Study Protocol

Name of Study: PrEP and Alcohol

Responsible Investigators:

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NOTE: This research is based on an NIH/NIAAA UH2/UH3 grant mechanism that involves a two-phased approach (i.e., UH2 Phase: Years 1-2; UH3 Phase: Years 3-5). REB approval for UH2 phase (years 1-2) was initially obtained on October 2, 2017 (CAMH REB# 101/2017; UHN REB#18-5014). Recruitment for this phase is now completed. The present protocol covers studies for the second phase of the grant, UH3, which was funded in September 2019 and has an anticipated end date of August 2022.

I. Introduction and Background

HIV continues to pose a significant public health concern in Canada, with recent estimates indicating approximately 75,500 Canadians living with HIV.[1] Within the context of this epidemic, HIV disproportionately impacts gay, bisexual, and other men who have sex with men (MSM), who comprise approximately half of all new and existing HIV infections in Canada.[2]

HIV-negative (HIV-) MSM have traditionally been reliant on condoms as their primary method of preventing HIV acquisition through sexual contact. More recently, however, biomedical strategies have moved to the forefront of prevention, with HIV pre-exposure prophylaxis (PrEP) offering those who are HIV- an effective new method of protection from the virus. PrEP entails taking a daily dose of tenofovir disoproxil fumarate/emtricitabine, which prevents HIV from replicating and taking hold inside one's body. Empirical support for PrEP has been strong, with several randomized controlled trials (RCTs) providing evidence for its efficacy; showing a reduction in the rate of HIV infection by 44%-86%.[3-7]

Although PrEP is an effective tool in preventing the acquisition of HIV,[3-7] its effectiveness has been shown to be dependent on a number of key behaviors, including adherence to the treatment,[4,6-9] attendance in follow-up care, and the continued use of condoms.

Hazardous alcohol use is prevalent among PrEP users in Canada,[10] which in turn has the potential to contribute to suboptimal PrEP adherence, poor retention in PrEP care, and condomless sex/STIs while on PrEP (e.g.,[11-17]). The impact of alcohol on these PrEP-related behaviours may also become exacerbated in the presence of concurrent issues such as substance use and depression, thus reflecting a potential syndemic effect (i.e., the combined presence of

multiple issues leads to a greater detrimental impact).[18] Substance use and depression frequently co-occur with alcohol consumption among MSM populations.[19] Addressing hazardous alcohol use and concurrent conditions in PrEP-prescribed hazardous MSM-drinkers is therefore crucial for maximizing the HIV-preventive benefits of PrEP treatment.

II. Rationale and Study Objectives

This investigation follows a syndemic approach and seeks to explore whether a brief, stand-alone, alcohol-reduction intervention (with modules on substance use and depression) would be feasible, acceptable, and potentially efficacious within the context of PrEP treatment. The impact of traditional alcohol-reduction interventions on HIV-related outcomes has been variable, potentially because other concurrent conditions that can adversely impact health outcomes may have remained unaddressed. Our proposed intervention will distinctly target alcohol consumption and address key concurrent conditions among hazardous drinking, PrEP-prescribed MSM; thereby attending to, and accounting for, the potential synergistic detrimental impact that these concurrent conditions may have on PrEP-related behaviors. As there is a high prevalence of these concurrent conditions among MSM populations, the comprehensiveness and uniqueness of our intervention will be particularly well-suited for MSM who rely on PrEP as an HIV risk-reduction strategy.

Findings from this research will have the potential to guide future initiatives to address hazardous alcohol use and concurrent conditions within the context of PrEP treatment. Improving PrEP treatment outcomes could ultimately help reduce the likelihood of HIV acquisition among this population.

III. Specific Aims

The specific aims of this study are to:

1) Assess the feasibility and acceptability of implementing an alcohol-focused brief intervention with a sample of hazardous drinking, PrEP-prescribed MSM.

2) Assess the preliminary impact of an alcohol-focused brief intervention on reducing alcohol consumption among a sample of hazardous drinking, PrEP-prescribed MSM.

3) Assess the preliminary impact of an alcohol-focused brief intervention on improving PrEP adherence and retention in PrEP-related care among a sample of hazardous drinking, PrEP-prescribed MSM.

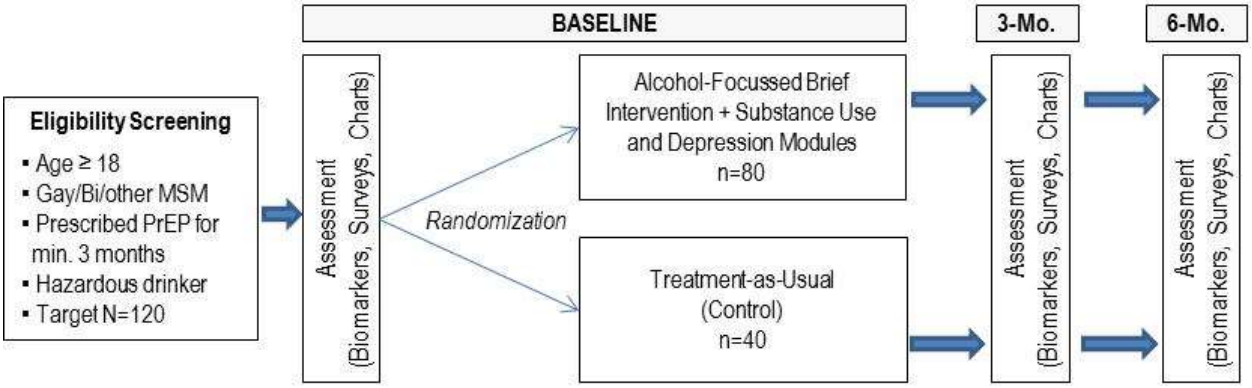
4) Assess the preliminary impact of an alcohol-focused brief intervention on reducing condomless sex and STIs among a sample of hazardous drinking, PrEP-prescribed MSM.

IV. Study Design

We will conduct a pilot randomized controlled trial (RCT) of an alcohol-focused brief intervention with supplementary modules that focus on concurrent substance use and depression.

A total of 120 PrEP-prescribed MSM who are hazardous drinkers will be recruited from two medical clinics, Toronto General Hospital (TGH) and Maple Leaf Medical Clinic (MLMC), located in downtown Toronto. Participants will be randomly assigned to either the intervention condition or treatment as usual (TAU) based on a 2:1 intervention:TAU ratio. All participants will complete biological and behavioral measures at baseline and at 3- and 6-months post-baseline to assess PrEP-related behaviors, alcohol consumption, substance use, and depression. An overview of the trial design is depicted in Figure 1.

Figure 1. Pilot RCT design overview.



Eligibility Criteria

To be included in the study, participants must be (a) aged 18 years or older, (b) be a patient of TGH or MLMC, (c) be a man who identifies as a gay or bisexual, and/or a man who has sex with other men, (d) have been prescribed PrEP for at least 3 months, and (e) meet the criteria for hazardous drinking, (i.e., based on a score of ≥4 on the Alcohol Use Disorders Identification Test – Consumption measures (AUDIT-C))[20]
Participants will be excluded if they do not meet all of the above-mentioned inclusion criteria.

Study Procedures and Measures

Men presenting for routine PrEP-related care at TGH and MLMC will be made aware of the study either through TGH/MLMC clinic staff members (e.g., doctors, nurses, clinic research staff) or via study information cards and/or posters (see "Recruitment Ad" attachment) at their respective clinics. Interested individuals will be referred to a CAMH research staff member. The CAMH research staff member will provide additional information about the study (see "Pre-Screening Script" attachment) and answer any questions that the individual may have.
Individuals who indicate that they would like to participate will complete either a brief, self-administered tablet-based eligibility screener or an over-the-phone screener (see "Pre-Screening Questionnaire" attachment), and qualifying individuals will be offered participation and asked to provide informed written consent (see "Consent Form" attachment). Potential participants will be encouraged to take as much time as they need to review the information and only give consent when they are ready to participate. The study comprises of a baseline session, and two follow-up visits at 3- and 6- months post initial visit. Designated CAMH staff members will conduct and oversee all study procedures.

Pre-Screening

A CAMH research staff member will introduce the study to the potential participant using the pre-screening script (see "Pre-Screening Script" attachment). Individuals interested to take part in the study will complete an eligibility pre-screening questionnaire (see "Pre-Screening Questionnaire" attachment) Pre-screening will take approximately 5 minutes to complete and will be conducted over the phone or in person. Questions in the screener ask participants about their age, time on PrEP, sexual orientation, and alcohol consumption patterns.

Baseline Session

During their baseline session, participants will provide samples of dried blood spots (DBS) via finger prick (see "Dried Blood Spot Testing" below and "Dried Blood Spot" attachment) and complete a self-administered tablet-based survey. The survey, which is based on the previously-approved survey that was employed in the first phase of this project (CAMH REB# 101/2017; UHN REB#18-5014), will include measures assessing PrEP-related behaviors and other key factors including alcohol use, substance use, and depression (see "Measures" below and the "Survey" attachment). Upon completion of the survey, the tablet-based program will randomly assign participants to either the intervention condition or TAU based on a 2:1 intervention:TAU ratio. Intervention condition participants will receive a one-time, alcohol-focused brief behavioural personalized feedback intervention delivered seamlessly on the same tablet, which will also embed supplementary modules focused on substance use and depression when necessary (see "Intervention" below and the "Intervention" attachment).

Intervention

The primary intervention component is The Check Your Drinking (CYD) intervention, a brief and personalized online intervention designed to assess and provide feedback on quantity and frequency of drinking, as well as the severity of hazardous drinking.[21] CYD has been previously approved by CAMH REB [Protocol # 075/2016]. In the intervention, after completing the alcohol assessment, participants will be provided with a personalized drinking feedback report that compares their drinking with other Canadian males of the same age. This report also includes other relevant feedback, including an assessment of severity of alcohol use, and provides recommendations for safe levels of alcohol consumption. The development of the CYD was led by CAMH Senior Scientist Dr. Cunningham (Co-Investigator), and it has been subjected to five randomized trials from two independent research groups, all of which displayed a significant impact of the intervention to reduce hazardous alcohol consumption compared to controls.[21-25]

An additional module will be appended to the CYD intervention and will appear for participants for whom a potential substance use- and/or depression-related issue is reflected in their self-reported survey responses. The module will be similar to components used in a previously validated, electronically-delivered ART adherence promotion intervention that the PI of the proposed research helped develop.[26] For the present trial, the module will include a list of local resources and support services for mental health and addictions concerns, along with contact information, web links, and other details for each of these entities. Participants in this arm only (intervention arm) can decide whether to include an email address of their choice if they would

like to receive an electronic copy of their personalized drinking feedback report and/or a list of local services for mental health- and substance-related concerns. Providing an email address will be completely voluntary. All email addresses collected will be deleted after the data have been downloaded to the CAMH secure server. To ensure participants are aware that their email address will be connected to their data, we have included the following text in the consent form: "It is recommended that for the report, you use an email address that does not identify you (for example, that you use an email that does not include your first or last name or other information that could identify you). This is because the email address you provide for the report will be temporarily stored in a secure Qualtrics database and will be connected with your data. If you use identifiable information in your email, the Qualtrics database may be able to link you to the data you provide (i.e., your data will be identifiable in the Qualtrics database). The choice is yours, and the research team would like to make you aware of this." TAU participants will receive no intervention.

Follow Up Sessions

At 3-month and 6-month follow-up visits, all participants will complete similar questionnaires to the baseline survey/screener measuring the same constructs in order to identify any changes in outcomes over time. DBS samples from finger prick will also be obtained at these follow up visits to test PrEP adherence and alcohol use biomarkers (see "Dried Blood Spot Testing" and "Measures" below, as well as the corresponding attachments). For participants in the intervention arm only, an additional questionnaire will be included at the end of the 6-month assessment to evaluate the perceived acceptability of the intervention (included in the "Survey" attachment). With participants' explicit written consent, retrospective chart reviews will be conducted by CAMH research staff for aspects pertaining to PrEP treatment-related factors; alcohol, substance use, and mental health-related aspects; incident STIs; and other relevant clinical indicators (see "Chart Review" attachment). Chart review items were previously approved in the first phase of this study (CAMH REB# 101/2017-03; UHN REB# 18-5014.3).

Dried Blood Spot Testing

Participants in both intervention and TAU arms will provide samples of dried blood spots (DBS) via finger prick to assess biomarkers of PrEP adherence and heavy alcohol consumption (see "Measures" below and "Dried Blood Spot" attachment). **S**amples will be sent to a lab in the United States for testing as there are no labs in Canada that conduct the tests. Tests will be performed on a fee for service basis. The samples will be identifiable only by participant ID number, with no personal identifiers. The US lab will be required to only use the samples for the purposes as defined by CAMH and the REB protocol; destroy the samples after the services are complete; and provide confirmation to the PI/designated CAMH project personnel that the samples have been destroyed. DBS testing for alcohol (PEth) will be done at USDTL laboratory located at 1700 S Mt Prospect Rd, Des Plaines, IL 60018, USA. PrEP testing will be done at one of the following three labs in the United States, 1) University of Colorado Denver located at: 12850 E. Monteview Blvd, Aurora; CO 80045; or 2) CPAC located at: 120 Mason Farm Road; University of North Carolina at Chapel Hill; NC 27599; or 3) University of Nebraska Medical Center located at: 42nd and Emile, Omaha, NE 68198. Detailed instructions on DBS collection, based from USDTL and University of Colorado protocols, are attached with this application (see "Dried Blood Spot" attachment).

Outcome Measures

Feasibility and acceptability. In accordance with **Specific Aim 1**, feasibility will be determined through an examination of 1) rates of eligible hazardous drinking PrEP-prescribed MSM who express a willingness to take part in the intervention trial; and 2) rates of those assigned to the intervention who subsequently complete it. Acceptability of the intervention will be measured using validated instruments,[27,28] as well as a small number of items developed by the researchers. The acceptability measure will query satisfaction with the intervention, perceived ease of use, perceived accuracy of intervention content, and the desire to use the intervention on an ongoing basis.

Alcohol consumption. Behavioral measures and a biomarker test will be employed to evaluate **Specific Aim 2**. The AUDIT,[20] included as part of the pre-screening process at baseline, will be incorporated into 3-month and 6-month follow-up assessments to identify changes in hazardous drinking over time. Two supplemental self-report alcohol items will be included in all assessments to measure 1) the number of drinks consumed in a typical week, and 2) the highest number of drinks consumed on a single occasion.[29] As an objective measure of alcohol use, an alcohol derivative, phosphatidylethanol (PEth), will be assessed from dried blood spots (DBS) obtained at baseline, 3-months, and 6-months. PEth has been shown to be highly correlated with several measures of alcohol consumption;[30] it has been used as a clinical marker for chronic excessive drinking and binge drinking;[30-34] and has been employed as a primary outcome in alcohol treatment trials.[35,36] The half-life of PEth has an estimated range of 4-12 days, and it has demonstrated a high degree of sensitivity (i.e., >95%) and specificity (i.e., 100%) when comparing patients presenting for alcohol treatment to those who abstain or only consume alcohol at low levels.[37-41] PEth levels will be measured using liquid chromatography-tandem mass spectrometry, and values will be examined based on a dichotomy using a cut-off of ≥35 ng/ml to identify hazardous drinking.[42]

PrEP adherence. Adherence to PrEP will be assessed at baseline, 3-months, and 6-months using a combination of behavioral and biological assessments to evaluate the adherence-focused component of **Specific Aim 3**. The behavioral assessment will be comprised of adapted versions of two well-validated measures of adherence,[43,44] identifying 1) the number of missed PrEP doses over the past seven days; and 2) the percent of PrEP doses taken over the past four weeks. These measures have been employed in a number of intervention trials and provide good estimates of adherence.[45] For both measures, suboptimal adherence will be defined as taking <80% of one's prescribed PrEP doses.[11] DBS samples obtained at baseline, 3-, and 6-months will be analyzed for quantities of PrEP components (e.g., tenofovir/emtricitabine (TFV/FTC)), using a validated liquid chromatography tandem mass spectrometry method widely used in PrEP research.[6,9,46-55] The half-life of TFV is 15 hours and that of FTC is 10 hours[50] which will allow the quantification of recent use of PrEP with a single DBS sample. Furthermore, blood plasma has been shown to provide a good indication of PrEP use for periods ranging from 24 hours to seven days.[50,51,54] A cut off for the concentration of ≤10ng/ml (for either TFV or FTC) will be employed, as this has been shown to be indicative of inconsistent PrEP intake.[50,51]

Retention in care. **Specific Aim 3** includes an additional focus on retention in PrEP-related care. Attendance at clinic visits that correspond with 3- and 6-month assessments, and attendance during any other regularly scheduled PrEP clinic visits during the 6-month follow-up period, will be used as an indicator of retention.

Engagement in condomless sex. In accordance with **Specific Aim 4**, condomless sex will be assessed at baseline and follow-up study visits using an adapted version of a validated MSM-focused sexual behavior assessment that queries condom use during the past three months.[56] Responses at each time point will be dichotomized to identify participants who engaged in any condomless anal sex. As an objective indicator of condomless sex, incident chlamydia, gonorrhea, syphilis, and HCV, diagnosed at each time point, will be identified through chart extraction.

Additional Measures

Participant characteristics. Demographic factors to be collected include age, race, educational background, and income. These factors will be queried during the baseline assessment.

Substance use and Depression. Substance use other than alcohol will be assessed using the National Institute on Drug Abuse (NIDA) - Modified Assist Screening Tool (NIDA M-ASSIST).[57] This measure queries lifetime use of a variety of substances, frequency of substance use during the past three months, and negative consequences experienced as a result of substance use. Participants will be identified as possessing a potential substance use issue based on NIDA M-ASSIST scoring. Participants will complete the Center for Epidemiologic Studies Depression Scale-10 (CESD-10).[58] A score ≥10 will be used as an indicator of the presence of marked depressive symptomatology.[58] Both measures will be administered at baseline and at the two follow-up time points.

It should be noted that the demographic and behavioral measures (i.e. alcohol consumption, PrEP adherence, retention in care and engagement in condomless sex) included in this study were previously approved in the first phase of this study (CAMH REB# 101/2017-02; UHN REB# 18-5014).

Data Analysis

Statistical power. As this is a feasibility study and not intended as a definitive clinical trial, sample size considerations focus on expected effect sizes detectable with the design. The following effect size for the variable that likely has the least power (i.e., adherence –**Aim 3**) can be detected based on the following assumptions: there is a combined effect of 1) the suggested alcohol intervention on alcohol intake,[59] and 2) the effect of lowered alcohol intake on PrEP adherence.[11] Suboptimal PrEP adherence, defined as taking <80% of all doses, was estimated based on the literature[11] and assumed to be 30% among heavy alcohol users.[8] With the current sample size, we would be able to significantly detect Odds Ratios of 3 and higher, and assuming confounding with an R^2 of other variables on the dependent variable, Odds Ratios of 3.5 and higher. We will be able to detect differences in proportions of about 20% with a 95% Confidence Interval between 2% and 28%.[60] Other factors in **Aims 2, 3,** and **4** can detect smaller effect sizes.

Statistical analyses. Analyses pertaining to feasibility and acceptability indicators (**Aim 1**) will be based on descriptive statistics involving frequency counts (e.g., intervention completion rates) and mean scores (i.e., acceptability measure). The anticipated patterns pertaining to **Aims 2, 3,** and **4** will be tested with generalized linear mixed effect models including random intercepts for every patient,[61,62] based on the expectation that the intervention group will have better outcomes at both follow-up time points. Mixed effect models have fewer assumptions compared to more

traditional repeated measures of analyses of variance[61] with respect to missing values.[63,64]

For the quantification of the causal impact of alcohol, we will additionally use path models, where alcohol consumption levels will be introduced into the equations, with the hypothesis that the introduction of this variable will make the differences between experimental and control groups disappear.

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