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## ASSOCIATION OF CANNABIS, STIMULANT, AND ALCOHOL USE WITH MORTALITY PROGNOSIS AMONG HIV-INFECTED MEN

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### Abstract

Questionnaires over a 9-year study period (2002–2010) were used to characterize cannabis, stimulant, and alcohol use among 3099 HIV-infected men participating in the Veterans Aging Cohort Study (VACS) to determine whether use of these substances is associated with changes in the VACS Index, a validated prognostic indicator for all-cause mortality. At baseline, 18% of participants reported no substance use in the past year, 24% lower risk alcohol use only, 18%

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#### Compliance with Ethical Standards

**Disclosure of potential conflicts of interest:** The authors declare that they have no conflict of interest.

**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.

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unhealthy alcohol use only, 15% cannabis use (with or without alcohol), and 24% stimulant use (with or without alcohol or cannabis). In adjusted longitudinal analyses, cannabis use [ $\beta=-0.97$  (95% CI:  $-1.93, 0.00$ ),  $p=0.048$ ] was not associated with mortality risk, while stimulant use [ $1.08$  (0.16, 2.00),  $p=0.021$ ] was associated with an increased mortality risk, compared to lower risk alcohol use. Our findings show no evidence of a negative effect of cannabis use on mortality risk, while stimulant use was associated with increased mortality risk among HIV-infected men. Interventions to reduce stimulant use in this patient population may reduce mortality.

## Keywords

alcohol; cannabis; drug use; men who have sex with men; HIV/AIDS

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## Introduction

Alcohol and drug use negatively affect HIV disease progression through mechanisms including poorer adherence to antiretroviral therapy (ART), higher rates of depressive symptoms, and physiological harms including immunosuppression, neurocognitive dysfunction, and a greater propensity for respiratory infections.<sup>1-9</sup> Of public health concern is the fact that alcohol and drug use are both prevalent among HIV-infected individuals.<sup>10,11</sup> Estimates for cannabis use in the past year among HIV-infected adults range from 24-56%; and a 2001 study using a nationally representative probability sample estimated that the prevalence of illicit drug use other than cannabis in the past year is approximately 40%.<sup>12-16</sup>

Particular types of drugs, such as cannabis, methamphetamine, and cocaine, may differentially impact HIV disease progression.<sup>11,17,18</sup> For example, use of methamphetamine among HIV-infected men who have sex with men (MSM) has been shown to negatively impact ART adherence and is associated with significant medical morbidity, including cardiovascular disease and impaired cognitive function.<sup>19,20</sup> In contrast, several studies have shown that cannabis use is not associated with poor viral suppression or other clinical outcomes in HIV-infected patients.<sup>21-23</sup> However, one longitudinal study examining trajectories of cannabis use over 29 years found that having a detectable HIV viral load was associated with cannabis use for HIV-infected MSM who increased their cannabis use over the follow-up period, even after controlling for other types of substance use.<sup>24</sup> In addition, alcohol use has been shown to impact both the clinical manifestations and management of HIV with potentially synergistic effects on HIV-related comorbidities.<sup>9</sup> While a growing body of literature has established the adverse effects of substance use on medication adherence, HIV disease progression, and HIV transmission risk, it is unclear whether specific types of substance use impact mortality prognosis among HIV-infected people in the current antiretroviral treatment era.

To address this research gap, the current study characterized cannabis, stimulant, and alcohol use among HIV-infected men participating in the Veterans Aging Cohort Study (VACS) to determine whether these substances were associated with changes in the VACS Index, a prognostic indicator for all-cause mortality. The VACS Index has been validated in numerous European and North American cohorts and a 5-point increase in the VACS Index

score has been shown to approximate a 20% increased risk of 5-year mortality.<sup>25–27</sup> VACS Index scores combine commonly collected clinical biomarkers into a cumulative index ranging from 0–164; incorporating the following: age, CD4 cell count, HIV RNA, hemoglobin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), platelet count, creatinine, and hepatitis C serologic status.<sup>26</sup> Our primary hypothesis was that the longitudinal association between substance use and mortality risk would differ by substance type. Specifically, we hypothesized that the impact of substance use on mortality risk over the study period would differ when examining the use of cannabis, stimulant, and alcohol as distinct substance use categories.

## Material and methods

### Study design and data sources

VACS is a longitudinal prospective cohort study conducted among mostly male HIV-infected veterans and age-, race-, and site-matched HIV uninfected controls attending eight US Veterans Administration (VA) medical facilities. From 2002 to 2010, participants were recruited from VA facilities in: Atlanta, Georgia; Baltimore, Maryland; New York (Bronx and Manhattan); Houston, Texas; Los Angeles, California; Pittsburgh, Pennsylvania; and Washington, D.C. VACS study design and methods have been described elsewhere.<sup>28,29</sup>

Given that the relationship between the type of substance use and mortality risk may differ by gender and by HIV-serostatus, we excluded female patients and HIV-negative patients participating in VACS. We also excluded individuals and/or observations missing information on covariates of interest (see below).

Self-administered questionnaires were scheduled approximately annually (a total of seven waves of data collection) and contained questions regarding sociodemographic characteristics, general health, sexual activity, and substance use. The VACS was approved by the institutional review boards at each participating VA medical center and affiliated academic institutions.

### Study measures

The primary outcome of interest was repeated assessment of the VACS Index score. The VACS Index score was recorded at time of the baseline assessment and each of the follow-up study visits. The score is re-calculated each time a lab is updated, with components of the index carried forward for up to a year to calculate the score. The exposure of interest was use of cannabis, stimulants, and alcohol reported at the baseline and each of the follow-up assessments. Alcohol use in the past year was determined using a component of the Alcohol Use Disorders Identification Test (AUDIT-C) reading: “How often do you have a drink containing alcohol?”.<sup>30</sup> Those replying “never” were categorized as abstaining from alcohol for the past year. Participants with an AUDIT-C score of 4 or above were categorized as engaging in unhealthy alcohol use.<sup>31</sup> For participants missing responses to the AUDIT-C, we evaluated alcohol use in the past year using responses to two additional questions: “When was the last time you had a drink?” and “In the last 12 months have you had a drink containing alcohol?”. Participants who reported alcohol use but lacked AUDIT-C

information were categorized as lower risk alcohol use. Those who skipped all alcohol-use related questions were categorized as abstaining from alcohol for the past year.<sup>32</sup>

Cannabis and stimulant use were evaluated at each assessment with the following question: “For each of the following drugs, please mark the box that best indicates how often in the past year you used each drug: marijuana or hashish; cocaine or crack; and stimulants (amphetamines, uppers, speed, crank, crystal meth, bam).” Response options for all substances included: have never tried, no use in the last year, less than once a month, 1–3 times a month, 1–3 times a week, 4–6 times a week, or every day. Endorsement of marijuana (i.e., cannabis) or hashish less than once a month to everyday was considered use of cannabis. As done in previous studies and due to considerable overlap in use of various kinds of stimulant drugs, any reported use of cocaine, crack, or other stimulant in the past year (less than once a month to everyday) was considered use of a stimulant.<sup>33,34</sup>

Time-updated, mutually exclusive substance use categories for the primary exposure were defined as: 1) no substance use (drugs or alcohol) in past year; 2) lower risk alcohol use only with a score <4 on the AUDIT-C questionnaire; 3) unhealthy alcohol use (AUDIT-C score 4) with no other substance use; 4) any reported cannabis use, with or without alcohol; and 5) any stimulant use, with or without alcohol or cannabis use.

Other covariates of interest were selected based on *a priori* hypotheses and informed by previous research on alcohol and drug use among HIV-infected individuals.<sup>10,11,18,34</sup> Sociodemographic (e.g., age, minority status, educational attainment) as well as behavioral (e.g., smoking status, MSM status) characteristics were included as covariates based on their association with type and frequency of substance use in previous studies.<sup>10,11,18,34</sup> MSM behavior was assessed at baseline. Specifically, respondents’ sexual behaviors were either classified as current MSM (at least one male sexual partner in the past twelve months), heterosexual (only female sexual partners in the past twelve months), or not sexually active (no sexual partners in the past twelve months). Other time-invariant sociodemographic variables assessed at baseline included: race/ethnicity (non-white or white), education level (high school or less, some college or greater), marital status (married/living with a partner, divorced/separated/widowed, never married), employment status (employed or self-employed, not employed or self-employed), and annual income (<\$6,000, \$6–11,999, \$12–24,999, \$25,000). Time-varying covariates used responses from every available assessment and included smoking status (current smoker, former smoker, never smoker), any opioid use (medical or non-medical) in the past year, and any history of injection drug use. Opioid use was included as a covariate rather than part of the substance use categorization schema because past year use, and in particular frequent use, was not as common as the other reported substances and survey questioning did not differentiate between medical and non-medical opioid use.

In addition, we identified participants who died during the follow-up period (2002–2010) using data available through Veterans Health Administration’s patient files, the Beneficiary Identification Records Locating System (which tracks Veterans Health Administration death benefits), the Medicare Vital Status file, and the Social Security National Death Index. Participants were considered lost to follow-up (for reasons other than death) if their last

assessment occurred more than two years prior to the end of the study period (i.e., their last assessment occurred before January 1, 2009).

### Statistical analyses

Initially, bivariate statistics were conducted to assess baseline cannabis, stimulant, and alcohol use by sociodemographic and behavioral characteristics using Pearson  $\chi^2$  and Wilcoxon rank-sum tests. Violin plots using BoxPlotR (available at [boxplot.tyerslab.com](http://boxplot.tyerslab.com)) were then used to plot the distribution of baseline VACS Index score by substance use category. Violin plots are box plots with the probability density incorporated within the figure.

Next, inverse probability weighted linear mixed effects models with a random intercept and slope were used to estimate the associations between substance use category and VACS Index score over time. Fitting a linear mixed effects model accounts for repeated measurements and yields parameters interpretable as the average difference in VACS Index score relative to the reference category.<sup>35,36</sup> This method is particularly appropriate as the number of follow-up assessments per respondent ranged from 0–6, and linear mixed effects modeling has built-in flexibility that can incorporate imbalance in longitudinal data.<sup>35</sup> Differences on measured factors between the respondents in the final study population and those excluded due to missing covariates or loss to follow-up were accounted for using inverse probability weights. Inverse probability weights were estimated as a function of substance use category at baseline and other baseline covariates using logistic regression models. Estimated inverse probability weights were subsequently evaluated based on their distributions (mean, range, minimum and maximum) and appeared to be well behaved, based on previously published guidelines.<sup>37,38</sup>

The lower risk alcohol-only group was chosen as the referent substance use category in response to evidence that those abstaining entirely from alcohol are a heterogeneous group comprising of lifetime abstainers, as well as individuals choosing to abstain due to health problems.<sup>39,40</sup> A 2006 population-based study found that non-current drinkers reported poorer physical and mental health compared to life-time abstainers and current drinkers.<sup>40</sup> Use of those abstaining from any substance use as the referent group could therefore bias results.

Multivariable models were then conducted to evaluate the independent effect of substance use category on VACS Index score, after adjusting for sociodemographic, behavioral, and other covariates. Covariates within the multivariable models were assessed for collinearity. Assessment of a substance use category and time interaction was also evaluated in multivariable analysis. Sensitivity analyses were conducted by excluding: 1) respondents who died during the follow-up period, 2) observations with VACS Index scores over 80, and 3) observations missing responses for the AUDIT-C score. In addition, we conducted two sensitivity analyses differing the categorization of substance use. One categorization used an AUDIT-C cut-off of 6, rather than 4, for unhealthy drinking and the other categorization accounted for frequency of cannabis and stimulant use. Statistical analyses performed using SAS statistical package (SAS Version 9.3, SAS Institute, Inc., Cary, NC).

## Results

A total of 7,324 patients were enrolled in VACS between June 1<sup>st</sup>, 2002 and September 30<sup>th</sup>, 2010. We excluded 3,693 (50.4%) HIV-uninfected participants, 94 (2.6%) female participants, and 79 (2.2%) participants missing exposure information due to non-response to all three drug-related questions at baseline. In addition, we excluded 86 (2.5%) individuals missing VACS Index information and 273 (8.1%) participants missing data on covariates of interest, resulting in a total study sample of 3,099 HIV-infected male VACS participants. The average number of surveys per respondent was 3.98 (SD: 1.91), with a median of 4 (IQR: 2, 6), including baseline visit. A total of 12,339 person-visits were included within the analysis.

### Substance Use Patterns

Sociodemographic, behavioral, and clinical characteristics by substance use category at baseline are presented in Table 1. Participant (N=3,099) median age was 49 (interquartile range: 44, 55), 79.6% were non-white, and 31.9% MSM. At baseline, 18.0% reported no substance use in the past year, 24.3% reported lower risk alcohol use only, 18.1% unhealthy alcohol use with no other substance use, 15.4% cannabis use (with or without alcohol), and 24.1% stimulant use (with or without alcohol and cannabis use). All measured sociodemographic and behavioral characteristics had statistically significant differences by substance use category ( $p < 0.0001$ ). Notably, a greater proportion of individuals reporting stimulant use also reported opioid (medical or non-medical) use in the past year compared to individuals within the other substance use categories. In addition, a greater proportion of individuals reporting stimulant use reported unhealthy alcohol use compared to individuals reporting cannabis use.

The distribution of baseline VACS Index scores differed by substance use category. Figure 1 presents violin plots of baseline VACS Index score distribution by substance use category at baseline. Overall, participants using stimulants and participants with unhealthy alcohol use had higher VACS index scores than other groups (Figure 1, Table 1). Median VACS Index was 5 points higher for the stimulants group compared to the lower risk alcohol use group. The distribution of VACS Index scores (i.e. the shape around the boxplot) was similar across substance use categories with the exception of cannabis use, which appeared to have a slight bimodal distribution.

### Mortality and loss to follow-up

By the end of the follow-up period in 2010, 952 (30.7%) of HIV-infected VACS participants included within this analytic sample had died. Of the 393 participants with only a baseline visit recorded, 253 (64.4%) died. In total, 468 (15.1%) participants included in the final study sample were lost to follow-up for reasons other than death. We accounted for potential biases arising from mortality by conducting a series of sensitivity analyses (see below).

### Multivariable Models

In a multivariable linear mixed effects model, factors independently associated with VACS Index score included substance use category, smoking status, history of injection drug use,

MSM status, race/ethnicity, marital status, employment status, and annual income at baseline (Table 2). The time-varying exposure variable (i.e., substance use category) was continually updated throughout follow up and not limited to the baseline assessment. A substance use category and time interaction term was not statistically significant in multivariable analysis and subsequently omitted from multivariable models. In adjusted analyses, cannabis use [ $\beta = -0.97$  (95%CL:  $-1.93, 0.00$ ),  $p=0.048$ ] was not independently associated with mortality risk, while stimulant use [ $1.08$  (0.16, 2.00),  $p=0.021$ ] was associated with an increased 5-year mortality risk, compared to lower risk alcohol use. Since a 5-point increase in the VACS Index score has been shown to approximate a 20% increased risk of 5-year mortality, stimulant use was associated with a 4.3% increase in 5-year mortality risk.<sup>25–27</sup> While not statistically significant, unhealthy alcohol use appeared to have negative impact [ $\beta = 0.52$  (95%CL:  $-0.43, 1.47$ ),  $p=0.281$ ] on VACS Index score. Current MSM at baseline [ $-4.03$  ( $-5.96, -2.10$ ),  $p < 0.001$ ] had a decreased mortality risk than heterosexual men (16.1% decreased 5-year mortality risk), while men who were not sexually active [ $4.87$  (3.08, 6.66),  $p < 0.001$ ] had an increased mortality risk compared to heterosexual men (19.5% 5-year increased mortality risk). A history of injection drug use [ $3.96$  (2.50, 5.41),  $p < 0.001$ ], non-white race/ethnicity [ $3.90$  (2.04, 5.75),  $p < 0.001$ ], being divorced, separated, or widowed at baseline [ $4.31$  (2.64, 5.98),  $p < 0.001$ ], or being unemployed [ $6.75$  (5.04, 8.45),  $p < 0.001$ ] were associated with increased mortality risk. Annual income at baseline was also associated—those making between \$6,000–11,999 [ $3.63$  (1.45, 5.80),  $p=0.001$ ] and \$12,000–24,999 [ $2.66$  (0.55, 4.77),  $p=0.014$ ] had higher VACS Index scores compared to those making \$25,000 or more annually.

### Sensitivity Analyses

Sensitivity analyses excluding participants who died during follow-up, observations with VACS Index scores over 80, and observations missing information on the AUDIT-C supported our main findings (Table 3). The impact of substance use category on VACS Index scores remained consistent; however, estimates were attenuated. When an AUDIT-C cut-off score of 6 was used rather than 4, unhealthy alcohol use had a greater negative impact [ $\beta = 1.10$ ,  $p=0.069$ ] on VACS Index score. A sensitivity analysis accounting for frequency of cannabis and stimulant use supported main findings and demonstrated increased mortality risk with frequent (at least once a week) use of stimulants. Results are presented in Supplemental Table 1.

### Discussion

The objective of this study was to determine whether use of alcohol, cannabis, and stimulants are associated with changes in the VACS Index, a validated prognostic indicator for all-cause mortality. We found no evidence of a negative effect of cannabis use on mortality risk among HIV-infected men in care. Although the effect size was small, stimulant use was associated with increased mortality risk (i.e., stimulant use was independently associated with a 1.08 increase in the VACS Index score compared to lower risk alcohol use, indicating a 4.3% increased risk of 5-year mortality). These findings suggest that interventions to reduce stimulant use in HIV-infected men may reduce mortality.

The legalization of cannabis or marijuana for medical or recreational use has renewed attention to potential harms associated with cannabis use.<sup>41</sup> Studies of cannabis use among HIV-infected populations have yielded mixed results.<sup>24,34,42</sup> In another study using the VACS cohort, Green et al. concluded that the participants who primarily used cannabis comprised a unique drug-using group due to the low prevalence of drug dependence and absence of negative consequences.<sup>34</sup> Furthermore, cannabis may be used for medical purposes to alleviate symptoms related to HIV disease and/or ART (e.g. nausea, appetite stimulation).<sup>12,43</sup> However, medical providers within the Veterans Health Administration system do not prescribe cannabis to treat HIV-related symptoms and we were unable to determine if participants used cannabis for this purpose, with or without a prescription. Nonetheless, further research is needed to determine whether recreational cannabis use has an impact on long-term mortality risk among HIV-infected patients.

Frequent stimulant use negatively impacted mortality risk for our study population. Supporting these findings, active cocaine use has been shown to predict poor ART adherence and viral rebound in HIV-infected patients.<sup>1,4,8</sup> Concerns regarding potential interactions between cocaine and ART medications or interactive toxicity beliefs may lead to non-adherence and subsequent HIV-related disease sequelae.<sup>3</sup> In addition, frequent use of stimulants might increase barriers to care engagement as well as ART adherence.<sup>44</sup> Cocaine and use of other stimulants have been associated with decreased ART adherence in several studies of HIV-infected adults.<sup>1,4</sup> Our study provides additional support for provision of treatment for stimulant use in HIV-infected patients.

Unhealthy alcohol use was prevalent within our study population. At the baseline assessment, over a third of our study population and half of those reporting stimulant use reported unhealthy alcohol use in the past year. Previous studies using the VACS cohort have found a high prevalence of unhealthy alcohol use and that alcohol use is associated with increased mortality risk and poorer HIV quality of care outcomes.<sup>45–47</sup> Notably, HIV-infected individuals have an increased risk of mortality and physiologic injury at lower levels of alcohol use compared to uninfected individuals.<sup>46</sup> Within our study, the increased mortality risk among individuals reporting stimulant use may be due, in part, to the prevalence of unhealthy alcohol use or a specific pattern of substance use which includes concurrent unhealthy alcohol and stimulant use.

Within our study, established social determinants of health (i.e., low income, unemployment, non-white race/ethnicity) had a greater impact on VACS Index score than any substance use category. Despite significant gains in improving survival for HIV-infected patients over the last two decades, disparities by race and socioeconomic status persist. Poverty-related stressors such as unstable housing, low health literacy, and food insecurity can negatively impact ART adherence and viral suppression.<sup>48–52</sup> A recent longitudinal study with over 10,000 HIV-infected patients found that black men and women had significantly greater 10-year all-cause mortality risk compared to white men.<sup>53</sup> Our study findings echo the need to identify modifiable factors through which to overcome observed disparities. An additional finding that warrants further research is the difference in mortality risk by MSM status. Within this analysis, men who reported MSM behavior at baseline had a decreased mortality



risk compared to other HIV-infected men. Future research will explore the potential reasons for differences in mortality risk between MSM and heterosexual men within the cohort.

This study has some limitations that warrant mentioning. First, substance use categories were based on self-report and may be impacted by social desirability or recall bias. However, use of self-administered paper-based surveys rather than in-person interviews is likely to have decreased the impact of such bias.<sup>54</sup> In addition, two of the substance use categories included multiple substances (i.e., cannabis with or without alcohol; stimulants with or without cannabis or alcohol) and this may have impacted findings. Second, biases related loss to follow-up and mortality can impact results from a large, ongoing cohort study such as VACS. However, inverse probability weighting to account for attrition and a sensitivity analysis evaluating the impact of mortality found that major findings were consistent. Finally, the study sample was restricted to male, HIV-infected U.S. veterans receiving care in the VA health care system which may limit generalizability to other HIV-infected populations, women, or veterans receiving care elsewhere. Nevertheless, at least two studies have found the VACS cohort comparable to other HIV-infected populations and combined the VACS cohort with other large HIV cohorts in Europe and North America for cross-cohort analyses.<sup>55,56</sup>

Despite these limitations, this study has several strengths. To the best of our knowledge, this is the first study to characterize substance use categories based on cannabis, stimulant, and alcohol use among HIV-infected men and evaluate the associated mortality risk. Longitudinal study design was employed with a median follow-up time of 6 years. Inverse probability weighting accounted for loss to follow-up and missing data within multivariable analyses. In addition, use of a time-varying substance use category variable and linear mixed effects modeling allowed for increased flexibility and the ability to discern associations that may not have been apparent using cross-sectional analyses.

Overall, cannabis use does not appear to negatively impact mortality prognosis while stimulant use is associated with greater mortality risk compared to lower risk alcohol use among HIV-infected men in care. Identifying the association of stimulant use with increased mortality risk can help inform targeted intervention and substance use treatment. Additionally, knowledge of the risks associated with frequent stimulant use may help motivate patients to decrease or discontinue use. However, sociodemographic characteristics appear to impact mortality risk to a greater degree than alcohol, cannabis, or stimulant use. Programs to lessen the impact of poverty and racial disparities continue to be vital components of improving the health of male veterans living with HIV/AIDS.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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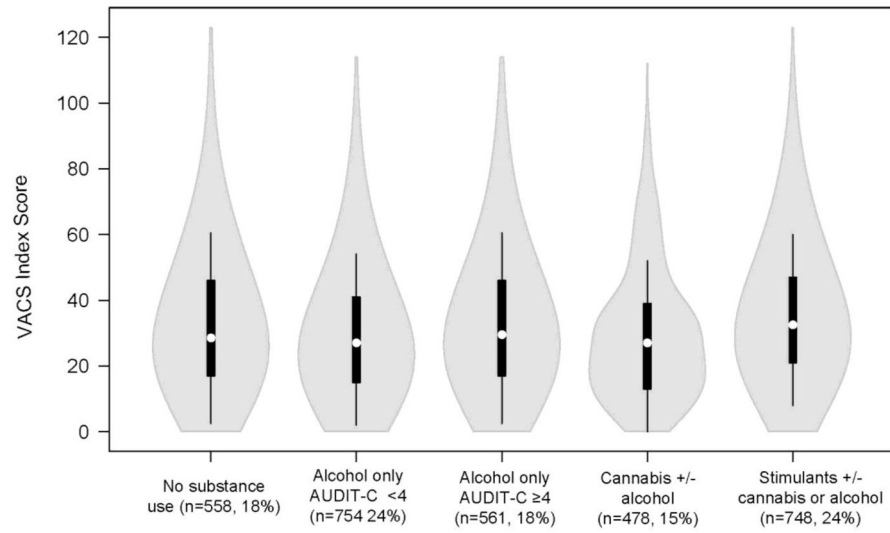
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**Figure 1.** Violin plots of baseline VACS Index score distributions by substance use category at baseline among HIV-infected male VACS participants (n=3,099).

**Table 1**

Baseline sociodemographic and behavioral characteristics associated with substance use category among HIV-infected male VACS participants (n=3,099).<sup>a,b</sup>

	Substance-use category at baseline					p-value <sup>c</sup>
	Total population (n=3,099, 100.0%)	No substance use (n=558, 18.0%)	Alcohol only, AUDIT-C <4 (n=754, 24.3%)	Alcohol only, AUDIT-C 4 (n=561, 18.1%)	Cannabis +/- alcohol(n=478, 15.4%)	
<b>VACS Index Score, median (IQR)</b>	28 (17, 45)	28 (17, 46)	27 (15, 41)	30 (17, 46)	27 (13, 39)	<0.0001
<b>Age, median (IQR)</b>	49 (44, 55)	50 (45, 56)	50 (43, 56)	50 (44, 55)	48 (42, 53)	<0.0001
<b>Smoking status, n (%)</b>						
Current smoker	1,658 (53.5)	220 (39.4)	295 (39.1)	292 (52.1)	257 (53.8)	<0.0001
Former smoker	731 (23.6)	158 (28.3)	204 (27.1)	181 (32.3)	117 (24.5)	71 (9.5)
Never smoker	710 (22.9)	180 (32.3)	255 (33.8)	88 (15.7)	104 (21.8)	83 (11.1)
<b>Any illicit opioid use in past year, n (%)<sup>d</sup></b>	309 (10.0)	23 (4.1)	27 (3.6)	24 (4.3)	40 (8.4)	<0.0001
<b>IDU ever, n (%)</b>	1,050 (33.9)	203 (36.4)	137 (18.2)	202 (36.0)	133 (27.8)	<0.0001
<b>Unhealthy alcohol use AUDIT-C 4, n (%)</b>	1,091 (35.2)	n/a	0 (0.0)	561 (100.0)	164 (34.5)	366 (49.1)
<b>MSM status<sup>e</sup></b>						
Current MSM	988 (31.9)	107 (19.2)	268 (35.5)	138 (24.6)	225 (47.1)	251 (33.6)
Heterosexual	1,166 (37.6)	230 (41.2)	227 (30.1)	234 (41.7)	139 (29.1)	336 (44.9)
Not sexually active	944 (30.5)	221 (39.6)	259 (34.4)	189 (33.7)	114 (23.9)	161 (21.5)
<b>Non-white race/ethnicity, n (%)</b>	2,467 (79.6)	464 (83.2)	558 (74.0)	448 (79.9)	338 (70.7)	659 (88.1)
<b>High school education/less than high school, n (%)</b>	1,233 (39.8)	234 (41.9)	240 (31.8)	250 (44.6)	160 (33.5)	349 (46.7)
<b>Marital status, n (%)</b>						
Married/living with partner	720 (23.3)	145 (26.0)	191 (25.3)	131 (23.4)	135 (28.2)	118 (15.8)
Divorced, separate, or widowed	1,257 (40.6)	235 (42.1)	286 (37.9)	226 (40.3)	154 (32.2)	356 (47.6)
Never married	1,122 (36.2)	178 (31.9)	277 (36.7)	204 (36.4)	189 (39.5)	274 (36.6)

	Substance-use category at baseline					<i>p</i> -value <sup>c</sup>
	Total population (n=3,099, 100.0%)	No substance use (n=558, 18.0%)	Alcohol only, AUDIT-C <4 (n=754, 24.3%)	Alcohol only, AUDIT-C 4 (n=561, 18.1%)	Cannabis +/- alcohol(n=478, 15.4%)	
<b>Unemployed/retired/other at baseline, n (%)</b>	2,074 (66.9)	364 (65.2)	443 (58.8)	370 (66.0)	310 (64.9)	<0.0001
<b>Annual income at baseline, n (%)</b>						
<\$6000	615 (19.9)	95 (17.0)	98 (13.0)	114 (20.3)	75 (15.7)	<0.0001
\$6000–\$11,999	955 (30.8)	174 (31.2)	185 (24.5)	170 (30.3)	148 (31.0)	
\$12,000–24,999	756 (24.4)	141 (25.3)	203 (26.9)	147 (26.2)	128 (26.8)	
\$25,000	773 (24.9)	148 (26.5)	268 (35.5)	130 (23.2)	127 (26.6)	

Abbreviations: VACS= Veterans Aging Cohort Study; MSM=men who have sex with men; IQR= interquartile range; IDU=intravenous drug use; AUDIT= Alcohol Use Disorders Identification Test-Consumption questionnaire

<sup>a</sup>Use or experiences in the past-year, reported at baseline.

<sup>b</sup>Percentages calculated excluding missing responses.

<sup>c</sup>Pearson  $\chi^2$  and Wilcoxon rank-sum tests compared variables by substance-use category at baseline.

<sup>d</sup>In response to the following question: “How often in the past year you used each drug - Opioids (heroin, morphine, codeine, opium)”

<sup>e</sup>Respondents were categorized at baseline as current MSM (at least one male sexual partner in the past twelve months), heterosexual (only female sexual partners in past twelve months) or not sexually active (no sexual partners in past twelve months).



**Table 2**

Inverse probability weighted longitudinal linear mixed effect models with adjusted factors associated with VACS Index score among HIV-infected male VACS participants (n=3,099).<sup>a</sup>

	$\beta$	95% CI	p - value
<b>Intercept</b>	18.81	15.59, 22.04	
<b>Time varying characteristics</b>			
<b>Substance-use category</b>			<0.001
No substance use	-0.61	-1.39, 0.18	0.129
Unhealthy alcohol use (AUDIT-C $\geq 4$ )	0.52	-0.43, 1.47	0.281
Any cannabis +/- alcohol	-0.97	-1.93, 0.00	0.048
Any stimulant +/- alcohol or cannabis	1.08	0.16, 2.00	0.021
Alcohol only <4 on AUDIT-C ( <i>reference</i> )	<i>ref</i>		
<b>Smoking status</b>			0.005
Current smoker	-0.80	-1.94, 0.35	0.172
Former smoker	0.67	-0.41, 1.75	0.225
Never smoker ( <i>reference</i> )	<i>ref</i>		
<b>Any illicit opioid use in past year (yes vs. no)</b>	0.19	-0.55, 0.94	0.612
<b>IDU ever (at baseline, updated through follow-up)</b>	3.96	2.50, 5.41	<0.001
<b>Time invariant or baseline characteristics</b>			
<b>MSM status<sup>b</sup></b>			<0.001
Current MSM	-4.03	-5.96, -2.10	<0.001
No sexual activity in past twelve months	4.87	3.08, 6.66	<0.001
Heterosexual ( <i>reference</i> )	<i>ref</i>		
<b>Non-white race/ethnicity vs. white race/ethnicity</b>	3.90	2.04, 5.75	<0.001
<b>High school education/less than high school vs. some college or greater</b>	0.81	-0.71, 2.33	0.296
<b>Marital status at baseline</b>			<0.001
Married/living with partner	1.88	-0.10, 3.86	0.063
Divorced, separated, or widowed	4.31	2.64, 5.98	<0.001
Never married ( <i>reference</i> )	<i>ref</i>		
<b>Unemployed/retired/other vs. employed at baseline</b>	6.75	5.04, 8.45	<0.001
<b>Annual income at baseline</b>			0.006
<\$6000	1.68	-0.76, 4.12	0.176
\$6000-\$11,999	3.63	1.45, 5.80	0.001
\$12,000-24,999	2.66	0.55, 4.77	0.014
\$25,000 ( <i>reference</i> )	<i>ref</i>		

Abbreviations: VACS= Veterans Aging Cohort Study; CL=Confidence Limits; MSM=men who have sex with men; IDU=intravenous drug user; AUDIT= Alcohol Use Disorders Identification Test-Consumption questionnaire; Ref=Reference value.

<sup>a</sup>Adjusted for year of recruitment.

<sup>b</sup>Respondents were categorized at baseline as current MSM (at least one male sexual partner in the past twelve months), heterosexual (only female sexual partners in past twelve months) or not sexually active (no sexual partners in past twelve months).

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**Table 3**

Sensitivity analyses using inverse probability weighted longitudinal linear mixed effect models with adjusted factors associated with VACS Index score among HIV-infected male VACS participants.<sup>a</sup>

	Excluding VACS Index Scores >80 (n= 3,053)		Excluding observations missing AUDIT-C scores (n= 3,040)	
	$\beta$	<i>p</i> - value	$\beta$	<i>p</i> - value
<b>Intercept</b>	19.90		19.45	
<u>Time varying characteristics</u>				
<b>Substance-use category</b>		<0.001		<0.001
No substance use	-0.23	0.517	-0.85	0.108
Unhealthy alcohol use (AUDIT-C $\geq$ 4)	0.09	0.846	0.36	0.488
Any cannabis +/- alcohol	-1.03	0.019	-1.39	0.010
Any stimulant +/- alcohol or cannabis	0.97	0.022	0.87	0.090
Alcohol only <4 on AUDIT-C ( <i>reference</i> )	<i>ref</i>		<i>ref</i>	
<b>Smoking status</b>		0.020		0.202
Current smoker	-0.91	0.082	-0.35	0.598
Former smoker	0.20	0.689	0.56	0.382
Never smoker ( <i>reference</i> )	<i>ref</i>		<i>ref</i>	
<b>Any illicit opioid use in past year (yes vs. no)</b>	0.26	0.453	0.34	0.441
<b>IDU ever (at baseline, updated through follow-up)</b>	3.63	<0.001	4.23	<0.001
<u>Time invariant or baseline characteristics</u>				
<b>MSM status<sup>b</sup></b>		<0.001		<0.001
Current MSM	-3.93	<0.001	-4.18	<0.001
No sexual activity in past twelve months	3.19	<0.001	4.62	<0.001
Heterosexual ( <i>reference</i> )	<i>ref</i>		<i>ref</i>	
<b>Non-white race/ethnicity vs. white race/ethnicity</b>	3.11	0.002	3.51	<0.001
<b>High school education/less than high school vs. some college or greater</b>	0.59	0.393	0.92	0.244
<b>Marital status at baseline</b>		<0.001		<0.001
Married/living with partner	1.56	0.081	1.75	0.088
Divorced, separated, or widowed	3.88	<0.001	4.26	<0.001
Never married ( <i>reference</i> )	<i>ref</i>		<i>ref</i>	
<b>Unemployed/retired/other vs. employed at baseline</b>	5.82	<0.001	6.40	<0.001
<b>Annual income at baseline</b>		0.007		0.011
<\$6000	1.72	0.117	1.59	0.209
\$6000-\$11,999	3.28	<0.001	3.41	0.002

	Excluding VACS Index Scores >80 (n= 3,053)		Excluding observations missing AUDIT-C scores (n= 3,040)	
	$\beta$	<i>p</i> - value	$\beta$	<i>p</i> - value
\$12,000–24,999	2.27	0.017	2.72	0.013
\$25,000 ( <i>reference</i> )	<i>ref</i>		<i>ref</i>	

Abbreviations: VACS= Veterans Aging Cohort Study; MSM=men who have sex with men; IDU=intravenous drug user; AUDIT= Alcohol Use Disorders Identification Test-Consumption questionnaire; Ref=Reference value.

<sup>a</sup> Adjusted for year of recruitment.

<sup>b</sup> Respondents were categorized at baseline as current MSM (at least one male sexual partner in the past twelve months), heterosexual (only female sexual partners in past twelve months) or not sexually active (no sexual partners in past twelve months).

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