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Title

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Permalink

<https://escholarship.org/uc/item/5rt2j5cv>

Journal

J AIDS Journal of Acquired Immune Deficiency Syndromes, 81(4)

ISSN

1525-4135

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Publication Date

2019-08-01

DOI

10.1097/qai.0000000000002049

Peer reviewed



Published in final edited form as:

J Acquir Immune Defic Syndr. 2019 August 01; 81(4): 448–455. doi:10.1097/QAI.0000000000002049.

HIV Disease Severity is Sensitive to Temporal Changes in Alcohol Use: A National Study of VA Patients with HIV

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Preliminary findings of this study were presented at the Research Society on Alcoholism (RSA) Conference in San Diego, CA in June 2018.

CONFLICTS OF INTEREST

All authors declare no potential conflicts of interest.

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Abstract

Background: Alcohol use influences HIV disease severity via multiple mechanisms. Whether HIV disease severity is sensitive to changes in alcohol use among people with HIV (PWH) is understudied.

Setting: National Veterans Health Administration.

Methods: Pairs of AUDIT-C screens within 9-15 months (2/1/08-9/30/14) were identified among PWH from the Veterans Aging Cohort Study (VACS). Initial and follow-up VACS Index 2.0 pairs obtained 0-270 days after initial and follow-up AUDIT-Cs, respectively, determined change in VACS Index 2.0, a composite HIV severity measure. Change in VACS Index 2.0 was regressed on AUDIT-C change scores (−12 to +12) adjusted for demographics, initial VACS Index 2.0, and days between VACS Index measures.

Results: Among 23,297 PWH (76,202 observations), most had no (51%) or low-level (38%) alcohol use initially. Most (54%) had no subsequent change; 21% increased and 24% decreased drinking. Initial VACS Index 2.0 scores ranged from 0-134, change scores ranged from −65 to +73, with average improvement of 0.76 points (SD 9.48). AUDIT-C change was associated with VACS Index 2.0 change ($p < 0.001$). Among those with stable alcohol use (AUDIT-C change | 1 | point), VACS Index 2.0 improvements ranged 0.36-0.60 points. For those with maximum AUDIT-C increase (change from 0 to 12), VACS Index 2.0 worsened 3.74 points (95% CI −4.71, −2.78); for those with maximum AUDIT-C decrease (change from 12 to 0), VACS Index 2.0 changed minimally [−0.60 (95% CI −1.43, 0.23)].

Conclusion: In this national sample, improvement in HIV severity was generally greatest among those with stable alcohol use (primarily those with no use).

Keywords

HIV; alcohol; HIV disease severity; VACS Index; alcohol use

INTRODUCTION

Alcohol use has substantial adverse influences on the health of people with HIV (PWH),^{1,2} but is highly prevalent in this population.³ Among myriad adverse HIV-related outcomes, higher levels of alcohol use are associated with greater HIV disease severity and risk of death.^{2,4-7}

Emerging longitudinal research has focused on understanding population-level patterns of alcohol use associated with increased HIV disease severity among PWH,⁸ and examining whether individual-level changes in alcohol use over time may influence HIV-relevant

outcomes,⁹ including disease severity.¹⁰ Research of this type is nascent but has potential to identify PWH with the greatest alcohol-related risk, and to determine levels of changes in alcohol use that may facilitate clinically-relevant improvements or decrements in markers of HIV severity. Thus, further work is needed to understand whether individual-level changes in reported alcohol use correspond to changes in markers of HIV disease severity, and to examine this relationship within important clinical subgroups (e.g., persons with uncontrolled or untreated HIV).

Alcohol use influences morbidity and mortality among PWH via both behavioral (e.g., ART adherence) and biological (e.g., immune suppression, chronic inflammation) mechanisms sometimes mediated through other common comorbid conditions.¹ We previously identified significant associations between individual-level changes in alcohol use and changes in traditional clinical markers of HIV severity—CD4 cells/ml and HIV RNA viral load.¹⁰ However, no study has evaluated a more-comprehensive, composite measure of HIV disease severity—an outcome that more broadly reflects the wide range of mechanisms via which alcohol use influences adverse outcomes among PWH.¹ The Veterans Aging Cohort Study (VACS) Index¹¹ is a composite measure of HIV disease severity that includes multiple clinical indicators (age, traditional markers of HIV severity—CD4 and HIV-1 RNA, hemoglobin, renal and hepatic function tests, and viral hepatitis C infection). Its original version predicts all-cause mortality, cause-specific mortality, and other clinical outcomes in PWH with proven reproducibility, accuracy, and validity.¹²⁻¹⁴ The recently-developed VACS Index 2.0 incorporates additional clinical indicators and uses continuous measures for greater precision,¹⁵ resulting in significantly improved discrimination for predicting mortality and better ability to detect change.^{15,16} Because it incorporates a broader range of clinical outcomes that influence health among PWH,^{1,17} this combined clinical measure is more sensitive to HIV disease severity than traditional markers of HIV severity alone,^{12,16,18} and, thus, provides improved clinical utility for understanding the dynamic and complex relationship between alcohol use and HIV disease severity.^{1,15,16} Finally, because all indicators included in VACS Index 2.0 are routinely monitored according to best care practices for PWH,^{12,19,20} this outcome can be applied across HIV care settings.^{15,16} Therefore, using VA clinical data from VACS, we sought to evaluate the association between individual-level changes in alcohol use and subsequent changes in the VACS Index 2.0 in a national sample of PWH.

METHODS

Data Source and Sample.

Following previously-reported methods,¹⁰ VA electronic health record (EHR) data from VACS were used to identify a national sample of PWH²¹ receiving VA care who had at least one documented Alcohol Use Identification Test Consumption (AUDIT-C) alcohol screen 2/1/2008 to 5/1/2014.¹⁰ Among these, we identified PWH with a follow-up AUDIT-C screen recorded 9-15 months after initial screening. For each initial screen, follow-up screens were identified as those documented closest to 12 (and within 9-15) months after initial screening to best approximate the AUDIT-C's past-year timeframe. Follow-up screens were identified through 7/31/2015. To maximize power, patients included in the sample could contribute

multiple pairs of alcohol screens during the study if there were at least 9 months between initial screens. For each pair of alcohol screens, an initial and follow-up VACS Index 2.0 was identified within 0-270 days after initial and follow-up AUDIT-C scores, respectively.

Measures

For each pair of observations, the primary exposure measure—change in alcohol use over time—was measured as the difference between each initial and follow-up AUDIT-C score. AUDIT-C scores range from 0 to 12, with increasing AUDIT-C scores reflecting increasing mean alcohol consumption levels and increased symptoms of alcohol use disorder.^{22,23} Possible *AUDIT-C change scores* ranged from -12 to 12 and were calculated as the change from follow-up to baseline so that negative values reflect increased drinking, positive values reflect decreased drinking, and 0 values reflect stable drinking over time. For descriptive purposes, AUDIT-C change scores were categorized as: -6 to -12, -3 to -5, -2, -1, 0, 1, 2, 3 to 5, and 6 to 12. Similarly, initial and follow-up AUDIT-C scores were categorized according to risk groups corresponding to increased risk of adverse outcomes: 0 non-drinking; 1-3 (1-2 for women) low-level alcohol use; 4-5 (3-5 for women), medium-level alcohol use; 6-7 high-level alcohol use; and 8-12 very high-level alcohol use.^{2,24,25}

The primary outcome was change in HIV disease severity measured using VACS Index 2.0. VACS Index 2.0 calculates HIV disease severity using traditional clinical measures of HIV severity (CD4 count and HIV-1 RNA), as well as hemoglobin, white blood cell count, estimated liver fibrosis (FIB-4) and liver injury (hepatitis C infection and albumin), estimated kidney injury (eGFR), and body mass index (BMI), and thus captures many of the major organ systems directly affected by microbial translocation, chronic inflammation, and its sequelae, key mechanisms influenced by alcohol use.^{1,15} VACS Index 2.0 scores range from 0 to 164; higher scores reflect higher disease severity and increasing risk of mortality.¹⁵ Change in VACS Index 2.0 was based on the difference between the initial and follow-up score and calculated so that negative change scores indicate increased disease severity over time while positive change scores indicate improvements, and 0 indicates no change.

Other measures included demographic characteristics measured using EHR documentation at initial AUDIT-C administration: age (<50, 50-65, >65), gender (male/female), and race/ethnicity (black, Hispanic, white, and other/unknown). We also measured depressive and anxiety disorders, serious mental illness, and substance use disorders (stimulant use disorder, opioid use disorder, other drug use disorder, and alcohol use disorder) using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes documented in the year prior to each patient's first initial AUDIT-C. Finally, two HIV clinical measures were derived for each AUDIT-C pair: a three-category variable measuring anti-retroviral treatment (ART) over time (treated with ART within a year prior to initial screen, initiated ART between initial and follow-up screens, and no documented ART treatment) based on having filled one or more prescriptions, and a dichotomous measure of detectable viral load at the time of initial screen, defined as HIV-RNA > 500 copies/ml at the most recent measurement within one year prior. Though changes in the sensitivity of tests for HIV-RNA have lowered commonly used cut-points,^{26,27} 500 copies/ml was a relevant target for all years of the study.

Analysis

We conducted descriptive analyses at the patient level at the time of each individual's first documented AUDIT-C. We summarized the distribution of initial and follow-up AUDIT-C scores, as well as AUDIT-C and VACS Index 2.0 change scores. We described mean initial VACS Index 2.0 scores across AUDIT-C risk group categories and tested their association using analysis of variance tests.

At the observation level, we evaluated the association between AUDIT-C change scores and VACS Index 2.0 change scores using linear regression. AUDIT-C change scores were flexibly modeled using restricted cubic splines to allow for a smooth association across levels of AUDIT-C change without assuming linearity.^{28,29} Spline knots where segments connect were set at scores -3, -1, 0, 1, and 3 based on examination of the unadjusted association.²⁹ Our model was first unadjusted and then adjusted for all measured demographic characteristics (age, gender, and race/ethnicity), initial VACS Index 2.0 score, and days between VACS Index 2.0 measures. The adjusted model was considered primary. Standard errors were estimated using the robust sandwich estimator to account for correlation due to multiple observations (i.e., screen pairs) per patient.³⁰ Because not all PWH receiving VA care who had an initial AUDIT-C screen also had a follow-up screen documented, inverse probability weights were estimated using logistic regression (an indicator for being in the analytic sample was regressed on demographic and clinical characteristics) and used to weight analyses back to the full sample of PWH with any alcohol screening.³¹

The significance of the association between AUDIT-C and VACS Index 2.0 change scores was tested using an overall (omnibus) Wald Test assessing significance of the spline terms. For the primary model, we estimated and plotted the mean estimated VACS Index 2.0 change for each possible AUDIT-C change score (-12 to +12). Mean changes were obtained based on fixed covariate values: mean age, male gender, black race, mean initial VACS Index 2.0 score, mean days between VACS Index 2.0 measures.

Based on prior research,³² we hypothesized that increases in AUDIT-C scores (reflecting increased drinking) would be associated with worsening HIV severity. On the other hand, due to possible social desirability bias in reported drinking reductions and the possibility that abstinence or decreases in drinking may result from illness³³ or reflect unstable drinking,³⁴ we hypothesized that decreases in AUDIT-C score might not be reflected in changes in HIV severity. Therefore, we tested *a priori*-specified contrasts of estimated mean VACS Index 2.0 change scores across several AUDIT-C change score combinations. Specifically, we tested whether mean change in VACS Index 2.0 differed for PWH with a 2-point increase in AUDIT-C (AUDIT-C change score -2) compared with those remaining stable (AUDIT-C change score 0); PWH with a 5-point increase in AUDIT-C (AUDIT-C change -5) relative to those remaining stable (AUDIT-C change 0); and PWH with a 5-point increase in AUDIT-C (AUDIT-C change -5) relative to those with an 8-point increase (AUDIT-C change -8).

We undertook three sets of secondary analyses. First, because alcohol use is associated both with being treated with and adherent to ART^{7,9,35} and ART treatment is reflected in HIV viral load,^{36,37} we repeated our primary model stratified by two factors: 1) treatment with

ART (ART at initial screen, ART initiation between screens, no ART treatment) and 2) detectable (500+ copies/ml) vs. non-detectable (<500 copies/ml) viral load at initial screening. Second, to minimize the likelihood that patients may have changed their drinking between an AUDIT-C and the calculation of VACS Index 2.0, we repeated primary analyses in the subgroup of patients with AUDIT-C and VACS Index 2.0 measurements 30 days apart at both initial and follow-up screening (n=64,944 observations; 85% of all observations). Finally, we repeated primary model stratified by initial AUDIT-C risk group based on previous research that found associations between changes in alcohol use and changes in medical outcomes depended on initial level of drinking.³²

All analyses were conducted using Stata Statistical Software, release 14.³⁸ This study was approved by Institutional Review Boards at VA Connecticut and VA Puget Sound Healthcare Systems, including waivers of written consent and HIPAA authorization.

RESULTS

Among 23,297 eligible PWH (contributing 76,202 observations), patients were largely male (97%) and 50 years (64%), and over half were black (49%) or Hispanic (8%) (Table 1). Nearly a third of patients had documented depressive disorder, and nearly one-tenth had anxiety disorders and/or serious mental illness. Approximately 14% had a documented alcohol use disorder and nearly 8% had other drug use disorders. Most (74%) were on ART at the time of their first initial AUDIT-C; 16% initiated ART between their first pair of screens, and another 9% had no documented ART at initial screening (Table 1).

The majority of PWH (87%) reported no (47% AUDIT-C=0) or lower-risk (40% AUDIT-C=1-3 men; 1-2 women) alcohol use at their first AUDIT-C (Table 1). Slightly more than half (54%) had no change in AUDIT-C over time; 21% increased drinking, and 24% decreased drinking. Most with no change (97%) had no (74% AUDIT-C=0) or low-level (23% AUDIT-C 1-3/1-2) alcohol use initially. First initial VACS Index 2.0 scores ranged from 0-134 with a mean of 51.1 (16.7 standard deviation). VACS Index 2.0 scores were generally higher for patients in higher AUDIT-C risk groups (ANOVA $p < 0.001$; Table 2). VACS Index 2.0 change scores ranged from -65 to +73, with improvement of 0.76 points (SD 9.48) average, reflecting a modest improvement in HIV severity over time. The mean time between initial AUDIT-Cs and VACS Index 2.0 measurement was 8.1 days (SD 26.9) and between follow-up AUDIT-Cs and VACS Index 2.0 was 10.4 days (SD 31.9).

Changes in VACS Index 2.0 were associated with AUDIT-C change scores in the unadjusted and adjusted model (p-values for spline terms < 0.001). In primary analyses, those with the smallest AUDIT-C change scores had the greatest improvements in HIV severity over time while changes in either direction were associated with worsening HIV disease severity (Figure 1). Those with increased alcohol use had worse estimated declines (Figure 1). Specifically, among those with relatively stable alcohol use (AUDIT-C change ± 1 point), VACS Index 2.0 improvements ranged from 0.36 to 0.60 points. For those with AUDIT-C change -12 indicating maximum increased alcohol use, VACS Index 2.0 worsened 3.74 points (95% CI -4.71, -2.78); for those with AUDIT-C change score +12

indicating maximum decreased alcohol use, VACS Index 2.0 changed minimally (estimated mean = -0.60 (95% CI -1.43, 0.23), Figure 1).

Results of contrast tests comparing mean estimated change in VACS Score 2.0 across specific AUDIT-C change scores are presented in Table 3. In *a priori* contrast tests, no statistically significant difference in estimated mean VACS Index 2.0 change was observed between those with AUDIT-C change scores of 0 [estimated mean VACS Index 2.0 change of 0.42 (95% CI, 0.31-0.52)] and those with AUDIT-C change score of -2 [estimated mean VACS Index 2.0 change of 0.46 (95% CI 0.27-0.65)] ($p=0.67$). However, differences were observed between those with AUDIT-C change scores of 0 and -5 and between those with AUDIT-C change scores of -5 and -8 (Table 3). We conducted several *post hoc* contrast tests to assess effects of decreases in drinking. Those with no change (AUDIT-C change score = 0) did not differ in mean VACS Index 2.0 change from those with a small decrease in drinking (AUDIT-C change score = +2), but did relative to those with a larger decrease in drinking (AUDIT-C change score = +5). Differences in mean VACS Index 2.0 change were also observed for those with AUDIT-C change scores of +1 relative to -1; +5 relative to -5, +5 relative to +8, and -8 relative to +8 (Table 3).

Secondary analyses stratified by ART treatment and viral load status resulted in similar findings (Figure 2) though precision was decreased for those initiating ART between screens and those without documented ART due to small sample sizes. Associations were unchanged when limited to those with AUDIT-C and VACS Index 2.0 measurements 30 days apart (data not shown) and similar when stratified by baseline AUDIT-C risk groups (Supplemental Figure).

DISCUSSION

In this national cohort of PWH receiving healthcare in the VA, individual-level changes in drinking measured by AUDIT-C scores were associated with changes in HIV disease severity measured by the VACS Index 2.0, a composite risk index that includes measurement of multiple mechanisms via which alcohol use influences HIV.¹ On average, HIV disease severity improved slightly among patients over time and improved the most among those who remained relatively stable in drinking, 97% of whom reported drinking at lower levels at the time of initial measurement. Those with increases in alcohol use worsened in HIV severity slightly more than those with decreases in alcohol use. Analyses stratified by ART treatment and viral load status, as well as initial alcohol use risk groups, resulted in generally similar findings.

Results of the present study extend a large literature that primarily has described cross-sectional associations between alcohol use and HIV disease severity⁴⁻⁶ and are consistent with prior longitudinal studies suggesting that stable or decreased alcohol use may result in the greatest health benefits.^{10,32} Though potentially surprising that greater improvements in HIV severity were not observed among PWH who decreased drinking, these results are possibly due to social desirability bias in reported drinking reductions, as well as the possibility that alcohol abstinence may result from illness³⁹ or may reflect unstable drinking and not be sustained.³⁴ Findings support and build on those of two previous longitudinal

This study has several limitations. Findings may not be generalizable to PWH not receiving care in VA or to women, given the small sample. Further work should assess gender-specific associations, given associations may differ for women and men.⁴³ Reliance on EHR data may have limited measurement of alcohol use as clinically documented screening may miss patients with any and unhealthy alcohol use, and patients may under-report alcohol use and/or report greater than experienced reductions in alcohol use over time.⁴⁴⁻⁴⁶ Additionally, findings from this study cannot be considered causal. Further work is needed to understand how individual-level changes in alcohol use influence HIV severity and whether observed associations reflect changes in alcohol use and/or changes in health that led to changes in alcohol use.³³ Finally, previous research suggests that a 5-point difference in VACS Index scores is associated with a 20% increased risk of 5-year mortality.⁴⁷ Investigation of the clinical relevance of changes in HIV severity observed at all levels of AUDIT-C change is needed among PWH.

Despite these limitations, this study found that changes in a practical widely-used alcohol screen are associated with changes in HIV severity over time in a large national sample of PWH receiving care in the VA, the nation's largest provider of HIV care. Findings from this study support and extend those of previous studies by using a validated, composite outcome measure that better reflects the multiple mechanisms via which alcohol use influences HIV severity and mortality risk and provides greater specificity regarding individual-level risk associated with changes in alcohol use. Findings highlight that stable low-level alcohol use over time may result in optimal stability of or improvements in HIV-related severity and risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

This research was funded by a grant from the National Institute on Alcohol Abuse and Alcoholism (R21AA022866-01; Williams/Bradley PIs) and COMpAAAS/Veterans Aging Cohort Study (U24-AA020794, U01-AA020790, U01-AA020795, U01-AA020799; U10 AA013566). Dr. Williams is supported by a Career Development Award from VA Health Services Research & Development (CDA 12-276), and Dr. Bradley is supported by a mid-career mentorship award from NIAAA (K24-AA022128). The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication. Dr. Bryant, the study's scientific collaborator, is employed by the funder (the National Institutes of Alcohol Abuse and Alcoholism) and helped guide analysis, interpretation and presentation of data and participated in the decision to submit the manuscript for publication.

SOURCES OF FUNDING

This research was funded by a grant from the National Institute on Alcohol Abuse and Alcoholism (R21AA022866-01; Williams/Bradley PIs) and COMpAAAS/Veterans Aging Cohort Study (U24-AA020794, U01-AA020790, U01-AA020795, U01-AA020799; U10 AA013566). Dr. Williams is supported by a Career Development Award from VA Health Services Research & Development (CDA 12-276), and Dr. Bradley is supported by a mid-career mentorship award from NIAAA (K24-AA022128). The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication. An employee of the funder (K. Bryant) served as a scientific collaborator and helped guide analysis, interpretation and presentation of data and participated in the decision to submit the manuscript for publication. Views presented in the manuscript are those of the authors and do not represent the official position of the U.S. Government, the Department of Veterans Affairs, or other affiliated institutions.

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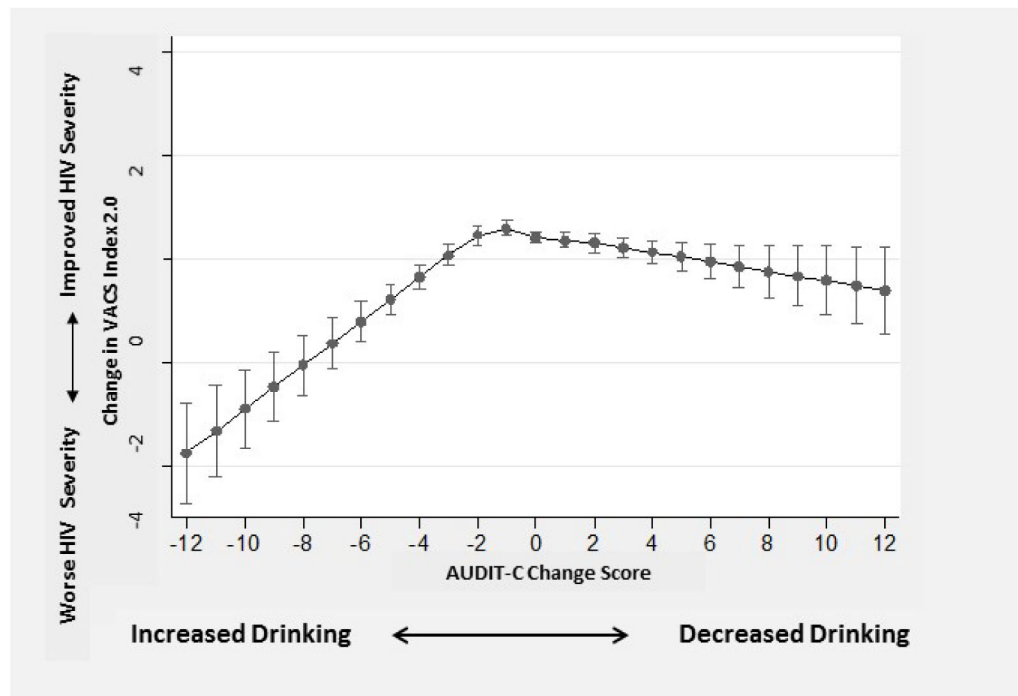


Figure 1.

Association* Between Change in AUDIT-C and Change in VACS Index 2.0 in a National Sample of VA Patients with HIV (n = 76,202 observations)

* adjusted for demographics (age, gender, and race), initial VACS Index 2.0 score, and time between VACS Index 2.0 measures.

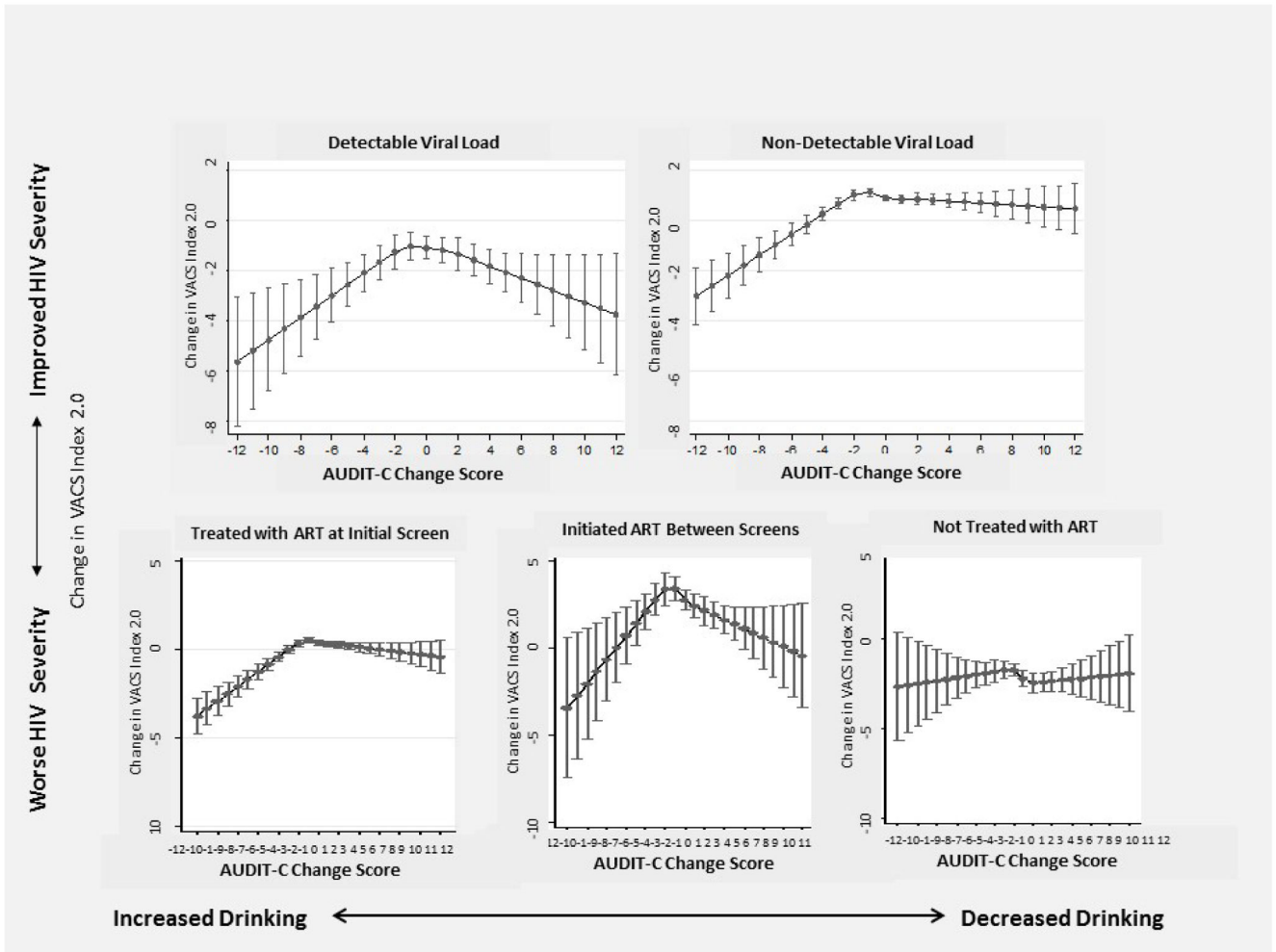


Figure 2.

Association* between Change in AUDIT-C and Change in VACS Index 2.0 in a National Sample of Patients with HIV: Stratified by Viral Load and ART Treatment Status, (n = 76,202 observations)

* adjusted for demographics (age, gender, and race), initial VACS Index 2.0 score, and time between VACS Index 2.0 measures.

Table 1.

Characteristics of eligible VA Patients with HIV at first Alcohol Use Disorders Identification Test Consumption (AUDIT-C) Measure during the study period (n=23,781 individuals)

Characteristic	N	(%)
Demographics		
Gender (Female)	659	(2.8)
Age		
<50	8,601	(36.2)
50 – 64	12,894	(54.2)
65	2,286	(9.6)
Race/Ethnicity		
Black	11,577	(48.7)
Hispanic	1,979	(8.3)
White	9,545	(40.1)
Other/Unknown	680	(2.9)
Mental Health and Substance Use Disorder		
Depressive Disorder	7,091	(29.8)
Anxiety Disorder	2,096	(8.8)
Serious Mental Illness	2,275	(9.6)
Stimulant Use Disorder	349	(1.5)
Opioid Use Disorder	885	(3.7)
Other Drug Use Disorder	1,822	(7.7)
HIV Clinical Measure		
On Antiretroviral Treatment (ART) at Initial Screen	17,604	(74.0)
Initiated ART Between Screens	3,871	(16.3)
Not on ART at Either Screen	2,306	(9.7)
Alcohol Use Severity		
Alcohol Use Disorder	3,311	(13.9)
Baseline AUDIT-C Category		
0	11,134	(46.8)
1-3 (1-2 for women)	9,441	(39.7)
4-5 (3-5 for women)	1,859	(7.8)
6-7	580	(2.4)
8-12	767	(3.2)

Table 2.

Mean Initial VACS Index 2.0 Score Across Initial AUDIT-C Score Risk Groups at the time of first AUDIT-C screen (n = 23,781 individuals)

	N	Initial VACS Index 2.0 Score Mean (SD)	
Total Sample	23,781	51.1 (16.7)	
Initial AUDIT-C Risk Group			p-value *
0	11134	52.9 (16.7)	<0.001
1-3 (1-2 for women)	9441	48.7 (16.3)	
4-5 (3-5 for women)	1859	49.9 (16.4)	
6-7	580	52.0 (18.6)	
8-12	767	56.6 (17.3)	

* Analysis of variance test

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Table 3.

Association between AUDIT-C change scores and change in VACS Index 2.0 score: Results of contrast tests* for comparison of mean changes in VACS Index 2.0 between *a priori*- and post hoc- specified AUDIT-C change scores among n = 76,206 observations

Specified AUDIT-C change scores		Predicted change in VACS Index 2.0 Score Associated with Specified AUDIT-C Change Scores		p-value comparing predicted change in VACS Index 2.0 Score estimated for specified AUDIT-C Change Scores*
A**	A'**	Y (95% CI)	Y' (95% CI)	
<i>A priori contrasts to test hypothesis</i>				
0	-2	0.42 (0.31, 0.52)	0.46 (0.27, 0.65)	0.6704
0	-5	0.42 (0.31, 0.52)	-0.77 (-1.08, 0.47)	<0.001
-5	-8	-0.77 (-1.08, 0.47)	-2.05 (-2.62, -1.47)	<0.001
<i>Post-hoc contrast tests to assess effects of decreases in drinking</i>				
0	+2	0.42 (0.31, 0.52)	0.31 (0.12, 0.50)	0.2939
0	+5	0.42 (0.31, 0.52)	0.04 (-0.23, 0.30)	0.0076
+1	-1	0.36 (0.21, 0.51)	0.60 (0.45, 0.75)	0.0140
+5	-5	0.04 (-0.23, 0.30)	-0.77 (-1.08, 0.47)	0.0001
+5	+8	0.04 (-0.23, 0.30)	-0.24 (-0.73, 0.26)	0.0444
+8	-8	-0.24 (-0.73, 0.26)	-2.05 (-2.62, -1.47)	<0.001

KEY: Above, mean change from initial to follow-up VACS Index 2.0 Score (Y) associated with one AUDIT-C change score (A) are compared to mean changes in VACS Index 2.0 Score (Y') associated with another AUDIT-C change score (A'); negative AUDIT-C change score indicates increased AUDIT-C; positive AUDIT-C change score indicates decreased AUDIT-C

* p-value for contrast, tested using primary model (Block 2) adjusted for demographics, initial VACS Index Score 2.0, and days between measures.

** N for AUDIT-C -8 = 173; N for AUDIT-C -5 = 408; N for AUDIT-D -2 = 3,479; N for AUDIT-C -1 = 9,157; N for AUDIT-C 0 = 41,466; N for AUDIT-C +1 = 9,963; N for AUDIT-C +2 = 3,939; N for AUDIT-C +5 = 510; N for AUDIT-C +8 = 220.