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Economic and relationship-strengthening intervention to reduce alcohol use in couples living with HIV in Malawi: a study protocol for a randomised controlled trial of Mlambe

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ABSTRACT

Introduction Heavy alcohol use has the potential to derail progress towards UNAIDS 95-95-95 targets for countries in sub-Saharan Africa (SSA). Within couples, alcohol use is closely linked with factors such as intimate partner violence and economic insecurity and can result in poor adherence to antiretroviral therapy (ART) and HIV clinical outcomes. We hypothesise that a combined economic and relationship intervention for couples that builds on the prior success of standalone economic and relationship-strengthening interventions will be efficacious for improving HIV clinical outcomes and reducing alcohol use. The synergy of these interventions has not been assessed in SSA—specifically among people living with HIV who drink alcohol. To test this hypothesis, we will test *Mlambe,* an economic and relationship-strengthening intervention, found to be feasible and acceptable in a pilot study in Malawi. We will conduct a full-scale, randomised controlled trial (RCT) to evaluate the efficacy and cost-effectiveness of *Mlambe*.

Methods and analysis We will enrol 250 adult married couples having at least one partner living with HIV and reporting heavy alcohol use. There will be two arms: *Mlambe* or an enhanced usual care control arm. Couples in the Mlambe arm will receive incentivised matched savings accounts and monthly sessions on financial literacy, relationship skills, and alcohol reduction education and counselling. Participants will be assessed at baseline, 11 months, 15 months and 20 months to examine effects on heavy alcohol use, HIV viral suppression, ART adherence and couple relationship dynamics. Study hypotheses will be tested using multilevel regression models, considering time points and treatment arms. Programmatic costs will be ascertained throughout the study and incremental cost-effectiveness ratios will be computed for each arm.

Ethics and dissemination The RCT has been approved by the University of California, San Francisco (UCSF) (Human Research Protection Program; Protocol Number 23-40642), and the study has been approved by the National Health Sciences Research Committee (NHSRC; Protocol Number 24/05/4431) in Malawi. Adverse events and remedial actions will be reported to authorities both in Malawi and at UCSF. Results will be disseminated to study participants, local health officials and HIV policy makers and through presentations at conferences and publications in peer-reviewed journals.

Trial registration number ClinicalTrials.gov Protocol Registration; NCT06367348 registered on 19 April 2024; https://register.clinicaltrials.gov/. Protocol Version 1.0: 22 October 2024.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Builds on the strong evidence of the prior pilot study to examine efficacy.
⇒ Uses a dyadic approach to intervene to collect and analyse intervention effects on both partners.
⇒ Uses biomarker (phosphatidylethanol) to validate self-reported heavy alcohol use.
⇒ Includes a cost and cost-effectiveness analysis of the intervention to assess scalability.

INTRODUCTION

Background

The inter-related issues of alcohol use, intimate partner violence (IPV) and economic insecurity threaten to derail progress towards UNAIDS 95-95-95 targets in sub-Saharan Africa (SSA). Rates of heavy drinking are alarmingly high among people living with HIV (PLWH), and almost twice that of the general population.[1] Heavy drinking is defined as having a positive AUDIT-C score of ≥4 for men and ≥3 for women. In Malawi, around 40% of adults report drinking alcohol, and among those who drink, half report heavy episodic drinking.[2] Heavy drinking has deleterious effects on antiretroviral therapy (ART) adherence and HIV clinical outcomes.[3–7] It also indirectly affects health by damaging the committed relationships needed for social

support, economic survival and well-being.[8–11] Brief alcohol interventions have shown to be effective, but most of these interventions treat heavy drinking as an individual-level issue.[12] However, for people in committed romantic relationships, research suggests an urgent need for interventions that consider alcohol use as a couple-level issue involving both partners.[13–15] Novel alcohol interventions are paramount for breaking cycles of IPV and poverty and creating stronger families to prevent HIV and reduce HIV mortality, morbidity and transmission.

Formative research from Malawi found that among HIV-affected married couples with a partner who drinks alcohol, almost 50% met the criteria for heavy alcohol use based on the AUDIT-C. The major drivers of heavy alcohol use suggested by qualitative interviews were unemployment, boredom and coping with the stress of poverty.[16] Moreover, men who drank alcohol expressed strong desires for intervention with an economic focus to reduce poverty stemming from drinking. Wives were also deeply concerned with how alcohol drains family resources and leads to couple conflict and noted how their communication skills were ineffective at changing their partners' alcohol use. Economic-strengthening interventions have been effective at improving household economics, family cohesion and ART adherence among young women in Uganda.[17–20] Relationship-strengthening interventions (eg, addressing couple communication) have reduced alcohol use and increased HIV testing among couples in South Africa.[21 22] Yet, no interventions to date have jointly addressed the economic and relationship context of drinking alcohol among people living with HIV in SSA, which may have synergistic effects on heavy alcohol use.

To assess the effect of a joint economic and relationship intervention, we developed and tested *Mlambe* as compared with enhanced usual care (EUC).[23] Our pilot study showed that *Mlambe* was highly feasible and acceptable, recording a 96% retention rate and 100% session attendance and satisfaction levels. At the 10-month follow-up, *Mlambe* participants had higher rates of viral suppression (100% vs 91.9%) and lower rates of heavy alcohol use compared with the EUC arm (89.5% vs 97.2%). From baseline to 15 months, *Mlambe* participants reported decreases in mean number of drinking days (from 6.8 to 2.1) and AUDIT-C scores (from 7.5 to 3.1), while ART adherence rates improved across the same period (from 63.2% to 73.9%).[24] We also found that couples in the *Mlambe* arm showed greater increases in couple communication, unity, sexual satisfaction, intimacy and trust (Cohen's d ranged from 0.36 to 0.56; $p<0.05$) as compared with EUC. Couples in the *Mlambe* arm showed significant decreases in physical and emotional IPV (Cohen's d ranged from 0.33 to 0.49; $p<0.05$) as compared with EUC.[25] Building on this evidence from the pilot study, we propose a full-scale randomised controlled trial (RCT) to carry out the following aims:

Aim 1: to evaluate the efficacy of *Mlambe* on heavy alcohol use, defined as self-reported drinking combined with an alcohol biomarker called phosphatidylethanol (PEth), and on viral suppression, ART adherence, number of drinking days, AUDIT-C score and PEth value.

Aim 2: to assess the effects of *Mlambe* on relationship dynamics (couple communication, alcohol-specific partner support, and IPV) and explore whether these factors mediate *Mlambe*'s effects on health outcomes.

Aim 3: to compare the costs in the intervention and control arms and assess the cost-effectiveness of *Mlambe* using cost-effectiveness analysis (CEA).

For Aim 1, our primary hypothesis is that the odds of heavy alcohol use will be lower in *Mlambe* as compared with EUC. Secondarily, we expect that *Mlambe* participants will have higher odds of ART and appointment adherence, and viral suppression, and lower number of drinking days, AUDIT-C score and PEth levels. For Aim 2, we hypothesise that *Mlambe* participants will report greater improvements in relationship dynamics (eg, better communication, less IPV) as compared with EUC participants. As a secondary hypothesis, we anticipate that *Mlambe* will impact alcohol and HIV treatment outcomes via the pathway of improved relationship dynamics.

METHODS AND ANALYSIS

Trial design

We will conduct a RCT with 250 married couples with a partner living with HIV and meeting criteria for heavy alcohol use. Couples will be randomised to one of two arms, *Mlambe* or the EUC control arm, which consists of usual care plus 10–15 min of brief alcohol counselling. To consider potential scale-up, we will incorporate a cost component. Couples will be assessed at baseline, 11 months, 15 months and 20 months to examine intervention impacts and costs.

Study setting

This study will take place in Zomba district where 15% of adults are living with HIV.[26] Heavy alcohol use is high among PLWH but rarely screened for in HIV clinics, with recent cross-sectional studies citing that almost 30% of people recruited from HIV clinics in Zomba screened positive for risky alcohol use or other mental disorders.[27] Couples will be recruited at high-volume HIV clinics in the Zomba district (public and private; a mix of urban, rural and peri-urban).

Eligibility criteria

Couples will be eligible if (1) in a married or cohabitating union; (2) aged 18 years or older; (3) have at least one partner with a positive AUDIT-C screen (score of ≥4 for men and ≥3 for women) and living with HIV. HIV status disclosure to primary partners will be required to openly discuss HIV issues as part of the intervention, which is high within married couples (>90%).[28] Because the intervention is not appropriate for couples experiencing severe IPV and to minimise the potential to increase the risk for IPV, we will exclude those who report severe IPV

in the past 3 months and/or fear that their safety would be at risk by participation. Based on the pilot findings, we do not expect to exclude many couples meeting these criteria. However, there is the possibility that findings may be more generalisable to couples without severe IPV; however, this decision to exclude was made balanced with the need to protect couples from harm. Couples who participated in the Mlambe pilot study will also be excluded.

Patient and public involvement

The *Mlambe* RCT was built on two previous research studies done in the same context and with a similar population.[15 24] Participants were engaged during the development of Mlambe through the development of the intervention and pilot study that followed.[23] At the conclusion of the pilot, we held community meetings to present the findings and obtain further feedback from participants and key stakeholders. In the *Mlambe* pilot study, we found the intervention to be both feasible and acceptable.[24] Based on the results of these studies, we developed and refined randomisation procedures, intervention manuals, training procedures, study procedures and study instruments.

Mlambe intervention arm

The intervention will consist of the following components:

Incentivised savings accounts

After being randomised, couples will be facilitated to open a couple's savings account at a national banking institution in Malawi. They will be encouraged to deposit savings into their couple's savings account every month for 10 months and will be eligible to receive a 1:1 savings match, capped at US$10 per couple per month. The incentivised/matched funds will be stored in a separate parallel account. To receive the matched contribution, couples must attend 75% of *Mlambe* sessions. Couples will have access to the matched funds at the end of the intervention period, allowing time to accumulate additional savings to meet financial goals depending on each family's business goal.

Financial Literacy Training (FLT)

We adapted a package of five FLT sessions based on the *Suubi and Bridges* interventions,[18 29–31] tailored for couples affected by HIV and heavy alcohol use. Topics include principles of financial management including savings, establishing financial goals, principles of banking, asset building and income-generating activities. Specifically, for the adapted package, we included illustrative sessions on alcohol use and HIV; for example, in one exercise, the couple creates a household budget (calculating expenses related to HIV) and calculates the amount that could be saved per month by reducing spending on alcohol.[23] Bank representatives and mobile money providers participate in the sessions to explain how to manage and conduct financial transactions. In the last FLT session, agricultural extension workers from the local communities help educate couples on their chosen IGAs (eg, a piggery, produce business) and link couples to local resources needed to develop and maintain their IGA after *Mlambe* ends. Prior to the last session, we will conduct a multiday training with extension workers on agriculture and livestock raising to ensure standardisation of skills and knowledge and to enhance existing training provided by the Malawi Ministry of Agriculture.

Relationship-strengthening activities (RSA)

RSA activities have been adapted from *Uthando Lwethu*.[32] The first two sessions are group-based with a combination of didactic and interactive activities on (a) alcohol use and relationships/HIV health (eg, harms of alcohol use on relationships and health (eg, missing ART); brainstorming strategies to reduce drinking such as avoiding the bar after getting paid); (b) positive relationship dynamics (eg, reflecting on what 'trust' or 'unity' means and why it matters; exercises to build love such as 'words from the heart' and expressing appreciation to a partner); and (c) gender and power imbalances (eg, defining types of power; brainstorming how to balance economic power). The last two sessions are one-on-one with a trained couple's counsellor and are more skills-based, which is essential for couples to learn to work together around alcohol use, family finances and adherence. In the first counselling session, couples learn constructive communication skills (ie, Initiator-Receiver technique, 'I' vs 'you' statements) and problem-solving skills (eg, the Problem Talk strategy; goal-setting guidelines), and practice on neutral topics. In the second session, the counsellor revisits skills and helps couples practice communication regarding sensitive issues related to alcohol, finances and ART adherence.

Brief alcohol counselling

Couples will also receive brief 15 min sessions of motivational enhancement therapy[33] by completing a 30-day calendar on alcohol use, reflecting on drinking levels and identifying alcohol reduction goals as a couple.

Control arm: enhanced usual care (EUC)

Control arm couples will receive EUC. Usual care is defined by the Ministry of Health Guidelines for Clinical Management of HIV and includes monitoring for ART non-adherence, treatment failure, and liver disease or failure.[34] Because guidelines do not call for routine counselling on alcohol use, we will enhance usual care by offering brief alcohol advice lasting 10–15 min, modelled on WHO recommendations.[35] Similar to our other study in South Africa,[36] we chose to balance our ethical obligation to provide brief counselling on alcohol, which will soon be routine care in other settings such as Uganda. While some experts recommend designs such as treatment-attention control (TAC) arms, our future objective is to evaluate the effectiveness of a scalable alcohol intervention and redefine usual care (UC) for unhealthy alcohol use. Thus, it is necessary to estimate

the total effects of the intervention rather than the specific effects by comparing it to another design such as TAC.[37 38] Furthermore, TAC designs use an active but different intervention, and therefore, there is a risk of biased results if the TAC distracts people from managing their alcohol use.[37 38] Comparing to EUC will also allow us to monitor for safety issues and risks to participants (such as IPV), which could be overlooked if compared with an active control with similar risks.

Training of staff

Facilitators will participate in a multiweek training with study investigators that will focus on implementation procedures, session content and activities, mock sessions, interpersonal communication with couples, and ethical issues. Following the training, all facilitators will complete a series of training mock sessions to practice the intervention sessions. These will be completed in English, recorded and reviewed by the investigative team. Ongoing refresher training will be held to improve facilitator skills and retrain on emerging challenges. We will hire and train a research manager in Malawi to supervise intervention and research activities and maintain regular communication with the study investigators. We will also train several teams of interviewers to assist with recruitment and study assessments, who will be gender-matched to the partners of the couple. All research staff will be trained on Good Clinical Practice and human subjects protection research guidelines.

Fidelity monitoring and supervision

After each session, facilitators will complete a form that tracks attendance, intervention content delivered and session length. Attendance issues and missed activities will be flagged for discussion in weekly meetings. During the initial roll-out of the intervention, we will closely monitor facilitator competency and fidelity by having the research manager attend sessions, complete a detailed checklist on content delivered and identify areas for retraining. Facilitators will also be required to complete one to two mock sessions in English for each intervention activity, which will be audio-recorded and evaluated by the lead investigators. Coaching and competency assessment will be provided through regular Zoom call meetings by investigators to support facilitators. Once the intervention period starts, facilitators will listen to audio-recordings of their sessions and complete a self-assessment, including written reflections (eg, challenges, successes) and ratings for session activities using a 5-point Likert scale, which will be discussed in weekly supervision meetings. The research manager will monitor competency and fidelity with unannounced visits to sessions. We will audio-record and randomly select 20% of recordings to be reviewed by an independent person not on the field team for completeness of session activities.

Recruitment

Our team has partnered with several high-volume HIV clinics in the Zomba district where this study will be conducted. A team of research assistants affiliated with the study (also known as study recruiters) matched by gender to the respondents will approach HIV clients or their partners attending clinic appointments or picking up medications at the HIV clinics in Zomba, Malawi. If the participant is interested and eligible, we will consider the couple to be eligible. Screenings will be administered by interviewers using computerised forms on tablet devices. Partners will be consented separately to ensure a lack of coercion within the couple. We will also place recruitment flyers for distribution to patients in clinics, pharmacies and other community locations so that potential participants can contact the study team for enrolment if interested.

Screening for participation

Following procedures from another couples' study in South Africa,[36] screening consists of two steps. The first screener will be conducted in person or by phone. Once deemed eligible to continue, the recruiter will inform the index participant that their partner must also be screened. Contact information for the recruited partner will be collected and permission to call them will be obtained. The partner could initiate contact via a 'please call me' SMS text message. The index participant will be provided with study information to share with the partner. Couples who meet eligibility criteria will be given a second screener to assess additional eligibility criteria. The purpose is to screen out ineligible couples, those who experienced severe IPV in the past 3 months, or those with safety concerns. In these cases, couples will not be informed of the reason for ineligibility to protect them from further harm. For the couple to be eligible for the study, both partners will need to meet eligibility criteria. In cases where both partners report unhealthy drinking and are on ART, the male partner will be assigned to be the index patient.

Randomisation

To ensure balance in study arms over time, we will use blocked randomisation with randomly permuted block sizes generated using a computerised and secure process. We will enrol couples in group sizes of around 20, who will then be randomly assigned to each arm (eg, 10 treatment; 10 control). The intervention is designed to be delivered to groups of approximately 10 couples. We will hold a randomisation ceremony for each groups, and couples will receive a sealed envelope containing their couple ID and random assignment group. Immediately after the randomisation ceremony, couples in the control arm will receive brief alcohol counselling, one-on-one as a couple, while couples in the *Mlambe* arm will receive an appointment card with a date for their next study visit.

Blinding

By the nature of the intervention, counsellors delivering the intervention cannot be blinded. Assessment staff will be different from the counsellors who administer

the intervention. However, because the assessment staff works in close collaboration with the counsellors, it is not possible to fully ensure that assessment staff will be blinded from the intervention condition. Participants will be informed after the randomisation process of their assigned group and thus are also not blinded.

Emergency unblinding

By nature of the intervention, there will be no blinding of staff and study participants.

Data collection

All surveys will be delivered in person using gender-matched interviewers who are fluent in English and Chichewa to be able to use the participants' preferred language. Study staff will enter data directly into REDCap using a tablet. The REDCap mobile app can be offline in areas without internet access. Measures collected will be the same across visits except for demographics collected only at baseline. Assessments will last 60–90 min and uploaded to a secure web-based storage system. Both partners will be assessed separately, but simultaneously, using versions of the survey tailored to their drinking and HIV status. All measures have already been pretested, tailored for Malawi and translated to Chichewa (local language). Assessments will occur at baseline, 11 months, 15 months and 20 months.

Cost data collection

We will adapt our materials from other studies and use an activity-based, microcosting approach, measuring all resources in the *Mlambe* and EUC arms. To best inform programme sustainability and future delivery, we will use a provider perspective,[39] as in our past work. This excludes any participant out-of-pocket expenditures that are not reimbursed, such as the opportunity cost of their time in *Mlambe* or EUC. While such costs are part of the full societal perspective, they should be small under *Mlambe*, and a provider perspective for the CEA is more policy-relevant. Costs will be carefully tracked in administrative and expenditure records, including staff time, wages/salaries, programme expenditures, implementation costs, transportation, communication (eg, cell phones), savings accounts, matching funds, ESA sessions, RSA sessions, and training. The importance of monitoring costs and procedures for measuring resources will be underscored during training with the field team.

Laboratory testing

We will collect blood samples to validate self-reported drinking using PEth testing.[40] PEth is highly sensitive (88%) and specific (88%) for any alcohol use, has a window of detection of 21 days and is correlated with number of drinking days (r=0.74).[41] Due to recent findings that PEth sensitivity may be associated with body mass index (BMI),[42] we will measure BMI at all visits and control for BMI in our analyses if indicated.

Nurses will conduct venous blood draws at every other visit for viral load. For efficiency of sample collection, we will pipette whole blood onto PEth dried blood spot (DBS) cards from the small tube of blood collected for viral load. DBS cards will be stored at room temperature in locked cabinets and transported every 6 months to a commercial laboratory in the USA for PEth quantification (16:0/18:1 analogue), with a lower limit of quantification of 8 ng/mL. For visits in which only PEth samples are collected (not viral load), trained research assistants will perform finger pricks to obtain blood for DBS cards.

Viral load samples will be stored at −80°C at a local laboratory in Malawi until processed. Viral load tests will be performed on plasma samples using machines such as the Abbott Real-time m2000, Abbott Alinity or Hologic Aptima Panther for HIV-1 RNA, with lower limits of detection under 40 copies/mL. Blood for PEth testing will be collected on all partners reporting heavy alcohol use at baseline (tests performed at every visit), while viral load tests will be performed for all partners living with HIV at baseline (tests at baseline and 15 months only).

Data management

Following procedures from Masibambisane,[36] we will use built-in controls within REDCap to restrict out-of-range values, and automatic alerts will inform the user of missing data or abnormal entries. The mobile application displays questions on the screen and then gives interviewers the ability to enter responses directly into the mobile phone or tablet. Once complete, the research instrument (ie, survey, baseline interview) is temporarily stored in a non-readable encrypted file on the device/tablet. When in an area with network coverage or back at the research office, completed forms are uploaded and removed from the tablets approximately every 60 s. If no network signal is present, the data are stored on the mobile device until it detects a network signal. Checks will be placed to ensure correct information has been entered by the local research manager before being uploaded to a secured server. The data will undergo both internal and external quality checks, conducted by the UCSF research manager. Additionally, incoming data will be monitored daily to identify any unusual or unexpected entries. In cases where such entries are detected, data queries will be generated, and the Malawi field team will be contacted to address and resolve these queries.

Retention

We will collect detailed contact information from couples at enrolment including village information, directions/map to the household, two cell phone numbers and contact information for up to three other individuals whom the participant designates that we can contact if necessary. Our prior work indicated that only 75% of couples have access to a cell phone. Therefore, we will provide couples with a basic cell phone, to be reached by staff for check-ins and appointment reminders. All participants will be contacted bimonthly with reminders and to update contact information, and 1–2 days before their next appointment. We will place two to three calls to participants who have missed appointments by 7 days. For those who are 14+ days late, special outreach workers will

be trained to visit participants' homes. We will also invoke the help of clinic staff, if necessary, who know the date of the participant's next clinic appointment. For the control arm participants, regular communication will be maintained throughout the study period. To maintain a high participation rate, we will track respondents who relocate within a 50 km radius of Zomba town. We will conduct follow-up assessments at their homes or another community-based location. We will continue also to support their transport costs to the intervention sessions.

We expect to lose a small number of couples due to break-ups or migration (less than 5% in the pilot study). Similar procedures will be followed from our prior studies.[36] For couples that break up, we will conduct one additional assessment with each partner following their break-up to understand factors contributing to their break-up and to identify any negative effects of participation on couples, including relationship dissolution. We will continue to follow dissolved couples (as individuals) as they will still be eligible for our outcomes of heavy alcohol use, viral suppression and ART adherence. In the case of break-ups, couples will not be asked questions on relationship dynamics.

Study outcomes

Primary outcomes

The primary outcome of the study is heavy alcohol use. Heavy alcohol use will be a composite measure, defined as having a positive AUDIT-C score and/or positive PEth value indicating heavy alcohol use. A positive AUDIT-C refers to a score of ≥4 for men and ≥3 for women, while a positive PEth value is based on a cut-off of ≥50 ng/mL, consistent with unhealthy drinking.[43 44] Refer to table 1 for details.

Table 1 Outcomes and domain definitions

Outcome variable	Domain	Measure
Primary outcome	Heavy alcohol use	AUDIT-C positive (score of ≥4 for men and ≥3 for women) and/or PEth positive.[43 44] A positive PEth value is based on a cut-off of 50 ng/mL, consistent with heavy/unhealthy drinking.[44]
Secondary outcomes	Drinking days	Number of drinking days in the past 30 (timeline follow-back method).
	AUDIT-C score	AUDIT-C score; the full 10-item AUDIT will also be collected.[56]
	PEth value	PEth value (ng/mL).
	Viral suppression	Viral suppression will be defined as a viral load value of <40 copies/mL.
	Adherence to ART	ART adherence (adapted Visual Analogue Scale[57] for low literacy populations[58]), dichotomised into 95–100% adherence.
Mediating variables	Intimate partner violence	Physical, sexual, emotional and financial IPV (WHO domestic violence module; validated with PLWH; α=0.75–0.83).[59 60]
	Couple communication	Constructive, avoidant and demand-withdraw communication (communication patterns questionnaire; α=0.69–0.72).[61] Couple illness communication.[62]
	Partner social support	General partner support (social provision scale; spouse version; α=0.88).[63] Alcohol-specific partner support (adapted from the HIV-specific partner support scale;[64] α=0.73).
	Relationship quality	Trust (dyadic trust scale; α=0.82).[65] Intimacy (emotional intimacy subscale of Sternberg love scale; α=0.90).[66] Commitment (commitment subscale of Sternberg love scale; α=0.82).[67] Equality (equality subscale of the relationship values scale; α=0.87).[68] Unity (inclusion of self-in-other measure).[69] Relationship and sexual satisfaction (developed in Malawi; α=0.89).[70]
	Stigma	Anticipated HIV Stigma[71] and Alcohol ART Stigma.[72]
	Alcohol behaviours	Readiness to change.[73]
	Savings behaviours	Financial literacy knowledge.[74] Household financial management.[75]
	Food insecurity	Household food insecurity access scale (HFIAS; validated in SSA; α=0.88).[76]
	Mental health	Stress (Perceived Stress Scale; validated in SSA;[77 78] α=0.78). Hopelessness (Beck Hopelessness Scale; validated in SSA with PLWH;[18 79] α=0.79). Depression (CES-D scale; validated in PLWH in SSA; α=0.90);[80 81] anxiety (GAD-7).[82]
Moderating variables	Demographics	Gender, education level, household asset index.[83]
	Couple variables	Relationship length, couple HIV status (concordant positive vs discordant).
Covariates	Control variables	Age, tribal affiliation, religion, living children in the household, clinical site, body mass index, Marlow-Crowne social desirability scale.[84]

Secondary outcomes

Secondary outcomes are viral suppression, ART adherence, care appointment adherence, number of drinking days, AUDIT-C score and PEth value. We will also assess the effects of *Mlambe* on relationship dynamics (couple communication, alcohol-specific partner support and IPV) and explore whether they mediate *Mlambe*'s effects on health outcomes. Refer to table 1 for details.

Process outcomes

In addition to tracking adverse events (eg, IPV, break-ups) and costs, we will track process outcomes that will be used to inform future implementation and scale-up. Outcomes tracked will include the following: (a) participation rates by session and the entire intervention; (b) financial outcomes (eg, number of savings accounts opened, mean number of deposits over 10 months, mean monthly savings, cumulative savings, total savings plus match, types of IGAs started); (c) topics selected by couples to practice communication skills in counselling sessions; (d) length of sessions; (e) participant distance/time to travel to sessions; (f) referrals into alcohol treatment services and linkages in care; and (g) total resources used in each arm, delineating major cost categories for a cost analysis.

Participant timeline

The study is expected to start participant recruitment in January 2025. The trial is planned to complete in 2029.

Sample size

The study will enrol approximately 250 couples (500 individuals). Each arm will have an equal number of couples to allow assessment of differential retention rates between arms.

Power analyses

Aim 1

We used NCSS PASS[45] to compute the minimum detectable effect size estimate for the proposed primary time-averaged comparison originating from the two-level generalised linear mixed model (GLMM). For power analyses for the proposed GLMMs, we assumed power=0.80, α=0.05 and two postbaseline repeated assessments from n=225 participants based on the conservative assumption of 10% attrition from our original sample of 250, even though in the pilot of *Mlambe*, we had only 4% attrition at 15 months. We assumed a baseline proportion of heavy alcohol use of 0.98 based on our *Mlambe* pilot study and an intraclass correlation (ICC) of 0.72 based on another alcohol study in Uganda that collected longitudinal data on PEth and self-reported drinking.[46] Under these assumptions, the minimum detectable raw difference in heavy drinking proportion was 8.3%. Conversion of the raw proportion differences to Cohen's standardised effect size metric h yields h=0.37 for heavy drinking, which is between thresholds for small (h=0.20) and medium (h=0.50) standardised effect sizes.[47] This effect size is similar to or smaller than effect sizes in studies conducted with PLWH who drink alcohol in Uganda,[46 48 49] suggesting we can detect clinically significant effects in line with comparable studies.

Aim 2

NCSS PASS[45] was used to compute the minimum detectable effect size estimate for the proposed primary time-averaged comparisons originating from LMMs. For power analyses for the proposed LMM, we assumed power=0.80, α=0.05 and two postbaseline repeated assessments from 450 participants from 225 couples following 10% attrition. In the pilot of *Mlambe*, we had only 4% attrition at 15 months; therefore, we conservatively assumed 10% attrition by our last follow-up visit of 20 months. Based on the maximum ICCs from our *Mlambe* pilot data, we further assumed ICCs of 0.13 at the couple level and 0.61 at the person level. Under these assumptions, we computed the minimum detectable standardised mean difference d=0.26 for the LMM-based repeated measures analyses proposed to address Aim 2. This minimum detectable effect size falls between benchmarks for small (d=0.20) and medium (d=0.50) standardised effect sizes,[50] suggesting that our study is powered to detect small to medium threshold effects.

Data analysis plan

Primary analysis for Aim 1

We will fit a two-level logistic GLMM for the binary outcome of heavy alcohol use. This model will include fixed effects for the study arm, time and their interaction, as well as BMI, if warranted. The unit of analysis will be at the individual level since we expect most couples to have only a male drinker (few women drink alcohol). To maximise rigor in our analyses, we will follow an intention-to-treat approach such that all participants who drink alcohol will be included in the analysis irrespective of whether they have complete or incomplete outcome data. A time-averaged comparison of repeatedly measured postbaseline observations across study arms will be performed to examine intervention effects over the duration of the postintervention study period at alpha=0.05.

Exploratory analyses for Aim 1

We anticipate *Mlambe* participants will have higher odds of viral suppression and ART adherence relative to the EUC arm. The same GLMM approach will be applied to the exploratory outcomes of viral suppression, ART adherence and missed HIV care visits. We also anticipate that *Mlambe* participants will have a lower mean number of drinking days, AUDIT-C scores and PEth values relative to participants in the EUC control arm. For PEth and AUDIT-C scores, which are likely to be skewed as shown in our prior work,[46] we will use a GLMM approach with gamma distribution and log link as is common for right-skewed distributions.[51] For the number of drinking days, we will use a GLMM with a negative binomial distribution as recommended for count-based outcomes of alcohol use.[52]

Primary analysis for Aim 2

We will fit a three-level LMM to the primary outcome of alcohol-specific social support. This model will include fixed effects for the study arm, time and their interaction. We will use random intercepts for couple ID to account for the clustering of participants within couples and include random intercepts, random slopes and their covariance for couple ID to account for the clustering of repeated measurements within participants. We will perform a time-averaged comparison of repeatedly measured observations across study arms to examine intervention effects over the duration of the postintervention study period at alpha=0.05.

Exploratory analyses for Aim 2

To explore hypothesised mediators and moderators, we will investigate whether psychosocial constructs (eg, depression, hopelessness) mediate the relationships between the intervention group assignment and heavy drinking/adherence and whether sociodemographic variables such as household assets moderate these associations. To maximise rigor, analyses will be conducted using structural equation modeling (SEM) and causal inference methods.[53] SEM allows for the creation of latent variables that represent shared variation among similar measures that are likely to be correlated (eg, couple communication). As part of our analyses, we will investigate whether mediators are sufficiently correlated to be treated as measures of one or more latent variables. We will use the specialised latent variable modelling program M*plus* to perform the mediation and moderation analyses because it unites SEM and latent variables with causal inference-based mediation methods in the same analysis platform[54] and can adjust SEs for clustering of participants within dyads.

Cost and cost-effectiveness analysis

We will measure and report the total resources used in each arm, delineating major cost categories. Results will be reported in Malawi Kwacha (MK) for the duration of the evaluation, and if necessary, adjusted for inflation using a Malawi price index and discounted for time at a standard annual rate of 3%. In final reports, cost results will also be shown in USD using current exchange rates, discounted and undiscounted, and in both nominal and inflation-adjusted dollars. To inform scalability, we will also report costs per participant.

To enable comparisons of the relative efficiency of *Mlambe* to other strategies for addressing alcohol use among PLWH, detailed intervention and programme costs for the *Mlambe* arm will be measured during its 10-month duration. We will also measure costs for the EUC control arm, including the session of brief alcohol advice. Research costs will be excluded, per standard practice,[39] and these may not be relevant for the scale-up of the programme. The CEA will combine cost data with programme effects (estimated over 20 months in Aim 1) to measure the additional resources required to deliver *Mlambe*, compared with EUC, and to achieve changes in primary and secondary outcomes. All analyses and reporting will follow best practices as well as the Consolidated Health Economic Evaluation Reporting Standards.[55]

For the CEA, we will compute an incremental cost-effectiveness ratio (ICER). The ICER calculation is $(cost_2 - cost_1)/(effect_2 - effect_1)$, where 2 is *Mlambe,* 1 is EUC, cost is the value of resources in each arm, and the difference in effect is the impact of *Mlambe* found in Aim 1. All CEA results will be reported as ICERs for cost per outcome achieved, including the cost per reduced heavy alcohol user, improvement in viral suppression, reduced drinking day, one-unit reduction in AUDIT-C score and one-unit reduction in PEth value.

Ethical considerations and dissemination

Informed consent

The study's consent form will be read and explained to participants by a research assistant to obtain participation consent from the participants. Consent will be sought to participate in the trial, to record intervention sessions, to collect biomarker specimens and to export samples to the USA for PEth testing. Even though participants did not report any major issues during the pilot study, participants will still be informed of possible risks of participating in the study, such as accidental disclosure of HIV results, pain when drawing the blood sample, potential couple tension, etc. The consent process will cover topics on the purpose of the study, potential risks and benefits, how confidentiality will be ensured, voluntary participation, the funding agency and study investigators, and contact information for the study investigators and the institutional review boards (IRBs). Participants will be informed that they have the option to refuse or withdraw from the study at any time they feel like doing so without any penalties or losing any social benefits.

Ancillary studies

We do not plan to conduct further studies on samples collected from participants beyond what they consent for. Therefore, we will not need to ask for further consent from participants for ancillary studies.

Confidentiality and privacy

Loss of confidentiality and privacy may lead to social, physical and/or emotional harm because, for example, one's HIV status has unexpectedly been revealed. To safeguard against loss of confidentiality and privacy at any point of the study, all staff will receive training on the protection of participants' information at the initiation of the study and throughout the study. Further steps will be taken to protect the identity of participants. For example, participant names will be replaced with a unique identification number, contact tracing information including signed consent forms will be stored separately from survey data and the physical copies will be stored in locked file cabinets in study offices at IKI, while electronic data will be

stored in password-protected computers only accessible to the research manager and the study investigators.

Since this study involves couples, partners will be interviewed simultaneously but separately in private rooms by a gender-matched interviewer. Research assistants will not be instructed to not share any information regarding each partner's interview. All couples will be given a list of support services available in the district and communities that they may contact, including the Zomba Mental Hospital in case of severe cases of distress.

Benefits of participation

There are no direct benefits to the study participants. However, couples may learn information and skills to reduce alcohol use, engage in communication better with their partner and reduce financial insecurity. As we found in the pilot, some participants might find it therapeutic to discuss alcohol and issues in their relationships. The larger public health community could benefit if the intervention is found efficacious at reducing alcohol use, improving HIV treatment outcomes and, potentially, reducing the burden of HIV in the community.

Data safety and monitoring

This study protocol has been approved by the NHSRC in Malawi and the UCSF HRPP and is registered with Clinicaltrials.gov. A Data Safety and Monitoring Board (DSMB) comprised of independent experts with expertise in HIV and alcohol use research will be assembled as required by the National Institute of Health (NIH) policy. The DSMB will routinely convene every 6–12 months and impromptu in response to the occurrence of any serious adverse events. Data on anticipated adverse events, including couple dissolution and IPV, will be gathered throughout the study and reported to the DSMB at regular meetings. The DSMB members are not affiliates of the funding agency, UCSF or the local implementing partner.

Harms

Any adverse events following participation will be tracked via referral and clinician follow-up. We will complete the standard NHSRC adverse event form to document the incident, actions taken and follow-up steps. This form, supplemented by any additional staff notes, will be provided to the appropriate agencies, including the UCSF, NHSRC (Malawi IRB) and the funding agency (NIH, USA). Any resulting recommendations from the IRB will be communicated to the NIH. The site PI will be responsible for monitoring and reporting any adverse events to the US PI and will involve the DSMB.

Auditing

The NHSRC conducts announced and unannounced inspection visits for studies they approve. The study team will cooperate with them in either scenario and work on their recommendations to keep the study safe for participants and staff. The local team will conduct weekly spot checks of intervention sessions, completed consents and standard operating procedures.

Trial modification and discontinuation

Major changes such as to eligibility criteria or key aspects of the trial design will require approval from the study sponsor and DSMB, and amendments will be sought from the UCSF and Malawi IRBs before implementation, and the clinicaltrials.gov record will be updated. The DSMB will monitor for adverse events and will make recommendations to halt or pause the study if needed.

Interim analysis

There are no a priori plans to conduct interim analysis.

Ancillary and post-trial care

A list of community-based services for HIV, couples and behavioural health will be provided to participants at the start of the study. Participants who experience for IPV or serious mental health concerns will be referred by the research staff for psychosocial support services in the community. The research team will contact the service provider to set up an appointment and then inform the participant of their appointment schedule. The team would follow up with participants to ensure they were linked to services if they expressed an interest in obtaining help.

Dissemination

The study findings will be made available on clinicaltrials.gov. We will also deposit de-identified data in the US National Institute of Mental Health Data Archive (NDA) as required by our funder. In collaboration with the Malawi field team, results will be presented to participants and stakeholders, and at meetings with health officials and HIV care providers. Finally, presentations will be given at HIV and alcohol use conferences and published in peer-reviewed journals.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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