



Published in final edited form as:

AIDS Behav. 2017 July ; 21(7): 2014–2022. doi:10.1007/s10461-016-1492-9.

What are the patterns between depression, smoking, unhealthy alcohol use, and other substance use among individuals receiving medical care? A longitudinal study of 5,479 participants

Kelly V Ruggles¹, Yixin Fang¹, Janet Tate², Sherry M Mentor¹, Kendall J Bryant³, David A Fiellin², Amy C Justice², and R Scott Braithwaite^{1,*}

¹Department of Population Health, New York University School of Medicine, New York, NY, US

²Yale University School of Medicine, New Haven, CT, US

³National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, MD, US

Abstract

Objective—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.

Methods—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).

Results—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 ($p = 0.01$; $OR = 0.75$).

* Corresponding Author: 227 East 30th street, Floor 6 Room 615, New York, NY 10016, Phone: 212-263-4964, Fax: 646-501-2706, Scott.Braithwaite@nyumc.org.

Compliance with Ethical Standards: The authors have no conflicts of interest to declare. 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.

Conclusions—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 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 6 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 ≥ 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 0–12 (a = 0 points, b = 1 point, c = 2 points, d = 3 points, e = 4 points). [32] We dichotomized AUDIT-C score using ≥ 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 & 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 4, current smoking, PHQ-9 score 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 10 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 8 models and therefore 1.23–1.30 was the range of 8 ORs between smoking and depression.)

Results

Among the 7,327 VACS participants, 5,479 met the study inclusion criteria of reporting ever drinking alcohol and smoking cigarettes. Of these, 52.5% (2,878) were HIV infected and 47.5% (2,601) were HIV uninfected. Within the 2,878 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 2,601 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). At baseline heroin and other opioids were combined into one question.

All 5,479 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 4,867, 3,647, 3,149, 2,581, 1,937 and 1,061 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 2–4). 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 (Table 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 2–5). Although we found only one instance in which the presence of a condition at the current time was associated with 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 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 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.[44] Epidemiological data and computer simulation suggest that unhealthy alcohol use, substance use and depression lead to new HIV infections and promote disease progression. [40,41] 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. [14,15,42,43] 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.

Acknowledgments

The authors have no conflicts of interest to declare.

References

1. Saitz R. Clinical practice. Unhealthy alcohol use. *N Engl J Med.* 2005; 352:596–607. [PubMed: 15703424]
2. Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, et al. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA.* 2003; 289:3095–105. [PubMed: 12813115]
3. Mokdad AH, Marks JS, Stroup DF, Gerberding JL. Actual causes of death in the United States, 2000. *JAMA.* 2004; 291:1238–45. [PubMed: 15010446]
4. Murray CJL, Atkinson C, Bhalla K, Birbeck G, Burstein R, Chou D, et al. The state of US health, 1990–2010: burden of diseases, injuries, and risk factors. *JAMA.* 2013; 310:591–608. [PubMed: 23842577]
5. Shu C, Cook BL. Examining the association between substance use disorder treatment and smoking cessation. *Addict Abingdon Engl.* 2015; 110:1015–24.
6. Cook BL, Wayne GF, Kafali EN, Liu Z, Shu C, Flores M. Trends in smoking among adults with mental illness and association between mental health treatment and smoking cessation. *JAMA.* 2014; 311:172–82. [PubMed: 24399556]
7. Sullivan LE, Fiellin DA, O'Connor PG. The prevalence and impact of alcohol problems in major depression: a systematic review. *Am J Med.* 2005; 118:330–41. [PubMed: 15808128]

8. Chowdhury PP, Balluz LS, Zhao G, Town M. Health behaviors and obesity among Hispanics with depression, United States 2006. *Ethn Dis.* 2014; 24:92–6. [PubMed: 24620454]
9. Braithwaite RS, Fang Y, Tate J, Mentor SM, Bryant KJ, Fiellin DA, et al. Do Alcohol Misuse, Smoking, and Depression Vary Concordantly or Sequentially? A Longitudinal Study of HIV-Infected and Matched Uninfected Veterans in Care. *AIDS Behav.* 2016; 20:566–72. [PubMed: 26187007]
10. Smith TC, LeardMann CA, Smith B, Jacobson IG, Miller SC, Wells TS, et al. Longitudinal assessment of mental disorders, smoking, and hazardous drinking among a population-based cohort of US service members. *J Addict Med.* 2014; 8:271–81. [PubMed: 24950137]
11. Lee RB, Sta Maria M, Estanislao S, Rodriguez C. Factors associated with depressive symptoms among Filipino university students. *PloS One.* 2013; 8:e79825. [PubMed: 24223198]
12. Hallfors DD, Waller MW, Ford CA, Halpern CT, Brodish PH, Iritani B. Adolescent depression and suicide risk: association with sex and drug behavior. *Am J Prev Med.* 2004; 27:224–31. [PubMed: 15450635]
13. Bohnert ASB, Miech RA. Changes in the association of drug use with depressive disorders in recent decades: the case of cocaine. *Subst Use Misuse.* 2010; 45:1452–62. [PubMed: 20438341]
14. Lev-Ran S, Roerecke M, Le Foll B, George TP, McKenzie K, Rehm J. The association between cannabis use and depression: a systematic review and meta-analysis of longitudinal studies. *Psychol Med.* 2014; 44:797–810. [PubMed: 23795762]
15. Martins SS, Keyes KM, Storr CL, Zhu H, Chilcoat HD. Pathways between nonmedical opioid use/dependence and psychiatric disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Drug Alcohol Depend.* 2009; 103:16–24. [PubMed: 19414225]
16. Amari E, Rehm J, Goldner E, Fischer B. Nonmedical prescription opioid use and mental health and pain comorbidities: a narrative review. *Can J Psychiatry Rev Can Psychiatr.* 2011; 56:495–502.
17. Brook DW, Brook JS, Zhang C, Cohen P, Whiteman M. Drug use and the risk of major depressive disorder, alcohol dependence, and substance use disorders. *Arch Gen Psychiatry.* 2002; 59:1039–44. [PubMed: 12418937]
18. Midanik LT, Tam TW, Weisner C. Concurrent and simultaneous drug and alcohol use: results of the 2000 National Alcohol Survey. *Drug Alcohol Depend.* 2007; 90:72–80. [PubMed: 17446013]
19. Bélanger RE, Akre C, Kuntsche E, Gmel G, Suris J-C. Adding tobacco to cannabis--its frequency and likely implications. *Nicotine Tob Res Off J Soc Res Nicotine Tob.* 2011; 13:746–50.
20. Richter KP, Ahluwalia HK, Mosier MC, Nazir N, Ahluwalia JS. A population-based study of cigarette smoking among illicit drug users in the United States. *Addict Abingdon Engl.* 2002; 97:861–9.
21. Log T, Hartz I, Handal M, Tverdal A, Furu K, Skurtveit S. The association between smoking and subsequent repeated use of prescribed opioids among adolescents and young adults--a population-based cohort study. *Pharmacoepidemiol Drug Saf.* 2011; 20:90–8. [PubMed: 21182157]
22. Goodwin RD, Sheffer CE, Chartrand H, Bhaskaran J, Hart CL, Sareen J, et al. Drug use, abuse, and dependence and the persistence of nicotine dependence. *Nicotine Tob Res Off J Soc Res Nicotine Tob.* 2014; 16:1606–12.
23. Schulz, DN., Kremers, SP., Vandelanotte, C., van Adrichem, MJ., Schneider, F., Candel, MJ., et al. Effects of a Web-Based Tailored Multiple-Lifestyle Intervention for Adults: A Two-Year Randomized Controlled Trial Comparing Sequential and Simultaneous Delivery Modes; *J Med Internet Res* [Internet]. 2014. p. 16[cited 2016 Mar 28]Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3936298/>
24. Hyman DJ, Pavlik VN, Taylor WC, Goodrick GK, Moye L. Simultaneous vs sequential counseling for multiple behavior change. *Arch Intern Med.* 2007; 167:1152–8. [PubMed: 17563023]
25. Oenema A, Brug J, Dijkstra A, de Weerd I, de Vries H. Efficacy and use of an internet-delivered computer-tailored lifestyle intervention, targeting saturated fat intake, physical activity and smoking cessation: a randomized controlled trial. *Ann Behav Med Publ Soc Behav Med.* 2008; 35:125–35.
26. Justice AC, Landefeld CS, Asch SM, Gifford AL, Whalen CC, Covinsky KE. Justification for a new cohort study of people aging with and without HIV infection. *J Clin Epidemiol.* 2001; 54(Suppl 1):S3–8. [PubMed: 11750202]

27. Conigliaro J, Madenwald T, Bryant K, Braithwaite S, Gordon A, Fultz SL, et al. The Veterans Aging Cohort Study: observational studies of alcohol use, abuse, and outcomes among human immunodeficiency virus-infected veterans. *Alcohol Clin Exp Res*. 2004; 28:313–21. [PubMed: 15112939]
28. Justice AC, Dombrowski E, Conigliaro J, Fultz SL, Gibson D, Madenwald T, et al. Veterans Aging Cohort Study (VACS): Overview and description. *Med Care*. 2006; 44:S13–24. [PubMed: 16849964]
29. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001; 16:606–13. [PubMed: 11556941]
30. Manea L, Gilbody S, McMillan D. Optimal cut-off score for diagnosing depression with the Patient Health Questionnaire (PHQ-9): a meta-analysis. *CMAJ Can Med Assoc J J Assoc Medicale Can*. 2012; 184:E191–6.
31. Bradley KA, DeBenedetti AF, Volk RJ, Williams EC, Frank D, Kivlahan DR. AUDIT-C as a brief screen for alcohol misuse in primary care. *Alcohol Clin Exp Res*. 2007; 31:1208–17. [PubMed: 17451397]
32. Bush K, Kivlahan DR, McDonell MB, Fihn SD, Bradley KA. The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project (ACQUIP). *Alcohol Use Disorders Identification Test Arch Intern Med*. 1998; 158:1789–95. [PubMed: 9738608]
33. Centers for Disease Control and Prevention. Sexual behavior and drug behavior questions. Atlanta, GA: Centers for Disease Control and Prevention; 2002.
34. Liang K-Y, Zeger SL. Longitudinal data analysis using generalized linear models. *Biometrika*. 1986; 73:13–22.
35. Rubin, DB. Multiple Imputation for Nonresponse in Surveys. John Wiley & Sons; 2004.
36. Grade Definitions - US Preventive Services Task Force [Internet]. [cited 2016 Mar 28]. Available from: <http://www.uspreventiveservicestaskforce.org/Page/Name/grade-definitions>
37. Lê AD, Kiiannaa K, Cunningham CL, Engel JA, Ericson M, Söderpalm B, et al. Neurobiological processes in alcohol addiction. *Alcohol Clin Exp Res*. 2001; 25:144S–151S. [PubMed: 11391064]
38. Narahashi T, Söderpalm B, Ericson M, Olausson P, Engel JA, Zhang X, et al. Mechanisms of alcohol-nicotine interactions: alcoholics versus smokers. *Alcohol Clin Exp Res*. 2001; 25:152S–156S. [PubMed: 11391065]
39. Dick DM, Agrawal A. The genetics of alcohol and other drug dependence. *Alcohol Res Health J Natl Inst Alcohol Abuse Alcohol*. 2008; 31:111–8.
40. Braithwaite RS, McGinnis KA, Conigliaro J, Maisto SA, Crystal S, Day N, et al. A temporal and dose-response association between alcohol consumption and medication adherence among veterans in care. *Alcohol Clin Exp Res*. 2005; 29:1190–7. [PubMed: 16046874]
41. Braithwaite RS, Conigliaro J, McGinnis KA, Maisto SA, Bryant K, Justice AC. Adjusting alcohol quantity for mean consumption and intoxication threshold improves prediction of nonadherence in HIV patients and HIV-negative controls. *Alcohol Clin Exp Res*. 2008; 32:1645–51. [PubMed: 18616666]
42. Coffey C, Carlin JB, Lynskey M, Li N, Patton GC. Adolescent precursors of cannabis dependence: findings from the Victorian Adolescent Health Cohort Study. *Br J Psychiatry J Ment Sci*. 2003; 182:330–6.
43. Patton GC, Coffey C, Carlin JB, Sawyer SM, Lynskey M. Reverse gateways? Frequent cannabis use as a predictor of tobacco initiation and nicotine dependence. *Addict Abingdon Engl*. 2005; 100:1518–25.
44. Koob GF. Brain stress systems in the amygdala and addiction. *Brain Res*. 2009; 1293:61–75. [PubMed: 19332030]

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*	-	NA*	-	-
- Opioid, %	218	8.0%	211	8.5%	0.51
- Benzodiazepines, %	NA*	-	NA	-	-

* 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

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

Parameter	Current Stimulant Use		Current Marijuana Use		Current Opioid Use		Current Heroin Use	
	OR ^a	p value	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	<0001
HIV status	2.48	<0001	1.39	<0001	0.87	0.05	1.14	0.31
Stimulant use at baseline	18.34	<0001	-	-	-	-	-	-
Marijuana use at baseline	-	-	15.57	<0001	-	-	-	-
Opioid use at baseline	-	-	-	-	2.99	<0001	-	-
Current unhealthy alcohol use	1.68	0.01	1.59	<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	<01
Current smoking at preceding survey ^c	1.21	0.42	1.09	0.24	1.05	0.55	2.02	<001
Current depression	2.06	<0001	1.35	<0001	1.55	<0001	1.60	<0001
Current depression at preceding survey ^d	1.35	0.09	0.93	0.27	1.33	<001	1.30	0.01

‘-’ indicates that predictor was not included in the model;

* Baseline data for heroin and prescription opioids are combined.

^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

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

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

Parameter	Current Depression							
	Model 1	Model 2	Model 3	Model 4	Model 1	Model 2	Model 3	Model 4
	OR ^a	p value	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	<.0001	0.76	<.0001	0.78	<.0001	0.72	<.0001
Depression status at baseline	6.39	<.0001	6.43	<.0001	6.26	<.0001	5.85	<.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	<.0001	1.29	<.0001	1.29	<.0001	1.30	<.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	<.001	-	-	-	-	-	-
Current stimulant use status at preceding survey ^d	1.09	0.61	-	-	-	-	-	-
Current marijuana use status	-	-	1.38	<.0001	-	-	-	-
Current marijuana use status at preceding survey ^e	-	-	0.92	0.17	-	-	-	-
Current opioid use status	-	-	-	-	1.51	<.0001	-	-
Current opioid use status at preceding survey ^f	-	-	-	-	1.24	<.01	-	-
Current heroin use status	-	-	-	-	-	-	1.62	<.01
Heroin use status at preceding survey ^g	-	-	-	-	-	-	1.03	0.85

‘-’ 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

ϵ Controlling for current marijuana use
 f Controlling for current opioid use
 g Controlling for current heroin use

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

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

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

Parameter	Current Smoking							
	Model 1	Model 2	Model 3	Model 4	Model 1	Model 2	Model 3	Model 4
	OR ^a	p value	OR ^a	P	OR ^a	P	OR ^a	P
Number of years from enrollment	0.91	<.0001	0.91	<.0001	0.91	<.0001	0.92	<.0001
HIV status	1.05	0.48	1.03	0.61	1.05	0.42	1.04	0.62
Smoking at baseline	22.34	<.0001	22.24	<.0001	22.33	<.0001	19.36	<.0001
Current unhealthy alcohol use	1.59	<.0001	1.58	<.0001	1.60	<.0001	1.65	<.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	<.0001	1.23	<.0001	1.24	<.0001	1.24	<.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

‘-’ 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

ϵ Controlling for current marijuana use
 η Controlling for current opioid use
 ξ Controlling for current heroin use

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

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

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

Parameter	Current Unhealthy Alcohol Use							
	Model 1	Model 2	Model 3	Model 4	Model 1	Model 2	Model 3	Model 4
Number of years from enrollment	OR ^a	p value	OR ^a	p	OR ^a	p	OR ^a	p
HIV status	0.96	<.0001	0.96	<.0001	0.96	<.0001	0.96	<.001
Unhealthy alcohol use at baseline	0.88	0.04	0.86	0.01	0.88	0.04	0.88	0.07
Current smoking	5.21	<.0001	5.27	<.0001	5.18	<.0001	4.82	<.0001
Current smoking at preceding survey ^b	1.70	<.0001	1.68	<.0001	1.71	<.0001	1.70	<.0001
Current depression	1.29	<.0001	1.27	<.0001	1.29	<.0001	1.31	<.001
Current depression at preceding survey ^c	1.09	0.07	1.08	0.11	1.11	0.03	1.09	0.11
Current stimulant use	1.01	0.91	1.00	0.96	1.02	0.67	1.03	0.59
Current stimulant use at preceding survey ^d	1.57	0.01	-	-	-	-	-	-
Current marijuana use	0.88	0.47	-	-	-	-	-	-
Current marijuana use at preceding survey ^e	-	-	1.63	<.0001	-	-	-	-
Current opioid use	-	-	1.08	0.27	-	-	-	-
Current opioid use at preceding survey ^f	-	-	-	-	0.84	0.06	-	-
Current heroin use	-	-	-	-	0.81	<.01	-	-
Current heroin use at preceding survey ^g	-	-	-	-	-	-	1.17	0.30
	-	-	-	-	-	-	0.83	0.24

-, * 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

ϵ Controlling for current marijuana use
 η Controlling for current opioid use
 ξ Controlling for current heroin use

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript