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Impact of alcohol use disorder severity on HIV viral suppression and CD4 count in three international cohorts of people with HIV

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Abstract

Background: Alcohol use has been linked to worse HIV immunologic/virologic outcomes, yet few studies have explored the effects of alcohol use *disorder* (AUD). This study assessed whether AUD severity is associated with HIV viral suppression and CD4 count in the three cohorts of the Uganda Russia Boston Alcohol Network for Alcohol Research Collaboration on HIV/AIDS (URBAN ARCH) Consortium.

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Methods: People with HIV (PWH) in Uganda (n=301), Russia (n=400), and Boston (n=251), selected in-part based on alcohol use, were included in analyses. Logistic and linear regressions were used to assess the cross-sectional associations between AUD severity (number of DSM-5 diagnostic criteria) and 1) HIV viral suppression and 2) CD4 count (cells/mm^3) adjusting for covariates. Analyses were conducted separately by site.

Results: The proportion of females was 51% (Uganda), 34% (Russia), and 33% (Boston); mean age (SD) was 40.7 (9.6), 38.6 (6.3), and 52.1 (10.5), respectively. All but 27% in Russia and 5% in Boston were on antiretroviral therapy. In Uganda 32% met criteria for AUD, 92% in Russia and 43% in Boston. The mean (SD) number of AUD criteria was 1.6 (2.4) in Uganda, 5.6 (3.3) in Russia, and 2.4 (3.1) in Boston. Most participants had HIV viral suppression (Uganda 92%, Russia 57%, Boston 87%); median (IQR) CD4 count was 673 (506;866), 351 (201;542), and 591 (387;881), respectively. In adjusted models, there were no associations between AUD severity and HIV viral suppression: AOR (95%CI) per 1 additional AUD criterion in Uganda was 1.08 (0.87;1.33); Russia 0.98 (0.92;1.04); and Boston 0.95 (0.84;1.08) or CD4 count: mean difference (95%CI) per 1 additional criterion: 5.78 (−7.47;19.03), −3.23 (−10.91;4.44), and −8.18 (−24.72;8.35) respectively.

Conclusions: In three cohorts of PWH, AUD severity was not associated with HIV viral suppression or CD4 count. PWH with AUD in the current era of antiretroviral therapy can achieve virologic control.

Keywords

Alcohol use disorder; HIV; CD4; viral suppression

INTRODUCTION

Among people with HIV (PWH), unhealthy alcohol use is common, with a quarter reporting heavy episodic drinking in the US (Williams, Joo et al. 2017). Alcohol use is an important aspect of HIV clinical care and prevention (Boscarino, Avins et al. 1995, Parsons, Rosof et al. 2008, Freeman 2016, Shuper, Joharchi et al. 2017) and has been associated with HIV seroconversion. In addition, the negative effect of alcohol on HIV disease progression is attributed to its impact on indirect processes such as reduced linkage to HIV care, delayed initiation of antiretroviral therapy (ART), worse treatment retention, and lower ART adherence (Lucas, Gebo et al. 2002, Chander, Lau et al. 2006, Williams, Hahn et al. 2016). Studies suggest there is a dose-response relationship between greater alcohol use and ART non-adherence (Braithwaite, McGinnis et al. 2005, Chander, Lau et al. 2006, Hendershot, Stoner et al. 2009, Hahn and Samet 2010, Williams, McGinnis et al. 2018). However, there is conflicting evidence on the degree to which alcohol use affects HIV outcomes via other mechanisms, such as the biological effect of alcohol itself on the immune system and nutritional deficencies (Hahn and Samet 2010, Hahn, Cheng et al. 2018). In a systematic review and meta-analysis, Rehm and colleagues concluded that, except for the link mediated by ART non-adherence, the contribution of other pathways from alcohol to HIV burden of disease could not be quantified given current knowledge (Rehm, Probst et al. 2017).

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Alcohol use disorder (AUD) is a condition characterized by impaired control over drinking and physical and emotional symptoms related to continued use despite negative consequences. Accordingly, diagnostic criteria for AUD focus on the consequences of use, without reference to the volume of alcohol consumption. As a result, the quantity and frequency of alcohol use varies widely among those with AUD. Consequences of use as reflected in diagnostic criteria may have a different association and mechanism of association with HIV outcomes than the quantity of alcohol use per se. Whether alcohol's impact on HIV outcomes is due to its disruptive effect on social and behavioral functioning as reflected by AUD diagnostic criteria -rather than direct effects of the volume of alcohol consumption itself on immunological and viral outcomes - has different implications for improving HIV outcomes among PWH who drink alcohol.

AUD is common worldwide among PWH. In a meta-analysis of 25 studies, the pooled prevalence of alcohol use disorder measured mostly by the AUDIT scale was 30%. The prevalence was even higher when analyses were limited to developed countries (Duko, Ayalew et al. 2019). Among PWH with either past 12-month alcohol and/or other drug dependence, the number of criteria met for the diagnosis, as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM) fourth edition (IV), was associated with detectable HIV viral load (Nolan, Walley et al. 2017) in a multivariable model that included number of DSM-IV alcohol dependence criteria and other measures of alcohol and other drug use. This suggests that social and behavioral effects of a substance use disorder as quantified by number of DSM criteria rather than non-dependent substance use are important.

AUD is a prevalent condition among PWH and one that could impact HIV disease progression with both direct biological effects as well as indirect effects on social, behavioral, and emotional dysregulation on medication adherence and treatment retention. The current study assessed the cross-sectional associations between AUD severity and HIV outcomes, specifically viral suppression and CD4 count, among PWH in three cohorts from different continents. We studied these internationally diverse cohorts because, in addition to quantifying alcohol exposure by the volume of alcohol consumption, the effects of alcohol may depend on and differ by sociocultural context, which may be more accurately quantified by the number of AUD symptoms (or DSM diagnostic criteria). The study hypotheses were that a greater number of AUD criteria would be associated with lower odds of viral suppression and lower CD4 count in three separate study cohorts. The study was conducted in the Uganda Russia Boston Alcohol Network for Alcohol Research Collaboration on HIV/AIDS (URBAN ARCH) Consortium. URBAN ARCH allows for evaluating the association between AUD and HIV outcomes in multiple cohorts from different geographic and socio-economic backgrounds.

MATERIALS AND METHODS

Study design

This cross-sectional study used baseline data from 3 cohorts from URBAN ARCH. PWH from Uganda (n=301), Russia (n=400) and Boston (n=251) were included. Uganda ARCH

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was conducted in Mbarara, Uganda, Russia ARCH in St. Petersburg, Russia and Boston ARCH in Boston, USA.

Participants, overview

The study population consisted of PWH with various levels of alcohol and other substance use, including abstinence. All participants provided informed consent. Assessments were conducted in-person by trained research personnel.

Uganda ARCH cohort: The Uganda participants were enrolled in the ADEPTT study (Alcohol Drinker's Exposure to Preventive Therapy for Tuberculosis, NCT 03302299), whose aim was to compare the safety and tolerability of tuberculosis preventive therapy in PWH with recent alcohol use (any use in past 3 months, n=201) compared to those with no alcohol use in the past year (n=100). Inclusion criteria included: age ≥ 18 years, fluency in English or Runyakole, HIV-infection on a non-nevirapine containing antiretroviral therapy (ART) regimen for at least six months, liver function tests (alanine aminotransferase and aspartate aminotransferase) <2 times the upper limit of normal, and living within 2 hours travel time from the Immune Suppression Syndrome (ISS) clinic of the Mbarara Regional Referral Hospital with no plans to move. Data for the present study were baseline visits, collected from May 2017 to January 2020.

Russia ARCH cohort: The Russia participants were enrolled in the St. PETER HIV study (Studying Partial agonists for Ethanol and Tobacco Elimination in Russians with HIV study) whose aim was to test the efficacy of varenicline, cytisine and nicotine replacement therapy for heavy alcohol use and tobacco use (Tindle, Freiberg et al. 2020). Inclusion criteria included: age 18–70 years old, HIV-infected, fluency in Russian, reporting daily tobacco use, >5 heavy drinking days over the past 30 days, provision of contact information for two contacts to assist with follow-up, stable address within St. Petersburg or districts within 100 kilometers of St. Petersburg, and possession of a home or mobile phone. Data for the present study were collected from July 2017 to December 2019.

Boston ARCH cohort: The Boston participants were enrolled in a study on alcohol use and falls. Inclusion criteria included: age ≥ 18 years, HIV-infection, and at least one of the following: any illicit drug use in the past 12 months, unhealthy alcohol use (AUDIT-C score (>3 for women, >4 for men) or enrollment in a previous Boston ARCH study (Kim, Walley et al. 2018). Other criteria were fluency in English, willingness to provide contact information for at least one person, and no plans to move from the area within the next year. Participants were recruited in-person from a hospital-based HIV primary care clinic. Data for the present study were collected from February 2018 to March 2020.

Outcomes

The study outcomes were HIV viral suppression and CD4 cell count. The definition of HIV viral suppression was cohort-specific based on local laboratory standards and was defined as < 40 copies/ml in the Uganda cohort, < 300 copies/ml in the Russia cohort and < 200 copies/ml in the Boston cohort. As these thresholds were used in the different cohorts, we kept the definition of HIV virologic control as defined in each cohort. CD4 cell count was

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examined as a continuous variable (in cells/mm^3). CD4 count and HIV viral load were collected by electronic health record review in the Boston ARCH cohort and phlebotomy in the Russia ARCH and Uganda ARCH cohorts.

Main independent variable

The main independent variable was the number of alcohol use disorder criteria (AUD) according to the DSM-5 (range 0–11) (American Psychiatric Association 2013) based on survey items measuring the DSM criteria. The number of AUD criteria was used as a proxy for AUD severity. AUD data was collected the same way in each cohort. Each DSM-5 AUD criteria was assessed in standardized structured interviews with a set of 11 questions based upon the MINI and AUDADIS questionnaires (Grant, Harford et al. 1995, Sheehan, Lecrubier et al. 1998, Sheehan, Janavs et al. 2010, American Psychiatric Association 2013) resulting in a score between 0 and 11. There were minor wording differences due to the different cultural backgrounds and languages.

Covariates

Covariates were selected based on the literature. Factors considered as potential confounders included sex, age, marital status (dichotomous, defined in Uganda as having a spouse, in Russia and Boston as being married or living with a partner), basic education level (defined in Uganda and Russia > 9 grades vs less and Boston as high school graduate or more vs less), employment status (currently employed or not), current (past 30 day use) of illicit opioids, cannabis, stimulants (amphetamines and/or cocaine), and tobacco.

The opioid, cannabis, and stimulant use covariates were included in the analyses of the Russia and Boston cohorts only (because it was rare in the Uganda cohort--0% opioid and stimulant use, 0.7% cannabis use). The tobacco use covariate was included for Uganda and Boston cohorts only (because tobacco use was 100% in the Russia cohort, as it was part of study inclusion criteria).

The Uganda, Russia and Boston ARCH cohorts all have individual level data. Nevertheless, covariates differed by cohort and could not be pooled into a single analysis without risking substantial bias, and because the relevant covariates differed by cohort as one might expect with cohorts from different parts of the world.

Logistic and linear regression models were used to assess the associations between each additional AUD criteria and HIV viral suppression and CD4 count, respectively. To attempt to separate out the effect of AUD severity from volume of drinking, additional models were conducted adjusting for volume of alcohol use (total grams of alcohol in the past 30 days calculated with a 14-day Timeline Followback for the Boston cohort and a 30-day Timeline Followback for the Uganda and Russia cohorts). These models were used as a sensitivity analysis but not as the primary analysis because we expected the volume of alcohol use to be strongly correlated with AUD severity. We used the same analytic strategy to test the association of AUD severity and viral suppression and CD4 count only among those with an AUD (i.e. at least 2 AUD DSM 5 criteria) rather than the entire sample.

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Russia ARCH was approved by the institutional review board (IRB) of Boston University Medical Campus, First St. Petersburg Pavlov State Medical University, and Vanderbilt University Medical Center. Uganda ARCH was approved by the IRB of Boston University Medical Campus, University of California, San Francisco, Mbarara University of Science and Technology, and the Uganda National Council of Science and Technology. Boston ARCH was approved by the IRB of Boston University Medical Campus.

RESULTS

The proportion of females was 51% (Uganda), 34% (Russia) and 33% (Boston); the mean age (SD) was 40.7 (9.6), 38.6 (6.3) and 52.1 (10.5) respectively. All but 27.3% in Russia and 5.2% in Boston were on ART (in the Uganda cohort being on ART was an inclusion criterion). The mean (Standard Deviation [SD]) number of AUD criteria was 1.6 (2.4) in Uganda, 5.6 (3.3) in Russia and 2.4 (3.1) in Boston. Viral suppression was achieved in 92% of the sample in Uganda, 57% in Russia and 87% in Boston; median (IQR) CD4 count was 673 (506, 866), 351 (201, 542) and 591 (387, 881) respectively. The sample characteristics, by cohort, are presented in Table 1. The prevalence of HIV virologic suppression and CD4 count differed across cohorts with the Russia cohort having the lowest prevalence of HIV viral suppression at 57% and the lowest mean CD4 cell count.

Associations between AUD severity and HIV outcomes:

In unadjusted models, there were no significant associations between the number of AUD criteria and either HIV viral suppression or CD4 count in the three cohorts. Similarly, in adjusted models, there was no significant cross-sectional association between the number of AUD criteria and HIV viral suppression: AOR (95%CI) per 1 additional AUD criterion in Uganda 1.08 (0.87, 1.33); Russia 0.98 (0.92, 1.04); and Boston 0.95 (0.84, 1.08) or CD4 count: beta (mean difference) (95%CI) per 1 additional criterion: 5.78 (−7.47, 19.03), −3.23 (−10.91, 4.44) and −8.18 (−24.72, 8.35), respectively. Detailed results of the regression models are presented in Table 2 and Table 3. Correlations between volume of alcohol use (grams of ethanol) and number of AUD criteria were 0.70 in Uganda, 0.45 in Russia, and 0.60 in Boston; despite these high correlations, adjusting for the volume of alcohol used did not change the results (Table 4). In the analyses restricted to those with an AUD, results were similar (Table 5).

DISCUSSION

Using data from three cohorts from different continents allowed us to examine of the relationship between AUD severity, as reflected by number of diagnostic criteria, and HIV outcomes in populations with vastly different socio-economic and cultural backgrounds and health care systems. The results were consistent in three cohorts of PWH, from Uganda, Russia and the US, and contrary to our hypothesis, we did not detect any associations between AUD severity and HIV viral suppression or CD4 counts. Our results indicate that PWH and AUD can achieve virologic control and suggest that AUD severity – as measured by DSM criteria – is not associated with HIV viral suppression and CD4 count. AUD did not appear to impact these two outcomes significantly in our cohorts of PWH most of whom were receiving ART. The observed measures of effect are close to 1 for the ORs of virologic

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suppression and the slopes for CD4 count are close to zero in all cohorts. Taking the volume of alcohol use into account did not change the results. Restricting analyses to those with an AUD did not either. This consistent absence of association across cohorts and different analyses reinforces these results.

By examining cohorts separately, we attempted to minimize the variability in access to ART one might expect in different countries, the effect of which could overwhelm any impact of AUD on viral suppression. While we did not see an association in cohorts with a spectrum of access to ART, most cohort participants were receiving ART. Accordingly, characteristics of the three samples may have played a role in these findings. Given that being on ART for 6 months or longer was a study entry criterion for the Uganda cohort, it is possible that the effects of AUD on viral suppression would be evident in other populations in Uganda with greater variability in ARV receipt because of alcohol's effect on disrupting care engagement, care-seeking, and ART prescribing. Participants enrolled in Uganda ARCH had managed to overcome those obstacles -at least enough to meet study criteria for Uganda ARCH eligiblity. It is notable, therefore, that the study results were consistent in the Russia cohort who had a broader range of ART use, from no ART prescription to full (self-reported) adherence.

The results differ from what has been hypothesized on the potential impact of alcohol use disorder and alcohol use on HIV disease progression. The literature has reported on the detrimental impact of alcohol use on HIV disease progression through biological and behavioral mechanisms (Hahn and Samet 2010). Earlier studies have shown associations between alcohol use (and any AUD) and lower engagement in HIV care and notably with ART adherence (Samet, Freedberg et al. 2003, Tucker, Burnam et al. 2003, Giordano, Visnegarwala et al. 2005, Mellins, Havens et al. 2009, Monroe, Lau et al. 2016). This is consistent with an effect of alcohol use on HIV viral suppression mediated by ART adherence (Deiss, Mesner et al. 2016, Rehm, Probst et al. 2017, Amirkhanian, Kelly et al. 2018). The assessment of this study's three cohorts revealed similarities among participants: most received ART and of those on ART, 78% or more were >=90% ART adherent. The latter may have precluded identification of an impact on HIV viral suppression. In addition, as recent research suggests, ART adherence level of 75–80% may allow achievement of viral suppression (Byrd, Hou et al. 2019).

Our approach was aimed at investigating the potential impact of AUD and not quantity of alcohol consumption. This is important because AUD is a widely used diagnosis in clinical care. While AUD and alcohol use are correlated, our approach aimed at taking into account the behavioral aspects of AUD (e.g., loss of control over drinking, giving up activities, interference with self-care, risk behavior taking), which are potentially linked to decreased adherence to treatment, ART discontinuation, and HIV care drop-out (Azar, Springer et al. 2010). Thus, our results are not directly comparable to studies assessing the impact of alcohol volume on HIV outcomes.

Research findings have been mixed when investigating the associations between alcohol use and HIV outcomes. Our results are in line with a parent cohort study of ART naïve participants in which unhealthy alcohol use was not associated with CD4 count (Hahn,

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Cheng et al. 2018). In a cross-sectional study of PWH from southern Brazil, there was an association between a proxy measure of AUD (AUDIT score) and CD4 count but not HIV viral load (da Silva, Mendoza-Sassi et al. 2017). Our results differ notably from a recent study by Williams et al showing, in a sample of PWH receiving VA healthcare, that higher levels of alcohol use were associated with a reduced likelihood of virologic control (Williams, McGinnis et al. 2019). The higher prevalence of viral suppression in the current study may have limited the ability to detect associations. While it has been hypothesized that the influence of alcohol use on HIV outcomes happens through reduced ART adherence, newer regimens are "more forgiving" such that adherence rates needed for viral suppression are lower compared to the regimens in earlier studies (Gordon, Gharibian et al. 2015, Byrd, Hou et al. 2019). Also, while we included cohorts from three different continents, the current study did not include participants from some regions where such associations have been previously shown (e.g., India and Vietnam) (Wagman, Wynn et al. 2020). Nonetheless, we did include Russia where the impact of alcohol on HIV outcomes has been described (Wagman, Wynn et al. 2020)

Although we found AUD severity was not associated with HIV viral suppression and CD4 count, the impact of AUD and alcohol use may still be significant among people who did not meet inclusion criteria for these cohorts and the most vulnerable fringe of the population that may not have been included in the studies. In addition, there are other ways in which alcohol use is detrimental with regard to HIV. Notably, alcohol use has been associated with poorer HIV care engagement and retention (Samet, Freedberg et al. 1998, Samet, Freedberg et al. 2001, Samet, Freedberg et al. 2003, Monroe, Lau et al. 2016). The current study did not allow the assessment of the impact of AUD on care initiation and timely diagnosis.

This study has limitations. While data from three different cohorts allowed for the study of populations from different backgrounds, the use of different definitions, notably for HIV viral suppression, was a limitation with comparing different cohorts. Models did not include the same covariates for each cohort due to important differences in the prevalence of illicit drug use. This study is cross-sectional in nature and thus did not allow for an examination of the effect of AUD severity on ART discontuation and HIV care drop-out over time. In addition, causality could not be assessed due to the study's cross sectional and observational design. While we did not detect an association with each additional DSM-5 criterion, our analyses assumed that each criterion would be additive and with the same value. It may well be that certain criteria such as tolerance, for example, would have little impact on adherence, while criteria that reflect life disorganization (failure to fulfill roles) would be more impactful. It would require a larger sample and variability of meeting criteria to study this question.

The current study has notable strengths. AUD was assessed systematically for research purposes – data that would be less reliably available in clinical samples. We did not use a proxy measure of AUD (like AUDIT-C) which would be less relevant to our study hypothesis. Instead we looked at clinical symptoms of an AUD (alcohol problems/disorder) extending the current literature. In addition, we were able to use unique data with similar research instruments used in 3 international cohorts.

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Given the high prevalence of alcohol use and AUD among PWH, further research could facilitate better understanding of how alcohol use and AUD impact clinical populations of PWH. Independent of its impact on HIV outcomes, AUD is a treatable disease that should be addressed and appropriately treated to prevent numerous complications. Our results do not indicate that AUD is not harmful for PWH.

Conclusions:

In cohorts from three different continents, we assessed the association between AUD severity and HIV outcomes (i.e., viral suppression and CD4 count). Our results suggest that quantifying AUD severity by number of DSM-5 criteria is not associated with these outcomes. We observed high rates of viral suppression even among those with AUD.

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Table 1:

Participants characteristics of the Uganda, Russia and Boston HIV+ cohorts

		Uganda (n=301)	Russia (n=400)	Boston (n=251)
Gender	Male, n (%)	147 (48.8%)	263 (65.8%)	169 (67.3%)
	Female, n (%)	154 (51.2%)	137 (34.3%)	82 (32.7%)
Age	Mean (SD)	40.7 (9.6)	38.6 (6.3)	52.1 (10.5)
Married or living with partner	n (%)	202 (67.3%)	197 (49.3%)	129 (51.6%)
Basic education *	n (%)	81 (26.9%)	390 (97.5%)	190 (75.7%)
Employed	Employed, n(%)	289 (96.0%)	260 (65.0%)	62 (24.7%)
Any illicit opioid use, 30 days	n (%)	0 (0.0%)	97 (24.3%)	40 (15.9%)
Any cannabis use, 30 days	n (%)	2 (0.7%)	46 (11.5%)	125 (49.8%)
Any stimulant use, 30 days	n (%)	0 (0.0%)	21 (5.3%)	70 (27.9%)
Any tobacco use, 30 days	n (%)	35 (11.6%)	400 (100.0%)	157 (62.8%)
ART adherence ***	Not on ART, n (%)	--**	109 (27.3%)	13 (5.2%)
	<90% adherence, n (%)	43 (14.3%)	24 (6.0%)	62 (24.8%)
	≥90% adherence, n (%)	258 (85.7%)	(66.8%)	175 (70.0%)
HIV viral Suppression§	n (%)	269 (92.1%)	228 (57.0%)	208 (86.7%)
CD4 count (in cells/mm^3)	Mean (SD)	706.2 (287.2)	391.3 (256.5)	664.0 (375.1)
Alcohol Use Disorder score (# of criteria)	Mean (SD)	1.6 (2.4)	5.6 (3.3)	2.4 (3.1)
Alcohol Use Disorder (2 or more criteria)	n (%)	96 (32.0%)	366 (91.5%)	106 (42.6%)
Total grams of alcohol, 30 days†	Mean (SD)	296.8 (926.7)	1018.8 (829.0)	525.7 (911.6)
Number of heavy drinking days, 30 days†	Mean (SD)	1.4 (4.8)	9.3 (5.8)	3.3 (6.5)

*Boston HS grad or more; Uganda and Russia > 9 grades

**Being on ART was an entry criterion for Uganda

***All cohorts used a visual analog scale for self-reported adherence. Adherence was defined as taking ART on ≥90% of days in the past month.

§Boston <200 copies/ml; Uganda < 40 copies/ml; Russia < 300 copies/ml

†Extrapolated from the 14-day Timeline Followback for the Boston cohort, a 30-day Timeline Followback for the Uganda and Russia cohorts

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Table 2:

HIV viral suppression - Unadjusted and adjusted logistic regressions, associations with the number of AUD criteria *

Unadjusted models						
	Uganda, n=291		**Russia, n=400**		**Boston, n=238**	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
AUD criteria (per 1 additional criterion)	1.03 (0.86, 1.24)	0.76	0.97 (0.91, 1.03)	0.26	0.90 (0.81, 1.01)	0.07
Adjusted models						
	Uganda, n=291		**Russia, n=400**		**Boston, n=238**	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
AUD criteria (per 1 additional criterion)	1.08 (0.87, 1.33)	0.50	0.98 (0.92, 1.04)	0.46	0.95 (0.84, 1.08)	0.44
Sex (ref=Male)	2.36 (0.85, 6.55)	0.10	1.19 (0.76, 1.84)	0.45	0.74 (0.30, 1.82)	0.51
Age (continuous)	1.02 (0.97, 1.08)	0.35	1.03 (1.00, 1.07)	0.05	1.03 (0.99, 1.08)	0.16
Marital Status (ref=No)	0.51 (0.16, 1.62)	0.25	1.14 (0.76, 1.72)	0.53	0.83 (0.37, 1.88)	0.66
Education (ref=Less than basic)	3.02 (0.85, 10.67)	0.09	0.26 (0.05, 1.31)	0.10	0.56 (0.18, 1.72)	0.31
Employment (ref=Unemployed)	1.75 (0.20, 15.51)	0.61	1.32 (0.85, 2.04)	0.22	0.70 (0.24, 2.04)	0.51
Current illicit opioid use (ref=No)	--	--	0.77 (0.48, 1.25)	0.29	0.29 (0.11, 0.77)	0.01
Current cannabis use (ref=No)	--	--	1.08 (0.56, 2.10)	0.81	1.75 (0.71, 4.30)	0.22
Current stimulant use (ref=No)	--	--	0.75 (0.28, 1.99)	0.56	0.59 (0.23, 1.48)	0.26
Current tobacco use (ref=No)	1.16 (0.30, 4.51)	0.83	--	--	0.53 (0.19, 1.47)	0.22

* Uganda < 40 copies/ml; Russia < 300 copies/ml; Boston <200 copies/ml

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Table 3:

Results of unadjusted and adjusted linear regressions examining associations between the number of AUD criteria and CD4 count (mean difference in cells/mm^3)

Unadjusted models						
	Uganda, n=299		**Russia, n=399**		**Boston, n=241**	
	Beta (95% CI)	p-value	Beta (95% CI)	p-value	Beta (95% CI)	p-value
AUD criteria (per 1 addl criterion)	−5.21 (−18.19, 7.77)	0.43	−4.03 (−11.59, 3.52)	0.29	−6.54 (−22.05, 8.98)	0.41
Adjusted models						
	Uganda, n=299		**Russia, n=399**		**Boston, n=241**	
	Beta (95% CI)	p-value	Beta (95% CI)	p-value	Beta (95% CI)	p-value
AUD criteria (per 1 addl criterion)	5.78 (−7.47, 19.03)	0.39	−3.23 (−10.91, 4.44)	0.41	−8.18 (−24.72, 8.35)	0.33
Sex (ref=Male)	192.37 (122.34, 262.39)	<.0001	28.33 (−26.63, 83.30)	0.31	−14.96 (−122.43, 92.51)	0.78
Age	−0.71 (−3.90, 2.48)	0.66	−2.09 (−6.17, 1.99)	0.31	−3.80 (−8.97, 1.38)	0.15
Marital Status (ref=No)	15.03 (−52.42, 82.48)	0.66	42.52 (−8.56, 93.59)	0.10	13.03 (−84.75, 110.82)	0.79
Education (ref=Less than basic)	97.66 (30.20, 165.13)	0.005	−52.98 (−220.01, 114.05)	0.53	−67.03 (−185.68, 51.62)	0.27
Employment (ref=Unemployed)	20.91 (−132.24, 174.07)	0.79	1.01 (−53.96, 55.98)	0.97	18.16 (−107.86, 144.19)	0.78
Current illicit opioid use (ref=No)	--	--	-78.91 (−139.03, −18.18)	0.01	48.36 (−95.68, 192.40)	0.51
Current cannabis use (ref=No)	--	--	56.58 (−25.92, 139.08)	0.18	21.48 (−81.72, 124.68)	0.68
Current stimulant use (ref=No)	--	--	61.29 (−129.79, 111.20)	0.88	−35.22 (−157.32, 86.89)	0.57
Current tobacco use (ref=No)	2.12 (−97.14, 101.37)	0.97	--	--	−2.16 (−111.67, 107.34)	0.97

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Table 4:

Results of logistic and linear regressions with and without adjustment for alcohol volume and other covariates

Associations with HIV viral suppression *						
	Uganda, n=290		**Russia, n=400**		**Boston, n=238**	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Unadjusted, AUD criteria continuous (per 1 addl criterion)	1.03 (0.86, 1.24)	0.76	0.97 (0.91, 1.03)	0.26	0.90 (0.81, 1.01)	0.07
AUD criteria + total grams of alcohol (not incl. covariates)	0.99 (0.81, 1.2)	0.94	0.96 (0.90, 1.03)	0.24	0.95 (0.84, 1.09)	0.47
AUD criteria + total grams of alcohol (incl. covariates **)	1.02 (0.82, 1.27)	0.84	0.97 (0.91, 1.04)	0.34	1.00 (0.87, 1.16)	0.97
Associations with CD4 count ***						
	Uganda, n=298		**Russia, n=399**		**Boston, n=241**	
	Beta (95% CI)	p-value	Beta (95% CI)	p-value	Beta (95% CI)	p-value
Unadjusted, AUD criteria (per 1 addl criterion)	−5.21 (−18.19, 7.77)	0.43	−4.03 (−11.59, 3.52)	0.29	−6.54 (−22.05, 8.98)	0.41
AUD criteria + total grams of alcohol§ (not incl. covariates)	−7.36 (−21.36, 6.65)	0.30	−2.80 (−11.08, 5.49)	0.51	−15.91 (−33.56, 1.73)	0.08
AUD criteria + total grams of alcohol (incl. covariates **)	1.61 (−12.11, 15.33)	0.82	−2.86 (−11.17, 5.45)	0.50	−17.54 (−35.88, 0.81)	0.06

*Uganda < 40 copies/ml; Russia < 300 copies/ml; Boston <200 copies/ml

**Covariates: sex, age, marital status, education level, employment, current opioid use, current cannabis use, current stimulant use, current tobacco use

***Beta = mean differences in CD4 cell count

§Total grams of alcohol was calculated with a14-day Timeline Followback for the Boston cohort, a 30-day Timeline Followback for the Uganda and Russia cohorts

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Table 5:

Analyses restricted to participants with AUD: logistic and linear regressions

Associations with HIV viral suppression *						
	Uganda, n=95		**Russia, n=366**		**Boston, n=103**	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Unadjusted, AUD criteria (continuous)	1.04 (0.75, 1.44)	0.80	0.94 (0.88, 1.00)	0.06	0.91 (0.76, 1.10)	0.34
AUD criteria (adjusted for covariates **)	1.04 (0.77, 1.40)	0.81	0.95 (0.89, 1.02)	0.13	0.97 (0.79, 1.20)	0.80
AUD criteria + total grams of alcohol § (not incl. covariates)	1.02 (0.74, 1.40)	0.92	0.93 (0.87, 1.00)	0.06	0.94 (0.77, 1.14)	0.52
AUD criteria (adjusted for covariates ** + total grams alcohol)	1.03 (0.77, 1.39)	0.84	0.94 (0.87, 1.01)	0.08	1.00 (0.80, 1.26)	0.98
Associations with CD4 count ***						
	Uganda, n=96		**Russia, n=365**		**Boston, n=103**	
	Beta (95% CI)	p-value	Beta (95% CI)	p-value	Beta (95% CI)	p-value
Unadjusted, AUD criteria (continuous)	5.24 (−16.71, 27.20)	0.64	−3.53 (−11.93, 4.86)	0.41	−17.03 (−44.46, 10.40)	0.22
AUD criteria (adjusted for covariates **)	7.52 (−14.76, 29.80)	0.50	−2.72 (−11.17, 5.74)	0.53	−18.30 (−47.82, 11.22)	0.22
AUD criteria + total grams of alcohol§ (not incl. covariates)	2.59 (−19.61, 24.78)	0.82	−2.06 (−11.19, 7.06)	0.66	−21.37 (−48.92, 6.18)	0.13
AUD criteria (adjusted for covariates ** + total grams alcohol)	4.84 (−16.95, 26.62)	0.66	−2.29 (−11.39, 6.81)	0.62	−23.12 (−52.42, 6.18)	0.12

* Uganda < 40; Russia < 300; Boston <200

** Covariates: sex, age, marital status, education level, employment, current opioid use, current marijuana use, current stimulant use, current tobacco use

*** Beta = mean differences in CD4 cell count

§ Total grams of alcohol was extrapolated from the 14-day Timeline Followback for the Boston Cohort, 30-day Timeline Followback for the Uganda and Russia cohorts