Innovative strategies to promote biomedical HIV prevention uptake and retention among high-risk adults at drinking venues in Kenya and Uganda

The Outreach and Prevention at ALcohol venues in East Africa study

(OPAL-East Africa study)

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Table of Contents

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Glossary of Terms

ART	Antiretroviral therapy
AUDIT-C	Alcohol Use Disorders Identification Test-Concise
DM	Diabetes mellitus
HLI	Healthy Living Intervention
HTN	Hypertension
MoH	Ministry of Health
PrEP	Pre-exposure prophylaxis
PEP	Post-exposure prophylaxis
PEth	Phosphatidylethanol

1. Study Synopsis

The project will rigorously test innovative interventions in Kenya and Uganda to increase uptake and use of biomedical HIV prevention, and assess facilitators, barriers, and cost-effectiveness of these approaches.

The project will have the following aims: **Aim 1**: Compare the effectiveness of two mobilization strategies to increase uptake of biomedical HIV prevention among adults at drinking venues. **Aim 2**: Determine the efficacy of the Healthy Living Intervention (HLI) to reduce heavy alcohol use vs. standard care (control) on retention in biomedical HIV prevention in a randomized trial among adults with heavy alcohol use. **Aim 3**: Determine the cost-effectiveness of interventions that increase biomedical HIV prevention uptake (Aim 1) and retention (Aim 2) among adults at high-risk for HIV who attend drinking venues.

The proposed research will address the critical intersection of alcohol use and HIV risk in SSA, by promoting reach, uptake and retention in biomedical HIV prevention and exploring associated facilitators and barriers.

1.1. Introduction

HIV incidence remains unacceptably high in sub-Saharan Africa (SSA) due in part to inadequate access, uptake, and retention in biomedical HIV prevention services, including pre- and post-exposure prophylaxis (PrEP/PEP), among persons at increased HIV risk. Alcohol use is a common risk factor for both HIV acquisition and poor HIV prevention uptake and retention in SSA. Interventions that promote biomedical HIV prevention among persons with heavy alcohol use and their sexual partners are urgently needed.

Alcohol-serving drinking venues play an important role as sites of HIV transmission in SSA and are ideal sites to engage women and men at increased risk of HIV in biomedical prevention services. However, despite long-standing awareness of drinking venues as transmission “hot spots”, few interventions exist to reach and engage persons in PrEP and PEP from drinking venues in SSA. Major barriers to reaching and engaging persons at high risk of HIV from community settings such as drinking venues in HIV testing – a critical first step to accessing biomedical HIV prevention – include HIV-associated stigma and poor perceptions of risk. To address these barriers, we have developed a mobilization strategy of integrating HIV testing within multi-disease screening that recruited >2,000 people from drinking venues in Kenya and Uganda, reaching >75% of adults recruited for HIV testing. We now need to determine whether multi-disease mobilization can promote uptake of HIV prevention for adults at drinking venues in the context of new biomedical prevention options.

Following uptake of biomedical HIV prevention, persons with heavy alcohol use face challenges with retention in care and adherence to PrEP/PEP. We have adapted a brief alcohol counseling intervention (Health Living) to reduce alcohol use and promote antiretroviral therapy (ART) adherence and HIV viral suppression among persons with HIV in Kenya and Uganda. We now need to determine whether this intervention can promote retention in biomedical prevention and PrEP/PEP adherence among adults with heavy alcohol use.

Problem Statement: HIV incidence remains above global targets for epidemic control in sub-Saharan Africa (SSA), and suboptimal retention in biomedical HIV preventive care undermines the promise of PrEP for HIV prevention. Alcohol use is a common risk factor for both HIV acquisition and poor HIV prevention uptake and retention in SSA. Interventions that promote biomedical HIV prevention among persons with heavy alcohol use and their sexual partners – persons at greatly increased risk of HIV – are urgently needed.
Justification of the study: This study will test innovative interventions to increase uptake and use of biomedical HIV prevention options by engaging women and men at drinking venues in rural Kenya and Uganda in care and evaluating a brief alcohol counseling intervention among adults with heavy alcohol use at high risk for HIV, while gaining insights into the facilitators, barriers, and cost-effectiveness of these approaches. The findings of this study will provide valuable information to policymakers and HIV prevention programs on the effectiveness of approaches – including strategies to mobilize and support prevention initiation and retention in prevention service care – to promote biomedical HIV prevention engagement among adults at drinking venues. Despite clear evidence that persons at drinking venues are at increased risk of HIV infection, there are very few

rigorous studies of strategies for engaging persons at risk of HIV from drinking venues. Similarly, despite increasing evidence that heavy alcohol use is a barrier to adherence to and retention in HIV biomedical preventive services, the effectiveness of brief alcohol counseling interventions to support retention and adherence to biomedical prevention remains unknown. Specifically, the first trial (Aim 1) will evaluate the relative effectiveness of offering multi-disease services vs. HIV-focused prevention services to promote biomedical HIV prevention uptake among persons from drinking venues, and the second trial (Aim 2) will evaluate whether a brief alcohol counseling intervention can improve retention in HIV preventive care.

2. Study Objectives

We will rigorously test innovative interventions in Kenya and Uganda to increase uptake and use of biomedical HIV prevention by engaging adults at drinking venues, evaluating the Healthy Living Intervention (HLI: brief alcohol counseling intervention) on PrEP/PEP retention and adherence in adults with heavy alcohol use at high HIV risk, and assessing facilitators, barriers, and cost-effectiveness of these approaches. We propose the following aims:

Aim 1: Compare the effectiveness of two mobilization strategies to increase uptake of biomedical HIV prevention among adults at drinking venues. We will compare *HIV-focused vs. multi-disease* mobilization to recruit adults at drinking venues for health center-based HIV or multi-disease testing, respectively. Participants in both arms (up to 5,000/arm) will be offered oral PrEP, the Dapivirine vaginal ring (women only) or PEP if HIV-uninfected, or ART if HIV-infected. The primary outcome will be PrEP/PEP initiation. Our hypothesis is that multi-disease mobilization will result in greater PrEP/PEP uptake. Secondary outcomes include HIV testing uptake, yield of persons with heavy drinking and with untreated HIV, and ART uptake. Qualitative research, including in-depth interviews among a stratified random sample of participants and observations at venues will be conducted to evaluate facilitators and barriers to prevention uptake and perceptions of the strategies. Aim 1 will address the research question: will mobilization of high-risk persons at drinking venues via a multi-disease approach be more effective than an HIV-focused approach in promoting biomedical prevention initiation?

Aim 2: Determine the efficacy of the Healthy Living Intervention (HLI) to reduce heavy alcohol use vs. standard care (control) on retention in biomedical HIV prevention in a randomized trial among adults with heavy alcohol use. We will compare a brief alcohol counseling intervention (already adapted to a Ugandan and Kenyan context) vs. control among 400 adults with heavy alcohol use initiating PrEP/PEP. The primary outcome will be HIV prevention coverage (proportion of time that a person is protected from HIV with PrEP/PEP) over 24 weeks. Our hypothesis is that the HLI will promote greater HIV prevention coverage. Secondary outcomes will include reductions in alcohol use (by AUDIT-C and phosphatidylethanol [PEth]) and HIV seroconversion. In-depth interviews in a stratified random sample of participants will evaluate facilitators and barriers to retention and adherence to HIV prevention. Aim 2 will address the research question: will a brief alcohol counseling intervention (the Healthy Living Intervention) promote greater retention in biomedical HIV prevention services - by reducing alcohol use and increasing healthy behavior – than standard care among adults at high risk for HIV with heavy alcohol use?

Aim 3: Determine the cost-effectiveness of interventions that increase biomedical HIV prevention uptake (Aim 1) and retention (Aim 2) among adults at high-risk for HIV who attend drinking venues. We will estimate the costs and cost-effectiveness of the interventions based on trial effectiveness measures.

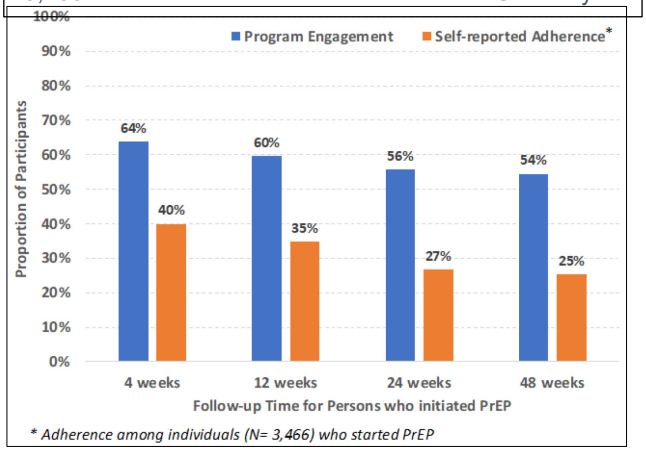
3. Background and Rationale

HIV incidence is high and well above global targets for epidemic control in sub-Saharan Africa (SSA), particularly among key populations at increased HIV risk, despite universal antiretroviral therapy (ART) eligibility for persons with HIV (PWH) and increasing availability of highly effective options for biomedical prevention.[1] In SSA, which accounts for 59% of new infections globally,[2] reducing HIV incidence requires strategies to optimize the effectiveness of biomedical HIV prevention, including pre-exposure prophylaxis (PrEP), in oral and injectable forms,[3-6] and post-exposure prophylaxis (PEP) among persons at risk for HIV.

Realizing the full potential of biomedical HIV prevention in SSA requires reaching and engaging persons at high risk of HIV. Despite increasing availability of biomedical prevention, several barriers exist to PrEP and PEP uptake among high-risk populations in SSA, including poverty, costs associated with accessing care, stigma, and inadequate knowledge about prevention (or how to access it) and about one's risk of HIV acquisition.[7-11] In implementation studies that have overcome access challenges and identified eligible adults at increased risk of HIV, PrEP uptake has been low to moderate, with <50% of eligible persons initiating PrEP. For example, in our large-scale Sustainable East Africa Research in Community Health (SEARCH) study of PrEP uptake, retention and adherence in Kenya and Uganda, we found that only 27% of PrEP-eligible adults initiated PrEP following population-wide HIV testing and risk assessment.[12] Notably, the likelihood of PrEP uptake among women was significantly lower for those working in bars or reporting alcohol consumption in this setting. Similarly, in a pilot study of PrEP uptake among adults with heavy alcohol use in South Africa, only 27% of eligible adults reached at drinking venues who were offered PrEP agreed to initiate it,[13] and in a cluster randomized trial in Zimbabwe that included community mobilization for female sex workers, 38% of sex workers who were screened and offered oral PrEP initiated it.[14] *Though some studies have found high acceptance and initiation of PrEP offered in clinical settings[15-17], how to effectively reach and engage adults at high HIV risk from community settings, such as drinking venues, to promote PrEP/PEP uptake is unclear.*

Suboptimal adherence to PrEP and retention in biomedical HIV preventive care also undermine the promise of PrEP for HIV prevention. Despite the high efficacy of PrEP, its effectiveness is dependent on adequate adherence and retention in care. In two oral PrEP trials among women in SSA, adherence was low (≤30%) and PrEP was not effective in reducing HIV risk.[18,19] In the majority of PrEP implementation studies (apart from those among mutually-disclosed discordant couples[20,21]), including the SEARCH study (**Figure 1**), adherence has dropped rapidly with <50% of PrEP initiators adhering by six months.[22] In one study in Kenya, PrEP uptake was 86% among eligible young women and 66% among female sex workers; however, only half continued at one month and 20% at six months.[23] Although PrEP use is ideally aligned with periods of HIV risk (i.e. "prevention-effective adherence"[24]), adherence has been found to be low even during periods of high risk.[25-27] As PrEP is now being brought to scale in SSA,[22] effective strategies to support retention in biomedical HIV prevention programs are critical.

Figure 1. PrEP program engagement and adherence in 3,466 adults who initiated PrEP in the SEARCH study.



Alcohol use is a common risk factor for *both* HIV acquisition and poor HIV prevention uptake, adherence, and retention in SSA. Multiple studies have found that alcohol use contributes to risk of HIV acquisition across SSA, including in Kenya and Uganda.[28-30] In prior meta-analyses, persons who consume alcohol are nearly two times more likely to be infected with HIV compared to those who abstain.[31,32] Several behaviors that increase HIV risk and have been associated with alcohol use include sex without a condom,[33] casual partnering and having multiple partners,[34] transactional sex[35], as well as impaired risk assessment, sexual negotiation and sexual decision-making.[34,36] In addition, a growing body of evidence suggests that alcohol use is associated with lower uptake and adherence to PrEP. As noted above, in our large-scale PrEP demonstration project

(SEARCH) in Kenya and Uganda, self-reported alcohol use of ≥1 day per month was associated with significantly lower odds of PrEP uptake among eligible women.[12] Alcohol use has been associated with decreased adherence to PrEP among sex workers in Uganda[37] and Zimbabwe[38], and HIV sero-discordant couples in Kenya and Uganda,[39] and non-retention in PrEP clinic among men who have sex with men in Kenya[40] and in PEP programs.[41] *Given the convergence of increased HIV risk and suboptimal PrEP uptake and retention, interventions to improve HIV prevention uptake and retention are urgently needed for persons with heavy alcohol use in SSA.*

Alcohol-serving drinking venues play an important role as sites of HIV transmission in SSA and are ideal sites to engage persons at increased risk of HIV in biomedical prevention services. In multiple studies and settings, attendance at drinking venues has been associated with increased HIV risk.[42] Increased risk of HIV has been found both among patrons and employees of drinking venues.[43-45] *Even after controlling for alcohol use*, attending drinking venues has been associated with high-risk sex.[46] However, despite these strong associations, there have been few HIV prevention interventions that have included drinking venues.[47] In addition, given the recency of PrEP availability in SSA, approaches to reach and engage persons in PrEP and PEP from drinking venues remain largely unexplored. *Furthermore, there are no studies evaluating implementation of flexible choice of prevention for engaging this high-risk population.* In a recent feasibility study of community-delivered PrEP in South Africa, study staff offered HIV testing and AUDIT screening outside of *shebeens* (drinking venues) 27 times over six months. Over this time, 162 *shebeen* patrons were screened of whom 136 (84%) were eligible for PrEP. Notably, only 37 patrons (27%) initiated PrEP, and the vast majority of *shebeen* patrons who participated in screening were men (92%).[13]

Common barriers to reaching and engaging persons at high HIV risk in biomedical HIV prevention from community settings in SSA are HIV-associated stigma and poor perceptions of HIV risk. HIV stigma is a well-established factor negatively impacting engagement in HIV-related services globally.[48-50] Mechanisms by which stigma results in lower HIV-related health engagement include enacted stigma from community members and health care providers, anticipated stigma (an expectation of stigma), and internalized stigma.[51] Fear of being perceived as HIV infected when accessing PrEP (as TDF/FTC are antiretroviral medications used in HIV treatment), or at high risk for HIV due to stigmatized behaviors when accessing HIV testing or other services, repeatedly emerge as barriers to care.[52,53] In drinking venues, HIV stigma may intersect with stigma associated with alcohol use[54] and commercial sex work, creating further challenges to reaching and engaging persons at risk for HIV. Poor perceptions of HIV risk and competing demands also contribute to low engagement,[55,56] and strategies to increase demand for HIV services among persons at risk are needed.

Offering multi-disease (*non-HIV-focused*) health services can be a compelling demand generating strategy that allows persons at risk for HIV to cope with stigma when engaging in HIV services. In Kenya and Uganda, we have shown that offering multi-disease services – such as screening for TB, malaria, diabetes and hypertension *in addition to* HIV – results in high uptake of testing in both men and women (**Table 1**).[57-60] In both the SEARCH universal HIV "test and treat" trial[57] and our trial engaging high-risk adults in Uganda[61], multi-disease services led to very high rates of HIV testing uptake, with *>95% population HIV testing coverage in SEARCH with this approach*.[62] Multi-disease screening may also alleviate stigma associated with accessing HIV testing and prevention services in isolation and engage persons with low perceptions of HIV risk. Qualitative data showed SEARCH community residents were drawn by non-HIV services and attracted those who reported prior reluctance to test for HIV.[63] While our prior studies are highly

Table 1. Multi-disease community-based testing uptake among census-enumerated residents in SEARCH trial communities in Kenya & Uganda

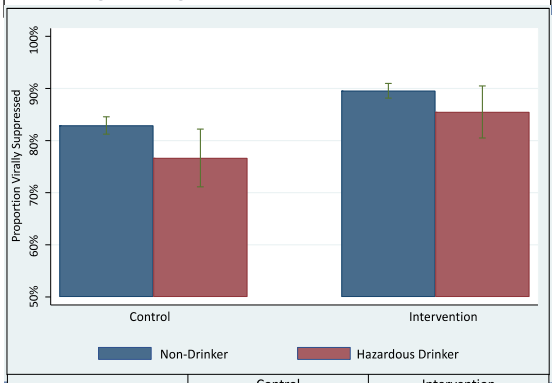
Multi-disease Service	Population accessing services	Demand: Population uptake (%)	Population uptake (%), by sex
Hypertension Screening	≥18 years	57,935 /68,121 (**85%**)	Women: **89%** Men: **79%**
Diabetes Screening	≥15 years	61,283 /77,788 (**79%**)	Women: **83%** Men: **74%**
Malaria Screening	All residents	*≥15 years:* 65,497 /77,788 (**84%**)	Women: **88%** Men: **79%**
TB Screening	≥15 years; Eastern Uganda only	22,269 /25,126 (**89%**)	Women: **90%** Men: **86%**

suggestive that offering multi-disease services can boost HIV testing and prevention service uptake compared to offering HIV-focused services alone,[64] *no randomized trials have evaluated this question.* In the proposed trial, we will directly test whether mobilization of high-risk persons at drinking venues via a multi-disease approach is more effective than an HIV-focused approach, in promoting biomedical prevention initiation.

In SSA, interventions to improve retention in biomedical HIV preventive care among persons with heavy alcohol use are limited. However, multi-session brief counseling for alcohol use interventions have been shown to be effective in reducing heavy alcohol use in multiple settings,[65] including studies in low- and middle-income countries.[66-68] Among PWH, such interventions can increase viral suppression via increased medication adherence,[68,69] suggesting that brief alcohol counseling interventions offer a potential, relatively low-cost intervention strategy for promoting retention in HIV preventive services and adherence to PrEP/PEP among persons with heavy alcohol use. The "Healthy Women Healthy Living" (HWHL) brief alcohol intervention demonstrated efficacy in reducing heavy drinking and unprotected vaginal sex among women living with HIV in the US.[70] It is based on an efficacious physician-delivered brief intervention in primary care.[71] Given its efficacy in reducing alcohol use and increasing HIV viral suppression,[68] our research group has adapted the HWHL intervention to a Ugandan context[72] and implemented this "Healthy Living" intervention (HLI) among PWH with heavy alcohol use in Uganda in a randomized trial of HLI vs. standard counseling to reduce heavy alcohol use (EXTEND study: NCT03928418). Our group has since further adapted it for Western Kenya, to evaluate the impact of HLI on viral suppression among PWH with heavy alcohol use in Kenya and Uganda in the SAPPHIRE trial (NCT04810650). *Whether this intervention could promote retention in biomedical HIV prevention services, including oral and injectable PrEP and PEP – by reducing alcohol use and increasing healthy behavior – among adults at high risk for HIV with heavy alcohol use remains unknown.*

Patient-centered care in which the needs and desired health outcomes of patients are central to care provision can improve multiple HIV-related outcomes, including medication adherence among persons with hazardous alcohol use. In the SEARCH HIV "test and treat" trial, providing patient-centered care – which included flexible clinic hours, phone access to a health care worker and a welcoming environment – resulted in improved retention in care and higher HIV viral suppression than standard care.[62,73-75] Furthermore, following population-wide HIV testing, *patient-centered care significantly reduced disparities in viral suppression among PWH with heavy alcohol used compared to those who abstain from alcohol* in the SEARCH trial (**Figure 2**).[76] Building on these findings, in the ongoing SAPPHIRE trial in Kenya and Uganda, we are evaluating a patient-centered approach to prevention – **"Dynamic Choice Prevention"** – that provides flexible access to biomedical HIV prevention options, including oral PrEP, the dapivirine vaginal ring and event-based PEP. The Dynamic Choice Prevention approach incorporates flexibility in choice to optimize uptake, adherence, and retention. Dynamic Choice Prevention provides an ideal context to evaluate interventions to engage and retain persons with hazardous alcohol use in biomedical HIV prevention.

Figure 2. HIV viral suppression at year 3, by SEARCH trial arm and baseline hazardous drinking among PWH.



	Control % (95% CI)	Intervention % (95% CI)
Non-Drinkers	83 (81-85)	90 (88-91)
Hazardous Drinkers	77 (71-82)	86 (81-91)

*Adjustment set included: sex, age, mobility, marital status, education level, occupation, and wealth quintile

In summary, interventions are urgently needed to ensure persons at high risk for HIV due to alcohol consumption are reached and engaged with effective biomedical HIV prevention tools. We are at a point in the HIV pandemic where, all too often, persons at greatest risk for HIV acquisition are not reached for or engaging with highly effective biomedical HIV prevention options. The relationship between alcohol use, drinking venues and HIV infection risk in SSA is clear and must be addressed. This study will test innovative interventions to increase uptake and use of biomedical HIV prevention by engaging persons at drinking venues

in care, evaluating the HLI intervention among adults with heavy alcohol use at high risk for HIV, and gaining insights into the facilitators, barriers, and cost-effectiveness of these approaches.

3.1 Preliminary Studies

We have developed and effectively implemented a recruitment card approach to mobilize adults from drinking venues in rural Kenya and Uganda for HIV testing followed by linkage to care for PWH. Using recruitment cards as proposed for the Aim 1 trial, we have implemented drinking venue mobilization in several studies.[61,77] We identified 61 drinking venues and distributed 960 cards with multi-disease messaging in a randomized trial to promote HIV retesting among adults at increased HIV risk in peri-urban Uganda. Of 960 persons who received cards at drinking venues, 773 (81%) adults presented to clinic within a week of card distribution, of whom 261 (34%) were adults with HIV.[45,61] Of the remaining 512 adults without HIV infection from drinking venues, 351 (69%) self-reported a significant risk for HIV in the prior 12 months, including multiple concurrent partners, sexual partners with HIV, diagnosis of ≥1 sexually transmitted infection and transactional sex. Using this same approach in Kenya in the ongoing SAPPHIRE trial (NCT04810650), we have distributed 1,131 recruitment cards with multi-disease messaging to formal and informal drinking venues in Western Kenya, and 863 adults (76%) have linked to our study clinics to date for screening and HIV testing. Of the 863 adults who linked to care, 270 (31%) were PWH, and 60 (7%) were identified with untreated HIV (**Table 3**).

Table 3. Yield of recruitment card approach to mobilize adults from drinking venues in Kenya and Uganda for HIV testing.

Setting	Drinking Venues		Health Center			
Country	Drinking venues visited	Recruitment cards distributed	Tested for HIV with recruitment card	HIV positivity	Adult at increased risk of HIV	
					Women	Men
Kenya	77	1131	863 (76%)	270 (31%)	110	478
Uganda	61	960	773 (81%)	234 (34%)	424	88

We have evaluated multi-disease strategies for community-based mobilization to promote HIV testing, prevention, and treatment for over 10 years. Such approaches have included large-scale community health fairs,[58,59,78,79] home-based testing[57] and community-based outreach and testing among key populations at increased risk of HIV.[61,80] Qualitative data from such strategies suggest that offering HIV testing and services within the broader context of maintaining health impacts community-level stigma associated with accessing HIV services.[81] *However, whether multi-disease screening can lead to improved uptake of HIV testing and prevention compared to standard, HIV-focused outreach,[47] by providing a means to cope with stigma and leveraging broader demand for services, particularly among adults at increased risk of HIV, has not been rigorously tested or adopted by programs to reach key populations such as adults at drinking venues.*

We have led one of the largest PrEP implementation studies to date and will leverage existing research infrastructure to implement and evaluate "Dynamic Choice" HIV prevention and measure prevention coverage, including use of oral PrEP, the dapivirine vaginal ring and PEP, for the proposed trial. In the SEARCH trial (NCT01864603), our team offered PrEP to >12,000 persons at elevated HIV risk during population-wide HIV testing in 16 rural communities in Kenya and Uganda.[12,82,83] Notably, the likelihood of PrEP uptake among women was significantly lower for those reporting alcohol consumption than those who abstain from alcohol (**Table 4**).[12] Among 3,466 people who initiated PrEP, there were substantial declines in PrEP program retention and adherence over time. Only 54% of PrEP initiators were engaged in care and 25% were adherent at 48 weeks. Even among a sub-group who reported

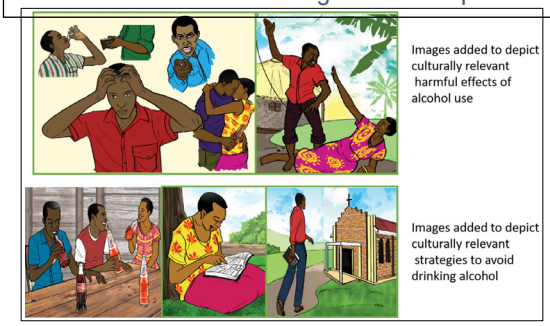
Table 4. Factors associated with PrEP uptake among women at elevated HIV risk in 16 communities in rural Kenya and Uganda in the SEARCH trial.

Women at elevated risk in rural Kenya & Uganda	Adjusted odds ratio of PrEP uptake (95% CI)	p value
Age, years		
15-24	0.43 (0.33-0.56)	<0.0001
25-34	0.52 (0.43-0.63)	<0.0001
35-44	1	..
≥45	0.79 (0.61-1.01)	0.065
Occupation		
Student or other formal sector	1	..
Fishing, **bar**, or transport	0.68 (0.52-0.89)	0.0048
Alcohol use		
None	1	..
≥1 day per month	0.74 (0.55-0.99)	0.040

ongoing high HIV risk and self-reported PrEP adherence, pill-taking was a challenge with 33% having hair levels consistent with taking <4 doses of PrEP/week. Our group has also studied PEP implementation in Kenya and Uganda and demonstrated high PEP retention (97%) and adherence (85%) at 4 weeks in adults following high-risk sexual exposures.[84] In the ongoing SAPPHIRE trial, we are evaluating a patient-centered "Dynamic Choice Prevention" approach to promote PrEP/PEP uptake and retention among adults at-risk for HIV that we will leverage for the proposed trial. This Dynamic Choice approach includes choice of oral PrEP (*with access to the dapivirine vaginal ring in all SAPPHIRE intervention communities to begin in 2023*) or event-driven PEP, and flexibility to *go back and forth* between current and emerging options when available (e.g., dapivirine vaginal ring). The well-developed, existing research infrastructure in the SAPPHIRE trial thus provides an opportunity to rigorously measure prevention uptake by adults at drinking venues and retention in biomedical HIV prevention among adults with heavy alcohol use.

We have adapted and implemented an intervention (Healthy Living Intervention [HLI]) to reduce heavy alcohol use and promote ART adherence and HIV viral suppression among PWH in Kenya and Uganda. Given the relative lack of interventions to reduce hazardous drinking in SSA, our group (led by Hahn and Camlin) has adapted a brief alcohol counseling intervention previously shown to be effective in reducing alcohol use in resource-limited settings,[66] to a Ugandan context (**Figure 3**).[72] The adapted HLI has now been effectively implemented in the EXTEND study (NCT03928418) among PWH, and adapted to a Kenyan context for PWH with heavy alcohol use in the SAPPHIRE trial. While the results of these trials are still pending, similar versions of this intervention have been shown to be effective to decrease alcohol use in PWH in low/middle income settings (Baltimore, Vietnam, India) and reduce viral suppression in one.[66,68,70] In addition, our team has extensive experience measuring alcohol use outcomes in SSA, including using biomarkers such as phosphatidylethanol (PEth). PEth is a phospholipid which is formed only in the presence of alcohol and thus is highly specific.[85] PEth is the most sensitive medium-term biomarker,[86] and PEth levels have been well correlated (Spearman's r= 0.6-0.8) with level of consumption in controlled studies.[87-90] We found that PEth was 95% sensitive and 73% specific for detecting prior 21-day heavy drinking, and highly correlated with the number of drinking days in PWH in Uganda.[90] It is tested from whole blood or dried blood spots which are easy to store and transport. We have subsequently used PEth to confirm suspected under-reporting in Uganda.[91,92] Our team is therefore well-positioned to rigorously test the HLI as an intervention to promote retention in HIV prevention services and adherence to PrEP and PEP among adults with heavy alcohol use at greatly increased HIV risk, and will include objective measures of the prime mediator, unhealthy alcohol use.

Figure 3. Example of images added to the HLI intervention workbook during cultural adaptation



We have integrated qualitative and costing measures and gained valuable insights into participant and provider facilitators and barriers to trial outcomes, cost-effectiveness and scalability. Qualitative and mixed method studies (led by Camlin) have provided rich understanding of local contexts, barriers and facilitators to engaging in HIV services, and perceptions of study interventions, including alcohol interventions. For example, in the SEARCH universal "test and treat" trial, focus group discussions and in-depth interviews among young adults who initiated vs declined PrEP revealed barriers such as HIV and ART-associated stigma, desire for "proof" of PrEP efficacy and misinformation/rumors,[93] that have informed interventions developed for the subsequent SAPPHIRE trial. Similarly, in SEARCH, costing studies (led by Shade) have provided valuable data for stakeholders and policymakers regarding the low added costs of adding multi-disease screening to HIV testing,[94] and of delivery of integrated hypertension/HIV care.[95]

4. Study Setting & Population

The study will take place in rural Kenya and Uganda (i.e., not defined as an urban municipality in either Uganda or Kenya) in eight geographically dispersed communities (each served by an ART/PrEP/PEP-providing health center) that are participating in the ongoing SAPPHIRE trial (NCT04810650). The study communities are in southwestern Uganda (4 communities) and western Kenya (4 communities) where adult HIV prevalence is 7% and 18%, respectively.[57] Uganda has one of the highest rates of alcohol use in SSA, and in both settings, heavy alcohol use is common, with an estimated 21% and 11% of the adult (≥15 years) population reporting heavy episodic drinking (i.e., >60 grams of pure alcohol on at least one occasion at least once a month),[96] and likely further unreported unhealthy alcohol use.[97,98] We have been at the forefront of implementing innovative HIV prevention and treatment approaches[12,74,84,99] and alcohol intervention[72,100] and measurement[97,101] studies in these regions. Access to Dynamic Choice Prevention (offered within the SAPPHIRE trial) and support from Ministries of Health (MoH) provide an optimal setting for the proposed study.

5. Study Design

5.1. Study Overview

We will determine the effectiveness of novel interventions to reach and engage adults who attend drinking venues in biomedical HIV prevention services, and then promote retention in preventive services, including adherence to oral PrEP and event-based PEP, among adults with heavy alcohol use in rural Kenya and Uganda. In **Aim 1**, we will compare two strategies – HIV-focused vs. multi-disease mobilization, testing and counseling – on initiation of PrEP or PEP among adults recruited from drinking venues. In **Aim 2**, we will determine the efficacy of a brief, multi-session alcohol counseling intervention on HIV prevention coverage (retention and adherence in PrEP/PEP), as well as reductions in heavy alcohol use, over 48 weeks. We will conduct in-depth qualitative interviews with a subset of participants from Aims 1 and 2, with stratified, random sampling based on key outcome measures, including perceptions of mobilization messaging, and barriers and facilitators to PrEP/PEP uptake and adherence among adults with heavy alcohol use. In **Aim 3** we will determine the costs and cost-effectiveness of interventions that promote HIV prevention uptake and retention among adults at high-risk for HIV who attend drinking venues (**Table 2**).

Table 2. Overview of proposed study aims, with study population, design, and outcome measures.

Aim	Study Population	Study Design	Outcomes
Aim 1	Adults (≥18 yrs) at drinking venues (patrons or workers) in study communities (N=up to 10,000 participants, from ~120 drinking venues)	Cluster randomized trial comparing drinking venue mobilization via HIV-focused (Arm 1) vs. Multi-disease (Arm 2) mobilization, testing, and counseling, on biomedical HIV prevention uptake	Primary: Initiation of PrEP or PEP at time of HIV testing among HIV-uninfected adults Secondary: a) HIV testing uptake; b) yield of adults with heavy EtOH use; c) yield of untreated HIV; d) ART uptake if HIV+ Qualitative: a) Perceptions of drinking venue mobilization strategies; b) barriers/facilitators of biomedical HIV prevention uptake
Aim 2	HIV-uninfected adults with heavy alcohol use (N=400) Eligible individuals who decline Aim 2 RCT participation but consent to	Randomized trial comparing the Healthy Living intervention to reduce hazardous alcohol use vs. standard care (control) on PrEP/PEP retention among heavy drinkers offered Dynamic Choice prevention	Primary: HIV Prevention coverage (retention in PrEP or PEP) over 24 weeks Secondary: a) Heavy alcohol use (AUDIT-C, PEth), b) HIV Prevention coverage (retention in PrEP or PEP) over 48 weeks, c)HIV seroconversion

	qualitative interview only (N=20)		Qualitative: a) Perceptions of intervention, alcohol use, and dynamic choice; b) barriers and facilitators to retention and adherence
Aim 3	Aim 1 and 2 study populations & care providers	Costing and Cost-Effectiveness Analyses (CEA)	CEA: Cost per HIV infection averted and cost per DALY averted

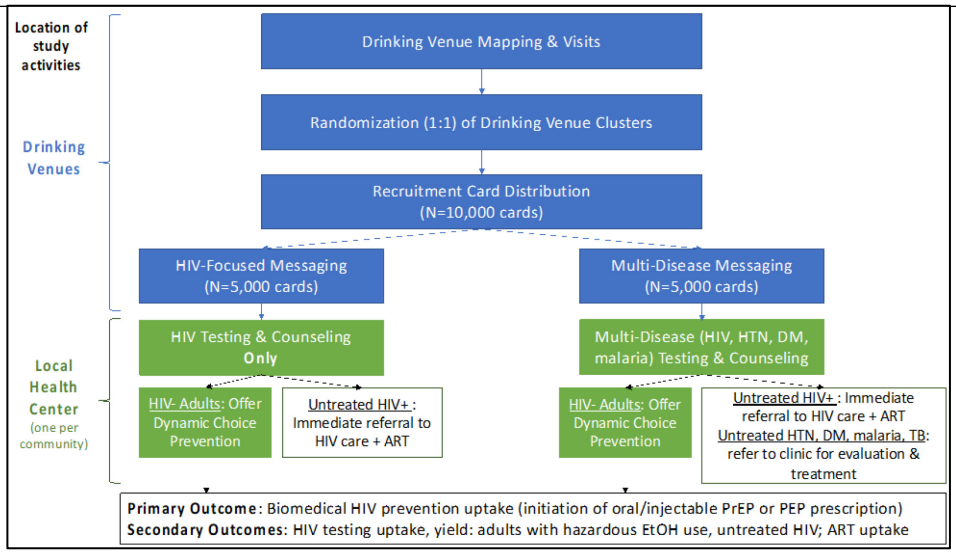
6. Drinking Venue Mobilization Strategies (Aim 1) Trial

Restatement of Aim 1: Compare the effectiveness of two mobilization strategies to increase uptake of biomedical HIV prevention among adults at drinking venues.

6.1 Aim 1 Study Design

We will conduct a two-arm, cluster randomized controlled trial of multi-disease vs. HIV-focused mobilization strategies to promote biomedical HIV prevention uptake among adults at drinking venues (**Figure 4: Schematic**).

Figure 4: Aim 1 Drinking Venue Mobilization Trial Schematic



6.2 Eligibility Criteria

Inclusion criteria: *Drinking venue eligibility*: venue within the study community at which alcohol is sold and consumed; Participant inclusion: a) adult (≥18 years); b) patron or worker at a drinking venue within the study community.

Participant exclusion criteria: a) age <18 years; b) inability to provide informed consent (e.g., if heavily intoxicated from alcohol use at time of health center-based screening).

6.3 Consent Process

a) Recruitment card distribution at drinking venues: When initiating interaction with persons at drinking venues within the study communities, study staff will identify themselves as members of the research team and, after verbally confirming a person is ≥18 years of age (in both Kenya and Uganda, persons <18 years old are not legally allowed to attend drinking venues), they will briefly describe the purpose of the study and proceed with recruitment card distribution.

b) Health screening at local health centers (written consent): Study staff working with each local health center's triage/check-in office will receive adults presenting with recruitment cards and obtain written consent for participation in additional health screening. Persons with gross inebriation or inability to provide informed consent *at the time of health center screening* will be ineligible to provide written consent and told they may return later (when no longer grossly inebriated) to undergo screening.

6.4 Community Engagement Plan

Study staff will engage community leaders, healthcare leaders, community members, and other key stakeholders in meetings to introduce and discuss the study, with approaches we have used in prior community-based studies in Kenya and Uganda.

Meetings with key leaders and stakeholders will be held in each region to introduce the study, answer questions, and engage leaders/stakeholders. In preparation for drinking venue mobilization activities (Aim 1), study staff will also meet with drinking venue owners, drinking venue managers, and key community representatives, to seek input on the following:

- Identification of potential challenges and solutions to implementation
- Communities and subgroups that may require special consideration
- Other issues tailored to individual regions

Dissemination**:** At the end of the study period, we will invite key community stakeholders to a dissemination meeting to share results of the study and discuss how the results of the study could be incorporated into routine clinical practice to improve care for persons at risk of HIV at drinking venues.

6.5 Enrollment & Randomization

a) Enrollment: Study recruitment will occur at the time of recruitment card distribution at drinking venues, following a brief verbal introduction. Staff will enroll participants and obtain written consent for study participation (including HIV testing and/or multi-disease screening) at the time that participants come to the clinic with recruitment cards. Study staff will continue to recruit participants and distribute recruitment cards until they have distributed recruitment cards to up to 10,000 drinking venue attendees/study participants.

b) Randomization: We will randomize drinking venue clusters, with specification of clusters based on neighborhood, parish/sublocation or geographic co-location to be determined upon completion of drinking venue mapping (see Section 6.6.1. Procedures: Drinking venue mapping, below). We anticipate a minimum of 16 clusters, and a maximum of 120 clusters (i.e., the anticipated number of drinking venues total in all 8 communities). Randomization will be conducted within strata defined by country, community, venue size (average number of persons at drinking venues within the cluster), and potentially other characteristics determined upon completion of the mapping, but prior to randomization. We will randomize clusters 1:1, using a random number generator, to either multi-disease mobilization messaging (intervention) or HIV-focused messaging (control) prior to initiation of participant recruitment and enrollment. Recruitment cards will be the same size, shape, and color, but messaging on one side of the cards will vary by mobilization strategy (randomization arm). Staff distributing the cards will aim to provide one card per adult encountered at the drinking venue.

6.6 Study Groups

a) HIV-focused messaging: Recruitment cards distributed at drinking venues will offer free HIV testing with access to biomedical HIV prevention. The cards will include the health center name, location, and hours. Participants who present to the health center with the HIV-focused recruitment cards will receive HIV-counseling and testing alone, emphasizing the risk of HIV infection and benefits of biomedical HIV prevention for adults who attend or work at drinking venues.

b) Multi-disease messaging: Recruitment cards distributed at drinking venues will offer a free health screening for multiple conditions, that may include: hypertension (HTN), diabetes mellitus (DM), HIV, tuberculosis (if symptomatic with cough, fever, weight loss or night sweats) and malaria (if febrile), with access to biomedical HIV prevention and multi-disease treatment services. Participants who present to the health center with the multi-disease recruitment cards will receive multi-disease (HTN, DM, HIV, TB and malaria) testing and counseling, with an emphasis on staying healthy and prevention and treatment of non-communicable and communicable diseases, including discussion of the risk of HIV infection and benefits of biomedical HIV prevention for adults who attend or work at drinking venues.

In both groups, participants who link to the health center for HIV or multi-disease screening with a recruitment card will receive a one-time travel voucher of up to US$5 for reimbursement of travel expenses.

All participants (both groups) who test HIV negative will be offered Dynamic Choice Prevention (see Procedures, below). Adults with untreated HIV who link to clinic will receive counseling emphasizing the benefits of antiretroviral therapy (ART) in preventing morbidity and HIV transmission with immediate referral to on-site HIV care and ART.

6.7 Procedures

1. Drinking venue mapping: Study staff will map all drinking venues, including bars, night clubs, hotels, and informal drinking dens (e.g., where commercial beer and local brews and spirits – *changaa* in Kenya, and *malwa/waragi* – are sold) in the study communities while recording global positioning system (GPS) location of each venue visited.[102,103] At each venue, staff will meet with venue owners prior to recruitment card distribution to describe the study and determine optimal times of the week and day for staff visits, based on attendance at drinking venues.

2. Recruitment card distribution: Staff will then visit each venue periodically throughout the Aim 1 trial to distribute recruitment cards to persons at drinking venues (based on randomization group assignment of the cluster), including patrons and employees, until all drinking venues have been visited at least once (with up to 10,000 cards distributed: up to 5,000 with HIV-focused messaging; up to 5,000 with multi-disease messaging. As noted above, recruitment cards will be the same size, shape, and color, but messaging on one side of the cards will vary by mobilization strategy. Staff will distribute cards and provide a brief, focused script that varies based on drinking venue randomization assignment, encouraging each adult to come to the local health center for screening (either HIV or multi-disease) with the recruitment card. The script, in both arms, may include brief messaging on availability of PrEP for HIV prevention at local clinics and the importance of ART for those with untreated HIV. All cards will indicate that travel costs (up to US$5) will be reimbursed for persons who come for screening and present a recruitment card. Prior to distribution, staff will record unique identifiers (recruitment card serial numbers) noting to which drinking venue each card was to be distributed and the date of mobilization (using procedures we have previously developed and implemented[45,61]). For each card distributed, staff will record the sex and age of the person to whom the card was given.

3. Clinic-based screening: Study staff working with each local health center's triage/check-in office will receive adults presenting with recruitment cards and obtain written consent for participation in additional health screening and a baseline survey to assess demographics, socio-economic status, HIV risk, HIV-related stigma and alcohol use. We will use digital fingerprint biometric metrics (with procedures used in prior studies[57,99]) or other personal identifiers (such as full name, age and household identification number) at time of screening to ensure participants enroll only once in the trial. Staff will provide clinic-based counseling and testing according to the approach indicated on the recruitment card, as follows:

a) *HIV testing and counseling*: Study staff will provide HIV testing performed according to national (Kenya or Uganda) MoH guideline rapid HIV antibody testing algorithms,[104,105] as well pre- and post-test counseling. Staff will focus on HIV risk and HIV counseling alone.

b) *Multi-disease testing and counseling*: Study staff will provide counseling emphasizing general health and wellbeing, and options for prevention and treatment of common communicable and non-communicable diseases. Staff may provide the following screening services: i) HIV testing performed according to national (Kenya or Uganda) MoH guideline rapid HIV antibody testing algorithms,[104,105] as well pre- and post-test counseling; ii) hypertension screening by automated sphygmomanometer; iii) diabetes mellitus screening by random blood glucose measure; iv) malaria screening by rapid diagnostic test, if febrile; v) option of TB screening (by sputum specimen collection for sputum microscopy or Xpert MTB/RIF assay, if symptomatic with fever, cough, night sweats or weight loss; and/or chest x-ray, depending on clinic availability); vi) option of urine pregnancy testing for pre-menopausal women; and vii) referral for sexually transmitted infection (STI)

testing for symptomatic men and women. We have offered similar multi-disease screening in prior studies.[57,59,61]

In both arms, study staff will offer eligible participants who test HIV negative initiation of oral PrEP or PEP if indicated, within the Dynamic Choice prevention service delivery model of the SAPPHIRE trial.

Study staff will also emphasize the importance of adherence to PrEP and PEP in preventing HIV infection, and the potential consequences associated with non-adherence (including HIV seroconversion).

4. Dynamic Choice Prevention is a patient-centered approach implemented in the intervention arm of the ongoing SAPPHIRE trial (NCT04810650) designed to address barriers to biomedical HIV prevention with PrEP and PEP that we identified when offering PrEP to >12,000 persons with risk factors for HIV acquisition in the study regions.[12] Components are delivered by study nurses and may include: a) choice of oral or injectable PrEP, the dapivirine vaginal ring (when available; women only) or event-driven PEP by country guidelines, and flexibility to *go back and forth* between current and emerging options once available (e.g., the dapivirine vaginal ring); b) client-centered care in which PrEP/PEP is offered in a supportive environment; c) flexibility in location of PrEP/PEP delivery over time; d) longer refills (up to 3 months) of oral PrEP; and e) HIV testing options of either rapid clinic-based testing or self-testing.

5. HIV treatment: Staff will refer all adults with untreated HIV to on-site HIV care for immediate offer of ART.

6. Qualitative interviews and observation at venues: Following clinic-based screening, study staff will recruit a subset of participants stratified by sex and uptake of PrEP/PEP from each study group for in-depth interviews to better understand motivations and stigma among adults at drinking venues for participating in screening and initiating PrEP/PEP. Study team members will also conduct qualitative observations during study activities at venues to gain insights into public reactions and interactions related to implementation.

6.8 Measurements

Outcome variables

1. Primary Outcome: The Aim 1 primary outcome will be **biomedical HIV prevention uptake**, defined as the proportion of HIV- adults, receiving a randomization card, who initiate PrEP or PEP after mobilization. The primary analysis will focus on a 4-week PrEP/PEP initiation period after recruitment card distribution; secondary analyses will consider initiation periods of 8 and 12 weeks.

2. Secondary Outcomes: By study arm, we will compare: a) **HIV testing uptake**: defined as presentation for clinic-based HIV testing with a recruitment card; b) **yield of adults with untreated HIV**: defined as the proportion of persons testing who are identified with newly diagnosed HIV or self-reported, known HIV infection but out of care and off of ART; c) **yield of adults with heavy alcohol use**, defined as AUDIT-C score of ≥4 for men and ≥3 for women; and d) **proportion of adults with untreated HIV that initiate ART** within one week of presenting for clinic-based screening with a recruitment card.

3. Qualitative inquiry. A.) In-depth semi-structured interviews: In accordance with principles of Grounded Theory[106], we will iteratively collect and rapidly analyze interview transcript data, continuing to randomly select participants within theoretically-informed categories (e.g. not only categories such as study group, age group and sex, but characteristics found to be salient for further sampling) until the data attain theoretical saturation. Based on our prior qualitative research in the setting, we anticipate adequate thematic saturation with N=10-20 participants with PrEP/PEP uptake and N=10-20 who declined PrEP/PEP initiation per study arm (N=80 total), with a 'ceiling' number of participants set based on practical study schedule requirements. The interview guide will be designed to elicit responses in two thematic areas: i) *perceptions, attitudes, and preferences related to the mobilization strategy received,* including perceptions of HIV-related stigma; and ii) *motivations and barriers related to biomedical HIV prevention uptake among adults who attend or work at drinking venues*, including qualitative exploration of risk preferences, effects of alcohol use, other psychosocial

factors (e.g. fatalism, coping style, stigma, and perceived gender norms) and other contextual factors. Trained interviewers will pursue lines of questioning following the domains of inquiry outlined above, while allowing participants to discuss salient subjects. Interviews will be audio-recorded, transcribed, and translated into English. B.) Participant observation at drinking venues: Following community entry and after obtaining local permissions, study team members will visit selected drinking venues (composed of a balanced number of venues across randomization groupings) during the recruitment card distribution activities described above. Team members will observe reactions of and interactions between individuals within venues during implementation in order to gain a deeper understanding of contextual factors that may influence study implementation and outcomes. Observations will be recorded in field notes following each exercise.

6.9 Data collection & management

Baseline survey data: Staff will collect questionnaire data using hand-held computers (tablets) or paper questionnaires (as back up, if tablets are not functioning, with subsequent data entry into computers or tablets). Data will be transferred via secure electronic transfer to our data center facilities in Kenya and/or Uganda and stored on a secure server.

Drinking venue GPS: Each drinking venue location will be mapped using a hand-held GPS receiver. Readings will be taken from the main entry door of the drinking venue, if possible, or from a point that is most representative of the venue. The GPS coordinates for each drinking venue will be recorded by the time of distribution of recruitment cards. GPS data will be synchronized from the GPS device to an electronic database and then transferred via a secure electronic transfer to the data center facilities in Kenya and/or Uganda and stored on a secure server.

Digital fingerprint biometric: A digital biometric identifier based on an electronic fingerprint of each participant at time of clinic-based screening will be captured in an electronic database and linked to the study participant's name. The biometric identifier will be saved into the study electronic database. The database will be transferred via a secure electronic transfer to the data center facilities in Kenya and/or Uganda and stored on a secure server. Alternatively, staff may obtain other personal identifiers (such as full name, age and household identification number) at time of screening.

HIV Test Results: Staff working at the study community clinics will record all lab test results, including HIV antibody test results, and HIV diagnosis status information, under each participant's study identification number (ID) in either paper lab logs or computers. Staff will also record non-HIV (multi-disease) screening/test results under each participant's study ID in either paper lab logs or computers. Data from these logs or devices will be transferred via a secure electronic transfer to our data center facilities in Kenya and/or Uganda and stored on a secure server. Staff will record PrEP/PEP initiation and ART start (when applicable) from clinical records, following HIV screening and referral to clinical services.

Qualitative Data: Staff will record interviews on audio devices using study IDs (not participant names), and transcribed interviews and translations, along with field notes, will be data entered into appropriate software on password-protected study computers. Data from interviews will be transferred via a secure electronic transfer to our data center facility and stored on a secure server.

6.10 Analysis

6.10.1 Primary Analysis

We will compare the primary outcome of biomedical HIV prevention (PrEP/PEP) uptake between the two study groups, accounting for clustering. We will evaluate the interventions using targeted maximum likelihood estimation (TMLE), a pre-specified approach to data-adaptively adjust for stratification factors used in randomization (country) as well as chance imbalances between randomized arms in additional baseline predictors of the outcome.[107,108] This approach provides precision and power gains over standard approaches

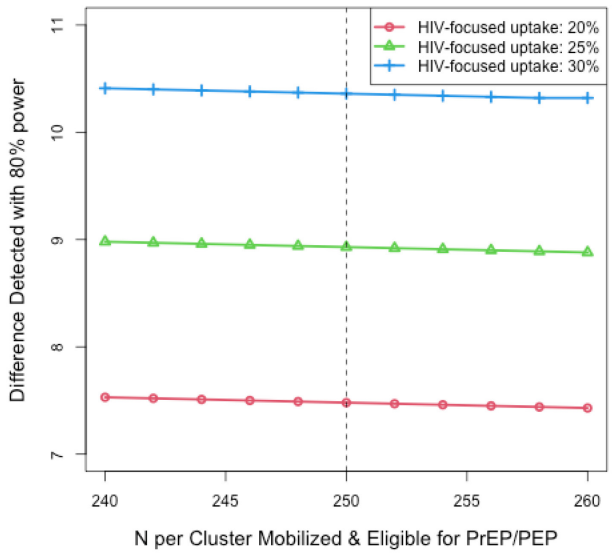
that only adjust for stratification factors. We will test the **null hypothesis** of no difference in HIV prevention uptake by mobilization strategy.

6.10.2 Analysis of qualitative data

Translated interview data and textual field note data will be imported into a qualitative analysis software program, for thematic analysis[109] guided by grounded theoretical approaches[106], in which research team members iteratively analyze transcripts and field notes and develop a common set of inductive codes describing patterns observed in the data. New codes proposed by research team members will be vetted and defined in relation to existing codes. As new data are collected and reviewed, and data reach analytic saturation, the research team members will independently code the interviews and field notes and discuss data segments that are particularly rich or difficult to code. Team members will discuss and resolve divergent coding and interpretations of findings to ensure that codes are applied consistently. Analytical memos will extract and summarize findings following the domains of inquiry outlined above, in order to extract themes and central ideas that explain the meaning of the data.

6.10.3 Power Calculations

We have powered our trial to identify enough eligible adults for enrollment in the Aim 2 trial and to detect a difference of ≥10% in HIV prevention uptake between the two arms. We plan to mobilize a minimum of 5,000 adults from a minimum of 16 drinking venue clusters (8 clusters, 60 venues, and 2,500 adults per trial arm). If we assume that ~20% of those mobilized are PWH or currently on PrEP/PEP, we expect ~4,000 adults mobilized to be eligible to initiate PrEP/PEP (~250 adults/cluster). Based on prior work[61,77], we anticipate that up to 80% of those mobilized will present for screening in the HIV-focused arm. Also based on prior studies,[12-14] we estimate that ~25% of adults offered prevention will initiate PrEP/PEP in the HIV-focused arm. Altogether, we anticipate 20% prevention uptake in the HIV-focused arm. With a coefficient of variation (k=0.175), we will estimate having 80% power to detect a ≥7.5% increase in prevention uptake in the multi-disease arm (2-sided, α=0.05). As shown in the Figure, these calculations are fairly robust to the uptake in the HIV-focused arm and the average number of participants per cluster. If, after drinking venue mapping, 32 drinking venue clusters (each with ~125 eligible participants) are selected as the unit of randomization, then we estimate having 80% power to detect a ≥5.6% increase. We expect these calculations to be conservative, because of the precision gained through stratified randomization and through covariate adjustment during the analysis.



7. Healthy Living Intervention for HIV prevention (Aim 2) Trial

Restatement of Aim 2: Determine the efficacy of the Healthy Living Intervention (HLI) to reduce heavy alcohol use vs. standard care (control) on retention in biomedical HIV prevention in a randomized trial among adults with heavy alcohol use.

7.1 Study Design

We will conduct a two-arm, individually randomized controlled trial of a brief alcohol counseling intervention adapted to a Ugandan and Kenyan context (the Healthy Living Intervention[72]) vs. control (standard alcohol

counseling per national MoH guidelines) on retention in biomedical HIV preventive care over 48 weeks among HIV-uninfected adults with heavy alcohol use initiating PrEP or PEP (**Figure 5**).

7.2 Study Population & Eligibility Criteria

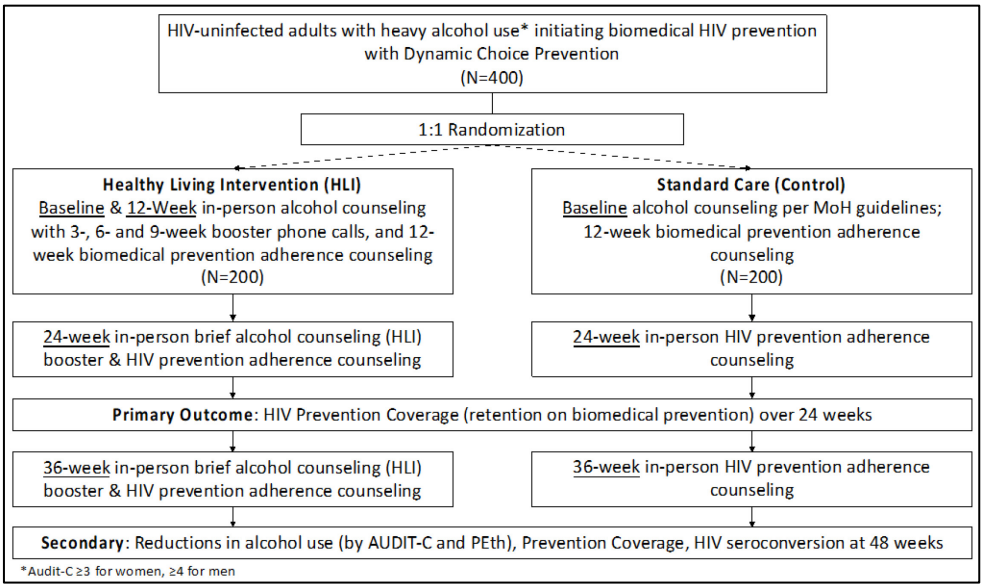
We will recruit HIV-uninfected adults with heavy alcohol use at the time of initiation of PrEP or PEP within Dynamic Choice Prevention (delivered by the SAPPHIRE trial) and screen for trial eligibility, as follows:

Inclusion: a) adult (≥18 years); b) HIV-uninfected (by rapid HIV antibody test); c) AUDIT-C score of ≥4 for men and ≥3 for women; d) attending a clinical visit for initiation of biomedical HIV prevention with oral PrEP, oral PEP, or the dapivirine vaginal ring; and e) has access to a mobile phone.

Exclusion: a) ineligible for PrEP based on MoH guidelines[104,105] (e.g., signs or symptoms concerning for acute HIV); b) intention to move away from the study community in the coming year; c) gross inebriation or inability to provide informed consent.

7.3 Recruitment & Screening Process

Figure 5: Aim 2 Healthy Living Intervention for HIV Prevention Trial Schematic



Study staff will recruit participants from the Aim 1 trial, from distribution of Aim 2 recruitment cards, or from the ongoing SAPPHIRE trial, who initiate PrEP, the dapivirine ring or PEP and administer the standardized 3-question AUDIT-C tool to assess alcohol use.[110] Those with an AUDIT-C score of ≥4 for men and ≥3 for women will be considered positive for heavy alcohol use and eligible for enrollment in the Aim 2 trial. Participants with AUDIT-C scores ≥8 will be invited to participate and will also be referred to their physician for a higher level of care for potential alcohol use disorder, regardless of their Aim 2 trial randomization.

7.4 Enrollment & Randomization

Study staff will obtain written informed consent and administer a questionnaire to collect baseline data on socio-economic and demographic information, HIV risk behavior and alcohol use, and obtain a baseline blood draw. Staff will then randomize participants 1:1, stratified by country, study community and sex, to either the alcohol counseling intervention (HLI) or standard care.

7.5 Study Groups

a) Healthy Living Intervention (HLI): In this arm, participants will receive brief alcohol counseling based on the Healthy Women Healthy Living (HWHL) study,[70] developed for women with HIV in the US, and adapted for use in a Ugandan (EXTEND)[72] and Kenyan context (SAPPHIRE) as the HLI.

The Healthy Living brief alcohol counseling intervention was developed using the Information, Motivation, and Behavioral skills (IMB) model, a framework in which information, motivation, and behavioral skills are key determinants of health behavior. In brief, in the intervention, information is provided about the harmful effects of alcohol use overall and on HIV risk, at baseline and during follow-up visits. Motivation is addressed

via an interactive discussion of reasons to cut down on drinking (e.g., money saved when not spent on alcohol) and the selection of specific drinking goals, to increase the likelihood that intervention participants will be inclined to act on the information they have received. Behavioral skills are developed with discussions of specific strategies to overcome drinking triggers (e.g., resisting peer pressure to drink, identifying non-drinking activities to reduce boredom, and engaging a support person). The motivation and behavioral skills components are reinforced during booster calls and in-person follow-up sessions.

b) Standard care (control): In this arm, participants will receive standard, brief unstructured advice regarding the health risks associated with heavy alcohol use, including risk of HIV acquisition.

In both groups, participants will have flexible access to oral PrEP, the dapivirine vaginal ring (once available) and PEP via Dynamic Choice Prevention (DCP) service delivery.

7.6 Procedures

Following randomization, study staff will perform the following study procedures:

1. Counseling:

In the HLI group, trained counselors will deliver the baseline and 3-month in-person counseling using the HLI workbook, as well as mobile phone-delivered booster sessions at 3-, 6- and 9-weeks post-baseline. Counselors will also deliver in-person or phone booster sessions at 24, 36 and 48-weeks post-baseline. The counselors will be trained by a licensed clinical psychologist in techniques to conduct the alcohol counseling sessions; training will include mock counseling sessions, with procedures used in the EXTEND and SAPPHIRE trials. The in-person sessions will be audio-recorded and 15% will be reviewed for fidelity, using a checklist of intervention components as in previous alcohol intervention trials.[111,112]

In the control group, study staff provide brief, standard of care advice regarding health risks associated with heavy alcohol use at baseline. *In both groups*, participants will receive PrEP/PEP adherence and HIV risk reduction counseling, provided through the SAPPHIRE trial (see **Figure 5**, above).

2. Monitoring: All participants will be monitored at 4- and 12-weeks, and then every 12 weeks thereafter for 48 weeks, with brief surveys regarding alcohol use (including AUDIT-C surveys). The week 4 monitoring visit will be conducted through SAPPHIRE DCP for the purpose of providing PrEP/PEP adherence and HIV risk reduction counseling; there will be no OPAL-specific surveys or activities at week 4. PrEP and PEP will be administered via enrollment in the SAPPHIRE trial. During the proposed study, the SAPPHIRE trial will be implementing the SAPPHIRE Dynamic Choice Prevention (DCP) intervention at each community's health center, whereas the present Aim 2 trial will be evaluating the Healthy Living brief alcohol intervention on PrEP/PEP adherence among persons with heavy alcohol use at increased risk for HIV. **Table 5** delineates the present (OPAL-East Africa) trial's activities from the SAPPHIRE trial activities.

Table 5: Delineation of OPAL trial study activities and SAPPHIRE trial activities

Key Study Activities	**OPAL Aim 2 HLI Trial**	**SAPPHIRE Trial**
Dynamic Choice Prevention: including initiation and maintenance of PrEP/PEP, adherence counseling and HIV-risk reduction counseling at 4 and 12 weeks, follow-up HIV testing during PrEP/PEP, pregnancy testing (for women), symptom screening for acute HIV, STI screening and follow-up creatinine testing		X
Health Living Intervention (brief alcohol counseling)	X	
Brief alcohol use survey (AUDIT-C) at baseline, 12, 24, 36 and 48-weeks	X	
PEth measurement (baseline and 48-weeks)	X	
Hair testing for tenofovir	X	
Aim 2 Qualitative Interviews	X	
PrEP/PEP Adherence Counseling	X	X

Study staff will work closely with SAPPHIRE trial and health facility staff and document follow-up visits, PrEP discontinuations (and reasons for discontinuation), and oral PrEP refills/administration and PEP use. All Aim 2 trial participants will also be provided a mobile number to call for PEP starts (7/days week, including holidays, provided by the SAPPHIRE trial). Any participants that test positive for HIV during follow-up will be referred for immediate initiation of ART at the local health center.

3. Qualitative interviews: After completion of trial participation, study staff will recruit a subset of participants stratified by sex and prevention modality (oral PrEP, dapivirine ring PrEP, and PEP) from each arm, as well as a sample of persons who are eligible for the Aim 2 trial but decline enrollment, for in-depth semi-structured interviews to better understand barriers and facilitators to retention in biomedical HIV preventive services, including perceived effects of heavy alcohol use, the HLI (intervention) and Dynamic Choice Prevention. We will also explore preferences, barriers, and facilitators regarding provision of PrEP/PEP on-site at drinking venues in the community compared to clinic, following qualitative data collection as described in Aim 1.

7.7 Measurements

1. Biomedical HIV Prevention coverage: The **primary outcome** will be PrEP/PEP "prevention coverage" defined as the proportion of time at risk during 24 weeks of follow up or until study end that an individual is protected from HIV infection with either PrEP or PEP, as assessed by prescription refills (with secondary analyses integrating drug levels from hair samples[113] for persons on oral PrEP). Prescription refill data will be collected from MoH medical and pharmacy records, augmented by OPAL trial case report forms, using procedures from the SAPPHIRE trial. Hair samples will be collected at 48 weeks among participants using oral PrEP. Each participant will be followed for 48 weeks; follow-up time will be censored at HIV seroconversion, death, or withdrawal from the trial.

2. Secondary Outcomes: a) Alcohol use: Study staff will assess AUDIT-C scores (modified to refer to the prior 3 months) with a standard drink guide adapted to local context at baseline and every 12-weeks post-baseline. Blood will also be collected, and dried blood spots prepared for phosphatidylethanol (PEth) testing at baseline and 48-weeks for confirmation of self-reported alcohol use. We will assess AUDIT-C,[114] and PEth as continuous variables, and explore social desirability[115] if AUDIT-C and PEth conclusions differ; b) PrEP/PEP "prevention coverage" (as defined above: see primary outcome) during 48 weeks of follow-up or until study end, as assessed by prescription refills and augmented by integrating drug levels from hair samples for persons on oral PrEP (as noted above); c) HIV seroconversion will be measured as documented rapid HIV antibody test positivity with Geenius confirmation[116] or documented detectable HIV viral load, with rapid HIV testing at PrEP refill and injection visits, or completion of a course of PEP.

3. In-depth semi-structured interviews: Using a similar approach to Aim 1, we will iteratively collect and rapidly analyze interview transcript data, continuing to randomly select participants within theoretically informed categories (e.g., not only study group but categories such as age group and level of alcohol use) until the data attain theoretical saturation. We anticipate that data in each study group will attain saturation with N=40 participants who chose oral PrEP/PEP or the dapivirine ring per study arm (N=80 total), plus an additional 20 adults who met eligibility criteria but declined trial enrollment (N=20 Aim 2 IDI-participants only). An overview of qualitative studies for Aims 1 and 2 are shown in **Table 6**.

Table 6. Overview of OPAL trial qualitative studies.

Aim	Behavior	Study population	Stratified random sampling strategy for in-depth interviews	Timing of in-depth interview
Aim 1	PrEP/PEP uptake	Adults recruited from drinking venues who are eligible for PrEP/PEP (N=80)	1. Sex: male/female 2. Uptake: initiated or declined PrEP/PEP 3. Aim 1 trial arm: multi-disease or HIV-focused recruitment	Following clinic-based screening for HIV and offer of PrEP/PEP

Aim 2	PrEP/PEP adherence	Adults with heavy alcohol use at increased risk of HIV (N=100)	1. Sex: male/female 2. Prevention modality: oral PrEP, dapivirine ring, or PEP 3. Aim 2 trial participation: HLI [intervention] arm, control arm, *or* eligible but declined to participate in trial	48-weeks after PrEP/PEP initiation

7.8 Data Collection & Management

Baseline survey data: Staff will collect questionnaire data using hand-held computers (tablets) or paper questionnaires (as back up, if tablets are not functioning, with subsequent data entry into computers or tablets). Data will be transferred via secure electronic transfer to our data center facilities in Kenya and/or Uganda and stored on a secure server.

HIV Test Results: Staff working at the study community clinics will record all lab test results, including HIV antibody test results, and HIV diagnosis status information, under each participant's study identification number (ID) in either paper lab logs or computers. Data from these logs or devices will be transferred via a secure electronic transfer to our data center facilities in Kenya and/or Uganda and stored on a secure server.

Qualitative Data: Staff will record interviews on audio devices using study IDs (not participant names), and transcribed interviews and translations will be data entered into appropriate software on password-protected study computers. Data from interviews will be transferred via a secure electronic transfer to our data center facility and stored on a secure server.

7.9 Analysis

1. Primary and secondary analyses: As in Aim 1, we will evaluate the intervention effects using TMLE, which provides precision and power gains over simple stratified approaches by adjusting not only for stratification factors but also for chance imbalance between randomized arms in additional baseline predictors of the outcome.[107] We may also use longitudinal causal mediation analysis to explore reductions in alcohol use as a potential mediator of the HLI intervention on increased HIV prevention coverage.[117,118] We will test the **null hypothesis** of no change in biomedical HIV prevention coverage due to the HLI with a two-sided test at the 5% significance level.

2. Analysis of qualitative data: We will conduct analyses using the same analytic approach described in Aim 1.

3. Power Calculations: We anticipate having 80% power to detect at least a 9.8% absolute increase in prevention coverage with a standard deviation of 0.35 and 200 participants/arm. Even with 25% attrition (from 200 down to 150 participants/arm) and higher than expected variability (e.g., standard deviation=0.40), these calculations suggest we would be well-powered to detect at least a 13% absolute increase in prevention coverage based on enrolling 400 participants in Aim 2 for measurement of the primary endpoint.

8. Costing (Aim 3)

Restatement of Aim 3. Determine the cost-effectiveness of interventions that increase biomedical HIV prevention uptake (Aim 1) and retention (Aim 2) among adults at high-risk for HIV who attend drinking venues.

8.1 Study Population

In Aim 3, we will evaluate the costs of delivering interventions to participants in Aims 1 and 2. No additional participants will be enrolled.

8.2 Measurements for Aim 3

Costs: We will employ rigorous, time-driven, activity-based methods[119] to determine intervention costs from the health system perspective. We will undertake micro-costing and time and motion (T&M) studies, using a uniform cost data collection protocol to quantify the resources needed to implement each intervention.[120,121] We will conduct two-week site visits in each community at three different times to assess the costs associated with each intervention component (e.g., training, implementation of bar-based recruitment, clinic-based screening, dynamic choice prevention, and HLI implementation). Cost will be organized in standard expenditure categories—personnel (e.g. wages, benefits and stipends), recurring goods (e.g. office supplies, testing supplies; PEP/PrEP medications, fuel), services (e.g. hiring advertisement, laboratory testing, utilities), equipment (e.g. vehicles, office equipment, computers, medical equipment) and facility costs (e.g. space rental). Information will be obtained through examination of expenditure records, discussion with program managers and staff and observation of service delivery for a sample of interactions for each intervention activity. "Economic" costs (the true value of resources consumed or "opportunity cost") will be assessed by identifying the value of subsidized resources using databases (e.g., wage rates) and, as needed, 3 price quotes from appropriate market sources. We will conduct T&M studies, using continuous self-reporting by providers, to allocate personnel effort toward each intervention component as well as to activities outside of intervention components. Personnel costs will be estimated as the sum of the product of resources (e.g., staff minutes) times unit costs. Costs for fixed costs (e.g., equipment) will be amortized on a straight-line basis over expected useful life and assume no salvage value.

8.3 Analytic approach for Aim 3

Costs: We will estimate the total incremental cost and the incremental cost per participant associated with each intervention. Costs will be organized in standard expenditure categories.

Efficiency: For each intervention, we will estimate the incremental cost per additional person: a) initiated on biomedical prevention b) identified with untreated HIV; c) linked to ART; and d) retained in PrEP/PEP services.

Health Effects: We will develop a decision model to explicitly define the paths and estimate the health effects associated with the health states defined in Aims 1 and 2 (i.e., heavy alcohol use, prevention uptake and adherence, HIV status, and ART use). We will use information from this study, our previous studies and the scientific literature to estimate the community prevalence of HIV, the risk of acquisition of HIV among individuals in our study, reduction in risk associated with PrEP/PEP uptake and adherence, reduction in risk associated with reduction in heavy alcohol use, morbidity and mortality associated with heavy alcohol use and/or HIV, and the reduction in morbidity and mortality associated with reduction in heavy alcohol use and/or treatment for HIV. We will translate each health state into a standard metric of burden of disease, Disability-Adjusted Life Years (DALYs),[122] which combines morbidity (and associated disability) with premature mortality (lost "life years"), as well as HIV transmissions averted in our study and if each intervention were scaled up to a population of 100,000 over 5, 10 and 20 years.

Cost-Effectiveness Analysis (CEA): We will compute the **incremental cost per DALY averted** (our incremental cost-effectiveness ratio, ICER) and per HIV transmission averted for each intervention in our study sample and if the intervention were scaled up in a population of 100,000. We will compute these estimates during the short (during the trial) and long term (5, 10 and 20 years). Costs will reflect **net cost per participant** by adjusting for added or averted health care costs over each period. Future costs and DALYs will be discounted at 3% per year. We will conduct extensive sensitivity analysis to estimate the variability of each of our estimates.

9. Human Subjects

9.1 Risks to Human Subjects

Potential risks: There are relatively few risks to study participants. The primary risks involved in study participation are inadvertent HIV status disclosure or HIV risk factor or heavy alcohol use disclosure with associated stigma. Given the sensitive and private nature of the HIV test results to be collected during implementation of the research aims, extra cautions will be put in place to ensure maintenance of privacy, confidentiality, and security of the data obtained. Data collection and storage procedures will include the use of encrypted, password-protected devices and servers.

PrEP/PEP Use. There are no "experimental" drugs in this study. We will be measuring the uptake of standard and approved drugs – TDF/3TC or TDF/FTC, the dapivirine vaginal ring for PrEP, and 3-drug antiretroviral regimens for 28-day PEP – that will be provided through the Kenya and Uganda health systems. The risk level associated with the offer and implementation of country guideline PrEP and PEP services to participants is classified as "Minimal", consisting of: blood sampling, hair collection for PrEP drug concentration measurement, and low risk behavioral questions.

Hair Collection: The risk of a cut to the skin from scissors during hair collection is extremely low. Our colleagues at UCSF have been collecting small hair samples from HIV-positive participants on antiretroviral therapy in the NIH- funded Women's Interagency HIV Study (WIHS), a large multicenter prospective study of HIV-infected and at-risk HIV-uninfected women, every six months since 2002. They have collected over 20,000 hair specimens in the WIHS via the collection procedure outlined in the research plan above and have never had an injury or any other adverse event reported from the collection process. The risk of cosmetic effects from hair collection is also extremely low. The human scalp loses an average of 100 strands of hair per day, so the amount of hair we propose to collect for this project is less than what a participant's scalp would typically lose on an average day. Moreover, the size of the hair sample collected for the tenofovir assays is extremely small and collection is usually easily accomplished from participants with short or limited amounts of hair. Over the past 12 years of collecting hair from participants in the WIHS cohort, our colleagues have never registered any complaints that the process has been disruptive to hair styles, and there are high rates of acceptability of hair collection in the overall study (ranging from 88-97%, depending on the site). We have also been collecting hair from HIV-infected women and their infants in Uganda,[123] HIV-infected pregnant women in South Africa, persons with HIV and heavy alcohol use in Uganda (in the DIPT trial)[100] and participants in PrEP trials.[12] We have experienced high rates of acceptability of hair collection in each of these studies (~95%), have not registered any reports of adverse events, including accidental skin cuts or disruption of hair styles, in any of these studies.

Phlebotomy associated risks include bruising, bleeding, infection, phlebitis, and pain. Bruising is common, minor pain with needle stick is universal, the other risks are rare.

Psychological stress could be caused by the interview in which participants will be asked sensitive questions regarding HIV, alcohol use, sexual behavior, and socio-economic status. Distress caused by the length of the interview is also possible. Study staff will be trained to address these issues with a calm, non-judgmental attitude. These minimal risks are not likely and will be minimized further by only selecting patients who understand the study and are willing to participate.

Potential risk of exposure to SARS-CoV-2 during clinic visits: SARS-CoV-2 virus is easily transmitted from person-to-person through infected respiratory droplets/airborne droplet nuclei via sneezing, coughing, talking, singing or through handling fomites recently contaminated by infected droplets. We will ensure that participants are well-informed regarding the potential risk of SARS-CoV-2 exposure when leaving their homes and visiting health centers and ensure a safe clinical environment for participants and study staff members.

9.2 Adequacy of protection against risks

Informed Consent: Written informed consent (Aims 1 and 2) will be obtained from all participants by trained research assistants. In Aim 2, the research assistants will find a private place; carefully explain the nature and

purpose of the study to each potential participant, potential risks and benefits, and will describe the study groups to which participants will be randomized. The consent process will be offered in English or local dialects (as per the participant's preferences). Our study team has prior experience in obtaining informed consent for research and clinical trials within the cultural contexts of Kenya and Uganda. The informed consent procedure has been designed to maximize understanding of potential risks. Participants will be told that they may decline to participate at any point.

Maintaining privacy and avoiding stigmatization: Recruitment at drinking venues (Aim 1 only) will occur within the eight study communities (4 in Kenya and 4 in Uganda), and study staff will be trained on community-based mobilization and engaging with adults at drinking venues safely and in a professional, non-judgmental manner to reduce stigmatizing patrons and workers at drinking venues, based on our prior experience conducting mobilization activities at these sites in >2000 adults in Kenya and Uganda to date. Aims 1 and 2 study visits with participants to screen, consent, enroll and follow-up participants will occur at the eight health centers participating in the SAPPHIRE (Phase B) trial, four in Kenya and four in Uganda, in order to reduce the unlikely possibility of stigmatizing study participants. Every effort will be made to ensure privacy is maintained during administration of questionnaires. Participants will be given a unique study identification number (their study ID number). Participants' names and study number, and thus their HIV status and name, will never appear in a dataset together.

Minimizing coercion to participate in research: To minimize the likelihood of persons feeling pressured to participate in research we will emphasize the concepts of individual voluntary choice to participate in research and the need for individuals to respect the voluntary choice of others during the process of obtaining informed consent. Study participants will also be informed that study enrollment can be stopped at any point during the study at their request.

Data Security: All information will be recorded using study identification numbers, rather than participant names, and stored securely in locked offices at the study data centers. All study computers are password encrypted and kept in locked offices.

SARS-CoV-2 Biosafety: We will follow MOH requirements and current local guidelines for infection control in clinical settings. To minimize any risk to participants or study staff, we will take the following precautions:

a) Participants: Interviews will take place in well-ventilated (by natural ventilation) clinical rooms. Face masks will be provided on-site for all participant interactions, in accordance local Kenyan and Ugandan guidelines for clinical care. Individuals may choose to wear a face mask to reduce droplet exposure during study visits.

b) Study staff: To minimize risk to study staff from potentially SARS-CoV-2 virus infected participants, masks will be made available to all participants (regardless of symptoms). Study staff will be offered SARS-CoV-2 vaccination (according to national guidelines in Kenya and Uganda), if not already vaccinated, and provided access to isolation masks to wear during participant interactions if they choose. All study staff will perform handwashing or alcohol-based hand disinfectant use between each participant encounter. Any face shield or mask that is contaminated by visible droplets (e.g. participant sneezes or coughs on the face mask/shield) will be disposed of and replaced or disinfected after that participant's encounter. Study staff will use disinfectant solution and paper towels or wipes to clean any electronic tablets or other equipment that is touched by study participants after each participant encounter.

Biosafety – Universal precautions: All study staff will be trained on universal precautions according to WHO guidelines to help prevent the spread of infectious diseases. Staff will perform handwashing or use an alcohol-based hand sanitizer before and after participant encounters, and after removing gloves. Staff will wear personal protective equipment like gloves, masks, and face shields as applicable during sample collection and processing to avoid exposure to blood and other bodily fluids. All sharps will be properly disposed of in sharp boxes which will be provided. Surfaces used for testing of participant specimens on-site will be cleaned daily. Medical waste will be conducted according to the health facility's medical waste disposal procedures.

Institutional Review Board Approval: Approval from the UCSF institutional review board, the Kenyan institutional review boards (the Scientific Ethics Review Unit [SERU] at KEMRI), and the Ugandan institutional review boards (the School of Medicine Research and Ethics Committee [SOMREC], and the Uganda National Council for Science and Technology [UNCST]) will be obtained prior to initiation of study activities. All study staff are required to undergo training in human subjects' research, and good clinical practice (GCP).

9.3 Potential benefits

The primary benefits of the proposed research to Aim 1 participants are support in engaging with HIV testing and biomedical HIV prevention in adults at increased risk of infection, along with post-test counseling and referral to HIV care if HIV-infected or prevention services if HIV-uninfected. For Aim 2 participants, the primary benefits are support in adherence to PrEP/PEP and retention in biomedical HIV prevention services, as well as counseling regarding heavy alcohol use. The benefits for the community may include increased engagement in HIV testing and biomedical prevention by adults at high risk of infection, decreases in heavy alcohol use among Aim 2 participants, and early diagnosis and prompt linkage to antiretroviral therapy for those who HIV-positive.

9.4 Importance of the knowledge to be gained

The minimal risk in this study is far outweighed by the importance of knowledge to be gained. Given the public health importance of improving uptake and use of biomedical HIV prevention among adults at drinking venues who are at high risk of infection, and reducing heavy alcohol use, it is vital to have effective, low-cost interventions that can be used to achieve these objectives.

9.5 Study Scientific Advisory Committee

The findings of this will be shared with the SAPPHIRE trial (NCT04810650) advisory scientific committee, as the OPAL trial is being implemented within the larger SAPPHIRE community cluster randomized trial. The SAPPHIRE trial scientific advisory committee meets annually and includes experts in HIV prevention and treatment; experts in PrEP and youth in Uganda and Kenya; and experts in economics/development in East Africa.

10. Publication of Research Findings

The findings from this study may be published in a medical journal. No individual identities will be used in any reports or publications resulting from the study. The researchers will publish results of the study in accordance with NIAAA, UCSF, Makerere University, UNCST and SERU/KEMRI guidelines.

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