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A-HACK Study: Addressing Heavy Alcohol use Consumption with Kudzu

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Study Protocol and Statistical Analysis Plan

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CLINICAL PROTOCOL

1.1 Overview and rationale for a pilot placebo-controlled trial and kudzu.

We propose to conduct a 12-week pilot with 1- and 3-month post-treatment follow-up, double-blind, placebo-controlled study of targeted kudzu extract among binge-drinkers with AUD at high risk for acquiring or transmitting HIV and other sexually transmitted infections (STIs). This intervention could benefit this population in two ways: reductions in binge drinking may limit harms associated with alcohol use and decrease alcohol-related sexual risk behaviors. This study will determine whether targeted oral kudzu extract (2 grams), taken on an as-needed basis, is an efficacious, tolerable and acceptable strategy among binge-drinkers who are at high risk for acquiring or transmitting HIV and other STIs. If kudzu extract is shown to be a viable strategy among binge-drinking individuals, it may ultimately expand the available interventions for this populations to reduce their alcohol consumption.

1.2 Specific Aims

The primary objectives of this study are as follows:

1. To determine the efficacy of targeted kudzu versus placebo in reducing binge drinking, as determined by number of binge drinking days in timeline follow-back (TLFB), by treatment arm.
2. To determine the efficacy of targeted kudzu versus placebo in reducing recent alcohol consumption, as determined by the proportion of ethyl glucuronide (EtG) positive urines, by treatment arm.
3. To determine the efficacy of targeted kudzu versus placebo in reducing alcohol-associated sexual risk behaviors and incidence of STIs, as determined by audio computer assisted survey instrument (ACASI) data and STI (syphilis, Neisseria gonorrhea, Chlamydia trachomatis testing, HIV) testing, by treatment arm.
4. To evaluate the tolerability and acceptability of targeted kudzu versus placebo, as determined by adverse clinical event rates and medication adherence (via data from MEMs cap dispenser monitoring and self-report from SMS texts and TLFB), by treatment arm.

1.3 Facilities and Investigator.

Study activities will take place at the Center on Substance Use and Health (CSUH) of the San Francisco Department of Public Health (SFDPH), a well-established clinical trial site. Dr. Santos has a joint appointment as a Senior Research Scientist at SFDPH. He has conducted research at this field site since 2008. The site is centrally located near multiple transit lines with convenient access for residents of multiple neighborhoods with high rates of alcohol use. We have had remarkable success recruiting and retaining alcohol and substance users at this location. Study staff have access to both **SFDPH** and **University of California, San Francisco**. The paired effort of these institutions has proven highly effective in both research and clinical care in San Francisco.

1.3.a. Form 1572

See Appendix B

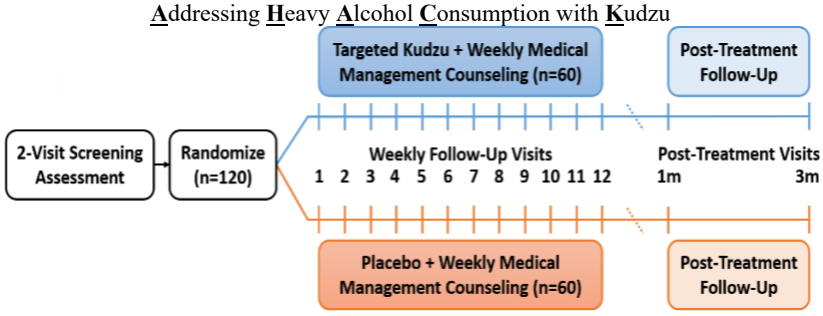
1.3.b. Sponsor-Investigator
Glenn-Milo Santos, PhD, MPH (See Appendix C for CV)

1.3.c. Sub-Investigator
Phillip O. Coffin, MD (See Appendix D for CV)

1.3.d. Form FDA 3454
See Appendix E

1.4 Study Design
This study is a double-blind, placebo-controlled, two-arm trial in which 120 binge drinkers with AUD will be randomly assigned to receive 12 weeks of kudzu or placebo, to be taken on an as-needed basis (see Figure 2) with 1- and 3-month post-treatment follow-up visits. This efficacy study will enroll sexually active, binge drinkers with AUD because they are the most likely population to benefit from this intervention by limiting harms associated with heavy alcohol use and decreasing alcohol-related sexual risk behaviors. A study clinician will perform the Structured Clinical Interview for the DSM-V (SCID) to screen for AUD and determine eligibility. Upon enrollment, 120 participants will be randomized 1:1 to kudzu extract (2 grams) or placebo for targeted administration. Participants will be seen weekly for behavioral surveys, urinalyses, study drug dispensing, and alcohol use counseling. Safety laboratory assessment, vital signs, and the audio computer assisted survey instrument (ACASI) will be completed monthly. Efficacy, tolerability, and acceptability (Specific Aims 1-4) will be assessed upon trial completion as measured by number of binge drinking occasions and numbers of drinks on drinking days via timeline follow-back at weekly visits; number of EtG-positive urine samples; sexual risk behavior data through monthly surveys via ACASI; frequency of adverse events; and cumulative medication adherence data at week 12. Durability of intervention effects will be evaluated at 1- and 3-month post-treatment visits.

Figure 2: Design of The **A-HACK Project**:
Addressing **H**eavy **A**lcohol **C**onsumption with **K**udzu



1.4.a. Study Participants, recruitment, and inclusion/exclusion criteria. We will recruit a total of 120 racially/ethnically diverse sexually active, binge drinkers with AUD will be enrolled in the study. Subjects will be San Francisco Bay Area residents between 18-70 years of age. The project is designed specifically for binge-drinkers at high risk for HIV transmission or acquisition.

1.4.b. Recruitment.
For this study, we will combine several strategies that have proven successful in our previous studies with alcohol- and substance-using individuals:

Advertisements: We will run advertisements in the local papers catering to the community and widely read by our participants.

Internet recruitment: As in our current studies, Internet-based recruitment will occur through strategic placement of banner ads on Web sites frequented by alcohol-using individuals, including craigslist.org, Facebook, manhunt.net, Adam4Adam.com, BarebackRt.com and tweaker.org, and on smart phone mobile applications for this population, including Grindr, Instagram, Manhunt Mobile, and BarebackRt Mobile. Additionally, we will use targeted ads for San Francisco Bay Area on Facebook and Google Adwords.

Active recruitment: We will recruit on the street in neighborhoods and at fairs frequented by alcohol-using individuals, collecting phone numbers of interested potential participants, and leaving cards and fliers in LGBT meeting places, local community-based organizations (CBOs), bars, and clubs. We will also recruit at clinics with many alcohol-using patients such as the Health Department's STD clinic (City Clinic) and the public HIV clinic at San Francisco General Hospital (SFGH).

Snowball sampling: Study participants are encouraged to refer their friends by taking cards and fliers so that potential participants can call us. This is a method to reach some people we may miss via our other recruitment strategies.

In addition, we will also recruit participants that screen ineligible for our other ongoing NIH-funded studies. Prospective and former participants from our ongoing trials will be asked if they are willing to be contacted for future studies; participants who provide consent will have their contact information saved in a database for future contact. Once this study is running, potential participants will be triaged with a pre-screening process that directs them to the study for which they are most likely to be eligible, an approach we have found to be effective and efficient for our parallel methamphetamine trials.

1.4.c. Retention.
We have a proven record of high retention rates in our studies, including among alcohol-using MSM. We anticipate an 80% retention rate over the 12 weeks of follow-up for this study. While we realize that retention among substance users is considerably challenging, we believe our goal is realistic and feasible. We acknowledge, however, that extra efforts will be needed to ensure

that our study participants adhere to the study protocol, and we will make every effort to meet and hopefully exceed our retention target.

First, study staff will be trained to be alert for any factors that signal a low likelihood of the participant being able to adhere to the study schedule; for example, participants who are unable to provide contact information or who miss or re-schedule screening visits are retention risks. Whether or not to enroll such persons will be determined on a case-by-case basis.

We will use a variety of up-front and long-term strategies from our prior studies to achieve excellent retention rates. At screening, participants will be asked to provide extensive locating information, including home addresses, cell and home phone numbers, and e-mail addresses for themselves, and to provide the names of two local persons to be contacted in the event that the participant cannot be reached. We will attempt to contact persons on this list only in the event that multiple attempts to reach the study participant directly fail; at no time will we divulge information about the study or the participant to these contacts. Contact information will be updated every four weeks, or more frequently as necessary. We have found these procedures to be highly acceptable to participants.

We have also found that scheduling out appointments in advance is useful for helping participants to understand the frequency of visits and for maintaining higher retention rates. This is easily done using our Wellsky® appointment scheduling software. Each participant is also provided with a wallet-sized appointment card containing study staff contact information. Future appointments are reviewed and rescheduled as needed. For missed or canceled visits, we contact participants by their selected form of communication (home telephone, cell phone, e-mail, text message, etc.) within 24 hours to reschedule by making up to three attempts to contact individuals at different times of day. We will also attempt to reach up to two alternate contacts provided by the participant at enrollment.

1.4.d. Inclusion Criteria.

Subjects must meet *all* of the following inclusion criteria to be eligible for participation in this study:

1. Self-reported anal or vaginal sex in the prior three months while under the influence of alcohol, or reported missing ART or PrEP due to alcohol use in the prior 3 months; ;
2. At least one binge-drinking (five or more drinks on a single occasion for men; four or more drinks for women) session per week in the prior three months;
3. Having an AUD by DSM-5 SCID criteria (includes hazardous and harmful use);
4. Interested in reducing binge alcohol consumption;
5. HIV negative by rapid antibody test or HIV positive with a medical record documentation of HIV infection*. For HIV-positive individuals, having a CD4 cell count >100 cells/mm3 and having suppressed HIV viral load with < 50 copies/mm3;
6. No current acute illnesses requiring prolonged medical care;
7. No chronic illnesses that are likely to progress clinically during trial participation;
8. Able and willing to provide informed consent and adhere to visit schedule;

9. Age 18-70 years;
10. Baseline CBC, total protein, albumin, glucose, alkaline phosphatase, creatinine, BUN, and electrolytes without clinically significant abnormalities as determined by study clinician in conjunction with symptoms, physical exam, and medical history.

**Note:* Participants newly diagnosed with HIV at screening are eligible for the study but we will postpone their enrollment until they are virally suppressed with HIV viral load < 50 copies/mm .

1.4.e. Exclusion Criteria.

Subjects who meet *any* of the following exclusion criteria are not to be enrolled in this study:

1. Any psychiatric (e.g., depression with suicidal ideation) or medical condition that would preclude safe participation in the study;
2. Known allergy/previous adverse reaction to kudzu;
3. Moderate/severe liver disease (AST, ALT $\geq$ 5 times upper limit of normal);
4. Impaired renal function (creatinine clearance < 50 ml/min);
5. Currently participating in another intervention research study with potential overlap;
6. Current severe substance use disorder (exclusive nicotine, cannabis and alcohol) as determined by DSM-V SCID criteria;
7. pregnant women;
8. HIV positive individuals who are not virally suppressed;
9. Any condition that, in the principal investigator and/or study clinician's judgment interferes with safe study participation or adherence to study procedures;
10. Not willing to learn how to send EMA surveys

*Eligible participants who have a partner currently in the study will be enrolled and randomized after their partner has completed their in-treatment follow-up, to reduce the concerns of contamination between treatment conditions.

1.4.f. Community input on recruitment and retention.

Center for Public Health Research's (CPHR) Community Consulting Group (CCG) is a panel of HIV treatment advocates, community stakeholders, and diverse staff from a range of community-based organizations that meets quarterly to share input about current and future research endeavors within the CPHR. The CCG includes health care providers, substance abuse experts, and other individuals familiar with the unique needs of substance-using individuals, and has a long history of partnership with the San Francisco Department of Public Health (SFDPH). This sustained association has afforded valuable opportunities for the community to provide substantial and pertinent input concerning our research and has been invaluable in helping to develop culturally competent intervention content and effective recruitment and retention strategies.

1.4.g Study Procedures.

Potential participants will be asked brief eligibility screening questions in person or over the phone after providing verbal consent. Potential participants will provide informed consent and be screened for eligibility during the pre-enrollment screening visit. The schedule for the study

procedures is shown in (see Figure 2). Participants will be compensated for their time at each visit (up to a total of $444). Participants will receive $50 for the 2 screening visits ($25 each visit), $50 for enrollment, $10 for weekly visits (1, 2, 3, 5, 7, 9, 10, and 11), $25 for weeks 4 (month 1) and 8 (month 2) visits, $30 week 6 safety lab visit and $50 for week 12. In addition, they will receive $1 for each day that they complete the text-messaging series throughout the 12-week treatment period (up to $84). Consistent with other trials, we will conduct 1- and 3-month post-treatment visits to evaluate durability of treatment.[139-142] For post-treatment visits, participants will receive $25 (see Figure 2).

We are currently implementing the Interim UCSF Policy on Human Subjects-Related Research visits during the COVID-19 outbreak. The A-Hack study is considered essential research. We have stopped screening and enrollment visits until the shelter-in-place order is lifted. The weekly and post-treatment visits are being conducted remotely according to the interim policy guidelines. We have given the active participants up to 6 weeks of study medication during the shelter-in-place order. The monthly visits (M1, M2 and M3) include safety labs to ensure that participants do not have any adverse events to study medication. We are proposing that these in-clinic visits are conducted at weeks 6 and 12 instead of monthly for the safety of our participants during the shelter-in-place order. We will evaluate the interim policy each two weeks or when necessary according to UCSF IRB guidelines.

1.5.a. Prescreening.
Potential participants will be asked brief eligibility screening questions in person or over the phone after providing verbal consent.

1.5.b. Consent.
The consent process will discuss the 1:1 random assignment of participants to receive kudzu or placebo and will detail the potential adverse effects of kudzu. It will also discuss the weekly substance use counseling sessions. The consent process also addresses participant rights, including the voluntary nature of participation and ability to decline without penalty. Mechanisms for maintaining confidentiality will also be discussed, as well as exceptions to confidentiality which is required by law. Participants will be given a copy of the Human Subject's Bill of Rights, along with a copy of the consent form. Participants are given the contact numbers of both the PI and the UCSF IRB to answer questions about the study or one's rights as a human subject. All participants will meet with a study clinician for an additional opportunity to ask questions. Similar to our prior pharmacologic studies, all participants must also correctly complete an "Assessment of Understanding" quiz. The quiz will include 10 to 12 true/false study-related questions that assess participants' understanding of basic study concepts, including the unknown efficacy of kudzu to reduce heavy alcohol use, its side effect profile, the randomization process, and the nature of placebos. After the assessment of understanding has been completed and staff are satisfied that the participant is able to give full informed consent (including, but not limited to, a participant completing the quiz with an 80% score or greater and a demonstrated ability to fully understand corrected answers), the consent form will be signed by the participant. The staff member obtaining consent will also sign both the original

and the copy as a witness, completing the informed consent process. A copy of the signed form will be given to the client; the original signed consent will be kept in a separate, locked file.

1.5.c. Screening.
Potential participants will be screened using the inclusion and exclusion criteria outlined above in sections I.2.d & I.2.e. The screening process will consist of two visits.

1.5.d. Randomization.
Participants will be randomly assigned, sequentially as they qualify for the study, to either kudzu or placebo in a 1:1 ratio per a computer-generated list, stratified by gender, provided by a biostatistician. Randomization will be balanced using permuted blocks. Stratification by gender will ensure balance of treatment assignment within genders. Participants and investigators will be blinded to assignment.

1.5.e. Procedures for assignment to a study group, and medication dispensing.
Participants will be assigned to kudzu or placebo by a double-blinded block randomization procedure, stratified by gender. The stratified randomization code, which will have variable blocks and 1:1 randomization, will be provided by the statistician directly to the pharmacy. No study staff will have access to the code. Study medication (kudzu and placebo) will be prepared by pharmacists at Natural Pharmacie International (NPI) in identical, absorbable gelatin caps to maintain the double-blind. The study drug will be dispensed by the study clinicians in MEMs cap dispensers with dosing instructions, date of dispensing, prescribing clinician, a 24-hour telephone study phone number for medical emergencies, and advisements against drug combinations. Participants will be trained on targeted dosing of medication during enrollment and be provided a quick guide instructional leaflet for reference. Consistent with prior targeted dosing studies, participants will be instructed to take a single 2 gram dose when they believe that drinking is imminent or anticipate a drinking session.[56] For the proposed study, a single dose of the study drug will be comprised of four 500 mg capsules of kudzu extract (NPI-031, Natural Pharmacia International, Belmont, MA) or matching placebo, which is consistent with a recent human laboratory study that established the quick-acting, protective effect of a single dose of kudzu.[88] Participants will be given seven 2 gram doses (28 500 mg capsules) per week and will be instructed to not exceed a single dose (4 capsules) every 24 hours.[56] Participants will be briefed about the importance of not sharing medications.

1.5.f. Medical Management.
This study's aim is to determine efficacy of an herbal intervention to reduce binge drinking, against a background of relatively brief counseling that would be feasible in a clinical setting with limited resources. Thus, we will adapt a manualized version of the MM brief counseling platform used in NIAAA's COMBINE study.[150,151] In that trial, pharmacotherapy with MM showed the most significant reductions in heavy drinking days compared to 7 other treatment arms.[150] MM has been used in a targeted pharmacotherapy trial 98 and our team has

successfully used MM in AUD trials. MM is a low-intensity supportive program designed to increase problem recognition and enhance motivation to change maladaptive alcohol use patterns. Participants will receive individual 20 minute MM sessions weekly from trained staff supervised by a clinical psychologist.

1.1. Measures and Schedule of Data Collection Overview.

1.1.a. Medical Safety Measures.

Blood specimens will be collected for monthly safety lab assessments via venipuncture by clinicians or research associates with certified phlebotomy training. Since San Francisco is facing the COVID-19 outbreak, we will collect safety lab assessments at 6 and 12 weeks* rather than monthly until the shelter-in-place order is lifted. This is for the safety of our participants.

Table 3: Summary of Measures	Data Source	Schedule*
OUTCOME VARIABLES		
Alcohol behavioral outcomes [152,153]		
No. of binge drinking sessions; drinks per drinking day	TLFB[154]; SMS texts	W, D, PT
Alcohol urinary biomarker		
Urine-positivity for ethyl glucuronide (EtG) for recent alcohol use (past 3 days)	Urine Sample	E, W-6, PT
Sexually Transmitted Infections outcomes		
Incident syphilis, gonorrhea, Chlamydia, or HIV; site of infections (urethral, oral or rectal).	Biologic Samples	E, M-3, PT
Behavioral outcomes[152,153] 155		
No. of sex partners and condomless sex acts; Event-level data on alcohol and recent episodes of sex[155]; Partners on PrEP or with undetectable viral load	ACASI, S MS texts	E, M, D, PT
PrEP use and adherence / Anti-retroviral Therapy (ART) use and adherence	ACASI	E, M
Reported days / episodes of other substance use	ACASI	E, M
Alcohol treatment (outside study)	ACASI	E, M
Adherence outcomes		
Frequency and timing of pill taking	MEMs cap Dispensers	D
Self-reported adherence	ACASI; SMS texts	M; D
Safety outcomes		
Adverse events[156]	Self-report	E, M
Safety labs (e.g., liver enzyme levels, renal function)[156]	Serum Sample	E, M*
Surrogate measures for hypothesized kudzu mechanisms		
Alcohol physiological effects, mood states and risk behaviors during drinking sessions [157]	ACASI	W
Alcohol subjective effects scale (SES) on *intensity of intoxication* and *of impairment*; Length of subjective effects of first alcohol drink;[158] Desire for alcohol[68]	ACASI	W
Binge-drinking score from Alcohol Use Questionnaire;[159,160] Speed of drinking/drinking rate;[161] Latency/time delay between first and second drink during drinking sessions[161]	ACASI	W
Biphasic alcohol effects scale (BAES) for subjective *nature of intoxication* (stimulation and sedation)[162]	ACASI	W
Trial process measures		
No. pre-screened, screened, enrolled; visits attended, overall retention; participant satisfaction with trial	Visit database, ACASI	Ongoing M 3
Additional covariates		
Demographics (e.g., age, race, education)	ACASI	E
Alcohol Use Disorders Identification Test (AUDIT)[163]	ACASI	E, M
Center for Epidemiologic Studies Depression Scale[164]	ACASI	E, M
Brief Symptom Inventory[165]	ACASI	E, M
Severity of Dependence Scale[166]	ACASI	E, M
Visual Analog Scale Craving Scores[167]	ACASI	E, W
Notes: E=Enrollment; M=Monthly; W=Weekly; D=Daily PT=Post-Treatment		

Medications taken 30 days prior to enrollment and while enrolled in the study will be documented on a concomitant medications form.

1.1.b. Potential Risks.

Adverse drug effects: A primary risk of participation in this study is the potential of AEs due to taking kudzu. As part of the informed consent process, participants will be informed of the potential risks of taking kudzu. As an edible plant, the roots, flowers and leaves of kudzu has long been used for a wide range of food recipes and consumed as tea in East Asia.[63] Hence, kudzu is believed to be extremely safe for human consumption.

Kudzu has been widely available as an oral, over-the-counter supplement in health food stores and pharmacies for many years. While its safety and efficacy has not been evaluated by the FDA, studies involving the use of oral kudzu have reported few AEs and side effects among study participants. One double-blind, placebo-controlled trial found no side effects and no changes in vital signs and blood chemistry, liver function, or urinalysis findings during the course of kudzu treatment.[66] Similarly, another double-blind, placebo controlled trial found a complete lack of side effects associated with taking kudzu.[80]. Another double-blind, placebo-controlled study reported low overall incidence of side effects (e.g. headache, shakes, chills, nausea), and no changes to vital signs, hematology, blood chemistry, and renal or liver function tests during the study period; there were also no reports of insomnia, sedation, dizziness, blurred vision, tinnitus, or altered libido among participants.[68] Finally, a double-blind, placebo-controlled trial of kudzu's isoflavones reported only mild side effects among participants that included headache, cold symptoms, and stomach/gastrointestinal distress, with an overall incidence of 1.8% (2.0% for placebo group).[89] It has also been found that kudzu does not disturb the sleep/wake cycles of moderate drinkers.[90] Kudzu has no known serious side effects, no known abuse potential, and no known sexual side-effects.[66,68,80,83,88,89]

One article has raised a concern regarding the use of over the counter hangover cures that contain kudzu, postulating that chronic use of such remedies may lead to increased acetaldehyde-related disorders, including development of neoplasms, due to the inhibitory action that kudzu has on ALDH-2.[187] However, studies have determined that levels of the kudzu isoflavones required to reduce alcohol consumption do not lead to an accumulation of acetaldehyde or changes in acetaldehyde metabolism[81] and no evidence of disulfiram-like effects associated with acetaldehyde accumulation have been reported in other kudzu studies.[80,83] Nevertheless, as a precaution, study subjects will be instructed to not take the study medication provided to alleviate hangover symptoms.

Other potential risks. All participants are informed of the risks involved in blood draws, including bruising around the needle site, the risk of infection at the needle site, and occasional equipment failure in the vacuum tubes. Other potential risks to participating in this study include: unauthorized disclosure of confidential information; discomfort or embarrassment related to specimen collection or questionnaires dealing with personal habits and lifestyle, including drug or alcohol use; and possible unwanted encounters with friends or associates in the research setting.

Alternative treatments and procedures. Participants have the alternative of not participating in the study; a decision to not participate will in no way influence their treatment by study staff. We will make it clear to all potential participants that they have the alternative of not participating in the study, emphasizing that their decision will in no way influence their treatment by the University of California San Francisco or the San Francisco Health Department. We will also offer referrals to inpatient and outpatient substance use treatment facilities and services in San Francisco.

Adequacy of Protection of Risks

Recruitment plans. As outlined above, participants will be recruited through clinic outreach, advertisements in newspapers and on the Internet, snowball sampling, and through other referrals. Participants will be recruited and pre-screened by trained outreach staff using IRB-approved procedures. In a confidential manner, staff will inform participants of the study, emphasize that participation is voluntary, and provide the individuals with IRB-approved fliers that describe the study. Interested potential participants will be scheduled for an office visit to meet individually with study personnel who will begin the informed consent process.

Informed consent process. For informed consent procedures, we will follow the 1991 Code of Federal Regulations (45 CFR 41.102) that defines research as a systematic investigation designed to develop or contribute to generalizable knowledge. Guiding principles include respect for persons, beneficence, and just selection of research participants. The informed consent process will conform to these policies and to SFDPH and UCSF's consent form standards, and it will be reviewed and approved by the UCSF IRB.

All staff have undergone the NIH-required training in human subject protections and good clinical practice (GCP) procedures,and are extensively trained on proper procedures for obtaining informed consent. Trained staff will obtain written informed consent prior to enrollment from all study participants using IRB-approved informed consent forms. The informed consent process involves a detailed verbal description of the study; an item-by-item reading of the consent form will be conducted by study staff while the participant reads along. Trained staff will explicitly cover the purpose, procedures, risks and benefits of the study. The consent process will discuss the random assignment of participants to receive kudzu or placebo and will detail the potential adverse effects of kudzu. It will also discuss the weekly urine testing throughout the study, weekly substance use counseling sessions and daily text messaging. The consent process also addresses participant rights, including the voluntary nature of participation and ability to decline without penalty. Mechanisms for maintaining confidentiality will also be discussed, as well as exceptions to confidentiality, which are required by law. Participants will be given a copy of the Human Subject's Bill of Rights, along with a copy of the consent form. Participants are given the contact numbers of both the Principal Investigator (PI) and the UCSF IRB to answer questions about the study or one's rights as a human subject. All participants will meet with a study clinician for an additional opportunity to ask questions.

Similar to our prior pharmacologic studies, all participants must also correctly complete an *assessment of understanding* quiz. The quiz will include 10-12 true/false study-related questions that assess participants' understanding of basic study concepts, including the unknown efficacy of kudzu to reduce alcohol use, its side effect profile, the randomization process, and the nature of placebos. After the assessment of understanding has been completed and staff are satisfied that the participant is able to give full informed consent (including, but not limited to, completing the quiz with an 80% score or greater and a demonstrated ability to fully understand corrected answers), the consent form will be signed by the participant. The staff member obtaining consent will also sign both the original and the copy as a witness, completing the informed consent process. A copy of the signed form will be given to the client; the original signed consent will be kept in a separate, locked file.

Plans for minimizing risks. All potential participants will be evaluated by the study clinician for physical or psychiatric illnesses or other medical criteria that would preclude study participation. Once enrolled, all participants will be provided with a 24-hour pager number by which a study clinician may be contacted to answer questions or to provide direction in case of emergency. Study staff follow an aggressive set of safety procedures to ensure that participants receive a high and consistent level of monitoring that also meets reporting requirements to the IRB. Potential safety issues are reviewed weekly in meetings during which staff discuss potential adverse events for all participants. At any time, persons judged by project investigators to be a danger to self or others, or who are otherwise judged to be in grave danger due to medical or other conditions, will be escorted to the SFGH Psychiatric Emergency Unit. All staff, including research assistants and counselors, receive yearly training for identifying suicide/homicide risk and/or dangerous intoxication, and de-escalation of agitated or angry persons. All staff are trained to appropriately respond to these situations by immediately contacting a study clinician to evaluate the participant.

Minimizing the risks of medication side effects. At all times, participants will be encouraged to contact the study clinician if they have questions or concerns about their medication dosage. During each study visit, participants are given the opportunity to discuss any adverse medication effects with the study clinician. Participants will have safety blood tests, including liver function tests, during the 12 weeks they are taking study drug. Participants who ultimately do not tolerate their medication may be taken of study medication if needed and will continue to be followed throughout the duration of the trial.

Minimizing the risks to privacy of individuals or confidentiality of data. The study consent form will inform participants of confidentiality guidelines. Strict confidentiality will be maintained. Records that have personal identifiers (e.g., clinical records) will be stored in a locked cabinet separate from the research record, which will contain only the participant's ID number. Only the research team and clinical staff assigned to the care of the participants will have access to non-anonymous records. All research data are maintained in binders in locked cabinets. Consent forms, which contain names, are stored separately. Screening and randomization ID numbers are used to identify specific research forms. Files that link participants' names with screening and randomization ID numbers will be kept in a locked file. No presentation or publication of the

study results will refer to participants individually. Exceptions to confidentiality for research participants are those required by law and include suspicion of child abuse, elder abuse, and threat of imminent action on suicidal or homicidal ideation. Participants will be informed of these exceptions in the informed consent process. In addition, representatives from NIH and the UCSF IRB will have limited access to the research records (i.e., in the event of an SAE, the IRB may request a review of the chart to assess adequacy of care during the trial). Prior to any sharing of the research dataset, all personal identifiers will be removed. Data will be shared only with researchers who have received IRB-approval for their studies, and who agree not to identify any specific study participant in any way, and who will destroy or return the dataset after completing their analyses.

We follow the Health Insurance Portability and Accountability Act of 1996 (HIPAA) regulations for the protection of private health information for individuals. All study participants screening or enrolling in our studies must sign the HIPAA Authorization Form (unless a waiver of authorization has been approved by the IRB). The Authorization Form is protocol-specific and must be signed along with the consent form when participants first screen or enroll into a study. Before participants sign the Authorization Form, study staff will explain the purpose of the Authorization Form and answer any of the participants' questions. Participants will receive a signed copy of the Authorization Form. Potential participants who choose not to sign the HIPAA Authorization form will be excluded from study participation.

Ensuring medical or professional intervention for adverse events. *The* study clinician(s) will review data forms daily to monitor safety during the conduct of the trial. If serious or unexpected AEs occur during the trial, the PI will report these occurrences within the specified time frames to the Data and Safety Monitoring Board (DSMB), IRB, NIH, and the FDA as required. All study materials and protocols will be reviewed and approved by the UCSF IRB prior to their use. AE reporting plans are described in the Data and Safety Monitoring plan in this section.

1.1.c. Adverse events (AE) and Serious adverse events (SAE) detection.

Because kudzu is not approved to treat binge drinking, we include extensive safety parameters, as is required by the Food and Drug Administration, when testing a medication for a new indication. AEs and concomitant medications will be elicited from participants verbally and documented weekly. As previously noted, participants will be given the 24-hour phone number to reach the study clinician in emergencies. Clinicians will follow the "Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events" and UCSF IRB reporting guidelines.[168] Safety monitoring will include the assessment, follow-up, and reporting of clinical/serious AEs.

AE Reporting. Each AE will be classified by the study clinician as serious or non-serious, and appropriate reporting procedures will be followed; these decisions will be reviewed on a real-time basis by the study clinicians. An AE is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial, whether or not the event is considered medication-related. A new illness, symptom, or worsening of a pre-existing condition or abnormality is considered an AE. Stable chronic conditions that are present prior to clinical trial

entry and do not worsen are not considered AEs. For this study, AEs will include symptoms reported by the patient and abnormal measures of clinical importance noted by study staff.

Study staff will assess participants for any medical or psychiatric side effects by asking the participant "How have you been feeling since I saw you last?" Study staff will also review the previous AE form and inquire whether any of those events are continuing. Study clinicians will follow all AEs, regardless of severity, until resolution or until four weeks following completion of the trial. Each new or unresolved AE will be recorded on the AE case report form according to standard procedures. All AEs will be assigned a severity (mild, moderate, severe or life-threatening), as defined by the DAIDS Table for Grading Severity of Adult Adverse Experiences for HIV Prevention Trials. 148 The study clinician will review the information and offer an educated opinion about the relatedness of the event to the study drug. These data will be reviewed by the PI or Co-Investigator on a weekly basis.

A summary report of all AEs (including SAEs) will be prepared at least every six months (frequency determined by our IRB, DSMB, and NIH), to be submitted to the DSMB, IRB and NIH.

SAEs. SAEs are defined as any fatal event, any immediately life-threatening event, any permanent or substantially disabling event, any event that requires or prolongs inpatient hospitalization, or any congenital anomaly. This category also includes any other important medical event that a study investigator judges to be serious because it may jeopardize the subject or require intervention to prevent one of the above reportable outcomes, or which would suggest a significant hazard, contraindication, side effect, or precaution. An unexpected event is one that is not described with respect to nature, severity, or frequency in the current protocol, investigator's brochure, or product labeling. All AEs that are both serious and unexpected will be reported to the DSMB and UCSF IRB, in writing, within 10 working days. If the SAE is fatal or life threatening, the PI will notify the FDA by telephone within 24 hours, with a follow-up written report within two working days.

As required, expedited reporting of SAEs to the NIH will adhere to the following guidelines:

1. Apply regardless of the investigator's assessment of the relatedness of the SAE to the intervention under study;
2. Apply equally to trials requiring an IND and those not requiring an IND;
3. Apply to any SAEs that occur during the post-treatment observation period defined by the protocol; and
4. Apply to suicidal or homicidal behavior that causes an SAE in the participant or someone else (e.g., hospitalization or death).

SAE reporting will include a narrative that will provide details of relevant screening measures, medical history and physical findings, treatment compliance, participant reports of SAEs, and any other required information. The completed SAE report will contain: subject's ID, gender, age, the title and date of the SAE, and narrative explanation. The SAE form will track how the research staff was notified of the event, dates of consent, randomization, study screening for inclusion/exclusion, treatment received, outcome of study treatment, dates and circumstances

of the hospitalization/death, whether alcohol or drugs were known to be involved, and participant status at last clinical or research contact. In cases of participant death, the report will also include appropriate substantiation from clinic records, and, whenever possible, copies of the death certificate, autopsy report, or medical record. As Medical Monitor for the study, Dr. Coffin, will state whether the event was expected and assess its relatedness to the study medication or intervention.

Reporting of other study events. As the study is being conducted, Dr. Santos (PI) will inform the NIH, IRB, and DSMB of any changes in recruitment or in the protocol that are relevant to safety, as well as any actions taken by the IRB as a result of its continuing review of the study. In the event of any major changes in the status of an ongoing protocol (which will occur only with IRB approval), the contact PI will inform the NIH's program officer and the DSMB immediately. Such changes would include, but are not limited to: amendments to the protocol; temporary suspension of patient accrual, or of the protocol; any change in informed consent or IRB approval status; termination of patient accrual or of the protocol; or other problems or issues that could affect the human subjects in the study.

Trial stopping rules: There are no formal trial stopping rules for this study. No formal interim efficacy analysis will be conducted. If it becomes clear that the trial puts undue safety risk on study participants, outcomes are poor, or the trial will not achieve its enrollment goals, consideration will be given to stopping the trial, after consultation with the DSMB, IRB, and NIDA PO. The overall safety risk to study participants will be determined through regular monitoring procedures. Safety issues will be evaluated as they arise; participants are given the pager number of the clinician on call which they can page in the event of an emergency or safety risk. Study clinicians will consult with Dr. Santos, the Principal Investigator and Dr. Coffin, the medical director, on these safety issues on a case-by-case basis as they are reported by the participant. Non-urgent clinical issues that arise during the course of the study are discussed by the team's research clinicians at the next weekly meeting with the PI Dr. Santos. During weekly meetings, study clinicians will review all the safety issues and incident adverse events (including lab abnormalities) for the study overall, by system category, and by possible relationship to the study drug. The PI will alert the DMSB and the NIDA PO immediately if at any point the team observes an unexpected frequency of serious AEs possibly related to kudzu. At that point, the PI will consult with the DSMB to determine if changes to the protocol or consent form are needed, or if additional safety data are needed to evaluate participant safety. The PI will consult the DSMB to determine if the trial should be stopped after the committee has reviewed available safety data to date.

1.5.d. Measures of adherence.

The study will collect self-reported adherence data via weekly modified TLFB assessments, similar to prior targeted dosing studies[94,98] and via daily SMS text messages. Pill counts at weekly visits will also assess adherence. **MEMs cap Dispensers**, as with our Project iN and Say When studies, will be used to track medication adherence daily; each dispenser opening is recorded as a medication event in a remote database in real time. MEMs cap Dispensers have been shown to be reliable for real time monitoring of medication adherence, even in resource-limited

settings.[169] We have had great success with electronic medical monitoring devices in prior studies.[125,126]

1.1.e. Text messaging procedure.
As with our study, participants will receive daily Ecological Momentary Assessments (EMA) to collect data on alcohol consumption, number of drinks on drinking days, targeted medication administration prior to anticipated drinking sessions, and sexual risk behaviors.. Participants will be trained on texting procedures, will receive a reference guide during enrollment, and will be encouraged to regularly delete texts and encrypt their phone with passwords for privacy. Participants will be compensated $1 per day for their time in responding to daily texts, or up to an additional $7 each week.

1.1.f. Urinalysis for novel alcohol biochemical markers for recent alcohol use
Urine samples will be collected weekly and tested for ethyl glucuronide (EtG) to determine recent alcohol consumption in the past three days. EtG is a relatively novel, highly sensitive indicator for recent alcohol consumption; this alcohol biomarker is detectable in urine for approximately 72 hours.[170-173] The PI and Co-I, Dr. Batki, have used EtG to evaluate the efficacy of another pharmacologic intervention in reducing alcohol consumption in a trial funded by the Department of Defense.[174] Urine samples will be tested via liquid chromatography-mass spectrometry through the Redwood Toxicology Laboratory, Inc., the same lab used by Dr. Santos and Batki in their ongoing pharmacologic trials to treat AUD. EtG quantitative results will be dichotomized using established cutoff values to distinguish between positive and negative specimens.[171,173] Whenever possible we will schedule weekly visits on Mondays and Tuesdays, given that binge drinking is likely to be more common during weekends.

1.1.g. Behavioral survey measurements.
Table 4 (page 7) summarizes the data source and collection schedule for the study measures. Standardized and validated behavioral measures[152-155,163,164,167] will be assessed using audio computer administered surveys (ACASI) to minimize underreporting of risk activities and standardize data collection.[152,153] To minimize potential social desirability bias, staff will not have access to data during the trial.

1.7. Statistical Plan and Data Analysis.
We will use generalized estimating equations (GEE) to estimate treatment effects on repeated study outcomes. Primary analyses will be by intention-to-treat, without regard to adherence to treatment. In our prior trials, we had excellent retention and visit adherence. Nonetheless, in this high risk population, missing data may be encountered.[175,176] We will conduct sensitivity analyses imputing all missing urine samples as positive, adjusting for baseline correlates of missingness, and using inverse probability of censoring weights.[177]

<u>*Aim 1*</u>: *To determine the efficacy of targeted kudzu versus placebo in reducing binge drinking among sexually active binge drinkers with AUD*, as determined by number of binge drinking days in timeline follow-back (TLFB), by treatment arm. GEE Poisson models with robust standard

errors will be used to assess reductions on weekly drinking outcomes**.** Baseline TLFB results will be included in the analysis. Minimum detectable effects (MDEs): Based on the prior Project iN trial (93% retention), we conservatively estimate that 80% of participants will be retained at 12 weeks. Using estimates based on Project ECHO for the within-subject correlation and over-dispersion of the outcomes, as well as the mean frequency among controls, we estimate that this study will have 80% power in 2-sided tests with a type-I error rate of 5% to detect 28% reductions in numbers of binge drinking occasions, as well as 11% reductions in the average number of drinks on drinking days. In exploratory analyses, we will evaluate the durability of intervention effects on drinking outcomes at 1- and 3-month post-treatment visits.

Aim 2: *To determine the efficacy of targeted kudzu versus placebo in reducing alcohol consumption among non-dependent individuals with AUD*, as determined by the proportion of ethyl glucuronide (EtG) positive urines, by treatment arm. GEE logistic models with robust standard errors will be used to assess reductions frequency of positive urine tests, accounting for within-subject correlation. *MDEs:* Using the assumptions for retention for Aim 1, as well as estimates based on biomarker data from Batki et al.'s study on topiramate for alcohol use disorders[174] for the within-subject correlation and control group urine positivity rate, we estimate that the study will have 80% power in 2-sided tests with a type-I error rate of 5% to detect 15-24% reductions in the urine positivity rate in the treatment arm.

Aim 3: *To determine the efficacy of targeted kudzu versus placebo in reducing alcohol-associated sexual risk behaviors and incidence of STIs*, by treatment arm, we will use GEE Poisson models with robust standard errors for the four monthly ACASI assessments on numbers of sex partners, HIV-serodiscordant condomless sex partners, condomless sex partners while intoxicated with alcohol, and condomless sex events with serodiscordant partners, including the baseline value. In the event that these outcomes are severely over-dispersed, we will analyze indicators for any self-report of each behavior, using GEE logistic models. We will use GEE logistic regression models to evaluate differences in incidence of STIs between kudzu and placebo arms over time. Incidence will be evaluated as a composite outcome (i.e., any incident STIs), as well as by type (i.e., incident syphilis, gonorrhea, or Chlamydia), and, for gonorrhea and Chlamydia, by site (i.e., urethral, oral, vaginal, or rectal). *MDEs*: Based on estimates of within-subject correlation and control prevalence from our Project Echo trial, we estimate that the study will have 80% power to detect 32% reductions in numbers of male anal sex partners, 59% reductions in serodiscordant condomless anal sex partners, 48% reductions in condomless anal sex partners while intoxicated with alcohol, and 58% reductions in condomless anal sex events with serodiscordant partners in the treatment arm. In analyses using GEE logistic models, we will have 80% power to detect reductions of 15% for any male anal sex partners, 39% for any HIV-serodiscordant condomless anal sex partners, 40% for any condomless anal sex partners while intoxicated with alcohol, and 31% for any condomless anal sex events with serodiscordant partners in the treatment arm. After accounting for expected loss to follow-up, we will have an estimated 80% power in 2-sided tests with a type-I error rate of 5% to detect reductions of 23-26 percentage points in the incidence of STIs at month 3, depending on the control rates, assumed to be in the range 30-40%, and within-subject correlation of these outcomes, assumed to be 0.1 to 0.3; both inputs were based on data in an ongoing PrEP demonstration project.

Aim 4: To evaluate the tolerability and acceptability of targeted kudzu versus placebo, as determined by adverse clinical event rates and medication adherence (via data from MEMs capmonitoring and self-report from EMA and TLFB), by study arm. While laboratory studies have demonstrated the tolerability and acceptability of ***daily*** kudzu, we will examine these outcomes in an outpatient setting for ***targeted*** (prn) dosing. Adverse clinical events (AEs) and other binary safety outcomes will be presented as percent of participants that experience the safety outcome by treatment arm. Binary adverse effect measures will be analyzed using exact methods, since they are expected to be uncommon. We will measure the acceptability of kudzu among participants by determining medication adherence via MEMs cap opening events, pill count and self-report. Adherence measures of interest will include percent of doses taken during reported drinking days, patterns of adherence and time to stopping medication. We will assess how these measures of adherence track with patterns of alcohol use and binge drinking as reported in TLFB. GEE logistic models will be used to estimate the proportions of kudzu participants taking medication during periods of reported alcohol use and binge drinking. Concordance of adherence measures based on MEMs cap and self-report measures will be examined using weighted Kappa and correlations.

Other Exploratory Outcomes: We will use linear mixed models to determine whether kudzu leads to changes in the subjective effects of alcohol and surrogate measures for our the hypothesized mechanisms, alcohol craving, as measured by the visual analog scale (VAS), and problematic drinking, as measured by AUDIT-10. We will then determine whether changes in these mediators are associated with current or later reductions in binge drinking, using GEE Poisson models with robust standard errors controlling for treatment as well as confounders of the mediator-outcome relationship. Additionally, we will explore whether changes in alcohol consumption mediate changes in sexual behaviors using similar methods described above. As-treated analyses. We will carry out an as-treated analysis, focusing on the effect of frequency of study medication use, calculated as the number of MEMs cap dispenser openings, as a time-dependent covariate, consistent with our prior targeted dosing study. This measure is also defined for the placebo group; this is in order to account for the placebo effect of frequency of medication use. The as-treated effect will be estimated by the interaction of frequency of use and treatment assignment. Cubic splines will be used if needed to account for non-linearity of the dose effects. Evidence of unblinding: We will tabulate the proportions of participants in each arm who correctly guess their treatment assignment, and determine if there is significant evidence of unblinding. Differential use of referral services: If targeted kudzu reduces binge drinking, placebo participants may be more likely to use referral services, potentially reducing the between-group differences. While we expect this effect to be small, such a bias toward the null would be of most concern if we found weak but not statistically significant evidence for the efficacy of kudzu. In this case, we will carry out a sensitivity analysis using marginal structural models to correct for imbalanced post-randomization use of an effective co-intervention. Consecutive weeks abstinent from drinking. There is increasing interest in looking at consecutive weeks of continued abstinence (termed as "number of beyond threshold weeks of success" (NOBWOS)) as part of pharmaceutical trials. We will use Wilcoxon rank-sum tests to compare NOBWOS in the 0-3 month intervals. Treatment effect modification by covariates: We will determine whether the effect of treatment on the

alcohol and sexual behavior outcomes is modified by the following pre-specified baseline covariates: frequency of binge drinking; HIV serostatus; polysubstance use, level of interest in cutting down alcohol use, motivation to participate in the study, severity of alcohol dependence, AUDIT-10 scores, history of alcohol treatment, PrEP use (among HIV negative), and having an undetectable HIV viral load (among HIV positive). Modification of treatment effect will also be assessed among the subsets of participants who engage in lower rates of counseling and study visits (e.g., less than 70%).

REFERENCES

1. Centers for Disease C, Prevention. Alcohol-attributable deaths and years of potential life lost--United States, 2001. *MMWR. Morbidity and mortality weekly report.* 2004;53(37):866-870.
2. Bouchery EE, Harwood HJ, Sacks JJ, Simon CJ, Brewer RD. Economic costs of excessive alcohol consumption in the U.S., 2001. *American journal of preventive medicine.* 2011;41(5):516-524.
3. Sacks JJ, Gonzales KR, Bouchery EE, Tomedi LE, Brewer RD. 2010 National and State Costs of Excessive Alcohol Consumption. *American journal of preventive medicine.* 2015;49(5):e73-79.
4. Kanny D, Liu Y, Brewer RD, Lu H, Centers for Disease C, Prevention. Binge drinking - United States, 2011. *MMWR supplements.* 2013;62(3):77-80.
5. Sionean C, Le BC, Hageman K, et al. HIV Risk, prevention, and testing behaviors among heterosexuals at increased risk for HIV infection--National HIV Behavioral Surveillance System, 21 U.S. cities, 2010. *MMWR Surveill Summ.* 2014;63(14):1-39.
1. Finlayson TJ, Le B, Smith A, et al. HIV risk, prevention, and testing behaviors among men who have sex with men--National HIV Behavioral Surveillance System, 21 U.S. cities, United States, 2008. *MMWR Surveill Summ.* 2011;60(14):1-34.
7. Raymond HF. Prevalence of Binge Drinking among Heterosexual Men and Women in National HIV Behavioral Surveillance. 2017.
8. Raymond HF. San Francisco National HIV Behavioral Surveillance Data - MSM and Binge-drinking. In: Santos GM, ed. San Francisco: San Francisco Department of Public Health; 2012.
9. Raymond HF. San Francisco National HIV Behavioral Surveillance Data - MSM and Binge-drinking 2014. In: Santos GM, ed. San Francisco: San Francisco Department of Public Health; 2015.
10. Jin H. San Francisco National HIV Behavioral Surveillance Survey Data Request - MSM3 Binge Drinking Data. In: Santos G, ed. San Francisco2014:1.
11. Raymond HF, Bereknyei S, Berglas N, Hunter J, Ojeda N, McFarland W. Estimating population size, HIV prevalence and HIV incidence among men who have sex with men: a case example of synthesising multiple empirical data sources and methods in San Francisco. *Sex Transm Infect.* 2013;89(5):383-387.
12. Wolitski RJ, Stall R, Valdiserri R. *Unequal Opportunity: Health Disparities affecting Gay and Bisexual Men in the United States.* New York: Oxford Press; 2008.
13. Leigh BC. Alcohol and condom use: a meta-analysis of event-level studies. *Sex Transm Dis.* 2002;29(8):476-482.
14. Woolf SE, Maisto SA. Alcohol use and risk of HIV infection among men who have sex with men. *AIDS Behav.* 2009;13(4):757-782.
15. Stueve A, O'Donnell L, Duran R, San Doval A, Geier J. Being high and taking sexual risks: findings from a multisite survey of urban young men who have sex with men. *AIDS Educ Prev.* 2002;14(6):482-495.
11. Fergus S, Lewis MA, Darbes LA, Butterfield RM. HIV risk and protection among gay male couples: the role of gay community integration. *Health Educ Behav.* 2005;32(2):151-171.
17. Voetsch AC, Lansky A, Drake AJ, et al. Comparison of demographic and behavioral characteristics of men who have sex with men by enrollment venue type in the National HIV Behavioral Surveillance System. *Sex Transm Dis.* 2012;39(3):229-235.
18. Maisto SA, Palfai T, Vanable PA, Heath J, Woolf-King SE. The Effects of Alcohol and Sexual Arousal on Determinants of Sexual Risk in Men Who Have Sex with Men. *Arch Sex Behav.* 2011.

19. George WH, Stoner SA. Understanding acute alcohol effects on sexual behavior. *Annu Rev Sex Res.* 2000;11:92-124.
20. Howard J, Taylor JA, Ganikos ML, Holder HD, Godwin DF, Taylor ED. An overview of prevention research: issues, answers, and new agendas. *Public Health Rep.* 1988;103(6):674-683.
21. Cooper ML. Alcohol use and risky sexual behavior among college students and youth: evaluating the evidence. *J Stud Alcohol Suppl.* 2002(14):101-117.
22. Scott-Sheldon LA, Carey KB, Cunningham K, Johnson BT, Carey MP, Team MR. Alcohol Use Predicts Sexual Decision-Making: A Systematic Review and Meta-Analysis of the Experimental Literature. *AIDS Behav.* 2016;20 Suppl 1:S19-39.
23. Rehm J, Shield KD, Joharchi N, Shuper PA. Alcohol consumption and the intention to engage in unprotected sex: systematic review and meta-analysis of experimental studies. *Addiction.* 2012;107(1):51-59.
24. Vosburgh HW, Mansergh G, Sullivan PS, Purcell DW. A Review of the Literature on Event-Level Substance Use and Sexual Risk Behavior Among Men Who Have Sex with Men. *AIDS Behav.* 2012.
25. Irwin TW, Morgenstern J, Parsons JT, Wainberg M, Labouvie E. Alcohol and sexual HIV risk behavior among problem drinking men who have sex with men: An event level analysis of timeline followback data. *AIDS Behav.* 2006;10(3):299-307.
21. Colfax G, Vittinghoff E, Husnik MJ, et al. Substance use and sexual risk: a participant- and episode-level analysis among a cohort of men who have sex with men. *Am J Epidemiol.* 2004;159(10):1002-1012.
27. Prestage G, Grierson J, Bradley J, Hurley M, Hudson J. The role of drugs during group sex among gay men in Australia. *Sex Health.* 2009;6(4):310-317.
28. Benotsch EG, Nettles CD, Wong F, et al. Sexual risk behavior in men attending Mardi Gras celebrations in New Orleans, Louisiana. *J Community Health.* 2007;32(5):343-351.
29. Benotsch EG, Mikytuck JJ, Ragsdale K, Pinkerton SD. Sexual risk and HIV acquisition among men who have sex with men travelers to Key West, Florida: a mathematical modeling analysis. *AIDS Patient Care STDS.* 2006;20(8):549-551.
30. Lambert G, Cox J, Hottes TS, et al. Correlates of unprotected anal sex at last sexual episode: analysis from a surveillance study of men who have sex with men in Montreal. *AIDS Behav.* 2011;15(3):584-595.
31. Vanable PA, McKirnan DJ, Buchbinder SP, et al. Alcohol use and high-risk sexual behavior among men who have sex with men: the effects of consumption level and partner type. *Health Psychol.* 2004;23(5):525-532.
32. Folch C, Esteve A, Zaragoza K, Munoz R, Casabona J. Correlates of intensive alcohol and drug use in men who have sex with men in Catalonia, Spain. *Eur J Public Health.* 2010;20(2):139-145.
33. Reisner SL, Mimiaga MJ, Case P, Johnson CV, Safren SA, Mayer KH. Predictors of identifying as a barebacker among high-risk New England HIV seronegative men who have sex with men. *J Urban Health.* 2009;86(2):250-262.
34. NYCDOHMH. *Alcohol use and risky sex in New York City.* New York City: New York City Department of Health and Mental Hygiene;2008.
35. Mackesy-Amiti ME, Fendrich M, Johnson TP. Symptoms of substance dependence and risky sexual behavior in a probability sample of HIV-negative men who have sex with men in Chicago. *Drug Alcohol Depend.* 2010;110(1-2):38-43.
31. Fisher JC, Bang H, Kapiga SH. The association between HIV infection and alcohol use: a systematic review and meta-analysis of African studies. *Sex Transm Dis.* 2007;34(11):856-863.

37. Fisher JC, Cook PA, Sam NE, Kapiga SH. Patterns of alcohol use, problem drinking, and HIV infection among high-risk African women. *Sex Transm Dis.* 2008;35(6):537-544.
38. Chersich MF, Rees HV. Causal links between binge drinking patterns, unsafe sex and HIV in South Africa: its time to intervene. *Int J STD AIDS.* 2010;21(1):2-7.
39. Bello B, Moultrie H, Somji A, Chersich MF, Watts C, Delany-Moretlwe S. Alcohol use and sexual risk behaviour among men and women in inner-city Johannesburg, South Africa. *BMC public health.* 2017;17(Suppl 3):548.
40. Kalichman SC, Simbayi LC, Kaufman M, Cain D, Jooste S. Alcohol use and sexual risks for HIV/AIDS in sub-Saharan Africa: systematic review of empirical findings. *Prevention science : the official journal of the Society for Prevention Research.* 2007;8(2):141-151.
41. Kalichman SC, Simbayi LC, Cain D. HIV transmission risk behaviours among HIV seropositive sexually transmitted infection clinic patients in Cape Town, South Africa. *Eur J Public Health.* 2010;20(2):202-201.
42. Kalichman SC, Simbayi LC, Cain D, Jooste S. Condom failure among men receiving sexually transmissible infection clinic services, Cape Town, South Africa. *Sex Health.* 2009;6(4):300-304.
43. Reisner SL, Mimiaga MJ, Bland S, et al. Problematic alcohol use and HIV risk among Black men who have sex with men in Massachusetts. *AIDS Care.* 2010;22(5):577-587.
44. Mimiaga MJ, Thomas B, Mayer KH, et al. Alcohol use and HIV sexual risk among MSM in Chennai, India. *Int J STD AIDS.* 2011;22(3):121-125.
45. Nelson KM, Simoni JM, Pearson CR, Walters KL. 'I've had unsafe sex so many times why bother being safe now?': the role of cognitions in sexual risk among American Indian/Alaska Native men who have sex with men. *Ann Behav Med.* 2011;42(3):370-380.
41. Shuper PA, Joharchi N, Irving H, Rehm J. Alcohol as a correlate of unprotected sexual behavior among people living with HIV/AIDS: review and meta-analysis. *AIDS Behav.* 2009;13(6):1021-1031.
47. Read TR, Hocking J, Sinnott V, Hellard M. Risk factors for incident HIV infection in men having sex with men: a case-control study. *Sex Health.* 2007;4(1):35-39.
48. Koblin BA, Husnik MJ, Colfax G, et al. Risk factors for HIV infection among men who have sex with men. *AIDS.* 2006;20(5):731-739.
49. Sander PM, Cole SR, Stall RD, et al. Joint effects of alcohol consumption and high-risk sexual behavior on HIV seroconversion among men who have sex with men. *AIDS.* 2013;27(5):815-823.
50. Baliunas D, Rehm J, Irving H, Shuper P. Alcohol consumption and risk of incident human immunodeficiency virus infection: a meta-analysis. *International journal of public health.* 2010;55(3):159-161.
51. Santos GM, Das M, Colfax GN. Interventions for non-injection substance use among US men who have sex with men: what is needed. *AIDS Behav.* 2011;15 Suppl 1:S51-51.
52. Paul JP, Barrett DC, Crosby GM, Stall RD. Longitudinal changes in alcohol and drug use among men seen at a gay-specific substance abuse treatment agency. *J Stud Alcohol.* 1996;57(5):475-485.
53. Fals-Stewart W, O'Farrell TJ, Lam WK. Behavioral couple therapy for gay and lesbian couples with alcohol use disorders. *J Subst Abuse Treat.* 2009;37(4):379-387.
54. Bux D. The epidemiology of problem drinking in gay men and lesbians: A Critical Review. *Clinical Psychology Review.* 1996;16(4):277-298.
55. Mark TL, Kranzler HR, Poole VH, Hagen CA, McLeod C, Crosse S. Barriers to the use of medications to treat alcoholism. *The American journal on addictions / American Academy of Psychiatrists in Alcoholism and Addictions.* 2003;12(4):281-294.

51. Mark TL, Kassed CA, Vandivort-Warren R, Levit KR, Kranzler HR. Alcohol and opioid dependence medications: prescription trends, overall and by physician specialty. *Drug Alcohol Depend.* 2009;99(1-3):345-349.
57. Jonas DE, Amick HR, Feltner C, et al. Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and meta-analysis. *Jama.* 2014;311(18):1889-1900.
58. Rychtarik RG, Connors GJ, Dermen KH, Stasiewicz PR. Alcoholics Anonymous and the use of medications to prevent relapse: an anonymous survey of member attitudes. *J Stud Alcohol.* 2000;61(1):134-138.
59. Harris AH, Oliva E, Bowe T, Humphreys KN, Kivlahan DR, Trafton JA. Pharmacotherapy of alcohol use disorders by the Veterans Health Administration: patterns of receipt and persistence. *Psychiatric services.* 2012;63(7):679-685.
60. Rubinsky AD, Chen C, Batki SL, Williams EC, Harris AH. Comparative utilization of pharmacotherapy for alcohol use disorder and other psychiatric disorders among U.S. Veterans Health Administration patients with dual diagnoses. *Journal of psychiatric research.* 2015;69:150-157.
61. Harris AH, Kivlahan DR, Bowe T, Humphreys KN. Pharmacotherapy of alcohol use disorders in the Veterans Health Administration. *Psychiatric services.* 2010;61(4):392-398.
62. San Francisco Department of Public Health. The SEEDS Study. 2015; https://www.snapsurveys.com/wh/s.asp?k=143837781982. Accessed 12/29/2015, 2015.
63. Keung WM, Vallee BL. Kudzu root: an ancient Chinese source of modern antidipsotropic agents. *Phytochemistry.* 1998;47(4):499-501.
64. Hayashino Y. Is herbal "root" effective for reducing alcohol drinking? *Alcoholism, clinical and experimental research.* 2005;29(10):1913; author reply 1914.
65. Lu L, Liu Y, Zhu W, et al. Traditional medicine in the treatment of drug addiction. *The American journal of drug and alcohol abuse.* 2009;35(1):1-11.
61. Lukas SE, Penetar D, Berko J, et al. An extract of the Chinese herbal root kudzu reduces alcohol drinking by heavy drinkers in a naturalistic setting. *Alcoholism, clinical and experimental research.* 2005;29(5):756-762.
67. Overstreet DH, Keung WM, Rezvani AH, Massi M, Lee DY. Herbal remedies for alcoholism: promises and possible pitfalls. *Alcoholism, clinical and experimental research.* 2003;27(2):177-185.
68. Lukas SE, Penetar D, Su Z, et al. A standardized kudzu extract (NPI-031) reduces alcohol consumption in nontreatment-seeking male heavy drinkers. *Psychopharmacology.* 2013;226(1):65-73.
69. Johnson RA, Lukens JM, Kole JW, Sisti DA. Views about responsibility for alcohol addiction and negative evaluations of naltrexone. *Substance abuse treatment, prevention, and policy.* 2015;10:10.
70. Edwards S, Kenna GA, Swift RM, Leggio L. Current and promising pharmacotherapies, and novel research target areas in the treatment of alcohol dependence: a review. *Current pharmaceutical design.* 2011;17(14):1323-1332.
71. Thomas CP, Wallack SS, Lee S, McCarty D, Swift R. Research to practice: adoption of naltrexone in alcoholism treatment. *J Subst Abuse Treat.* 2003;24(1):1-11.
72. Lin RC, Li TK. Effects of isoflavones on alcohol pharmacokinetics and alcohol-drinking behavior in rats. *The American journal of clinical nutrition.* 1998;68(6 Suppl):1512S-1515S.
73. Xie CI, Lin RC, Antony V, et al. Daidzin, an antioxidant isoflavonoid, decreases blood alcohol levels and shortens sleep time induced by ethanol intoxication. *Alcoholism, clinical and experimental research.* 1994;18(6):1443-1447.

74. Keung WM, Vallee BL. Daidzin and daidzein suppress free-choice ethanol intake by Syrian golden hamsters. *Proceedings of the National Academy of Sciences of the United States of America.* 1993;90(21):10008-10012.
75. Keung WM, Klyosov AA, Vallee BL. Daidzin inhibits mitochondrial aldehyde dehydrogenase and suppresses ethanol intake of Syrian golden hamsters. *Proceedings of the National Academy of Sciences of the United States of America.* 1997;94(5):1675-1679.
71. Lin RC, Guthrie S, Xie CY, et al. Isoflavonoid compounds extracted from Pueraria lobata suppress alcohol preference in a pharmacogenetic rat model of alcoholism. *Alcoholism, clinical and experimental research.* 1996;20(4):659-663.
77. Heyman GM, Keung WM, Vallee BL. Daidzin decreases ethanol consumption in rats. *Alcoholism, clinical and experimental research.* 1996;20(6):1083-1087.
78. Overstreet D, Lee D, Chen Y, Rezvani A. The Chinese herbal medicine NPI-028 suppresses alcohol intake in alcohol-preferring rats and monkeys without inducing taste aversion. *J Perfusion.* 1998;11:381–389.
79. Kushner S, Han D, Oscar-Berman M, et al. Declinol, a Complex Containing Kudzu, Bitter Herbs (Gentian, Tangerine Peel) and Bupleurum, Significantly Reduced Alcohol Use Disorders Identification Test (AUDIT) Scores in Moderate to Heavy Drinkers: A Pilot Study. *Journal of addiction research & therapy.* 2013;4(3).
80. Penetar DM, Toto LH, Lee DY, Lukas SE. A single dose of kudzu extract reduces alcohol consumption in a binge drinking paradigm. *Drug Alcohol Depend.* 2015;153:194-200.
81. Keung WM, Lazo O, Kunze L, Vallee BL. Daidzin suppresses ethanol consumption by Syrian golden hamsters without blocking acetaldehyde metabolism. *Proceedings of the National Academy of Sciences of the United States of America.* 1995;92(19):8990-8993.
82. Keung WM, Vallee BL. Daidzin: a potent, selective inhibitor of human mitochondrial aldehyde dehydrogenase. *Proceedings of the National Academy of Sciences of the United States of America.* 1993;90(4):1247-1251.
83. Penetar DM, Maclean RR, McNeil JF, Lukas SE. Kudzu extract treatment does not increase the intoxicating effects of acute alcohol in human volunteers. *Alcoholism, clinical and experimental research.* 2011;35(4):726-734.
84. Overstreet DH, Kralic JE, Morrow AL, Ma ZZ, Zhang YW, Lee DY. NPI-031G (puerarin) reduces anxiogenic effects of alcohol withdrawal or benzodiazepine inverse or 5-HT2C agonists. *Pharmacology, biochemistry, and behavior.* 2003;75(3):619-625.
85. Shen XL, Witt MR, Nielsen M, Sterner O. Inhibition of [3H] flunitrazepam binding to rat brain membranes in vitro by puerarin and daidzein. *Yao xue xue bao = Acta pharmaceutica Sinica.* 1996;31(1):59-62.
81. Wong KH, Li GQ, Li KM, Razmovski-Naumovski V, Chan K. Kudzu root: traditional uses and potential medicinal benefits in diabetes and cardiovascular diseases. *Journal of ethnopharmacology.* 2011;134(3):584-607.
87. Wu XD, Wang C, Zhang ZY, Fu Y, Liu FY, Liu XH. Puerarin attenuates cerebral damage by improving cerebral microcirculation in spontaneously hypertensive rats. *Evidence-based complementary and alternative medicine : eCAM.* 2014;2014:408501.
88. Penetar DM, Teter CJ, Ma Z, Tracy M, Lee DY, Lukas SE. Pharmacokinetic profile of the isoflavone puerarin after acute and repeated administration of a novel kudzu extract to human volunteers. *Journal of alternative and complementary medicine.* 2006;12(6):543-548.
89. Penetar DM, Toto LH, Farmer SL, et al. The isoflavone puerarin reduces alcohol intake in heavy drinkers: a pilot study. *Drug Alcohol Depend.* 2012;126(1-2):251-251.

90. Bracken BK, Penetar DM, Maclean RR, Lukas SE. Kudzu root extract does not perturb the sleep/wake cycle of moderate drinkers. *Journal of alternative and complementary medicine.* 2011;17(10):961-961.
91. Leeman RF, Palmer RS, Corbin WR, Romano DM, Meandzija B, O'Malley SS. A pilot study of naltrexone and BASICS for heavy drinking young adults. *Addict Behav.* 2008;33(8):1048-1054.
92. Kranzler HR, Armeli S, Feinn R, Tennen H. Targeted naltrexone treatment moderates the relations between mood and drinking behavior among problem drinkers. *J Consult Clin Psychol.* 2004;72(2):317-327.
93. Kranzler HR, Armeli S, Tennen H, et al. Targeted naltrexone for early problem drinkers. *J Clin Psychopharmacol.* 2003;23(3):294-304.
94. Kranzler HR, Tennen H, Armeli S, et al. Targeted naltrexone for problem drinkers. *J Clin Psychopharmacol.* 2009;29(4):350-357.
95. Kranzler HR, Tennen H, Penta C, Bohn MJ. Targeted naltrexone treatment of early problem drinkers. *Addict Behav.* 1997;22(3):431-431.
91. Heinala P, Alho H, Kiianmaa K, Lonnqvist J, Kuoppasalmi K, Sinclair JD. Targeted use of naltrexone without prior detoxification in the treatment of alcohol dependence: a factorial double-blind, placebo-controlled trial. *J Clin Psychopharmacol.* 2001;21(3):287-292.
97. Santos GM, Coffin P, Santos D, et al. Feasibility, acceptability and tolerability of targeted naltrexone for non-dependent methamphetamine-using and binge-drinking men who have sex with men. *Journal of acquired immune deficiency syndromes.* 2015.
98. Karhuvaara S, Simojoki K, Virta A, et al. Targeted nalmefene with simple medical management in the treatment of heavy drinkers: a randomized double-blind placebo-controlled multicenter study. *Alcoholism, clinical and experimental research.* 2007;31(7):1179-1187.
99. Trial watch: Nalmefene reduces alcohol use in phase III trial. *Nat Rev Drug Discov.* 2011;10(8):561.
100. Mansergh G, Koblin BA, Colfax GN, McKirnan DJ, Flores SA, Hudson SM. Preefficacy use and sharing of antiretroviral medications to prevent sexually-transmitted HIV infection among US men who have sex with men. *Journal of acquired immune deficiency syndromes.* 2010;55(2):e14-11.
101. Wilson DP, Prestage GP, Gray RT, et al. Chemoprophylaxis is likely to be acceptable and could mitigate syphilis epidemics among populations of gay men. *Sex Transm Dis.* 2011;38(7):573-579.
102. Carballo-Dieguez A, Bauermeister J, Ventuneac A, Dolezal C, Mayer K. Why Rectal Douches May Be Acceptable Rectal-Microbicide Delivery Vehicles for Men Who Have Sex With Men. *Sex Transm Dis.* 2009.
103. Molina JM, Capitant C, Spire B, et al. On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection. *The New England journal of medicine.* 2015;373(23):2237-2241.
104. Stall R, Purcell D. Intertwining epidemics: A review of research on substance use among men who have sex with men and its connection to the AIDS epidemic. *AIDS and Behavior.* 2000;4:181-192.
105. Santos GM, Emenyonu NI, Bajunirwe F, et al. Self-reported alcohol abstinence associated with ART initiation among HIV-infected persons in rural Uganda. *Drug Alcohol Depend.* 2014;134:151-157.
101. Hahn JA, Bwana MB, Javors MA, Martin JN, Emenyonu NI, Bangsberg DR. Biomarker testing to estimate under-reported heavy alcohol consumption by persons with HIV initiating ART in Uganda. *AIDS Behav.* 2010;14(6):1265-1268.

107. Hahn JA, Fatch R, Kabami J, et al. Self-Report of Alcohol Use Increases When Specimens for Alcohol Biomarkers Are Collected in Persons With HIV in Uganda. *Journal of acquired immune deficiency syndromes.* 2012;61(4):e63-64.
108. Armstrong AW, Watson AJ, Makredes M, Frangos JE, Kimball AB, Kvedar JC. Text-message reminders to improve sunscreen use: a randomized, controlled trial using electronic monitoring. *Arch Dermatol.* 2009;145(11):1230-1231.
109. Cocosila M, Archer N, Haynes RB, Yuan Y. Can wireless text messaging improve adherence to preventive activities? Results of a randomised controlled trial. *Int J Med Inform.* 2009;78(4):230-238.
110. Franklin VL, Waller A, Pagliari C, Greene SA. A randomized controlled trial of Sweet Talk, a text-messaging system to support young people with diabetes. *Diabet Med.* 2006;23(12):1332-1338.
111. Granholm E, Ben-Zeev D, Link PC, Bradshaw KR, Holden JL. Mobile Assessment and Treatment for Schizophrenia (MATS): A Pilot Trial of An Interactive Text-Messaging Intervention for Medication Adherence, Socialization, and Auditory Hallucinations. *Schizophr Bull.* 2011.
112. Miloh T, Annunziato R, Arnon R, et al. Improved adherence and outcomes for pediatric liver transplant recipients by using text messaging. *Pediatrics.* 2009;124(5):e844-850.
113. Petrie KJ, Perry K, Broadbent E, Weinman J. A text message programme designed to modify patients' illness and treatment beliefs improves self-reported adherence to asthma preventer medication. *Br J Health Psychol.* 2011.
114. Rodgers A, Corbett T, Bramley D, et al. Do u smoke after txt? Results of a randomised trial of smoking cessation using mobile phone text messaging. *Tob Control.* 2005;14(4):255-261.
115. Shapiro JR, Bauer S, Andrews E, et al. Mobile therapy: Use of text-messaging in the treatment of bulimia nervosa. *Int J Eat Disord.* 2010;43(6):513-519.
111. Wei J, Hollin I, Kachnowski S. A review of the use of mobile phone text messaging in clinical and healthy behaviour interventions. *J Telemed Telecare.* 2011;17(1):41-48.
117. clinicaltrial.gov. N-acetylcysteine Treatment of Hazardous or Harmful Alcohol Use In Veterans With TBI (NAC). 2016; https://clinicaltrials.gov/ct2/show/NCT02791945. Accessed 10/25/2017, 2017.
118. Batki SL, Dimmock JA, Wade M, et al. Monitored naltrexone without counseling for alcohol abuse/dependence in schizophrenia-spectrum disorders. *The American journal on addictions / American Academy of Psychiatrists in Alcoholism and Addictions.* 2007;16(4):253-259.
119. Batki SL, Dimmock JA, Ploutz-Snyder R, Meszaros ZS, Canfield K. Directly Monitored Naltrexone Reduces Heavy Drinking in Schizophrenia: Preliminary Analysis of a Controlled Trial. *Alcoholism Clinical and Experimental Research.* 2009;33(6):116A.
120. Batki SL, Dimmock JA, Meszaros ZS, et al. Extended-Release Naltrexone for Alcohol Dependence in Serious Mental Illness. *Alcoholism Clinical and Experimental Research.*
121. Batki SL, Pennington DL, Lasher B, et al. Topiramate treatment of alcohol use disorder in veterans with posttraumatic stress disorder: a randomized controlled pilot trial. *Alcoholism, clinical and experimental research.* 2014;38(8):2169-2177.
122. clinicaltrial.gov. Treatment With Lorcaserin for Cocaine Use: The TLC Study (TLC). 2017; https://www.clinicaltrials.gov/ct2/show/NCT03192995. Accessed 10/25/2017, 2017.
123. clinicaltrial.gov. Accelerated Development of Additive Pharmacotherapy Treatment (ADAPT-2) for Methamphetamine Use Disorder (ADAPT-2). 2017; https://www.clinicaltrials.gov/ct2/show/NCT03078075. Accessed 10/25/2017, 2017.
124. Coffin PO, Santos GM, Hern J, et al. Extended-release naltrexone for methamphetamine dependence among men who have sex with men: a randomized placebo-controlled trial. *Addiction.* 2017.

125. Das M, Santos D, Matheson T, et al. Feasibility and acceptability of a phase II randomized pharmacologic intervention for methamphetamine dependence in high-risk men who have sex with men. *AIDS.* 2010;24(7):991-1000.
121. Colfax GN, Santos GM, Das M, et al. Mirtazapine to reduce methamphetamine use: a randomized controlled trial. *Arch Gen Psychiatry.* 2011;68(11):1168-1175.
127. clinicaltrial.gov. Mirtazapine for the Treatment of Methamphetamine Dependence Among MSM (M2.0). 2013; https://www.clinicaltrials.gov/ct2/show/NCT01888835. Accessed 10/25/2017, 2017.
128. Coffin PO, Santos GM, Das M, et al. Aripiprazole for the treatment of methamphetamine dependence: a randomized, double-blind, placebo-controlled trial. *Addiction.* 2013;108(4):751-761.
129. Coffin PO, Santos GM, Colfax G, et al. Adapted Personalized Cognitive Counseling for Episodic Substance-using Men Who Have Sex with Men: A Randomized Controlled Trial. *AIDS & Behavior.* 2014; In press.
130. Mansergh G, Koblin BA, McKirnan DJ, et al. An intervention to reduce HIV risk behavior of substance-using men who have sex with men: a two-group randomized trial with a nonrandomized third group. *PLoS Med.* 2010;7(8):e1000329.
131. Das M, Dadasovich R, Matheson T, et al. Adapting an Effective HIV Prevention Intervention, Personalized Cognitive Counseling, for Episodic Substance-Using Men who have Sex with Men (SUMSM). XVIII International AIDS Conference; 07/14/2010, 2010; Vienna, Austria. Abstract #WEPE0324.
132. Santos GM, Das M, Santos D, Chu P, G. C. Social network analysis of methamphetamine-using men who have sex with men in San Francisco. 2011 National HIV Prevention Conference. Abstract# 1463 August, 2011., 2011; Atlanta, GA.
133. Santos GM, Das M, Matheson T, Vittinghoff E, Dilley J, Colfax G. High-risk sexual behaviors associated with increasing combinations of polysubstances among substance-using men who have sex with men (SUMSM). Abstract# A-452-0270-13751. XIX International AIDS Conference (AIDS 2012). ; July, 2012, 2012; Washington, D.C.
134. Santos GM, Das M, Santos D, Chu P, Vittinghoff E, G. C. Adherence in pharmacotherapy trials among methamphetamine-dependent men who have sex with men (MSM). . North American Congress of Epidemiology. Abstract# 00003039 June, 2011 2011; Montreal, QC.
135. Santos GM, Do T, Beck J, et al. Syndemic conditions associated with increased HIV risk in a global sample of men who have sex with men. *Sex Transm Infect.* 2014.
131. Santos GM, Beck J, Wilson PA, et al. Homophobia as a barrier to HIV prevention service access for young men who have sex with men. *Journal of acquired immune deficiency syndromes.* 2013;63(5):e167-170.
137. Colfax G, Santos GM, Chu P, et al. Amphetamine-group substances and HIV. *Lancet.* 2010;376(9739):458-474.
138. Santos GM, Coffin PO, Das M, et al. Dose-response associations between number and frequency of substance use and high-risk sexual behaviors among HIV-negative substance-using men who have sex with men (SUMSM) in San Francisco. *Journal of acquired immune deficiency syndromes.* 2013;63(4):540-544.
139. Baltieri DA, De Andrade AG. Acamprosate in alcohol dependence: a randomized controlled efficacy study in a standard clinical setting. *J Stud Alcohol.* 2004;65(1):136-139.
140. Anton RF, Moak DH, Latham PK, et al. Posttreatment results of combining naltrexone with cognitive-behavior therapy for the treatment of alcoholism. *J Clin Psychopharmacol.* 2001;21(1):72-77.

141. Kiefer F, Andersohn F, Otte C, Wolf K, Jahn H, Wiedemann K. Long-term effects of pharmacotherapy on relapse prevention in alcohol dependence. *Acta neuropsychiatrica.* 2004;16(5):233-238.
142. Tempesta E, Janiri L, Bignamini A, Chabac S, Potgieter A. Acamprosate and relapse prevention in the treatment of alcohol dependence: a placebo-controlled study. *Alcohol and alcoholism.* 2000;35(2):202-209.
143. Lee T. NPI-031 information request. In: Walker J, ed. San Francisco: Natural Pharmacia, Inc (NPI),; 2011.
144. Kamb ML, Fishbein M, Douglas JM, Jr., et al. Efficacy of risk-reduction counseling to prevent human immunodeficiency virus and sexually transmitted diseases: a randomized controlled trial. Project RESPECT Study Group. *Jama.* 1998;280(13):1161-1167.
145. Freeman AH, Bernstein KT, Kohn RP, Philip S, Rauch LM, Klausner JD. Evaluation of self-collected versus clinician-collected swabs for the detection of Chlamydia trachomatis and Neisseria gonorrhoeae pharyngeal infection among men who have sex with men. *Sex Transm Dis.* 2011;38(11):1036-1039.
141. Moncada J, Schachter J, Liska S, Shayevich C, Klausner JD. Evaluation of self-collected glans and rectal swabs from men who have sex with men for detection of Chlamydia trachomatis and Neisseria gonorrhoeae by use of nucleic acid amplification tests. *Journal of clinical microbiology.* 2009;47(6):1657-1662.
147. Soni S, White JA. Self-screening for Neisseria gonorrhoeae and Chlamydia trachomatis in the human immunodeficiency virus clinic--high yields and high acceptability. *Sex Transm Dis.* 2011;38(12):1107-1109.
148. Barbee LA, Tat S, Dhanireddy S, Marrazzo JM. Effectiveness and patient acceptability of a self-testing intervention for STI in an HIV primary care setting. 2014 National STD Prevention Conference; 2014; Atlanta GA.
149. Sexton ME, Baker JJ, Nakagawa K, et al. How reliable is self-testing for gonorrhea and chlamydia among men who have sex with men? *The Journal of family practice.* 2013;62(2):70-78.
150. Anton RF, O'Malley SS, Ciraulo DA, et al. Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial. *Jama.* 2006;295(17):2003-2017.
151. Pettinati HM, Weiss R, Miller WR, Donovan D, Ernst DB, Rounsaville BJ. *Medical Management Treatment Manual: A Clinical Research Guide for Medically Trained Clinicians Providing Pharmacotherapy as Part of the Treatment for Alcohol Dependence. .* Bethesda, MD: NIAAA;2004.
152. Koblin B, Chesney M, Coates T, et al. Effects of a behavioural intervention to reduce acquisition of HIV infection among men who have sex with men: the EXPLORE randomised controlled study. *Lancet.* 2004;364(9428):41-50.
153. Macalino GE, Celentano DD, Latkin C, Strathdee SA, Vlahov D. Risk behaviors by audio computer-assisted self-interviews among HIV-seropositive and HIV-seronegative injection drug users. *AIDS Educ Prev.* 2002;14(5):367-378.
154. Sobell L, Sobell M. Timeline follow-back: a technique for assessing self-reported alcohol consumption. In: Litten R, Allen J, eds. *Measuring Alcohol Consumption*. New York: Humana Press; 1992:41-72.
155. Koblin B, Chesney MA, Husnik MJ, et al. High-risk behaviors among men who have sex with men in 6 US cities: baseline data from the EXPLORE Study. *American Journal of Public Health.* 2006;93(6):926-932.

151. DAIDS. Table for grading severity of adult adverse experiences for prevention research programs. 2003; http://www.hptn.org/Web%20Documents/Regulatory_Resources/VPRP_toxtables.pdf. Accessed December, 2004.
157. Peacock A, Bruno R, Martin FH. The subjective physiological, psychological, and behavioral risk-taking consequences of alcohol and energy drink co-ingestion. *Alcoholism, clinical and experimental research.* 2012;36(11):2008-2015.
158. Forward J, Akhurst J, Bruno R, et al. Nature versus intensity of intoxication: Co-ingestion of alcohol and energy drinks and the effect on objective and subjective intoxication. *Drug Alcohol Depend.* 2017;180:292-303.
159. Mehrabian A, Russell JA. A questionnaire measure of habitual alcohol use. *Psychological reports.* 1978;43(3 Pt 1):803-801.
160. Lake SL, Hill-Kapturczak N, Liang Y, et al. Assessing the Validity of Participant-Derived Compared to Staff-Derived Values to Compute a Binge Score. *Alcohol and alcoholism.* 2015;50(4):413-419.
161. Townshend JM, Duka T. Patterns of alcohol drinking in a population of young social drinkers: a comparison of questionnaire and diary measures. *Alcohol and alcoholism.* 2002;37(2):187-192.
162. Martin CS, Earleywine M, Musty RE, Perrine MW, Swift RM. Development and validation of the Biphasic Alcohol Effects Scale. *Alcoholism, clinical and experimental research.* 1993;17(1):140-141.
163. Maisto SA, Saitz R. Alcohol use disorders: screening and diagnosis. *The American journal on addictions / American Academy of Psychiatrists in Alcoholism and Addictions.* 2003;12 Suppl 1:S12-25.
164. Cheng ST, Chan AC, Fung HH. Factorial structure of a short version of the Center for Epidemiologic Studies Depression Scale. *Int J Geriatr Psychiatry.* 2006;21(4):333-331.
165. Derogatis LR, Melisaratos N. The Brief Symptom Inventory: an introductory report. *Psychol Med.* 1983;13(3):595-605.
161. Gossop M, Darke S, Griffiths P, et al. The Severity of Dependence Scale (SDS): psychometric properties of the SDS in English and Australian samples of heroin, cocaine and amphetamine users. *Addiction.* 1995;90(5):607-614.
167. Han DH, Bolo N, Daniels MA, et al. Craving for alcohol and food during treatment for alcohol dependence: modulation by T allele of 1519T>C GABAAalpha1. *Alcoholism, clinical and experimental research.* 2008;32(9):1593-1599.
168. DAIDS. Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events 2009.
169. Haberer JE, Kahane J, Kigozi I, et al. Real-time adherence monitoring for HIV antiretroviral therapy. *AIDS Behav.* 2010;14(6):1340-1341.
170. Litten RZ, Bradley AM, Moss HB. Alcohol biomarkers in applied settings: recent advances and future research opportunities. *Alcoholism, clinical and experimental research.* 2010;34(6):955-967.
171. SAMHSA. The Role of Biomarkers in the Treatment of Alcohol Use Disorders, 2012 Revision. *SAMHSA Advisory.* 2012;11(2):1-8.
172. Kalapatapu RK, Chambers R. Novel Objective Biomarkers of Alcohol Use: Potential Diagnostic and Treatment Management Tools in Dual Diagnosis Care. *J Dual Diagn.* 2009;5(1):57-82.
173. Jatlow P, O'Malley SS. Clinical (nonforensic) application of ethyl glucuronide measurement: are we ready? *Alcoholism, clinical and experimental research.* 2010;34(6):968-975.

174. Santos GM, Lasher BA, Heinz AJ, et al. Urinary Ethyl Glucuronide and Ethyl Sulfate Testing to Evaluate the Efficacy of Topiramate for Alcohol Dependence Among Veterans with Post-Traumatic Stress Disorder. Research Society on Alcoholism; June 22, 2013, 2013; Orlando, FL.
175. Laird NM. Missing data in longitudinal studies. *Stat Med.* 1988;7(1-2):305-315.
171. Little RJA. Modeling the drop-out mechanism in repeated-measures studies. *J Amer Stat Assoc.* 1995;90(431):1112-1121.
177. Robins JM, Rotnizky A, Zhao LP. Analysis of semiparametric regression models for repeated outcomes in the presence of missing data. *J Amer Stat Assoc.* 1995;90(429):106-121.
178. Hartz DT, Frederick-Osborne SL, Galloway GP. Craving predicts use during treatment for methamphetamine dependence: a prospective, repeated-measures, within-subject analysis. *Drug Alcohol Depend.* 2001;63(3):269-271.
179. Cole SR, Hernan MA. Fallibility in estimating direct effects. *Int J Epidemiol.* 2002;31(1):163-165.
180. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology.* 2000;11(5):550-560.
181. Hernan MA, Brumback B, Robins JM. Marginal structural models to estimate the joint causal effect of nonrandomized treatments. *J Amer Stat Assoc.* 2001;96(454):440-448.
182. McCann DJ, Li SH. A Novel, Nonbinary Evaluation of Success and Failure Reveals Bupropion Efficacy Versus Methamphetamine Dependence: Reanalysis of a Multisite Trial. *CNS Neurosci Ther.* 2011.
183. Charney DA, Heath LM, Zikos E, Palacios-Boix J, Gill KJ. Poorer Drinking Outcomes with Citalopram Treatment for Alcohol Dependence: A Randomized, Double-Blind, Placebo-Controlled Trial. *Alcoholism, clinical and experimental research.* 2015;39(9):1756-1765.
184. Kenna GA, Haass-Koffler CL, Zywiak WH, et al. Role of the alpha blocker doxazosin in alcoholism: a proof-of-concept randomized controlled trial. *Addiction biology.* 2015.
185. Wallace TC. Twenty Years of the Dietary Supplement Health and Education Act--How Should Dietary Supplements Be Regulated? *The Journal of nutrition.* 2015;145(8):1683-1681.
181. Frankos VH, Street DA, O'Neill RK. FDA regulation of dietary supplements and requirements regarding adverse event reporting. *Clinical pharmacology and therapeutics.* 2010;87(2):239-244.
187. McGregor NR. Pueraria lobata (Kudzu root) hangover remedies and acetaldehyde-associated neoplasm risk. *Alcohol.* 2007;41(7):469-478.

APPENDIX A: Form 1571

APPENDIX B: Form 1572

APPENDIX C: Sponsor-Investigator

Appendix D: Sub-Investigator CV

APPENDIX E: Form 3554

APPENDIX F: Form 3674

APPENDIX G: Manufacture's Letter Of Support

APPENDIX H: COA and BSE/TSE

APPENDIX I: Investigational New Drug Label

CAUTION:

New Drug

Limited by Federal (or United States) law to investigational use only.

Study medication for "A-HACK Study: Addressing Heavy Alcohol use Consumption with Kudzu"

Capsules, 500 mg

May contain: Kudzu 500 mg, or PLACEBO