Trials

STUDY PROTOCOL

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A Brief Alcohol Intervention (BAI) to reduce alcohol use and improve PrEP outcomes among men who have sex with men in Vietnam: study protocol for a randomized controlled trial

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Abstract

Background In Vietnam and other global settings, men who have sex with men (MSM) have become the population at greatest risk of HIV infection. Although HIV pre-exposure prophylaxis (PrEP) has been implemented as a prevention strategy, PrEP outcomes may be affected by low persistence and adherence among MSM with unhealthy alcohol use. MSM have a high prevalence of unhealthy alcohol use in Vietnam, which may affect PrEP outcomes.

Methods

Design: We will conduct a two-arm hybrid type 1 effectiveness-implementation randomized controlled trial of a brief alcohol intervention (BAI) compared to the standard of care (SOC) at the Sexual Health Promotion (SHP) clinic Hanoi, Vietnam.

Participants: Sexually active MSM (n=564) who are newly initiating PrEP or re-initiating PrEP and have unhealthy alcohol use will be recruited and randomized 1:1 to the SOC or BAI arm. A subgroup of participants (n=20) in each arm will be selected for longitudinal qualitative interviews; an additional subset (n=48) in the BAI arm will complete brief quantitative and qualitative interviews after completion of the BAI to assess the acceptability of the intervention. Additional implementation outcomes will be assessed through interviews with clinic staff and stakeholders (n=35).

Intervention: Study participants in both arms will receive standard care for PrEP clients. In the BAI arm, each participant will receive two face-to-face intervention sessions and two brief booster phone sessions, based on cognitive behavioral therapy and delivered in motivational interviewing informed style, to address their unhealthy alcohol use.

Outcomes: Effectiveness (PrEP and alcohol use) and cost-effectiveness outcomes will be compared between the two arms. Intervention implementation outcomes (acceptability, feasibility, adoption) will be assessed among MSM participants, clinic staff, and stakeholders.

Discussion This proposed trial will assess an alcohol intervention for MSM with unhealthy alcohol use who initiate or re-initiate PrEP, while simultaneously preparing for subsequent implementation. The study will measure

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the effectiveness of the BAI for increasing PrEP persistence through reducing unhealthy alcohol use in a setting where excessive alcohol consumption is a normative behavior. If effective, implementation-focused results will inform future scale-up of the BAI in similar settings.

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Keywords Brief alcohol intervention (BAI), Motivational interview (MI), Men who have sex with men (MSM), HIV pre-exposure prophylaxis (PrEP)

Background

In Asia, the HIV epidemic has shifted from people who inject drugs (PWID) to men who have sex with men (MSM) [1, 2]. HIV prevalence among Vietnamese MSM tripled from 2011 (4%) to 2021 (13.5%) [3]. The prevalence is even higher in urban areas, at 15% [4, 5]. In 2021, MSM comprised 43% of new HIV cases in Vietnam [6].

In 2018, Vietnam was the second country in Asia to start a program for HIV pre-exposure prophylaxis (PrEP), which is a medication that if taken as prescribed, is highly effective for preventing HIV. By the end of 2022, over 60,000 people at high risk for HIV had access to PrEP in Vietnam; 80% of those using PrEP were MSM. Effective PrEP use requires persistence in care and adherence to the prescribed regimen, whether daily oral, event-driven, or injectable. PrEP persistence (maintaining PrEP use over time) has been a challenge for Vietnamese MSM. In Hanoi, PrEP persistence among MSM is only 42 and 33% at 6 and 12 months, respectively.

Unhealthy alcohol use may contribute to poor PrEP persistence [7, 8]. Unhealthy alcohol use is defined as a spectrum of use from risky/hazardous (drinking more than the recommended daily, weekly or per-occasion amounts resulting in increased risk for health consequences) to alcohol use disorder [9]. In Asia, unhealthy alcohol use is common among MSM with about 25–50% of MSM engaging in heavy alcohol use (defined as having 5 or more drinks on any day or 15 or more per week) and binge drinking (defined as having 6 standard drinks for men, 4 for women). Unhealthy alcohol use is normative in Vietnam—men often feel pressured to drink and drink to excess. In Hanoi, 63% of MSM attending a sexual health clinic reported unhealthy alcohol use [10], which is higher than data from a national survey on alcohol use. These data indicated that 40.1% men in urban and 40.9% men in rural drank alcohol at hazardous (4–6 standard drinks) or harmful (≥ 6 standard drinks) levels in the last year [11].

Unhealthy alcohol use impairs cognition and affects behavior, often leading to poor decision making [12–14]. Unhealthy alcohol use also causes substantial morbidity and mortality and affects every step of the HIV prevention and care cascade [15], including PrEP persistence and PrEP adherence (using PrEP consistently as prescribed). In multiple settings, unhealthy alcohol use has been found to be associated with reduced oral PrEP persistence [16, 17], thereby potentially impairing PrEP's effectiveness in preventing HIV infection. Thus, an effective alcohol intervention for MSM using PrEP is needed to address both unhealthy alcohol use and low PrEP persistence issues. In addition to causing consequences related to PrEP, alcohol use at high levels before sex is consistently linked to condomless anal intercourse [8], more sex partners, and commercial sex acts [18–21], increasing the risk of HIV and sexually transmitted infections (STIs) among MSM [22–25]. People with unhealthy alcohol use are also less likely to engage in health care and to take medications appropriately [26]. Yet, few interventions to reduce alcohol use in MSM have been evaluated [7].

The brief alcohol intervention (BAI) is an alcohol reduction intervention that was developed [27] and piloted in primary care settings [28, 29, 30, 31]. Studies in the USA [31] and Vietnam [28–30] have found that the BAI is an effective intervention for reducing alcohol use and improving HIV-related outcomes among people with HIV (PWH). In our randomized controlled trial (RCT) of the BAI among 440 Vietnamese PWH on antiretroviral therapy (ART) with unhealthy alcohol use, PWH who received the intervention were more likely to be virally suppressed 12 months [28]. Since findings from our previous study suggested that the BAI reduced alcohol use, which in turn improved ART adherence among PWH, we hypothesize that the BAI would also help improve adherence and persistent of PrEP among MSM. In two-arm effectiveness-implementation type 1 hybrid RCT, we will extend the use of the BAI to improve PrEP use. Our aims are (1) to assess the effectiveness of the BAI for increasing PrEP persistence and adherence among MSM in Vietnam; (2) to assess the impact of the BAI on alcohol use among MSM; (3) to estimate the cost-effectiveness, feasibility, and acceptability of scaling up the BAI in PrEP clinics throughout Vietnam via in-depth interviews with relevant stakeholders.

In this paper, we describe the guiding theories and conceptual frameworks, study setting, design, randomization, and types of participants involved in this study. We discuss the interventions, study outcomes,

data collection, and analysis plan. We end this paper by describing this study's innovations and potential challenges. We follow the SPIRIT checklist in reporting the protocol for this study [32].

Methods

Study setting

This study will be based at the SHP (Sexual Health Promotion) clinic at the Hanoi Medical University hospital, Hanoi, Vietnam. The clinic offers comprehensive sexual health care services to key populations, with a focus on MSM. Since May 2019, the clinic has provided oral PrEP free of charge to people at risk of HIV infection. As of February 2024, the clinic has provided oral PrEP to 5025 clients, 95% of whom are MSM. Unhealthy alcohol use is common in this population. In Hanoi, 72% of MSM PrEP clients drink alcohol at risky levels based on the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) scale [33]. In addition, data from the SHP clinic indicated that almost 50% of MSM discontinued PrEP within 6 months.

The BAI will be delivered to SHP clinic MSM PrEP clients initiating or reinitiating PrEP who report unhealthy alcohol use based on the AUDIT-C (The Alcohol Use Disorders Identification Test-Concise) score [34]. In-person BAI sessions will be administered in a private room in a building adjacent to the SHP clinic. Evaluation activities to measure BAI effectiveness will be conducted in a separate room in the same building to mask PrEP clinic staff from study participants' assigned trial arm and minimize potential contamination. Intervention (e.g., BAI counselors) and evaluation teams will also not overlap.

Study design

This study is a hybrid type 1, two-arm effectiveness-implementation randomized controlled trial (RCT). A total of 564 MSM participants will be recruited and randomly assigned to either the BAI (target n=282) or standard of care (SOC) (target n=282) arms.

Prior to RCT implementation, the BAI as well as the outcome assessment tools will be adapted and piloted among MSM from other PrEP clinics in Hanoi (Fig. 1).

Randomization

Randomization will be conducted following the completion of study consent and baseline data collection. Randomization will use a stratified, permuted block design with randomly assigned block sizes. Details of blocking will be provided to the data manager who has no direct role in the study. Stratification will account for initiation or re-initiation of PrEP. Random allocation will be implemented by study statisticians, who use a random number generator to assign each participant to an arm at a single point in time. The randomization sequence is concealed from study team members and allocation is determined from a randomization list generated prior to study start. RCT enrollment is completed upon allocation to the study arm.

Study arm allocation will be masked to PrEP clinic staff, data analysts, and investigators. Emergency unblinding would only occur in the case of a severe adverse event that might have been related to the intervention. As the intervention is behavioral, we expect this to be extremely rare. Unblinding would require the clinic staff caring for the person to contact the study team that has access to the allocation assignments.

Participants

MSM participants

MSM newly initiating PrEP or reinitiating PrEP who have unhealthy alcohol use will be recruited (N=564). A subgroup of participants from both study arms (N=20 for each arm) will be purposively selected and enrolled in a qualitative cohort to evaluate their change in alcohol use and PrEP use over 12 months. An additional subset of MSM in the intervention arm (N=48) will be selected to assess the acceptability of the BAI. We will engage MSM-focused community-based organizations in Hanoi to encourage PrEP-eligible MSM to present to the SHP PrEP clinic.

Eligibility criteria for MSM participants includes (1) newly initiating PrEP or re-initiating PrEP after at least 3 months from a missed PrEP appointment, based on Vietnamese PrEP guidelines; (2) assigned male sex at birth; (3) identifying as male; (4) receptive or penetrative anal intercourse with a man in the past 6 months; (5) AUDIT-C≥4, indicating unhealthy alcohol use [34]; (6) 16 years of age or older; (7) intention to receive PrEP care in Hanoi for 12 months; and (7) willingness to provide informed consent. In accordance with the Vietnam law on medical examination and treatment [35], which requires parental consent for PrEP initiation of minors, participants from 16–17 years old will be eligible for study participation with parental written informed consent. MSM will not be enrolled if they meet one of these criteria: (1) psychological disturbance, cognitive impairment, or threatening behavior; (2) unwilling to provide locator information; (3) current participation in alcohol programs or studies; (4) current participation in other research studies unless specifically approved by the principal investigators; (5) current or previous participation in an HIV vaccine study; or (6)

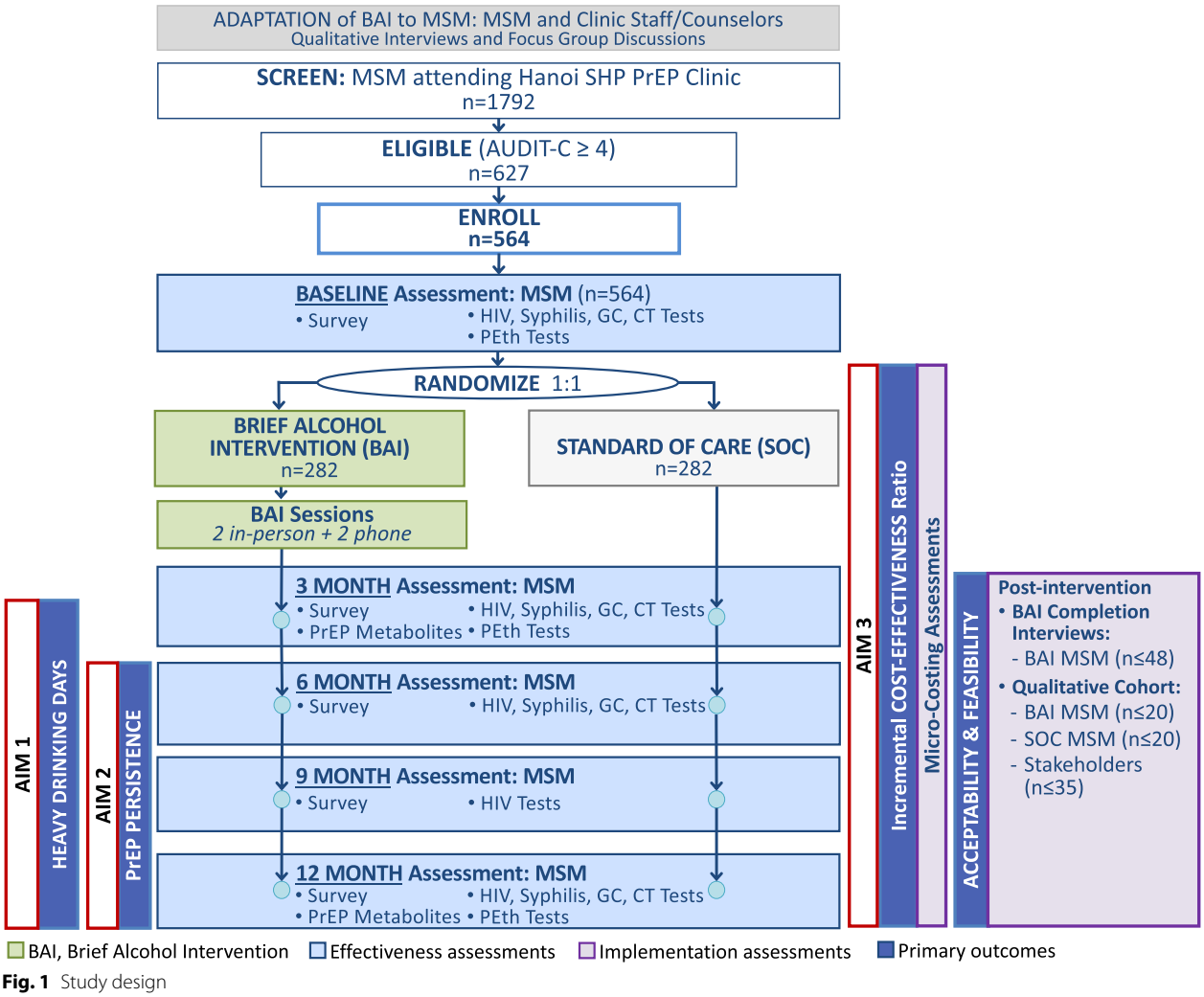

Fig. 1 Study design

Clinical Institute Withdrawal Assessment for Alcohol (CIWA) ≥ 10, indicating risk for alcohol withdrawal.

Stakeholder participants for pre and post implementation assessment

We will recruit health care staff working in PrEP clinics in Hanoi for in-depth interviews on alcohol use among MSM PrEP users, availability of alcohol screening and intervention services, and their comments for the BAI manual at pre-implementation phase. Staff from the Vietnam Authority for HIV/AIDS Control (VAAC) (which directs and provides support for initiatives in HIV/AIDS prevention and care in Vietnam), Hanoi Center for Disease Control, and the SHP PrEP clinic will be recruited prior to and upon completion of the main RCT to examine implementation-related outcomes. Stakeholders will be recruited through referral and well-established connections with governmental HIV agencies in Vietnam.

Intervention: BAI

The BAI is based on Project TrEAT [27]—an effective alcohol intervention was adapted for PWH in the USA [31]. In 2016, the BAI was further adapted in Vietnam as part of REDART, a 3-arm RCT among 440 adults with unhealthy alcohol use receiving ART in 7 HIV outpatient clinics in Thai Nguyen, Vietnam [28–30]. Results of the study showed that the BAI significantly reduced alcohol use compared to the SOC. The BAI arm also increased viral suppression compared to the SOC and was found to be cost-effective [29].

Guiding conceptual frameworks

The BAI draws from motivational interviewing (MI) [36]/motivational enhancement therapy (MET) [37, 38] and cognitive behavioral therapy (CBT) [39]. The BAI leads to increased alcohol-related readiness to change and coping skills, which will, in turn, decrease alcohol use [28]. Since our previous study suggested that reduced alcohol

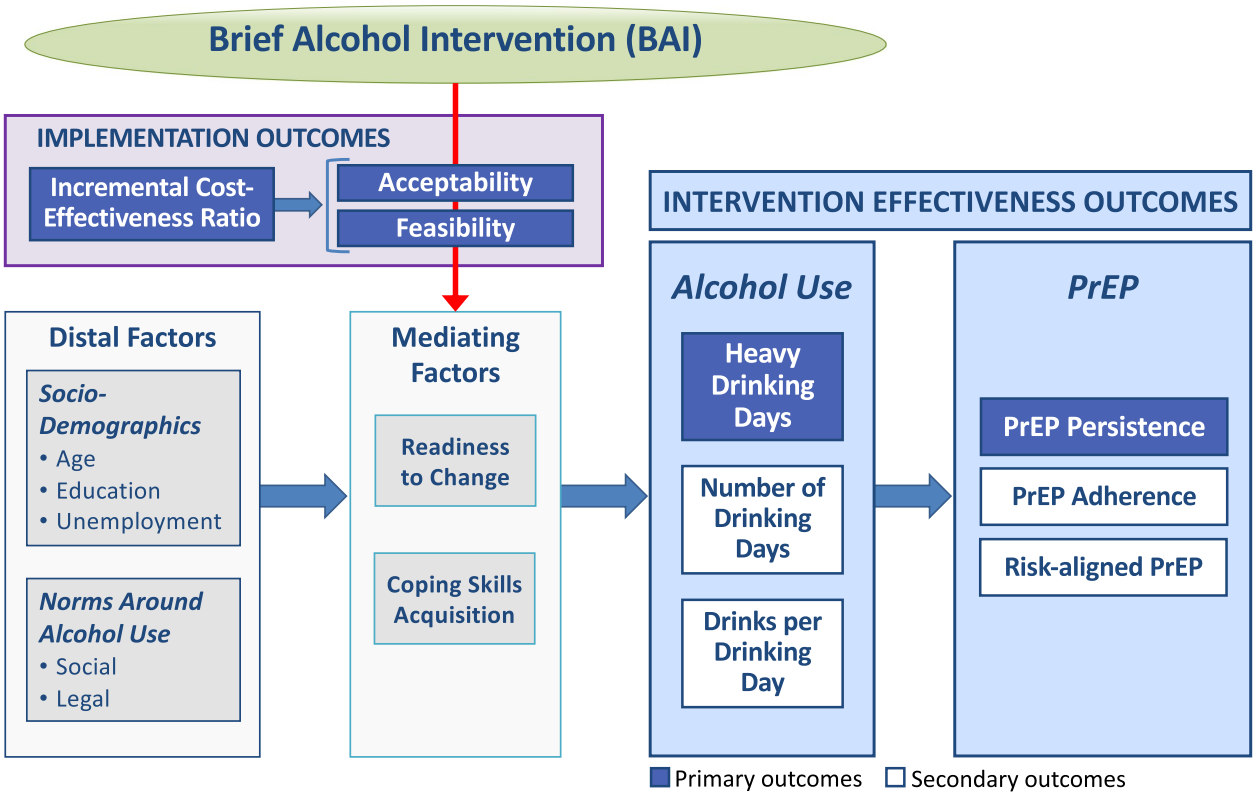

Fig. 2 Conceptual model

use increases ART adherence among PWH, we extended these findings to hypothesize that the BAI will reduce alcohol use and increase PrEP uptake among MSM. As the BAI is implemented in the real world, its effectiveness will depend, in part, on its acceptability and feasibility from the perspective of MSM and stakeholders.

MI [36] and MET [37, 38]

MI is a therapeutic approach that is directive, yet client-centered, and is based in enhancing individuals' intrinsic motivation to change behavior by exploring and resolving their ambivalence [36–38]. The goal of MI is to elicit self-motivational statements and behavioral change from the client through four principles: empathy, collaboration, evocation, and autonomy support. MET, based on the MI approach and practice, provides clients with normative-based feedback on alcohol use, explores client motivation to change in light of this feedback, and consolidates client commitment to change [37, 38]. In Vietnamese settings where drinking is normative, this feedback supports change [30].

Cognitive behavioral therapy (CBT) [39]

CBT emphasizes clients' development of skills to modify problematic cognitions and maladaptive behaviors. Specifically, CBT targets cognitive, affective, and environmental risks for alcohol use and develops clients' behavioral skills to cope with these risks (Figs. 2 and 3) [39].

Intervention components

The BAI comprises two in-person sessions and two booster telephone sessions. The two in-person, face-to-face sessions are approximately 45 min each, and occur about 1 month apart. The two booster telephone sessions are approximately 20 min each, and each telephone session occurs 2 to 3 weeks after each face-to-face session. The sequence and schedule of BAI sessions are in-person session 1 (~0–2 weeks following study enrollment), booster session 1 (~2–4 weeks), in-person session 2 (~4–6 weeks), and booster session 2 (~6–8 weeks).

The BAI's core components (Table 1) reflect the theoretical and empirical mechanisms responsible for behavior change.

In session 1, the BAI includes information about personalized feedback, alcohol facts, decisional balance, managing risky moods and situations, target behaviors, and optional goal setting. In session 2, events since session 1 and previously set goals are reviewed, followed

	STUDY PERIOD							
				Post-allocation				
	Screening	Enrollment & Baseline (Month 0)	Allocation	Month 1-2	Month 3	Month 6	Month 9	Month 12
TIMEPOINT	*-t2*	*-t1*	*0*	*t1*	*t2*	*t3*	*t4*	*t5*
ENROLMENT								
Screening informed consent	X							
Enrollment informed consent		X						
Contact information	X	X			X	X	X	X
Randomization			X					
INTERVENTION								
Brief Alcohol Intervention (2 in-person and 2 booster telephone session) for participants of intervention arm				←→				
Treatment for STIs, when detected for participants of both arms	X	X			X	X		X
Referrals to treatment – for HIV, STIs, chemsex, mental health problems, as needed for participants of both arms	X	X			X	X	X	X
ACCESSMENT								
Behavioral assessment procedure								
Baseline questionnaire		X						
Follow-up questionnaire					X	X	X	X
TLFB – for alcohol use		X			X			X
Review medical records at PrEP clinic – for HIV and STI testing results		X			X	X	X	X
Review pharmacy and medical records at PrEP clinic - for PrEP refills and PrEP clinic attendance					X	X	X	X
Social impact assessment		X			X	X	X	X
Cost-effectiveness questionnaire		X				X		
Qualitative assessment – among Qualitative Cohort only					X			X
Clinical Procedures								
CIWA, as needed	X	X			X	X	X	X
Urine (or urethral) swab, rectal, and pharyngeal swabs for Gonorrhea/Chlamydia (GC/CT) testing		X			X	X		X
Dried blood spot (DBS) collection		X			X			X
AE assessment					X	X	X	X
Laboratory procedures								
HIV testing		X			X	X	X	X
Gonorrhea/chlamydia (GC/CT) testing – rectal and pharyngeal swabs and urine		X			X	X		X
Syphilis testing with confirmation		X			X	X		X
PEth (DBS)		X			X			X
PrEP metabolites (DBS)					X			X
DBS storage		X			X			X

Fig. 3 Schedule of enrolment, intervention, and assessment

by discussion of developing an alcohol independent lifestyle, engaging supportive others, and building coping skills. Booster phone sessions check the participant's perception of progress towards goals (or needed goal revisions), elicit self-motivational statements and strategies for coping with high-risk situations, and/or review effective coping skills.

Intervention arm

BAI counselors, who were not working as PrEP counselors at the SHP clinic, were identified and trained. MSM will receive BAI sessions delivered by BAI counselors with timeframe and contents describe above. In addition, MSM in the BAI arm will receive the same procedures with participants in the standard of care

Table 1 BAI core components

Session 1
Introduction
Alcohol use
Reflecting on alcohol use
Figuring out drinking
What could change if you cut down or stopped drinking
Moods and situations that could lead to drinking
Managing moods and situations that could lead to drinking
Summarize
Make a personal action plan
Home practice
Session reflection and ending
Session 2
General review
Client evaluation of their alcohol use and PrEP use since last visit
Since last visit: what went well
What barriers did client have or did not meet goals
Client's updated/new personal action plan
Session reflection

arm. A counseling supervisor from UNC Vietnam will provide specific feedback on BAI competencies that meet or need improvement as well as on adherence to the BAI content. This supervisor will in turn be supervised by protocol team members with expertise in behavioral interventions and alcohol use.

Standard of care arm

Participants in the SOC arm will receive all counseling sessions that are normally offered within the PrEP clinic, including PrEP counseling. Those identified with substance use disorders (exclusive of alcohol use disorder) or mental health problems will receive care, as needed, using a four-tiered approach currently in place at SHP: (1) information and leaflets focusing on the specific issue; (2) brief intervention; (3) intensive intervention; (4) referral. None of these activities address alcohol use or alcohol use disorder.

All MSM participants will have regular screening for HIV and STI (gonorrhea, chlamydia, and syphilis) at baseline and months 3, 6, and 12. They will also receive HIV testing at 9 months. Any positive tests will be treated (STI) or referred for treatment (HIV) according to Vietnamese guidelines. All participants will receive pre- and post-test counseling for HIV testing and brief counseling for STI risk reduction. Condoms and lubricant will be offered to all participants.

Study procedure

As a part of routine clinic activities at SHP clinic, clients who would like to initiate or re-initiate PrEP will be pre-screened for risk behaviors including a brief screening for alcohol use. Those who have elected to start PrEP and are eligible for the study will have the study explained to them. Screening for study participants may occur at their PrEP initiation visit or within 1 month of PrEP initiation. For each potential MSM participant, independent informed consent for screening will be obtained before screening procedures are initiated.

During screening, MSM will undergo a brief screening questionnaire, including the AUDIT-C and CIWA. MSM will also be offered condoms and lubricant. Sobriety will be clinically assessed. MSM identified as acutely intoxicated will not be able to proceed with the screening or enrollment process. MSM who screen positive for unhealthy alcohol use (AUDIT-C $\geq$ 4) will be assessed for severe alcohol use disorder with the Mini International Neuropsychiatric Interview (MINI) [40]. Individuals in danger of alcohol withdrawal (CIWA $\geq$ 10) will be further evaluated with the CIWA and will not be able to proceed with enrollment at that time. For these individuals, rescreening for study eligibility may occur after the danger of alcohol withdrawal has passed—participants will be asked to be re-screening following completion of their withdrawal treatment.

Participants who meet all the eligibility criteria for enrollment will proceed with enrollment visit procedures, including written informed consent for RCT study procedures. Study participants are requested to remain in the study for 12 months with study visits at months 3, 6, 9, and 12. However, participants may voluntarily withdraw from the study for any reason at any time. The enrollment visit will typically occur on the same day but may occur up to 1 month after screening. If enrollment occurs on a different date from screening, the CIWA will be administered again prior to enrollment.

As part of each study visit, participants will complete a standardized questionnaire on topics including demographic information, PrEP use, alcohol use, and sexual behaviors. At enrollment, 3 months, and 12 months, participants will be asked to complete a 30-day Timeline Followback (TLFB) to assess recent alcohol use and they will be asked to provide dried blood spots (DBS).

We will use a variety of procedures to maximize retention, including compensating participants for their time to complete study visit, tracking of scheduled and missed visits in a computerized follow-up program, updating locator information at every study visit and using appropriate and timely visit reminder mechanisms.

Table 2 Study outcomes

Outcome	Definition	Measure or scale
Primary effectiveness outcome		
PrEP persistence	Details in the Table 3	Medical and pharmacy record review
Heavy drinking days (binge drinking)	Number of days with ≥ 6 standard drinks of alcohol per occasion	30-day TLFB
Secondary effectiveness outcomes		
PrEP adherence	Details in the Table 3	• Standardized questions • PrEP metabolites in DBS
Risk-aligned PrEP use	Details in the Table 3	• Medical and pharmacy record review • Standardized questions
Number of drinking days	Number of days with any alcohol use	30-day TLFB
Drinks per drinking day	Number of standard drinks of alcohol consumed on a drinking day	30-day TLFB
Primary implementation outcome		
Incremental cost-effectiveness ratio (ICER)	Incremental cost per quality-adjusted life-year (QALY) gained. ICER is defined as $[C_i - C_a]/[E_i - E_a]$ with C_i and C_a being the respective costs of the intervention [i] and assessment only [a], and E_i and E_a the corresponding effectiveness [48].	Direct observation and time-and-motion (TAM) studies, detailed prospective budgetary analysis, and surveys of both participants and key staff
Acceptability of BAI among clinic staff and MSM	Perception that BAI is agreeable, palatable, or satisfactory	For MSM: • AIM scale at post-BAI • Mental Health Implementation Science Tools (mhIST) Acceptability Scale for consumers For clinic staff: • AIM scale at post-implementation. • mhIST Acceptability Scale for providers • Qualitative interview
Feasibility of BAI at the clinic level	Rate of BAI completion among MSM study participants who are assigned in BAI.	For MSM: • Visit tracking form For clinic staff: • Qualitative interview
Secondary implementation outcomes		
Penetration	Completion of at least one session among those assigned to the BAI arm.	Visit tracking form
Adoption		For clinic staff: • Qualitative interview

Stakeholder participants

In the RCT phase, implementation outcomes will be assessed prior to and following completion of the RCT. All stakeholders will provide informed consent prior to participation in study interviews.

Outcomes

Effectiveness outcomes

PrEP Use and Sexual Behavior/STIs (Aim 1) The primary effectiveness outcome among MSM participants is PrEP persistence (Table 2, Table 3). The secondary effectiveness outcomes are PrEP adherence and risk-aligned PrEP use. Risk-aligned PrEP use is defined as persistent oral, event-driven (2+1+1) [41] or injectable PrEP, or clinician-supervised PrEP discontinuation for reduced sexual risk. Supplemental effectiveness outcomes, which are pre-specified for analyses, include condomless anal intercourse, as well as incident HIV, gonorrhea, chlamydia, and syphilis.

All PrEP outcomes will be measured at 3, 6, and 12 months. Because self-report may overestimate adherence, we will also measure PrEP metabolites in DBS at 3 and 12 months. Condomless anal intercourse will be measured at baseline and every quarterly study visit. Incident HIV will be measured at 3, 6, 9, and 12 months, and incident gonorrhea, chlamydia, and syphilis will be measured at 3, 6, and 12 months.

Alcohol use (Aim 2)

The primary alcohol-related effectiveness outcome is heavy drinking days (binge drinking), measured by

Table 3 Definitions of PrEP outcomes

PrEP route	Persistence definition
Oral daily	Consistent PrEP prescription refills, from a participant's PrEP initiation (or re-initiation) until a missed refill by >14 days for any reason
Event-driven	Consistent attendance at each quarterly clinic visits with refills as provided by the clinician until a missed visit by >14 days for any reason
LAI	Consistent receipt of injection every 8 weeks until missed injection by >14 days for any reason
PrEP route	**Adherence definition**
Oral daily	Two thresholds: ≥ 4 days/week, a threshold consistent with HIV prevention among MSM, and 7 days/week, indicating perfect adherence [57].
Event-driven	Completion of the 2+1+1 regimen for every reported anal or vaginal intercourse event.
All routes of PrEP uptake	**Risk-aligned PrEP use definition**
	PrEP use is consistent with concurrent risk behavior, including: • persistent oral, event-driven or injectable PrEP ➢ clinician-approved PrEP discontinuation for reduced sexual risk

self-report with the TLFB (Table 2). Secondary alcohol-related effectiveness outcomes include self-reported number of drinking days and self-reported drinks per drinking day. Supplemental alcohol-related effectiveness outcomes include self-reported alcohol before sex and alcohol abstinence stigma.

Alcohol outcomes will each be measured at 0, 3, and 12 months. Phosphatidyl ethanol (PEth) levels, a biomarker of alcohol consumption [42–44], will be measured using DBS as a process measure.

Implementation outcomes

The study has two primary implementation outcomes: acceptability of the BAI among clinic staff and MSM, and feasibility of the BAI at the clinic level. Secondary implementation outcomes include adoption and penetration.

Acceptability will be measured both qualitatively and quantitatively. MSM and clinic staff will complete the 4-item Acceptability of Intervention Measure (AIM) [45] after receiving the BAI, and after BAI implementation, respectively. The 15-item Mental Health Implementation Science Tools Acceptability Scale (mhIST), consumer version [46] and the mhIST 13-item provider version will also be administered simultaneously. Clinic staff will address acceptability in in-depth interviews as well.

Feasibility will be measured qualitatively among clinic staff at within 6 months of the final BAI delivery to an MSM participant, and quantitatively based on the BAI completion rate among MSM participants. The BAI completion rate will be defined as (1) completion of all four sessions among those who initiated at least one session and (2) completion of all four sessions among those who were assigned to the BAI arm; (3) completion of at least two sessions among those who were assigned to the BAI arm.

Adoption will be measured qualitatively among clinic staff within 6 months of the final BAI delivery to an MSM participant. Penetration will be measured among all MSM participants and defined as completion of at least one session among those assigned to the BAI arm.

Economic evaluation and measurements

The BAI has been found to be cost-effective for PWH [29]; however, implementation costs and its value in MSM clients with alcohol use problems has not been studied. In our study, we incorporated a suite of economic evaluation sub-studies to assess (1) the cost of BAI implementation, (2) the intervention delivery, (3) patient perspective costs during their care, (4) health-related quality of life (HRQoL), and (5) the cost-effectiveness of the BAI in the study's target population. For the health systems costing, key outcome measure will be total implementation process cost of the BAI and per-patient intervention delivery cost. For patient cost, the primary outcome will be cumulative total direct and indirect patient costs associated with care-seeking from screening to maintaining PrEP. For HRQoL, we will use EQ-5D-5L-based health profiles collected for each patient into a value on a scale anchored at 1 (full health) and 0 (worst health state = death) based on the value set for Vietnam, which will represent the quality-adjusted-life years (QALY) estimate for each participant on average during the study participation [47]. For the cost-effectiveness analysis, we will estimate the incremental cost-effectiveness ratio (ICER), defined as $[C_i - C_a]/[E_i - E_a]$ with C_i and C_a being the respective health systems costs of the intervention [i], inclusive of implementation costs, and assessment only [a], and E_i and E_a the corresponding effectiveness, measured in terms of QALY [48]. The ICER estimates will be measured against varied levels of the willingness to pay thresholds (WTP) to assess the overall cost-effectiveness

of the BAI in our study population. Costs will be measured using direct observation and time-and-motion (TAM) studies, detailed prospective budgetary analysis, and surveys of both participants and key staff.

We will estimate the human resource requirements (using activity-based time estimates) and costs of all intervention-related activities, including the BAI, PrEP (including long-acting injectable, event-driven, and risk-aligned approaches, accounting for adherence), screening for and treatment of HIV, and management of HIV-associated complications.

Data collection and analysis

Formative data collection and BAI adaptation

Prior to RCT recruitment, adaptive and pilot phases were conducted to adapt intervention package and study tools to the context of MSM on PrEP in Vietnam. In-depth interviews were conducted with clinic staff and MSM PrEP clients to ensure that concepts, language, examples, and context of the BAI is culturally relevant to MSM, HIV risk, and PrEP persistence in adaptive phase. Data were analyzed to systematically adapt key BAI characteristics to MSM in Vietnam acceptability while maintaining the core structure [30, 49–51]. Key characteristics were the population-specific elements and structural factors that increase intervention efficacy, relevance. Two focus group discussions, one with MSM on PrEP and one with counselors from PrEP clinics from the four clinics (around 8 participants per focus group) to test component of the adapted BAI. Feedback from the focus groups was utilized to further revise the adapted intervention package for pilot.

In the pilot phase, trained BAI counselors delivered the adapted BAI package to eight MSM on PrEP to assess intervention flow, comprehension, utility of information, motivation changes, and utility of behavioral skill training. We also did pilot survey items, interview procedures to assess survey length, check response distribution, item comprehension, and data collection procedures with up to 10 MSM on PrEP. The results informed refinement and finalization of the BAI package and assessment tools for use in the RCT. Individuals who take part in the pilot did not participate in the RCT phase.

RCT data

Quantitative data At baseline and each quarterly visit, we will measure PrEP use, alcohol use, and sexual behaviors. PrEP use will be monitored from the participant's medical record, and from self-report at each study visit. HIV screening status will be conducted at every quarterly visit and STI testing for gonorrhea, chlamydia, and syphilis will be performed at baseline, and months 3, 6, and 12.

Analytically, we will conduct intention-to-treat comparisons between the two arms to assess effectiveness of the BAI at months 3, 6, and 12 for the PrEP outcomes and months 3 and 12 for the alcohol outcomes. All tests will be based on a nominal 5% two-sided type 1 error probability. Confidence intervals (CI) will have a nominal 95% coverage. Additional multivariable analyses will adjust for potentially important predictors of persistence, determined a priori, which include age, prior PrEP use, partner living with HIV, perceived PrEP need, use of event-driven PrEP, AUDIT-C score, number of sex partners, and frequency of condomless sex. Alternative predictors may be chosen if any of the proposed predictors have substantial statistical issues, such as low response frequency or substantial missing data. We will also examine overall persistence using a generalized estimating equations (GEE) model with a logit link function and binomial error distribution to assess the outcome across time at 3, 6, and 12 months.

TLFB hand-on training was conducted online in total nine 1-hour sessions at the beginning of the pilot phase to equip knowledge and skill for assessment team of study. To examine the primary outcome of number of heavy drinking days, we will use GEE with a Gaussian error distribution and identity link to compare the means of heavy drinking days between the two arms at 3 and 12 months. The primary model will estimate effects across all time points; a secondary model will include an interaction term with time.

Quantitative tools used to measure acceptability were described above. Although a specific AIM cutoff has not been established [45], we provisionally consider an AIM score of $\geq$ 16 to reflect adequate acceptability. We will use descriptive analysis to determine if the intervention is acceptable and feasible.

For assessment of health systems perspective costs, we will perform an activity-based cost analysis for both implementation costs and intervention delivery costs using ingredients approach scale-up planning. Capital assets and start-up costs will be annuitized based on their expected useful life years (between 2 and 15 years) and discounted at 3–10%. All other resource use will be assessed as costs using ingredients approach. Common costs multiple activities and procedures will be apportioned based on ratios of cumulative human resource time commitment measured from time assessment study. Patient costs include data on socio-economic status,

costs associated with the participants' alcohol use, direct health care costs, and indirect costs associated with the participants' illness. Cumulative total costs for each period and overall follow-up will be assessed for individual patients. We will calculate the differences in the proportion of participants experiencing patient costs exceeding 20% (sensitivity analysis performed at different % levels) of individual and household income as well as income levels assessed based on the social capital approach between the intervention and control arms of the trial.

Leveraging individual participant level data on costs and effectiveness, we will evaluate the cost-effectiveness of the BAI intervention against the SOC, from the health systems perspective. Cumulative health systems costs measured for individual participants in the study will be used to estimate the differences in health systems costs between the BAI and SOC groups. Differences in effectiveness will be assessed based on differences in HRQoL estimate obtained from EQ-5D-5L between the two groups, as an estimated number of QALYs gained by the BAI among MSM initiating PrEP relative to the SOC. As the WTP is largely unknown for the BAI in our study population context, we will explore a range of WTPs, starting with 1 x Vietnam's Gross Domestic Product (GDP) per capita in the "net benefits" (NB) or "net-monetary benefit" (NMB) approach (via generalized linear models with log-link) [52, 53] and generate the cost-effectiveness acceptability curve.

For PrEP persistence and adherence, MSM lost to follow-up will be considered not persistent and non-adherent. For other outcomes, if there are missing >10% of observations, we will assess predictors of loss to follow-up and apply multiple imputation under the assumption that data are missing at random conditional on observed data.

Qualitative data To monitor the process of change in PrEP and alcohol-related outcomes, as well as BAI acceptability, we will conduct qualitative interviews with a subset of 40 RCT study participants, with 20 MSM in each arm. In this qualitative cohort, qualitative interviews will be conducted at months 3 and 12. At each in-depth interview, we will ask participants about personal drinking and sexual behaviors, attitudes towards and perceptions around drinking, PrEP use, and if and how they have changed over time as well as their experiences in the study. Participants in the BAI arm will also be asked about BAI acceptability, including how they experience BAI, if the BAI is useful and acceptable for them and if the BAI would be applied for those with unhealthy alcohol.

We will also conduct in-depth interviews with SHP clinic staff (up to 15) and stakeholders from policy-oriented agencies (up to 20) in Hanoi to explore feasibility and adoption of the BAI. In-depth interviews with SHP staff, including those who are BAI counselors, will be conducted after BAI training and within approximately 1 month prior RCT initiation. These interviews will focus on BAI implementation barriers and facilitators, staff's intent to sustain use of the BAI, and competing health priorities, resources, counselor skills, and clinic space for intervention implementation. We will also conduct in-depth interviews with staff from policy-oriented agencies when the BAI is completed for all MSM participants. These interviews will explore and assess the feasibility of scaling up the BAI throughout Vietnam and intention to adopt the BAI, if it is effective.

All qualitative interviews will be audiotaped, transcribed, and translated, for analysis using NVivo or similar software. Analysis will begin as data are collected so that topics for further exploration can be incorporated into ongoing fieldwork. Textual data analysis will involve five steps: (1) reading for content; (2) deductive and inductive coding; (3) data display to identify emerging themes; (4) data reduction; and (5) interpretation. Coded interviews will be compared and triangulated within study participants with multiple interviews and across all study participants. Findings from qualitative interviews will inform our understanding of the context and processes that may underlie successful mechanisms for the BAI to be effectively delivered to MSM PrEP clients as well as refinements that may be needed for future scale-up efforts.

Data management, safety monitoring, and adverse event reporting

Standard operating procedures (SOPs) will be created to outline procedures for data and forms processing, adverse event assessment, management, and other study operations. Data will be transferred to the central UNC-Vietnam office in Hanoi, processed, and cleaned. The data manager will be responsible for coordinating Quality Control reports and data queries resolutions. All participant information will be stored in locked file cabinets in areas with access limited to study staff. All records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored

separately from study records identified by code number. All local databases will be secured with password-protected access systems.

Safety monitoring will be performed by an independent Data and Safety Monitoring Board (DSMB) committee comprised of researchers and persons in Hanoi with expertise in issues relevant to this study. The committee will meet before the trial begins, 1 year of commencing enrollment and at least annually thereafter. Blind interim analyses of the data will be conducted halfway through the follow-up period, when virtually all participants will have provided 6-month behavioral interim endpoints and presented blinded for the DSMB by an external statistician. All adverse events and social harms will be documented and reported to the principal investigators (PIs), Institutional Review Board (IRB), and DSMB according to the SOPs.

Trial conduct is reviewed regularly by independent boards as well as the study team. The trial will be monitored by an independent DSMB at least annually. The university and local IRBs review the trial progress annually to ensure ethical conduct and participant safety. The DSMB and IRB members and their review processes are independent from investigators and the sponsor. Additionally, the data management and assessment teams conduct various study procedures and data quality checks at each participant study visit. The data management team submits quality assurance/quality control (QA/QC) reports monthly to the Evaluation Team and Operational Coordinating Center and biannually to the Protocol Committee for review and feedback.

Study committees' roles and responsibilities

The study team comprises the Protocol Committee, Operations Team, and Community Advisory Board (CAB). The Protocol Committee leads the study and consists of the PIs and co-investigators. The Protocol Committee has primary responsibilities of overseeing and facilitating the overall conduct of the study, developing the study protocol, making study decisions, and reporting the study results.

The Operations Team consists of the Operational Coordinating Center, Evaluation Team, and Clinical Team. The Operational Coordinating Center is primarily responsible for reviewing all study materials and procedures; facilitating regular meetings among the Protocol Committee and Operations Team; facilitating and/or leading staff trainings; ensuring study activities are meeting protocol requirements; tracking study progress, timelines, and decisions; preparing progress reports for the sponsor; and ensuring that all relevant IRB regulations are followed. The Evaluation Team directly oversees all day-to-day study activities, with primary responsibilities of conducting the study assessment visits and obtaining informed consent with study participants; developing SOPs; data management; quality assurance and quality control of data and procedures; and coordinating local IRB approvals. The Evaluation Team Research Manager supervises this team. The Clinical Team is responsible for conducting all recruitment and intervention activities with study participants and managing the intervention team. The Clinical Team Research Manager supervises this team.

The Protocol Committee meets weekly with the Operations Team to discuss study conduct, progress, and challenges. Additionally, the Operational Coordinating Center meets weekly with the Evaluation Team to discuss specific study issues and operations, and the Evaluation Team and Clinical Team meet weekly to coordinate day-to-day study activities.

The CAB includes MSM eligible for PrEP, organizations serving MSM in Hanoi, and community and health leaders from Hanoi, and meets every 2 months. The CAB serves as a voice for the community and study participants and provides input on how the study can best serve and protect the interests and welfare of study participants and the community.

Sample size

RCT sample size and power calculation

For the primary effectiveness outcomes, the total number of MSM participants enrolled into the RCT will be 564, with a target of 282 participants in each of the two arms. Power calculations are based on a two-sided α=0.05, 80 and 90% power, and a minimum clinically important difference in proportions of 0.15 for our primary outcome of PrEP persistence. We estimate study retention to be 80% at 12 months, based on data retention in our previous trials [28]. With these assumptions, a sample of 564 provides an analytical sample of 450 and 90% power to detect a prevalence proportion difference of 0.15 for our primary outcomes. Power for secondary outcomes is greater. For the number of heavy drinking days, we have sufficient power to detect a difference of ~0.3 days.

Discussion

To the best of our knowledge, this study is the first to assess the effectiveness and cost-effectiveness of the BAI among MSM with unhealthy alcohol use who initiate PrEP in Vietnam or similar settings where alcohol use is widely accepted. This trial will simultaneously test the effectiveness of the BAI for addressing two important public health issues for MSM: PrEP persistence and unhealthy alcohol use. The BAI was effective, cost-effective, and feasible for PWH on ART in Vietnam [28]—extending the use of the BAI to MSM initiating

or re-initiating PrEP is a logical step. The study population of our previous BAI trial with PWH on ART was primarily people with a history of injection drug use; this BAI trial with MSM who initiate PrEP will develop a culturally acceptable manual for this new population. This trial will also assess appropriate mechanisms for the BAI to be effectively delivered to MSM initiating PrEP and provide information needed for future scale-up if the intervention is shown to be effective.

In our previous trial, the effect of the BAI on PWH on ART was mediated through alcohol use and increased ART adherence. We expect there to be a similar mechanism for the BAI among MSM initiating/re-initiating PrEP. We hypothesize that the BAI will lead to reduced alcohol use, better alcohol-related decision-making which in turn increase PrEP persistence. If MSM's behavioral risks change after receiving the BAI, we will identify those changes through HIV and STI testing, as well as detailed behavioral assessments. We anticipate that through its impact on alcohol use, the BAI may also lead to fewer STIs. Taken together, we believe that the BAI may have important health implications for MSM with unhealthy alcohol use.

This study addresses priorities for the future health of MSM in several ways:

First, the BAI has the potential to alter multiple health outcomes among MSM. Interventions to address alcohol reduction among MSM are "alarmingly scarce" [54, 55]. Yet, excessive alcohol use is both common and consequential among MSM. This proposed study has the potential to improve three interlinking health outcomes [7] for MSM: excessive alcohol use, STIs, and HIV prevention.

Second, this intervention study is designed as a type 1 hybrid RCT to expedite scale up of this study if the BAI is found effective. Many interventions are never taken to scale after their effectiveness is shown. Bringing an evidence-based intervention to scale requires careful implementation assessment. By combining the effectiveness evaluation with preparation for implementation, the timeline for scale up is shortened dramatically, allowing a greater impact on MSM health in a shorter time.

Third, the study will evaluate a cost-effective and likely sustainable intervention model. As seen in REDART with PWH on ART, the short duration, feasibility, and acceptability of the BAI are keys to its potential for sustained impactful benefit to MSM in resource-limited settings.

Finally, the trial is designed to be integrated into an existing structure within the SHP clinic and enroll MSM who initiate or re-initiate PrEP at the clinic, providing an opportunity to evaluate the intervention in a real-world clinic setting to inform future scale-up [56]. By integrating the BAI into an existing structure and enrolling current PrEP clients, we will have the opportunity to access BAI acceptability among both MSM and the clinic staff.

Since the study is being conducted in a setting where alcohol use is considered a normative behavior, MSM PrEP clients with unhealthy alcohol use may not realize that their alcohol consumption is at a level that requires intervention. As a result, they may be reluctant to undergo the BAI. To help address this concern, our study staff will provide complete information about what excessive alcohol use is, potential consequences of excessive alcohol use, and how the BAI is delivered, including its relatively short duration in screening session.

One of the expected benefits of the BAI is that MSM will reduce their alcohol use. If alcohol-related decision-making is positively affected, MSM may also reduce their sexual risk behaviors, potentially eliminating their need for PrEP or shifting the need to event-driven PrEP. We will measure these changes in behavior and conduct secondary analyses to describe the potential mediators of changes in PrEP use over time.

Currently in Vietnam, long-acting injectable PrEP (LAI-PrEP) is not available. LAI-PrEP may become available during the study and the protocol has included adaptations for that possibility. Recently, the United State President's Emergency Plan for AIDS Relief (PEPFAR) has proposed a donation of long acting injectable cabotegravir for conducting a demonstration study evaluating acceptability and feasibility of LAI-PrEP implementation in Vietnam. While we have not seen challenges when the demonstrated study is conducted, our study team will keep eyes on preparation process for this demonstration study and decide on adjustment for our study if needed.

Conclusions

PrEP is an effective HIV prevention strategy for MSM when it is used as prescribed and persistently. Interventions to support PrEP adherence and persistence are crucial to ensure effective implementation of PrEP worldwide. In regions where heavy alcohol use is normative, alcohol reduction interventions may be needed to improve PrEP adherence among MSM PrEP clients. The BAI, which improved HIV outcomes among PWH with unhealthy alcohol use, is a logical intervention to adapt to the context of MSM using PrEP. This study will provide insight regarding the adaptation of the BAI to a new population. The trial will also shed light on the potential impact of targeting alcohol use reduction to improve PrEP persistence among MSM worldwide.

Trial status

Protocol version 4.0 (2/22/2024). Recruitment is expected to begin on April 3, 2024, and complete in February 28, 2026.

Abbreviations

AIM	Acceptability of intervention measure
AUDIT	Alcohol use disorders identification test
ART	Antiretroviral therapy
BAI	Brief alcohol intervention
CAB	Community advisory board
CBT	Cognitive behavioral therapy
CIWA	Clinical Institute Withdrawal Assessment for Alcohol
DBS	Dried blood spot
DSMB	Data and safety monitoring board
GEE	Generalized estimating equation
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
ICER	Incremental cost-effectivenes ratio
IRB	Institutional review boards
MET	Motivational enhancement therapy
mhIST	Mental health implementation science tools acceptability scale
MSM	Men who have sex with men
LAI	Long acting injectable
MI	Motivational interview
MINI	Mini International Neuropsychiatric Interview
PIs	Principal investigators
PWH	People living with HIV
PrEP	Pre-Exposure Prophylaxis
QALY	Quality-adjusted life-year
RCT	Randomized controlled trial
TLFB	Timeline follow back
SHP	Sexual Health Promotion
SOC	Standard of care
SOP	Standard operating procedure
STIs	Sexually transmitted infections
UNC	University of North Carolina

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-024-08382-5.

Supplementary Material 1.

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Authors' contributions

WCM, VFG, and LMG conceived the study and obtained the funding. WCM, VFG, LMG, HTMB, JSC, TS, HTTN, NTKN, SMB, SLR, HS, OF, HVT, MXN, KDN, SER, SL, IFH, BJP, and BWP contributed to research design and protocol development. HH and GC helped conceptualize the intervention conditions, contributed to the grant writing, and informed all implementation materials. HTMB drafted the manuscript, and VFG, WCM, LMG, and MXN revised it critically with important intellectual contents. All authors read and approved the final manuscript.

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Availability of data and materials

Data collection for this study is ongoing, so no data and materials are currently available. During study implementation, deidentified data will be made available in accordance with NIAAA policies. This study will comply with all NIH and U.S. Federal governments requirements related to the dissemination of the research findings upon completion of the study. The International Committee of Medical Journal Editors (ICMJE) guidelines for authorship will be applied. In addition to publications, primary results of the study will be presented to stakeholders and study participants through a dissemination workshop and/or dissemination materials. All informed consent forms will include a statement referencing that this study will be registered in clinicaltrials.gov and will provide a link to the site to enable interested participants to review the trial information on the website.

Declarations

Ethics approval and consent to participate

The study was approved by the IRBs at the University of North Carolina, Chapel Hill and Hanoi Medical University. The study will be conducted in full compliance with the protocol. The protocol will not be amended without prior written approval by the PIs. All protocol amendments must be submitted to and approved by the relevant IRB(s)/Ethical Committees prior to implementing the amendment. Informed consent for both MSM participants and stakeholders will be obtained by research staff in the assessment team who have prior experience with obtaining informed consent. All consent forms will be translated into Vietnamese. The informed consent procedures will be conducted with all MSM who are eligible and interested in participating in the study, prior to participation in any study visit activities. Stakeholder participants will be consented prior to any quantitative or qualitative interviews.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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