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ORIGINAL PAPER

Point-of-Care Urine Ethyl Glucuronide Testing to Detect Alcohol Use Among HIV-Hepatitis B Virus Coinfected Adults in Zambia

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Abstract
In an HIV-hepatitis B virus (HIV-HBV) coinfection cohort in Zambia, we piloted a qualitative point-of-care (POC) test for urine Ethyl glucuronide (uEtG), assessed concordance between uEtG and alcohol use disorders identification test-consumption (AUDIT-C), and identified epidemiological factors associated with underreporting (defined as uEtG-positivity with last reported drink > 7 days prior). Among 211 participants (40.8% women), there were 44 (20.8%) lifetime abstainers, 32 (15.2%) former drinkers, and 135 (64.0%) current drinkers, including 106 (50.2%) with unhealthy drinking per AUDIT-C. Eighty-seven (41.2%) were uEtG-positive including 64 of 65 (98.5%) who drank ≤ 3 days prior and 17 of 134 (12.7%) underreported, all of whom admitted to recent drinking when results were discussed. uEtG was moderately concordant with AUDIT-C. Past drinking (versus lifetime abstinence) and longer time on antiretrovirals (≥ 12 months) were associated with underreporting. These data support further use of POC alcohol biomarkers in HIV and hepatitis research and clinical settings.

Keywords Alcohol use disorder · HIV/AIDS · Africa · Hepatitis B virus · Ethyl glucuronide · Alcohol biomarker

Background

Unhealthy alcohol consumption, defined as hazardous/heavy alcohol use and alcohol use disorder, is an unaddressed barrier to controlling the HIV/AIDS epidemic and achieving an AIDS-free generation in Africa [1]. Heavy drinking increases the risk of HIV acquisition and drives high HIV incidence among young people [2]. Among HIV-infected individuals unhealthy drinking is associated with reduced adherence to antiretroviral therapy (ART) [3, 4], reduced immune recovery during treatment [5], and increased all cause mortality [6, 7]. Liver disease is a leading cause of non-AIDS mortality among HIV-infected individuals in part due to heavy drinking [8]. Unhealthy drinking also accelerates liver disease progression in chronic hepatitis B virus (HBV) infection [9], a common HIV coinfection.

Reliance on self-report is one of the challenges to diagnosis of unhealthy alcohol use among HIV-affected individuals [10]. In HIV prevention and care settings, underreporting of alcohol consumption may occur due to a number of social, psychological, and contextual factors [11]. In Uganda, HIV-infected individuals feared being denied ART if they openly reported drinking alcohol [12]. Once alcohol use is revealed and ART is initiated, social desirability bias may lead to inaccurately reported reductions in drinking as patients receive group and individual counseling that includes alcohol reduction messages.

Ethyl glucuronide (EtG) is an alcohol metabolite that can be measured in urine and may have the potential to augment screening for alcohol use in HIV care settings [13]. EtG becomes detectable in urine within hours of alcohol consumption and remains detectable for up to 2-5 days, depending on the specific assay used. Historically, urinary EtG (uEtG) was measured using high performance liquid chromatography with mass spectrometry [14] or an

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immunoanalyzer [15]; however, a point-of-care (POC) dipstick uEtG immunoassay recently became available. Within an HIV-HBV coinfection cohort in Lusaka, Zambia, we piloted the use of the POC uEtG test and compared uEtG results with self-reported measures of drinking. Based on HIV studies in Uganda [16] and Kenya [17] that utilized another alcohol biomarker Phosphatidylethanol (PEth), we hypothesized that 20–30% would underreport alcohol use. We also hypothesized that men and former drinkers would be more likely to underreport.

Methods

Since 2013, HIV-HBV coinfected adults aged 18 years and older, who were ART naïve have been prospectively enrolled in a cohort in Lusaka, Zambia [18]. HBV coinfection was defined as hepatitis B surface antigen positivity. Patients were prescribed ART according to national guidelines [19]. Alcohol consumption was assessed longitudinally at ART initiation and 6-month intervals thereafter using the Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) [20, 21], modified to measure drinking in the prior 6 months. Current abstinence was an AUDIT-C of 0 points, moderate drinking was 1–2 points for women and 1–3 for men, and unhealthy consumption was 3+ for women and 4+ for men. Patients who reported never having consumed a single alcoholic drink were classified as lifetime abstainers.

From August-2016 to May-2017, at routine cohort visits, additional informed consent was obtained, and we also documented the date of each participant's last alcohol drink. A fresh urine sample was collected in a 4-ounce specimen cup and within 20 min of collection a counselor or nurse dipped a uEtG test strip (Rapid ETG, Premier Biotech, Cottage Grove, USA) into the urine according to manufacturer instructions. This uEtG test provides a qualitative (positive/negative) result at a threshold of 500 ng/ml, a conservative cutoff designed to be highly specific for alcohol use and to reduce false positives due to alcohol-based mouthwash, hand sanitizer, or other products [13, 22]. Results became available within several minutes and were communicated to the participant. Participants reporting abstinence and found to be uEtG-positive were re-interviewed regarding recent alcohol consumption.

Participant characteristics were compared by sex with the Wilcoxon rank sum test for continuous measures and the Chi square test for categorical ones. We reported the proportion of uEtG tests that were positive in current abstainers, moderate drinkers, and unhealthy drinkers. Separately we described uEtG positivity according to the date of last drink. We assessed the concordance of uEtG and AUDIT-C using the kappa coefficient. For this analysis, we defined underreporting of alcohol use as uEtG positivity with last reported drink > 7 days ago and we explored patient and HIV care factors associated with underreporting using multivariable logistic regression. In bivariable analysis we considered patient age, sex, smoking status, time on ART (< versus > 1 year), staff member doing the testing (nurse versus counselor) and lifetime abstinence (versus former drinker) as potential correlates of underreporting. A stepwise logistic regression model was used to identify factors associated with underreporting with forward selection algorithm. The probability of removal was set at 0.2 using likelihood ratio test. The study was approved by the ethics committee at University of Zambia (011-11-14).

Results

Among the 295 HIV-HBV patients enrolled in the cohort, 211 (71.5%) underwent uEtG testing. Median age, sex, and current drinking status were similar between those tested and not tested for uEtG (all $P > 0.05$). Among those tested median age was 35 years (interquartile range, 29–40), 125 (59.2%) were men, and median time on ART was 11.4 months (IQR, 0–29). Most participants reported previous or current alcohol consumption with only 44 (21.0%) reporting lifetime abstinence (Table 1).

According to the AUDIT-C, 29 individuals (13.7%) reported moderate and 106 (50.2%) reported unhealthy levels of alcohol consumption. Current abstinence was more common among women than men (45.4 vs. 29.6%; $P = 0.019$) and unhealthy alcohol consumption was more common among men than women (60.0 vs. 36.0%; $P < 0.001$). AUDIT-C scores imperfectly correlated with recent consumption as only 64 (60.4%) unhealthy drinkers reported their last drink in the past 7 days and 5 (6.6%) participants with an AUDIT-C of 0 points (i.e., current abstinence) reported having a drink in the prior week.

Overall, uEtG was positive for 87 (41.2%) of participants. Self-reported drinkers (i.e., AUDIT-C > 0) were more likely to test positive than abstainers (57.8 vs. 11.8%, $P < 0.001$); however, positivity was similar between unhealthy and moderate drinkers (60.4 vs. 48.3%, $P = 0.242$). When AUDIT-C scores were dichotomized at 0 or > 0, concordance with the uEtG result was modest at 68.7% (kappa = 0.404) and similar concordance (69.2%; kappa = 0.384) was observed when comparing abstainers and moderate drinkers to heavy ones. Test positivity strongly decreased with increased time from last reported drink (Table 2). Concordance between self-reported last drink within 7 days and uEtG was 88.6% (kappa = 0.756). Nearly all (98.5%) patients reporting a drink in the last 3 days tested positive compared with 50.0% who reported drinking 4–6 days earlier (Table 2).

Among the 134 who reported last drink 7+ days prior, 17 (12.7%) were found to be uEtg-positive and were suspected

Table 1 Characteristics of HIV-HBV coinfected adults tested for urinary ethyl glucuronide in Lusaka, Zambia

	All (n = 211)	Women (n = 86)	Men (n = 125)	P
Median age, years (IQR)	35 (29–40)	32 (27–40)	35 (31–40)	0.001
Body mass index, n (%)				
< 18.5	55 (26.1)	21 (24.4)	34 (27.2)	< 0.001
18.5–25	128 (60.7)	42 (48.8)	87 (68.8)	
> 25	28 (13.3)	23 (26.7)	5 (4.0)	
WHO stage at ART start, n (%)				
1 or 2	72 (35.1)	26 (31.3)	46 (37.7)	0.348
3	133 (64.9)	57 (68.7)	76 (62.3)	
Alcohol consumption, n (%)[a]				
Abstinent (lifetime abstainer)	44 (20.8)	26 (30.2)	18 (14.4)	0.003
Abstinent (former drinker)	32 (15.2)	13 (15.1)	19 (15.2)	
Moderate	29 (13.7)	16 (18.6)	13 (10.4)	
Unhealthy	106 (50.2)	31 (36.0)	75 (60.0)	
Recentness of last drink[b]				
7+ days ago	63 (46.7)	27 (57.4)	36 (40.9)	0.150
4–6 days ago	11 (8.2)	4 (8.5)	7 (8.0)	
0–3 days ago	61 (45.2)	16 (34.0)	45 (51.1)	
Cigarette smoker, n (%)	31 (14.9)	3 (3.6)	28 (22.6)	< 0.001
Time on ART, n (%)				
≤12 months	106 (50.2)	39 (45.4)	67 (53.6)	0.239
> 12 months	105 (49.8)	47 (54.6)	58 (46.4)	

HIV human immunodeficiency virus, *HBV* hepatitis B virus, *IQR* interquartile range, *ART* antiretroviral therapy, *WHO* World Health Organization

[a]Alcohol consumption was assessed with the alcohol use disorders identification test-consumption (AUDIT-C) over the previous 6 month timeframe. An AUDIT-C score of 0 was considered abstinence, 1–3 for women and 1–4 for men was moderate drinking, and 4+ for women and 5+ for men were unhealthy alcohol consumption. Abstinent patients were categorized as lifetime abstainers or former drinkers

[b]Among current (moderate or unhealthy) drinkers

Table 2 Point-of-care urinary EtG results according to AUDIT-C score and timing of last alcoholic drink among 211 HIV-HBV coinfected individuals in Zambia

	No. tested	uEtG positivity, n (%)		
		All	Women	Men
Average alcohol use per AUDIT-C[a]				
Abstinent (lifetime abstainer)	43	1/43 (2.3)	1/25 (4.0)	0/18 (0)
Abstinent (former drinker)	33	8/33 (24.2)	4/14 (28.6)	4/19 (21.0)
Moderate	29	14/29 (48.3)	3/16 (18.8)	11/13 (84.6)
Unhealthy	106	64/106 (60.4)	18/31 (58.1)	46/75 (61.3)
Timing of most recent drink				
7+ days ago	134	17/134 (12.7)	6/63 (9.5)	11/71 (15.5)
4–6 days ago	12	6/12 (50.0)	3/5 (60.0)	3/7 (42.9)
0–3 days ago	65	64/65 (98.5)	17/18 (94.4)	47/47 (100)

The assay used (Rapid ETG, Premier Biotech, Cottage Grove, USA) provides a qualitative result (positive/negative) had a positivity cutoff of 500 ng/ml

uEtG urinary ethyl glucuronide, *AUDIT-C* alcohol use disorders identification test-consumption, *HIV* human immunodeficiency virus, *HBV* hepatitis B virus

[a]Unhealthy alcohol consumption was defined as AUDIT-C ≥ 3 for women and ≥ 4 for men; moderate drinking was defined as 1–2 for women and 1–3 for men

to have underreported. When a positive result was discussed with these patients, all admitted to having a drink in the past week. A larger proportion of men underreported compared to women (15.5 vs. 9.5%; P = 0.30); however, this

difference was not statistically significant. In multivariable analysis, lifetime abstainers had reduced odds (adjusted odds ratio 0.09; 95% CI 0.01–0.70) and patients on ART > 1 year (adjusted odds ratio 3.01; 95% CI 1.00–9.12) had increased odds of underreporting (Table 3).

Discussion

In an HIV-HBV coinfection cohort in Zambia, unhealthy alcohol consumption was common and 1 in 8 current abstainers were found to be underreporting by POC uEtG test. These data highlight that [1] alcohol use is an important comorbidity in HIV-HBV coinfection, [2] underreporting is a significant barrier to diagnosis of alcohol use and measurement of its impact on outcomes, and [3] POC uEtG testing is feasible and potentially implementable at HIV and viral hepatitis research and care settings in Africa.

We documented 40% prevalence of unhealthy alcohol consumption among HIV-HBV coinfected Zambians, a group at high risk of liver-related mortality. These data are supported by another Zambian study where 18% of TB or HIV-infected adults had alcohol dependence [23] and a South African study where 33% of HIV-infected adults taking ART reported hazardous drinking [24]. Our data highlight that 1 in 10 women reported heavy drinking in Zambia which is important as women experience alcohol's effects at lower doses due to differences in alcohol metabolism [25].

In this study underreporting of alcohol consumption was not uncommon. Although not a new phenomenon [11], underreporting has been measured with highly specific biomarkers in relatively few HIV studies. Our data build on a study in Kenya where following a 3-month alcohol reduction intervention for HIV-infected drinkers, 30.0% of women and 65.5% of men who reporting abstinence had detectable PEth [17]. Similarly in Uganda self-reported alcohol reduction was found to be partially inaccurate when PEth testing was performed [16]. As the POC uEtG test we used has a high detection threshold, we likely underestimated the degree of underreporting. Underreporting was more common with longer time on ART possibly due to social desirability bias. Also, individuals reporting that they had quit drinking in the past were more likely to underreport compared to lifetime abstainers. Underreporting by former drinkers may introduce bias in epidemiological studies as they have diverse risk of outcomes compared to lifetime abstainers [26].

Finally, these data provide feasibility data on the POC uEtG test that was relatively inexpensive ($5–8 per test), easy to use in field settings, and provided rapid results in the clinic that strengthened the counseling provided. The test appeared highly sensitive as 98% of participants who reported drinking in the past 3 days had a positive result. Not surprisingly the test was only modestly concordant with

Table 3 Patient factors associated with underreporting of recent alcohol consumption among HIV-HBV coinfected individuals in urban Zambia

	n (%) underreporting	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Age, in years			
18–29	5/44 (11.4)	Reference	
30–39	8/58 (13.8)	1.25 (0.38–4.12)	
40 and above	4/32 (12.5)	1.11 (0.27–4.53)	
Sex			
Female	6/63 (9.5)	Reference	Reference
Male	11/71 (15.5)	1.74 (0.60–5.02)	1.71 (0.55–5.31)
Lifetime abstainer			
No	16/90 (17.8)	Reference	Reference
Yes	1/44 (2.3)	0.11 (0.01–0.84)	0.09 (0.01–0.70)
Current smoking			
No	16/120 (13.3)	Reference	
Yes	1/11 (9.1)	0.65 (.078–5.42)	
Time on ART			
≤ 12 months	7/74 (9.5)	Reference	Reference
> 12 months	10/60 (16.7)	1.91 (0.68–5.38)	3.01 (1.00–9.12)
Staff member testing			
Counselor	15/107 (14.0)	Reference	
Nurse	2/27 (7.4)	0.49 (0.11–2.29)	

HIV human immunodeficiency virus, *HBV* hepatitis B virus, *ART* antiretroviral therapy, *CI* confidence interval

AUDIT-C scores that reflect chronic drinking patterns and could not distinguish moderate from unhealthy levels of use.

POC uEtG testing may have several applications in research and clinical care settings. First, the test could augment the information from self-report [27] and facilitate alcohol reduction counseling or referral to interventions. It could also be used in alcohol reduction interventions where contingency management is used (i.e., participants receive a reward contingent on having a negative uEtG) [28]. The test could also be utilized in clinical trials of potentially-hepatotoxic drugs where unhealthy alcohol use could elevate aminotransferases. In epidemiological studies, uEtG testing could be used to reduce the bias introduced by underreporting among non-drinkers and improve estimation of effect size.

The POC uEtG test and our study have several limitations that warrant discussion. EtG is a marker of recent alcohol use rather than chronic consumption. The qualitative POC test we used requires combination with another measure like AUDIT-C to determine levels of alcohol consumed. Documenting not only the last drink date but quantity of alcohol consumed in the prior week would have strengthened our analysis. Finally, we assumed but did not document whether participants were exposed to alcohol-containing products that could have caused a false positive result [22]. It was reassuring that those reporting abstinence and then testing uEtG-positive admitted to drinking.

In summary, among Zambian HIV-HBV patients taking ART, ongoing and heavy alcohol use was common. POC uEtG testing revealed underreporting of recent drinking and may have promise in both epidemiologic and interventional efforts to understand and intervene upon unhealthy alcohol use among HIV-infected individuals in Africa.

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