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Long-term alcohol use patterns and HIV disease severity

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Abstract

Objective—We examined the relationship between alcohol use trajectories and HIV disease severity among men and women participating in the Veterans Aging Cohort Study (VACS).

Design—Prospective cohort of HIV-infected persons in care at eight US Veterans Health Administration sites.

Methods—Between 2002 and 2010, we assessed alcohol consumption annually using the alcohol use disorders identification test-consumption (AUDIT-C). HIV disease severity was ascertained using the VACS index, a validated measure of morbidity and all-cause mortality. We examined the relationship between alcohol use and HIV disease severity patterns using joint trajectory modeling. Alcohol use trajectories were validated using phosphatidylethanol – a biomarker of alcohol consumption – measured between 2005 and 2006 among a subset of participants. We examined associations between membership in alcohol use and VACS index trajectories using multinomial regression.

Results—Among eligible participants, we identified four alcohol consumption trajectories: abstainers (24% of the sample), lower risk (44%), moderate risk (24%), and higher risk drinkers

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Conflicts of interest

There are no conflicts of interest.

(8%). Alcohol use trajectories were highly correlated with phosphatidylethanol (Cramér's V = 0.465, $P < 0.001$): mean concentrations were 4.4, 17.8, 57.7, and 167.6 ng/ml in the abstainer, lower risk, moderate risk, and higher risk groups, respectively. Four VACS index trajectories were identified: low (2%), moderate (46%), high (36%), and extreme (16%). Higher risk drinkers were most common in the extreme VACS index group, and were absent in the low index group. In multivariable analysis, the association between alcohol use and VACS index trajectory membership remained significant ($P = 0.002$).

Conclusion—Alcohol use trajectories characterized by persistent unhealthy drinking are associated with more advanced HIV disease severity among HIV-infected veterans in the United States.

Keywords

alcohol; HIV infection; morbidity; trajectories; trends; veterans

Introduction

Unhealthy alcohol use – the spectrum of alcohol consumption characterized by at-risk and heavy episodic drinking, along with alcohol use disorder [1] – is prevalent among people living with HIV [2]. The effects of unhealthy alcohol use on HIV disease progression have been studied extensively [3]. Studies have demonstrated a significant detrimental impact of unhealthy alcohol use on viral load suppression, primarily mediated through antiretroviral therapy adherence [4–7], as well as retention in care [8]. In addition, unhealthy alcohol use has direct effects on the immune system [9], and has been associated with $CD4^+$ cell count decline in individuals on antiretroviral therapy [10,11]. Compared with uninfected individuals, those living with HIV experience increased mortality at lower levels of alcohol consumption [12]. This body of research provides strong evidence that unhealthy alcohol use negatively influences HIV disease progression through a combination of behavioral (i.e. adherence) and biological processes.

Nonetheless, elucidating the relationships between long-term patterns of alcohol use and HIV disease severity has been limited by several factors. For example, many studies only measure alcohol use at a single time point. Furthermore, in longitudinal studies of alcohol use among HIV-infected populations, traditional analytic methods are often unable to differentiate reductions in alcohol consumption because of declining health (i.e. 'sick quitters') from the potentially deleterious effects of unhealthy alcohol use on HIV disease progression [3]. Alcohol use trajectories have begun to be explored, but their associations with HIV disease progression have yet to be fully elucidated [13]. The classification of alcohol use phenotypes may lead to more precise efforts to identify patients with distinct patterns of alcohol consumption that place that them at increased risk of long-term HIV disease morbidity and mortality.

In this cohort study of HIV-infected patients in care, we sought to characterize alcohol use trajectories and their relationship with HIV disease severity over time. To achieve these objectives, we employed a joint trajectory modeling approach in which two longitudinal outcomes are analyzed contemporaneously [14]. We hypothesized that, independent of other

relevant behavioral factors, persistent unhealthy patterns would be associated with more advanced HIV disease severity over time.

Methods

Study design and eligibility criteria

The study utilized data collected from the Veterans Aging Cohort Study (VACS) survey sample, which enrolled HIV-infected participants receiving medical care at Veterans Health Administration (VHA) facilities in Atlanta, Baltimore, Houston, Los Angeles, Manhattan and The Bronx, Pittsburgh, and Washington, DC. Design of the VACS has been described in detail elsewhere [15,16]. In brief, the open cohort began enrolment in 2002 with follow-up assessments scheduled approximately annually. For this analysis, we used data from six waves of data collection, representing an 8-year (2002–2010) study period.

At each assessment participants completed a detailed questionnaire that elicited information regarding socio-demographics, general health status, health conditions, and behavioral factors including alcohol and other substance use. Participant survey data were then linked with VHA electronic medical records, which include information on all clinical encounters, laboratory data, and diagnoses recorded using the International Classification of Diseases, 9th Revision codes [17]. The VACS was approved by the institutional review boards at each participating VHA Medical Center and affiliated academic institutions.

Measures

We assessed two outcome measures. First, we examined each participant's set of scores on the alcohol use disorders identification test-consumption (AUDIT-C) questionnaire [18]. Scores range from 0 to 12; values at least 3 and 4 are considered positive for unhealthy alcohol use in women and men, respectively [19]. The AUDIT-C is a reliable and valid measure to assess risk of unhealthy alcohol use among HIV-infected individuals, and has been used in previous VACS studies [13,20].

The second outcome was the VACS index, a composite measure that predicts all-cause mortality, cause-specific mortality, and other clinical outcomes in those with HIV [21]. Validation studies show the VACS index has reproducible accuracy and validity in HIV-infected populations [22–24]. As shown in Table S1, http://links.lww.com/QAD/B70 the score is created by summing points for age, indicators of HIV disease (i.e. $CD4^+$ cell count and HIV-1 RNA), general indicators of organ system injury, as well as history of hepatitis C virus (HCV) coinfection [21]. Each five-point increment indicates an approximately 20% increase in 5-year mortality risk [21,22]. Thus, the VACS index is a clinically relevant measure of overall HIV disease severity. At each survey wave, the VACS index was calculated as previously reported [12], using laboratory values closest to the participant's AUDIT-C assessment. The score is recalculated each time a lab is updated, with components of the index carried forward up to a year to calculate the index.

In addition to exploring associations between the two outcome measures, we also considered the following independent covariates. These included: age at baseline, sex, race (white, African American, vs. other), Hispanic/Latino ethnicity (yes vs. no) educational attainment

(high school or less education, yes vs. no), marital status, and lifetime homelessness. We also examined current smoking status at baseline (defined as any smoking in the past week), and self-reported history of injection drug use. We assessed depressive symptomatology using the Patient Health Questionnaire, where a score at least 10 is considered positive for moderate or greater depressive severity [25]. Finally, we assessed HCV coinfection status (positive vs. negative, based on a combination of International Classification of Diseases, 9th Revision codes for this diagnosis and laboratory data indicating positive HCV antibody or HCV–RNA positivity), $CD4^+$ cell count (cells/μl), and viral suppression, defined as less than 400 copies/ml. Finally, any participant who filled a prescription for an antiretroviral on the Veterans Affairs (VA) formulary and within the VA between 90 days prior and 7 days following the date of the baseline interview were considered to be on highly active antiretroviral therapy at baseline.

As conducted previously [13], we identified participants who died during the study period (between 2002 and up to September 2010) from the VA vital status file. Finally, we defined loss to follow-up (for reasons other than death) as failing to complete a study assessment within 1 year prior to the end of the study period (i.e. their last assessment occurred before September 2009).

Statistical analyses

We used a semiparametric, group-based mixture modeling approach (Proc TRAJ) to identify joint AUDIT-C and VACS index score trajectories [26]. In brief, the modeling procedure sorts each participant's set of AUDIT-C values and VACS index scores into 'clusters' and estimates distinct trajectories. The time scale was follow-up time (in years) from study enrolment. The procedure calculates each individual's probability of belonging in each trajectory and assigns the one for which they have the highest probability of membership [27]. We used a zero-inflated Poisson model for AUDIT-C scores and a censored normal model for VACS index scores (minimum = 0, maximum = 164, with higher scores indicating greater HIV disease severity).

After each outcome had been separately modelled, we used the joint modeling procedure in Proc TRAJ [14]. This model permits analysis of two outcomes that evolve contemporaneously over time. First, the model estimates the trajectories for each outcome and the conditional probabilities of membership in each combination of trajectories. Second, the model assigns each individual to the combination with the highest probability of membership. Additional details regarding the determination of the optimal number of trajectory groups and each trajectory's shape are provided in the supplemental file.

Once trajectory groups were assigned, we used the χ^2 test and the Wilcoxon rank sum test to compare the baseline characteristics of individuals in each VACS index trajectory group. Then, we used multinomial logistic regression to estimate odds of membership in each VACS index trajectory, conditional on membership in each AUDIT-C group, and other covariates. As there were no persons assigned to the higher risk AUDIT-C/low VACS index subgroup, we were unable to use either of these classes as the referent level for the multivariable model. As such, the moderate AUDIT-C and moderate VACS index classes were chosen as the referent categories. The final multivariable model was chosen using an

iterative, manual backwards selection procedure. First, variables significant at $P < 0.05$ in bivariable analyses were included in a preliminary model. Baseline HCV status, HIV treatment status, $CD4^+$ cell count, and viral load were not considered for inclusion in the multivariable model as they are components of the VACS index. Next, variables with the highest P value were removed sequentially, with the final model based on that with the lowest Akaike information criterion. Finally, we calculated and applied inverse probability of censoring weights to account for potential biases arising from differential loss to follow-up (see Supplemental File, http://links.lww.com/QAD/B70). All analyses were performed in SAS 9.4 (SAS Institute Inc., Cary, North Carolina, USA) and all P values are two-sided.

Validation and sensitivity analyses

To validate AUDIT-C trajectories, we conducted a subanalysis of participants enrolled in the VACS tissue repository. As described previously [28], blood and DNA specimens were collected from a subset of 1532 VACS participants between 2005 and 2006. All samples were tested for phosphatidylethanol (PEth), a direct biomarker of alcohol exposure with high specificity for alcohol abstinence that modestly correlates with dose of alcohol consumed in the past 21 days [29,30]. Additional details are provided in the supplemental file. We examined mean PEth concentrations and the proportion with PEth above the limit of detection (≥ 4 ng/ml), stratified by AUDIT-C trajectory membership.

In *post hoc* analyses, we compared the characteristics of persons classified in specific subgroups of interest (i.e. ‘healthy abstainers’, ‘sick quitters’). In addition we examined the proportion in each subgroup who reported sexual activity in the past year. Next, in a series of sensitivity analyses, we used last observation carried forward (LOCF) to account for potential biases arising from individuals who were lost to follow-up. The LOCF approach carries forward the last observation to the last time point for each participant who dropped out, treating these carried forward data as observed data [31]. Then, we restricted the trajectory analyses to persons who completed at least two study assessments during the study period (87% of the analytic sample). Finally, to determine whether mortality affected the shape of each VACS index and AUDIT-C score pattern, we re-estimated the trajectories excluding those participants who died during the study period.

Results

Patient characteristics

Of 3631 HIV-infected participants, 3539 (97%) had at least once AUDIT-C and one VACS index score and were thus included in this analysis. The 3539 eligible participants contributed 13 090 AUDIT-C observations and 12 958 VAC index score values for a total of 15 354 person-years over the 8-year study period. A total of 3072 (86.8%) participants completed at least two assessments. The median age was 49 [interquartile range (IQR) = 44–55], 98% were men, and 68% were African American. At baseline, median $CD4^+$ cell count was 367 cells/μl (IQR = 213–555) and median viral load was 413 copies/ml (IQR = 75–14500). The median AUDIT-C score was 1 (IQR = 0–4), and the median VACS index score was 29 (IQR = 17–46).

Alcohol use disorders identification test-consumption score trajectories

In the joint model, we identified four distinct AUDIT-C score trajectories (Fig. 1, Table S2, http://links.lww.com/QAD/B70). We labelled the AUDIT-C trajectories as abstainers, lower risk, moderate risk, and higher risk. The abstainer group (24% of the sample) had consistently low mean AUDIT-C scores. The lower risk group (44%) had an AUDIT-C trajectory indicative of stable, lower risk drinking. The moderate risk group (24%) had an average AUDIT-C score between 3.2 and 3.9, just below the standard cutoff of 4 for men. Finally, we identified a higher risk group (8%), who had a consistently elevated AUDIT-C score, indicative of persistent unhealthy alcohol use. The baseline characteristics of persons in each of the four AUDIT-C groups are shown in Table S3, http://links.lww.com/QAD/B70.

Validation of alcohol use disorders identification test-consumption score trajectories

Among 1525 persons included in the VACS tissue repository, 1499 (98.3%) were included in this analysis. The distribution of trajectories and characteristics of persons included in the subsample were similar to those of the overall analytic sample (Table S4, http://links.lww.-com/QAD/B70). We observed significant correlations between measures of PEth concentration and membership in the AUDIT-C trajectories (Figure S1, http://links.lww.com/QAD/B70). For example, the mean PEth concentrations were 4.4, 17.8, 58.8, and 167.6 ng/ml among persons classified in the abstainer, lower risk, moderate risk, and higher risk groups, respectively ($P < 0.001$). Over 90% of participants in the higher risk group were above the PEth limit of detection, compared with only 18% in the abstainer group ($P < 0.001$).

Veterans Aging Cohort Study index trajectories

We identified four distinct VACS index trajectories (Table S2 http://links.lww.com/QAD/B70 and Fig. 2). We characterized these groups as low, moderate, high, and extreme. The low group (2%) had an average VACS index score of 0 at baseline, increasing to 4 at the last follow-up. Almost half of participants (46%) belonged to the moderate group, which was characterized by a slightly decreasing VACS index trajectory from an average of 19 to 16. One-third of participants (36%) were classified as belonging to the high group, with a stable VACS index score. Finally, we identified an extreme group (16%), who had consistently elevated VACS index scores.

Bivariable analyses

We observed a significant association between membership in AUDIT-C and VACS index trajectories ($\chi^2 = 73$, $P < 0.001$, see Fig. 3). Persons in the abstainer and higher risk AUDIT-C trajectories were most likely to belong to the extreme VACS index trajectory. Notably, there were no individuals classified as higher risk drinkers in the Low (i.e. healthiest) VACS index trajectory.

As expected (as age, $CD4^+$ cell count, viral load, and HCV status are components of the VACS index), we observed significant associations between age, baseline $CD4^+$ cell count, viral suppression, and HCV coinfection with VACS index trajectory membership (Table 1). Providing further validation of the VACS index trajectories, the proportion of participants who died over the study period was only 6% in the healthiest group increasing to over 70%

in the Extreme group ($P < 0.001$). We also observed significant associations between race, educational attainment, marital status, history injection drug use, lifetime homelessness, and smoking status by membership in the VACS index trajectory groups ($P < 0.001$).

Multivariable results

As shown in Table 2, AUDIT-C trajectory group membership was independently associated with VACS index trajectory groups ($P = 0.002$). Specifically, compared with the moderate risk AUDIT-C group, Abstainers were more likely to be assigned to the low and extreme groups compared with the moderate VACS index group. Furthermore, membership in the lower risk AUDIT-C class was marginally associated with membership in the extreme VACS index group (adjusted odds ratio = 1.35, 95% confidence interval: 1.02–1.79), compared with the moderate group. Finally, the association between membership in the higher-risk AUDIT-C group and the extreme VACS index trajectory group was significant (adjusted odds ratio = 1.83, 95% confidence interval: 1.21–2.78).

Post hoc and sensitivity analyses

In *post hoc* analyses, we compared the characteristics of persons in the abstainer category who were also classified in the low and extreme VACS index groups, respectively. Persons in the abstainer/extreme subgroup were older (mean = 56 years) compared with those in the abstainer/low subgroup (mean = 41). Furthermore, persons in the abstainer/extreme subgroup were significantly less likely than those in the abstainer/low subgroup to report any sexual activity in the past year at baseline (45.3 vs. 79.0%, $P < 0.001$). Notably, over 74.0% of persons in the abstainer/extreme subgroup died over the study period, compared with only 10.5% of the abstainer/low VACS index subgroup. In the entire abstainer group, 809 (94.7%) reported abstinence from alcohol throughout the entire study period, a proportion that did not vary significantly between the abstainer/low and abstainer/extreme subgroups (89.5 vs. 97.8%, $P = 0.114$).

In several sensitivity analyses, we found no substantive difference in our findings. Applying LOCF values did not meaningfully alter the shape or composition of the AUDIT-C and VACS index trajectories (Figures S2, S3, http://links.lww.com/QAD/B70). Restricting the analysis to the 3072 participants who completed at least two assessments during the study period did not substantially alter our results (Figures S4, S5, http://links.lww.com/QAD/B70), nor did excluding those who died (Figures S6, S7, http://links.lww.com/QAD/B70).

Discussion

In this 8-year prospective cohort study of HIV-infected patients engaged in care, long-term alcohol use patterns were associated with HIV disease severity trajectories. Notably, no individuals belonging to the healthiest trajectory (indicative of normal immune system functioning and well controlled HIV disease) were classified as consistently higher risk drinkers. Moreover, persons with long-term unhealthy alcohol use were over-represented in the extreme VACS index trajectory (in which over 70% of participants died). Finally, abstainers were overrepresented in both the low and extreme VACS index trajectories, suggesting distinct groups of ‘sick quitters’ and ‘healthy abstainers’. The observed alcohol

use trajectories were highly correlated with PEth – a biomarker of alcohol consumption assessed in a subsample of VACS participants – demonstrating that trajectory-based approaches are a valid method for discriminating between different patterns of long-term alcohol exposure.

These results extend previous work demonstrating that unhealthy alcohol use is associated with increased physiologic injury among HIV-infected persons [12]. One possible explanation for this finding is that alcohol consumption may adversely affect medication adherence and thus promote greater HIV disease severity. Prior studies have shown that alcohol use, including moderate consumption, has been associated with poorer adherence to therapy among HIV-infected individuals [4,5]. Alcohol exposure may also influence HIV disease severity through biological effects not mediated by adherence. For example, animal and human studies have shown that alcohol-mediated alterations in immune function can result in chronic inflammation and T-cell activation that may accelerate HIV disease progression [32]. Finally, previous studies have shown fewer drinks to get a 'buzz' among HIV-infected individuals [33], suggesting greater exposure to alcohol at lower levels of consumptions.

A key strength of this study was the use of PEth to validate the observed alcohol use trajectories. This finding demonstrates that trajectory-based approaches based on self-reported alcohol use offer promise as an empirical method to identify distinct behavioral phenotypes of long-term alcohol consumption. Future work should seek to identify genetic, social, and other risk factors for persistent unhealthy drinking in HIV-infected populations. Another strength was the use of the VACS index to measure HIV disease severity. The index is a more comprehensive assessment than either $CD4^+$ or viral suppression and accounts for both HIV-specific measures and general organ system injury.

The 'sick quitter' phenomenon, in which individuals consume less alcohol as they become too sick to drink [34], has been hypothesized to explain the apparent protective effect of alcohol use on physical functioning [35] and mortality [36] among people living with HIV. To our knowledge, this study, the first to provide empirical support for a distinct subgroup of 'sick quitters' among HIV-infected individuals. Specifically, in *post hoc* analyses, we found that almost three in four 'sick quitters' died over the study period, compared with only 10% of the 'health abstainers'. Future studies assessing the relationship between alcohol use and HIV disease outcomes should account for 'sick quitters' by either excluding nondrinkers or by identifying individuals who abstain from alcohol as a result of poor health.

The observed association between membership in the lower risk AUDIT-C class and the extreme VACS index class was unexpected and requires further investigation. It is possible that unmeasured confounding may explain the association. Alternatively, this finding may reflect a distinct subgroup of persons who continue to consume alcohol at relatively healthy levels despite the prevalence of other comorbidities. Finally, it is possible that this marginally significant association ($P = 0.035$) is because of random chance.

The study has a number of important limitations. First, although a validated measure was used to assess alcohol consumption, alcohol use patterns were self-reported. However, in a

subanalysis of persons involved in the VACS biomarker cohort, AUDIT-C group membership was highly correlated with PEth concentrations. These findings increase confidence in the observed AUDIT-C patterns. Second, there may be unmeasured confounding affecting the observed associations between membership in the alcohol use and VACS index score trajectories. For example, we were not able to assess family history of alcohol problems, which may affect both long-term drinking patterns and overall health. Third, the trajectory-based approach did not permit analysis of whether specific changes in drinking behavior result in subsequent changes in VACS index scores. Fourth, differential loss to follow-up may have affected the shape and classification of alcohol and VACS index trajectories, particularly as the proportion who dropped out varied across the groups. We evaluated the extent to which these biases influenced our results by conducting a series of sensitivity analyses, and found that the differences in trajectory membership, shape, and effect estimates were minimal. Fifth, the small number of persons assigned to the low VACS index class is in part a function of the fact that persons 50 years and older are assigned at least 12 points on the VACS index. Research is underway to refine how age is accounted for in the scoring algorithm. Finally, our study was restricted to HIV-infected veterans receiving care in the Veterans Healthcare System and who were primarily men. Thus, the results may not necessarily be generalizable to all veterans or populations living with HIV.

In conclusion, long-term alcohol consumption and VACS index trajectories were linked and interrelated among HIV-infected patients in care. A pattern of persistent unhealthy alcohol use was most common among persons with greater HIV disease severity, whereas abstainers were overrepresented in the healthiest and unhealthiest groups (suggesting distinct groups of ‘healthy abstainers’ and ‘sick quitters’). Future research should explore motivations and reasons for alcohol abstinence among HIV-infected populations to more fully understand this relationship. Second, studies should seek to determine the extent to which changes in alcohol consumption may impact long-term HIV disease progression. Finally, further research is needed to identify whether interventions that successfully reduce alcohol consumption improve HIV-related morbidity and mortality.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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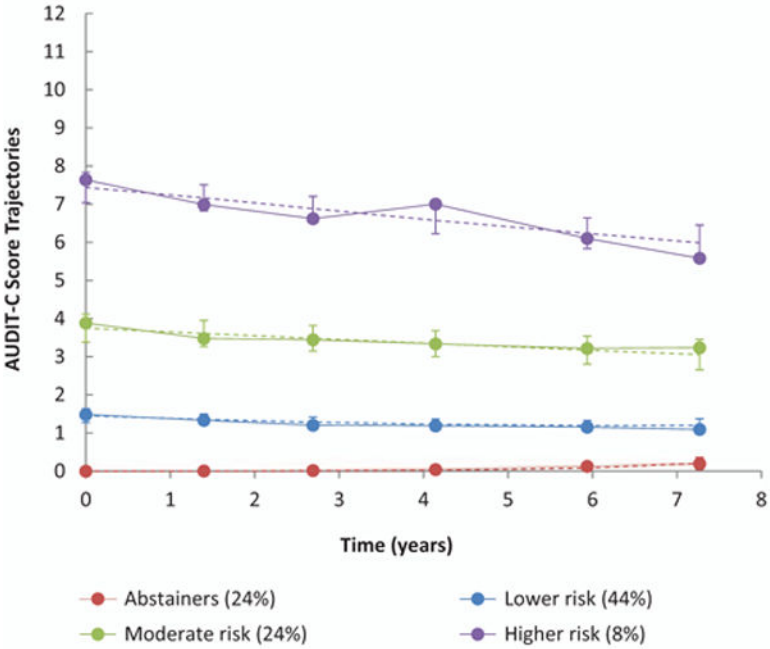

Fig. 1. AUDIT-C score trajectories among 3539 HIV-infected participants in the VACS, 2002–2010. AUDIT-C; alcohol use disorders identification test-consumption; VACS, Veterans Aging Cohort Study

Dashed lines represent predicted values and error bars represent 95% confidence intervals for each wave's estimate; solid lines represent empirical averages. Time points are based on the average time since baseline for each of the six waves of data collection during the 8-year study period.

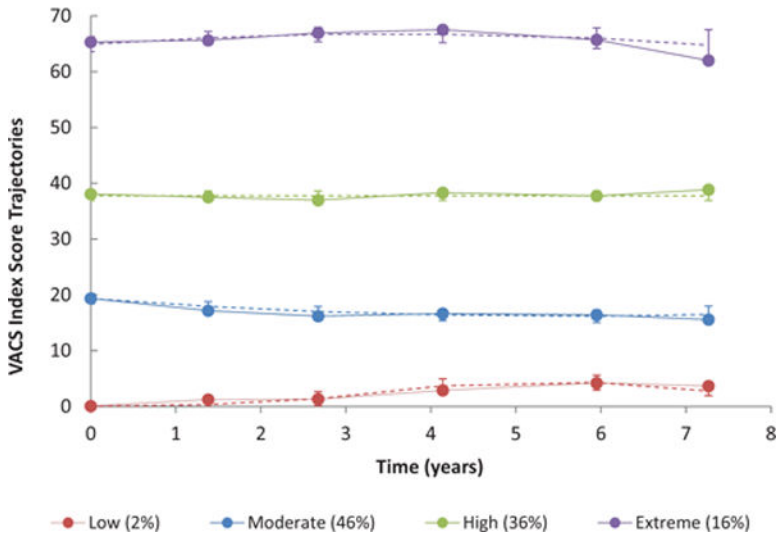

Fig. 2. VACS index score trajectories among 3539 HIV-infected participants in the VACS, 2002–2010. AUDIT-C; alcohol use disorders identification test-consumption; VACS, Veterans Aging Cohort Study

Dashed lines represent predicted values and error bars represent 95% confidence intervals for each wave's estimate; solid lines represent empirical averages. Time points are based on the average time since baseline for each of the six waves of data collection during the 8-year study period.

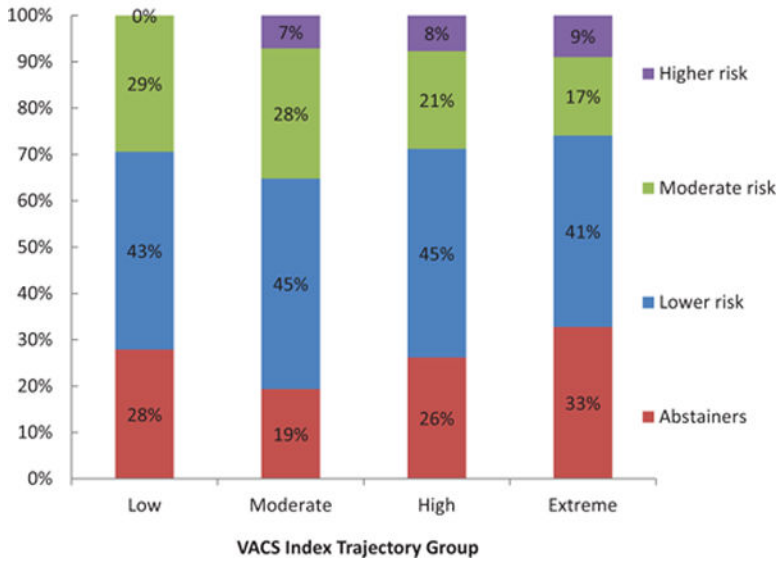

Fig. 3. Relationship between membership in trajectories by VACS index and AUDIT-C among 3359 HIV-infected participants in the VACS. AUDIT-C; alcohol use disorders identification test-consumption; VACS, Veterans Aging Cohort Study

Association between membership in VACS index score trajectory and AUDIT-C score trajectory was statistically significant ($\chi^2 = 73$, $P < 0.001$).

Table 1

Baseline characteristics, alcohol use disorders identification test-consumption trajectory group, death, and loss to follow-up among eligible participants, overall and by Veterans Aging Cohort Study index score trajectory group (*n*, % except as noted).

	VACS index trajectory group					
	Overall	**Low**	**Moderate**	**High**	**Extreme**	
Characteristic	***N* = 3,539**	***N* = 68 (2%)**	***N* = 1629 (46%)**	***N* = 1290 (36%)**	***N* = 552 (16%)**	***P* value**
Age (median, IQR)	49 (44–55)	42 (38–44)	46 (41–51)	52 (47–56)	53 (48–58)	< 0.001
Baseline VACS index (median, IQR)	17 (29–46)	0 (0–0)	12 (18–24)	30 (38–46)	65 (56–76)	< 0.001
Female	90 (3)	2 (3)	45 (3)	31 (2)	12 (2)	0.858
Race						< 0.001
White	827 (23)	26 (39)	447 (28)	271 (22)	83 (16)	
African American	2395 (68)	37 (55)	1042 (66)	909 (73)	407 (78)	
Other	182 (5)	4 (6)	91 (6)	58 (5)	29 (6)	
Hispanic/Latino	332 (9.4)	9 (13)	162 (10)	110 (9)	51 (9)	0.405
On HAART at baseline	2615 (73.9)	56 (82.4)	1177 (72.3)	963 (74.7)	419 (75.9)	0.075
$CD4^+$ cell count (median, IQR cells/μl)	367 (213–555)	719 (638–904)	450 (310–620)	309 (187–483)	170 (6–331)	< 0.001
Virally suppressed (< 400 copies/ml)	1482 (42)	48 (71)	782 (48)	484 (38)	169 (30)	< 0.001
HCV positive	1790 (51)	0 (0)	599 (37)	799 (62)	394 (71)	< 0.001
Current smoker	1880 (53)	27 (40)	838 (52)	709 (55)	306 (56)	< 0.001
Injection drug use, ever	1170 (33)	10 (15)	400 (25)	517 (41)	243 (52)	< 0.001
Depressive symptomatology[a]	790 (22)	9 (13)	357 (22)	289 (23)	135 (25)	0.147
Education, high school or less	1476 (42)	18 (27)	585 (36)	590 (46)	283 (51)	< 0.001
Marital status						< 0.001
Married/living with partner	806 (23)	13 (19)	397 (25)	300 (24)	96 (18)	
Divorced/separated/widowed	1432 (40)	17 (25)	563 (35)	567 (45)	285 (53)	
Never married	1249 (35)	38 (56)	649 (40)	407 (32)	155 (29)	
Homeless, ever	1388 (39)	15 (22)	606 (37)	542 (42)	225 (41)	< 0.001
Baseline AUDIT-C (median, IQR)	1 (0–4)	1 (0–3)	2 (0–4)	1 (0–3)	1 (0–4)	< 0.001
AUDIT-C trajectory group						< 0.001
Abstainers	854 (24)	19 (28)	316 (19)	338 (26)	181 (33)	
Lower risk	1576 (45)	29 (43)	739 (45)	580 (45)	228 (41)	

	VACS index trajectory group					
	Overall	**Low**	**Moderate**	**High**	**Extreme**	
Characteristic	***N* = 3,539**	***N* = 68 (2%)**	***N* = 1629 (46%)**	***N* = 1290 (36%)**	***N* = 552 (16%)**	***P* value**
Moderate risk	843 (24)	20 (29)	458 (28)	272 (21)	93 (17)	
Higher risk	266 (7)	0 (0)	116 (7)	100 (8)	50 (9)	
Died during study period	1105 (31)	4 (6)	241 (15)	469 (36)	391 (71)	< 0.001
Loss to follow-up	772 (22)	20 (29)	461 (29)	244 (19)	47 (9)	< 0.001

Not all cells add to 100% because of missing values. AUDIT-C; alcohol use disorders identification test-consumption; HAART, highly active antiretroviral therapy; HCV, hepatitis C virus; IQR, interquartile range; VACS, Veterans Aging Cohort Study.

[a]Patient Health Questionnaire-9 score at least 10 indicates moderate depressive severity [25].

Table 2

Weighted multinomial logistic regression of factors associated with membership in Veterans Aging Cohort Study index score trajectories among HIV-positive participants.

	VACS index trajectory group, adjusted odds ratio (95% CI)				
Characteristic	**Low**	**Moderate**	**High**	**Extreme**	***P* value**
Age (per unit increase)	0.94 (0.91–0.96)	REF	1.12 (1.10–1.12)	1.13 (1.12–1.15)	< 0.001
Race (ref: White)					< 0.001
African American	0.42 (0.26–0.66)	REF	1.80 (1.52–2.14)	2.58 (1.98–3.38)	
Other	0.41 (0.16–1.05)	REF	1.44 (1.01–2.04)	2.41 (1.47–3.95)	
High school education	1.30 (0.80–2.13)	REF	0.77 (0.66–0.90)	0.69 (0.56–0.84)	< 0.001
Marital status (ref: Married)					0.006
Divorced/separated/widowed	1.35 (0.71–2.58)	REF	1.03 (0.85–1.24)	1.56 (1.18–2.07)	
Never married	2.06 (1.16–3.64)	REF	1.00 (0.82–1.21)	1.28 (0.96–1.73)	
IDU, ever	0.57 (0.31–1.08)	REF	1.77 (1.52–2.07)	2.03 (1.64–2.52)	< 0.001
AUDIT-C group		REF			0.002
Abstainers	1.92 (1.07–3.44)	REF	1.18 (0.96–1.47)	1.90 (1.40–2.57)	
Lower risk	1.07 (0.64–1.79)	REF	1.14 (0.95–1.36)	1.35 (1.02–1.79)	
Moderate risk	REF	REF	REF	REF	
Higher risk	*a*	REF	1.21 (0.89–1.63)	1.83 (1.21–2.78)	

Final model chosen using a manual backwards selection procedure based on the AIC, starting with all variables significant at $P < 0.05$ in Table 1. Inverse probability of censoring weights were used to account for loss to follow-up for reasons other than death. Final model also adjusted for year of recruitment. AIC, Akaike information criterion; AUDIT-C; alcohol use disorders identification test-consumption; CI, confidence interval; REF, reference; VACS, Veterans Aging Cohort Study.

[a]Effect estimate could not be calculated because of zero cell counts.