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ORIGINAL PAPER

What are the Patterns Between Depression, Smoking, Unhealthy Alcohol Use, and Other Substance Use Among Individuals Receiving Medical Care? A Longitudinal Study of 5479 Participants

Kelly V. Ruggles[1] · Yixin Fang[1] · Janet Tate[2] · Sherry M. Mentor[1] · Kendall J. Bryant[3] · David A. Fiellin[2] · Amy C. Justice[2] · R. Scott Braithwaite[1]

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Abstract To evaluate and characterize the structure of temporal patterns of depression, smoking, unhealthy alcohol use, and other substance use among individuals receiving medical care, and to inform discussion about whether integrated screening and treatment strategies for these conditions are warranted. Using the Veterans Aging Cohort Study (VACS) we measured depression, smoking, unhealthy alcohol use and other substance use (stimulants, marijuana, heroin, opioids) and evaluated which conditions tended to co-occur within individuals, and how this co-occurrence was temporally structured (i.e. concurrently, sequentially, or discordantly). Current depression was associated with current use of every substance examined with the exception of unhealthy alcohol use. Current unhealthy alcohol use and marijuana use were also consistently associated. Current status was strongly predicted by prior status ($p < 0.0001$; OR = 2.99–22.34) however, there were few other sequential relationships. Associations in the HIV infected and uninfected subgroups were largely the same with the following exceptions. Smoking preceded unhealthy alcohol use and current smoking was associated with current depression in the HIV infected subgroup only ($p < 0.001$; OR = 1.33–1.41 and $p < 0.001$; OR = 1.25–1.43). Opioid use and current unhealthy alcohol use were negatively associated only in the HIV negative subgroup ($p = 0.01$; OR = 0.75). Patterns of depression, smoking, unhealthy alcohol use, and other substance use were temporally concordant, particularly with regard to depression and substance use. These patterns may inform future development of more integrated screening and treatment strategies.

Keywords Substance use · Alcohol use · Depression · Smoking · HIV

Introduction

Depression, smoking and unhealthy alcohol use [1] account for 21.6 % of the population mortality burden globally and 23.1 % of the population morbidity burden in the United States [2–4]. An emerging question is whether these conditions comprise a distinct syndrome drawing on their widely observed associations [5–7], particularly in individuals with chronic illnesses related to risky behaviors such as HIV infection [8, 9]. For example, analysis of depression, smoking, and unhealthy alcohol use in the Veterans Aging Cohort Study (VACS) found that cessation of any of the three was associated with discontinuation of any of the other two conditions [9]. Further, depression has been closely associated with smoking and unhealthy alcohol use in several large cohort studies [10, 11]. In addition to this triad, substance use, including stimulants, non-medical use of prescription opioids, heroin, and marijuana use, has been associated with increased depression [12–16], alcohol use [17, 18], and smoking [19–22].

However, few of these studies assessed whether temporal patterns underlie the associations, and if so, whether these patterns have a particular structure (e.g. concordant, sequential, or discordant). Elucidating and characterizing temporal patterns is particularly important when thinking

✉ R. Scott Braithwaite
Scott.Braithwaite@nyumc.org

[1] Department of Population Health, New York University School of Medicine, New York, NY, USA

[2] Yale University School of Medicine, New Haven, CT, USA

[3] National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, MD, USA

about integration of screening and treatment strategies. If conditions have temporal concordance, an integrated screening strategy is likely to yield a greater health advantage over a nonintegrated strategy. For example, if a patient screens positive for one condition, automatic screening and/or enhanced surveillance for the other characteristics could improve downstream health. Moreover, integrated treatment of associated conditions could result in a greater health impact if discontinuation of one behavior makes discontinuation of another behavior more likely. Bundled therapy designs have been shown to be effective in smoking and alcohol reduction [23] and in simultaneous interventions targeting diet and physical activity [24, 25]. However, there is still limited evidence on where and how to target simultaneous and sequential intervention strategies, particularly in regards to the HIV infected population.

To address these questions, we used the VACS cohort, a multi-site study of individuals in care, with high representation of chronic diseases related to risky behavior (half HIV-infected) and more than a decade of follow-up. We used longitudinal analyses to identify whether temporal patterns underlie associations between depression, smoking, unhealthy alcohol use, and other substance use; and if so, whether these patterns have a particular structure (e.g. concordant, sequential, or discordant).

Methods

Sample

We used data from the Veterans Aging Cohort Study (VACS) [26–28], a prospective, longitudinal, observational study of United States veterans receiving care in the Veterans Health Administration. The overall goal of VACS is to inform interventions to improve medical outcomes for patients infected with HIV [28]. An HIV uninfected control group was matched by age, race, gender and site to the HIV infected sample to study comorbidities in aging patients with HIV [26, 28]. All VACS patients completed a baseline survey and follow-up surveys were launched every 12–18 months. Depending on when a patient enrolled, they could participate in up to six follow-up surveys. Study enrollment began in 2002, and the first annual follow-up survey occurred between September 2003 and September 2004.

Our study focused on the temporal relationship between depression, smoking, unhealthy alcohol use and other substance use in this cohort. Only patients reporting that they had ever smoked and consumed alcohol at baseline were included in this analysis.

Measures

Depression was measured using the patient health questionnaire (PHQ-9) score, a self-administered diagnostic instrument for mental disorders [29]. Scores range between 0 and 27 and a cutoff between 8 and 11 has been found to accurately detect major depressive disorder [30]. Therefore, we used a PHQ-9 score $\geq$8 to indicate depression. Smoking status was determined from survey questions and categorized as never (0), current smoker (1) and past smoker (2). Alcohol use was measured using the Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) score [31]. This test consists of three questions: (1) How often do you have a drink containing alcohol? (a. never, b. monthly or less, c. 2–4 times a month, d. 2–3 times a week, e. 4 or more times a week); (2) How many standard drinks containing alcohol do you have on a typical day? (a. 1 or 2, b. 3 or 4, c. 5 or 6, d. 7 to 9, e. 10 or more); and (3) How often do you have six or more drinks on one occasion? (a. never, b. less than monthly, c. monthly, d. weekly, e. daily or almost daily). A score is calculated as the sum across questions, ranging from 0 to 12 (a = 0 points, b = 1 point, c = 2 points, d = 3 points, e = 4 points) [32]. We dichotomized AUDIT-C score using $\geq$4 as the cutoff for unhealthy alcohol use [31].

The VACS survey included items on the frequency of drug use: marijuana, heroin, opioids (heroin, morphine, codeine, opium and prescription opioids/painkillers), cocaine, crack, and stimulants (amphetamines, speed, and crystal methamphetamine) [33]. We grouped cocaine and crack with other stimulants, referred to as simply stimulants. At baseline heroin and opioids were queried as single question. Subsequent surveys separated heroin and opioids, allowing for downstream analysis specific to heroin use. However, since there was no baseline question specifically querying heroin use, we were unable to assess the effect of heroin use at baseline in any of our analyses. For all substances, responses were collapsed into yes/no based on whether or not the individual reported any past year use.

Quantitative Analyses

Our study focused on identifying and characterizing temporal relationships between depression, smoking, unhealthy alcohol use, and other substance use in VACS participants. The seven outcomes (AUDT-C score $\geq$4, current smoking, PHQ-9 score $\geq$8, current marijuana use, current stimulant use, current heroin use, and current opioid use) were evaluated using multiple logistic regression. Predictor variables included in the model were (1) the outcome of interest at baseline; (2) HIV status; (3) other characteristics reported in the same survey; (4) other characteristics reported in the immediately preceding survey; and (5) number of years from enrollment to the current

survey. Here 'other' characteristics were the three remaining characteristics after excluding the outcome in a model; for example, if depression was the outcome in a model then other characteristics were smoking, unhealthy alcohol use, and other substance use. Demographic variables such as age, gender and race were not included in the final models, because they were not found to be significant when included. We used the generalized-estimation-equation method (GEE) for binary outcomes [34] to account for repeated measures on the same patients across seven surveys using PROC GENMOD in SAS 9.3. Multiple-imputations was used to address missing data [35] using PROC MI to generate ten imputed datasets and PROC MIANALYZE to summarize the statistical results from analyzing these imputed datasets. To alleviate the bias due to the assumption of an implicit imputation model, we did not impute missing data due to loss to follow up. Instead we only imputed missing values in cases where the survey was taken by the participant but there was missing data for a specific condition (e.g. patient participated in follow-up surveys 1–3 but missed the alcohol question on survey 2, we imputed missing data for alcohol at survey 2 without imputing missing data for surveys 4–6).

Because of the multitude of comparisons, the values of the odds ratio (OR) between any two characteristics that appeared in different models were summarized in terms of their range (e.g., smoking and depression appeared in eight models and therefore 1.23–1.30 was the range of eight ORs between smoking and depression.)

Results

Among the 7327 VACS participants, 5479 met the study inclusion criteria of reporting ever drinking alcohol and smoking cigarettes. Of these, 52.5 % (2878) were HIV infected and 47.5 % (2601) were HIV uninfected. Within the 2878 HIV infected participants meeting the study criteria, 97.3 % were male with average age of 49.8 years and two-thirds were African American (67.5 %). Of 2601 HIV uninfected VACS participants reporting tobacco smoking and alcohol use, 94.5 % were male, 63.8 % were African American and had an average age of 51.4 years. HIV infected participants were significantly younger (49.8 vs. 51.4; $p < 0.0001$), more male (97.3 vs. 94.5 %; $p < 0.0001$), and more likely to be black (67.5 vs. 63.8 %; $p = 0.001$), but these differences were not clinically significant. Further, HIV infected participants, compared to uninfected, reported more current use of marijuana (19 vs. 13 %) and cocaine (18 vs. 14 %), and similar use of stimulants (defined as amphetamines, speed, and crystal methamphetamine) (3 vs. 2 %) and opioids (8 % for both) (Table 1). At baseline heroin and other opioids were combined into one question.

All 5479 of included VACS participants completed the first survey, and follow-up survey numbers declined as expected in a cohort with continuous enrollment. Subsequent survey completion was 4867, 3647, 3149, 2581, 1937 and 1061 for the first through sixth follow-up surveys, respectively.

We observed concordant temporal patterns between many of the conditions of interest. Current depression was associated with current use of nearly every other substance examined (smoking (OR = 1.23–1.30), stimulants (OR = 1.83–2.06), marijuana (OR = 1.35–1.38), opioids (OR = 1.51–1.55), and heroin (OR = 1.60–1.62), $p < 0.001$ for all) regardless of which variable was treated as the outcome and which variables were predictors (Tables 2, 3, 4). Depression was not significantly associated with unhealthy alcohol use (Table 5). Additionally, current heroin and opioid use were found to be associated with previous depression ($p < 0.01$; OR = 1.30–1.33) (Table 2). Current unhealthy alcohol use and current marijuana use were consistently associated ($p < 0.0001$; OR = 1.59–1.63) (Tables 2, 5).

Opioid use was linked to a qualitatively distinct network of co-occurring conditions, with previous opioid use negatively associated with current unhealthy alcohol use ($p < 0.01$; OR = 0.81) and current opioid use not associated with current use of other substances (Tables 2, 5). Heroin use was associated with current ($p < 0.01$, OR = 1.56) and previous smoking ($p < 0.001$, OR = 2.02) (Table 2). Only one finding suggested a sequential temporal structure (i.e. presence of one condition at a prior time associated with presence of another condition at present time, but when relationship is not reciprocal). Smoking preceded unhealthy alcohol use but unhealthy alcohol use did not precede smoking (Tables 4, 5).

When investigating the impact of HIV infection on these relationships, we found the associations in HIV infected and uninfected subgroups to be broadly the same with a few notable exceptions. The sequential temporal relationship in which smoking precedes unhealthy alcohol use and the relationship between current smoking and current depression was only identified in the HIV infected population ($p < 0.001$; OR = 1.33–1.41 and $p < 0.001$; OR = 1.25–1.43, respectively). Additionally, the negative association between previous opioid use and current unhealthy alcohol use was only found in the HIV negative subgroup ($p = 0.01$; OR = 0.75).

Discussion

We observed numerous and pervasive temporally concordant patterns between depression, smoking, unhealthy alcohol use and other substance use (Tables 2, 3, 4, 5). Although we found only one instance in which the presence of a condition at the current time was associated with

Table 1 Baseline characteristics of VACS participants who reported ever drinking alcohol and smoking cigarettes

	HIV+		HIV−		p value
	N	Mean or %	N	Mean or %	
Age, mean (SD)	2878	49.8 (8.3)	2601	51.4 (9.0)	<0.0001
Male, %	2800	97.3 %	2457	94.5 %	<0.0001
Race white, %	548	19.0 %	592	22.8 %	0.001
Race black, %	1942	67.5 %	1659	63.8 %	–
Race other, %	388	13.5 %	350	13.5 %	–
HCV+, %	1603	55.7 %	894	34.4 %	<0.0001
Died, %	882	30.7 %	476	18.3 %	<0.0001
AUDIT-C ≥4	1100	45.5 %	944	50.5 %	0.001
Current smoking, %	1805	64.5 %	1248	58.6 %	<0.0001
PHQ-9 ≥8	913	32.0 %	777	30.2 %	0.14
Substance use, %	954	33.9 %	684	26.8 %	<0.0001
Marijuana, %	531	19.1 %	325	12.9 %	<0.0001
Cocaine, %	488	17.7 %	351	14.0 %	0.0003
Stimulants, %	78	2.8 %	45	1.8 %	0.01
Heroin, %	NA[a]	–	NA[a]	–	–
Opioid, %	218	8.0 %	211	8.5 %	0.51
Benzodiazepines, %	NA[a]	–	NA	–	–

[a] Baseline data for heroin and prescription opioids are combined. Benzodiazepine use is not available at baseline

Table 2 Logistic regression analysis of current drug use and the current and prior status of unhealthy alcohol use, smoking and depression

Parameter	Current stimulant use		Current marijuana use		Current opioid use		Current heroin use	
	Model 1		Model 2		Model 3		Model 4	
	OR[a]	p	OR[a]	p	OR[a]	p	OR[a]	p
Number of years from enrollment	0.98	0.54	0.99	0.49	1.01	0.24	**0.93**	**<0.0001**
HIV status	2.48	<0.0001	1.39	<0.0001	0.87	0.05	1.14	0.31
Stimulant use at baseline	**18.34**	**<0.0001**	–	–	–	–	–	–
Marijuana use at baseline	–	–	**15.57**	**<0.0001**	–	–	–	–
Opioid use at baseline[e]	–	–	–	–	**2.99**	**<0.0001**	–	–
Current unhealthy alcohol use	**1.68**	**0.01**	**1.59**	**<0.0001**	**0.82**	**0.02**	1.22	0.09
Current unhealthy alcohol use at preceding survey[b]	1.28	0.15	0.99	0.86	0.88	0.07	0.90	0.32
Current smoking	1.16	0.55	1.20	0.02	1.01	0.89	**1.56**	**<0.01**
Current smoking at preceding survey[c]	1.21	0.42	1.09	0.24	1.05	0.55	**2.02**	**<0.001**
Current depression	**2.06**	**<0.0001**	**1.35**	**<0.0001**	**1.55**	**<0.0001**	**1.60**	**<0.0001**
Current depression at preceding survey[d]	1.35	0.09	0.93	0.27	**1.33**	**<0.001**	**1.30**	**0.01**

Four logistic regression models were fitted for four outcome variables (current stimulant use, current marijuana use, current prescription opioid use, and current heroin use), respectively, with the status of the corresponding outcome variable at baseline, and the status of unhealthy alcohol, smoking, and depression at the current and preceding surveys, adjusting for number of years from enrollment and HIV status

Bold values correspond to $p < 0.05$

'–' indicates that predictor was not included in the model

[a] Adjusted for HIV status and number of years from enrollment

[b] Controlling for current unhealthy alcohol use

[c] Controlling for current smoking

[d] Controlling for current depression

[e] Baseline data for heroin and prescription opioids are combined

Table 3 Logistic regression analysis of current depression and the current and prior status of smoking, depression and drug use

Parameter	Current depression							
	Model 1		Model 2		Model 3		Model 4	
	OR[a]	p	OR[a]	p	OR[a]	p	OR[a]	p
Number of years from enrollment	0.98	0.02	0.98	0.02	0.98	0.01	0.97	<.01
HIV status	**0.76**	**<0.0001**	**0.76**	**<0.0001**	**0.78**	**<0.0001**	**0.72**	**<0.0001**
Depression status at baseline	**6.39**	**<0.0001**	**6.43**	**<0.0001**	**6.26**	**<0.0001**	**5.85**	**<0.0001**
Current unhealthy alcohol use status	**1.13**	**0.03**	1.11	0.06	**1.15**	**0.01**	1.11	0.10
Current alcohol use status at preceding survey[b]	1.09	0.10	1.09	0.08	1.10	0.06	1.10	0.13
Current smoking status	**1.30**	**<0.0001**	**1.29**	**<0.0001**	**1.29**	**<0.0001**	**1.30**	**<0.0001**
Current smoking status at preceding survey[c]	1.01	0.85	1.01	0.89	1.01	0.91	0.96	0.57
Current stimulant use status	**1.83**	**<0.001**	–	–	–	–	–	–
Current stimulant use status at preceding survey[d]	1.09	0.61	–	–	–	–	–	–
Current marijuana use status	–	–	**1.38**	**<0.0001**	–	–	–	–
Current marijuana use status at preceding survey[e]	–	–	0.92	0.17	–	–	–	–
Current opioid use status	–	–	–	–	**1.51**	**<0.0001**	–	–
Current opioid use status at preceding survey[f]	–	–	–	–	**1.24**	**<0.01**	–	–
Current heroin use status	–	–	–	–	–	–	**1.62**	**<0.01**
Heroin use status at preceding survey[g]	–	–	–	–	–	–	1.03	0.85

Four logistic regression models were fitted for the status of depression as outcome variable, with the depression status at the baseline, and the statuses of unhealthy alcohol use, smoking, and one of the four drug uses (1. stimulant use; 2. marijuana use; 3. prescription opioid use; 4. heroin use) at the current and preceding surveys

Bold values correspond to $p < 0.05$

'–' indicates that predictor was not included in the model

[a] Adjusted for HIV status and number of years from enrollment

[b] Controlling for current unhealthy alcohol use

[c] Controlling for current smoking

[d] Controlling for current stimulant use

[e] Controlling for current marijuana use

[f] Controlling for current opioid use

[g] Controlling for current heroin use

the presence of another condition at a previous time (smoking tended to precede unhealthy alcohol use, Table 5), we identified several associations between conditions that may have important implications for integration of screening and treatment.

Screening

Our results underscore the importance of integrating screening strategies for depression, smoking, unhealthy alcohol use and other substance use. Screening positive for depression should increase the index of suspicion for concomitant substance use of any type. Conversely, incidental discovery of substance use (e.g. uncovering non-medical use of prescription opioids) may constitute a circumstance in which the US Preventative Services Task Force (USPSTF), a panel of experts who develop recommendations for preventive medicine, considers depression screening as a "B" (service recommended, high certainty that the net benefit is moderate or moderate certainty that the net benefit is moderate to substantial) rather than a "C" (service selectively offered, at least moderate certainty that the net benefit is small) [36]. Indeed, these relationships raise the question of whether existing screening algorithms for depression, smoking and unhealthy alcohol use should be additionally integrated. While it is impractical to perform experimental trials of all plausible permutations of these screening strategies, mathematical models may offer a means of identifying the most promising candidate strategies for additional evaluation.

Treatment

Our results also underscore the concept of integrating treatment strategies for depression, smoking, unhealthy alcohol use and other substance use. Some depressive symptoms will likely improve with effective treatment of an underlying substance use disorder. Our results reinforce the known precept that, if a patient has both substance use

Table 4 Logistic regression analysis of current smoking and the current and prior status of alcohol, depression and drug use

Parameter	Current smoking							
	Model 1		Model 2		Model 3		Model 4	
	OR[a]	p	OR[a]	p	OR[a]	p	OR[a]	p
Number of years from enrollment	0.91	<0.0001	0.91	<0.0001	0.91	<0.0001	0.92	<0.0001
HIV status	1.05	0.48	1.03	0.61	1.05	0.42	1.04	0.62
Smoking at baseline	**22.34**	**<0.0001**	**22.24**	**<0.0001**	**22.33**	**<0.0001**	**19.36**	**<0.0001**
Current unhealthy alcohol use	**1.59**	**<0.0001**	**1.58**	**<0.0001**	**1.60**	**<0.0001**	**1.65**	**<0.0001**
Current unhealthy alcohol use at preceding survey[b]	1.06	0.26	1.05	0.28	1.06	0.21	1.13	0.06
Current depression	**1.24**	**<0.0001**	**1.23**	**<0.0001**	**1.24**	**<0.0001**	**1.24**	**<0.001**
Current depression at preceding survey[c]	**1.12**	**0.02**	**1.12**	**0.02**	**1.12**	**0.02**	1.11	0.06
Current stimulant use	1.09	0.71	–	–	–	–	–	–
Current stimulant use at preceding survey[d]	1.35	0.18	–	–	–	–	–	–
Current marijuana use	–	–	**1.22**	**0.01**	–	–	–	–
Current marijuana use at preceding survey[e]	–	–	1.13	0.10	–	–	–	–
Current opioid use	–	–	–	–	1.06	0.44	–	–
Current opioid use at preceding survey[f]	–	–	–	–	1.10	0.24	–	–
Current heroin use	–	–	–	–	–	–	1.32	0.11
Current heroin use at preceding survey[g]	–	–	–	–	–	–	1.36	0.06

Four logistic regression models were fitted for the status of smoking as outcome variable, with the smoking status at the baseline, and the statuses of unhealthy alcohol use, depression, and one of the four and drug uses (1. stimulant use; 2. marijuana use; 3. prescription opioid use; 4. heroin use) at the current and preceding surveys

Bold values correspond to $p < 0.05$

'–' indicates that predictor was not included in the model

[a] Adjusted for HIV status and number of years from enrollment

[b] Controlling for current unhealthy alcohol use

[c] Controlling for current depression

[d] Controlling for current stimulant use

[e] Controlling for current marijuana use

[f] Controlling for current opioid use

[g] Controlling for current heroin use

and persistent depression it may be particularly important to ensure that treatment encompasses depression. An example of an existing strategy is bupropion, which has Food and Drug Administration approval for treatment of both depression and smoking cessation. Counseling strategies, such as cognitive behavioral therapy, have demonstrated efficacy for both mood and substance use disorders. Additionally, Naltrexone, a drug approved for the treatment of alcohol and opioid dependence, has been shown to decrease smoking behavior [33].

Previous studies using VACS have identified consistent, significant relationships between current depression and current unhealthy alcohol use, whereas the current analyses, which incorporate substance use, find less consistent relationships [9]. Indeed, substance use appears to attenuate the magnitude of the relationship between depression and unhealthy alcohol use, since removing drug variables produced similar odds ratios as those previously reported ($p = 0.02$, OR = 1.13).

Unhealthy alcohol use, smoking, and stimulant use often co-occur, tending to start and stop together [9]. If their concordance manifests a common causal mechanism rather than a common external factor, it may improve outcomes if they are addressed simultaneously. For example, if a causal relationship between two such conditions exists, we can interpret the odds ratio as a likelihood of discontinuing use of one condition given the cessation of another. This suggests the possibility that stopping unhealthy alcohol use is associated with an increased odds of discontinuing stimulant use of 57 % (Table 5; OR = 1.57), and smoking by 70 % (Table 5; OR = 1.68–1.71).

Basic science research also supports the idea that these conditions may be mutually reinforcing [8, 22]. All substances of abuse, including alcohol and nicotine, affect the central reward pathways based in the ventral tegmental area and the nucleus accumbens [37, 38] and involve common genetic liability [39]. Further, the significant co-occurrence identified between depression and substance

Table 5 Logistic regression analysis of current unhealthy alcohol use and the current and prior status of smoking, depression and drug use

Parameter	Current unhealthy alcohol use							
	Model 1		Model 2		Model 3		Model 4	
	OR[a]	p	OR[a]	p	OR[a]	p	OR[a]	p
Number of years from enrollment	0.96	<0.0001	0.96	<0.0001	0.96	<0.0001	0.96	<0.001
HIV status	0.88	0.04	0.86	0.01	0.88	0.04	0.88	0.07
Unhealthy alcohol use at baseline	**5.21**	**<0.0001**	**5.27**	**<0.0001**	**5.18**	**<0.0001**	**4.82**	**<0.0001**
Current smoking	**1.70**	**<0.0001**	**1.68**	**<0.0001**	**1.71**	**<0.0001**	**1.70**	**<0.0001**
Current smoking at preceding survey[b]	**1.29**	**<0.0001**	**1.27**	**<0.0001**	**1.29**	**<0.0001**	**1.31**	**<0.001**
Current depression	1.09	0.07	1.08	0.11	**1.11**	**0.03**	1.09	0.11
Current depression at preceding survey[c]	1.01	0.91	1.00	0.96	1.02	0.67	1.03	0.59
Current stimulant use	**1.57**	**0.01**	–	–	–	–	–	–
Current stimulant use at preceding survey[d]	0.88	0.47	–	–	–	–	–	–
Current marijuana use	–	–	**1.63**	**<0.0001**	–	–	–	–
Current marijuana use at preceding survey[e]	–	–	1.08	0.27	–	–	–	–
Current opioid use	–	–	–	–	0.84	0.06	–	–
Current opioid use at preceding survey[f]	–	–	–	–	**0.81**	**<0.01**	–	–
Current heroin use	–	–	–	–	–	–	1.17	0.30
Current heroin use at preceding survey[g]	–	–	–	–	–	–	0.83	0.24

Four logistic regression models were fitted for the status of unhealthy alcohol use as outcome variable, with the unhealthy alcohol use status at the baseline, and the statuses of smoking, depression, and one of the four drug uses (1. stimulant use; 2. marijuana use; 3. prescription opioid use; 4. heroin use) at the current and preceding survey

Bold values correspond to $p < 0.05$

'–' indicates that predictor was not included in the model

[a] Adjusted for HIV status and number of years from enrollment

[b] Controlling for current smoking

[c] Controlling for current depression

[d] Controlling for current stimulant use

[e] Controlling for current marijuana use

[f] Controlling for current opioid use

[g] Controlling for current heroin use

use are in line with negative reinforcement models of addiction, which posit that negative emotional states associated with withdrawal may trigger dependence-induced drug intake and/or relapse [40]. Epidemiological data and computer simulation suggest that unhealthy alcohol use, substance use and depression lead to new HIV infections and promote disease progression [41, 42]. Therefore, these conditions not only "travel together" but substantially impact HIV progression and treatment.

Limitations

There are notable limitations to our study. Not every survey was completed by every patient and the intervals between surveys were variable. Additionally, these results may be affected by survivor bias and attrition bias, particularly for persons with depression. As this study was completed in a veteran population with a large representation of a particular condition (HIV), it is possible that these results are not generalizable to the larger population of individuals in care with behavioral risk-based chronic diseases. However, many of the relationships identified have been shown to occur in the general population [14, 15, 43, 44]. We examined substance use and not the presence of substance use disorders. Some individuals may have had low or intermittent levels of substance use that could remit spontaneously and not require treatment. Use of opioids was asked in the same survey section as marijuana and cocaine, with the intent of capturing non-medical use. Patients may have answered in the affirmative when referring to opioids prescribed for pain. We note that only 30 % of patients endorsing current opioid use had an active prescription for an opioid at that time.

In conclusion, patterns of depression, smoking, unhealthy alcohol use and other substance use were temporally concordant, particularly with regard to depression and

substance use. Our results, if reproduced in an independent analyses, have implications for clinical care and mechanistic insight.

Compliance with Ethical Standards

Conflict of Interest The authors have no conflicts of interest to declare.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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

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