Title

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Journal

AIDS and Behavior, 21(Suppl 2)

ISSN

1090-7165

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Publication Date

2017-11-01

DOI

10.1007/s10461-017-1895-2

Peer reviewed

Alcohol types and HIV disease progression among HIV-infected drinkers not yet on antiretroviral therapy in Russia and Uganda

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Word count: Abstract=331; Text=3,976

Running title: Alcohol types and clinical outcomes in HIV-infected drinkers

ABSTRACT

Objectives: In HIV-infected drinkers, alcohol types more likely to cause inflammation could plausibly increase the risk of HIV disease progression. We therefore assessed the association between alcohol type and plasma HIV RNA level (HIV viral load) among HIV-infected drinkers not on antiretroviral therapy (ART) in Russia and Uganda.

Methods: We analyzed the data of participants from cohorts in Russia and Uganda and assessed their HIV viral load at enrollment by the alcohol type predominantly consumed. We defined predominant alcohol type as the alcohol type contributing >50% of total alcohol consumption in the 1 month (Russia) or 3 months (Uganda) prior to enrollment. Using multiple linear regression, we compared $\log_{10}$ HIV viral load by predominant alcohol type, controlling for age, gender, socioeconomic status, total number of standard drinks, frequency of drinking ≥6 drinks/occasion, and in Russia, history of injection drug use.

Results: Most participants (99.2% of 261 in Russia and 98.9% of 352 in Uganda) predominantly drank one alcohol type. In Russia, we did not find evidence for differences in viral load levels between drinkers of fortified wine (n=5) or hard liquor (n=49), compared to drinkers of beer/low-ethanol-content cocktails (n=163); however, wine/high-ethanol-content cocktail drinkers (n=42) had higher mean $\log_{10}$ viral load than beer/low-ethanol-content cocktail drinkers (β=0.38, 95%CI: 0.07 to 0.69; p=0.02). In Uganda, we did not find evidence for differences in viral load levels between drinkers of locally-brewed beer (n=41), commercially-distilled spirits (n=38), or locally-distilled spirits (n=43), compared to drinkers of commercially-made beer (n=218); however, wine drinkers (n=8) had lower mean $\log_{10}$ HIV viral load (β=-0.65, 95% CI -1.36 to 0.07, p = 0.08), although this did not reach statistical significance.

Conclusions: Among HIV-infected drinkers not yet on ART in Russia and Uganda, we observed an association between the alcohol type predominantly consumed and the HIV viral load level in the Russia sample. These exploratory results suggest that, in addition to total number of drinks and drinking patterns,

alcohol type might be a dimension of alcohol use that merits examination in studies of HIV and alcohol related outcomes.

Key words: Alcohol types; HIV-infected patients; HIV-disease progression; Uganda; Russia; HIV viral load

Background

Heavy alcohol consumption can increase risk of HIV transmission and acquisition [1, 2]. In HIV-infected individuals, heavy drinking may also affect disease progression [3] and adherence and response to antiretroviral therapy (ART) [4]. While previous studies assessing the negative effects of alcohol consumption have tended to quantify alcohol use via either the volume of alcohol consumed or the drinking pattern [5, 6], the type of alcohol consumed may also be important. Alcohol types vary widely in ethanol concentration, processing methods, and ingredients [7]. Such differences may explain why certain alcohol types have been reported to be more strongly associated with negative clinical outcomes in general population studies [8] and in studies of HIV-infected patients [9].

Associations between alcohol type and clinical outcomes might be explained by variations in either the total volume of pure ethanol consumed or the drinking patterns by alcohol type. For example, those drinking certain types might consume larger amounts of pure ethanol or be more likely to binge-drink [10, 11]. However, different alcohol types could also exert different biological effects independent of both volume of ethanol consumed and the drinking pattern. For example, fermented alcohols, especially wines, are suggested to have polyphenols that can reduce inflammation [12, 13]. Alcoholic beverages that are made through distillation (i.e., “purification”) processes, such as liquor, might be deficient of such “beneficial” chemicals, and the ethanol in such drinks could in turn be more inflammatory [14]. Alternatively, imperfectly processed “locally-made” drinks may retain excessive levels of harmful non-ethanol chemicals like methanol [15], which could promote inflammation. Such differences in the propensity to cause inflammation may be important in HIV-infected drinkers, since inflammation plays a key role in HIV disease progression [16, 17].

Previous studies have examined the association between heavy alcohol use and HIV disease progression, but findings remain inconclusive. In the systematic review by Azar et al., 2010, HIV-infected patients with AUDs were more likely to experience decreased adherence to ART and poor treatment outcomes [18]. However, in a narrative review by Hahn et al., 2010, studies in the pre-ART era generally found no associations between heavy drinking and either viral load or CD4, while studies in the ART era found some associations between heavy drinking and CD4+ cell count declines and viral suppression [19]. Such associations could be mediated by behavioral factors like adherence to ART or biological factors like immune activation, microbial translocation or overlapping metabolic pathways between alcohol and ART [20].

If alcohol types are differently associated with inflammation, then alcohol type is a possible biologic mediator of observed associations between heavy drinking and HIV disease progression. In one study in the United States involving 165 HIV-infected drinkers on ART, those drinking only liquor (N = 55) were less likely to achieve viral suppression after 6 months of ART than those drinking only beer or wine [9]. The liquor-only drinkers were also less likely to increase their thymic volumes, further suggesting diminished responses to ART [21]. These associations were adjusted for total volume of alcohol consumed, but not drinking patterns. We are not aware of any studies reporting on the association of "locally-made" alcohols with health outcomes; these "locally-made" alcohols are commonly consumed in Uganda [22].

Both Russia and Uganda have high per capita alcohol consumption (15.1 and 9.8 liters of pure ethanol in Russia and in Uganda, respectively, in 2014) [23] . HIV prevalence is high (7.4 % in 2013) in Uganda and increasing (~1%) in Russia [24, 25]. In addition to allowing the exploration of pathways through which heavy drinking might be associated with HIV disease progression, studying the association of alcohol type with health outcomes in these settings could potentially expand the range of available interventions for unhealthy drinking e.g., through beverage substitution interventions or through beverage specific volume reduction messaging.

We thus took advantage of existing cohort studies in Russia and Uganda to describe the alcohol type preferences of HIV-infected drinkers and to assess associations between the alcohol type predominantly consumed prior to enrollment and the HIV viral load at enrollment. Based on the hypothesis that alcohols with higher ethanol content are more likely to promote inflammation and, through this, increase HIV viral load, we evaluated whether compared to drinkers of commercially-brewed beers, drinkers of higher ethanol content drinks had higher viral loads.

METHODS

Study design

We analyzed the baseline data of HIV-infected adults enrolling into 3 cohort studies between 2011 and 2015 in Russia (1 cohort of 360 participants) and Uganda (2 cohorts with a total of 352 participants). These studies were separate studies with differing eligibility criteria, but all recruited HIV-positive participants not yet on ART. For this analysis, we selected participants who reported consuming any alcohol prior to enrollment (past 30 days in Russia, past 3 months in Uganda, per the individual study enrollment criteria). The Ugandan studies used a longer time frame of alcohol consumption prior to enrollment to allow us identify drinkers, since drinking in this setting is often underreported and a longer time period was considered more socially acceptable to mitigate the risk of under-reporting [26]. Participants in both countries completed interviewer-administered structured questionnaires and provided blood samples at the time of the interview, and received HIV care independently of study activities. We restricted our analysis to only the self-reported drinkers since only those would have provided alcohol type information. Given the distinct alcohol types consumed in the two countries, the analysis was stratified by country.

Ethics statement

All participants provided written informed consent to participate in their respective cohort study; those who had a cognitive impairment resulting in inability to provide informed consent were excluded. The Russian study was approved by Institutional Review Boards (IRBs) at Boston University School of Medicine/Boston

Medical Center, and The First St. Petersburg Pavlov State Medical University. The Ugandan studies were approved by IRBs at The University of California San Francisco, Boston Medical Center, and Mbarara University of Science and Technology, and by Uganda's National Council for Science and Technology.

Setting and study population

URBAN ARCH Russia cohort

The Russia sample included participants from the Uganda Russia Boston Alcohol Network for Alcohol Research Collaboration on HIV/AIDS (URBAN ARCH) consortium's Russia cohort, a prospective observational cohort study of HIV-infected individuals from St. Petersburg, Russia, to assess the longitudinal association between alcohol consumption and biomarkers of microbial translocation and inflammation/altered coagulation. Eligibility criteria were: documented HIV infection, 18-70 years of age, not yet on ART, living within 100km of St. Petersburg, providing contacts of at least 2 relatives or close friends who could assist with follow-up, having a telephone and being fluent in Russian. Participants were enrolled irrespective of their CD4+ T cell count levels and alcohol consumption. URBAN ARCH's Russia cohort started enrollment in 2012 and is still ongoing. For this analysis, we included participants enrolled from 2012 to 2015.

The ADEPT and BREATH cohorts (Uganda Cohorts)

The Uganda sample included participants from the URBAN ARCH consortium's Uganda cohort, known as the Alcohol Drinking Effects on Progression prior to Treatment (ADEPT) study, and from the Biomarker Research of Ethanol among Those with HIV (BREATH) study. Both studies were prospective observational cohorts of HIV-infected adults at the Immune Suppression Syndrome (ISS) clinic in Mbarara, Uganda. ADEPT's aim was to determine the effect of alcohol consumption on pre-ART HIV disease progression; BREATH aimed to describe changes in alcohol consumption during the first year of HIV care [22, 27, 28]. Eligibility criteria for both cohorts included: HIV-infected adult (age ≥ 18), enrolled into care at the ISS clinic and not yet on ART, fluent in English or Runyankole (the local language), living within 60km of the

clinic, and for BREATH only, new to the ISS Clinic and HIV care, and reporting past-year alcohol use. ADEPT initially (August 2011-February 2014) recruited only patients with CD4+ T cell count >350 cells/mm^3. After February 2014, Uganda's national guidelines for ART initiation were changed such that patients with CD4+ T cell counts ≤500 became eligible for ART; we thus then recruited only those patients with CD4+ T cell counts >500. By this time, however, all but 68 patients had already been enrolled. Participation in ADEPT ended and participants were exited from the study once the clinic booked them for ART initiation. BREATH enrolled patients irrespective of CD4+ T cell count.

Measurements

Alcohol type

The primary independent variable was the alcohol type predominantly consumed. We defined the predominant alcohol type per participant as the type contributing >50% of the participants' overall absolute alcohol consumption. The total number of standard drinks, and the frequency of drinking 6 or more drinks per occasion, were also measured and used as covariates in the analysis.

In Russia, alcohol consumption survey questions were based on the hypothesized ethanol concentrations of different drinks (the ethanol concentration estimates were based on previous studies [29] and container labels for all commercially-produced alcohols) and included 4 alcohol types as (from lowest to highest alcohol concentration): beer or low-ethanol-content cocktails; wine or high-ethanol-content cocktails; fortified wine; and hard liquor (e.g., vodka). "Cocktails" refers to canned or bottled mixed drinks sold in commercial alcohol stores. They were classified as either "high-ethanol-content cocktails" (~9% ethanol by volume), or "low-ethanol-content cocktails" (~5.5% ethanol by volume). On the study survey, a question was asked about drinking low-ethanol-content cocktails and commercial beer together since these were thought to have similar ethanol concentrations. The two are thus grouped into one alcohol type: "beer or low-ethanol-content cocktails". Similarly, a question was asked about high-ethanol-content cocktails and wine together leading to the "wine or high-ethanol-content cocktails" category.

In Uganda, the classification of alcohol types on the study surveys depended on the methods of production (commercial vs. local/traditional), as well as whether a drink was a beer, a spirit, or a wine. Data on 5 alcohol types were collected (from lowest to highest estimated alcohol concentration): commercially-brewed beer, locally-brewed beer, wine, commercially-distilled spirits, and locally-distilled spirits.

Total alcohol volume consumed

In both countries, measurements of alcohol volumes were beverage-specific, and illustrations of common containers in which different drinks are sold were used to aid recall (Figure 1). In Russia, a beverage-specific timeline follow-back method with 30-day recall was used [30]. With the aid of a calendar, participants were asked to report the volume of each alcohol type that they drank yesterday, the day before yesterday, *etc.*, for the past 30 days [31]. The daily amounts were added to obtain monthly beverage-specific total volumes of alcohol. In Uganda, a beverage-specific quantity frequency method was used. Participants were asked to report volumes consumed for each alcohol type on a "typical drinking day" in the past 3 months and their frequency of drinking in the past 3 months. These two quantities were used to calculate the total (beverage-specific) alcohol volumes consumed in the past 3 months as previously described [22].

Total number of standard alcoholic drinks

To obtain the total number of standard alcoholic drinks consumed by a participant, we first estimated the beverage-specific grams of alcohol by multiplying the volume of each drink type consumed by estimated ethanol content per drink as previously described [29]. The following estimates were used for each drink type: in Russia, beer/low-ethanol-content cocktails (3.92%), wine/high-ethanol-content-cocktails (9.52%), fortified wine (13.44%), and hard liquor (31.50%), respectively; in Uganda, beers (3.95%), wines (9.87%), and spirits (31.57%). Beverage-specific grams of alcohol were then summed into a total for the reference period and divided by 14, the US National Institutes on Alcohol Abuse and Alcoholism (NIAAA) standard number of grams for one alcoholic drink.

Defining a participant's predominant alcohol type

To determine each participant's predominant alcohol type, we assessed fractional contributions to the total number of standard drinks by each alcohol type. The type contributing more than half of the participant's total standard drinks was their predominant type. For example, if a participant reported consuming 8 standard drinks of alcohol from wine in the reference period out of a total consumption (from all drink types) of 10 standard drinks, the fraction of absolute alcohol due to wine was 0.8, and wine was their predominant alcohol type. If no single type accounted for >50% of reported alcohol consumption, the participant was considered as "having no predominant alcohol type".

Drinking patterns

In both countries, we assessed the number of days when a participant drank 6 or more drinks on one occasion as a proxy measure of drinking patterns [32]; we categorized responses into three groups: never, less than monthly or once to thrice a month, and weekly or more often. For this question, we defined a drink for the participant as a 140ml glass of 12%-alcohol wine, a 40ml container of hard liquor, or a 360ml bottle or can of beer, also using illustrations of relevant containers (Figure 1).

Other covariates

We also obtained the participants' age and socioeconomic status (SES). In Russia, we used individual-level monthly income to measure SES. In Uganda we created a household asset index based on household ownership of durable goods, housing quality, and available energy sources as a proxy measure of SES (in this setting, the asset index is suggested to be a better measure of SES) [33]. We also asked about history of injection drug use in both countries (although this was not reported by any participants in the Uganda cohorts). Participants reported the date of first HIV-positive diagnosis; from this, we calculated the years since diagnosis, at enrollment. As underreporting of alcohol use is common in HIV-infected patients in Uganda, we measured levels of the alcohol biomarker phosphatidylethanol (PEth) as previously described [22], and controlled for this variable in a sensitivity analysis. In both countries, we also measured

participants' CD4+ T-cell count levels (APC-H7, BD Biosciences, for the Russia sample, and Beckman Coulter, Brea, California, for the Uganda sample).

Plasma HIV RNA level

The outcome was the plasma HIV RNA level measured on frozen and batched samples by the RIBO-sorb AmpliSens HIV-Monitor-FRT, for the Russia samples (Federal Budget Institute of Science, Central Research Institute for Epidemiology, Moscow), and the Versavt HIV-1 RNA 3.0 Assay, for the Uganda samples (Bayer system 340 bDNA analyzer, Bayer HealthCare Corporation, Whippany, NJ). Log_{10}-transformed values of the HIV viral load were used in the regression analyses.

Analysis

We described the participants' characteristics and assessed the association between predominant alcohol type and the log_{10} viral load stratified by country. In linear regression models comparing the log_{10} HIV viral load by predominant alcohol type, beer/low-ethanol-content cocktails (in Russia) and commercially-made beer (in Uganda) were used as the reference categories. Participants without a predominant alcohol type were excluded from the regression analyses.

In the adjusted analysis, we controlled for covariates which we believed *a priori* to be correlates of both alcohol type preference and HIV disease progression (i.e., potential confounders) based on the literature and clinical knowledge. These included age, gender, SES (income/asset index), total number of standard alcoholic drinks, frequency of drinking ≥6 drinks per occasion, and injection drug use (Russia only). Numeric covariates (age, SES, and number of standard drinks) were all modelled as restricted cubic splines. Since HIV-infected patients in Uganda may underreport volumes of alcohol consumed [34], we repeated the analysis in the Uganda sample further adjusting for PEth concentrations, also modelled as a restricted cubic spline. Since some descriptive differences in years since diagnosis were observed by alcohol type, we performed a second sensitivity analysis post-hoc, adding years since diagnosis to the adjusted model, also

modelled as a restricted cubic spline. Analyses were performed in Stata 13 (College Station, Texas), and, for all analyses, p-values <0.05 were considered statistically significant.

Three participants in Russia and 12 in Uganda were missing income information; one participant in Russia and two in Uganda were missing date of HIV diagnosis; and one participant in Uganda lacked PEth measurements. We substituted the missing values with sample's median for these variables so as to retain these observations in the adjusted analyses [35]. One participant in Russia and 6 in Uganda lacked HIV viral load (outcome) measurements. For these participants, we chose not to impute their viral load values, given that the viral load was the main outcome of interest, and we did not have other appropriate biological data to rely on during the imputations. The 7 participants were thus excluded from the analysis.

RESULTS

Participants' characteristics

Russia

In Russia, a total of 360 participants were enrolled between 2012 and 2015. We excluded 99 individuals (50 who were HIV antibody negative or had undetectable viral loads at enrollment, suggesting either HIV negativity or ART positivity; 49 who did not report any alcohol consumption in the past month). A total of 261 individuals were thus analyzed. Median age was 33 years (interquartile range (IQR) 30 to 37), and 69.4% were male. Median CD4+ T-Cell count was 465 cells/mm^3 (IQR 299 to 683).

Uganda

ADEPT enrolled a total of 484 participants; we excluded 255 from these analyses (37 were ineligible because they were either ART-positive or HIV-antibody negative/indeterminate, and 218 did not report any alcohol consumption in the past 3 months). BREATH enrolled a total of 213 participants; we excluded 90 from these analyses (8 for not meeting study eligibility criteria, 42 for being co-enrolled in ADEPT, and 40 for not reporting any alcohol consumption in the past 3 months). Consequently, the Uganda sample comprises 352 self-reported ART-naïve HIV-infected drinkers assessed between 2011 and 2014 (229 from

ADEPT and 123 from BREATH). Their median age was 31 years (IQR 25 to 38); 45.5% were male (Table 1). Median CD4+ T-Cell count was 486 cells/mm^3 (IQR 332 to 626).

Alcohol type preferences

In both countries, nearly all participants predominantly drank one alcohol type; only 2 participants (0.8%) in Russia and 4 participants (1.1%) in Uganda did not have a predominant alcohol type. In Russia, beer/low-ethanol-content cocktails were the most common type consumed (163/261; 62.5%). In Uganda, most participants predominantly drank commercially-brewed beer (218/352; 61.9%) (Table 1).

Alcohol type and participant characteristics

Distributions of participant characteristics, by predominant alcohol type, are presented in Table 2 among participants reporting a predominant alcohol type. There appeared to be some differences by alcohol type. For example, in Russia, more wine/high-ethanol-content-cocktail drinkers (52.4%) reported injection drug use (versus 42.3% among beer/low ethanol content cocktail drinkers). In Uganda, drinkers of commercially distilled spirits were more likely to be male (76.3% of all commercial spirit drinkers were male versus 37.6% for commercial beer). Drinkers of wine and commercially distilled spirits had slightly higher income (median monthly income ~ 65 USD, IQR, 32 to135, for wine, and median monthly income ~ 55 USD, IQR, 30 to 90, for commercial spirits versus 30 USD, IQR, 18 to 60, for commercial beers. Drinkers of the locally made alcohols were on the lower side of the asset index distribution (median score -1.2, IQR, -2.1 to 0.0, for locally-brewed beers, and median score -1.7, IQR, -2.9 to 0.3, for locally distilled spirits versus median score 0.3, IQR -1.6 to 1.7, for commercial beers). Liquor drinkers had higher PEth levels (median 167 ng/ml, IQR 26 to 730, for commercial spirits, and 181 ng/ml, IQR 59-510, for locally distilled spirits, versus median 56 ng/ml, IQR 10-148, for commercial beer).

Alcohol type and plasma HIV viral load

In the unadjusted analysis in both countries, the HIV viral load varied according to the alcohol type predominantly consumed. Drinkers of wine/high-ethanol-content cocktails and liquor (Russia), and

commercially- and locally-distilled spirits and locally-made beer (Uganda) tended to have higher levels than drinkers of beer/low-ethanol-content cocktails (Russia) or commercially-made beer (Uganda). Drinkers of fortified wine in Russia (n = 5) and wine in Uganda (n = 8) had substantially lower HIV viral load levels (Table 3).

In the adjusted analysis in Russia, those drinking wine/high-ethanol-content cocktails had higher $\log_{10}$ HIV viral load levels than those drinking beer/low-ethanol-content cocktails (β = 0.38, 95% CI 0.07 to 0.69, p = 0.02) (Table 4). There was no significant difference between those drinking beer/low–ethanol-cocktails and those drinking liquor or fortified wine. In the adjusted analysis in Uganda, compared to commercially-brewed beer drinkers, wine drinkers appeared to have lower HIV viral load levels (β = -0.65, 95% CI -1.36 to 0.07, p = 0.08) (Table 4). This result did not reach statistical significance, likely due to the small number of wine drinkers (n=8), but was consistent even after adding PEth concentrations to the model (β = -0.65 95% CI -1.36 to 0.07, p = 0.08). We did not find evidence of differences between those drinking commercially-brewed beer and those drinking spirits or the locally-brewed beers in the adjusted analysis in Uganda.

In a sensitivity analysis adding years since HIV diagnosis to the adjusted models, the results from models with and without years since HIV diagnosis were similar in Russia. In Uganda, there was some attenuation in the observed association among wine drinkers (β = -0.44, 95% CI -1.15 to 0.27, p = 0.22).

DISCUSSION

Alcohol consumers tend to prefer specific alcohol types [36]; their preferred type may expose them to varying health risks [12]. In particular, among HIV-infected individuals, alcohol types that are more likely to promote inflammation [37] could impact HIV disease progression [38]. In this analysis, we assessed the alcohol types used by ART-naïve HIV-infected patients enrolling into three separate cohort studies at HIV treatment clinics in Russia and Uganda. We evaluated the association between the alcohol type predominantly consumed in the one month (Russia) or three months (Uganda) prior to enrollment and the HIV viral load at enrollment. Notably, nearly all participants predominantly drank one alcohol type,

supporting the presumption that alcohol consumers, including those with HIV infection, have preferred alcohol types.

In our analysis, we assessed whether those drinking higher-ethanol-content drinks would have higher viral loads. Alcohol types with high ethanol content might be more likely to cause inflammation irrespective of the overall amount of alcohol consumed. Some experimental studies suggest that ethanol concentrations above 30%, a threshold that is lower than the ethanol concentrations of most liquors, are more likely to damage biological membranes than lower concentrations [39]. In theory, such damage could promote increased microbial translocation, which in HIV-infected patients is associated with HIV disease progression [40]. In Russia, those consuming wine/higher-ethanol-content cocktails had significantly higher HIV viral load levels than those consuming beer/lower-ethanol-content cocktails; however, those consuming liquor, contrary to our expectation, did not have significantly higher viral loads. Similarly, we did not find a significant association between high ethanol content and HIV viral load in the Uganda sample.

Although wine may have considerably high ethanol levels, participants consuming wine might have lower HIV viral loads, since wine is believed to have some anti-inflammatory properties [12]. In Uganda, a small number (n=8) of participants who reported predominantly drinking wine had lower HIV viral loads than those drinking commercially-brewed beer. In Russia, a small number of participants (n=5) predominantly drank fortified wine, and had lower viral loads than those drinking beer/lower-ethanol-content cocktails. However, neither of these results were statistically significant ($p = 0.08$ and $p = 0.78$, respectively). Due to the small number of participants in both wine groups, further investigation is warranted. If confirmed, such an observation would be consistent with suggestions that fermented drinks like wine may be less likely to promote inflammation than other types of alcohol [12, 13] and thus may be least associated with risk of HIV disease progression. In Russia, drinkers of wine/higher-ethanol-content cocktails had significantly higher viral loads than those drinking beer/lower-ethanol-content cocktails. Unfortunately, wine and high-ethanol-content cocktails were combined during patient interviews in Russia and thus their associations with HIV

viral load cannot be assessed separately. Consequently, this observation in Russia may be due to either the high ethanol content inherent in both high-ethanol-content cocktails and wine (perhaps less likely given the lack of higher viral load observed among liquor drinkers), or, it could be due primarily to unknown constituents in the cocktail drinks. Further studies assessing the cocktail drinks separately from wine and beer are thus recommended.

In the Uganda, sample, we expected that those consuming locally-made alcohols would have higher viral loads, possibly due to differences in methods of production or methods of distribution. We did not find evidence of differences in HIV viral load level by production method (i.e. whether the alcohol type was locally- or commercially-made).

We suggest that our results be interpreted with consideration given to the limitations in our data and study design. First, we were only able to assess associations with HIV viral load, which may be an imperfect marker of both HIV disease progression and the overall effects of inflammation in HIV-infected patients. Future studies should assess whether differences by alcohol type consumed exist in aspects or markers of HIV disease progression other than the viral load. For example, in Uganda, we recently found increased levels of monocyte activation among ART-naïve persons consuming unhealthy amounts of alcohol compared to those consuming lower amounts [41]. Whether such associations are driven by the consumption of specific alcohol types remains unknown.

Secondly, the number of participants consuming some alcohol types in our study was small (e.g., fortified wine in Russia and wine in Uganda). Also, as noted earlier, wine and high-ethanol-content cocktails were assessed together during interviews in Russia, as were beer and low-ethanol-content cocktails. As such, associations with HIV viral load could not be assessed separately for these types.

Thirdly, the estimated ethanol concentrations used in both countries may not be accurate. This may affect how the total number of standard ethanol drinks is estimated, leading to insufficient adjustment in our

analyses. In Uganda, for example, locally-brewed beers are estimated to have similar ethanol concentrations as commercially-brewed beers, but the former has been reported to have higher ethanol concentrations [29].

We excluded participants who were suspected to be either HIV-negative or to have been already exposed to ART (based on either undetectable viral load results, or testing HIV-antibody negative), since this would have otherwise classified them as ineligible for these studies. This excluded a substantial number of participants (50 in Russia and 37 in Uganda); for those testing HIV-negative, their earlier results could possibly be due to false positive rapid tests [42]. While this affected our sample size, excluding these participants allowed us to better reflect those who were truly HIV-positive and not yet on treatment in both locations.

Finally, as our measurements of alcohol type, total number of standard drinks, and frequency of binge drinking were self-reported, social-desirability could lead to misreporting on any of the variables, and this could bias our estimates. In our previous study in this setting, we found only moderate correlation between self-reported measures of drinking and PEth [22].

The overall impact of these limitations could be that we missed differences in viral load levels by alcohol type consumed, especially in the adjusted analyses, even where such differences might actually exist. We suggest that future alcohol surveys in similar settings consider separate categories for locally- versus commercially-made alcohols, as well as different drink types (i.e. wine versus cocktails), as well as give due consideration to inherent ethanol concentrations in these drink types.

Despite these limitations, we adjusted for both the overall amount of ethanol consumed and the drinking pattern, suggesting that any observed associations are unlikely to be due to these two dimensions of alcohol-related risk. Assessing volumes in a beverage-specific fashion allowed us to identify drinkers of each alcohol type. In Uganda, our findings were consistent even when adjusting for PEth, a direct metabolite of alcohol, which may suggest that observed associations are unlikely to be mediated by alcohol *per se* but quite possibly something else that may be inherent in specific alcohol types.

Conclusions

Among HIV-infected drinkers not on ART enrolling into cohort studies in Russia and Uganda, we observed an association between the alcohol type consumed and the HIV viral load in the Russia sample. In Russia, those consuming wine/higher-ethanol-content cocktails had higher HIV viral load levels than those consuming beer/lower-ethanol-content cocktails. In Uganda, compared to those drinking commercially-brewed beer, those drinking wine appeared to have somewhat lower HIV viral load levels, but this was not statistically significant. Our observations suggest that in addition to assessing total number of standard drinks and drinking patterns, it may also be important to assess alcohol type when investigating alcohol use and HIV disease progression. We recommend further study to evaluate the possible link between alcohol type and clinical outcomes among HIV-infected patients, and what relevance this might have to interventions to reduce alcohol-related harm in this population.

Author contributions

SBA conceptualized the study, performed the analyses, wrote and edited the manuscript, and led the study. JH is the PI for ADEPT and BREATH cohort studies in Uganda; JS is the PI for the URBAN ARCH Russia cohort study. Both JH and JS provided mentorship to SBA, conceptualized the study, and wrote and edited the manuscript. RF, CLT, and GP, conceptualized the study, prepared and cleaned the data, assisted with data analysis, and wrote and edited the manuscript. NG, WM, NA, EK, DC, and AK, conceptualized the study, prepared the data, and wrote and edited the manuscript. All authors read and approved the final version of the manuscript.

Funding

Funding was provided by the NIH to: Judith Hahn (R01 AA018631, U01AA020776, K24 AA022586), Jeffrey Samet (U01AA020780, U01AA021989, U24AA020778), and Debbie Cheng (U24AA020779)

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Figure legends

Figure 1.

Illustrations of containers that were used to aid patient recall during interviews for both the number of standard drinks and the total alcohol volume consumed.

In Russia, a complex chart was used, as shown. The captions in the top left and top right corners are Russian text translating to: “Examples of standard drink types (alcohol beverages)” and “Picture 1”, respectively. The pictures on the chart show actual beverages: the first two (cans) are beers and are labelled “beer”, the next three bottles are wines, labelled as “table wine”, the red bottles are “fortified wine” and are labelled as such. The two cans at the end of the chart are cocktail drinks and are each labelled with Russian text for “cocktail”. The illustrations of glasses represent how the associated drinks are commonly consumed in this setting, with the small glass on the left side representing a “shot of liquor” (1 standard drink), the one on the left representing a “glass of wine” (one standard drink), while the one in the middle represents a “glass of fortified wine” (1.5 standard drinks). The numbers at the bottom of the chart represent the total number of standard alcoholic drinks in the associated container. For example, the 0.3L beer-can is 1.0 standard drink, while the 0.5L can is 1.5 standard drinks, etc.

In Uganda, simple illustrations showing a beer bottle, a wine glass, and a shot of liquor were used without any associated text as shown. Volumes and standard drink quantities were explained to participants by the interviewer.

Table 1. Characteristics of participants at cohort entry by country. The table shows the characteristics at cohort entry of HIV-infected participants enrolling in 3 cohort studies in Russia and Uganda. The reference period for drinking reports was past month in Russia and past 3 months in Uganda.

	Russia (n=261)	**Uganda (n = 352)**
Year of enrollment	2012 to 2015	2011 to 2014
Age	33 (30 to 37)*	31 (25 to 38)
Male sex	181 (69.4%)	160 (45.5%)
Monthly income (USD)	309.6 (123.8 to 464.4)	30 (17 to 60)
Asset index score	-	0.0 (-1.7 to 1.7)
History of injection drug use		
No	154 (59.0%)	352 (100.0%)
Yes	107 (41.0%)	0 (0.0%)
Years since first HIV-positive diagnosis	6.8 (2.7 to 11.6)	0.2 (0.0 to 2.9)
Total number of standard drinks	62.3 (36.8 to 116.4)	32.1 (8.5 to 126.9)
Frequency of 6+ drinks		
Never	22 (8.4%)	228 (64.8%)
Less than monthly or once to thrice a month	121 (46.4%)	78 (22.2%)
Weekly or more often	118 (45.2%)	46 (13.1%)
Alcohol type predominantly drank†		
Russia		
Beer or low-ethanol-content cocktails‡	163 (62.5%)	-
Wine or high-ethanol-content cocktails	42 (16.1%)	-
Fortified wine	5 (1.9%)	
Liquor such as vodka ∞	49 (18.8%)	
No specific predominant type	2 (0.8%)	
Uganda		
Commercially-brewed beer‡	-	218 (61.9%)
Locally-brewed beer	-	41 (11.7%)
Wine	-	8 (2.3%)
Commercially-distilled spirits∞	-	38 (10.8%)
Locally-distilled spirits∞	-	43 (12.2%)
No specific predominant type	-	4 (1.1%)
Phosphatidylethanol (PEth) (ng/mL)	-	73.0 (14.4 to 265.5)
CD4+ T cell count (cells/mm^3)	465.0 (298.9 to 683.4)	485.5 (332.0 to 625.5)
HIV viral load (log_{10} copies/ml)	4.6 (4.0 to 5.2)	3.9 (3.2 to 4.5)

* Median (Interquartile range) unless otherwise specified

† Contributing >50% of total alcohol volume in the reference period; listed in order of lowest to highest estimated alcohol content

‡ Lowest ethanol concentration

∞ Highest ethanol concentration (in Uganda, unclear whether locally distilled spirits considered to have the same concentration as commercially distilled spirits, but the former's ethanol concentrations may be more variable).

Table 2. Descriptive table of study participant characteristics at cohort entry by predominant drink type and stratified by country*. The reference period for drinking reports was past month in Russia and past 3 months in Uganda.

	Russia‡				
	Overall	**Beer/low-ethanol cocktails**	**Wine/high-ethanol cocktails**	**Fortified wine**	**Hard liquor (e.g., vodka)**
Characteristic.	n = 259	n = 163	n = 42	n = 5	n = 49
Male sex	180 (69.5%)	116 (71.2%)	24 (57.1%)	5 (100.0%)	35 (71.4%)
Age	33 (30 to 37)∞	33 (30 to 36)	32 (29 to 35)	31 (29 to 39)	36 (32 to 39)
Monthly income (USD)	310 (124 to 464)	232 (77 to 464)	310 (124 to 464)	310 (155 to 929)	310 (155 to 464)
History of injection drug use					
No	152 (58.7%)	94 (57.7%)	20 (47.6%)	3 (60.0%)	35 (71.4%)
Yes	107 (41.3%)	69 (42.3%)	22 (52.4%)	2 (40.0%)	14 (28.6%)
Years since first HIV-positive diagnosis	6.8 (2.8 to 11.4)	7.1 (3.8 to 12.0)	7.2 (2.6 to 9.9)	3.9 (1.2 to 5.9)	4.4 (1.6 to 9.7)
Total number of standard drinks	62 (37 to 116)	59 (34 to 100)	74 (48 to 167)	115 (53 to 220)	72 (37 to 126)
Frequency of 6+ drinks					
Never	22 (8.5%)	10 (6.1%)	4 (9.5%)	1 (20.0%)	7 (14.3%)
Less than monthly or once to thrice a month	119 (46.0%)	82 (50.3%)	19 (45.2%)	2 (40.0%)	16 (32.7%)
Weekly or more often	118 (45.6%)	71 (43.6%)	19 (45.2%)	2 (40.0%)	26 (53.1%)
HIV viral load (log_{10} copies/ml)	4.6 (4.0 to 5.2)	4.5 (3.9 to 5.0)	4.8 (4.2 to 5.7)	4.1 (4.0 to 4.7)	4.5 (3.6 to 5.3)
CD4+ T cell count (cells/mm^3)	462 (299 to 683)	448 (292 to 668)	486 (354 to 642)	632 (471 to 839)	478 (278 to 724)

	Uganda†					
	Overall	**Commercially-brewed beer**	**Locally-brewed beer**	**Wine**	**Commercially-distilled spirits**	**Locally-distilled spirits**
Characteristic.	n = 348	n = 218	n = 41	n = 8	n = 38	n = 43
Male sex	157 (45.1%)	82 (37.6%)	24 (58.5%)	3 (37.5%)	29 (76.3%)	19 (44.2%)
Age	30 (25 to 38)	30 (25 to 36)	34 (29 to 43)	29 (26 to 34)	34 (27 to 44)	32 (27 to 39)
Monthly income (USD)	30 (18 to 60)	30 (18 to 60)	24 (14 to 54)	65 (32 to 135)	55 (30 to 90)	27 (12 to 45)
Asset index score	0.0 (-1.7 to 1.7)	0.3 (-1.6 to 1.7)	-1.2 (-2.1 to 0.0)	1.2 (-0.2 to 4.2)	1.1 (-0.5 to 3.0)	-1.7 (-2.9 to 0.3)
Years since first HIV-positive diagnosis	0.2 (0.0 to 2.8)	0.2 (0.0 to 2.5)	0.6 (0.1 to 3.6)	3.9 (0.6 to 6.2)	0.2 (0.0 to 3.3)	0.1 (0.0 to 2.0)
Total number of standard drinks	32 (8 to 127)	21 (7 to 80)	40 (17 to 190)	17 (2 to 27)	172 (71 to 358)	45 (12 to 176)
Frequency of 6+ drinks						
Never	227 (65.2%)	146 (67.0%)	29 (70.7%)	8 (100.0%)	16 (42.1%)	28 (65.1%)
Less than monthly or once to thrice a	76 (21.8%)	51 (23.4%)	7 (17.1%)	0 (0.0%)	11 (29.0%)	7 (16.3%)

month						
Weekly or more often	45 (12.9%)	21 (9.6%)	5 (12.2%)	0 (0.0%)	11 (29.0%)	8 (18.6%)
HIV viral load (log_{10} copies/ml)	3.9 (3.2 to 4.5)	3.9 (3.3 to 4.5)	4.1 (3.4 to 4.9)	3.2 (2.9 to 3.7)	3.9 (3.1 to 4.9)	3.9 (3.4 to 4.7)
CD4+ T cell count (cells/mm^3)	486 (332 to 625)	488 (354 to 618)	436 (307 to 634)	495 (434 to 554)	493 (322 to 672)	431 (326 to 588)
Phosphatidylethanol (PEth) (ng/mL)	73 (14 to 257)	56 (10 to 148)	88 (23 to 334)	25 (6 to 51)	167 (26 to 730)	181 (59 to 510)

* Limited to participants with a predominant alcohol type

∞Median (Interquartile range) unless otherwise specified

‡ Excludes 2 Russia participants without a predominant alcohol type

† Excludes 4 Uganda participants without a predominant alcohol type

Table 3. Mean HIV viral load by alcohol type predominantly consumed among HIV infected drinkers in Russia and Uganda

Predominant alcohol type	N	Mean HIV viral load (SD) (copies/ml)
*Russia**		
Beer/Low-ethanol content cocktails‡	162	161,178 (413,293)
Wine/High-ethanol content cocktails	42	505,434 (1,183,791)
Fortified wine	5	66,980 (113,228)
Liquor∞	49	286,239 (749,554)
No predominant alcohol type	2	14,031 (4,242)
Uganda†		
Commercially-made beer‡	215	42,712 (102,845)
Locally-made beer	41	52,611 (95,054)
Wine	8	4,549 (6,458)
Commercially-distilled spirit∞	35	112,245 (314,840)
Locally-distilled spirit∞	43	46,232 (79,833)
No predominant alcohol type	4	2,595 (3,193)

*excludes n = 1 Russia participants missing viral load.

† excludes n = 6 Uganda participants missing viral load.

‡ Lowest ethanol concentration

∞ Highest ethanol concentration (in Uganda, unclear whether locally distilled spirits considered to have the same concentration as commercially distilled spirits, but the former's ethanol concentrations may be more variable).

Table 4. Unadjusted and adjusted mean differences in $\log_{10}$ HIV viral load level (coefficients of linear regression) and 95% confidence intervals by alcohol type among HIV-infected patients in Russia and Uganda.

Variable	Unadjusted β (95% CI)	P	Adjusted* β 95% CI	P
Predominant alcohol type				
Russia (n=258)†				
Beer or low-ethanol cocktails‡	Ref	Ref	Ref	Ref
Wine or high-ethanol cocktails	0.42 (0.11 to 0.72)	0.008	0.38 (0.07 to 0.69)	0.018
Fortified wine	-0.23 (-1.03 to 0.57)	0.571	-0.12 (-0.95 to 0.72)	0.782
Hard liquor (e.g., vodka)∞	0.04 (-0.25 to 0.33)	0.783	0.00 (-0.30 to 0.30)	0.989
Uganda (n=342) ε				
Commercially-brewed beer‡	Ref		Ref	
Locally-brewed beer	0.17 (-0.17 to 0.51)	0.327	0.07 (-0.27 to 0.42)	0.672
Wine	-0.58 (-1.30 to 0.14)	0.115	-0.65 (-1.36 to 0.07)	0.076
Commercially-distilled spirits∞	0.04 (-0.32 to 0.41)	0.818	-0.08 (-0.47 to 0.32)	0.704
Locally-distilled spirits∞	0.05 (-0.29 to 0.38)	0.779	0.01 (-0.33 to 0.35)	0.951

*Adjusted for age, sex, asset index (or monthly individual-level income in Russia), number of standard drinks, frequency of drinking 6 or more drinks per occasion, and in Russia only, history of injecting drugs.

†Excludes 1 participant without HIV viral load measurement and 2 participants without a predominant alcohol type.

‡Lowest ethanol concentration

[∞] Highest ethanol concentration (in Uganda, unclear whether locally distilled spirits considered to have the same concentration as commercially distilled spirits, but the former's ethanol concentrations may be more variable).

[ε]Excludes 6 participants without HIV viral load measurements and 4 participants without a predominant alcohol type.

Figure 1. Illustrations of alcoholic drinks which we used in both countries to aid participant recall

Russia

Uganda