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## Validating self-reported unhealthy alcohol use with phosphatidylethanol (PEth) among patients with HIV

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### Abstract

**Background:** We sought to compare self-reported alcohol consumption using Timeline Followback (TLFB) to biomarker-based evidence of significant alcohol use (phosphatidylethanol (PEth) >20 ng/mL). Using data from patients with HIV (PWH) entering a clinical trial, we asked whether TLFB could predict PEth >20 ng/mL and assessed the magnitude of association between TLFB and PEth level.

**Methods:** We defined unhealthy alcohol use as any alcohol use in the presence of liver disease, at-risk drinking, or alcohol use disorder. Self-reported alcohol use obtained from TLFB interview was assessed as mean number of drinks/day and number of heavy drinking days over the past

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Conflicts of interest  
None.

21 days. Dried blood spot samples for PEth were collected at the interview. We used logistic regression to predict PEth >20ng/mL and Spearman correlation to quantify the association with PEth, both as a function of TLFB.

**Results:** Among 282 individuals (99% men) in the analytic sample, approximately two-thirds (69%) of individuals had PEth >20 ng/mL. The proportion with PEth >20ng/mL increased with increasing levels of self-reported alcohol use; of the 190 patients with either at-risk drinking or alcohol use disorder based on self-report, 82% had PEth >20 ng/mL. Discrimination was better with number of drinks/day than heavy drinking days (AUC: 0.80 [95%CI: 0.74–0.85] vs. 0.74 [95%CI: 0.68–0.80]). The number of drinks/day and PEth were significantly and positively correlated across all levels of alcohol use (Spearman's R ranged from 0.29 to 0.56, all p values <0.01).

**Conclusions:** In this sample of PWH entering a clinical trial, mean numbers of drinks/day discriminated individuals with evidence of significant alcohol use by PEth. PEth complements self-report to improve identification of self-reported unhealthy alcohol use among PWH.

### Keywords

Alcohol use; Biomarker; Timeline Followback; TLFB; Phosphatidylethanol; PEth; HIV

## INTRODUCTION

Unhealthy alcohol use extends across a spectrum that ranges from low-risk drinking in the presence of a health problem caused or exacerbated by alcohol (e.g. liver disease) to alcohol use disorder; its negative consequences on individual and public health is well established (World Health Organization (WHO), 2014, Saitz, 2005). Despite the growing body of evidence suggesting that individuals with HIV may be at greater risk of harm from unhealthy alcohol consumption compared to their uninfected counterparts (Justice et al., 2016, Williams et al., 2016, Conigliaro et al., 2003), unhealthy alcohol use remains common among this population. Among patients with HIV (PWH), unhealthy alcohol use is associated with worse outcomes at each stage of the HIV care continuum and independently increases risk of death (Williams et al., 2019, Justice et al., 2016, Rentsch et al., 2016, Braithwaite and Bryant, 2010, Samet et al., 2007, Saitz, 2005, Conigliaro et al., 2003), as well as risky sexual behaviors and ongoing HIV transmission (Cook et al., 2006).

Given the health consequences associated with unhealthy alcohol use, it is important that alcohol exposure is accurately assessed. This is particularly critical in clinical settings – where care is provided and individuals may be recruited for clinical trial studies, to ensure that those at risk of harm are identified and offered appropriate interventions, including counseling and medications. Accurate measurement of unhealthy alcohol use is challenging (Justice et al., 2016) and alcohol consumption may be inconsistently reported due to social desirability bias, recall bias, and/or misinformation related to social norms. Under-reporting may be common especially among PWH or those with hepatitis C virus (HCV) infection for whom alcohol use may be discouraged by clinicians for reasons including concerns about viral disease progression, liver injury, and risk behaviors (Justice et al., 2016, Pellowski et al., 2016, Kalichman et al., 2012). Accordingly, self-report of alcohol consumption used to

assess intervention eligibility and efficacy may be biased. While self-reported calendar based methods, such as those employed with the Alcohol Timeline Followback (TLFB) (Sobell et al., 1996), are the gold standard for assessing alcohol use among patients in clinical trials (Witkiewitz et al., 2015), biomarkers of alcohol, such as phosphatidylethanol (PEth), may serve to improve confidence in the accuracy of patient-reported alcohol consumption.

PEth is a direct metabolite of alcohol use and has high sensitivity, with near perfect specificity for assessing any alcohol use in the recent past (Hahn et al., 2012a, Aradottir et al., 2006). PEth can detect alcohol exposure up to 21 days after consumption (Hahn et al., 2016, Wurst et al., 2015, Winkler et al., 2013). PEth >20 ng/mL reflects significant alcohol use ranging from an average of 2 to 4 drinks per day for several days a week to 4 or more drinks per day several days a week (Ullwelling and Smith, 2018, Piano et al., 2015, Stewart et al., 2009). PEth levels can vary between persons consuming the same amount of alcohol likely because of individual differences in alcohol metabolism (Javors et al., 2016). PEth does not differentiate alcohol consumption patterns (e.g. heavy episodic drinking vs. constant daily ingestion). However, its performance does not appear related to demographic factors such as age and sex, or other ingested substances (Viel et al., 2012). It has been demonstrated to be superior to other alcohol biomarkers (Walther et al., 2015, Wurst et al., 2015, Viel et al., 2012, Aradottir et al., 2006). Although PEth is an objective measure and may improve assessment of unhealthy alcohol use, data on the correlation between PEth and self-reported alcohol use among PWH have been mixed. While some studies have shown evidence of strong correlation (Bajunirwe et al., 2014, Hahn et al., 2012a, Aradottir et al., 2006), others have not (Wang et al., 2018, Littlefield et al., 2017, Papas et al., 2016). Explanations which have been proposed for these mixed results point to a number of PEth related characteristics that may vary across studies including individual differences in PEth formation and elimination (Javors et al., 2016, Stewart et al., 2010); differences in PEth measurement and cutoffs in studies (Papas et al., 2016, Hahn et al., 2012a, Isaksson et al., 2011); imperfect overlap of window of alcohol detectability by self-report and PEth (Bajunirwe et al., 2014); as well as the heterogeneity of the type and level of alcohol consumed (Aradottir et al., 2006). In addition to these, we suspect the mixed results are likely also a reflection of the validity of self-reported alcohol measures (Littlefield et al., 2017), which could be under-reported or over-reported depending on the context of the study.

Therefore, in the context of the Starting Treatment for Ethanol in Primary care Trials (STEP Trials), where PWH were eligible for study enrollment across the spectrum of unhealthy alcohol use, we sought to test the degree of consistency between self-reported alcohol consumption and PEth >20 ng/mL. Specifically, we were interested in the magnitude of association between self-reported alcohol consumption by TLFB and PEth >20 ng/mL and whether TLFB could be used to predict PEth >20 ng/ml. Given that PEth may not be readily accessible across all settings due to cost or other feasibility issues, the latter objective of this study seeks to address the uncertainty around the use of self-report measures in clinical research settings and thus increase our understanding of how well self-report measures predict clinically relevant alcohol use.

## METHODS

### Study Design and Setting

This study uses baseline data collected as part of the STEP trials, described in detail elsewhere (Edelman et al., 2019a, Edelman et al., 2019b, Edelman et al., 2017). Briefly, the STEP Trials consists of three multi-site, parallel, randomized controlled trials designed to evaluate the effectiveness of integrated stepped alcohol treatment compared to treatment as usual to address unhealthy alcohol use (see criteria below) among individuals with HIV. Ethics approval was received from the institutional review boards of the coordinating center at Yale University, New Haven, CT, the Veterans Affairs (VA) Connecticut Healthcare System, West Haven, CT, and from the participating clinical sites. The study is registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (ClinicalTrials.gov Identifier: NCT01410123).

### Study Participants

Participants were recruited at VA Infectious Disease clinics in Washington, DC; Atlanta, GA; Brooklyn/Manhattan, NY; Dallas and Houston, TX. Potentially eligible patients were identified based on the Alcohol Use Disorder Identification Test-Consumption (AUDIT-C) with score >0 and then assessed for eligibility. Eligible participants had to be: 1) HIV-positive adults; 2) a patient at one of the five clinics; 3) English speaking and able to provide written informed consent; and 4) with unhealthy alcohol use based on established criteria and recommendations (National Institute on Alcohol Abuse and Alcoholism, 2005, American Psychiatric Association, 2013). Each of the three trials focused on a specific type of unhealthy alcohol use which were defined in increasing order of alcohol use severity as: 1) moderate alcohol use with liver disease [MALD] trial, defined as report of any alcohol consumption in the past 30 days and are either HCV coinfecting, confirmed by HCV antibody and a detectable HCV RNA viral load, or have evidence of liver fibrosis, defined as a FIB-4 score >1.45 (Lim et al., 2014, Mendeni et al., 2011, Sterling et al., 2006), and who do not meet criteria for at-risk drinking or alcohol use disorder; 2) at-risk drinking trial, defined as alcohol consumption that is 14 or more drinks per week or 4 or more drinks per occasion in men younger than or equal to 65 years old or 7 or more drinks per week or 3 or more drinks per occasion in women or men older than 65 years old (National Institute on Alcohol Abuse and Alcoholism, 2005); and 3) alcohol use disorder trial, defined as meeting Diagnostic and Statistical Manual (DSM)-IV TR criteria for alcohol abuse or dependence (as DSM-5 was released after initiation of the trial) (American Psychiatric Association, 2013). TLFB was used to assess alcohol use pattern and frequency; participants were assessed for presence of alcohol use disorder based on their AUDIT-C score (>4 for men; >3 for women and men over 65 years old).

Participants were excluded if: 1) suicidal; 2) unable to provide informed consent or participate in counseling; 3) currently enrolled in treatment for unhealthy alcohol use excluding self or mutual-help groups; 4) had any medical condition(s) that would preclude completing the study or cause harm during the course of the study; or 5) a woman who is pregnant, nursing or does not agree to use birth control.

### Self-reported alcohol use

Self-reported alcohol use was measured at baseline using the TLFB during face-to-face, in-person interview by a research assistant trained in TLFB methods. TLFB is a validated, calendar-based, self-report method of assessing daily alcohol consumption in the past month and has good psychometric properties (Sobell and Sobell, 1996). Research assistants were trained to use probes, such as birthdays, holidays and weekends with use of a printed calendar, to improve recall. Our primary analysis considered two key measures of alcohol use at baseline, namely: (i) mean number of drinks per day in the past 21 days; and (ii) heavy drinking days, defined as  $\geq 5$  drinks in a given day, over the past 21 days. We used the last 21 days TLFB measure for this analysis to align with the 21-days PEth detection window. Additional measures included AUDIT-C score, collected at baseline screening for eligibility.

### PEth

To quantify PEth, dried blood spots obtained by fingerstick on the same day as TLFB were collected by the same research assistant or as needed by phlebotomist, and sent to United States Drug Testing Laboratories (USDTL), in Des Plaines, IL, and assayed using a previously described method (Jones et al., 2011). The order in which PEth and TLFB were collected was determined on a participant-participant basis to optimize data collection and minimize logistical hurdles. As no single PEth cutoff uniformly correlates with the spectrum of alcohol use (Gnann et al., 2012, Stewart et al., 2010, Aradottir et al., 2006), several different PEth thresholds have been used in previous studies (Eyawo et al., 2018, Asiimwe et al., 2015, Bajunirwe et al., 2014, Hahn et al., 2012a). Whereas PEth  $\geq 8$  ng/mL – excess of the lower limit of quantitation – is frequently used as an indicator of any alcohol use in the past 21 days, a PEth value  $< 8$  ng/mL is consistent with alcohol abstinence (Asiimwe et al., 2015, Bajunirwe et al., 2014, Stewart et al., 2014). Given our interest in alcohol use that impacts health rather than detecting any alcohol use, and coupled with our desire to minimize risk of false positive results (Hahn et al., 2016), we selected a PEth cutoff of 20 ng/ml, as values above reflect clinically significant alcohol use (Ulwelling and Smith, 2018). PEth results were not used to determine study eligibility.

### Sociodemographic and other clinical characteristics

Additional information on sociodemographic and biomarkers specific to HIV were also collected at baseline and included age, sex, race, HIV viral load, CD4 cell count, and the VACS Index score. The VACS Index is a validated, composite measure of morbidity and mortality that incorporates weighted values of routinely collected laboratory test results and measures of organ system injury, including age, CD4 cell count, HIV viral load, hemoglobin, platelets, aspartate transaminase, alanine transaminase, creatinine, and hepatitis C serostatus (Justice et al., 2013, Tate et al., 2013). The VACS Index is a reliable predictor of hospitalization and mortality with higher scores indicating higher risks (Eyawo et al., 2018, Akgun et al., 2013, Justice et al., 2013, Tate et al., 2013). We categorized HIV viral load as detectable ( $\geq 50$  copies/mL) vs. undetectable ( $<50$  copies/mL).

## Statistical Analysis

Baseline characteristics of participants were evaluated using descriptive statistics and compared according to PEth ( $\leq 20$  ng/mL vs.  $>20$  ng/mL) using Chi-square or Fisher's exact test for categorical variables and t test or Wilcoxon rank sum test for continuous variables, as appropriate. To summarize mean number of drinks per day in the past 21 days, we constructed dot plots by PEth status. As no sociodemographic or clinical variables satisfied the criteria of a confounder, we did not include any of these variables in subsequent models. We examined the association between PEth  $>20$  ng/mL and TLFB self-report as the independent variable using logistic regression. Discrimination was assessed using receiver operating characteristics (ROC) curves. Area under the curve (AUC) and corresponding 95% confidence intervals were calculated to evaluate discrimination. We used Spearman correlation to explore the relationship between mean number of drinks per day and PEth as a continuous value. We performed these analyses for the whole sample, as well as individually for the three defined subgroups of unhealthy alcohol use (MALD, at-risk drinking, and alcohol use disorder). In sensitivity analyses we used a TLFB time window covering the past 14 and 7 days (Fiellin et al., 2013). We also repeated all analyses using a less conservative PEth cutoff of 8 ng/mL. All p-values were 2-tailed and were considered statistically significant if less than 0.05. All analyses were performed using SAS version 9.4 (SAS, Cary, North Carolina, USA).

## RESULTS

### Sample Characteristics

Of 315 participants randomized into one of the three STEP trials, 33 were missing baseline PEth data as they were not collected or unable to be processed. This resulted in a total sample of 282 (MALD: 92, at-risk drinking: 85, and alcohol use disorder: 105). Characteristics of the study participants, overall and stratified by baseline PEth ( $\leq 20$  ng/mL vs.  $>20$  ng/mL) are presented in Table 1 and Figure 1. Most study participants were male (99%), African-American (81%) with median age of 59 years (interquartile range [IQR]: 53, 63). Compared to those with PEth  $\leq 20$  ng/mL, participants with baseline PEth  $>20$  ng/mL were more likely to have a lower VACS Index score (median [IQR]: 28 [18, 40] vs. 30 [21, 48],  $p = 0.021$ ); higher AUDIT-C score (mean [SD]: 6.3 [2.7] vs. 3.9 [2.4],  $p < 0.001$ ); less likely to be in MALD group (20% vs. 61%,  $p < 0.001$ ); and were more likely to fall into the more severe spectrum of unhealthy alcohol consumption, namely; in the at-risk drinking (35% vs. 19%,  $p < 0.001$ ) and alcohol use disorder groups (45% vs. 19%,  $p < 0.001$ ) (Table 1).

### Characterization of alcohol exposure by PEth compared to TLFB self-report

Approximately two-thirds (69%, 194/282) of individuals had PEth  $>20$  ng/mL. Of these, 20% were in the MALD, 35% in at-risk drinking, and 45% in the alcohol use disorder group (Table 1). Accordingly, the percent of participants with PEth  $>20$  ng/mL increased with severity of unhealthy alcohol use across the three subgroups (Table 1, Figures 2 to 4). Among the 190 patients with either at-risk drinking or alcohol use disorder (i.e. the upper spectrum of unhealthy alcohol use), approximately 82% had PEth  $>20$  ng/mL. In sensitivity analyses using a cutoff of 8 ng/mL, 77% of participants had PEth  $>8$  ng/mL. The percent of



participants with PEth >8 ng/mL also increased with severity of unhealthy alcohol use (48% of MALD, 87% of at-risk drinking, and 93% of alcohol use disorder). Of 190 patients with either at-risk drinking or alcohol use disorder, 91% had PEth >8 ng/mL.

Among 176 participants reporting at least one drink per day in the prior 21 days, 84% had baseline PEth >20 ng/mL compared to 42% of 104 participants who reported less than one drink per day ( $p < 0.0001$ ). Irrespective of the TLFB look-back window (21 vs. 14 vs. 7 days), we observed that participants with baseline PEth >20 ng/mL had on average two extra drinks per day more than the daily amount consumed by those with PEth  $\leq 20$  ng/mL (Table 1). Similarly, the mean number of heavy drinking days based on TLFB were higher among those with a PEth >20 ng/mL, regardless of the look-back window. For example, the mean number of heavy drinking days in the prior 21 days was 5.8 among participants with a baseline PEth >20 ng/mL compared to 1.6 among those with a PEth  $\leq 20$  ng/mL ( $p < 0.0001$ , Table 1).

In general, we observed differences in the distribution of the mean number of drinks per day among those with a PEth  $\leq 20$  ng/mL compared to PEth >20 ng/mL (Figures 1 – 4) and no individual with a PEth  $\leq 20$  ng/mL reported 10 or more drinks per day (Figure 1). Among MALD or at-risk drinking subgroups, no individual with a PEth  $\leq 20$  ng/mL reported 4 or more drinks per day (Figures 2 and 3); among those in the alcohol use disorder subgroup, no individual with a PEth  $\leq 20$  ng/mL reported 9 or more drinks per day (Figure 4).

### Associations between PEth >20 ng/mL and self-report TLFB measures

We found strong associations between self-reported alcohol use and PEth >20 ng/mL (or PEth >8 ng/mL – data not shown). The odds of a PEth >20 ng/mL was 1.73 (95% CI: 1.41, 2.11) with each unit increase in the mean number of drinks per day (Table 2). This varied by subgroup from 4.31 (95% CI: 1.61, 11.54) for MALD, 1.57 (95% CI: 1.04, 2.36) for at-risk drinking and 1.26 (95% CI: 1.01, 1.57) for alcohol use disorder (Table 2). The association was similar in sensitivity analyses using TLFB look-back windows of 14 and 7 days (Table 2). Here, for each unit increase in the mean number of drinks per day in the past 14 or 7 days, the odds ratio of having a PEth >20 ng/mL was 1.66 (95% CI: 1.37, 2.00) and 1.60 (95% CI: 1.34, 1.91) respectively. We observed similar results when the analysis was repeated using the mean number of heavy drinking days; each unit change was associated with odds ratio of 1.24 (95% CI: 1.13, 1.36) for having PEth > 20 ng/mL.

These results were also confirmed in the ROC curves (Figure 5) and corresponding AUC (Table 2). ROC curves and AUC estimates demonstrate that both mean number of drinks per day and heavy drinking days may be used to distinguish individuals with a PEth >20 ng/mL from those with a PEth  $\leq 20$  ng/mL. However, based on AUC our results suggest mean number of drinks per day has better discriminatory ability (AUC: 0.80, 95% CI: 0.74, 0.85) compared to mean number of heavy drinking days (AUC: 0.74, 95% CI: 0.68, 0.80). Mean number of drinks per day also performed well in sensitivity analysis using a 14- or 7-day look back window with AUC of 0.79 (95% CI: 0.73, 0.85) and 0.78 (95% CI: 0.72, 0.84), respectively. Considering the subgroups separately, the highest AUC, and thus the greatest discriminatory ability was observed among participants in MALD with AUC of 0.78 (95% CI: 0.69, 0.88).

### Association between self-reported alcohol exposure and PEth

In the overall sample, there was a moderate but statistically significant positive correlation between the mean number of drinks per day and PEth (Spearman's  $R = 0.55$ ,  $p < 0.0001$ ). Within subgroups, moderate and positive correlation was observed among participants in MALD (Spearman's  $R = 0.56$ ,  $p < 0.0001$ ) and at-risk (Spearman's  $R = 0.41$ ,  $p < 0.0001$ ). Weak but statistically significant positive relationship was observed among participants with alcohol use disorder (Spearman's  $R = 0.29$ ,  $p = 0.003$ ) (Table 3). This was unattenuated in sensitivity analyses where we limited the time window to the past 14 and 7 days (Table 3). We also observed a significant positive correlation with PEth when estimated using mean number of heavy drinking days instead of mean number of drinks per day (Table 3).

## DISCUSSION

Using baseline data collected among PWH with unhealthy alcohol use entering alcohol trials in a clinical setting, we examined the association between self-report alcohol use and PEth and whether self-report alcohol use data could predict clinically significant alcohol use as defined by a PEth  $>20$  ng/mL. Several key findings emerged. First, our results underscore the potential for misclassification of unhealthy alcohol use based on self-report data alone. Among those that met the criteria for at-risk drinking and alcohol use disorder based on established criteria, only 82% had PEth  $>20$  ng/mL, and 91% had PEth  $>8$  ng/mL. Second, we found a low to moderate positive correlation between self-report mean number of drinks per day or heavy drinking days and PEth  $>20$  ng/mL. Third, our results suggest that better discrimination is found with self-reported mean number of drinks per day than number of heavy drinking. These results highlighting the association between self-report and PEth are strengthened by the fact that our 21 days look-back window for the measurement of self-report alcohol use by TLFB coincide with the 21-days window of detectable PEth, and the results remained robust in sensitivity analyses using shorter look-back windows of 14 and 7 days to minimize the effect of recall bias in self-reports. Taken together, these findings highlight the potential role of alcohol biomarkers such as PEth as a complementary measure to improve the assessment of alcohol consumption in clinical settings (e.g., use of biomarker feedback to patients) and patients entering clinical trials.

Although under-reporting of alcohol consumption based on self-report may occur in the setting of HIV due to social desirability bias, social norms, misinformation (Papas et al., 2016, Bajunirwe et al., 2014, Hahn et al., 2012b) and among patients with liver disease, we found a substantial proportion of the participants self-reporting levels consistent with at-risk drinking and alcohol use disorder and yet, did not have a PEth  $>20$  ng/mL. Our observation suggestive of self-reported over-reporting of alcohol use in the context of baseline assessments for a clinical trial may be due to several potential reasons. Although issues of recall bias are common in settings where retrospective assessment of behaviors such as drinking is performed (Greenfield and Kerr, 2008), the structural features of TLFB including calendar and other memory aids to improve recall may have minimized this issue. It is not improbable that our mode of administration of TLFB via face to face interview with participants (instead of self-administration) may have contributed to the observed trend, although the direction of such an effect should have been more towards an under-



reporting as opposed to over-reporting (Bradley et al., 2011). It is also possible that some participants exaggerated their drinking due to perceived social norms (Chung and Rimal, 2016) or to qualify for the alcohol treatment trials given potential reimbursements, but have had low- to moderate-level drinking in the recent past. A different but somewhat related reason was reported from a study conducted in Uganda, where participants overreported drinking for secondary gain of transportation reimbursement (Papas et al., 2016), although our study did not provide such incentives. To reduce demand characteristics that might lead to overreporting during participant recruitment or administration of the TLFB, our recruitment materials did not specify any particular level of drinking to be eligible for study participation; participants were eligible across a range of alcohol use. Furthermore, the research assistants were trained to competence to collect TLFB and were not involved in participants' medical care, thereby minimizing any perceived incentive to disclose. Another potential reason for the self-reported over-reporting of alcohol use may have to do with our choice of PEth cutoff. Although we chose a cutoff of 20 ng/mL to reflect clinically significant alcohol exposure, previous studies have used lower cutoffs of 8 ng/mL (Asiimwe et al., 2015, Bajunirwe et al., 2014) including suggesting that drinking at PEth cutoffs 8 ng/mL may be associated with some harms (Eyawo et al., 2018). The extent of the observed overreporting was cut by half when we used a less conservative cutoff of 8 ng/mL in sensitivity analyses thereby improving the concordance between PEth and self-report. In the study by Asiimwe and colleagues that used a PEth cutoff of 8 ng/mL (Asiimwe et al., 2015), only 10% of self-reported unhealthy drinkers had a PEth at or below the 8 ng/mL cutoff, compared to 9% of individuals with at-risk drinking and alcohol use disorder in our sensitivity analysis that used a 8 ng/mL cutoff. We also observed that having a PEth >20 ng/mL appeared to be directly related to the severity of unhealthy alcohol use based on self-report. This corroborates previously reported findings from other studies in terms of the correlation between self-report alcohol intake and PEth (Aradottir et al., 2006). Prior research has demonstrated the association between increasing severity of unhealthy alcohol use and adverse health outcomes including mortality (Eyawo et al., 2018, Justice et al., 2016).

A key objective of our study was to investigate whether self-reported alcohol use data could predict clinically relevant use, resulting in a PEth >20 ng/mL. Our findings that unit increases in the self-reported mean number of drinks per day in the past 21 days has better discriminatory ability for predicting PEth >20 ng/mL than use of heavy drinking days may likely be related to the mechanism of formation and elimination of PEth. Findings from previous studies have shown that there is inter-individual variability in the absorption and elimination of PEth, both of which have an impact on the PEth concentration that is measured at a given point in time (Javors et al., 2016, Stewart et al., 2010). With this in mind, it makes sense that the mean number of drinks per day has better discriminatory power, as it more closely reflects changes in daily alcohol concentration in the blood compared to heavy drinking days that may be episodic and less regular in frequency. Although the mean number of drinks per day in the past 21 days appears to have better discriminatory ability over the heavy drinking days, it does not necessarily mean that the latter is not useful. Given the fair discriminatory power of PEth for heavy drinking days, it

could also be used in settings where information on the mean number of drinks per day in the past 21 days are unavailable.

We also found the mean number of drinks per day in the past 21 days to have greater discriminatory power for predicting PEth >20 ng/mL among individuals meeting the criteria for MALD (AUC: 0.78, 95% CI: 0.69, 0.88), compared to the other subgroups. Given that these individuals are co-infected with HCV or have evidence of liver fibrosis, it is possible that their underlying health status may have directly or indirectly impacted how sensitive they are to changes in blood alcohol levels (Stewart et al., 2014). We have previously demonstrated that individuals co-infected with HCV may be at particularly high risk of mortality (Eyawo et al., 2018). Nevertheless, at least one study has suggested that liver disease severity does not modify the effect of alcohol use on PEth concentration and thus the validity of PEth in the presence of liver disease (Stewart et al., 2014). However, given the small sample size of that study and that all patients included in the analysis had liver disease, confirmatory analyses are needed. It would be interesting to examine whether factors such as FIB-4 score might impact the correlation between TLFB and PEth among individuals with unhealthy alcohol use and liver disease. This will be particularly relevant for patients with clinically important alcohol exposure that could harm the liver or exacerbate other liver-related conditions. Furthermore, given the current limited knowledge of inter-individual differences in PEth synthesis and elimination, additional research is needed to better understand this and improve our understanding of the relationship between self-reported alcohol use and PEth concentrations. Additionally, given that liver disease is associated with shortened red cell survival (Bhattacharjee et al., 2018), our findings that self-reported alcohol use was more strongly associated with PEth among the MALD participants may be explained by the fact that PEth reflects alcohol use over shorter period of time among patients with HIV and comorbid liver disease and would thus be less subject to recall bias.

Our study has some limitations. Most importantly, we were only able to evaluate PEth among those reporting at least some alcohol use. Given social desirability bias, PEth may be particularly important for detecting harmful alcohol use among those reporting abstinence. Approximately 99% of the participants in the study were men. As such, the findings are not generalizable to women. Furthermore, our sample included only individuals who were currently receiving HIV care. It is possible that this sample is systematically different from those that are not in care. Furthermore, the results presented are based on data from a relatively small sample of 282 participants, therefore it would be interesting to replicate these analyses in a larger sample with more women. Despite these limitations, our study has shed light on some important relationship between alcohol self-report and PEth.

In summary, our study demonstrated self-reported alcohol use overestimates alcohol consumption compared to PEth in approximately 9% to 18% of HIV-positive individuals entering alcohol clinical trials supporting the role of confirming self-report with PEth, irrespective of the PEth cutoff used (8 ng/mL or 20 ng/mL). Specific to PEth > 20 ng/mL – a level that reflects clinically significant alcohol use, our results suggest that better discrimination is found with self-reported mean number of drinks per day than number of heavy drinking. Using a biomarker such as PEth to complement self-report measures could

improve the measurement of alcohol use and be an effective way to accurately measure unhealthy alcohol use in clinical settings and trials.

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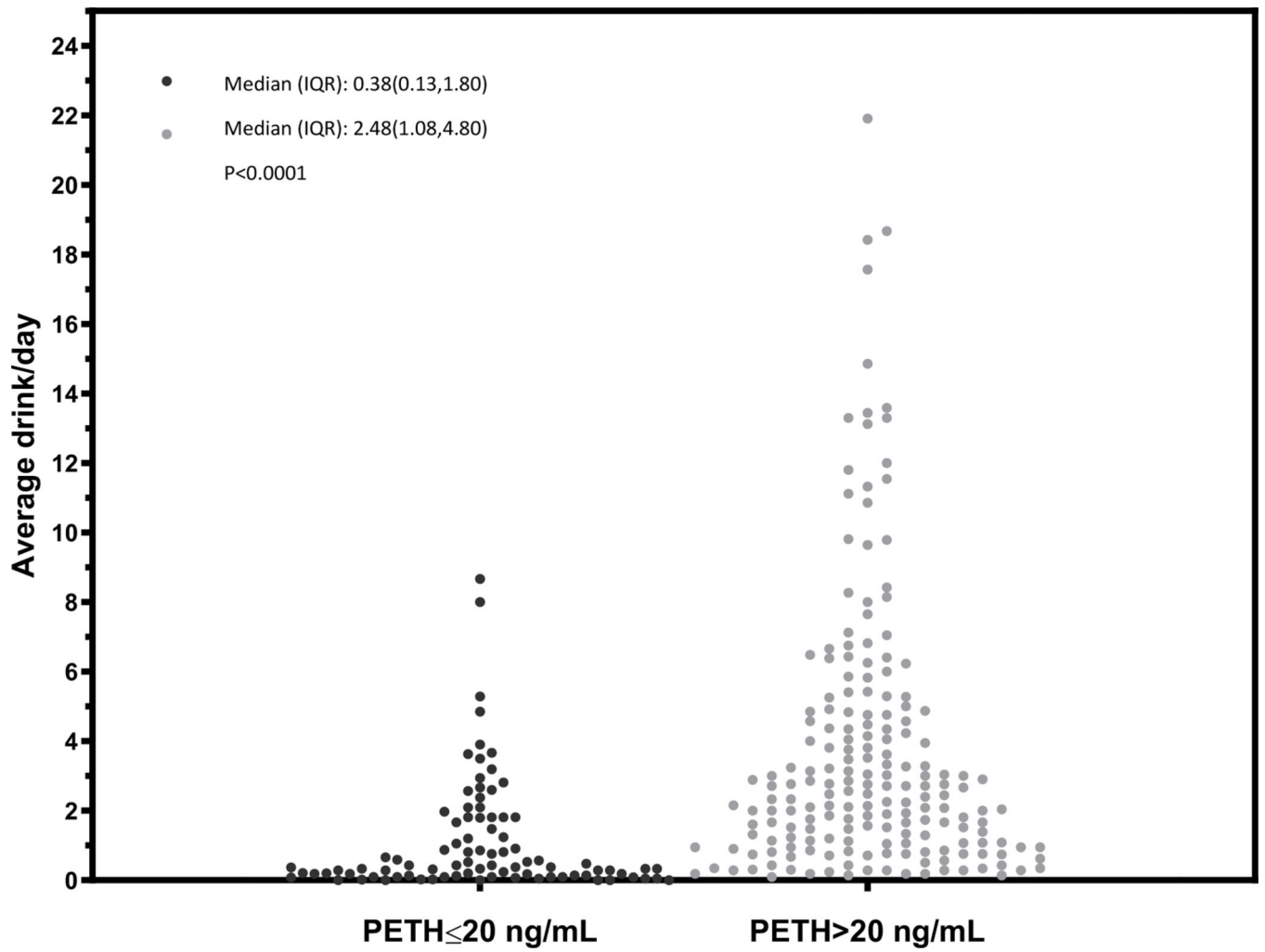
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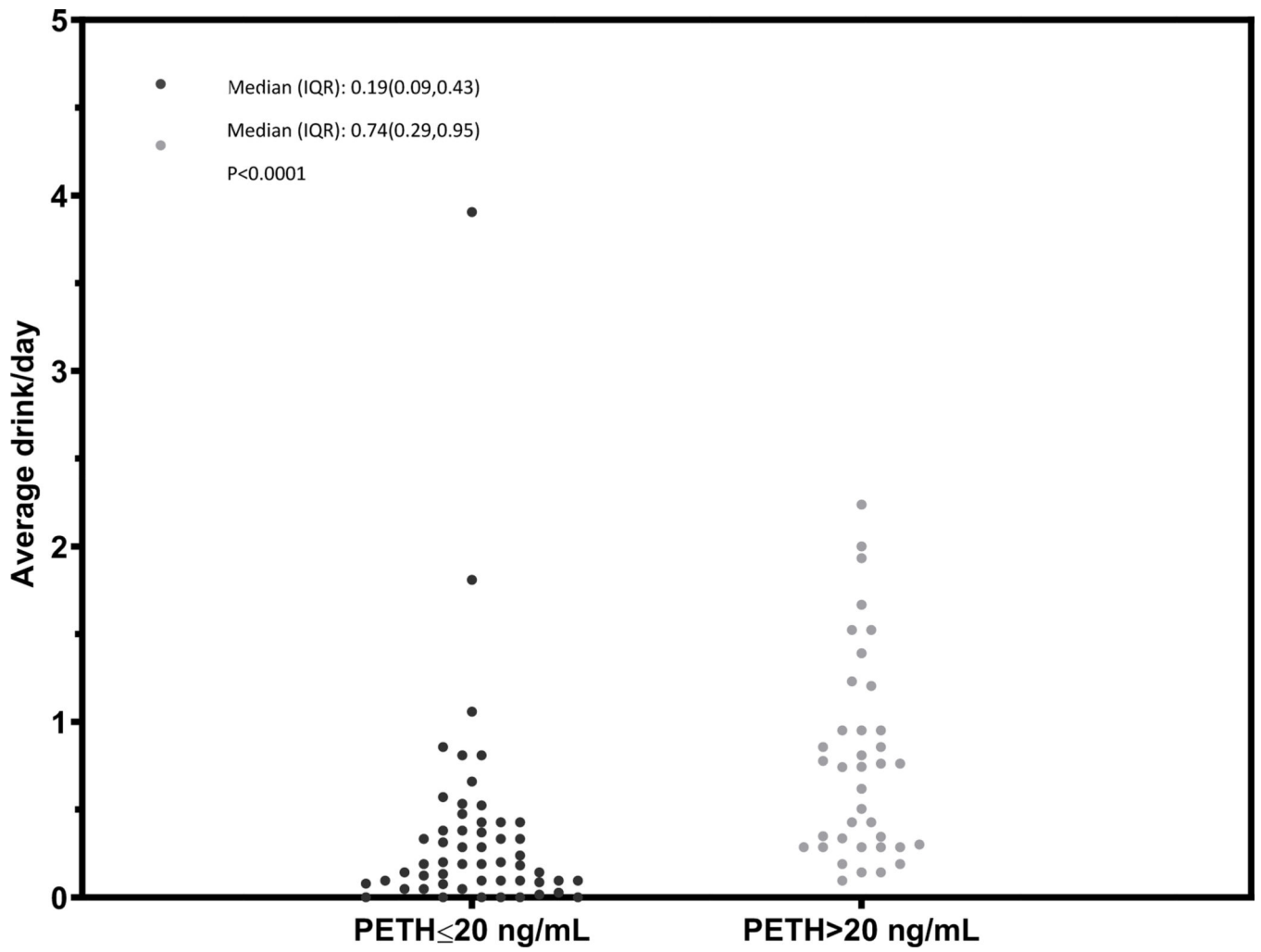
**Figure 1.** Dot plot characterizing the mean number of drinks per day over the prior 21 days before the PEth test for overall sample, stratified by PEth ≤20 or >20 ng/mL

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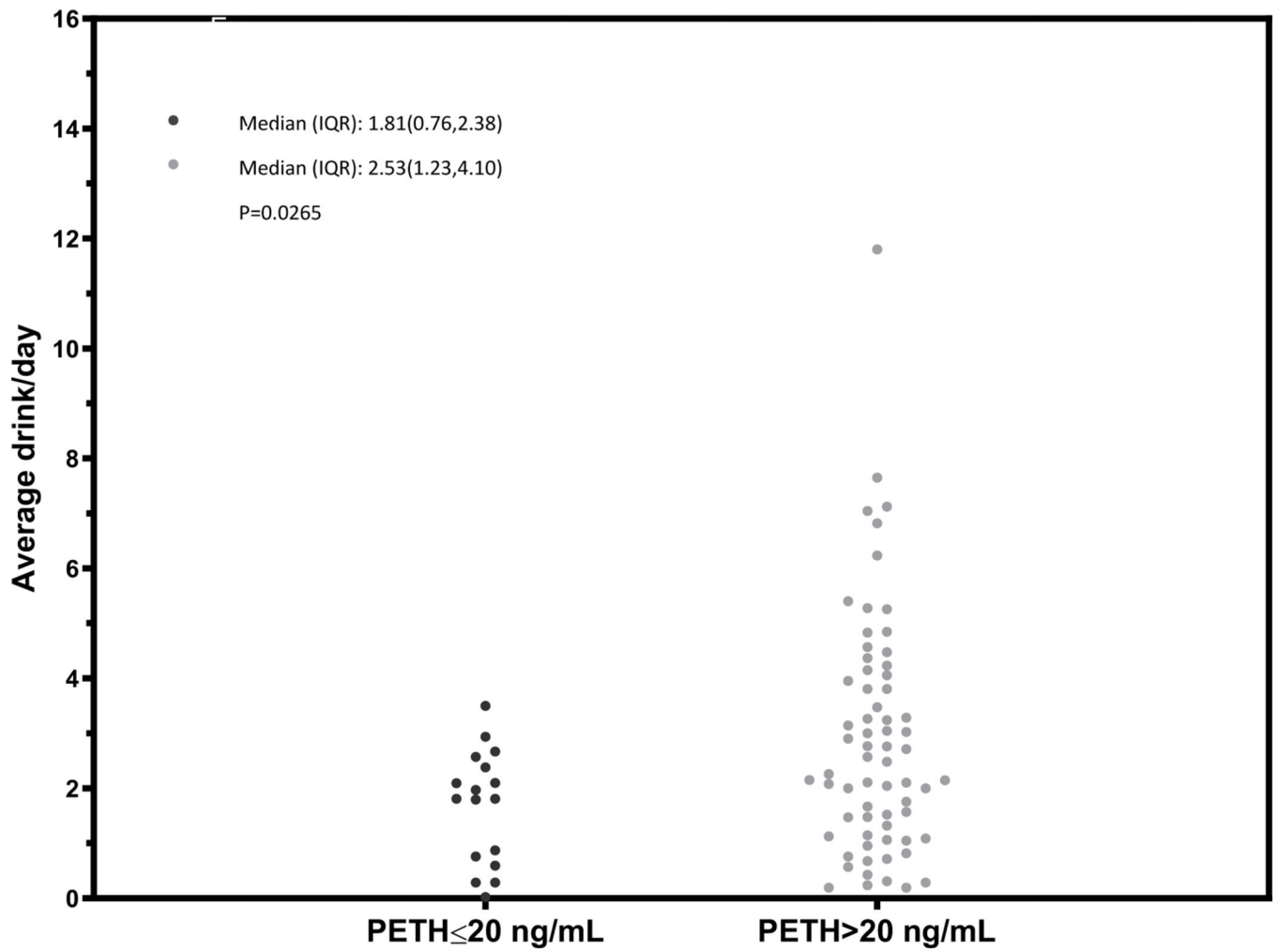
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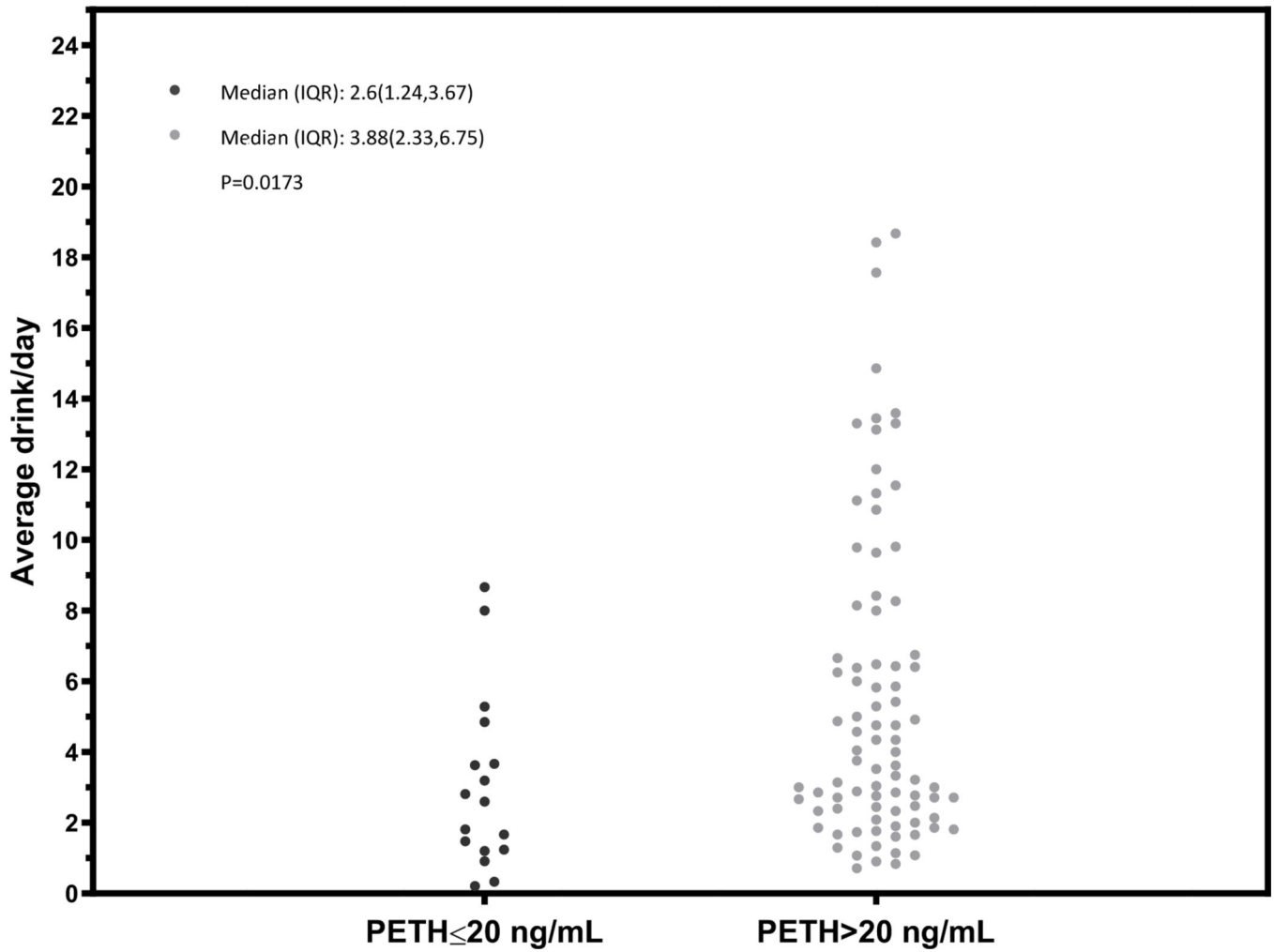
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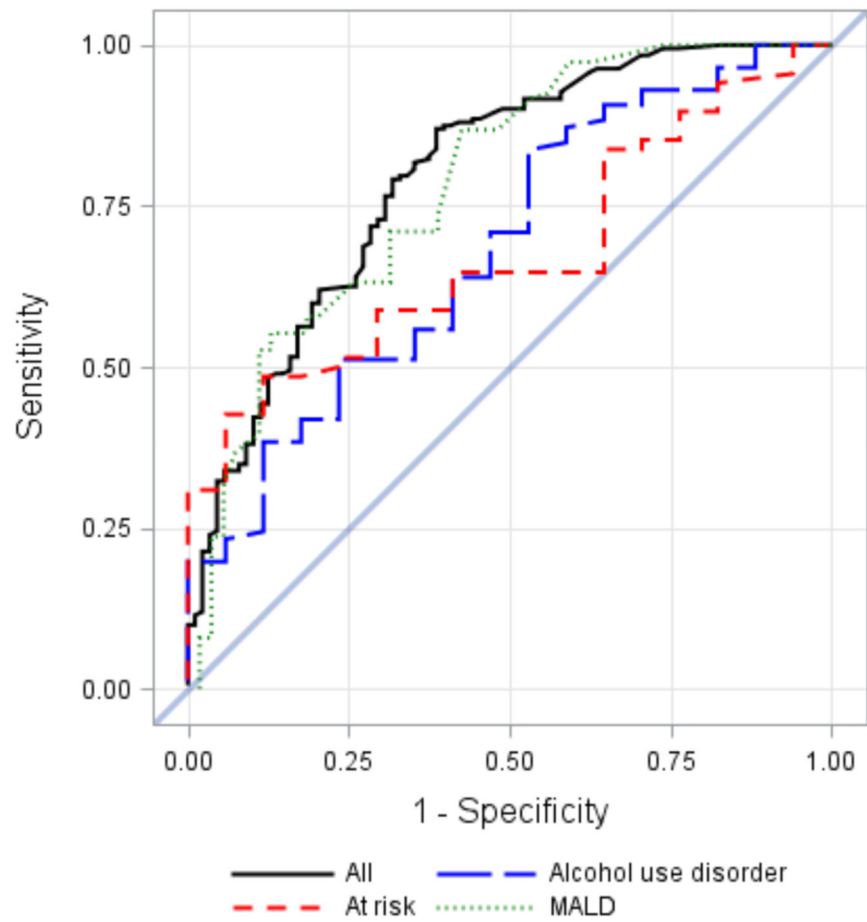
**Figure 2.** Dot plot characterizing the mean number of drinks per day over the prior 21 days before the PEth test among participants with MALD, stratified by PEth ≤ 20 or >20 ng/mL



**Figure 3.** Dot plot characterizing the mean number of drinks per day over the prior 21 days before the PEth test among participants with at-risk drinking, stratified by PEth ≤ 20 or >20 ng/mL



**Figure 4.** Dot plot characterizing the mean number of drinks per day over the prior 21 days before the PEth test among participants with alcohol use disorder, stratified by PEth ≤ 20 or >20 ng/mL



**Figure 5.** ROC curves for predicting PEth > 20 ng/mL in the overall (all), MALD, at-risk and alcohol use disorder sample (note: the diagonal line represents chance level, or probability of 0.5)

**Table 1.**

Baseline characteristics of the study participants, overall and by PEth

| Characteristic, n (%)                         | Overall sample | PEth (ng/mL)   |                | P-value |
|---|----------------|----------------|----------------|---------|
|   |                | 20             | > 20           |         |
| Sample size                                   | 282            | 88             | 194            |         |
| Age, median (IQR)                             | 59 (53, 63)    | 59 (54, 65)    | 58 (53, 63)    | 0.26    |
| Sex   |                |                |                | 1.00    |
| Female  | 4 (1.4)        | 1 (1.1)        | 3 (1.6)        |         |
| Male  | 278 (98.6)     | 87 (98.9)      | 191 (98.5)     |         |
| Race  |                |                |                | 0.24    |
| White   | 48 (17.0)      | 17 (19.3)      | 31 (16.0)      |         |
| African-American                              | 227 (80.5)     | 67 (76.1)      | 160 (82.5)     |         |
| Other   | 7 (2.5)        | 4 (4.6)        | 3 (1.6)        |         |
| Undetectable viral load (< 50 copies/mL)      | 186 (66.2)     | 54 (62.1)      | 132 (68.0)     | 0.33    |
| CD4 cell count, median (IQR)                  | 534 (373, 750) | 510 (370, 749) | 543 (379, 760) | 0.41    |
| VACS index score, median (IQR)                | 29 (18, 43)    | 30 (21, 48)    | 28 (18, 40)    | 0.021   |
| Unhealthy alcohol use (trial groups)          |                |                |                | < 0.001 |
| MALD  | 92 (32.6)      | 54 (61.4)      | 38 (19.6)      |         |
| At-risk drinking                              | 85 (30.1)      | 17 (19.3)      | 68 (35.1)      |         |
| Alcohol use disorder                          | 105 (37.2)     | 17 (19.3)      | 88 (45.4)      |         |
| <b>Self-reported alcohol use, * mean (SD)</b> |                |                |                |         |
| AUDIT-C score                                 | 5.53 (2.8)     | 3.85 (2.4)     | 6.29 (2.7)     | < 0.001 |
| Drinks per day, past 21 days                  | 2.91 (3.6)     | 1.13 (1.6)     | 3.73 (3.9)     | < 0.001 |
| Drinks per day, past 14 days                  | 2.89 (3.5)     | 1.14 (1.6)     | 3.70 (3.8)     | < 0.001 |
| Drinks per day, past 7 days                   | 2.86 (3.6)     | 1.13 (1.8)     | 3.65 (4.0)     | < 0.001 |
| Heavy drinking days, past 21 days             | 4.48 (6.0)     | 1.61 (3.2)     | 5.80 (6.5)     | < 0.001 |
| Heavy drinking days, past 14 days             | 3.03 (4.1)     | 1.13 (2.2)     | 3.91 (4.4)     | < 0.001 |
| Heavy drinking days, past 7 days              | 1.50 (2.1)     | 0.52 (1.1)     | 1.95 (2.2)     | < 0.001 |

\*assessed using Alcohol Timeline Follow back (TLFB) except for AUDIT-C score;

IQR, Interquartile range; MALD, Moderate alcohol use with liver disease; SD, Standard deviation

Note: several participants had missing data for a small number of variables as follows: 4 for VACS index score; 1 for viral load status; and 2 participants with missing TLFB measures data, respectively



**Table 2.**

Logistic regression analysis and area under the curve of the ROC curves predicting PEth > 20ng/mL based on self-reported alcohol use by TLFB

| Self-reported alcohol use**                                    | Odds ratio (95% CI)* | P-value | Area under the curve (95% CI) |
|--|----------------------|---------|-------------------------------|
| Mean number of drinks per day, <i>past 21 days</i>             |                      |         |                               |
| • Overall sample   | 1.73 (1.41, 2.11)    | <0.0001 | 0.80 (0.74, 0.85)             |
| • Individual trial samples                                     |                      |         |                               |
| ◦ MALD   | 4.31 (1.61, 11.54)   | 0.004   | 0.78 (0.69, 0.88)             |
| ◦ At-risk drinking   | 1.57 (1.04, 2.36)    | 0.035   | 0.68 (0.55, 0.80)             |
| ◦ Alcohol use disorder   | 1.26 (1.01, 1.57)    | 0.04    | 0.68 (0.54, 0.82)             |
| <u><i>Sensitivity analyses (among overall sample only)</i></u> |                      |         |                               |
| Mean number of drinks per day, <i>past 14 days</i>             | 1.66 (1.37, 2.00)    | <0.0001 | 0.79 (0.73, 0.85)             |
| Mean number of drinks per day, <i>past 7 days</i>              | 1.60 (1.34, 1.91)    | <0.0001 | 0.78 (0.72, 0.84)             |
| Mean number of heavy drinking days, <i>past 21 days</i>        | 1.24 (1.13, 1.36)    | <0.0001 | 0.74 (0.68, 0.80)             |

CI, Confidence interval; ROC, Receiver operating characteristics curve; TLFB, Alcohol Timeline Followback;

\* this is the OR of PEth > 20ng/mL. The OR are calculated based on 1 unit increase in each of the TLFB measures

**Table 3.**

Spearman correlation for the relationship between TLFB self-reported alcohol use by TLFB and PEth on a continuous scale

| Self-reported alcohol use                                      | Spearman Correlation (95% CI)* | P-value for H <sub>0</sub> : Rho=0 |
|--|--------------------------------|------------------------------------|
| Mean number of drinks per day, past 21 days                    |                                |                                    |
| • Overall sample   | 0.55 (0.46, 0.63)              | <0.0001                            |
| • Individual trial samples                                     |                                |                                    |
| ◦ MALD   | 0.56 (0.40, 0.68)              | <0.0001                            |
| ◦ At-risk drinking   | 0.41 (0.22, 0.58)              | <0.0001                            |
| ◦ Alcohol use disorder   | 0.29 (0.10, 0.45)              | 0.0034                             |
| <b><i>Sensitivity analyses (among overall sample only)</i></b> |                                |                                    |
| Mean number of drinks per day, past 14 days                    | 0.53 (0.44, 0.61)              | <0.0001                            |
| Mean number of drinks per day, past 7 days                     | 0.52 (0.43, 0.60)              | <0.0001                            |
| Mean number of heavy drinking days, past 21 days               | 0.44 (0.34, 0.530)             | <0.0001                            |

CI, Confidence interval; TLFB, Alcohol Timeline Followback

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