Trials

STUDY PROTOCOL

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Gabapentin to achieve HIV viral load suppression in people with risky drinking in Mbarara, Uganda: study protocol for a randomized, double-blinded, placebo-controlled trial (GRAIL)

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Abstract

Background Ending the HIV epidemic requires achieving HIV viral load (HVL) suppression for key populations including those with risky drinking. Gabapentin can decrease alcohol use and thus holds potential for improving medication adherence and HIV viral load suppression for individuals with HIV and risky drinking.

Methods The aim of this paper is to describe the protocol for a randomized, double-blinded, placebo-controlled trial (GRAIL [Gabapentin to Reduce Alcohol and Improve viral Load suppression]), to test the efficacy of gabapentin versus placebo on achieving undetectable HIV viral load among people with HIV with risky drinking. We will recruit and randomize 220 people with detectable HIV viral loads (≥ 200 copies/ml) and risky drinking. Participants will be randomized 1:1 to receive either gabapentin (1800 mg/day target dose) or placebo for 3 months in a double blind design. Both arms will receive a 5-min evidence-based counseling session aimed at reducing alcohol use. The primary outcome is undetectable viral load (< 200 copies/ml) at 3 months. Other secondary outcomes include undetectable viral load at 6 and 12 months, biomarker-confirmed recent alcohol consumption, antiretroviral therapy (ART) adherence, engagement in HIV care and pain severity. This study will take place in Mbarara, Uganda, as the country ranks among the top five for alcohol consumption globally and has 1.4 million people living with HIV.

Discussion GRAIL tests the efficacy of gabapentin, a medication to decrease alcohol use to achieve HIV viral load suppression. This trial may identify a treatment strategy to prevent the transmission of HIV and improve health outcomes among a high-risk HIV population, specifically those with risky drinking.

Trial registration This trial has been registered at ClinicalTrials.gov (NCT05443555) on June 29, 2022.

Keywords Uganda, HIV, Alcohol use, Viral load suppression , Gabapentin, RCT

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Background

Over 1.4 million people in Uganda are living with HIV. Among this group, 90% are aware of their HIV status, 84% report receiving antiretroviral therapy (ART), and 79% of people with HIV (PWH) have achieved HIV viral load (HVL) suppression [1]. These statistics represent great progress, yet the country is facing barriers on its path to achieving the UNAIDS 95-95–95 HIV targets (i.e., detection, on medication, HVL suppression) [2]. The prevalence of heavy drinking is high in Uganda, with more than half of the adult population who drink (56.9%) reporting heavy episodic drinking [3]. As of 2020, total per capita consumption of pure alcohol among drinkers over the age of 15 years in Uganda is 27L [4], and total per capita consumption of pure alcohol among the general population over the age of 15 years is 12.2L [5]. This places Uganda at the top of the list among African countries for alcohol consumption [6] and in the top five countries globally [7]. Alcohol consumption has negative impacts across the HIV care cascade, including effects on engagement in HIV care, medication adherence, and HVL suppression [8, 9]. The quantitative effect of alcohol use on viral non-suppression was significant in one meta-analysis (pooled odds ratio: 2.47; 95% confidence interval: 1.58–3.87) [8]. An intervention targeting alcohol consumption in PWH with risky drinking and without HVL suppression has the potential to improve HIV outcomes such as medication adherence and HVL suppression. Increasing viral suppression rates could decrease the incidence of new HIV infections exemplifying "treatment as prevention". Prior studies have demonstrated that gabapentin is efficacious for decreasing alcohol consumption [10–13], mitigating neuropathic pain [14], and promoting relapse prevention after alcohol cessation [15] but its impact on outcomes in PWH with risky drinking has not been evaluated [10–13]. By reducing alcohol consumption among PWH who are not virally suppressed, gabapentin may support improved engagement in medical care and adherence to ART, and in turn, promote HIV viral load suppression. Uganda's high HIV and alcohol use burden make this setting suitable for studying gabapentin in this population. This paper describes the protocol of the Gabapentin to Reduce Alcohol and Improve viral Load suppression (GRAIL) – Promoting "Treatment as Prevention."

Methods

GRAIL is a randomized, double-blinded, placebo-controlled clinical trial designed to evaluate the efficacy of gabapentin versus placebo in achieving undetectable HVL in 220 PWH who engage in recent risky drinking. Risky drinking is operationalized as a positive Alcohol Use Disorders Identification Test - Concise (AUDIT-C) [16–18] and urine ethyl glucuronide (EtG) test [19, 20]. Participants will be randomized 1:1 to receive either gabapentin or placebo for 3 months; both arms will receive a brief intervention to reduce alcohol use.

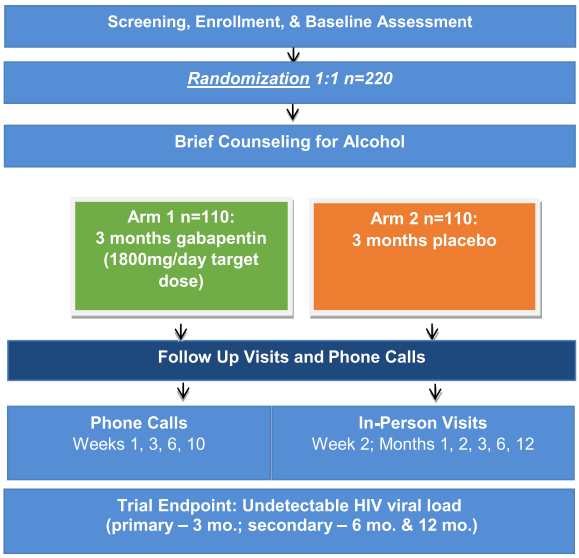


Fig. 1 GRAIL study design

Study setting

The study will be implemented at Mbarara University of Science and Technology (MUST) in Mbarara, Uganda. MUST is a major educational, scientific, and clinical medical institution. Recruitment will occur at the Immune Suppression Syndrome (ISS) Clinic at the Mbarara Regional Referral Hospital in Uganda, HIV Care Clinics (e.g., Mbarara City Council Health Centre 4 and others within and outside the city and district), as well as through snowball recruitment. The ISS Clinic has provided HIV care since November 1998. The adult care section of the clinic currently cares for over 11,500 adults with HIV. The SPIRIT checklist of recommended items to address in a clinical trial protocol is available as Additional File 1. See Fig. 1 for study flow and Fig. 2 for the planned schedule of enrollment, intervention and assessments.

Participants and recruitment

In Uganda, clinics typically initiate ART for patients newly diagnosed with HIV. Therefore, our criteria require that a participant has been diagnosed with HIV for at least six months, and their detectable HVL must be recorded at least six months post-diagnosis to strongly suggest non-adherence to ART. Participants will be eligible if they meet the following additional criteria: 18 years

	STUDY PERIOD						
	Enrollment	**Allocation**	**Baseline**	**Medication visits**	**Study visits**		
TIMEPOINT	0	0	0	1w-10w	3m	6m	12m
ENROLLMENT:							
Eligibility screen	X						
Informed consent	X						
Randomization		X					
INTERVENTION:							
Active gabapentin			X	X			
Placebo			X	X			
ASSESSMENTS:							
Demographics (e.g., age, sex, education, relationship status, etc.)			X				
Primary outcomes (undetectable HVL)					X		
Secondary outcomes (undetectable HVL, alcohol consumption, pain severity, ART adherence, engagement in HIV care)						X	X

Fig. 2 Schedule of enrollment, intervention, and assessments (SPIRIT figure)

or older; positive EtG urine test (300 ng/ml cutoff); able and willing to comply with all protocols and procedures; and living within 2 hours travel time of the study site as a practical criterion to facilitate retention and enable follow-up visits in this rural Ugandan setting. They will be excluded for the following: not fluent in English or Runyankole; cognitive impairment resulting in inability to provide informed consent based on research assistant assessment; pregnant, planning to become pregnant in the next 3 months, or breastfeeding; taking gabapentin/pregabalin in past 30 days; taking any medication for alcohol use disorder; known hypersensitivity to gabapentin; enrolled in another HIV research study seeking viral load suppression; and has an unstable psychiatric illness. Study eligibility criteria are detailed in Table 1. A clinic staff member will review electronic medical records to identify patients with upcoming clinic appointments who potentially meet eligibility criteria. Patients meeting the initial eligibility criteria (i.e., HIV diagnosis and most recent detectable HVL) will be approached during their appointment to assess interest in study participation. Those interested will be screened by a study research

Table 1 GRAIL eligibility criteria

Inclusion criteria
18 years or older
Having an HIV diagnosis for at least 6 months (assessed via medical charts)
Current (within 2 months) detectable HIV viral load at least 6 months after HIV diagnosis (assessed via medical charts or study test)
Positive ethyl glucuronide (EtG) urine test (300 ng/ml cutoff)
Able and willing to comply with all study protocols and procedures
Living within 2 hours travel time of the study site
Exclusion criteria
Not fluent in English or Runyankole
Cognitive impairment resulting in inability to provide informed consent based on research assistant assessment
Pregnancy, planning to become pregnant in next 3 months, or breast feeding (pregnancy assessed via study test)
Taking gabapentin/pregabalin in past 30 days (self-report)
Taking any medication for alcohol use disorder (self-report)
Known hypersensitivity to gabapentin (self-report)
Enrolled in another HIV research study seeking viral load suppression (self-report)
Unstable psychiatric illness (i.e., answered yes to any of the following: past 3 months active hallucinations; mental health symptoms prompting a visit to the ED or hospital; mental health medication changes due to worsening symptoms; presence of suicidal ideations)

assistant (RA), who is a clinical officer, to determine further eligibility. In addition, the GRAIL study data manager and project coordinator will consult with clinic counselors overseeing the non-suppression registry to identify patients with a recent detectable HVL test who were not captured through the initial screening process.

RAs will either meet potential participants at the clinics following their routine clinic visit or will make an appointment to meet in person at a later date at one of the recruitment clinics. For participants unable to travel to the clinic, RAs will provide transportation from their home to the clinic. RAs will introduce the study to eligible participants, gauge their interest and explain the purpose of the study. If further eligibility is established, the RA will seek informed consent. Randomization follows the completion of the baseline assessment.

Randomization

Randomization will be conducted and monitored by the data management team. Participants will be randomized in a 1:1 ratio using permuted blocks with a fixed block size of two, stratified by: i) self-reported alcohol use severity score (Alcohol Use Disorders Test (AUDIT) > 20 vs. ≤ 20) and ii) clinic site. We assume that participants with severe alcohol use may be less likely to reach HVL suppression over the study period than those who are drinking less alcohol.

Randomized group allocations will be concealed using scratch-off cards. Before recruitment, the study pharmacist will receive a randomization list, generated by our data management team. This list will link each sequential card number to a unique 5-digit randomization code corresponding to the assigned treatment arm (gabapentin and placebo). Each scratch-off card will display only the card number and the randomization code will remain hidden until the participant scratches off the covering. The AUDIT score stratum is distinguished by the color of the scratch card (i.e., yellow for AUDIT > 20 and green for AUDIT ≤ 20).

During randomization, the RA will present the participant with the top four sequential scratch-off cards from the appropriate AUDIT pile. The participant will pick one card, scratch it off, and reveal the randomization assignment, ensuring transparency and participant engagement in the randomization process. The RA will then dispense the medication package labeled with the corresponding randomization number. The next sequential card will be added to the pile, ensuring that four cards are consistently available for subsequent participants.

Intervention

Eligible participants will be randomly assigned into one of two study arms: (1) gabapentin (up to 600 mg (2 pills) three times a day [i.e., 1800 mg/day target dose]) for 3 months vs. (2) placebo for 3 months. A review article by Quintero (2017) examined potential drug-drug interactions involving gabapentin and found that multiple studies indicated gabapentin has little interaction with other medications [21]. No specific timing adjustments relative to ART medications are generally necessary and gabapentin may be useful for specific patient populations, including individuals with HIV.

At study initiation, the medication will be provided by trained clinical officers, who will instruct participants in proper medication administration and adherence. Study medications were purchased from EVA Pharma, in Cairo, Egypt. Placebo medications do not contain active ingredients. The placebo and active study medications are indistinguishable by packaging, appearance and taste to allow for double blinding. The study pharmacist will package study medications into paper envelopes. Participants and study team members will be blinded to assigned treatment.

Medication dosing is based on Mason et al. [11]. Dosing is titrated up over 3 weeks, starting with a daily dose of 300 mg (1 capsule/day) in week 1, followed by a daily dose of 900 mg (3 capsules/day) in week 2, up to a target daily dose of 1800 mg (6 capsules/day) in week 3. The target dose of 1800 mg per day is sustained from weeks 3 through day 4 of week 12. Then, the dose is tapered down to 900 mg in days 5–7 of week 12, and medication is discontinued at the end of week 12. If a participant in any group experiences an adverse event, the symptom is documented and monitored at each study visit. If reductions in medication are required due to side effects, the participant will be advised to reduce their dose to that of the prior week. The GRAIL medication schedule can be seen in Table 2. Participants will be instructed to bring any unused capsules to their upcoming in-person study visit.

In addition to the study medications, all participants will receive brief (5 minutes) evidence-based counseling based on the severity of their alcohol use disorder (per DSM-5) from the study assessment at baseline. This counseling approach was adapted from the NIAAA Clinician's Guide [22]. We will offer additional counseling sessions conducted by the GRAIL study counselors to participants who report any current drinking at the 3-month time point.

Adherence

Medication adherence will be assessed at each medication check-in using capsule counts and self-report. At each medication check-in visit, medication instructions will be reviewed with the participant and strategies to support adherence will be discussed. To further

Table 2 GRAIL medication dosing schedule

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Week 1: 1 capsule per day; 7 capsules total							
Morning	1 capsule	1 capsule	1 capsule	1 capsule	1 capsule	1 capsule	1 capsule
Afternoon							
Evening							
Total	1	1	1	1	1	1	1
Week 2: 3 capsule per day; 21 capsules total							
Morning	1 capsule	1 capsule	1 capsule	1 capsule	1 capsule	1 capsule	1 capsule
Afternoon	1 capsule	1 capsule	1 capsule	1 capsule	1 capsule	1 capsule	1 capsule
Evening	1 capsule	1 capsule	1 capsule	1 capsule	1 capsule	1 capsule	1 capsule
Total	3	3	3	3	3	3	3
Week 3, 4, 5, 6, 7, 8, 9, 10, 11: 6 capsule per day; 42 capsules total							
Morning	2 capsules	2 capsules	2 capsules	2 capsules	2 capsules	2 capsules	2 capsules
Afternoon	2 capsules	2 capsules	2 capsules	2 capsules	2 capsules	2 capsules	2 capsules
Evening	2 capsules	2 capsules	2 capsules	2 capsules	2 capsules	2 capsules	2 capsules
Total	6	6	6	6	6	6	6
Week 12: 33 capsules total							
Morning	2 capsules	2 capsules	2 capsules	2 capsules	1 capsule	1 capsule	1 capsule
Afternoon	2 capsules	2 capsules	2 capsules	2 capsules	1 capsule	1 capsule	1 capsule
Evening	2 capsules	2 capsules	2 capsules	2 capsules	1 capsule	1 capsule	1 capsule
Total	6	6	6	6	3	3	3

increase medication adherence, a text message will be sent out daily reminding participants to take their study medication. To ensure participant privacy and to accommodate those who may not wish to disclose their involvement in a research study or share their phones, the message will read: "Please remember GRAIL." Participants will be able to reduce the frequency to 2 days per week or opt out of text message reminders entirely at any time throughout the study.

Study outcomes

The primary outcome is undetectable HVL (< 200 copies/ml) at 3 months, with secondary outcomes being undetectable HVL at 6 and 12 months. We chose the 3-month time-point as our primary outcome for two reasons. First, gabapentin's impact on alcohol use begins to occur in the first four weeks [23] of its use. Second, 3 months is a sufficient amount of time for ART medications to suppress HVL, if adherence is adequate and viral resistance is not an issue. Secondary outcomes will be assessed at 6 and 12 months to evaluate the durability of the intervention and its longer-term clinical impact. In order to explore potential mechanisms by which gabapentin may lead to HVL suppression, we will assess the impact of gabapentin compared to placebo on the following secondary outcomes: (a) alcohol consumption; (b) pain severity; (c) ART adherence; and (d) engagement in HIV care.

Study visits

Participants will be assessed at baseline, 3, 6, and 12 months post enrollment, along with shorter medication visits by phone at weeks 1, 3, 6 and 10 and shorter medication visits in-person at weeks 2, 4, and 8. All follow-up study visits will take place at the clinic from where the participant was recruited or by phone.

Participants will receive a meal at each study visit, along with either 1 kg of rice and one bar of soap, or two bars of soap, as compensation. Transport costs will also be reimbursed: 20,000 UGX (5.33 USD) for those living within 20 km, 30,000 UGX (8 USD) for 20–40 km, and up to 45,000 UGX (12 USD) for 40–60 km from the study site.

The study will employ a driver to provide transportation to the clinic for participants who require a ride to their study visit appointments.

Questionnaires

Components of the baseline and follow-up assessments are listed in Table 3. At baseline and at follow-up visits, we will collect participants' ART history and adherence via questionnaire, including the timing of ART initiation, current ART use, and self-reported adherence assessed

Table 3 GRAIL data and sample collection

Administered assessment		Baseline	Short check ins	3 months	6 months	12 months
Demographics [24]		X				X
Income level		X				X
HIV testing		X				
ART medication history and adherence [25]		X	X	X	X	X
Healthcare utilization		X		X	X	X
Alcohol Use Disorders Identification Test (AUDIT) [26]		X		X		X
DSM-5 Alcohol Use Disorder		X		X		X
30-day Alcohol Timeline Followback (TLFB) [27]		X		X	X	X
Penn Alcohol Craving Scale[28]		X		X	X	X
Readiness to quit alcohol [29]		X		X	X	X
Tobacco use (Fagerström) [30]		X		X	X	X
HIV risk categories		X				
Depressive symptoms (CESD-10) [31]		X		X		X
Anxiety (GAD-7)[32]		X		X		X
Perceived Alcohol Stigma Scale [33]				X		
HIV stigma [34–36]				X		
Co-morbidities [37]		X				
Brief Pain Inventory (BPI-SF) [38]		X		X	X	X
Medications in past 7 days (prescription and non-prescription medications)		X		X	X	X
Other substance use (e.g., mairungi, marijuana, hookah, powder, kerosene) Drug use		X		X	X	X
Social Support Scale [39]		X				X
Veterans Rand 12-Item Health Survey [40]		X				X
Symptoms/events checklist		X	X	X		
Study medication adherence (pill count and visual analog scale)			X	X		
Medication Satisfaction Questionnaire [41]				X		
Study medication tolerability			X	X		
Willingness to continue study medication				X		
Clinical values						
	Screening	**Baseline**	**Short check ins**	**3 months**	**6 months**	**12 months**
EtG	X					
HVL		X		X	X	X
CD4		X				
Creatinine		X				
HIV drug resistance				X		
PEth		X		X	X	
Urine for pregnancy test	X		X			

using a visual analog scale. At each in-person study visit, RAs will measure and record participants' weight and blood pressure. Height will be measured at the baseline visit. Over the course of the study, we will review medical charts to obtain HIV treatment history. Participants will be asked to provide consent so that their data may be used for potential future ancillary studies.

Laboratory testing and results

Blood will be collected throughout the study. CD4 count and creatinine will be tested at baseline. Phosphatidylethanol (PEth, an alcohol biomarker) [42] will be tested at baseline and 3 months. HIV viral loads will be tested at 3, 6, and 12 months. Participants with a creatinine clearance of < 60 mL/min will have their study medication dose reduced per clinical recommendations for prescribing gabapentin for patients with chronic kidney disease. Additionally, at the 3-month study visit, all participants will be asked to provide blood for an HIV drug resistance test, however, the test will only be conducted for those with a detectable HVL at 3 months to assess if the HIV is resistant to that participant's ART regimen. A copy of the HIV drug resistance results will be filed in participants' medical charts, which is standard research practice with the local team. The participant's medical team will be notified when necessary or if urgent follow-up is needed.

Urine samples will be collected during screening to test for pregnancy and alcohol use, the latter by using an ethyl glucuronide (EtG) dip test. An EtG dip test is a type of urine test used to detect the presence of alcohol. In this study, we will use a test with an 80-hour detection window and a 300 ng/mL cutoff. Additionally, urine will be collected for women during in-person medication check-ins and at 3 months to confirm the participant is not pregnant. Participants found to be pregnant will discontinue their study medication but will continue follow-up assessments for the duration of the study.

Retention of study participants

Participants will be asked to provide contact information for 2–3 alternative contacts (e.g., friends and family) who can assist in the event of being lost to follow-up. Efforts to improve retention for all participants will include the provision of refreshments during study visits, reimbursements for travel expenses, and conducting home visits when necessary.

Adverse events and safety monitoring

At baseline, participant symptoms will be assessed to document any chronic conditions or symptoms that existed prior to the introduction of study medication. These will be documented on the baseline event form and will be reviewed and compared to reported adverse events throughout the study. During follow-up, symptoms will be assessed weekly for the first month, and biweekly thereafter while the participants are administered study medication. If a participant experiences a severe or medically significant but not immediately life-threatening symptom, the RA will increase monitoring frequently for safety, and the team will consider adjusting the medication dose or stopping it. Participants may be unblinded if there is an urgent medical need, as determined by the clinician evaluating the participant. If a participant is unblinded, study medication may be discontinued if deemed medically necessary.

Any event that meets the criteria for an adverse event (AE), serious adverse event (SAE), or unanticipated problem will be recorded. All events will be reviewed by a study physician. AEs and SAEs will be periodically presented to and reviewed by an external Data and Safety Monitoring Board (DSMB), the Institutional Review Boards (IRBs), and the Uganda's National Drug Authority.

Data management

The Biostatistics and Epidemiology Data Analytics Center at Boston University will provide statistical collaboration in the design and analysis of the GRAIL trial. Electronic questionnaires will include programmed skip patterns and range checks, minimizing errors at data capture. Participant screening, assessment, tracking, and randomization will utilize Research Electronic Data Capture (REDCap) mobile.

Analytic methods

The study will use an intention-to-treat analysis that includes all participants according to their randomized assignment. Descriptive statistics (e.g., depressive symptoms, income level, and social support) will be calculated for variables at baseline and follow-up to assess whether there appear to be any differences across treatment arms. Spearman correlation analyses will be performed to identify pairs of variables that may be collinear. In addition, the variance inflation factor will be assessed to detect possible collinearity.

The primary outcome for this study is undetectable HVL (<200 copies/ml) at 3 months. The primary analysis will use multivariable logistic regression analyses to control for the randomization stratification factors to improve efficiency (i.e., AUDIT >20, clinic site). If any baseline factors appear to differ by randomized group, additional sensitivity analyses will be conducted controlling for these factors to assess for potential confounding. We will conduct a preliminary analysis for the primary binary outcome using chi-square test. Other binary outcomes (e.g., heavy alcohol consumption [defined as PEth ≥ 50 ng/mL], adherence to ART [defined as taking $\geq 80\%$ of prescribed medication via visual analog scale], engagement in HIV care [defined as ≥ 1 HIV visit in the past 3 months]) will be analyzed using the same approach. Number of heavy drinking days (assessed using the Timeline Followback [TLFB] method) in the past month will be analyzed using negative binominal regression, to account for overdispersion in the data. Percentage of ART pills taken (assessed by self-report), a continuous outcome, will be analyzed using multiple linear regression if the data are normally distributed. However, if the distribution is skewed, transformations of the data will be performed (e.g., log transformation). If an appropriate transformation is not identified, a median regression model will be used. A secondary analysis will be conducted using a per protocol approach that includes only those participants who were adherent to their assigned intervention (i.e., defined as taking at least 80% of the assigned medication), as determined by self-report (i.e., visual analog scale).

Given the repeated measures of our primary outcome (i.e., 3, 6, and 12 months), additional exploratory analyses using longitudinal regression models will be used to incorporate repeated measures for each outcome in the same model and will test for possible gabapentin by time interactions. For the dichotomous undetectable HIV viral

load outcome, we will use generalized estimating equations (GEE), with an autoregressive working correlation matrix, a logit link; standard errors will be based on the empirical-sandwich estimator. Longitudinal analyses of heavy alcohol consumption will be analyzed using the same approach. For number of heavy drinking days, we will use GEE negative binomial regression models. For continuous outcomes, such as percentage of ART taken, we will use generalized linear mixed effects models that include subject-specific random intercepts and slopes to account for the correlation due to having repeated observations from each subject.

Sample size, power, and effect size

We present power calculations for the primary outcome of HVL suppression at 3 months post-randomization. Calculations assume a two-sided alpha of 0.05 and were originally based on enrolling 300 participants. The GRAIL trial was initially designed to be conducted in Russia, with sample size assumptions derived from prior research in the Russian population. Based on data from our previous study of 400 Russian people with HIV and risky drinking [43], we expected 40% of control participants to have undetectable HVL at 3 months. Assuming 15% loss to follow-up at 3 months (i.e., 255 evaluable participants), the study was powered at 80% to detect an absolute difference of 19% in the proportion with undetectable HVL at 3 months (59% vs. 40% in the gabapentin and control arms, respectively) using a chi-square test with continuity correction. Because the observed 3-month follow-up was better than anticipated (2.3% loss to follow-up vs. 15%), before unblinding we performed a blinded re-estimation based on the observed follow-up rate. In addition, given the sufficiently large expected cell counts, the updated calculations use the chi-square test without continuity correction. In this case, enrolling 220 participants yields approximately 215 evaluable participants at 3 months and the minimum detectable difference for 80% power remains 19%. Larger effects would yield even higher power. For example, in our prior Russian study, among participants on ART who reduced alcohol consumption, approximately 76% achieved HVL suppression at 3 months. If a similar proportion is observed in the gabapentin arm, the study would have > 99% power to detect this 36% difference (76% vs. 40%). All re-assessment of the minimum detectable difference was conducted without examining treatment-group outcomes and prior to unblinding. Thus, the trial remains adequately powered to detect clinically meaningful differences as small as 19% between arms.

Missing data

Participants who meet eligibility criteria and agree to participate will be compared with participants who were determined to be eligible but declined enrollment on data captured during eligibility assessment. Missing data patterns will be evaluated including the frequency and percentage of participants missing for each variable and the distribution of the number of variables missing for participants. In addition, data collected to the point of loss to follow-up will be compared to the data of those who complete the study to examine missing data mechanisms. The proposed study has accounted for a 15% random non-informative loss to follow-up and will still have sufficient power with this potential loss in size. It may be reasonable to assume that data are missing at random, albeit not completely. If this is the case, multiple model-based imputation methods will be applied to account for the missing data, if needed. We will also consider the use of pattern mixture models, which is applicable when the data are not missing at random. Pattern mixture models involve classifying subjects based on their longitudinal missing data patterns and assessing whether there appears to be an interaction between a randomized group and missing data pattern.

Protection of study data

All study data will be captured electronically on computers via a secure, web-based data capture system. The study data will be located on a secure server within the Boston University Medical Center domain. Identifiers needed to track participants will be kept separate from research data.

Data safety monitoring board (DSMB)

To ensure the safety of the participants and the validity and integrity of the data, an external DSMB was established to assume oversight of the study. The DSMB operates independently of the study sponsor and study investigators and its members have no competing interests that could affect their objectivity in monitoring the safety and integrity of the study. The Board will meet every 6 months and will be charged with evaluating the quality of trial administration, monitoring safety issues, and providing guidance on scientific, methodological, and ethical issues. Specifically, the Board will review investigators' plans and processes for identifying individual or patterns of adverse events as well as accumulating safety data. They may use results from an interim analysis to recommend that the study proceed as planned, be temporarily suspended, or be terminated. The DSMB charter is available as Additional File 2.

Auditing

The research team will employ a study monitor to conduct monitoring visits at study recruitment sites and research office. These will typically occur annually in order to review study documents and collaborate with the research team to ensure compliance with protocols and regulations. The study monitor will provide input without influence from investigators or sponsor.

Participant graduation, withdrawal, and disenrollment

Participant disenrollment can occur at any time during the study upon a participant's request to withdraw from study participation. Graduation for participants will occur after all procedures for the 12-month follow-up visit are complete or when a participant is withdrawn or terminated from the study. At their final study visit, participants will receive a graduation certificate in appreciation of their contribution to the research.

Dissemination plans

De-identified trial data will be uploaded into the NIAAA Data Archive biannually. Study results will be submitted for publication in peer-reviewed journals relevant to the research topic. Abstracts will be submitted to national and international conferences relevant to the field.

Discussion

The GRAIL study seeks to establish whether gabapentin can achieve HVL suppression among PWH with risky drinking. Suppressing HIV viral load is an efficient approach to preventing new HIV transmission. The challenge clinically is identifying populations engaged in HIV care but without effective delivery of ART. This study will be conducted in a setting of high HIV prevalence with unmet needs for treatment and the opportunity to prevent unhealthy alcohol use, thus mitigating its negative impact on HIV care.

We previously conducted a pilot, randomized, double-blinded, three-arm trial among 45 PWH in St. Petersburg, Russia, in which participants with chronic pain and past-year heavy alcohol use were randomized to low-dose naltrexone, gabapentin, or placebo [44]. In that pilot study, gabapentin was well tolerated, but we did not observe significant differences between groups in changes in the percentage of heavy drinking days over 30 days. The current GRAIL trial builds on this earlier work. First, it is conducted in Uganda, a different setting with high burden of both alcohol use and HIV. Second, GRAIL integrates brief alcohol counseling along with pharmacotherapy. Third, GRAIL is designed to evaluate HIV viral load suppression as the primary outcome, therefore directly assessing the intervention's impact on a clinically meaningful HIV outcome.

This study also has several limitations. First, our sample size justification and power calculations were based on data from a Russian cohort of people with HIV, rather than the African cohort from which this study is implemented. Second, adherence to gabapentin was assessed using self-report and pill counts. While these are commonly used adherence measures, they can introduce reporting and measurement biases.

If the GRAIL study demonstrates efficacy for gabapentin in PWH who engage in risky drinking, this highly generalizable HIV care approach, with the potential of rapid deployment of an affordable medication, can be added to the HIV prevention toolkit and implemented within existing medical infrastructure, advancing HIV care.

Trial status

The study was initially approved by the BUMC IRB on August 13, 2022 (version 1.1). The current version was approved on July 22, 2024 (version 1.6). Recruitment started on November 20, 2023 and is expected to complete in May 2026.

Abbreviations

AE	Adverse event
ART	Antiretroviral therapy
AUDIT	Alcohol Use Disorders Identification Test
AUDIT-C	Alcohol Use Disorders Identification Test- Concise
BPI-SF	Brief Pain Inventory-Short Form
CD4	Cluster of differentiation 4
CESD-10	Center of Epidemiologic Studies Depression Scale, 10-item version
DSMB	Data Safety Monitoring Board
DSM-5	Diagnostic and Statistical Manual of Mental Disorders
EtG	Urine ethyl glucuronide test
GAD-7	Generalized Anxiety Disorder-7
GEE	Generalized estimating equations
HVL	HIV viral load
IRB	Institutional Review Board
ISS	Immune Suppression Syndrome Clinic
MUST	Mbarara University of Science and Technology
NIAAA	National Institute on Alcohol Abuse and Alcoholism
PEth	Phosphatidylethanol
PWH	People with HIV
RA	Research assistant
REDCap	Research Electronic Data Capture
SAE	Serious adverse event
TLFB	Timeline Followback
UGX	Ugandan Shilling
USD	United States dollar

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-026-09813-1.

Additional file 1.

Additional file 2.

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Not applicable.

Authors' contributions
VT, AK, WM, NG, NE, DC, KL, and JS were responsible for study conception and design and will be responsible for implementation of the trial analysis and interpretation of trial data. JS and KL are the principal investigators of this study. VT drafted and revised the manuscript. JS, KL, AK, NG, WM, JT, DC, OA, and JH contributed to the revision of successive drafts of the manuscript. All authors read and approved the final manuscript.

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Data availability
Data and materials will be provided upon reasonable requests to the corresponding author.

Declarations

Ethics approval and consent to participant
The GRAIL study was approved by the Institutional Review Boards of Boston University Medical Campus (H-42904), Mbarara University of Science and Technology Research Ethics Committee (MUST-2022-668) and the Uganda National Council for Science and Technology (HS2622ES). The study was also approved by the Uganda's National Drug Authority. All study participants will complete the informed consent process and provide their consent in writing or use their fingerprint in cases where writing may not be feasible.
The IRBs and Council will be informed of any substantial modifications and deviations. Participants will be informed of any modifications that may have an impact on them and further permissions and consents will be requested if needed. ClinicalTrials.gov records will be updated accordingly. The funder will be notified of any deviations through the progress report, submitted every 6 months.

Consent for publication
Not applicable, personal and clinical details of participants will not be provided in the reporting of trial results.

Competing interests
The authors declare that they have no competing interests.

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