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BMJ Open

Efficacy of alcohol reduction interventions among people with HIV as evaluated by self-report and a phosphatidylethanol (PEth) outcome: protocol for a systematic review and individual participant data meta-analysis

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ABSTRACT

Introduction Unhealthy alcohol use is associated with a range of adverse outcomes among people with HIV (PWH). Testing the efficacy and promoting the availability of effective interventions to address unhealthy alcohol use among PWH is thus a priority. Alcohol use outcomes in intervention studies are often measured by self-report alone, which can lead to spurious results due to information biases (eg, social desirability). Measuring alcohol outcomes objectively through biomarkers, such as phosphatidylethanol (PEth), in addition to self-report has potential to improve the validity of intervention studies. This protocol outlines the methods for a systematic review and individual participant data meta-analysis that will estimate the efficacy of interventions to reduce alcohol use as measured by a combined categorical self-report/PEth variable among PWH and compare these estimates to those generated when alcohol is measured by self-report or PEth alone.

Methods and analysis We will include randomised controlled trials that: (A) tested an alcohol intervention (behavioural and/or pharmacological), (B) enrolled participants 15 years or older with HIV; (C) included both PEth and self-report measurements, (D) completed data collection by 31 August 2023. We will contact principal investigators of eligible studies to inquire about their willingness to contribute data. The primary outcome variable will be a combined self-report/PEth alcohol categorical variable. Secondary outcomes will include PEth alone, self-report alone and HIV viral suppression. We will use a two-step meta-analysis and random effects modelling to estimate pooled treatment effects; I^2 will be calculated to evaluate heterogeneity. Secondary and sensitivity analyses will explore treatment effects in adjusted models and within subgroups. Funnel plots will be used to explore publication bias.

Ethics and dissemination The study will be conducted with deidentified data from completed randomised controlled trials and will be considered exempt from additional ethical approval. Results will be disseminated through peer-reviewed publications and international scientific meetings.

PROSPERO registration number CRD42022373640.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This meta-analysis will be conducted with individual participant data (ie, meta-analysis using raw data), which is considered the gold-standard methodological approach for reviews.
⇒ The analysis approach will provide the ability to permit examination of the efficacy of alcohol interventions in improving HIV viral suppression, overall and as mediated by alcohol use.
⇒ The Grading of Recommendations Assessment, Development and Evaluation approach will be used to rate the quality of outcomes across studies.
⇒ Although studies from all over the world are eligible for inclusion, we will include studies that have abstracts in English and it is expected that the vast majority of included studies will be from the USA and other high-income countries, which limits generalisability.

INTRODUCTION

Engaging in unhealthy alcohol use, defined as drinking above the recommended limit of 14 drinks per week or 4 drinks per day for men and 7 drinks per week or 3 drinks per day for women,[1] is common among people with HIV (PWH) with an estimated prevalence of 42% in high-income and 25% in low-income and middle-income countries.[2 3] Unhealthy alcohol use among PWH is associated with worse adherence to HIV antiretroviral therapy (ART), viral non-suppression, increased HIV transmission risk and several comorbidities prevalent in HIV such as liver disease, cancer, cardiovascular disease, poor infectious disease outcomes (eg, tuberculosis), mental health problems, intimate partner violence and all-cause mortality.[4–8] While a substantial fraction of mortality is attributable to alcohol use in the overall population (5%),[9] the impact of alcohol use on morbidity and mortality is greater for PWH compared with people without HIV.[5] Collectively, these findings show that alcohol use is a major threat to the health of PWH and research on alcohol intervention efficacy in PWH is thus a priority.

A major challenge to the accurate evaluation of alcohol interventions is the valid measurement of alcohol consumption. Typically measured by self-report, alcohol consumption can be under-reported in both research[10–12] and clinical settings[13–16] due to social desirability bias, and this can be a particularly acute challenge among populations where alcohol is stigmatised[17] or prohibited by religious guidelines.[18] Recall bias (not remembering the amount or frequency of consumption)[19–21] and lack of knowledge/awareness of standard drink sizes and content may also bias self-report.[22–24] In randomised controlled trials (RCTs), such information bias can be particularly problematic if it is differential by treatment group and can cause an intervention to falsely appear to be more or less effective than it is, or mask a true effect.[25] Under-report of alcohol use can also have severe clinical implications as it can delay entry into evidence-based care and has been associated with increased mortality risk.[26]

Given the limitations of using self-report alone to measure alcohol use, objective alcohol measurements are critical to alcohol/HIV health outcomes and intervention research. One of the most promising objective measures is the biomarker phosphatidylethanol (PEth), an abnormal phospholipid formed in the blood only in the presence of alcohol use. It is detectable for 2–4 weeks after repeated high-risk (≥4 drinks/day) alcohol consumption and has a half-life of 4–10 days.[27 28] PEth has high sensitivity and specificity as a biomarker to identify unhealthy alcohol use[29–31] and is also detectable at low levels of alcohol use (eg, after a single drink).[32] PEth can be used as a continuous or categorical variable, with cut-offs of ≥8 ng/mL for any prior month alcohol use, ≥20 to ≥80 ng/mL for unhealthy alcohol use,[33–35] and ≥200 ng/mL for repeated high-risk alcohol use.[33 34] In alcohol intervention research, PEth combined with self-report (eg, Alcohol Use Disorders Identification Test (AUDIT), Alcohol Timeline Followback (TLFB))[26 36–39] may be an optimal approach to identify unhealthy alcohol use if either PEth or self-report scales exceed their respective thresholds because the combination of two specific measures increases the sensitivity beyond using either measure alone.[40 41] Both PEth and self-report have high specificity: PEth is highly specific because it is formed only in the presence of ethanol, and self-reported alcohol use is very specific because it is typically more prone to under-report than over-report.[42]

A meta-analysis of behavioural interventions to reduce alcohol use among PWH found that the interventions modestly reduced the quantity of alcohol consumption among 11 studies (Cohen's d=0.11).[43] The alcohol outcomes from these studies were all measured by self-report alone, and thus could be subject to the biases described above. The use of PEth has increased in recent years, including in new alcohol intervention trials among PWH. This provides an opportunity for the first time to conduct pooled analyses with PEth data to evaluate alcohol intervention efficacy among PWH. In this paper, we describe a protocol for an individual participant data (IPD) meta-analysis of alcohol intervention RCTs among PWH that included both PEth and self-report data. IPD meta-analyses are considered the gold standard of reviews and have several advantages compared with aggregate data systematic reviews and meta-analyses including greater quantity of data, the ability to standardise outcomes across trials, more flexibility in analysis approaches, the ability to conduct subgroup/moderator analyses and an enhanced ability to detect and address bias.[44] The review aims to:

- Estimate the efficacy of interventions to reduce alcohol use as measured by a combined self-report/PEth variable among PWH. Efficacy estimates will be compared with those generated when alcohol is measured by self-report alone and PEth alone.
- Estimate the efficacy of interventions to reduce alcohol use in improving HIV viral suppression among PWH, overall and as mediated by alcohol use measured via a combined self-report/PEth variable.

METHODS AND ANALYSIS

Patient and public involvement

Patients and the public were not involved in the design of the IPD meta-analysis protocol.

Protocol guidance and registration

This systematic review and IPD meta-analysis protocol was developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocol (PRISMA-P).[45 46] Results of the review will follow guidelines established through the PRISMA-IPD statement, which was developed specifically for IPD meta-analyses.[47] The protocol has been registered with the International Registration of Systematic Reviews (PROSPERO) on 30 November 2022 with registration number CRD42022373640. Any future modifications to the review procedures will be documented in updates to the PROSPERO registration.

Eligibility criteria

Study design

We will include RCTs (both individual and cluster RCTs) that feature two or more arms, at least one post-baseline assessment, and included alcohol use as a primary or secondary outcome. Cross-over and single-arm trials will be excluded as will quasi-experimental (ie, non-randomised) and observational study designs, systematic reviews and meta-analyses.

Participants

We will include RCTs that enrolled adult and adolescent participants (15 years of age or older) with HIV. Studies that only include children and/or only include people without HIV (or did not determine HIV status) will be excluded.

Interventions

We will include RCTs that test the efficacy of an intervention or multiple interventions in reducing alcohol use compared with an active or inactive control condition. We will include both behavioural and pharmacological interventions.

Outcomes

We will include RCTs that measure PEth AND self-reported alcohol use. Studies that only measured PEth or studies that only measured self-report will be excluded.

Timing

Included RCTs must have at least one follow-up time point after baseline. There are no restrictions on the length of time between baseline and follow-up. Studies can have single or multiple follow-up time points.

Setting

There are no restrictions on study setting.

Language

We will include studies that have abstracts reported in English.

Dates

We will include studies that complete data collection by 31 August 2023.

Information sources and search strategy

We will conduct tailored searches in the following academic databases: PubMed, PsycINFO, Cochrane Central, Embase, CINAHL and Lilacs. Table 1 displays the expected search terms. We will include all possible combinations of search terms within six categories (A+B+C+D+E+F) in the title, abstract and/or full text: (A) study design, (B) alcohol use, (C) intervention, (D) PEth, (E) self-report and (F) HIV. We will also search ClinicalTrials.gov for ongoing studies that may have data

Table 1 Expected search terms for meta-analysis

(A) Study design	(B) Alcohol use	(C) Intervention	(D) PEth	(E) Self-report	(F) HIV
Clinical trial	Alcohol	12-step	1-palmitoyl-2-oleoyl-sn-glycero-3-phosphoethanol	Alcohol, Smoking, and Substance Involvement Screening Test	AIDS
Experimental design	Alcoholism	Acamprosate	PETH	Alcohol Use Disorders and Associated Disabilities Interview	HIV
Randomised trial	Alcohol abuse	Antabuse	PEth	Alcohol Use Disorders Identification Test	CD4
Randomized trial	Alcohol addiction	Brief intervention	Peth	Alcohol Use Disorders Identification Test-Consumption	Viral load
Randomised clinical trial	Alcohol consumption	Chantix	Phosphatidylethanol	ASSIST	Adherence
Randomized clinical trial	Alcohol dependence	Cytisine Intervention	Phosphatidyl ethanol	AUDADIS	ART
Randomised controlled trial	Alcohol intoxication	Cognitive behavioral therapy		AUDIT	
Randomized controlled trial	Alcohol misuse	Contingency management		AUDIT-C	
	Alcohol-related disorders	Counseling		CAGE	
	Alcohol use	Counselling		CIDI	
	Alcohol use disorder	Detoxification		Composite International Diagnostic Interview	
	Binge drinking	Disulfiram		Timeline Followback	
	Drinking	Gabapentin		TLFB	
	Ethanol	Medical management		Self-report	
	Harmful alcohol use	Motivational interviewing		Short Inventory of Problems	
	Hazardous alcohol use	Naltrexone		SIP	
	Heavy alcohol use	Prevention		SCID-AUD	
	Heavy drinking	Psychotherapy			
	Heavy episodic drinking	Program			
	Problem drinking	Rehabilitation			
	Risky drinking	Self-help			
	Unhealthy alcohol use	Therapy			
		Treatment			
		Varenicline			

collected prior to 31 August 2023 using the following keyword search: peth OR phosphatidylethanol AND alcohol AND HIV.

In preparation for this review, the authors identified 15 studies (ongoing or completed) that meet the established eligibility criteria. The search strategy will first be piloted to ensure it results in those studies being identified (among the studies known to have been published). If the search strategy fails to identify the known studies, we may modify the search terms and/or information sources. Any modifications will be recorded in the PROSPERO registration.

The search strategy will be executed by a health services librarian with experience in systematic reviews. The librarian will upload results from all databases to Covidence. We will record the total number of records (titles and abstracts) that were identified. Duplicate entries will be removed. Two reviewers will independently conduct a review of all titles/abstracts in the list. The initial screening will consist of evaluating the TITLE and ABSTRACT (if available) of the documents that resulted from the search. Discrepancies will be resolved through discussion or, if necessary, by a third reviewer. Reviewers will classify studies as 'yes' if the title and abstract describe an alcohol intervention RCT that includes persons with HIV and both self-report and PEth were measured. Studies will be labelled 'maybe' if they describe an alcohol intervention RCT among persons with HIV but it is not clear from the abstract if self-report and/or PEth were measured. Studies will be marked 'no' if they are not an alcohol intervention RCT among PWH.

We will retain all articles classified as 'yes' or 'maybe' for full-text review. Two reviewers will independently screen the full text of retained articles based on the full eligibility criteria. Full-text review screening will similarly be completed using Covidence software. Reviewers will meet to discuss any discrepancies. If needed, a third reviewer will resolve discrepancies that were not resolved through discussion. During the full text review process, we will record reasons for excluding studies.

Once the list of included full texts from the searches is finalised, two independent reviewers will search the reference lists of all included studies and include any additional eligible articles. Discrepancies will be resolved through discussion or by a third reviewer, if needed. The review results will then be shared with the full investigator team and additional articles may be included based on investigator input and knowledge of known papers or studies that are relevant and that meet eligibility criteria. We will contact the principal investigators of all included studies to inquire about participating and their willingness to contribute data for the IPD meta-analysis. Studies for which we will not be able to have access to IPD or for which data collection will not be completed by 31 August 2023 will be excluded from the IPD meta-analysis but published data may be used in a sensitivity meta-analysis (not using IPD). The search strategy is summarised in the PRISMA flow chart (figure 1). The search will take place prior to 31 August 2023.

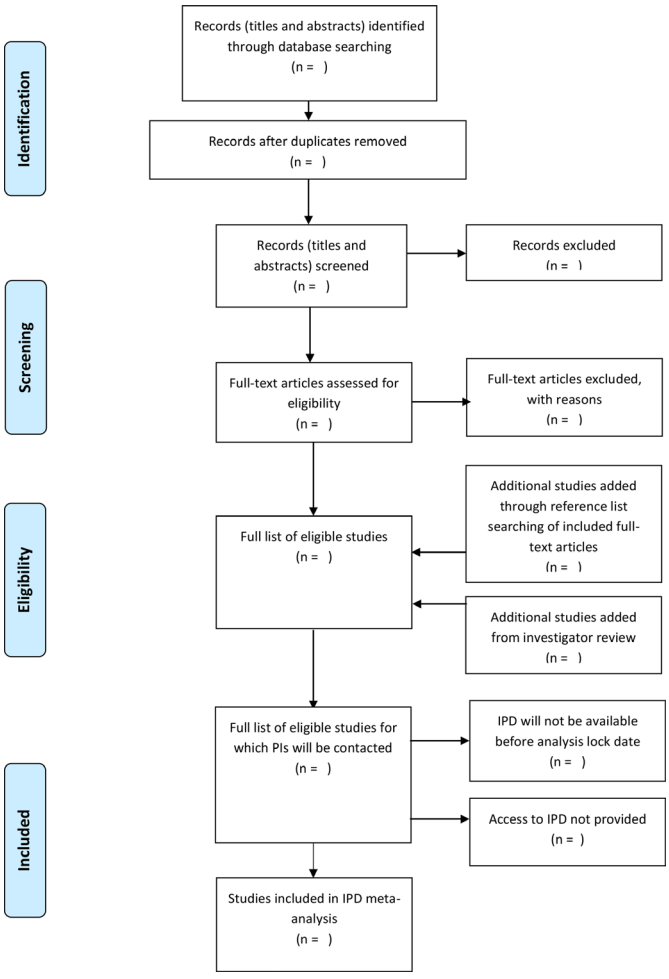

Figure 1 Flow diagram. IPD, individual participant data.

Data extraction and management

Data use agreements will be completed with all principal investigators who have agreed to share IPD. We will obtain raw, participant-level, deidentified data and study protocols from all included studies. Data from eligible studies will be merged and harmonised into a central database for which common variable names are created. Variables to be requested from all studies include: randomisation status (intervention or control), PEth level, self-reported alcohol consumption (eg, AUDIT, AUDIT-Consumption (AUDIT-C), Alcohol TLFB, quantity/frequency measures), HIV viral suppression, age, biological sex, race/ethnicity, setting (eg, low/high resource), intervention content (eg, cognitive behavioural therapy, motivational interviewing, pharmacological), intervention dose (eg, number and duration of sessions), intervention format (eg, individual vs group, in-person vs remote). For studies that were eligible for inclusion but for which we could not access IPD, we will enter study characteristics and relevant data into standardised forms for possible use in a sensitivity analysis.

Outcomes

The primary outcome variable will be a combined self-report/PEth categorical variable. The choice of the combined categorical variable as primary was made because PEth measured continuously can be heavily skewed with wide CIs, and because PEth is not 100% sensitive.[29] We will construct a self-report/PEth composite variable representing unhealthy alcohol use, as in prior studies.[36–38] This variable will be positive for unhealthy alcohol use if PEth is ≥50 ng/mL, a cut-off used previously for unhealthy alcohol use[37] and/or if AUDIT-C is positive (≥4 among males; ≥3 among females).[48] We expect that most included trials will have the full AUDIT (which includes AUDIT-C) or AUDIT-C itself as a self-report measure. If AUDIT-C was not measured in a trial, we will transform the self-report measure that was included to create a categorical variable of unhealthy alcohol use using established guidelines when possible (eg, number of drinks/day in the Alcohol TLFB). We will also explore using cut-offs consistent with high-risk/excessive alcohol use, for example, PEth ≥200 ng/mL[49] and AUDIT-C ≥6.[50] We will additionally explore weighting the self-reported alcohol use variables by the concordance of self-report with PEth. The weights will be the differences between the z-standardised volume of alcohol consumed and the z-standardised PEth. We expect most studies will have detected the most common PEth homologue (16:0/18:1), however, if a different homologue was used, we will transform to approximate 16:0/18:1.

A secondary outcome will be PEth measured continuously. For example, we may measure the relative difference in PEth level from baseline to follow-up (PEth at baseline—PEth at follow-up)/(PEth at baseline). Because PEth is not linear above 1000 ng/mL, we may first truncate all observations at this value. This relative difference approach will help account for interperson PEth variability in PEth formation,[27] and the percent difference will measure changes in alcohol use that are clinically important (eg, a change of 50 ng/mL is more meaningful at the lower levels of PEth), while retaining the maximum amount of information from the original PEth measurements. We may also conduct a log transformation of the continuous PEth variable.

We will also conduct analyses using self-report as the outcome variable, using methods comparable to those in the previously published aggregate meta-analysis on alcohol interventions among PWH.[43] We will qualitatively compare the results obtained using the combined PEth/self-report variable to self-report alone and PEth (measured continuously) alone. Finally, HIV viral suppression (yes/no, cut-off test dependent) will also be a secondary outcome to evaluate the effectiveness of interventions on viral suppression, overall and as mediated by alcohol use (measured using the combined variable, PEth alone and self-report alone).

Data synthesis

All randomised patients will be included following an intention-to-treat principle. We will analyse all studies separately to confirm our results with those of the original trial analysis and resolve any discrepancies. Analyses will be conducted by using R[51] and Stata (version 15).[52]

The main statistical analysis will be a two-step meta-analysis, in which treatment effects (intervention vs control) are calculated using the IPD within each study using generalised linear models and an intent to treat approach. We will then combine these in a random effects model (using restricted maximum likelihood) and create summary forest plots using I^2 to estimate heterogeneity. We will conduct adjusted and unadjusted analyses and examine effect modifiers in a similar fashion. We will construct these models for the primary outcome and all the secondary outcomes, using the appropriate models: linear models for PEth differences and the volume of alcohol consumed, logistic models for viral non-suppression and dichotomous measures of alcohol use (including the combined self-report/PEth variable). We will compare the strength of the effect of the intervention using PEth versus self-report alone, and in combination with PEth calculating Cohen's d statistics for continuous models and ORs for categorical models. Primary analyses will be conducted separately among the behavioural intervention studies and among the pharmacological intervention studies when possible.

For studies that have multiple follow-up visits with PEth measurements, we will also examine relative differences from baseline PEth level at each time point using an interaction term with time in regression models and mixed-effects models. To examine the potential mediating effect of changing alcohol use (measured by PEth) on an effect of the interventions on viral suppression, we will conduct mixed effects regression with an interaction between intervention arm and time (as above), and another interaction between intervention arm and PEth levels, within each participant in models of viral suppression. The coefficient for the latter interaction will represent the effect of changes in PEth level over time on viral suppression.

Heterogeneity/sensitivity/risk of bias analyses

Statistical heterogeneity will be examined using the t^2 statistic to provide an estimate of between-study variance and the I^2 statistic providing an estimate of the proportion of total variance of the treatment effects. In addition, the p value for Cochran's Q statistic will be assessed. If moderate heterogeneity is observed (I^2>50%), possible causes will be examined by selectively eliminating studies in the analysis. We will explore whether there are differences in covariates such as demographics, location/region or patient mix that might explain the heterogeneity.

We will conduct sensitivity analyses that exclude studies judged to be of low quality. We will construct funnel plots to examine the risk of publication bias and small study effects using Begg's and Egger's statistics.[53] We will conduct influence analyses to determine whether one

or more study unduly influences the results by removing individual studies and recalculating the analyses. We will conduct meta-regressions by sample size, study year and other covariates to examine bias.

Additionally, we may conduct the following secondary analyses: (A) adjusting for time reference variation of alcohol use self-report measurements at follow-ups across studies (eg, past 3-month reference period and past 12-month reference period) and (B) per-protocol analysis in which only treatment completers are included. Finally, if a sufficient number of studies are identified for which IPD are not available (ie, >3), we may conduct a secondary analysis that will combine the RCTs without IPD with the summary statistics from the IPD analyses to identify possible significant differences between the strictly IPD meta-analysis and the overall summary meta-analysis.

Missing data

There are likely to be some studies that are eligible but do not provide data. From these studies we are unlikely to be able to extract effect sizes for our primary outcome (self-report/PEth combined variable), but we may be able to obtain self-report outcomes, and/or viral suppression. We will examine the effect of including these data in the analyses where possible. We will also examine the extent and pattern of missing individual-level data. We will conduct multiple imputation using chained equations (within each study) if the missing at random assumption seems reasonable.[54]

Confidence in cumulative estimate

We will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to rate the quality of outcomes across studies.[55] GRADE accounts for metrics including risk of bias (including checking the integrity of the data, such as the randomisation pattern, as recommended by the PRISMA-IPD statement), inconsistency, indirectness, imprecision, publication bias, effect size, dose response and confounding in determining the quality rating (high, moderate, low, very low) for each outcome across included studies. We will enter these data into statistical software and use these scores in the sensitivity analyses described below.

ETHICS AND DISSEMINATION

No human subjects will be involved in this research. The meta-analysis will be conducted among coded data. Wide dissemination of review results will be conducted through peer-reviewed publications and presentations at international scientific fora.

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Contributors JK is the first and corresponding author. JAH conceived of the study. JAH, JK and IA designed the review. JK wrote the first draft of the article, which was critically edited and approved by IA, RF, AS, NE, SP, PC, KS-A, CK, JM, AAC, EJE, SW-K, CP, SMK, GC, JA, VFG, RLC, WM, NM, EB, EK, DF and JAH.

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