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ORIGINAL PAPER

Do Symptoms of Depression Interact with Substance Use to Affect HIV Continuum of Care Outcomes?

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Abstract

Few studies examine how depression and substance use interact to affect HIV control. In 14,380 persons with HIV (PWH), we used logistic regression and generalized estimating equations to evaluate how symptoms of depression interact with alcohol, cocaine, opioid, and methamphetamine use to affect subsequent retention in care, maintaining an active prescription for ART, and consistent virologic suppression. Among PWH with no or mild depressive symptoms, heavy alcohol use had no association with virologic suppression (OR 1.00 [0.95–1.06]); among those with moderate or severe symptoms, it was associated with reduced viral suppression (OR 0.80 [0.74–0.87]). We found no interactions with heavy alcohol use on retention in care or maintaining ART prescription or with other substances for any outcome. These results highlight the importance of treating moderate or severe depression in PWH, especially with comorbid heavy alcohol use, and support multifaceted interventions targeting alcohol use and depression.

Keywords Alcohol · HIV · Depression · Illicit drug use · Viral suppression

Introduction

Persons with HIV (PWH) consistently adhering to antiretroviral therapy (ART) and sustaining virologic suppression have an almost normal lifespan [1, 2]. In order to achieve virologic suppression, PWH must proceed through the HIV care continuum: diagnosis of HIV, linkage to HIV care, retention in care, and receipt of and adherence to ART [3]. However, a substantial proportion of PWH linked to care (15–25%) are not retained in care, and of those who are, a significant subset (9–24%) fail to achieve or maintain virologic suppression [4–7]. PWH who fail to suppress their viral load represent a missed opportunity to optimize individual health and prevent new HIV infections and are thus a priority for intervention.

Depression and misuse of substances, such as alcohol, opioids, cocaine, and methamphetamine are highly prevalent, modifiable risk factors for poor HIV outcomes. In a nationally representative sample, 36% of PWH in care screened positive for depression [8]. Depression is associated with decreased retention in HIV care [9, 10], decreased adherence to ART [11, 12], and failure to achieve virologic suppression [12–19].

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Similarly, nearly 50% of PWH in care report substance use [20, 21], with 8–27% reporting heavy or hazardous alcohol use [20, 22, 23], and 10–40% reporting use of an illicit drug other than marijuana [8, 20, 23, 24]. Alcohol misuse is associated with decreased retention in care, and decreased utilization of and adherence to ART, with a more pronounced effect for hazardous drinking [25–29]. Use of cocaine, opioids, and methamphetamine are associated with decreased receipt of and adherence to ART, as well as worse virologic response to ART in some studies [24, 29–41]. Further, alcohol misuse is highly comorbid with depression in PWH [32, 42–45], as are use of cocaine, opioids, and methamphetamine [32, 45–47].

Both depression and substance use reduce engagement at multiple steps in HIV care and engender behaviors that impede the ability of PWH to ultimately achieve virologic suppression [36, 48]. Furthermore, comorbid depression and substance use may work synergistically in reducing engagement or promoting behaviors that impede the continuum of care. For example, use of alcohol and other substances may have direct effects on HIV replication and immune system activation [49–51], which may render PWH who use substances particularly vulnerable to interruptions in ART as a result of comorbid depression. However, relatively few studies have examined the specific ways in which depression and substance use interact to affect care continuum outcomes [11, 52, 53]. Our objective for this study was to identify how symptoms of depression interact with alcohol, cocaine, illicit opioid, and methamphetamine use to affect three care continuum outcomes in PWH: retention in care, having an active prescription for ART, and achievement of virologic suppression.

Methods

Study Population

We studied patients enrolled in the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS), a racially diverse cohort of PWH engaged in routine HIV medical care across 8 clinical US sites. CNICS has been described in detail elsewhere [54]. Briefly, the CNICS data repository integrates longitudinal data including comprehensive clinical information from outpatient and inpatient encounters, demographic, clinical, medication, laboratory, and socioeconomic data obtained from each site's electronic health record and other institutional data sources [54]. Additionally, approximately every 6 months, as part of routine clinical care visits, a majority of the cohort completes a patient-reported outcome (PRO) computer-assisted survey, which includes the Patient Health Questionnaire 9 (PHQ-9) [55], the Alcohol Use Disorders Identification Test consumption questions (AUDIT-C) [56, 57], and the National Institute on Drug Abuse modified Alcohol, Smoking And Substance Involvement Screening Test (NIDA-ASSIST) [58, 59].

Our study sample consisted of all individuals with a PRO completed between Feb. 17, 2005 (when PROs were first collected in the cohort) and July 31, 2016, to allow for at least a year of potential observation afterward (although individuals included in the sample may not have been retained in care). Individuals could appear multiple times in the sample if they completed multiple PROs, and were included whether or not they were previously established in care or receiving ART. We excluded PROs that fell within 90 days of a previously completed PRO for an individual.

Outcome Definitions

Outcomes for a particular individual and PRO were defined relative to the time the PRO was recorded. We used the Institute of Medicine (IOM) definition of retention in care: at least two HIV primary care visits at least 90 days apart within the year following the PRO [60]. We defined an active prescription for ART as a prescription for any ART at any time between 150 and 180 days after the PRO by pharmacy records. As almost all CNICS subjects take ART, we did not restrict to ART-naïve; having an active prescription for ART principally reflects continued receipt of ART. We chose a 30-days window so that a gap of a few days between prescriptions would not be counted as lacking an active prescription; we lagged the outcome as antidepressants take a few months to reach full effect [61], and other studies of depression and ART have looked at receipt and adherence ranging from 1 to 15 months, with a number looking at outcomes at 6 months [12, 62–66]. We defined consistent virologic suppression as having all viral loads drawn in the subsequent year < 200 copies/mL [67]. No subjects were censored for the outcomes of retention in care or active prescription for ART; whether or not subjects died or stopped following in clinic, their outcomes were defined based on the criteria above. Subjects were not included in the analysis of virologic suppression if they were retained in care but had no viral loads drawn in the year following a PRO; we made the conservative assumption that subjects who had no viral loads checked within the subsequent year and were not retained in care had unsuppressed viral loads.

We evaluated each of the three outcomes for all subjects, rather than nesting them (i.e., evaluating ART receipt only in those retained in care, and evaluating virologic suppression only in those on ART). Over the course of year, the outcomes do not nest neatly: the overwhelming majority of CNICS subjects are on ART even without meeting the IOM definition of retention in care, and a large proportion also achieve virologic suppression without being retained in

care. Our analysis of virologic suppression therefore reflects failures to suppress viral load due to all upstream drivers (engagement in care, receipt of ART, and adherence).

Independent Variables

The PHQ-9 asked about symptoms over the prior 2 weeks, the NIDA-ASSIST asked about behaviors in the past 3 months, and the AUDIT-C asked about behaviors in the preceding year. Consistent with prior studies, we dichotomized symptoms of depression as "moderate-severe"—a score of ≥ 10 on the PHQ-9—versus "no-mild"—a score of < 10 on the PHQ-9 [55]. We categorized alcohol use as "none"—a score of 0 on the AUDIT-C—"moderate"—a score of 1 or 2 in women or 1–3 in men—and "heavy"—a score of ≥ 3 in women or ≥ 4 in men, consistent with recommended scoring [57]. We defined recent use of cocaine, opioids, and methamphetamine as any reported recreational use in the preceding 3 months on the NIDA-ASSIST; opioid use includes abuse of prescription opioids but not opioids prescribed by a medical provider.

We also adjusted for clinic site, age, sex, race, and whether subjects were men who have sex with men (MSM), which have been associated in prior studies with retention in care, receipt of ART, and virologic suppression [68–71]. Because subjects who have been enrolled for longer in the cohort may be more likely to continue in care and comply with therapy, we additionally adjusted for time since enrollment in the cohort, as has been done in prior CNICS studies [25].

In a secondary analysis, we considered use of antidepressants, defined as an active prescription at the time of PRO completion for any of the following: a selective serotonin reuptake inhibitor, serotonin–norepinephrine reuptake inhibitor, tricyclic antidepressant, serotonin modulator and stimulator, monoamine oxidase inhibitor, bupropion, or nefazodone. Antidepressants may have been prescribed by any provider, not just HIV providers; CNICS captures prescriptions by other providers, such as psychiatrists, in the health care networks of CNICS sites.

Statistical Methods

We built a logistic model for each of our three outcomes, with indicator variables for recent symptoms of depression, moderate or heavy alcohol use, cocaine use, opioid use, and methamphetamine use as well as product terms for depressive symptoms and each of the four substances. We adjusted for age and time since enrollment in the cohort, both as restricted quadratic splines with knots at the 20th, 40th, 60th, and 80th percentiles [72]. We additionally adjusted for clinic site, sex, race, and whether subjects were men who have sex with men (MSM). To account for repeated measurements on subjects, we used generalized estimating equations; because outcomes were defined based on the 6–12 months following a PRO and our sample included repeated PROs as close as 90 days apart, we used an autoregressive-1 correlation structure and robust standard errors [73].

Because some outcomes for virologic suppression were missing (subjects who were retained in care but had no viral load measured in the subsequent year), we weighted the logistic model for virologic suppression with inverse probability of observation weights [74]. We constructed the weights using a logistic regression model with the same covariates and interaction terms as in the main model. Use of inverse probability of observation weights relaxes the assumption that viral load measurements are missing completely at random and instead assumes they are missing at random conditional on covariates in the weight model.

For missing PRO components, we performed multiple imputation by chained equations [75] with 10 imputations based on demographic characteristics, the three care continuum outcomes, and responses to the PRO question on the previous and subsequent evaluation (when there was a previous or subsequent evaluation). We imputed the PROs at the levels of individual questions (e.g., the 9 individual PHQ questions) rather than the aggregate score. We fit our models on each of the 10 imputed datasets, and report the pooled estimates [76]. We re-ran the models with 20 imputations to make sure our estimates were stable. We assessed collinearity among model covariates by calculating variance inflation factors averaged across imputations [77].

Because symptoms of depression are a modifiable risk factor with respect to the care continuum, we conducted a secondary analysis in which we stratified depressive symptoms according to whether subjects were concurrently on antidepressant therapy. We also conducted post hoc analyses in which we further explored the relationship between depressive symptoms and alternative measures related to retention in care: number of scheduled visits, number of kept visits, proportion of kept visits, and 6-month visit constancy over a year (the number of 6-month intervals in the following year in which a patient had at least one visit—which could take values 0, 1, or 2) [78]. These analyses mirrored the covariates and imputation scheme of the primary analyses.

We tested for departures from multiplicative interaction (i.e., sub- or super-multiplicativity) between substance use and depressive symptoms on care continuum outcomes by assessing whether the product terms for moderate-severe symptoms of depression with each of the substances were significantly different than zero on the log scale. Because five interactions for each of three outcomes induces a large number of comparisons, we used the Quasi Information Criterion (QIC) [79, 80] a global test of model fit for each outcome to account for multiple comparisons. The QIC is analogous to the Aikake Information Criterion, representing a

trade-off between goodness-of-fit and model complexity, and is appropriate for use with GEEs. If the mean QIC (across imputations) for a model with interaction terms was higher (worse) than for the corresponding model without interactions, we concluded that there was not compelling evidence of a departure from multiplicative interaction. We used a global test rather than a Bonferroni or other multiple comparison adjustments because global tests are generally more efficient and sensitive than multiple comparison adjustment which can greatly increase the type II error rate [81, 82].

All statistical analyses were conducted in R version 3.4.0 [83], using the packages *mice* [75], *geepack* [84], *geem* [85], and *car* [86].

Results

Our study sample comprised 14,380 individuals who completed 56,208 PROs. A plurality of subjects were white (47.5%) and the majority were male (83.0%) (Table 1). Of all completed PROs, 8996 (16.0%) were missing one or more PRO components, and had values imputed (Fig. 1). Overall, 11,420 (22.0%) of 51,838 PROs with a complete PHQ-9 score indicated moderate-severe symptoms of depression. Among PROs with moderate-severe symptoms of depression, the prevalence of recent substance use was: moderate alcohol, 30.5%; heavy alcohol, 32.2%; cocaine, 9.8%; opioids, 4.3%; and methamphetamine, 13.9%. Among PROs with no-mild symptoms of depression, prevalence of recent substance use was: moderate alcohol 34.9%; heavy alcohol, 28.6%; cocaine, 5.2%; opioids, 1.4%; and methamphetamine, 6.3%.

472 subjects (0.8%) died within 1 year of completing a PRO. Of those, 148 (31%) met the definition for retention in care prior to death, 441 (93%) had an active ART script 5–6 months after the index PRO, and 251 (53%) had all viral loads subsequent to the PRO suppressed. In the fitted models no covariate (except splines for age and time since enrollment in cohort) had an average variable inflation factor greater than 8, indicating minimal collinearity among covariates.

Retention in Care

Following 39,739 PROs (70.8% of the study sample), subjects were retained in care in the subsequent year. There

Table 1 Characteristics of study population based on encounters from Feb. 17, 2005 to July 31, 2016 in which a PHQ-9 was completed

	Initial visit		All visits	
	Moderate-severe symptoms of depression (PHQ-9 ≥ 10)	No-mild symptoms of depression (PHQ-9 < 10)	Moderate-severe symptoms of depression (PHQ-9 ≥ 10)	No-mild symptoms of depression (PHQ-9 < 10)
All, % (n)	25.5% (3522)	74.5% (10,265)	22% (11,420)	78% (40,418)
Age, mean [IQR]	43.0 [35.6–50.2]	44.7 [36.4–52.4]	45.6 [39–52.3]	46.6 [38.9–54.1]
Female	18.2% (641)	16.6% (1700)	18.7% (2139)	16.8% (6802)
Race, % (n)				
White	51.1% (1801)	46.2% (4746)	51.2% (5843)	46.5% (18,810)
Black	28.5% (1004)	36.1% (3710)	29.4% (3353)	36.8% (14,888)
Hispanic	15.2% (537)	13% (1331)	15.4% (1753)	12.8% (5193)
Other	5.1% (180)	4.7% (478)	4.1% (471)	3.8% (1527)
MSM, % (n)	68.5% (2414)	65.8% (6756)	67.8% (7740)	67% (27,078)
Years since enrollment in cohort, mean [IQR]	3.5 [0.3–6]	4.4 [0.5–7.6]	5.5 [1.5–8.6]	6.4 [2–10.1]
On antidepressant therapy, % (n)	32.3% (1139)	17.4% (1783)	40.8% (4664)	22% (8898)
Alcohol use, % (n[a])				
None	33.2% (1110)	35.4% (3504)	37.3% (4045)	36.5% (14,240)
Moderate	29.7% (993)	32.7% (3240)	30.5% (3305)	34.9% (13,585)
Heavy	37.1% (1240)	31.9% (3165)	32.2% (3487)	28.6% (11,136)
Recent cocaine use, % (n[a])	12.6% (425)	6.6% (659)	9.8% (1078)	5.2% (2036)
Recent opioid use, % (n[a])	5.0% (164)	1.9% (178)	4.3% (462)	1.4% (546)
Recent methamphetamine use, % (n[a])	18.5% (620)	8.0% (796)	13.9% (1518)	6.3% (2462)

IQR—interquartile range

[a]Not all subjects completed the PRO questions for alcohol, cocaine, opioid, and methamphetamine use, so the denominators are less than the total numbers of subjects

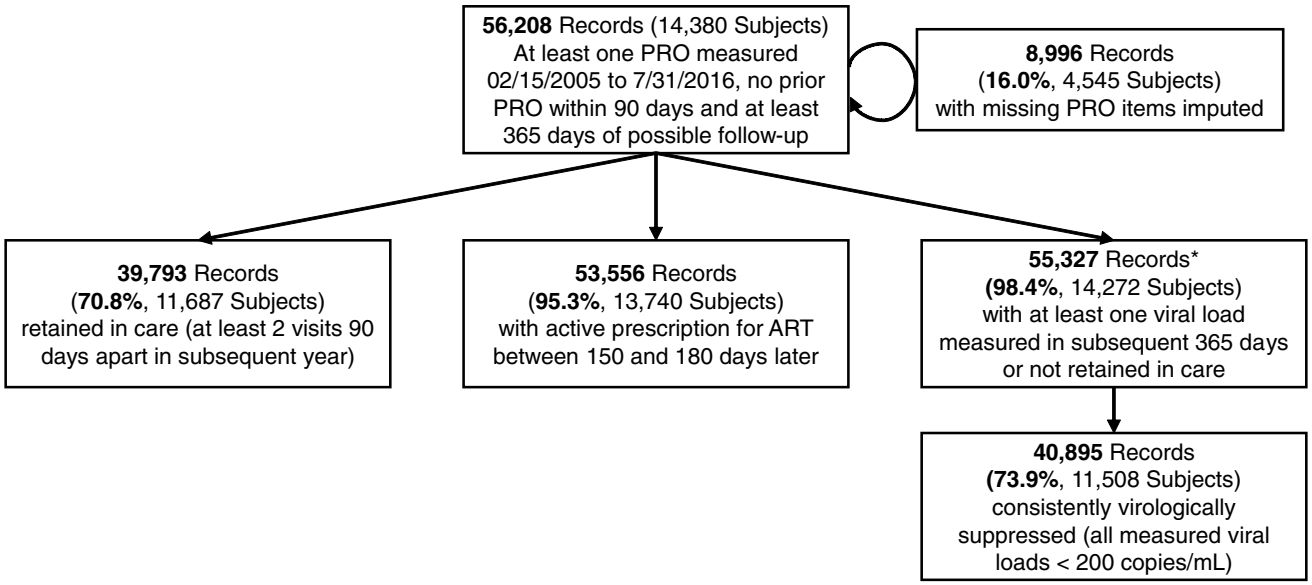

Fig. 1 Consort diagram. 53,213 (94.7% of the total sample) records had at least one viral load drawn in the subsequent year. Of those that had no viral load drawn, 2114 (3.8% of the total sample) were not subsequently retained in care—these were assumed to be not consistently virologically suppressed

were no statistically significant departures from multiplicativity for the relative odds of retention in care associated with symptoms of depression and substance use (Table 2). These associations were consistent when symptoms of depression were stratified by concurrent use of antidepressants (Table 3).

Moderate-severe symptoms of depression (in the absence of substance use) were associated with higher odds of retention (OR 1.20, 95% confidence interval [CI] 1.11–1.29) (Table 2). In contrast, both moderate and heavy alcohol use were associated with lower odds of subsequent retention in care (OR for moderate use vs. no use 0.85, 95% CI 0.81–0.90, OR for heavy use 0.79, 95% CI

Table 2 Effect of symptoms of depression and substance misuse on HIV continuum of care

Substance use	Symptoms of depression (n)	Retention in care, AOR, 95% CI	Receipt of ART, AOR, 95% CI	Virologic suppression, AOR, 95% CI
No substance use	No-mild (17,544)	1.0 (ref)	1.0 (ref)	1.0 (ref)
	Moderate-severe (4315)	1.20 [1.11–1.29]	0.97 [0.87–1.08]	0.90 [0.84–0.96]
Moderate alcohol use	No-mild (17,281)	0.85 [0.81–0.90]	0.99 [0.91–1.08]	1.02 [0.97–1.08]
	Moderate-severe (4154)	1.09 [1.00–1.19]	0.89 [0.78–1.01]	0.86 [0.79–0.93]
Heavy alcohol use	No-mild (14,268)	0.79 [0.74–0.83]	0.90 [0.82–0.99]	1.00 [0.95–1.06]
	Moderate-severe (4439)	0.93 [0.85–1.01]	0.85 [0.75–0.96]	0.80 [0.74–0.87][a]
Recent cocaine use	No-mild (2899)	1.01 [0.93–1.11]	0.81 [0.71–0.93]	0.82 [0.75–0.90]
	Moderate-severe (1437)	1.26 [1.08–1.47]	0.86 [0.70–1.05]	0.76 [0.66–0.87]
Recent opioid use	No-mild (912)	1.12 [0.95–1.32]	1.11 [0.87–1.41]	0.89 [0.77–1.03]
	Moderate-severe (664)	1.07 [0.88–1.30]	0.96 [0.71–1.30]	0.87 [0.73–1.03]
Recent meth-amphetamine use	No-mild (3131)	0.95 [0.87–1.05]	1.00 [0.88–1.13]	0.72 [0.65–0.78]
	Moderate-severe (1950)	1.15 [1.00–1.32]	0.93 [0.77–1.11]	0.62 [0.54–0.70]

Models adjusted for clinic site, age, sex, race, whether subjects were men who have sex with men (MSM), and time since enrollment in the cohort

AOR adjusted odds ratio, *CI* confidence interval

[a]The association between substance use and the outcome in the presence of moderate-severe symptoms of depression is significantly lower than would be expected from the associations with substance use and symptoms of depression alone (p-value for interaction is 0.019)

Table 3 Effects of symptoms of depression, use of antidepressants, and substance misuse on HIV continuum of care

Substance use	Symptoms of depression	Concurrent antidepressant use (n)	Retention in care, AOR, 95% CI	Receipt of ART, AOR, 95% CI	Virologic suppression, AOR, 95% CI
No substance use	No-mild	No (13,357)	1.0 (ref)	1.0 (ref)	1.0 (ref)
		Yes (4187)	1.28 [1.18–1.40]	2.53 [2.03–3.15]	1.13 [1.03–1.23]
	Moderate-severe	No (2514)	1.19 [1.08–1.31]	0.97 [0.85–1.11]	0.85 [0.78–0.92]
		Yes (1801)	1.45 [1.29–1.63]	2.20 [1.78–2.72]	1.09 [0.98–1.21]
Moderate alcohol use	No-mild	No (13,901)	0.85 [0.80–0.90]	1.04 [0.95–1.14]	1.04 [0.98–1.11]
		Yes (3380)	1.15 [1.05–1.27]	2.00 [1.59–2.51]	1.08 [0.99–1.19]
	Moderate-severe	No (2533)	1.08 [0.97–1.20]	0.87 [0.76–1.00]	0.76 [0.69–0.84]*
		Yes (1621)	1.34 [1.18–1.51]	2.02 [1.50–2.72]	1.14 [1.01–1.28]
Heavy alcohol use	No-mild	No (11,648)	0.79 [0.74–0.84]	0.93 [0.84–1.03]	1.00 [0.94–1.07]
		Yes (2620)	1.05 [0.94–1.16]	2.00 [1.57–2.55]	1.14 [1.03–1.27]
	Moderate-severe	No (2824)	0.92 [0.83–1.03]	0.84 [0.72–0.98]	0.74 [0.67–0.82]†
		Yes (1615)	1.12 [0.98–1.27]	1.85 [1.46–2.33]	0.99 [0.88–1.11]
Recent cocaine use	No-mild	No (2274)	1.03 [0.92–1.14]	0.83 [0.72–0.96]	0.79 [0.71–0.88]
		Yes (625)	1.21 [0.99–1.48]	1.71 [1.17–2.51]	1.00 [0.82–1.21]
	Moderate-severe	No (946)	1.30 [1.07–1.58]	0.83 [0.65–1.05]	0.73 [0.61–0.86]
		Yes (491)	1.42 [1.12–1.80]	2.06 [1.32–3.23]	0.91 [0.74–1.12]
Recent opioid use	No-mild	No (690)	1.06 [0.87–1.30]	1.06 [0.81–1.38]	0.86 [0.72–1.03]
		Yes (222)	1.58 [1.16–2.17]	3.76 [1.67–8.46]	1.09 [0.82–1.46]
	Moderate-severe	No (446)	0.97 [0.76–1.24]	0.99 [0.68–1.44]	0.85 [0.69–1.06]
		Yes (218)	1.52 [1.13–2.06]	2.10 [1.32–3.33]	0.97 [0.75–1.26]
Recent methamphetamine use	No-mild	No (2584)	0.97 [0.87–1.07]	1.02 [0.89–1.16]	0.71 [0.64–0.79]
		Yes (547)	1.15 [0.94–1.42]	2.45 [1.75–3.44]	0.80 [0.65–0.98]
	Moderate-severe	No (1440)	1.18 [1.00–1.40]	0.97 [0.79–1.19]	0.60 [0.52–0.70]
		Yes (510)	1.30 [1.03–1.65]	1.91 [1.31–2.79]	0.73 [0.59–0.92]

Models adjusted for clinic site, age, sex, race, whether subjects were men who have sex with men (MSM), and time since enrollment in the cohort

AOR—adjusted odds ratio, *CI*—confidence interval

*,†The association between substance use and the outcome in the presence of symptoms of depression given antidepressant use is significantly different than would be expected from the associations with substance use and symptoms of depression alone. *p-value for interaction is 0.016. †p-value for interaction is 0.040

0.74–0.83). Cocaine, opioid, and methamphetamine use were not associated with retention in care.

In light of finding that symptoms of depression were associated with higher odds of retention in care, we conducted post hoc analyses to further explore the relationship between depression and attendance at HIV primary care visits. In the year following a PRO indicating moderate-severe symptoms of depression, subjects had an average of 4.9 scheduled HIV primary care visits and 4.2 kept visits versus 3.4 scheduled visits and 3.2 kept visits following a PRO indicating no-mild symptoms of depression. In multivariate analyses, subjects with moderate-severe symptoms of depression had on average 10% (95% CI 7–13%) more scheduled visits in the subsequent year, and despite having lower odds of keeping an appointment (OR 0.88, 95% CI 0.84–0.92), they had on average 8% more kept visits (95% CI 6–11%) and were more likely to have a kept appointment in the two following 6-month intervals (OR 1.15, 95% CI 1.09–1.23).

Receipt of ART

Following 53,556 PROs (95.3% of the study sample), subjects had an active prescription for ART 150–180 days later. There was no evidence of non-multiplicative interactions between depression and substance use overall nor in models that considered antidepressant use.

There was no association between moderate-severe symptoms of depression and having an active prescription for ART (OR 0.97, 95% CI 0.87–1.08). Heavy alcohol use and cocaine use were associated with lower odds of subsequently having an active prescription for ART (OR for heavy alcohol use vs. no use 0.90, 95% CI 0.82–0.99, OR for cocaine 0.81, 95% CI 0.71–0.93] (Table 2). When depressive symptoms

were stratified by antidepressant use, both use of antidepressants with no-mild symptoms of depression (OR 2.53, 95% CI 2.03–3.15) and use of antidepressants with moderate-severe symptoms of depression symptoms (OR 2.20, 95% CI 1.78–2.72) were associated with increased odds of subsequently having an active prescription for ART relative to no use of antidepressants with no-mild symptoms (Table 3).

Virologic Suppression

Following 40,895 PROs (73.9% of the 55,327 PROs where at least one viral load was measured or the subject was not retained in care over the following year), all viral loads were < 200 in the subsequent year. There was significant super-multiplicative interaction between depression and heavy alcohol use for the odds of virologic suppression. With no-mild symptoms of depression, heavy alcohol use had no independent association with virologic suppression (OR 1.00, 95% CI 0.95–1.06). However, reporting both moderate-severe symptoms of depression and heavy alcohol use was associated with 0.80 times the odds of virologic suppression (95% CI 0.74–0.87) compared to reporting neither. This was lower than the association expected if each exposure acted independently on a multiplicative scale (the ratio of odds ratios for the interaction term was 0.89, 95% CI 0.81–0.98, p = 0.019). After stratifying depressive symptoms according to concurrent use of antidepressants, the super-multiplicative interaction between heavy alcohol use and moderate-severe symptoms of depression persisted only in the absence of antidepressant use (Table 3). In the absence of antidepressant use there was also a significant interaction between moderate alcohol use and moderate-severe symptoms of depression. Interactions with cocaine, opioid, or methamphetamine use were all non-significant.

Moderate-severe symptoms of depression were independently associated with lower odds of subsequently achieving virologic suppression (OR 0.90, 95% CI 0.84–0.96), as were cocaine use (OR 0.82, 95% CI 0.75–0.90) and methamphetamine use (OR 0.72, 95% CI 0.65–0.78) (Table 2). Neither moderate nor heavy alcohol use nor opioid use had a significant association with virologic suppression.

Discussion

In a longitudinal study of PWH in medical care, the association between heavy alcohol use and consistent virologic suppression during the subsequent year depended on concurrent symptoms of depression. With no-mild symptoms of depression, heavy alcohol use had no association with subsequent virologic suppression. However, the combination of both moderate-severe symptoms of depression and heavy alcohol use was associated with lower odds of subsequent virologic suppression than would be expected based on their independent associations. Our secondary analysis suggested that the interaction between symptoms of depression and heavy alcohol use was present only in PWH not taking antidepressants. Cocaine, opioid, and methamphetamine use did not interact super- or sub-multiplicatively with symptoms of depression when estimating the odds of virologic suppression, and no substance interacted super- or sub-multiplicatively with symptoms of depression for the odds of either retention in care or receipt of ART. These results highlight the need for antidepressant treatment and multifaceted interventions that target alcohol misuse and depression simultaneously.

Few studies have examined the interaction of depression and substance misuse on the HIV care continuum, and they have all been cross-sectional. Two studies in the HIV Research Network, with 10,284 and 5119 subjects, did not find significant interactions between any mental illness (of which 84–88% were depression) and illicit drug use in either receipt of ART or virologic suppression, consistent with our results [36, 52]. A study of 1710 women with HIV found a significant interaction between probable depression, by the Center for Epidemiologic Studies Depression Scale (CES-D) scale, and recent illicit drug use in lowering the odds of receiving ART [35], whereas we found no significant interaction. This difference may be due to the fact that the study included only women, or to the different assessment tools used to measure depression; in specific populations, the Pearson correlation between PHQ-9 and CES-D scores has ranged from 0.77 to 0.85 [87–89]. To our knowledge, no prior studies have evaluated the interaction between alcohol use and depression in PWH.

The interaction between symptoms of depression and heavy alcohol use raises mechanistic questions. Poor adherence to ART is the most cited potential mechanism for the effect of depression on virologic suppression, although in several studies depression has been associated with decreased virologic suppression even after adjusting for self-reported adherence [13]. Additionally, depression may affect the timing of ART initiation and interruptions to ART [13, 90]. Depression has also been associated with high-risk sexual behaviors [31, 91], which may predispose to super-infection with multiple strains of HIV, increasing the risk of resistance [91]. Alcohol likely has similar effects on adherence, timing of ART, and high-risk behaviors [26, 31, 92]. Furthermore, in vitro studies and studies of simian immunodeficiency virus suggest that alcohol may have more direct effects on viral burden by increasing viral replication and promoting chronic, systemic immune activation [49]. Lastly, both depression and alcohol misuse are associated with psychosocial comorbidities that can impair engagement in care [36, 48]. Alcohol and depression may work synergistically in worsening adherence, or it may be that the direct biological

effects of alcohol have a more pronounced impact when layered onto poor adherence to ART engendered by depression. The interaction may also represent a confluence of psychosocial factors or that alcohol use patterns in patients with depression differ from use in non-depressed patients in a manner not captured by the AUDIT-C. It is important to note that CNICS measures of depressive symptoms and alcohol use reflect recent trends; as they are measured concurrently, we cannot infer temporal directionality regarding the mechanism of interaction.

Regardless of the mechanism, our results have several implications. Our findings that the interaction between depression and heavy alcohol use persisted in patients not on antidepressants reinforces the imperative of diagnosing and treating depression, especially in the setting of alcohol misuse. Our results also argue for the use of multifaceted interventions that target both depression and alcohol misuse. Integrated interventions that target both psychiatric and substance use disorders simultaneously are more successful than multiple separate interventions [48, 93], and are most effective if they target both clinical and psychosocial aspects of disease in a multidisciplinary fashion [48, 94].

Our findings regarding the main effects of depression and substance use on virologic suppression and receipt of ART are largely consistent with the published literature. We found that depression and use of cocaine or methamphetamine were associated with lower odds of virologic suppression, and that cocaine use and heavy alcohol use were associated with lower odds of being on ART. Other longitudinal studies have found that depression and use of cocaine are associated with failure to achieve virologic suppression [12–19, 30, 33], whereas studies of the association between alcohol, opioid, or methamphetamine use and viral load have had mixed results [24, 33, 38, 40, 95–97]. Other studies have also found illicit drug use (including cocaine use and intravenous opioid use) to be associated with lower odds of PWH in care being on ART [24, 34, 35, 52], while finding no such association for depression [35, 36, 52].

Existing literature on retention in care is more mixed, owing in part to multiple definitions of retention. We found that moderate and heavy alcohol use were associated with decreased retention in care, and found no association of retention in care with either cocaine, opioid, or methamphetamine use. Further, we found that symptoms of depression were associated with increased retention in care. A previous study in the CNICS cohort found, as we did, that heavy alcohol use (as defined by the AUDIT-C) is associated with decreased retention in care [25], although other studies with alcohol misuse abstracted from the medical record have not found such an association [98, 99]. In contrast to our findings, prior studies have generally found illicit substance use (both all substances in aggregate, and cocaine and opioids individually) to be associated with worse retention in care [98–100], and have either found depression to be associated with decreased retention in care [9], or found no association [98, 99]. With the exception of the analysis done in CNICS, these studies have all used different definitions for retention in care than we did: having a visit in all four 3-month intervals over a year, not being lost to follow-up for 60 days, or visit constancy (the number of intervals in which subjects had at least one visit). Our discordant findings, particularly the association between depressive symptoms and increased retention in care, may be due in part to the fact that the IOM's definition (at least two HIV care visits at least 90 days apart within the subsequent year [60]) depends on the total number of kept visits. In our sample, patients with moderate-severe symptoms of depression had more primary care visits scheduled, and, despite having lower odds of keeping an appointment, had more kept visits. This may reflect the fact that depression is associated with higher health services utilization [101], and in a population of PWH in care, a higher depressive symptom burden may prompt more primary care visits. With respect to substance misuse, as many CNICS subjects have been in care for years and we use repeated observations in our study, those who have managed to negotiate HIV care while using illicit drugs likely contribute more observations than those who drop out of care [54]. Furthermore, our exposure for drug use (any reported use in the past 3 months) may represent a different pattern of use than in other studies, many of which use a shorter time frame or restrict to IV drug use [98–100].

Our study has a number of potential limitations. First, depression and substance use were based on patient reported instruments, and are subject to possible underreporting. However, the instruments are all validated, and electronic self-report permits integration into care and decreases underreporting of risk behaviors due to social desirability bias [102]. Second, we used the PHQ-9 to categorize depression rather than criteria from the Diagnostic and Statistical Manual of Mental Disorders, which differs from some prior studies. However, the PHQ-9 cutoff of 10 has high sensitivity and specificity relative to a clinical diagnosis [55], and current depression symptom burden is arguably more important to HIV outcomes than a clinical diagnosis in which symptoms may or may not be controlled. Third, we combined moderate and severe depression into a single exposure, which might overlook nonlinear associations with depression severity, as have been found in sexual risk behaviors among MSM [103]. Fourth, it is possible that some patients leave the cohort to establish care at another clinical site, and are incorrectly categorized as not retained. To skew our results, such transitions would have to be more or less likely for PWH with depression or substance misuse. Fifth, although our analysis accounts for repeated measures within individuals, we do not account for the cumulative effect or duration of depressive symptoms or substance use. Sixth, we

do not consider possible mediation of the effect of substance use by depressive symptoms or consider bidirectional effects (e.g. alcohol use increasing depressive symptoms which in turn might increase alcohol use). Seventh, we do not adjust for overall disease severity and comorbidities, which may confound the relationship between depression, substance use, and HIV control outcomes. Finally, we used logistic regression with a common outcome, so odds ratios should not be assumed to estimate risk ratios; odds ratios will generally be greater in magnitude than risk ratios when the risk of the outcome is > 10%.

Our study also has a number of strengths. The CNICS cohort comprises patients in routine HIV care and is roughly representative of patients in care for HIV in the United States with both geographic and clinical diversity. Furthermore, within CNICS, PROs are incorporated into regular clinical care. Thus our results are likely to generalize to patients in care for HIV in the United States [104, 105]. Additionally, because the PROs are collected via computer-assisted self-interview, social desirability is less likely to influence patients' responses to sensitive questions like recent illicit substance use. Lastly, we used robust statistical analyses to account for repeated measurements and missing data.

Conclusions

Depression and misuse of substances play a significant role in preventing PWH from sustaining HIV control. We found that symptoms of depression and heavy alcohol use interact to lower the chances of achieving virologic suppression, yielding a more detrimental effect of heavy alcohol use in patients with moderate-severe symptoms of depression than in those without. When considering antidepressant use, the interaction persisted only in those not on antidepressants. These results underscore the importance of recognizing and treating depression in PWH, particularly among persons with heavy alcohol use, and suggest that deploying integrated, multifaceted interventions that target both depression and alcohol misuse could greatly benefit a subset of PWH at high risk for poor outcomes.

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Compliance with Ethical Standards

Conflict of interest Anthony T. Fojo, Catherine R. Lesko, Keri L. Calkins, Richard D. Moore, Mary E. McCaul, Heidi E. Hutton, William C. Mathews, Heidi Crane, Karen Cropsey, Michael J. Mugavero, Kenneth Mayer, Brian W. Pence, Bryan Lau, and Geetanjali Chander declares that they have no conflict of interest. Katerina Christopoulos has been scientific advisory board member for Roche Pharmaceuticals and a community advisory board member for Gilead Sciences Inc.

Ethical Approval This article does not contain any studies with animals performed by any of the authors.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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