6, 9–13]. Depression is also frequently undiagnosed, untreated, or undertreated in HIV-infected populations [14–16], raising the likelihood that depression will adversely affect outcomes across the HIV treatment cascade.

Engagement in care is essential to improve outcomes across the HIV treatment cascade. Viral suppression has long been

recognized as a biological indicator of ART adherence and the ultimate goal of HIV treatment [17, 18]. However, achieving sustained viral suppression also requires attendance at regularly scheduled HIV clinic visits. HIV appointment adherence has increasingly been recognized as an important, and distinct, indicator of engagement in care along the HIV treatment cascade [19–21]. Missed HIV clinic visits have been associated with delays in starting ART and achieving viral suppression, as well as development of AIDS-defining illnesses and mortality [22, 23]. Understanding how depressive symptoms affect both viral suppression and HIV appointment adherence over time is therefore essential to optimize outcomes across the HIV treatment cascade.

In this analysis, we used data from a large cohort of HIV-infected adults in the United States to investigate how presenting with recent, clinically meaningful depressive symptoms affects the risk of the following 2 important markers of engagement in HIV care over time: having a detectable viral load and missing an HIV appointment. We hypothesize that recent depressive symptoms may affect these distinct aspects of engagement in care differently over time.

Received 29 March 2018; editorial decision 29 May 2018; accepted 11 June 2018; published online June 12, 2018

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Clinical Infectious Diseases® 2019;68(3):475–81

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METHODS

Data for the present analysis come from the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort. The CNICS cohort includes more than 32 000 HIV-infected adults in routine HIV clinical care at 8 academic medical centers across the United States [24]. Since 1997, CNICS has collected detailed information on demographic characteristics, medication (including ART) prescriptions, HIV/AIDS clinical events, comorbid conditions, CD4 count, HIV viral load, and vital status of patients who consent to participate. Between 2005 and 2011, CNICS introduced self-administered questionnaires, called patient-reported outcomes (PROs), across 7 of the 8 sites for patients to complete on touchscreen tablets or personal computers every 4–6 months as part of routine clinical visits. PRO assessments typically begin around entry into CNICS care, with some variation by site. Participants provided written informed consent to participate in CNICS. The institutional review board at each CNICS site provided ethical approval for the use of routinely collected clinical data.

Study Population

For the present analysis, we included HIV-infected adults in CNICS initiating ART (n = 11 038) with a viral load measured at least 28 days after ART initiation (n = 10 549) and at least 1 PRO measure in the 6 months before or after initiating ART (n = 2357). The majority of participants excluded for not having a PRO measure (64%) were participants who initiated ART

prior to PRO data collection beginning at their CNICS site. To identify ART-naive participants, we excluded participants with incomplete information on ART use (n = 1821); those with an undetectable viral load (<75 copies/mL) at ART “initiation” (n = 246 excluded), possibly indicating prior ART use; and those who did not have a viral load measure within 28 days of initiating ART (n = 518 excluded). Our final study population when examining detectable viral load (henceforth, “detectable viral load analysis”) included 1057 participants. Of the 1057 participants, 7 did not have an HIV appointment scheduled after ART initiation and were excluded from the analysis of HIV appointment adherence (henceforth, “appointment adherence analysis”; n = 1050 participants; Figure 1). Participants from 6 of the 8 CNICS sites were included in our study population (1 site did not collect PRO information and 1 site did not collect PROs around the time of ART initiation).

Participants were followed from ART initiation through the first of the following events: lost to follow-up from CNICS (defined as the date 12 months after their last HIV care appointment), death, administrative censoring (2014–2015 depending on site), or 5 years of follow-up. We assessed multiple outcomes for each participant using a repeated measures framework.

Depressive Symptoms Exposure

For both the detectable viral load and appointment adherence analyses, the exposure of interest was a binary measure

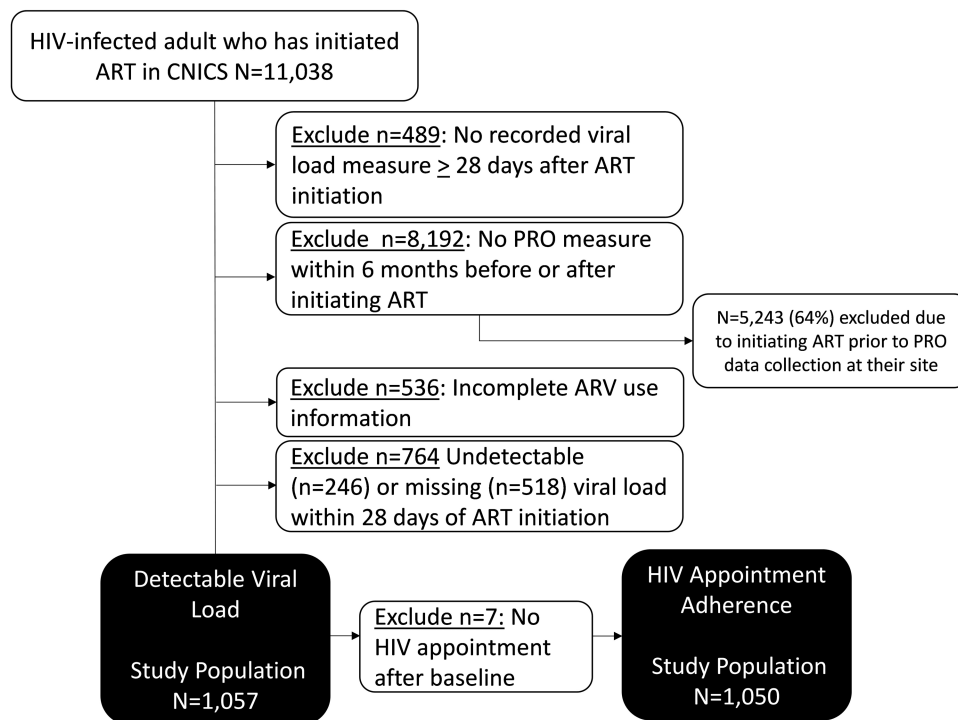


Figure 1. Study population for new antiretroviral therapy users in the Centers for AIDS Research Network of Integrated Clinical Systems included in the detectable viral load (n = 1057) and human immunodeficiency virus appointment adherence (n = 1050) analyses. Abbreviations: ART, antiretroviral therapy; ARV, antiretroviral; CNICS, Centers for AIDS Research Network of Integrated Clinical Systems; HIV, human immunodeficiency virus; PRO, patient-reported outcome.

of recent depressive symptoms, measured using the Patient Health Questionnaire-9 (PHQ-9) [25]. The PHQ-9 is used to assess the presence of the 9 Diagnostic and Statistical Manual of Mental Disorders-V criteria symptoms for depression in the past 2 weeks and has been widely validated, including in HIV-infected populations [26]. The PHQ-9 ranges from 0 to 27, with higher scores indicating more severe depressive symptoms. Participants with a score of ≥ 10 were considered to have clinically meaningful depressive symptoms; a cutoff of ≥ 10 has 88% sensitivity and 88% specificity to indicate probable major depressive disorder and is considered a clinical threshold for beginning antidepressant treatment [25, 27]. We considered a continuous measure of recent depressive symptoms as a secondary exposure, modeled using both a linear term and locally weighted scatterplot smoothing regression after investigating the functional form.

Depressive symptoms are measured in CNICS approximately every 6 months, during the PRO administration. Therefore, we allowed depressive symptom measures to be valid (eg, carried forward) for up to 6 months (eg, 183 days) or until the patient's next PRO measure; we defined this as recent depressive symptoms. One pathway that depressive symptoms affect having a detectable viral load is through reduced ART adherence [4, 5], a process that may take several weeks to become evident. Therefore, for the detectable viral load analysis, we assessed each participant's depressive symptoms 30 days prior to when each viral load measurement was taken. For the HIV appointment adherence analysis, we assessed depressive symptoms on the day of a given attended HIV appointment to estimate the likelihood that the next scheduled appointment would be kept or missed. For all observations without a valid depressive symptoms measure, the exposure was considered missing and accounted for in sensitivity analysis.

HIV Treatment Cascade Outcomes

The outcome of interest for the detectable viral load analysis was having a detectable viral load, defined as ≥ 75 copies of HIV-1 RNA per milliliter of plasma. In the HIV appointment adherence analysis, the outcome of interest was missing, as opposed to keeping, the next scheduled HIV appointment (walk-in or rescheduled appointments were excluded). Multiple outcomes per participant were assessed over time.

Covariates

Both the detectable viral load and appointment adherence analyses included time-fixed and time-varying covariates. Time-fixed covariates were measured at enrollment into CNICS or ART initiation (baseline) and included site, gender, race/ethnicity (white, non-Hispanic; black, non-Hispanic; Hispanic; or other), HIV acquisition risk group (intravenous drug user, male-to-male sexual contact, heterosexual contact, or other), and having a preexisting mental health, diabetes, or hypertension

diagnosis documented by a provider, likely around the time of HIV care initiation, in the medical record at the time of ART initiation. Preexisting mental health diagnosis was defined as any previously documented anxiety, depression, bipolar disorder, post-traumatic stress disorder, psychosis, or other uncategorized mood or mental health disorders. Chronic comorbid medical diagnoses may also affect patients' depressive symptoms status and engagement in clinical care [28–30]. Therefore, we also controlled for chart-documented comorbid medical diagnoses available in our data, namely, hypertension and diabetes.

Time-varying covariates collected via CNICS PROs included symptoms of panic disorder (measured using the PHQ-5, defined as no panic symptoms, some panic symptoms, or panic disorder) [31]; high-risk alcohol use (measured using the alcohol use disorders identification test [AUDIT-C], defined as an AUDIT-C score ≥ 4 for males and ≥ 3 for females) [32]; and current, past, or no illicit drug use, excluding marijuana (measured using the alcohol, smoking, and substance involvement screening test) [33, 34]. CNICS also collects time-updated information on whether a participant has a current antidepressant prescription, CD4 count, and viral load laboratory values (viral load was only used as a covariate in the appointment adherence analysis). Poor ART adherence is more likely to result from depressive symptoms rather than precede them; therefore, ART adherence (measured via PROs) was not considered as a potential confounder in our analysis [35, 36]. Information on counseling or other behavioral health treatment is not available in CNICS.

Values for all time-varying covariates were considered valid (eg, carried forward) for 6 months. To ensure appropriate temporal ordering, all time-varying covariate values were lagged and assessed 6 months prior to each depressive symptom measure. If time-varying covariate information was not available 6-months prior, the time-varying covariate values were considered missing and accounted for in sensitivity analyses.

Statistical Analysis

The goal of our analysis was to estimate how time-varying recent depressive symptoms affect engagement in care over time. We estimated the relationship between recent depressive symptoms and having a detectable viral load over time and separately estimated the relationship between recent depressive symptoms and missing a subsequent HIV appointment over time. For both analyses, we estimated unadjusted and adjusted risk ratios (RRs) and 95% confidence intervals (CIs) using generalized estimating equations for log binomial models, with a robust variance estimator and an exchangeable correlation matrix. All covariates considered for inclusion in multivariable models were identified a priori using directed acyclic graphs [37].

Due to model convergence issues, we empirically investigated which time-fixed and time-varying covariates were associated with both recent depressive symptoms and each outcome (ie, were confounders). For the detectable viral load analysis,

multivariable models included site; preexisting chart-documented mental health, diabetes, and hypertension diagnoses; HIV acquisition group; and lagged PRO measures of depressive symptoms, anxiety, drug use, alcohol risk, as well as lagged antidepressant prescription information. For the appointment adherence analysis, we considered 2 adjustment sets. The first included preexisting chart-documented diabetes or hypertension diagnoses, gender, race/ethnicity, age, HIV acquisition group, and lagged PRO measures of drug use and alcohol risk, as well as lagged antidepressant prescription, CD4 count, and detectable viral load. The second adjustment set additionally included preexisting chart-documented mental health diagnoses and lagged PRO measures of anxiety and depressive symptoms in order to understand how including preexisting and lagged mental health–related factors influenced effect estimates. Time-fixed and time-varying continuous confounders were modeled using restricted cubic splines with 4 knots.

In sensitivity analysis, we used multiple imputation to account for all missing data and inverse probability of visit weights (IPVW) to account for the fact that some participants had more frequent viral load measures or HIV appointments than others [38]. Additional details about sensitivity analysis are available in the [Supplementary Materials](#). All statistical analyses were conducted in Stata, version 13 (StataCorp, College Station, TX) or SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

We included 1057 HIV-infected adults who initiated ART in CNICS between 2005 and 2015 with a valid viral load measure and 1050 who had both a valid viral load and HIV appointment measure ([Figure 1](#)). Participants contributed 2424 person-years (median follow-up time, 735 days) to the detectable viral load analysis and 2416 person-years (median follow-up time, 744 days) to the appointment adherence analysis.

At ART initiation, 30% of participants reported clinically meaningful depressive symptoms ([Table 1](#)). Over the follow-up period, 1057 participants had 7733 viral load measures, 28% of which indicated a detectable viral load (≥ 75 copies/mL), and 1050 participants had 14 131 HIV appointments, 18% of which were missed. Participants had a median of 5 viral load measures (interquartile range [IQR], 3–8), with a median of 104 days (IQR, 64–161) between measures, and a median of 9 HIV appointments (IQR, 4–18), with a median of 41 days between appointments (IQR, 15–92). More than half (53%) of participants were administratively censored, 29% were lost to follow-up, 1% died, and 17% were censored at 5 years of follow-up.

Study participants were primarily male (88%), white non-Hispanic (49%), and reported contracting HIV through male-to-male sexual contact (69%; [Table 1](#)). At ART initiation (baseline), 35% of participants had a preexisting mental health diagnosis, 14% had PRO-measured panic disorder, and 15% had

an antidepressant prescription. Of the 320 participants (30%) with depressive symptoms at baseline, 47% had a preexisting mental health diagnosis documented in their chart at the time of ART initiation and 27% had a preexisting chart-documented depression diagnosis. Nearly a quarter (23%) of participants reported current drug use, and 20% reported at-risk alcohol use on PRO measures at baseline.

Undetectable Viral Load Analysis

In the unadjusted (crude) model, recent depressive symptoms were associated with a 37% average increase in the risk of having a detectable viral load over time (RR, 1.37; 95% CI, 1.20, 1.56). After adjustment for time-fixed and time-varying confounders, recent depressive symptoms remained associated with an increased risk of having a detectable viral load over time (RR, 1.28; 95% CI, 1.07, 1.53; [Table 2](#) and [Supplementary Table 1](#)). Effect estimates did not change meaningfully when missing data were imputed (RR, 1.22; 95% CI, 1.04, 1.42) or when IPVW were used (RR, 1.23; 95% CI, 1.01, 1.49; [Supplementary Table 2](#)). When depressive symptoms were considered as a continuous measure, higher (worse) depressive symptom scores were associated with an increasing risk of having a detectable viral load. However, data were sparse at the highest depressive symptom scores ([Supplementary Figure 1](#)).

Appointment Adherence Analysis

In the unadjusted model, recent depressive symptoms were associated with a 24% average increase in the risk of missing a subsequent HIV appointment over time (RR, 1.24; 95% CI, 1.07, 1.39). The effect estimate was similar (RR, 1.20; 95% CI, 1.05, 1.36; [Table 2](#) and [Supplementary Table 1](#)) in multivariable analysis that did not include lagged PRO measures of depressive or anxiety symptoms and preexisting mental health diagnoses (adjustment set 1). When these variables were additionally included (adjustment set 2), the RR for the association between recent depressive symptoms and HIV appointment adherence moved to the null (RR, 1.00; 95% CI, 0.85, 1.18). Effect estimates with the full multivariable adjustment set (adjustment set 2) did not change meaningfully when missing data were imputed (RR, 1.07; 95% CI, 0.95, 1.21) or when IPVW were used (RR, 1.10; 95% CI, 0.97, 1.23; [Supplementary Table 2](#)).

DISCUSSION

In a large cohort of HIV-infected adults initiating ART, we observed that impaired mental health adversely affected engagement in care along the HIV treatment cascade. Over a median of approximately 2 years on ART, recent, clinically meaningful depressive symptoms were associated with an increased risk of having a detectable viral load over time, controlling for socio-demographic and clinical factors and for preexisting mental health diagnoses. For HIV appointment adherence, recent depressive symptoms were also associated with an increased

Table 1. Characteristics at Antiretroviral Therapy (ART) Initiation and Over Follow-up of 1057 Human Immunodeficiency Virus–Infected Adults Who Initiated ART Between 2005 and 2015 in the Centers for AIDS Research Network of Integrated Clinical Systems Cohort

Characteristic	At Antiretroviral Therapy Initiation,	Over Follow-up,
	(n = 1057) Participants	(n = 2424) Person-Years
	n (%)	n (%)
Time-fixed		
Site		
Fenway	103 (9.7)	...
University of Alabama, Birmingham	286 (27.1)	...
University of North Carolina, Chapel Hill	20 (1.9)	...
University of California, San Diego	427 (40.4)	...
University of California, San Francisco	54 (5.1)	...
University of Washington	167 (15.8)	...
Age in years, median (IQR)	36 (28, 45)	...
Gender		
Male	929 (87.9)	...
Female	128 (12.1)	...
Race/ethnicity		
White, non-Hispanic	509 (48.6)	...
Black, non-Hispanic	288 (27.5)	...
Hispanic	191 (18.2)	...
Other	59 (5.6)	...
HIV risk group		
Intravenous drug user	109 (10.4)	...
Men who have sex with men	721 (68.7)	...
Heterosexual	187 (17.8)	...
Other	33 (3.1)	...
Previous mental health diagnosis		
No	687 (65.0)	...
Yes	370 (35.0)	...
Previous medical diagnosis		
No	941 (89.0)	...
Yes	116 (11.0)	...
Time-updated		
Depressive symptoms		
No (PHQ-9, <10)	737 (69.7)	3755 (74.3)
Yes (PHQ-9, ≥ 10)	320 (30.3)	1299 (25.7)
Viral load		
Undetectable (<75 copies/mL)	0 (0.0)	5964 (77.1)
Detectable (≥75 copies/mL)	1057 (100.0)	1769 (22.9)
HIV appointment status		
Missed appointment	...	2492 (17.6)
Kept appointment	...	11 639 (82.4)
Depressive symptom score (PHQ-9, range 0–27), median (IQR)	5 (1, 11)	4 (1, 10)
Panic disorder		
No symptoms	716 (68.9)	4032 (71.5)
Some symptoms	179 (17.2)	864 (15.3)
Panic disorder	145(13.9)	746 (13.2)
Antidepressant prescription		
Not on antidepressants	900 (85.2)	6101 (78.9)
On antidepressants	157 (14.9)	1632 (21.1)

Table 1. Continued

Characteristic	At Antiretroviral Therapy Initiation,	Over Follow-up,
	(n = 1057) Participants	(n = 2424) Person-Years
	n (%)	n (%)
Drug use		
No current use	437 (46.2)	2676 (50.2)
Current use	218 (23.0)	998 (18.7)
Past use	291 (30.8)	1656(31.1)
Alcohol use^a		
Not at risk drinking	816 (80.5)	4710 (84.9)
At risk drinking	198 (19.5)	840 (15.1)
CD4 count, cells/mm ³ , median (IQR)	334 (167, 488)	426 (258, 616)

Abbreviations: HIV, human immunodeficiency virus; IQR, interquartile range; PHQ-9, Patient Health Questionnaire-9.

^aDefined as alcohol use disorders identification test score >4 for males and >3 for females.

risk of missing the next HIV visit after adjustment for sociodemographic and clinical confounders. However, this association moved to the null after further adjustment for preexisting mental health diagnoses and lagged measures of depressive and anxiety symptoms. These results suggest that for new ART users, recent depressive symptoms are a risk factor for unsuppressed viral load, while preexisting mental health conditions may play a larger role in HIV appointment adherence.

For clinicians who treat people living with HIV, understanding how depression affects engagement in HIV care and progression through the HIV treatment cascade is complex. Depressive symptoms change over time and frequently reoccur, particularly among HIV-infected adults [39–41]. The episodic nature of depression raises questions for clinicians about whether a patient's depression status at a given HIV visit or mental health history is a more clinically relevant risk factor for disengagement from HIV care. Further, patients may disengage from HIV care in multiple ways, all of which may have distinct risk factors. Our analysis helps to clarify these important relationships by demonstrating that recent depressive symptoms and preexisting mental health conditions are likely both risk factors for adverse outcomes but affect aspects of engagement in HIV care differently.

In our analysis, recent depressive symptoms consistent with major depressive disorders were associated with an increased risk of detectable viral load but not with HIV appointment adherence. Depressive symptoms have been linked to reduced ART adherence [4, 5] and subsequent unsuppressed viral load in the past [6–8]. However, the extent to which suboptimal adherence may affect clinic attendance or whether missing HIV visits also increases the risk of detectable viral load is not clear. Our results suggest that the increased risk of detectable viral load among persons with current depressive symptoms is most likely

Table 2. Risk Ratios and 95% Confidence Intervals for the Association Between Having Recent Depressive Symptoms and the Risk of an Adverse Outcome Over Time Along the Human Immunodeficiency Virus Treatment Cascade

Depressive Symptom Status	Detectable Viral Load ^a		Missed Human Immunodeficiency Virus Visit		
	Unadjusted RR (95% CI)	Adjusted ^b RR (95% CI)	Unadjusted RR (95% CI)	Adjusted Set 1 ^c RR (95% CI)	Adjusted Set 2 ^d RR (95% CI)
No depressive symptoms (PHQ-9 <10)	1.00	1.00	1.00	1.00	1.00
Depressive symptoms (PHQ-9 ≥ 10)	1.37 (1.20, 1.56)	1.28 (1.07, 1.53)	1.24 (1.07, 1.39)	1.20 (1.05, 1.36)	1.00 (0.85, 1.18)

RRs and 95% CIs estimated from a generalized estimating equation log binomial model with a robust variance estimator and an exchangeable correlation matrix to account for repeated measures.

Abbreviations: CI, confidence interval; PHQ-9, Patient Health Questionnaire-9; RR, risk ratio.

^aDetectable viral load defined as ≥75 copies/mL.

^bAdjusted for site; preexisting mental health, hypertension, or diabetes diagnoses; human immunodeficiency virus (HIV) acquisition group; lagged anxiety level; lagged drug use; lagged alcohol risk; lagged antidepressant use; and lagged depressive symptoms.

^cAdjustment set 1: preexisting hypertension or diabetes diagnoses, gender, race/ethnicity, age, HIV acquisition group, lagged CD4 count, lagged drug use, lagged alcohol risk, lagged antidepressant use, and lagged detectable viral load.

^dAdjustment set 2: all variables in adjustment set 1, as well as preexisting mental health diagnoses, lagged anxiety level, and lagged depressive symptoms.

driven by reduced ART adherence or possibly the deleterious effect of depression on viral replication [8, 42], and not on an inability to regularly attend HIV visits. Conversely, preexisting mental health conditions, rather than recent depressive symptoms, may be more likely to affect HIV appointment adherence.

Our analysis has several strengths and limitations. Strengths include the use of a large, diverse cohort of HIV-infected adults across the United States; the ability to account for recent depressive symptoms, as well as preexisting mental health diagnoses and comorbid panic disorder symptoms; and the use of a validated measure for clinically meaningful depressive symptoms, as well as a range of other time-fixed and time-varying covariates. Limitations of our analysis include not having information on counseling or other behavioral health assistance, income, or other measures of instability, such as homelessness or insurance status. Participants in our analysis were enrolled in routine HIV care at 6 large, academic medical centers across the United States. Our results may be less generalizable to care settings that serve different populations of HIV-infected adults (ie, a larger population of HIV-infected women).

CONCLUSIONS

When it comes to engaging HIV-infected adults in care across the HIV treatment cascade, both recent and preexisting mental health conditions matter. For new ART users, recent clinically meaningful depressive symptoms may be a risk factor for detectable viral load over time, while having preexisting mental health conditions may be more likely to affect HIV appointment adherence over time. In order to keep HIV-infected adults engaged in care and virally suppressed, routine, ongoing depressive symptom screening and treatment by HIV providers are essential. For patients with a history of mental health conditions, even if they are not currently depressed, additional supportive services such as peer navigators and transportation assistance may be important to help ensure regular HIV visit attendance. A number of interventions exist to improve

depression in HIV-infected adults, including counseling and pharmacotherapy [43–45]. Future studies should explore how such interventions could be combined with additional supportive services to optimize engagement and HIV care outcomes.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Financial support. We thank the National Institutes of Health (NIH; grants R01MH100970, R24AI067039, L30 MH110572, K99MH112413) for their support of this work. We also thank the Center for AIDS Research sites involved in CNICS including the University of Alabama at Birmingham (P30 AI027767), University of Washington (P30 AI027757), University of California–San Diego (P30 AI036214), University of California–San Francisco (P30 AI027763), Case Western Reserve University (P30 AI036219), Johns Hopkins University (P30 AI094189, U01 DA036935), Fenway Health/Harvard (P30 AI060354), and University of North Carolina Chapel Hill (P30 AI50410).

Potential conflicts of interest. K. C. reports grants from the NIH during the conduct of the study and grants and personal fees from Gilead and personal fees from Roche outside the submitted work. H. C. reports grants from the NIH during the conduct of the study and grants from the NIH and Patient-Centered Outcomes Research Institute, and from VIIV, outside the submitted work. All other authors report no conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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