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Risk of mortality and physiologic injury evident with lower alcohol exposure among HIV infected compared with uninfected men

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ABSTRACT

Background: HIV infected (HIV+) individuals may be more susceptible to alcohol-related harm than uninfected individuals.
Methods: We analyzed data on HIV+ and uninfected individuals in the Veterans Aging Cohort Study (VACS) with an Alcohol Use Disorders Identification Test-Consumption AUDIT-C score from 2008 to 2012. We used Cox proportional hazards models to examine the association between alcohol exposure and mortality through July, 2014; and linear regression models to assess the association between alcohol exposure and physiologic injury based on VACS Index Scores. Models were adjusted for age, race/ethnicity, smoking, and hepatitis C infection.
Results: The sample included 18,145 HIV+ and 42,228 uninfected individuals. Among HIV+ individuals, 76% had undetectable HIV-1 RNA (<500 copies/ml). The threshold for an association of alcohol use with mortality and physiologic injury differed by HIV status. Among HIV+ individuals, AUDIT-C score ≥4 (hazard ratio [HR] 1.25, 95% CI 1.09–1.44) and ≥30 drinks per month (HR, 1.30, 95% CI 1.14–1.50) were associated with increased risk of mortality. Among uninfected individuals, AUDIT-C score ≥5 (HR, 1.19, 95% CI 1.07–1.32) and ≥70 drinks per month (HR 1.13, 95% CI 1.00–1.28) were associated with increased risk. Similarly, AUDIT-C threshold scores of 5–7 were associated with physiologic injury among HIV+ individuals (beta 0.47, 95% CI 0.22, 0.73) and a score of 8 or more was associated with injury in uninfected (beta 0.29, 95% CI 0.16, 0.42) individuals.
Conclusions: Despite antiretroviral therapy, HIV+ individuals experienced increased mortality and physiologic injury at lower levels of alcohol use compared with uninfected individuals. Alcohol consumption limits should be lower among HIV+ individuals.

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1. Introduction

The health impact of alcohol use is well described (Dawson et al., 2008; Rehm et al., 2003; Saitz, 2005). While the impact of alcohol on cause-specific mortality can vary by condition, most large observational studies demonstrate a dose-dependent association

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between higher levels of alcohol consumption and all-cause mortality (Di Castelnuovo et al., 2006; Harris et al., 2010; Knott et al., 2015; Plunk et al., 2014; Rogers et al., 2015). However, alcohol use is common among those with HIV infection (HIV+ individuals) and may be uniquely harmful in this population (Braithwaite and Bryant, 2010; Braithwaite et al., 2008, 2005; Cook et al., 2001). Among other effects, alcohol use is associated with poor adherence to life preserving combination antiretroviral treatment (ART; Braithwaite and Bryant, 2010; Braithwaite et al., 2008, 2005; Cook et al., 2001; Samet et al., 2004) and increases risk for liver fibrosis (Lim et al., 2014), a leading cause of death. Further, compared with uninfected individuals, HIV+ individuals report fewer drinks required to experience intoxication (McGinnis et al., 2015). As a result, some have suggested that "safe limits" for alcohol use among those with HIV infection should be lower than among uninfected individuals (Samet et al., 2007, 2004).

Further, health effects of alcohol among HIV+ individuals appear to vary depending on whether viral suppression is attained. Given a unit dose of alcohol, HIV+ individuals experience higher blood alcohol concentrations before, compared to after, initiating ART (McCance-Katz et al., 2012). In addition, having a detectable HIV viral load is associated with a lower number of drinks to feel intoxicated among HIV+ individuals (McGinnis et al., 2015). Since many the prior studies were dominated by HIV+ individuals who had not achieved viral suppression, it is important to determine whether differential harms from alcohol use persist among a more current sample of HIV+ individuals, most of whom have achieved HIV-1 RNA suppression on ART, compared with uninfected individuals.

Finally, all-cause mortality is an important health outcome, but it is not the only one of interest (Kinder et al., 2009). HIV+ individuals in care are aging (Justice, 2010) and experiencing increasing physiologic injury resulting in cumulative frailty or a greater vulnerability to stressors (Clegg et al., 2013). The Veterans Aging Cohort Study (VACS) Index incorporates weighted values of routinely available clinical biomarkers including age, CD4 count, HIV-1 RNA, hemoglobin, platelets, aspartate transaminase, alanine transaminase, creatinine, and hepatitis C sero-status (Justice et al., 2013; Tate et al., 2013). The Index provides reliable estimates of 5-year mortality in HIV+ individuals (Tate et al., 2013) and has been shown to predict hospitalization (Akgun et al., 2013a), physical and cognitive performance (Marquine et al., 2014; Oursler et al., 2013), and fragility fractures (Womack et al., 2013). The Index also predicts hospitalization and mortality among uninfected individuals (Akgun et al., 2013a). As a result, the VACS Index is a clinically applicable measure of overall physiologic injury and may be a meaningful indicator of frailty (Akgun et al., 2013a; Escota et al., 2014; Shaper, 1990; Shaper and Wannamethee, 1998; Womack et al., 2013). The Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) is a commonly used tool to screen for alcohol use in large clinical populations (Bradley et al., 2007). We use mortality, the VACS Index, and self-reported alcohol data, to compare health outcomes associated with patterns of alcohol use among HIV+ and uninfected individuals. Our first aim is to determine whether level of alcohol use is associated with all-cause mortality and physiologic injury as measured by the VACS Index. Our second aim is to determine whether AUDIT-C thresholds for physiologic injury differ by HIV status.

2. Methods

2.1. Data

We used data from the Veterans Aging Cohort Study (VACS), a large electronic medical record (EMR) based cohort study of 47,805 HIV + and 99,061 uninfected patients receiving care in the Veterans Health Administration (2006) (VHA) from fiscal years 1997 to 2014 (Conigliaro et al., 2004; Justice et al., 2006a,b). We identified those who reported alcohol use based on having a non-zero AUDIT-C score after enrollment into the cohort and from October, 2008 to March, 2012. Observations with an AUDIT-C score of zero were excluded since those who abstain from alcohol may be an inappropriate referent group (Knott et al., 2015) as they often include individuals who became abstinent due to comorbidities and other health issues (Fillmore et al., 2007; Shaper, 1990; Shaper and Wannamethee, 1998). We elected not to use alcohol-related diagnoses from the EMR for the current analysis due to concerns over low sensitivity (Kim et al., 2012; Quan et al., 2008). Women were excluded because they represent less than 3% of VACS subjects and sensitivity to the effects of alcohol varies by gender (Midanik, 1999).

2.2. Main outcomes

Outcomes included: (1) all-cause mortality and (2) physiologic injury as measured by the VACS Index. Mortality rates were calculated using follow-up time starting with date of first AUDIT-C and ending with date of death or July 31, 2014, whichever came first. Deaths were identified from four sources: (1) the Patient Treatment File, which records hospital deaths in the VHA healthcare system, (2) the Beneficiary Identification Records Locating System, which tracks VHA death benefits, (3) the Medicare Vital Status File, and (4) the Social Security National Death Index. The VACS Index was calculated as previously reported using laboratory values from closest to (±90 days) date of AUDIT-C measurement. Of note, VACS Index is calculated for uninfected individuals by assuming a normal CD4 count (i.e., greater than 500 cells/mm3) and an undetectable HIV-1 RNA VL (Akgun et al., 2013a,b).

2.3. Main predictor

Alcohol exposure was assessed based on self-reported responses to the AUDIT-C. AUDIT-C data are collected nationally in the VHA using automated clinical reminders in the EMR that providers must complete on their patients on a regular basis (Bradley et al., 2006). For each of the 3 questions in the AUDIT-C, 0–4 points are assigned based on the response and summed for a total score ranging from 0 to 12. Item 1 is: "How often do you have a drink containing alcohol?" Choices (points) include: never (0), monthly or less (1), 2–4 times a month (2), 2–3 times a week (3); or 4 or more times a week (4). Item 2 is: "How many standard drinks containing alcohol do you have on a typical day?" Choices (points) include: 0 (0), 1 or 2 (0); 3 or 4 (1); 5 or 6 (2); 7 to 9 (3); 10 or more (4). The original AUDIT-C Item 2 had no option for 0 number of drinks; therefore, we combined the responses of 0 and 1 or 2. Item 3 is: "How often do you have six or more drinks on one occasion?" Choices (points) include: never (0); less than monthly (1); monthly (2); weekly (3); daily or almost daily (4).

AUDIT-C has been evaluated using multiple cutoffs including 3+, 4+, and 5+ (Bradley et al., 2007; Bush et al., 1998; Gordon et al., 2001; Gual et al., 2002). Heavy episodic drinking (HED) has been assessed using a cutoff based on any positive response to AUDIT-C item 3 (McGinnis et al., 2013). Further, recommended cutoffs for AUDIT-C vary based on the population (male vs. female, 65 years), the different modes in which the AUDIT-C is asked (face to face vs. confidential survey), and the purpose for using the AUDIT-C (initial screening prior to further assessment vs. the only assessment). Because of the diversity of cutoffs used in prior literature, we initially employed integer categories of AUDIT-C to evaluate multiple candidate cutoff(s) (1, 2, 3, 4, 5–7, and 8+) for predicting mortality and physiologic frailty.

Table 1
Demographic characteristics of HIV infected and uninfected men in VACS with an AUDIT-C score of at least 1.

Characteristic	HIV infected	Uninfected	*p*-Value
N	18,145	42,228	
Mean age (SD)	52.5 (10.5)	54.0 (10.0)	<.001
Race/ethnicity (%)			<.001
White	40.7	38.6	
African–American	47.1	48.5	
Hispanic	7.5	8.2	
Other/unknown	4.8	4.6	
AUDIT-C scores (%)			<.001
1	42.2	37.8	
2	20.9	19.7	
3	13.1	13.7	
4	9.2	10.0	
5–7	8.6	10.1	
8–12	6.2	8.8	
Median (IQR)	2 (1,3)	2 (1,4)	
Number of drinks containing alcohol consumed per month (%)			<.001
1–2	45.7	41.5	
3–7	21.1	19.6	
8–29	15.5	16.7	
30–69	10.1	12.1	
70+	7.5	10.1	
Heavy episodic drinking* (define below) HED (%)			<.001
Never	77.5	74.4	
<Monthly	11.2	10.8	
Monthly	3.8	4.6	
Weekly	3.9	5.4	
Daily	3.6	4.9	
Drug related diagnosis code (%)	16.3	13.3	<.001
Hepatitis C infection (%)	31.2	16.1	<.001
Smoking (%)			<.001
Never	27.5	26.6	
Past	13.8	16.9	
Current	58.7	56.5	
Deaths (%)	7.2	4.7	
Deaths/100 person year	2.7	1.8	<.001
Median follow-up time (IQR)	4.7 (3.5–5.3)	4.8 (3.7–5.3)	<.001
*N	9216	12,841	
Mean VACS Index score (SD)	29.8 (21.4)	20.7 (16.2)	<.001
Mean estimated 5 year mortality based on VACS Index score (SD)	15.0 (14.6)	9.4 (9.6)	<.001
Hemoglobin (%)			<.001
<10	2.0	1.7	
10–11.9	8.8	6.8	
12–13.9	32.2	29.9	
14+	57.0	61.7	
Estimated glomerular filtration (%) rate			.03
<30	1.7	1.8	
30–44.9	1.8	1.9	
45–59.9	6.5	5.5	
60+	90.1	90.8	
FIB4 (%)			<.001
<1.45	52.1	65.0	
1.45–3.249	38.1	29.5	
3.25+	9.8	5.5	
CD4 (%)		–	
<50	2.9		
50–99	3.3		
100–199	9.6		
200–349	20.5		
350–499	21.8		
500+	41.8		
HIV viral load (%)		–	
<500	75.7		
500–99,999	20.0		
100,000+	4.3		

* Includes those who had VACS Index score w/in 90 days after their AUDIT-C.

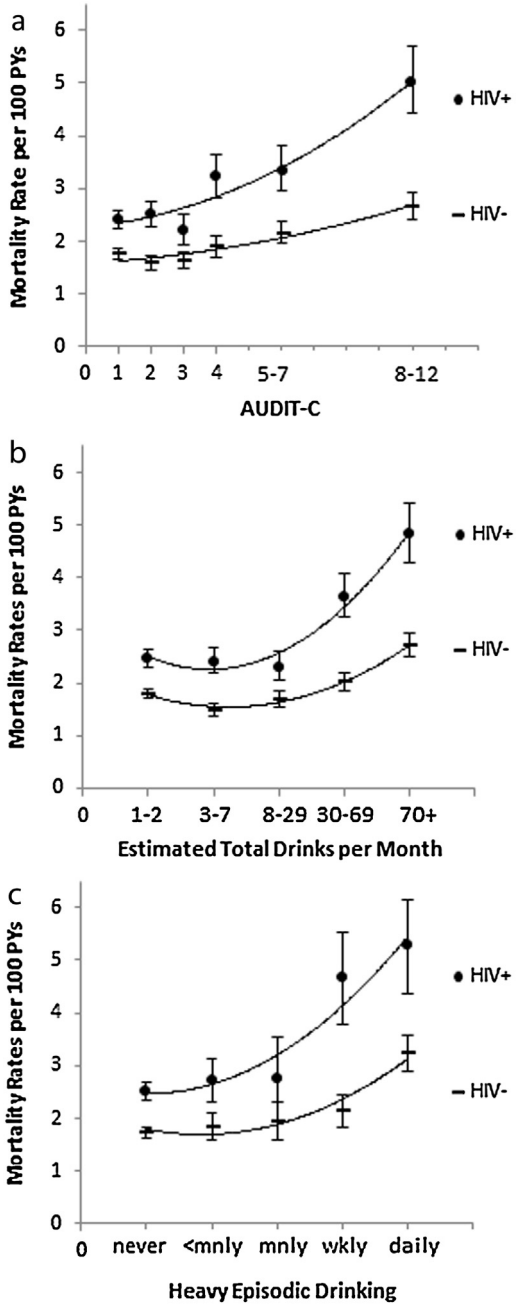

Fig. 1. (a–c) Mortality per 100 person years (PYs) by AUDIT-C level and HIV status.

Alcohol use is often evaluated using quantity-frequency measures (i.e., total number of drinks over a certain timeframe) and an average of more than 2 drinks per day is considered potentially unhealthy alcohol use for men (Saitz, 2005; NIAAA, 2005). Therefore, we also created a variable for estimated total number of drinks per month using the first two items in the AUDIT-C. Cate-

Table 2
Adjusted *mortality* by AUDIT-C level among HIV infected and uninfected men.

Variable	HIV infected (n = 18,145)		Uninfected (n = 42,228)	
	HR	95% CI	HR	95% CI
AUDIT-C score (reference is 1–3)				
4	1.25	1.09–1.44	1.01	0.90–1.13
5–7	1.29	1.12–1.48	1.19	1.07–1.32
8–12	1.71	1.49–1.98	1.35	1.22–1.50
Age (reference is <50 years)				
50–64 years	2.40	2.13–2.71	2.94	2.63–3.28
65+ years	5.92	5.11–6.85	7.29	6.39–8.26
Race/ethnicity (reference is white)				
African–American	0.94	0.85–1.03	0.83	0.77–0.89
Hispanic	0.78	0.64–0.93	0.73	0.64–0.85
Other	0.88	0.69–1.12	0.71	0.58–0.87
Smoking (reference is never smoked)				
Current	1.85	1.64–2.10	2.21	1.99–2.45
Past	1.22	1.04–1.44	1.39	1.23–1.58
Unknown/missing	1.81	1.31–2.50	1.54	1.17–2.03
Hepatitis C infection	1.90	1.74–2.09	1.89	1.75–2.05

gories included 1–2, 3–7, 8–29, 30–69, and 70+ drinks per month. We also considered HED (Smith et al., 2009) frequency separately.

2.4. Covariates

Covariates assessed include HIV status, age, race/ethnicity, smoking status, drug dependence-related diagnosis, and hepatitis C. HIV status is based on a previously validated group of International Classification of Diseases, Ninth Revision (ICD-9) codes. Like AUDIT-C for alcohol, smoking status (current/past/never) is an automated EMR-based clinical reminder; drug dependence-related diagnoses are based on ICD-9 codes, and hepatitis C is based on a combination of ICD-9 codes and laboratory data. Age was measured at the time of AUDIT-C and used as a continuous variable for descriptive statistics and categorized as <50, 50–64 and 65 years and over for regression models.

2.5. Analysis

We compared characteristics of participants by HIV status using chi-square tests, *t*-tests and Wilcoxon rank-sum tests. We compared number of participants identified with unhealthy alcohol use based on AUDIT-C 4+ vs. a combination of HED and 30+ drinks per month. Mortality rates were summarized and compared graphically by HIV status and alcohol use levels (AUDIT-C scores, estimated quantity-frequency, and HED) and using Cox proportional hazard (PH) models. Multivariate Cox PH models for time to death were adjusted for age, race/ethnicity, smoking status, and hepatitis C infection. Interactions between HIV and alcohol use levels were tested. Drug dependence-related diagnoses were not associated with the outcomes in the multivariate models, nor did their exclusion change the association of interest, so they were not included in the final models. VACS Index Scores were summarized graphically by HIV status and alcohol exposure (AUDIT-C scores, estimated quantity-frequency, and HED). Ordinary least squares linear regression models were used to quantify the association between alcohol exposure and VACS Index Scores. Multivariate models were adjusted for age, race/ethnicity, smoking status, and hepatitis C. Since sensitivity to alcohol varies with age, and recommended drinking limits are lower for those older than 65 years of age, we repeated all analyses excluding those over age 65.

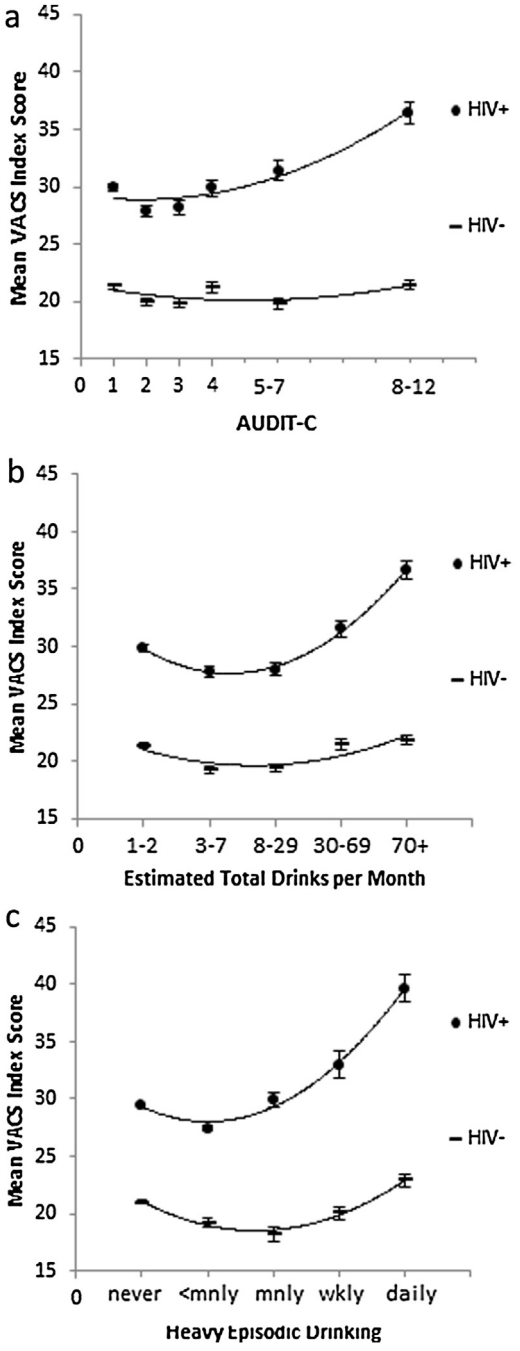

Fig. 2. (a–c) Mean VACS Index by AUDIT-C level and HIV status.

3. Results

3.1. Demographics and characteristics

There were 18,145 HIV+ and 42,228 uninfected individuals with an AUDIT-C score greater than zero. Mean age was 52.5 years for HIV+ and 54.0 years for uninfected individuals. The distribution of race/ethnicity and AUDIT-C scores was generally similar by HIV status. Hepatitis C was more prevalent among HIV+ (31%) than uninfected individuals (16%, $p < .001$). Among HIV+ and uninfected individuals, 16% and 13% had a drug dependence-related diagnosis code ($p < .001$), respectively. Most HIV+ individuals (76%) had achieved HIV-1 RNA suppression demonstrating effective ART. Mean VACS Index was 30 for HIV+ and 21 for uninfected individuals

Table 3
Adjusted *mortality* by level of alcohol exposure among HIV infected and uninfected men.

Variable	HIV infected (n = 18,145)		Uninfected (n = 42,228)	
	HR	95% CI	HR	95% CI
Number of alcoholic drinks per month (reference is 1–2)				
3–7	1.03	0.91–1.16	0.86	0.78–0.95
8–29	0.96	0.83–1.10	0.92	0.83–1.02
30–69	1.30	1.14–1.50	0.96	0.86–1.07
70+	1.50	1.28–1.76	1.13	1.00–1.28
HED weekly or more	1.12	1.00–1.25	1.17	1.07–1.27
Age (reference is <50 years)				
50–64 years	2.39	2.12–2.69	2.93	2.62–3.28
65+ years	5.86	5.06–6.79	7.27	6.39–8.26
Race/ethnicity (reference is white)				
African–American	0.94	0.85–1.03	0.83	0.77–0.89
Hispanic	0.78	0.65–0.94	0.73	0.63–0.84
Other	0.88	0.70–1.12	0.71	0.58–0.87
Smoking (reference is never smoked)				
Current	1.86	1.64–2.10	2.21	1.99–2.45
Past	1.22	1.04–1.44	1.39	1.23–1.58
Unknown/missing	1.82	1.32–2.51	1.54	1.17–2.04
Hepatitis C infection	1.91	1.74–2.09	1.89	1.75–2.05

Table 4
Adjusted *VACS Index*, by AUDIT-C level among HIV infected and uninfected men.

Variable	HIV infected (n = 9216)		Uninfected (n = 12,833)	
	Beta coefficient	95% CI	Beta coefficient	95% CI
AUDIT-C (ref 1)				
4	0.10	−0.14 to 0.35	0.08	−0.06 to 0.22
5–7	0.47	0.22–0.73	0.04	−0.09 to 0.17
8–12	1.05	0.77–1.34	0.29	0.16–0.42
Age (ref <50 years)				
50–64 years	3.29	3.14–3.44	3.26	3.17–3.36
65+ years	7.26	7.00–7.52	7.63	7.48–7.78
Race/ethnicity (ref white)				
African–American	1.28	1.13–1.43	0.67	0.58–0.75
Hispanic	0.18	−0.09 to 0.45	−0.03	−0.17 to 0.11
Other	0.40	0.03–0.76	0.01	−0.23 to 0.24
Smoking (ref never)				
Current	0.14	−0.03 to 0.30	−0.16	−0.25 to (−0.06)
Past	−0.04	−0.28 to 0.19	0.16	0.03–0.29
Unknown/missing	−0.40	−0.99 to 0.20	−0.31	−0.66 to 0.03
Hepatitis C	2.20	2.05–2.36	1.98	1.88–2.08
Constant	1.92	1.75–2.10	0.58	0.47–0.70

(p < .001) (Table 1). Among HIV+ individuals, considering HED and drinks per month as separate criteria results in identifying 30% with unhealthy alcohol use compared to 24% using the overall AUDIT-C threshold of 4 or higher.

3.2. Mortality

Median follow-up was 4.8 years (interquartile range (IQR) 3.6 to 5.3). Mortality per 100 person-years was 2.7 among HIV+ and 1.8 among uninfected individuals (p < .001, Table 1). Mortality rates increased with increasing AUDIT-C scores for both HIV+ and uninfected individuals (Fig. 1a). However, the difference in mortality rates between HIV+ and uninfected individuals widened with higher AUDIT-C scores (interaction term from Cox PH model: p = .02). Similar patterns and significant interactions were found using number of drinks per month (Fig. 1b) or HED (Fig. 1c) as the measure of alcohol exposure.

In multivariable models, based on hazard ratios (HRs), the association between AUDIT-C scores of one, two, and three with the outcomes were similar, so the categories were combined so that the AUDIT-C referent group contains individuals with an AUDIT-C of 1–3. Among HIV+ individuals, adjusted HRs for mortality were significantly higher for those with AUDIT-C of 4, 5–7, and 8–12 compared to those with AUDIT-C of 1–3. Among uninfected individuals, HRs were significantly higher for those with AUDIT-C scores of 5–12 (Table 2). In a combined model HIV infection was associated with mortality (HR 1.35: 95% CI 1.26–1.45) and the interaction term for HIV and AUDIT-C was significant (p = .02). Age, smoking, and hepatitis C infection were also significant predictors of mortality in all three models.

Number of drinks per month and HED in the past 12 months were also important predictors of mortality. Among HIV+ individuals, HRs for mortality were significantly higher for those drinking an estimated 30 or more drinks per month compared to those drinking 1–2 drinks per month (Table 3). Among uninfected individuals, HRs were significantly higher for those drinking an estimated 70 or more drinks per month compared to those drinking 1–2 drinks per month. Notably, a "J-shaped" relationship between drinks per month and risk of mortality was only observed for the uninfected, whereby 3–7 drinks per month (compared to 1–2 drinks per month)

Table 5
Adjusted *VACS Index*, by level of alcohol exposure among HIV infected and uninfected men.

Variable	HIV infected (n = 9216)		Uninfected (n = 12,833)	
	Beta coefficient	95% CI	Beta coefficient	95% CI
#Drinks/men (ref 1–2)				
3–7	−0.14	−0.32 to 0.05	−0.23	−0.33 to (−0.12)
8–29	−0.03	−0.24 to 0.17	−0.16	−0.27 to (−0.04)
30–69	0.22	−0.03 to 0.47	−0.05	−0.19 to 0.08
70+	0.99	0.68–1.29	0.19	0.04–0.34
HED weekly or more	0.05	−0.14 to 0.24	0.08	−0.02 to 0.18
Age (ref <50 years)				
50–64 years	3.27	3.12–3.43	3.26	3.17–3.35
65+ years	7.23	6.97–7.49	7.62	7.47–7.77
Race/ethnicity (ref white)				
African–American	1.28	1.13–1.43	0.68	0.59–0.76
Hispanic	0.20	−0.07 to 0.47	−.03	−0.17 to 0.12
Other	0.40	0.03–0.77	0.02	−0.22 to 0.26
Smoking (ref never)				
Current	0.15	−0.02 to 0.31	−0.15	−0.25 to (−0.05)
Past	−0.04	−0.28 to 0.19	0.16	0.03–0.29
Unknown/missing	−0.38	−0.98 to 0.21	−0.30	−0.65 to 0.04
Hepatitis C	2.21	2.06–2.36	1.98	1.88–2.08
Constant	1.97	1.78–2.15	0.65	0.53–0.77

was found to be protective (HR 0.86: 95% CI 0.78–0.95). In combined models, HIV infection was associated with higher risk of mortality (HR 1.28: 95% CI 1.18, 1.40). Both drinks per month and HED in the past 12 months were independently associated with mortality and the interaction term for HIV and drinks per month was significant ($p < .001$). Age, smoking, and hepatitis C infection were also significant predictors of mortality in all three models.

3.3. Physiologic injury

Among HIV+ individuals, physiologic injury, as measured by VACS Index, increased with increasing AUDIT-C scores (Fig. 2a). Similarly, injury increased with increasing number of drinks per month and increasing frequency of HED (Fig. 2b and c). Additionally, the difference in physiologic injury between HIV+ and uninfected individuals was greater as all three measures of alcohol use increased (Fig. 2a–c). In linear regression models adjusting for the same factors as models predicting all-cause mortality, the levels of alcohol use associated with injury were lower among HIV+ than among uninfected individuals (Tables 4 and 5). AUDIT-C scores of 5–7 and 8–12 were significantly associated with physiologic injury among HIV+ individuals compared to those with AUDIT-C 1–3 (beta 0.47: 95% CI 0.22, 0.73; and beta 1.05: 95% CI 0.77, 1.34, respectively). In contrast, only a score of 8–12 was associated with injury among uninfected individuals (beta 0.29: 95% CI 0.16, 0.42) (Table 4). Interestingly, after adjusting for HED (which was not independently associated with VACS Index), drinking between 3 and 29 drinks a month was protective against injury among uninfected individuals (beta −0.23: 95% CI −0.33 to (−0.12) and beta −0.16: 95% CI −0.27 to (−0.04), respectively) whereas no level of use was protective among HIV+ individuals. Drinking 70 or more drinks per month was associated with injury among HIV+ individuals (beta 0.99: 95% CI 0.68–1.29) and HIV uninfected individuals (beta 0.19: 95% CI 0.04–0.34). The J-shaped associated between alcohol and physiologic injury was only observed for the uninfected group.

4. Discussion

Compared with uninfected individuals, mortality and physiologic injury associated with discrete levels of alcohol exposure were higher among HIV+ individuals. While we found evidence of a J-shaped association between alcohol use, mortality, and physiologic injury among uninfected subjects, there was little evidence suggesting a protective effect of alcohol at any level of use among HIV+ individuals. Further, lower levels of alcohol exposure were associated with more harm among HIV+ individuals. Thresholds for risk were also lower among HIV+ individuals when physiologic injury was estimated using the VACS Index. Based on our findings, HIV+ individuals consuming more than 30 drinks per month are at increased risk of all-cause mortality and physiologic frailty. This would translate to a recommended drinking limit for HIV+ individuals of no more than 1 drink containing alcohol per day. This is lower than the current limits by the National Institute on Alcohol Abuse and Alcoholism recommended for men, which is no more than 14 drinks per week (equivalent to 2 drinks per day), and similar to the recommendations for women and those over 65 years pf age (NIAAA, 2005). This is the first study to demonstrate an association between low levels of alcohol use and mortality or physiologic injury among HIV+ individuals in the modern antiretroviral treatment era.

This is the most comprehensive study of the question of unhealthy alcohol consumption among HIV+ individuals to date. The VHA benefits from one of the largest and most comprehensive electronic health information systems in the world with some of the longest follow up (Corrigan et al., 2003; McQueen et al., 2004). Our group has developed and validated a national multisite cohort of HIV+ individuals engaged in HIV treatment with demographically matched uninfected comparators. Drawing from the VHA EMR, we have clinical data supporting careful adjustment for important confounders including tobacco exposure and hepatitis C infection. We were able to use national AUDIT-C data collected in the course of routine clinical care to assess varying levels and patterns of alcohol exposure.

There are several, likely overlapping, reasons why HIV+ individuals might be more susceptible to physiologic harm from alcohol. First, they may experience higher blood alcohol levels given a unit exposure. This has been demonstrated among those with untreated HIV infection (McCance-Katz et al., 2013, 2012). Recent analyses in VACS have demonstrated that HIV+ individuals with unsuppressed HIV-1 RNA report the lowest number of drinks required to feel intoxicated, HIV+ individuals with suppressed HIV-1 RNA

report a higher number to experience intoxication and uninfected individuals report an even higher number of drinks to experience intoxication (McGinnis et al., 2015). Further, even modest alcohol use is associated with poorer adherence to antiretroviral therapy (Braithwaite and Bryant, 2010; Braithwaite et al., 2008, 2010) which can in turn increase susceptibility to harm. Collectively, these data suggest that HIV+ individuals are more susceptible to physiologic harm from alcohol. Our results support this hypothesis.

The VACS Index, an integrated measure of physiologic injury, has been widely recognized as a means of estimating physiologic injury and risk of frailty related outcomes among HIV+ individuals in care (Akgun et al., 2014; Escota et al., 2014; Womack et al., 2013). The VACS Index includes many biomarkers known to be directly or indirectly influenced by alcohol exposure. CD4 count and HIV VL are altered by non-adherence to antiretroviral therapy which is strongly associated with alcohol use (Braithwaite and Bryant, 2010; Braithwaite et al., 2008). Hemoglobin, platelets, aspartate transaminase and alanine transaminase are altered by direct toxicity of alcohol and by non-adherence to antiretroviral treatment (Anderson et al., 2014; Conigliaro et al., 2003; Lo et al., 2014; Schmitt et al., 1999; Sullivan et al., 2008). Given this dual effect of alcohol among HIV+ individuals, we might expect the VACS Index to be sensitive to adverse health effects from increasing alcohol exposure in this population and that is what we observed. Importantly, 76% of HIV+ individuals had achieved HIV virus suppression, suggesting that this susceptibility to alcohol does not disappear once suppressed. HIV+ individuals, even those on ART, are more susceptible to physiologic harm from alcohol.

An AUDIT-C score of 4 or more is often considered consistent with unhealthy alcohol use (Gordon et al., 2001) and 24% of HIV+ individuals in our study had scores at or above this threshold. However we found that HED and drinks per month were also independently associated with mortality suggesting that these criteria should be considered individually. When these were considered as separate criteria, 30%, or an additional 6%, of HIV+ individuals in VACS were identified with unhealthy alcohol use.

4.1. Limitations

Accurate measurement of exposure to alcohol is challenging. While self-report has limitations, it remains the standard in clinical settings. We used the AUDIT-C from the VHA EMR. At most sites AUDIT-C is asked face to face by a healthcare provider or health technician who records the patient's response, an approach that may be subject to social desirability bias. There may also be quality issues related to how screening is conducted in routine clinical settings (non-verbatim screening, assumptions/inferences being made about patient responses, and inputting responses not reported; Williams et al., 2015). When compared with responses on a confidential survey, clinical AUDIT-C data tends to under report alcohol exposure equally by HIV status (Bradley et al., 2011). In addition, we did not separate out patients with alcohol use disorder in the current analysis. Because detection of alcohol use disorder in routine clinical settings is poor we were not confident that separating out those assigned a diagnosis of alcohol use disorder based on ICD-9 codes would help (Kim et al., 2012; Quan et al., 2008). While higher AUDIT-C scores have been proposed for this purpose, the AUDIT-C is not intended as a diagnostic tool for alcohol use disorder (Johnson et al., 2013; McGinnis et al., 2013; Rubinsky et al., 2010). These limitations would introduce misclassification which would dampen observed associations suggesting that the differences we were able to observe by HIV status may be under estimated. Finally, these data reflect information available to the clinician in the course of care.

Another important limitation was the need to exclude those who reported no exposure to alcohol in the past 12 months. By excluding non-drinkers, we are not able to determine whether there is a level of alcohol exposure measured by AUDIT-C that is "safe". All our analyses were compared with the lowest score on the AUDIT-C among those reporting current alcohol use (a score of 1). Non-drinkers were excluded because non-drinkers are often people who quit drinking because they experienced adverse outcomes related to alcohol (so called, "sick quitters"; Fillmore et al., 2007; Shaper, 1990; Shaper and Wannamethee, 1998). For instance, in a recent VACS survey, 29% of subjects reported that they stopped drinking because they had problems due to alcohol (data not otherwise shown). Our results may only apply to men and those receiving care in the Veterans Healthcare System.

4.2. Conclusion

In conclusion, among HIV+ individuals on ART, lower thresholds of alcohol use are associated with mortality and physiologic injury than among uninfected individuals. In both groups HED and drinks per month are independently associated with mortality and considering each as separate criteria identifies more individuals with unhealthy alcohol use.

Conflicts of interest

The manuscript has not been previously published and is not being considered for publication elsewhere. The authors have all approved the manuscript and have no conflicts of interest to declare.

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Contributors

- Amy C. Justice—Dr. Justice's roles for this submission were conception and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, statistical analysis, obtaining funding, administrative, technical or material support and supervision.
- KathleenA. McGinnis—Dr. McGinnis' contributions to this submission were conception and design, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content and statistical analysis.
- JanetP. Tate—Dr. Tate's contributions to this submission were conception and design, acquisition of data, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, and supervision.
- R. Scott Braithwaite—Dr. Braithwaite's contributions to this submission were analysis and interpretation of data and critical revision of the manuscript for important intellectual content.
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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.drugalcdep.2016.01.017.

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