


# Phosphatidylethanol (PEth) as a Biomarker of Alcohol Consumption in HIV-Infected Young Russian Women: Comparison to Self-Report Assessments of Alcohol Use

Andrew K. Littlefield<sup>1</sup>  · Jennifer L. Brown<sup>2</sup> · Ralph J. DiClemente<sup>3,4,5</sup> · Polina Safonova<sup>6</sup> · Jessica M. Sales<sup>3,4</sup> · Eve S. Rose<sup>3</sup> · Nikolay Belyakov<sup>7</sup> · Vadim V. Rassokhin<sup>8</sup>

Published online: 18 April 2017

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**Abstract** Alcohol use is particularly deleterious for HIV-infected individuals and thus accurate assessment of alcohol consumption is crucial in this population. Phosphatidylethanol (PEth) provides an objective assessment of drinking and can be compared to self-reported alcohol assessments to detect underreporting. The purpose of this study was to identify underreporting and its potential predictors in an HIV-infected sample of young Russian women. The current study examined the concordance between a quantitative measure of PEth and self-reported recent alcohol consumption in a prospective sample of HIV-infected young women ( $N = 204$ ) receiving medical care in Saint Petersburg, Russia. At baseline, 53% of

participants who denied drinking in the prior 30 days tested positive for PEth (i.e., underreporters), although this rate decreased significantly at a three-month follow-up assessment. Further exploration did not identify consistent predictors of underreporting status. Quantitative PEth levels showed, at best, modest overlap to self-reported alcohol consumption among those reporting alcohol use (e.g., Spearman's  $r = 0.27$  between PEth and total drinks past-30 days at baseline). Objective measures of alcohol consumption demonstrate modest overlap with self-report measures of use in HIV-infected young Russian women. Incorporating objective and quantifiable biological markers are essential for valid assessments of alcohol use.

**Keywords** Biomarker · Alcohol drinking · HIV · Phosphatidylethanol

✉ Andrew K. Littlefield  
andrew.littlefield@ttu.edu

<sup>1</sup> Department of Psychological Sciences, Texas Tech University, 2500 Broadway, Lubbock, TX 79409, USA

<sup>2</sup> Addiction Sciences Division, Department of Psychiatry & Behavioral Neuroscience, University of Cincinnati College of Medicine, Cincinnati, OH, USA

<sup>3</sup> Department of Behavioral Sciences and Health Education, Rollins School of Public Health, Emory University, Atlanta, GA, USA

<sup>4</sup> Centers for AIDS Research, Emory University, Atlanta, GA, USA

<sup>5</sup> Department of Pediatrics (Division of Infectious Diseases, Epidemiology and Immunology), Emory University School of Medicine, Atlanta, GA, USA

<sup>6</sup> Saint Petersburg AIDS Center, Saint Petersburg, Russia

<sup>7</sup> North-West Regional Center for Control and Prevention of AIDS, Saint Petersburg, Russia

<sup>8</sup> First Pavlov State Medical University, Saint Petersburg, Russia

## Introduction

The World Health Organization (WHO) estimates there are 980,000 people living with HIV in Russia (480,000 women), with an HIV prevalence rate exceeding 1% (based on 2010 data; see 1). Russia is believed to be the nation with the greatest alcohol consumption per capita [2]. Elevated rates of hazardous drinking have been found among cohorts of HIV-infected individuals [3] and HIV-uninfected women [4, 5] in Russia. The WHO estimates that 10.3% of all Russian women (and 16.6% of female Russian drinkers) are heavy episodic drinkers (defined as drinking  $\geq 60$  g [or  $\sim 4.3$  standard drinks] of pure alcohol on at least one occasion during the past 30 days) and 6.2% have an alcohol use disorder [6]. Disordered alcohol use may lead to a variety of deleterious health consequences for HIV-infected individuals [7, 8]. Alcohol dependence

results in neurocognitive impairment, diminished cerebral cortex functioning, and increased prevalence of HIV-associated dementia [9, 10]. Heavy alcohol use is also linked to malnutrition among HIV-infected individuals [11]. In addition to health complications posed by alcohol directly, interactions between alcohol and antiretroviral (ARV) medications heighten the health risks posed to HIV-infected individuals who engage in harmful alcohol use. Alcohol and ARV medication interactions may contribute to hepatotoxicity and liver disease [12–14], which may be accelerated by co-morbid Hepatitis C infection [15]. Hazardous alcohol use also produces peripheral neuropathic pain, which may be further exacerbated by ARV medications [16]. Alcohol use is also a prominent factor associated with HIV transmission behavior [3, 17–19]. Despite epidemiological data suggesting elevated prevalence of alcohol use among HIV-infected women in Russia and the potential for negative health consequences, there is a lack of empirical investigations regarding alcohol consumption in this population, with no studies (to our knowledge) examining biomarkers of alcohol use.

Given their importance in providing objective measures of alcohol consumption, a variety of alcohol biomarkers have been proffered and examined (see 20–25). One such alcohol biomarker is phosphatidylethanol (PEth). The precursor of PEth, phosphatidylcholine, is typically converted to phosphatidic acid; however, in the presence of ethanol, PEth is produced (26–28; see 29 for further details). The half-life of PEth appears to be approximately 4–5 days [29, 30], though estimates of the half-life of PEth has varied across studies (with evidence of marked differences in half-life estimates across assessed individuals; see 29, 31, 32).

Numerous studies indicate the PEth is a valid marker of recent alcohol consumption (33; see 34 for a review and meta-analysis), with evidence that the most common molecular species of PEth (1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphatidylethanol; PEth 16:0/18:1; 35) has higher sensitivity to detect recent alcohol consumption compared to other alcohol biomarkers [36, 37]. Studies indicate PEth can be used as an alcohol biomarker for several purposes, including neonatal screening for prenatal alcohol exposure [38, 39], to assess alcohol intake in emergency rooms [40], to measure alcohol consumption in patients with liver disease and hypertension [41–43], to estimate driver risk among those previously convicted of driving while intoxicated [35], and to assess alcohol consumption among individuals who are HIV-infected [44, 45].

Although several studies have used laboratory-based alcohol administration paradigms to test PEth as a marker of alcohol consumption (e.g., 29–31, 37), several research groups have compared PEth to self-reported assessments of alcohol use (e.g., 40, 42, 43, 45–48). For example, receiver

operating characteristic curve (ROC) and contingency table analyses to assess the ability of PEth to detect self-reported alcohol consumption has been used in an effort to validate PEth as an alcohol consumption biomarker in those with liver disease [43]. These analyses yielded reasonable levels of sensitivity and specificity across several alcohol outcomes (e.g., PEth was 91% sensitive and 77% specific for detecting an average of at least four drinks/day during the past 30 days at the optimal cutpoint; see 43 for more details). The seminal study to assess the potential usefulness of PEth in HIV-infected individuals found high receiver operator characteristic area under the curve (ROC-AUC) for several self-reported alcohol outcomes (e.g., for any prior alcohol consumption across three weeks, PEth ROC-AUC was 0.92, with 88% sensitivity and 88.5% specificity) among 77 HIV-infected patients in Uganda [45]. Notably, this study [45] corroborated self-report with collateral reports of drinking by a friend or family member and by breath alcohol concentration. Overall, these studies indicate that PEth and self-reported alcohol consumption can show strong concordance, at least in certain samples.

Importantly, the aforementioned studies that validated PEth against self-report measures of alcohol consumption made the assumption that these self-reports are valid. However, it is possible that some individuals may not accurately report their actual alcohol consumption, limiting the usefulness of validating PEth against self-report measures. Indeed, other studies have used PEth as the “gold standard” to determine underreporting of self-reported alcohol use. For example, one study [40] found that 38.5% of male patients recruited in emergency room settings who denied drinking in the past 12 months tested positive for PEth. A recent article [44] compared self-reported alcohol consumption (that was not corroborated with additional assessments) to PEth among 150 HIV-infected patients initiating antiretroviral treatment (ART) in Uganda. Startlingly, 51.7% of individuals who were positive for PEth denied alcohol use in the past month. Additional analyses indicated that men (compared to women) and those in the lowest category of economic assets (compared to those in higher economic asset categories) were more likely to underreport alcohol consumption. Among individuals who did not deny alcohol use, quantitative PEth showed significant and high magnitude rank correlations with several indices of self-reported alcohol use, including self-reported drinking days. Based on these results, the authors concluded that men and those lower in economic status should undergo higher scrutiny for possible alcohol use (when alcohol use is denied via self-report) and reassurance needs to be provided that reporting alcohol consumption will not impact ART initiation. Based on the high magnitude correlation with quantitative PEth, the authors also concluded that self-reported drinking days is a useful measure among

those who do not deny recent drinking. More recently, the association between PEth and self-reported alcohol use at 2 time points in 127 HIV-infected outpatient drinkers in western Kenya was examined [49]. Similar to other findings [45], this more recent study found considerable disagreement between self-reported alcohol consumption and PEth status (e.g., at follow-up, 45% who denied drinking tested positive for PEth; 49).

In sum, some studies have shown significant overlap between self-report measures of alcohol consumption and PEth (e.g., 43, 45) whereas other studies have shown discrepancies between self-report and PEth (e.g., 40, 44). To our knowledge, the use of PEth as a biomarker of alcohol use among individuals who are HIV-infected has been limited to the work involving participants in Sub-Saharan Africa. Thus, it remains unclear if substantive underreporting extends to HIV-infected individuals drawn from other populations, such as individuals recruited from different regions, particularly in countries with elevated prevalence of alcohol use such as Russia.

In addition to assessing rates of underreporting alcohol use, it is also important to identify predictors of this phenomenon. Although one study [44] found several significant predictors of underreporting (e.g., gender, economic status) in an HIV-infected cohort, it is unclear the extent to which these findings extend to other cultural contexts. Further, additional variables that may distinguish underreporters from others could be explored, including self-report of other substance use, constructs related to alcohol involvement (e.g., alcohol outcome expectancies), and multi-method assessments of health (e.g., self-reported health as well as biological measures of viral load and CD4 count). Ideally, the same participants would also be assessed at multiple time points. A prospective design would allow for the examination of several novel research questions, such as whether underreporting at baseline predicts underreporting at a follow-up assessment, whether the rate of underreporting changes across time, as well as whether predictors of underreporting are consistent across time.

In sum, PEth has been identified as a viable biomarker of alcohol consumption in several populations. Although some studies indicate strong relations between PEth and self-reported alcohol consumption, the accuracy of self-report assessments of alcohol consumption may vary, such that in some settings (e.g., cross-cultural research) there may be significant difficulties in precisely measuring content and volume of alcohol consumed. Further, some populations may be particularly susceptible to social desirability bias. For example, consistent with recent work [44], HIV-infected individuals may under-report their alcohol consumption out of concern of being denied critical treatment (e.g., ART). Although there is some evidence

that underreporting may be significantly linked to specific participant characteristics, these findings are limited to data among modestly-sized samples of participants from a specific geographic region [45, 49].

Thus, the current study examined the concordance between a quantitative measure of PEth and recent alcohol consumption in a sample of HIV-infected young women assessed at two time points receiving comprehensive HIV medical care in Saint Petersburg, Russia. Several self-report and biological variables were examined as potential predictors of underreporting status. To our knowledge, this is the first study to examine PEth among HIV-infected individuals in Russia (and any location other than Sub-Saharan Africa) and to utilize prospective assessments of PEth among HIV-infected individuals.

## Methods

### Participants

Participants were HIV-infected young women ( $N = 250$  at baseline;  $N = 217$  at three-month follow-up) receiving HIV medical care in a comprehensive HIV care center in Saint Petersburg, Russia (see 50 for more details). Given the focus on PEth and self-reported alcohol use, analyses are limited to participants with non-missing PEth and self-reported alcohol use scores at both baseline and follow-up ( $N = 204$ ; 81.6% of the baseline sample; 42 missing on both variables; 3 missing on PEth only; 1 missing on self-reported alcohol only; underreporting at baseline among the full sample did not significantly predict study attrition, and median level of baseline PEth did not significantly differ between study attriters and those who remained in the study).

### Procedures

Participants were recruited during their regularly scheduled medical appointments at a comprehensive HIV care center in Saint Petersburg, Russia. A study staff member approached female patients in the clinic, described the study, and assessed eligibility. Eligibility criteria included: (a) aged 18–35 years; (b) reported vaginal sex in the previous three-months; (c) not pregnant; and (d) currently prescribed antiretroviral medication. Participants completed an initial baseline data collection and then a follow-up data collection three-months later. Data collection at baseline and follow-up consisted of a 45-min survey administered via an audio computer assisted self-interview (ACASI). All measures were translated from English to Russian and back translated from Russian to English. A pilot study was first conducted to refine the measures (e.g.,

wording). The finalized ACASI provided the questions visually with accompanying Russian audio presentation. To measure phosphatidylethanol (PEth) levels, participants provided blood spot samples using U.S. Drug Testing Laboratory standardized procedures (USDTL, Des Plaines, IL). Participants also provided biological specimens to test for prevalent STI, HIV viral load, and CD4 counts. Written informed consent was obtained from all participants; participants were informed about the alcohol biomarker assessment by both research staff and as part of the study's consent form. The Institutional Review Boards of participating institutions (Emory University Institutional Review Board and the St. Petersburg AIDS Centre Institutional Review Board) approved all study procedures.

### PEth Measure of Alcohol Use

#### *Specimen Collection*

Per USDTL standardized collection procedures, participants first washed their hands with soap and water. A single finger was then wiped with an isopropyl alcohol pad. A laboratory staff member used a sterile lancet to puncture the finger. The participant then provided blood to fill the five collection circles on the collection card provided within the USDTL BloodSpot collection kit. The collection card was then placed in the USDTL BloodSpot Drying Box and labeled with the participant's identification number. Specimens were stored in a temperature controlled refrigerator before shipment to USDTL for processing. The timeline varied for the length of time the specimens were stored based on when participants completed the study visits, and it is possible some degradation occurred (see "[Discussion](#)" section).

#### *Assay Procedures*

Specimens were analyzed at U.S. Drug Testing Laboratories using a previously published method [51]. Briefly, the method monitored a single isomer of PEth (palmitoyl/oleoyl), which is the most prevalent PEth species. The limit of detection was 2 ng/mL, the limit of quantitation was 8 ng/mL, and the assay was linear up to 800 ng/mL.

### Other Biological Measures

#### *Viral Load and CD4 Counts*

Participants' HIV viral load (ng/mL) and CD4 cell count (obtained via blood draw) at the baseline and three-month follow-up assessments were obtained via medical chart abstraction.

#### *Hepatitis C Virus (HCV) Antibody Status*

Participants' medical charts were abstracted to obtain their HCV antibody status. Research staff recorded whether the participant had a documented reactive HCV antibody result or not.

### Self-Report Measures

#### *Demographics*

To characterize the sample, participants reported their age, relationship status, and current employment status (no/yes) at baseline.

#### *Monthly Income*

At baseline, participants were asked to "Indicate the average monthly income per one member of your family" Based on the provided response options, a binary variable was created such that individuals indicating a monthly income of 10,000 rubles or less (closely corresponding to the Russian poverty line of 9662 rubles) were coded "0" whereas those reporting income greater than 10,000 rubles were coded "1".

#### *Alcohol Use*

At both baseline and follow-up, participants were asked, "During the past 30 days, on how many days did you have at least one drink of alcohol?" Individuals who reported "zero" were coded as "no" for past 30 day self-reported alcohol use, whereas individuals who reported one or more days were coded as "yes". Among those who endorsed past 30-day alcohol use, the count of number of drinking days was used. Participants were also asked, "On days when you drank in the past 30 days, about how many drinks did you drink on the average day?" This response was multiplied by the number of drinking days variable to calculate total drinks in the past 30 days. To be consistent with prior work [44], typical drinks on the average drinking day was also examined separately. Responses to the question, "On how many days (0–31) in the last month have you had 4 or more drinks on one occasion?" were used to provide an estimate of heavy episodic drinking in the current sample; participants who reported one or more days of consuming four or more drinks were coded as heavy episodic drinkers at each wave.

Additionally, alcohol consumption was assessed using the AUDIT-C scoring of the Alcohol Use Disorders Inventory Test (AUDIT; 52). More specifically, the AUDIT-C comprises the three consumption questions from the full AUDIT (see 52). Each question is scored 0 to 4

points and summed for a total possible score ranging from 0 to 12 points. In this study, the three consumption questions (“How often do you have a drink containing alcohol?”; “How many drinks containing alcohol do you have on a typical day when you are drinking?”; “How often do you have six or more drinks on one occasion?”) did not specify a timeframe (e.g., past 12 months). Further, individuals who responded “Never” to the question “How often do you have a drinking containing alcohol?” were then asked “Have you ever tried drinks containing alcohol?”; participants who responded “No” were then not asked the remaining AUDIT-C questions and were scored as a “0”. Given the entire sample consisted of females, a binary variable was used with a cut score of three for the current analyses.

#### *Alcohol Expectancies*

At both baseline and follow-up, participants reported on their expectancies regarding the effects of alcohol on sexual behaviors [53]. Participants responded to four items indicating their agreement with statements regarding the effects of alcohol on sex (e.g., “If I were under the influence from drinking alcohol I would enjoy sex more.”) on a four-point scale from Disagree to Agree. A total score was calculated such that higher scores indicate greater expectancies that alcohol affects sexual behaviors. Participants who denied a lifetime history of alcohol use were not assessed on this measure.

#### *Drug Use in the Past Year*

At both baseline and follow-up, participants were asked, “IN THE LAST YEAR, have you used drugs other than those required for medical reasons?” This item, taken from the Drug Abuse Screening Test (DAST; 54), was used as a binary measure of drug use in the past year.

#### *Tobacco Use*

At both baseline and follow-up, participants were asked, “During the past 30 days, on how many days did you smoke cigarettes?” This item was used to create a binary variable indicating any smoking versus no smoking in the past 30 days.

#### *HIV-Related Symptom Burden*

At both baseline and follow-up, HIV-relevant physical and cognitive complaints were assessed using a self-report measure based on the AIDS Clinical Trials Group symptom checklist [55, 56]. Participants were asked whether they have experienced each of 20 possible symptoms in the

preceding 30 days and, if so, how much it bothered them on a 5-point scale with higher scores indicative of greater discomfort or intrusion. Sample items include: fatigue or loss of energy, difficulty falling or staying asleep, problems with weight loss or wasting, and loss of appetite or a change in the taste of food. A total score is calculated across the 20 items such that higher scores are indicative of experiencing a greater number of HIV-related symptoms and symptom burden.

#### *Overall Health*

At baseline and follow-up, participants were asked, “During PAST MONTH, how would you rate your general health?” Responses on a 5-point scale ranged from “Excellent” to “Poor”, with higher scores indicating lower perceived health.

#### *Self-Efficacy for ART Medication Adherence*

At both baseline and follow-up, self-efficacy for ART medication adherence was assessed using the HIV-Adherence Self-Efficacy Scale [57]. A composite score was created by summing across fourteen items, with higher scores indicating greater self-efficacy for ART medication adherence.

#### **Analytic Approach**

Consistent with prior work [44], participants were coded as underreporters (at both baseline and follow-up) if they tested positive for PEth ( $\geq 8$  ng/mL, the limit of quantification) but denied alcohol consumption in the prior 30 days. We first examined the extent to which underreporting status at baseline predicted underreporting status at follow-up using logistic regression (conducted in SAS PROC MIXED). Additionally, to quantify the magnitude of agreement between underreporting status across assessments, kappa and the phi coefficient were also calculated. We also tested whether the prevalence of underreporting significantly changed from baseline to follow-up using McNemar’s test (in SAS PROC FREQ). Underreporters were then compared on a range of variables across waves to participants who reported alcohol consumption (regardless of PEth status) and participants who tested negative for PEth and denied prior month alcohol consumption. More specifically, generalized estimating equations (GEE, conducted in SAS PROC GENMOD using an unstructured correlational structure and a binomial link function) were used to predict underreporting status across both timeframes. All GEE analyses adjusted for study visit (i.e., time) and considered each predictor separately. Analyses also examined differences in quantitative viral load and

CD4 counts as a function of underreporting status using a nonparametric approach (i.e., a two-sample median test, using SAS PROC NPAR1WAY). To make comparisons to existing work [44], Spearman’s rank correlation between several indices of self-reported alcohol consumption and quantitative PEth were calculated (using SAS PROC CORR) among individuals who self-reported alcohol consumption in the prior 30 days.

**Results**

**Demographics**

The 204 participants were between the ages of 20 and 35 years old with mean (SD) age of 30.11 (2.91); 47.06% of participants were married. The majority of participants were employed (62.75%), with 32.84% working 40 or more hours a week.

**Self-Report of Alcohol Consumption and PEth**

Self-reported alcohol consumption in the prior 30 days (yes vs. no) by PEth status (positive vs. negative) is shown in Table 1 for the baseline and follow-up assessment. The median number of total drinks consumed among those reporting any drinking in the past month at baseline ( $n = 134$ ) was 4 (range 1–80); at follow-up, the median number of total drinks reported among those reporting past-month drinking ( $n = 118$ ) was 4.5 (range 1–375). At baseline, 25.4% reported heavy episodic drinking during the past month, and 27.9% exceeded the cutoff for hazardous drinking based on the AUDIT-C. At follow-up, 19.6% reported heavy episodic drinking during the past month, and 18.1% exceeded the cutoff for hazardous drinking based on the AUDIT-C. Of those denying alcohol consumption in the prior 30 days at baseline ( $n = 70$ ), 37 (52.9%) tested positive for PEth. At follow-up, 21 of the 86

(24.4%) individuals who denied drinking in the past 30 days were positive for PEth. Thus, rates of underreporting were more than double at baseline versus follow-up; results from McNemar’s test indicated this difference was statistically significant (McNemar 5.82,  $df = 1$ ,  $p = 0.02$ ). Interestingly, there was generally low overlap between underreporting status at baseline and follow-up ( $kappa = 0.13$ ; Phi coefficient = 0.13). Indeed, logistic regression analysis indicated that underreporting status at baseline did not significantly predict underreporting at follow-up ( $b = 0.94$ ,  $p = 0.06$ ); only seven participants (24.3% of underreporters at baseline and 3.4% of the total sample) were underreporters at both assessments.

**Potential Covariates of Underreporting Status**

Descriptive data (frequencies for binary variables; means for continuous self-report variables; medians for quantitative biological measures) that were used to predict underreporting status are shown in Table 2. Results from the GEE are shown in Table 3. Across waves, individuals who were AUDIT-C positive had lower odds of being an underreporter versus reporting alcohol consumption in the past-30 days (see Table 3). No other variables from the GEE were significantly related to underreporting status. Further, supplementary analyses (not shown) that combined the comparison groups, such that underreporters were compared to all other participants, failed to identify predictors of underreporting status.

**Biological Measures and Underreporting Status**

Wilcoxon rank-sum tests indicated the distributions CD4 counts and viral load did not significantly differ between underreporters and other comparison groups across both waves of assessment (absolute value of  $z$ s ranged from 0.04 to 1.13;  $p$ s ranged from 0.26 to 0.97).

**Quantitative PEth and Past 30 day Drinking**

At both baseline and follow-up and among individuals who self-reported alcohol consumption in the prior 30 days, Spearman rank correlations were calculated between quantitative PEth and: (a) total days drinking in the prior 30 days, (b) total number of drinks in the past 30 days, (c) typical number of drinks per drinking day. At baseline, number of drinking days was significantly correlated with quantitative PEth, though the magnitude of this correlation was small (Spearman’s  $r = 0.19$ ,  $p = 0.03$ ); at follow-up, the magnitude of the relation was higher though still modest (Spearman’s  $r = 0.38$ ,  $p < 0.001$ ). At baseline, total drinks in the past 30 days significantly and modestly correlated with quantitative PEth (Spearman’s  $r = 0.27$ ,

**Table 1** Self-reported alcohol use (past 30 days) by PEth status (N = 204)

Assessment				PEth status		Total
				PEth+	PEth–	
Baseline	SR. AU	Yes	Count	104	30	134
		No	Count	37	33	70
	Total	Count	141	63	204	
Follow-up	SR. AU	Yes	Count	69	49	118
		No	Count	21	65	86
	Total	Count	90	114	204	

SR. AU self-reported alcohol use, past 30-days. PEth+ positive for PEth. PEth– negative for PEth

**Table 2** Descriptives by underreporting status (N = 204)

	Baseline			Follow-up		
	Underreporters (n = 37)	SR+ (n = 134)	SR-/PEth- (n = 33)	Underreporters (n = 21)	SR+ (n = 118)	SR-/PEth- (n = 65)
Binary measures, n (%)						
Low income	13 (35.1)	40 (29.9)	11 (33.3)	8 (38.1)	37 (31.4)	19 (29.2)
AUDIT-C	5 (13.5)	47 (35.1)	5 (15.2)	1 (4.8)	33 (28.0)	3 (4.6)
Past-year drug use	2 (5.4)	25 (18.7)	3 (9.1)	5 (23.8)	18 (15.3)	7 (10.8)
Past-month smoking	18 (48.7)	79 (59.0)	18 (54.6)	8 (38.1)	68 (57.6)	30 (46.2)
HCV antibody positive	22 (59.5)	68 (51.9)	23 (69.7)	13 (61.9)	61 (52.1)	40 (61.5)
Self-reported quantitative measures, mean (SD/interquartile range)						
Alcohol outcome expectancies	6.1 (3.0/4)	7.2 (3.1/5)	6.9 (2.8/6)	6.5 (3.5/5)	7.3 (3.4/5)	7.1 (3.4/6)
HIV symptom scale score	30.7 (8.6/12)	36.0 (13.3/18)	40.3 (13.4/16)	35.3 (14.8/22)	32.2 (12.8/15)	32.7 (9.5/13)
Overall health	2.8 (1.0/1)	2.9 (0.9/1)	3.3 (1.0/1)	3.1 (1.0/1)	3.0 (0.9/2)	3.1 (0.9/1)
Self-efficacy	48.2 (9.2/9)	46.8 (8.3/12)	45.0 (7.4/10)	47.1 (10.0/11)	46.9 (8.2/12)	44.5 (10.6/14)
Biological quantitative measures, medians (interquartile range)						
Viral load	40.0 (98)	40.0 (25)	40.0 (130)	40.0 (50)	40.0 (37)	40.0 (42)
CD4 count	459.0 (258)	423.0 (256)	444.0 (296)	513.0 (368)	440.5 (319)	454.0 (268)
PEth	18.0 (11)	23.5 (38)	–	14.0 (10)	17.0 (42)	–

*Underreporters* negative on self-reported alcohol use and positive on PEth; *SR+* positive self-reported alcohol use, PEth positive or negative; *SR-/PEth-* negative on both self-reported alcohol use in the past 30 days and PEth. For alcohol outcome expectancies, total *n* at baseline (follow-up) = 199 (193). For HCV Antibody positive, total *n* at baseline (follow-up) = 201 (203)

**Table 3** Results from univariate generalized estimating equations predicting underreporting status

Independent variables	Underreporters versus SR+	UR versus SR-/PEth-
	Odds ratio ( <i>p</i> value)	
Low income	1.31 (0.44)	1.26 (0.53)
AUDIT-C	0.29 (<0.01)	0.93 (0.91)
Past-year drug use	0.79 (0.57)	1.60 (0.43)
Past-month smoking	0.59 (0.08)	0.76 (0.39)
HCV antibody positive	1.33 (0.38)	0.79 (0.52)
Alcohol outcome expectancies	0.90 (0.09)	0.93 (0.26)
HIV symptom scale score	0.99 (0.40)	0.97 (0.10)
Overall health	0.96 (0.83)	0.75 (0.14)
Self-efficacy	1.01 (0.69)	1.04 (0.11)

*Underreporters* negative on self-reported alcohol use and positive on PEth; *SR+* positive self-reported alcohol use, PEth positive or negative; *SR-/PEth-* negative on both self-reported alcohol use in the past 30 days and PEth

$p < 0.01$ ); the magnitude of this relation was higher at the follow-up assessment (Spearman's  $r = 0.40$ ,  $p < 0.001$ ). Finally, PEth and typical number of drinks per drinking day were significantly and modestly correlated at both baseline (Spearman's  $r = 0.25$ ,  $p < 0.01$ ) and follow-up (Spearman's  $r = 0.20$ ,  $p = 0.03$ ).

Supplementary analyses were then conducted based on two observations: (1) compared to the estimates above, another study [44] found much higher Spearman correlations (0.73 and 0.72 between quantitative PEth and number

of drinking days and total number of drinks, respectively) in their sample of HIV-infected individuals despite also comparing to a 30 day assessment window for self-reported alcohol consumption and (2) in the prior study [44], only four of the 150 participants (4.4%) self-reported alcohol use and tested negative for PEth. However, the current data indicate that approximately 15% of the sample indicated drinking in the past 30 days at baseline but tested negative for PEth; at follow-up, this was true for nearly a quarter of the participants (24%). Given these observations,

Spearman correlations between quantitative PEth and self-reported alcohol indices were calculated only among participants with both positive PEth and positive self-reported alcohol use. At baseline, findings were very consistent with the results reported above (i.e., Spearman correlations of 0.19, 0.27, and 0.26 between quantitative PEth and number of drinking days, total drinks, and average number of drinks per drinking day, respectively). However, at follow-up, correlations between quantitative PEth and self-reported alcohol use were lower in magnitude and non-significant (Spearman correlations of 0.11, 0.09, and  $-0.02$  between quantitative PEth and number of drinking days, total drinks, and average number of drinks per drinking day, respectively). Thus, it does not appear the lower magnitude correlations between PEth and self-reported drinking outcomes in this sample compared to prior work [44] can be attributed to differences in rates of individuals that self-report alcohol consumption yet test negative for PEth.

## Discussion

Prior work has examined the link between PEth and self-reported alcohol consumption, with some studies indicating considerable overlap between these approaches to assess alcohol use (e.g., 43, 45) whereas other studies have shown marked discrepancies between self-report and PEth (e.g., 40, 44). Consistent with prior work [44], there was considerable evidence of underreporting of alcohol use among HIV-infected individuals. At the initial assessment, over 50% of the participants who denied drinking in the past 30 days tested positive for PEth. Perhaps the three most interesting findings from the current work are: (1) the prevalence of underreporting significantly decreased between the first and second assessment, (2) there was low overlap of underreporting status across assessments, and (3) correlations between quantitative PEth and self-reported alcohol assessments were much lower in magnitude compared to existing work focused on HIV-infected individuals. Further, with the exception of hazardous drinking based on the AUDIT-C (in which individuals who were AUDIT-C negative were more likely to be underreporters; this is not entirely surprising, given that individuals who ever denied drinking would be AUDIT-C negative and, in combination of with a positive PEth score, be coded as an underreporter), none of the broad range of variables considered as potential predictors of underreporting significantly differentiated underreporters from other comparator groups across both assessments. Implications of these findings are discussed below.

There are several potential motives for socially desirable reporting in this sample of HIV-infected individuals. For

example, participants may have been concerned that if they accurately report their substance use, they may be denied ARV (and other crucial) medications or health care services. Prior to study initiation, clinic staff raised concerns that patients may inaccurately believe that they would face negative consequences (e.g., denial of ARV medications) if their doctors became aware of potential alcohol or other substance use. Given the significant declines in underreporting, it is possible that participants “learned” that study participation did not impact clinical services and thus participants were more likely to report alcohol use accurately at the follow-up assessment. Indeed, over 80% of participants who underreported at baseline did not underreport at follow-up, whereas only about 8% of those who did not underreport at baseline did so at the follow-up assessment. It is also important to note that the frequency of positive PEth results in the entire sample decreased across the two waves of the assessment (from  $\sim 69$  to  $\sim 44\%$ ; see Table 1); of the 37 underreporters at baseline, 26 ( $\sim 70\%$ ) tested negative for PEth at the follow-up, indicating these individuals may have quit (or reduced their) drinking during the course of the study.

Interestingly, underreporting at the first assessment did not significantly relate to underreporting status at the follow-up assessment; only seven of the 204 participants (3.43%) appeared to consistently underreport alcohol use. In light of these findings (and taken together with the low magnitude of the agreement statistics), it is not entirely surprising that the majority of the examined variables failed to distinguish underreporters from other participants, given the tendency to be an underreporter appears to be more of a “state” rather than a “trait.” In contrast with prior findings [44], economic status (as indexed by monthly income) did not distinguish underreporters from other comparison groups at either wave of assessment. Although [44] found that those lower in economic asset categories were more likely to be underreporters, it is important to note that their index involved several indicators (e.g., electricity in the home, asset category; see 44) and was only examined at one time point. Thus, it remains unclear the extent to which lower economic status is a reliable covariate of underreporting status; this relation may vary across HIV-infected populations (e.g., male and female participants recruited in Africa vs. Russian women), assessment approaches, or even across repeated assessments among the same individuals.

As noted in the results, the correlations between quantitative PEth and self-reported alcohol consumption among those who did not deny alcohol use in the prior 30 days were much lower in magnitude compared to prior estimates found in [44]. Supplementary analyses indicated that the discrepant magnitudes across studies cannot be attributed to study differences regarding the number of participants



who reported past month drinking yet tested negative on PEth. Based on the observed correlations, it was concluded that self-reported drinking days is a useful measure among those who do not deny recent drinking in their sample of HIV-infected individuals recruited in Uganda [44]. However, implementing the same logic and in light of the current findings, the same conclusion cannot be reached for the current sample of HIV-infected Russian females. These findings highlight the utility of the current work and suggest caution should be taken when generalizing findings regarding PEth and other assessments of alcohol use across samples of HIV-infected individuals.

As noted in the introduction, half-life estimates for PEth have varied across studies and across individuals. For example, [29] found the half-life of combined PEth homologues (PEth 16:0/18:1, the homologue considered in this study as well as PEth 16:0/18:2) was about 4.6 days; however, estimates ranged from one to 13.1 days across individuals. Thus, the extent to which self-reported alcohol consumption maps onto PEth levels may vary across samples (and individuals) for a multitude of reasons, including half-life differences of PEth homologues; additional laboratory-based, cross-cultural research is needed to further examine this potential. It is also possible that the PEth half-life for some individuals may be significantly higher than current estimated averages, resulting in detection of drinking via PEth that occurred prior to the 30 day assessment window (i.e., it is possible that some individuals who denied drinking in the past 30 days but were PEth positive were not underreporting). Despite this possibility, supplemental analyses indicate that it is doubtful that our estimates of underreporting are significantly and positively biased as a function of the 30 day assessment window. More specifically, at the first assessment 58 participants reported “never” to the question “How often do you have a drink containing alcohol?”; of these participants, 30 (51.72%) had quantifiable levels of PEth.

This study had several notable strengths, including (to our knowledge) this being the first examination of PEth among HIV-infected individuals outside of Sub-Saharan Africa. Indeed, given Russia is considered to be the country with the highest alcohol consumption per capita (2) and HIV-infected women may be at particular risk to engage in hazardous alcohol use, we consider it a strength that this study (to our knowledge) is the first to use an alcohol biomarker in this population to evaluate possible rates of underreporting. As noted in the introduction, WHO estimates that approximately 10.3% of all Russian women (and 16.6% of female Russian drinkers) are heavy episodic drinkers and 6.2% have an alcohol use disorder (6). Highlighting the alcohol involvement among the current sample of HIV-infected Russian women, at either the baseline or follow-up assessment about 16% of the sample

reported consuming four or more drinks on the “average” drinking day, about 33% met criteria for heavy episodic drinking, and about 34% exceeded the AUDIT-C cutoff indicating hazardous consumption. Given these estimates are based on self-reported assessments and in light of the PEth findings, these rates may be considered lower bound estimates of actual rates of problematic alcohol use in this sample. Indeed, the low correlations between PEth and self-reported alcohol consumption among those who did not deny drinking completely may indicate that quantity of alcohol consumption may be underreported to some extent, even among these participants. Further, this study is the first (to our knowledge) to utilize prospective assessments in a detailed examination of alcohol underreporting in HIV-infected Russian women, which yielded several novel findings. Additionally, we examined a broad range of potential predictors (based on both self-report and biological assessments) of underreporting that extended beyond basic demographic characteristics.

Despite these strengths, the current study has some limitations. This sample was limited to women, which prohibited us from testing gender differences in underreporting. As with other studies examining underreporting, PEth may not be entirely sensitive or specific, which may lead to inaccurate underreporting estimates, though notably other types of alcohol biomarkers also have measurement limitations (e.g., alcohol breathalyzers may only detect very recent drinking; see [20–25] for further discussion of relative strengths and limitations of various alcohol biomarkers). Although all PEth specimens were stored in temperature-regulated refrigerators using USDTL recommended procedures before being batched shipped at the end of the study, some degradation could have occurred during the storage and shipping process. As noted previously, the self-report assessments of past 30 day drinking behavior may not be optimal given the half-life estimates of PEth; as feasible, future studies should use more refined assessments of self-reported alcohol use (e.g., ecological momentary assessment) or consider alternative methods to assess alcohol consumption via self-report (see 58) to better understand the links between self-reported alcohol consumption and PEth. It should also be noted that, to some extent, the evidence of inaccurate reporting on alcohol calls into question the validity of reports on all other self-reported assessments; thus, the “true score” relation between the examined variables and underreporting may be biased to some unknown extent, though this is always a possibility for assessments with measurement error. Notably, the presence of an objective biomarker magnifies this possibility in this sample; soberingly, the extent to which underreporting may be common in samples that lack objective biological measures of alcohol use is difficult if not impossible to determine with high accuracy.

Clearly, obtaining accurate measures of alcohol consumption is essential to both clinical and research efforts. Inaccurate reporting by patients can hamper intervention efforts and skew findings in epidemiological and other treatment studies. The current findings indicate that a large portion of HIV-infected women from Russia denied drinking yet tested positive for PEth. When feasible, incorporating alcohol biomarkers as part of initial screening for HIV treatment may be beneficial to identify individuals who would benefit from additional alcohol-focused interventions. Perhaps somewhat reassuringly, rates of underreporting decreased across time, and chronic underreporting was infrequent. However, inconsistent with prior work among HIV-infected individuals, quantitative PEth showed (at best) modest overlap with several self-reported indices of alcohol use, suggesting that it is important to examine the relation between PEth and self-reported alcohol outcomes in a variety of samples representing different populations of individuals who are HIV-infected. Overall, these findings highlight the need for objective assessments of alcohol use (and by extension, other phenotypes of interest) and additional research to determine what factors contribute to enhanced accuracy of self-report assessments.

**Funding** Jennifer L. Brown was supported by R03DA0377860 from the National Institute on Drug Abuse. Ralph J. DiClemente was supported by Grant 1U01DA0362233 from the National Institute on Drug Abuse and 1R01AA018096 from the National Institute on Alcohol Abuse and Alcoholism.

#### Compliance with Ethical Standards

**Conflicts of interest** All authors declare that they have no conflict of interest.

**Ethical Approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed Consent** Informed consent was obtained from all individual participants included in the study.

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