Study Protocol and Statistical Analysis Plan

Behavioral Interventions to Reduce Heavy Drinking Among MSM in HIV Primary Care

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Description and Purpose of the Project

The purpose of this project is to conduct a randomized clinical trial in which 224 heavy drinking men who have sex with men (MSM), who receive their HIV primary care at Fenway Health or other health care facilities in the greater Boston area or Jackson Memorial Hospital Medical Center or other health care facilities in Miami (N = 112 per site), are randomly assigned in a 2 X 2 X 2 design to receive either (1) Brief Advice about their drinking (BA) or Motivational Interviewing (MI) with personalized normative feedback specific to their drinking and HIV. Participants will also be assigned to receive either (2) an interactive text messaging (ITM) system that facilitates behavioral self-monitoring versus no ITM and (3) a standard (1-month) vs. an extended intervention (9 months; EI). BA and MI will be delivered by interventionists at Brown University using a webcam-enabled telemedicine system, as well as over the phone. Both BA and MI will involve one individual session of up to an hour, conducted using videoconferencing, and a follow-up counseling session delivered over the phone a month later that can last up to 20 minutes (5-10 minutes for BA, 10-20 minutes for MI). BA will involve counseling patients that they are drinking more than recommended limits for safe consumption and that staying below these limits is important for those with HIV. The MI intervention involves a more in-depth discussion of alcohol use, including providing feedback on health indicators and alcohol and other substance use. The ITM program involves sending/receiving text messages about participants' drinking daily for 30 days. The EI conditions involve extended versions of either counseling approach (BA vs. MI) and the ITM program. Beyond the "standard" counseling participants receive, those in the EI conditions will receive additional 5-20 minute phone-based counseling sessions at 3- and 9- months, and participate in an additional 5-20 minute videoconference session at 6 months. Those in the EI+ITM condition will participate in an extended version of the ITM program that provides interactive text messages each week for 8 additional months after the initial 30 days (months 2-9).

The primary aims of the study are as follows:

Aim 1: To test the hypothesis that MI compared to BA, ITM compared to no ITM, and EI compared to no EI, will result in significantly greater reductions in (1) the number of alcoholic drinks consumed and (2) the number of heavy drinking days at 6- and 12-month follow ups.

Aim 2: To test the effects of MI, ITM, and EI on engagement in unprotected anal intercourse, ART adherence and viral suppression.

Procedures

A number of procedures will mirror many of those previously approved. There will only be slight changes made to the explanation of the study in the study screener (see attached) with the primary change being the addition of text messaging, delivery of intervention by videoconferencing, and inclusion of at least minimal counseling for all participants. New consent forms are attached that reflect those changes. We will recruit heavy drinking HIV-infected MSM receiving primary care at Fenway Health or other health care facilities in the greater Boston, Massachusetts area and at Jackson Memorial Hospital Medical Center or other health care facilities in Miami, Florida. Participants will be recruited through fliers posted throughout the clinics and at HIV support groups and on community bulletin boards, as well as through proactive screening and recruitment during primary care visits at Fenway Health and at outside organizations that cater to HIV+ individuals. Screening procedures at outside organizations will only take place in either private rooms, hallways, or corners of rooms that are all out of the earshot of others. Study recruiters at Fenway Health will work closely with providers and CFAR Network of Integrated Clinical Systems (CNICS) staff to identify patients who would be eligible and interested in participating in this study. We will also advertise the study on social media websites like Facebook and Tumblr, online community bulletin boards like Craigslist, as well as on location-based, sex-seeking websites/apps (e.g. Grindr and SCRUFF) to further assist us with recruitment efforts. The online advertisement will include a link to a secure REDCap form that will request only the interested

individual's contact information so that the study team could then reach out to the person (instead of requiring him/them to initiate contact). The REDCap form describes the main details of the study at the top of it. The REDCap form will not request an individual's protected health information and the form and its associated database will not have "HIV" or "Alcohol" in their names. Participants will be randomly assigned to one of each of three conditions in a 2 X 2 X 2 between-subjects design (BA vs. MI, ITM vs. no ITM, and EI vs. standard intervention) and followed for 12 months.

Participant population

Inclusion criteria: For inclusion, subjects must: (1) be at least 18 years of age; (2) drink heavily at least once per month on average (≥5 drinks) or have drunk more than 14 drinks per week over the past 3 months; (3) have a confirmed diagnosis of HIV with a documented viral load test result drawn within six months of the date of screening; (4) receive HIV clinical care at Fenway Health or other health care facilities in the greater Boston area; (5) be a biological male who identifies as male; (6) report having had sex (oral or anal) with a male partner in the past 12 months and/or identify as gay or bisexual. For those on ART, they must be on the same ART regimen for at least 3 months prior to study enrollment, with the exception of patients who switch from one medication to another medication that shares the same active moiety. Additionally, prospective participants who, at the time of the baseline visit, have the results of a viral load test completed in the last seven months, but not the past six months, may be allowed to enroll in the study with the approval of a Principal Investigator or co-Investigator provided they are willing to complete a viral load test at the time of the baseline visit.

Exclusion criteria: Participants will be excluded if they: (1) reported past 3 month intravenous drug use; (2) are currently psychotic, suicidal, or manic; (3) are currently being treated or have been treated in the past 3 months for an HIV-related opportunistic infection; or (4) are currently receiving treatment for an alcohol or drug problem. We will allow those in maintenance methadone or Suboxone programs to enroll provided that they have been using the medication for at least one year and are not receiving counseling in conjunction with the treatment. We also will exclude participants who have characteristics that might make supervised alcohol detoxification necessary, specifically, having a history of severe withdrawal symptoms such as hallucinations, seizures, or delirium tremens. Withdrawal symptoms will be assessed using the Clinical Institute Withdrawal Assessment for Alcohol, revised (CIWA-Ar) [1], and those with scores over 7 will be excluded. Participants must abstain from alcohol the night before the baseline assessment and have a BrAC of 0.00 g/dl. Participants reporting psychosis or suicidality, or who have CIWA-Ar scores greater than 7, will be referred to appropriate treatment. Participants must agree to be available for 12 months. Participants will not be asked to refrain from seeking treatment for an alcohol problem during the study if they decide to do so, and treatment utilization during follow-up will be assessed. We will also maintain a list of local addictions and mental health treatment resources (both Fenway Health and JMHMC have in-house substance abuse treatment programs), and any participant requesting referral to drug, alcohol, or other mental health treatment at any point during the study will be provided the referral list. Participants are not required to use text messaging to participate as lack of text messaging is an occasional limitation to the approach that should not be eliminated when testing its potential impact. Participants will be randomized to ITM vs. no-ITM without regard for whether they have access to text messaging on their phones. Subjects reporting substance dependence, psychosis, or suicidality or who have CIWA-Ar scores greater than 7 will be referred to appropriate treatment.

Inclusion of Women, Minorities, and Children.

This research will involve youth between the ages of 18 and 20 inclusive. Youth in this age range have been included in numerous clinical trials of brief alcohol interventions for heavy drinkers. HIV-infected MSM who receive care in Boston or Miami were chosen as the focus of this study because of high rates of HIV-infection and co-occurring elevated alcohol use and heavy drinking among this

population, and the elevated risk of unprotected sexual encounters while under the influence of alcohol. We did not include women or heterosexual men in the current study because the intervention approach may vary in different communities.

Recruitment Procedures

Prospective participants at both sites will be screened during HIV primary care visits or by phone if responding to a study advertisement. Patients at Fenway Health and JMHMC are given a Notice of Privacy Practices which informs them that their protected health information may be utilized for research when the research proposal is approved by the IRB and conducted in accordance with established rules on privacy and confidentiality (i.e. Health Insurance Portability and Accountability Act of 1996 -HIPAA). Under HIPAA, as employees of the covered entities (Fenway Health/JMHMC), the study staff may utilize the medical records to identify potential participants and flag their providers to alert them to the study. Providers will work closely with the study staff to gauge their client's interest for participation during the next scheduled visits. If patients are interested, they will be referred to the study staff during the clinic visits. For potential study participants who receive their HIV care elsewhere, we will require them to confirm their HIV diagnosis with a documented viral load lab drawn within six months of the date of screening. Potential participants have the option to request that information on their own from their providers and bring it with them to the baseline visit or study staff could request that information from their medical providers with their authorization by having them sign a medical records release form. If a participant plans to bring documentation of the viral load test to the study visit, it must include the participant's name and date of birth, the name of medical provider who ordered the test, the viral load lab value and the date of the blood draw, and a logo or letterhead or something identifying the health care facility or lab where the test was performed. Once they are enrolled in the study at the baseline visit, we will ask all participants who receive care outside of Fenway Health to sign what will for some be a second medical records release form to allow us to access their medical information. We will ask permission to access their medical records from one year before the scheduled study visit through one year after their study visit. If the participant agrees, we will request medical information from the medical record concerning treatment for HIV and other conditions, such as hepatitis. This medical information will not be shared with anyone outside of our research team. The participant's name and other identifying information will not be associated with the information from the medical record. Once we receive the medical information, it will be coded and stored with a code number instead of the participant's name in order to maintain confidentiality.

Prior to screening, the study staff will explain the study and obtain consent for completing the screening questionnaire. No identifying information will be collected on the screening questionnaire. Those who appear eligible based on their responses will be invited to participate in the study and asked to schedule a baseline (intake) appointment at Fenway Health/JMHMC within the next one to two weeks, which would last up to 4 hours: up to three hours are for the assessment and up to one hour is for counseling. This visit can be completed in one or two days.

Intake visit

At the baseline interview, participants will first complete informed consent. Subjects will be asked to abstain from alcohol for 24 hours before this assessment, and an alcohol breathanalysis will be conducted. Those with a positive breath alcohol concentration (BrAC >.00 g/dl) will not be assessed and will be asked to re-schedule their baseline assessment. Then subjects will complete a limited battery of other assessments, including having blood drawn, completing a urine drug screen, and completing a few questionnaires and interviews and will be interviewed and screened as to exclusion criteria using the MINI 7.0 and the CIWA-Ar. Subjects who appear eligible based on the interview will complete

additional questionnaires, interviews, and neurocognitive assessments. Interview assessments will be audio recorded for training purposes.

We aim to randomize 112 participants at each site using block randomization (16 per block) to ensure an equal number of participants in each of the treatment cells. Participants will receive their first session of MI/BA videocounseling immediately upon completion of the baseline interview. Research staff will share with the interventionist participant's information that is necessary for conducting the counseling session (drinking level, viral load, etc.) by uploading a report to a restricted and secure folder on the Brown server. Participants will be seated in a private room in the clinic that is equipped with a computer, speakers, a microphone, and a webcam. Research staff will instruct participants about how to use the videoconferencing tool on this computer. The videoconferencing software provides a secure, HIPAA compliant connection with the study's interventionists, who will be housed at Brown University. The software also allows secure sharing of the conferencing patient's medical information, which allows video counselors to share, present, and discuss this information, as relevant to the conversation. Each session conducted will be audio recorded for research and training purposes.

After the videoconference, participants in all conditions will be informed that they will be contacted by this same counselor by phone in 1 month, and that they will come back in for in-person interviews and questionnaires in 6 and 12 months. Those in the EI condition will be informed that they will receive an additional phone call from their counselor at 3 months, meet again with their counselor during their 6 month appointment, and then receive a final phone call at 9 months. Those in the ITM conditions will also be informed that they should expect to receive daily text messages beginning the next day. Those in the EI+ITM group will be told to expect the frequency of these messages to be reduced to weekly after the first 30 days.

Brief Intervention

Counselors. Counseling sessions will be delivered by master's-level interventionists. Detailed treatment manuals will be used at all times to ensure standardization of treatment delivery. Drs. Kahler and Mastroleo will provide interventionists extensive training in treatment protocols and motivational interviewing including readings and role-playing exercises, and conduct weekly clinical supervision along with Drs. Pantalone and Hernandez. Interventionist training also includes education about HIV, medication adherence, and high-risk sexual behaviors, which will be led by Drs. Mayer and Pantalone. Dr. Mastroleo will review session recordings on a weekly basis and provide detailed feedback to interventionists; Dr. Hernandez will provide feedback on sessions conducted in Spanish. For emergent psychosocial problems such as family conflict, unemployment, or loss of residence, a brief problem-solving discussion will be conducted in session and referrals to relevant local agencies and community therapists will be provided, including services available at Fenway Health and JMHMC. Interventionists will intervene immediately in the event that participants are an immediate threat to themselves or others and will discuss any cases of clinical deterioration with Drs. Mastroleo, Pantalone or Kahler (licensed clinicians) in order to determine whether more intensive treatment is required.

Brief Advice – Session 1 (Video conferencing): Brief advice entails a largely scripted intervention lasting 5-10 minutes (see attached script). The interventionist will inform the participant that he is drinking more than the recommended limits for safe consumption and that staying below these limits is particularly important for those with chronic health conditions such as HIV. The interventionist will then gauge readiness to change drinking. For those willing to change, the interventionist will help them choose a change goal, will send educational materials to their home address, and offer to provide local referrals (both Fenway Health and JMHMC have substance abuse treatment programs), including recommending (a) 12-step programs for those willing to quit drinking or (b) discussing alcohol pharmacotherapy with the participant's HIV care provider. At the end of BA, the interventionist will inform participants assigned to ITM about the text messaging program, initiating a text at that time to ensure that the participant receives the message and texts back in the appropriate way to complete

initiation of the program. The interventionist will schedule a follow-up phone call 1 month later and inform the participant how many more conversations they will be having: for those not assigned to EI, 1 phone call; for those in EI, 3 phone calls and 1 more videoconference at 6 months.

Brief Advice – Follow-Up sessions. Follow-up session(s) entail a brief check in on progress towards reducing drinking, reinforcement for changes made, encouragement to make changes for those whose drinking has remained heavy, and offers of referral to treatment for those who have been unsuccessful in their efforts to change. All follow-up sessions of BA, regardless of assignment to ITM or EI, will last 5-10 minutes.

Motivational Intervention – Session 1 (Video Conferencing): MI follows the same intervention outline that we have utilized in the ongoing approved study with minor modifications to mention text messaging when appropriate. The intervention draws heavily from techniques of motivational interviewing intended to minimize resistance and support self-efficacy for change. Interventionists will provide feedback and advice in a non-confrontational manner that avoids labeling and stresses personal responsibility for change. This MI relies heavily on the impact of alcohol use on HIV-relevant outcomes in building motivation for change. The interventionist first asks participants to describe their current drinking patterns and its positive and potential negative aspects and how drinking relates to their HIV treatment. Participant statements supporting change in drinking are reflected and amplified. Personalized feedback is then presented on the person's drinking level relative to norms from a national sample of urban MSM. Personalized feedback on viral and immune function, ART adherence, sexual risk behaviors, liver function, neurocognitive function, and other substance use is provided highlighting areas where the participant is currently doing well and where there may be concerns that are potentially related to drinking. These data are used to develop discrepancies between a goal of living successfully with HIV and continued heavy drinking. The interventionist provides a "grand summary" of the discussion, reflecting the participant's stated pros and cons of drinking and the key feedback results. The interventionist will clearly state there is no known "safe" level of drinking for those with HIV and recommend reducing or avoiding alcohol use to the greatest extent possible, especially if there is hepatitis coinfection. The provider will ask participants to choose a drinking goal, providing a menu of alternative goals to those who have difficulty formulating a goal. The session then focuses on increasing self-efficacy for changing drinking and problem-solving regarding drinking goals, including identifying supportive people, addressing barriers to change, and engaging in alternative activities to drinking alcohol. As in BA, the interventionist will mail the participant the NIAAA self-help pamphlet "Tips for Cutting Down on Drinking," and those indicating an intention to quit drinking or to stop drug use also will be provided referrals to AA and local addictions treatment programs if desired. Participants also will be directed to a website where they can view question and answer videos we have developed, which are tailored for MSM, focusing on alcohol, health, and HIV.

Motivational interviewing (Follow-Up sessions). Follow-up session(s) begin with a brief summary of the prior session and discussion of their current drinking goal. Progress in making changes in drinking is reviewed and reinforced and barriers to changing drinking are discussed and addressed with problem solving discussions. Where relevant, the interventionist highlights potential benefits of reducing drinking, including benefits unrelated to HIV treatment such as saving money, improving energy levels, and enhancing productivity. As with BA, referral to additional treatment resources is provided in the event the participant has been unsuccessful in efforts to moderate or stop drinking. At the last session of MI (session 2 for those not in EI and session 5 for those in EI), there is a brief discussion of strategies for maintaining changes in drinking over the longer term.

Interactive Text Messaging. The ITM program will be housed as Brown University and uses Qualtrics'™ text messaging program. In the first 30 days of the program, participants will receive daily texts that ask them to report the number of drinks they consumed in the prior day, whether they plan to drink that day, and how much they plan to drink. Tailored messages are used to reinforce abstinence and moderate drinking and drinking goals. At the end of each 7 days of ITM, the system will provide the

participant feedback on the number of drinks consumed during the week with a tailored message based on whether the participant has stayed under 15 drinks, avoided heavy drinking (≥5 drinks) or reduced drinking relative to baseline. The results of the ITM assessments of drinking will also provide data that the interventionists can present to participants to reinforce positive changes in drinking and address potential difficulties in changing drinking. Once each week, the ITM system will ask participants the number of missed doses of ART in the prior week. Based on participant response, a text will be sent that either (a) reinforces/congratulates the participant for not missing any doses or (b) for those missing any doses, states the importance of taking every dose of ART regardless of whether drinking alcohol that day. In addition, two times each week, the system will send a message randomly selected from a bank of affirming messages and quotes on health, well-being, and sexual/gay identity. These positive messages have been cited as important to include during focus groups with former trial participants. Once each week, a tip for reducing drinking will be sent.

For those assigned to EI, ITM will continue beyond 30 days but change in intensity. Daily assessments of drinking will be replaced by weekly assessments of number of days drinking alcohol, number of drinks consumed, heavy drinking, and ART adherence. The system will reinforce positive changes in drinking and ART adherence. Positive affirming messages run twice a week throughout EI, and tips for changing drinking run once a week.

Follow-up Assessments

All participants in the main trial, regardless of treatment condition, will be assessed on a variety of interview, self-report, and biochemical measures at 6 and 12 months after the baseline interview. Interviewers conducting follow-ups will be different from those conducting the baseline session when feasible and will not be informed of subjects' treatment condition assignment. To ensure that the accuracy of self-reports is not affected by intoxication, alcohol breathanalysis will be conducted at all assessments. Subjects with a BrAC >.02 g/dl (an alcohol level that may affect assessment) will not be assessed and their follow-up appointment will be re-scheduled for the following day or at the next available time. All subjects will provide serum samples at each follow-up.

In order to maximize study participant retention, we will offer follow-up 6- and 12-month visits by phone for any participant who, in the course of the 12-months of study participation, moves to a location that makes it impossible to travel to Fenway Health or JMHMC for in-person visits. These phone visits will include a subset of assessments as well as referrals for mental health or substance abuse services. In addition, for those participants in EI, they will be given counseling by phone at the 6-month visit rather than by videoconference. We will then mail the full compensation check to an address specified by the participant. Participants will be compensated $100 for the baseline interview, $50 for the 6-month interview, and $60 for the 12-month interview, for a total of $210 in the form of checks or gift cards. Those found ineligible at baseline will be compensated $50 for their time given the eligibility is confirmed within the first half of the baseline interview. Participants will also receive a Charlie Ticket in the amount of the cost of a round-trip T ride at each study visit that they attend in person.

Using procedures and assessments already approved, collateral informants will be interviewed to corroborate self-reports of drinking. All participants will complete two collateral letter forms at the intake session with the option to opt out completely or to only provide one collateral informant. If a visit is not scheduled after a minimum of three attempts using the participant's preferred mode of contact, or if a visit is not scheduled by the remaining two weeks of their visit window, collateral letters will be either mailed or emailed to informants depending on the contact information provided by the participant. These letters inform the collateral that the subject is participating in this study and that he has given the study personnel permission to call them should there be a loss of contact with the participant. These letters also note that the participant has given us permission to ask them questions regarding the participant's drinking. If a follow-up visit is not scheduled after a minimum of three attempts using the participant's preferred mode of contact, or if a visit is not scheduled by the remaining two weeks of their

visit window, collaterals will be contacted in order to ask them questions regarding the participant's drinking. Participants will be instructed to provide names of individuals who see them often enough to know about their alcohol use and their current contact information. These individuals do not have to know about participants' HIV status, and that information will not be provided to them. Participants will be informed that collateral informants will be told that they are participating in a study being conducted at Fenway Health or Florida International University, and so they should choose people with whom they are comfortable sharing that information.

Measures

Assessment focuses on six domains: (a) screening and background measures; (b) measures of alcohol use and problems, other substance use, and motivation to change; (c) measures of risky sexual behavior and ART adherence; (d) clinical assays and biomarker assessment; (e) measures of neurocognitive function; and (f) measures of treatment utilization. To reduce subject burden and potential assessment reactivity effects, assessments have been reduced to only those measures that are essential to study purposes. The interviews at baseline, 6 months, and 12 months should not exceed 120 minutes.

We will primarily use *measures that have already been approved as part of this protocol*. A description of each of the measures is provided below. We are not including copies of the measures that have been previously reviewed. Any additional measures will be submitted for approval prior to their implementation. Table 1 shows the schedule of assessments, indicating when each measure will be administered.

Table 1. Schedule of Main Study Assessments

Assessment:	Screening	Baseline - Session 1	6-Month Follow-up	12-Month Follow-up
Measure				
Chart Review	X			
Initial Screening	X			
Medical Record Review		X	X	X
Alcohol Consequences Scale		X		
Alcohol Contemplation Ladder		X	X	X
Alcohol-ART Interaction Beliefs and Behaviors		X	X	X
Alcohol and Drug Use History		X		
Alcohol Withdrawal (SAWS/CIWA)		X		
Antiretrovial Therapy (ART) Adherence		X	X	X
Childhood Sexual Abuse		X		
Conflict Tactics Scale (CTS)		X		X
Demographics		X		
Depressive Symptoms (CES-D 10)		X	X	X
Drinking Motives		X	X	X
HIV History		X	X	X
HIV Stigma		X	X	X
Important People Assessment (IPA)		X	X	X
Internet and Communications Use (Use of Technology)		X		
LGBIS Internalized Homonegativity Subscale		X		
MINI 7.0 (DSM-V)		X		

Multiple Discrimination Scale		X		X
Neurocognitive Assessment		X	X	X
Quantity-Frequency Survey (Computer Assisted Self-Interview, CASI via Qualtrics)		X	X	X
ReACH Website Access			X	X
Serum collection		X	X	X
Short Inventory of Problems (SIP)		X	X	X
Smoking History Questionnaire		X		
Smoking Status Questionnaire			X	X
Timeline Followback Interview		X	X	X
Treatment Services Review		X	X	X
UCLA Loneliness Scale		X	X	X
Urine Drug Screen		X	X	X
Vital Signs & BrAC		X	X	X
Payment:		$100	$50	$60

Screening and Background Measures

Participants approached during HIV care visits or calling in to the study will complete a brief screen assessing primary inclusion criteria, namely that they are male, are receiving HIV care at Fenway Health or other health care facilities in the greater Boston or Miami area , meet drinking criteria, had oral or anal sex with a man in the past 12 months and/or identify as a gay or bisexual man, have no current or past 3 month opportunistic infection(s), and, if receiving ART, have been on a stable regimen for at least 3 months. When a participant completes informed consent at the baseline interview, he will be asked to provide permission for staff to access his medical record in the clinic to confirm eligibility and to obtain key HIV treatment information, including, but not limited to, duration of illness, CD4 nadir, medication history, and whether he has had any other illnesses such as sexually transmitted diseases. If a participant receives dental care at Fenway Health, he will be asked to provide permission for staff to view his future dental appointments in order to able to schedule study follow-ups that are potentially more conveniently-timed for when he is already scheduled for appointments at this location.

We will obtain complete demographic information on each participant who is eligible and will also assess depressive symptoms using the Center for Epidemiologic Studies – Depression scale [CES-D;[2]]. Depressive symptoms, which can sometimes result from excessive alcohol consumption, have been associated with poor ART adherence and are therefore important to assess as a covariate. The Treatment Services Review will assess use of major medical care outside of the health care facility where the participant normally receives care. Internet and Communication Use (use of technology) will be asked in order to learn what means of communication may be most effective in administering interventions in this population and whether there are potential barriers to the text messaging program. We will also ask participants how often they accessed the ReACH project website for information on alcohol use and HIV in the past 6 months. Experienced discrimination due to HIV status, race/ethnicity, and sexual orientation will be assessed with the Multiple Discrimination Scale [3]. Internalized homonegativity will be measured using a 5-item subscale from the Lesbian, Gay, and Bisexual Identity Subscale (Mohr & Fassinger, 2000).

Measures of Alcohol Use and Problems, Other Substance Use, and Motivation to Change

We will gather information about age of onset of alcohol use, period of heaviest drinking, most drinks consumed on a single day, and number of lifetime drug classes used. Current and past alcohol and substance use disorders (as well as screening for mania and psychosis) will be assessed at baseline using the MINI 7.0.1 [4]. Urine Drug Screen. In addition to providing a breath sample for alcohol concentration analysis at each in-person assessment, participants also will provide a urine sample for testing for recent

drug use: PCP, ecstasy, barbiturates, methadone, oxycodone, benzodiazepines, methamphetamine, THC, opiates, and cocaine. Alcohol withdrawal symptoms will be assessed using the Clinical Institute Withdrawal Assessment for Alcohol, revised [1].

Timeline Followback (TLFB). The TLFB interview [5] will be used to assess past 30 day alcohol use. The TLFB interview is a valid and reliable calendar-assisted structured interview which provides a way to cue memory so that accurate recall is enhanced [6-8]. It will provide data on the percentage of drinking days, drinks consumed per week, and the percentage of heavy drinking days. The TLFB also will be used to provide a valid assessment of drug use behavior [9]. The Short Inventory of Problems [SIP; [10]] will be used to assess the extent to which subjects have experienced problems related to their alcohol use in the 3 months prior to each interview. The SIP assesses 15 negative consequences of alcohol use and has good psychometric properties [10,11]. Cigarette smoking will be assessed at baseline including whether participants consider themselves "smokers", age of initiation, current smoking rate, and number of years of regular smoking, quitting attempts and corresponding methods. At follow-ups, the questionnaire will query current smoking rate and whether any quit attempts have been made since the last follow-up. Perceptions of alcohol related consequences and motivation to change alcohol use will be assessed using the 28 item validated Alcohol Consequences Scale (12) and the Alcohol Contemplation Ladder which consists of one item where participants indicate the statement which best reflects their motivation to make changes in their alcohol use (13). The inclusion of these two scales at will allow us to better understand the motivations for change in the sample.

The short form of the Conflict Tactics Scale (14). We have previously received approval to administer the Conflict Tactics Scale (CTS) Short Form to assess intimate partner violence (IPV) but, in the new segment of this project, we had not sought approval to continue using it. We are asking for this approval now. We have modified the response options to be consistent with other studies of IPV with HIV-positive gay and bisexual men, which have often used a combination of response-choices that track past year and past 5 year experiences (15).

The CTS contains some questions about physical violence and sexual coercion. Consistent with our procedures, participants reporting significant injury victimization in a relationship (items 5, 11, 15, or 17) will be offered referrals to local and national domestic violence abuse shelters and resources, such as the Massachusetts domestic violence hotline and the national domestic violence hotline. Those who have current concerns for their safety (e.g., since many men may no longer be in the relationship in which the violence occurred) will be given the opportunity to talk with a doctoral level clinician (Kahler, Pantalone, Monti, or Mayer) on the study if they choose to do so. Responses to questions on the CTS would not require reporting to authorities given that they do not reflect intent to harm or imminent risk or reflect child or elder abuse.

HIV History: Participants will be asked 6 self-report items about their HIV medication history, including when they first tested HIV-positive, their recent viral load test, when they began taking ART medications and number of doses at their Baseline visit, and 5 self-report items at 6-month and 12-month follow up. These data are important to understand the impact of the intervention on ART adherence, which is a key outcome of our study. Antiretroviral Therapy (ART) Adherence: We are including a 3-item measure of ART adherence (16), which is a secondary outcome of the study; therefore, the inclusion of this variable is critical for our study. HIV Stigma: This 12-item scale assesses the internalization of negative messages about one's HIV status, and has been associated with substance use, sexual risk, and suboptimal adherence in samples of HIV-positive adults (17,18). The addition of this scale will enable us to better understand the ways in which stigma impacts key outcomes of the intervention.

UCLA Loneliness Scale: This 20-item self-report measure will be administered to assess perceptions of loneliness and isolation (19) [12] (12) to will enable us to better understand the social factors contributing to alcohol use, which a key outcome of the study. Important People Assessment (IPA): Social networks have a strong impact on substance use behaviors; therefore, we are including a 7-item

IPA which has been widely used in studies addressing alcohol and other substance use behaviors (20). [13] (13) The inclusion of this measure will allow us to better understand participant's social network characteristics of participants and whether they change over time as a function of the intervention. Childhood Sexual Abuse (CSA) (21): Numerous studies document a high prevalence of childhood sexual abuse (CSA) among HIV-positive gay and bisexual men, and has been associated with HIV risk and substance use behaviors (22, 23). We will administer an 8 item measure of CSA to better understand whether the intervention has a different impact on participants who have experienced CSA compared to those who have not

Collateral Reports. Collateral informants will be interviewed regarding the participant's drinking. These interviews will be confidential, and no information regarding the participant will be provided to the collateral. Collaterals will estimate the number of drinking days in the past month, the average number of drinks consumed per drinking day, and the number of heavy drinking days. They will indicate their level of confidence in their knowledge of the participant's drinking and only reports for which the collateral was at least "fairly confident" will be considered. The use of collaterals may increase honesty in reporting by participants and provides an index of the validity of self-reported drinking.

Measures of ART Adherence and Sexual Behavior

Timeline Followback (TLFB). The TLFB administered will be used to assess medication adherence and sexual risk behaviors as we have been doing in our current study. Due to the cognitive demands of completing a TLFB with alcohol, drug, sex, and adherence behavior, we will only go back 30 days from the interview for these measures. The TLFB has been shown to be a valid measure of adherence [14,15] and facilitates examination of alcohol-adherence associations on a daily basis [16-18]. Participants will review each of the 30 days on the calendar, indicating the number of doses prescribed and taken each day. The dependent variable will be the percent of days with missed ART doses.

The TLFB interview for sex risk behaviors has previously been shown to be feasible, reliable, and valid [19], even in a high-risk population (psychiatric outpatients) [20]. In order to better assess sexual risk reduction strategies, this assessment asks whether their HIV-negative partners are on PrEP, in addition to whether participants engaged in other deliberate risk reduction strategies (i.e., strategic positioning, having oral instead of anal sex). This interview assesses each occasion of sexual activity over the past 30 days, with detailed information on the type of partner (long-term, dating, casual, or anonymous); HIV status of partner (positive, negative, or unknown); type of sexual activity (anal, insertive or receptive); condom use; and whether the participant was under the influence of alcohol and/or other substances. Three variables will be derived from this measure: occasions of unprotected anal intercourse (UAI), and occasions of UAI with a partner of negative or unknown status. The latter variable captures occasions of sex that carry the highest risk of HIV transmission [21].

Computer-Assisted Self Interviewing (CASI). We will use a brief CASI to provide a secondary assessment of alcohol, sex, and ART adherence that may reduce under-reporting of behaviors due to social desirability. The CASI queries behavior over the prior 6 months. The Sexual Risk Assessment queries the number and gender of partners with whom the participant reported having sex and the number of times the participant had unprotected insertive or receptive anal sex or vaginal sex with a partner of HIV-negative or unknown HIV status. The CASI also assess alcohol and drug use using a quantity-frequency interview, and adherence using a recent questionnaire that has recently been validated in a large sample of MSM by collaborators at Brown [22].

Cross-behavioral measures. We will assess alcohol-ART interactive toxicity beliefs with a scale by Kalichman et al. that predicts non-adherence on drinking days [23]. We will assess motives for drinking [24,25], including our newly validated scale for sexual drinking motives [26].

Standard Clinical Assays and Research Biomarker Assessment

We will collect serum samples from all participants. Some clinical assays will be run in real time and will include immunologic profiling (CD4/CD8 enumeration) and complete blood count while others

including virologic assays (serologic HBV/HCV status, HIV-1 PVL and if required HBV, HCV viral loads) and a full liver profile (liver enzymes, bilirubin) will be processed and frozen before sent to labs for analysis. When possible and within the appropriate timeframe, all clinical values will be taken from patients' electronic medical records for patients who receive care at Fenway Health. For those who receive care at other health care facilities in the greater Boston or Miami area, we will ask their permission to request those values from their providers. Clinical lab values obtained through this study will be added to participants' medical records if they receive care at Fenway Health. For those receiving care at other health care facilities in the greater Boston area, we will request their permission to notify their providers of abnormal lab values. We also will use the samples to obtain serum biomarkers of inflammation (21-plex cytokine/chemokine assay); oxidative stress (4-HNE/LPO, 8-OHdG, AGE, carbonyl); insulin resistance and metabolic dysfunction; neurodegeneration (BDNF, ICAM, VCAM, GDNF, NGF, HGF, bFGF); and ceramide levels/profiles (see Virology Core for further details), as well as recent alcohol use (phosphotidyl ethanol). The non-clinical assays will be used only for research purposes and not entered into participants' medical records.

Measures of Neurocognitive Functioning

We will conduct a brief battery of neurocognitive tests that are likely to be sensitive to the effects of heavy alcohol consumption and HIV. The neurocognitive test results from baseline will be used for feedback for those in MI as we have been doing in our current study and has been done in other trials. The battery takes a total of 20 minutes to complete and includes the WTAR [27,28], Trails A and B [29], Digit Symbol [30], Hopkins Verbal Learning test [31-33], and the Controlled Oral Word Association Test [34-36]. All of these measures are well-established neurocognitive measures that have each been widely used in numerous studies of HIV [37-41] and alcohol [42-55] effects on brain functioning.

Measures of Treatment Utilization

Concurrent Treatment. Use of other treatments for alcohol or other substance use will be assessed including use of pharmacotherapy for excessive drinking (type and duration), number of sessions of counseling received for drinking or substance use, and the number of Alcoholics Anonymous or Narcotics Anonymous meetings attended. Those seeking alcohol or other substance use treatment beyond that offered in the study will be retained following the intent to treat principle.

Safety Monitoring

In an effort to meet the NIH policy for Data and Safety Monitoring, we have created a system for oversight of the project. Oversight of internal monitoring of the participants' safety will be conducted by the PI, Dr. Christopher Kahler. Drs. Monti (Brown), Mayer (Fenway Health), Pantalone (Fenway Health), and Míguez (Florida International University (FIU), Miami) also will participate in the development and administration of the plan. Investigators on this application have extensive experience with clinical trials for excessive drinking and clinical and observational studies with HIV-infected patients.

Entities Conducting Monitoring:

The Institutional Review Boards (IRBs) at Brown University, Fenway Health, FIU, Jackson Memorial Hospital Medical Center, and the University of Miami will review this protocol and all procedures and will provide oversight. Monitoring will be done by the Principal Investigator, Dr. Christopher Kahler, the Brown University IRB, and the respective site IRBs. Drs. Monti, Mayer, Pantalone, and Míguez (Co-I's) will also participate in the administration of the monitoring plan.

What is Monitored?

Monitoring is done of all procedures to ensure that they conform to the approved protocol; of unforeseen circumstances that might arise and affect safety; of all reports of serious adverse events as defined in 38 CFR 46 and the FDA 312.32 (death, life-threatening experience, new or prolonged hospitalization, persistent or significant disability/incapacity); of other significant adverse events

(adverse events that lead to drop out by participant or termination by the investigator); of unexpected adverse events resulting from the study; and of expected adverse events.

Monitoring is done of all study inclusion and exclusion criteria. During this clinical trial, we will notify officials, as mandated by law, if a participant reports intentions to harm him/herself or others, or reports child abuse or abuse of an elder. The PI (Dr. Kahler) is a licensed clinical psychologist, who will be available on call in case of any psychological adverse events. In the event a participant were to report a need or interest in treatment for alcohol/substance dependence, psychiatric disorder, or distress, an appropriate referral to resources will be provided based on an extensive list of referral resources maintained at each study site.

Frequency of Monitoring:

All adverse events will be continuously monitored by the PI. Participants will be given contact information so that they can inform us of events that occur in between study visits. Dr. Kahler will conduct daily oversight of participant safety. He will videoconference weekly with staff to review participant progress and their experiences with the experimental procedures, including adverse events. Any adverse events that are observed and/or reported will be immediately reported to Dr. Kahler. The Investigators will be available to meet outside of the weekly meetings, if necessary, due to concerns regarding a particular participant or any problems that may arise for participants. If necessary, they will make appropriate recommendations for changes in protocol.

The Brown University and collaborating IRBs conduct the monitoring at the continuing reviews as scheduled, whenever modification requests are considered, and upon receiving reports of serious adverse events from the PI or anyone else. NIAAA monitors the study upon receipt of annual progress reports and whenever other information is received.

Reporting Plan:

Any serious adverse events that are observed and/or reported will be immediately reported to Dr. Kahler. Unexpected serious adverse events are reported to Brown University, the site IRBs, and to NIH by telephone and by written report within 48 hours of our receipt of information regarding the event. All other adverse events related to the study will be reported at the continuing review. All serious adverse events related to the study will be reported annually in the Progress Report sent to the NIAAA Project Officer.

Any actions taken by the IRB, other than acceptance of the adverse event report, will be reported to NIAAA along with any changes or amendments to the protocol requested by the IRB in response to these reports. Proposed changes or amendments to the protocol in general must be requested first in writing to the Brown and site IRBs, which will then grant or deny permission to make the requested change or amendment in protocol. NIAAA will subsequently be informed of any substantive changes or amendments in approved protocol.

Data Quality Assurance and Confidentiality

(a) Procedures to ensure the validity and integrity of the data. Several procedures currently in practice in our laboratory will also be utilized for this study to guarantee the validity, integrity, accuracy, and completeness of the data. It will be made clear to all participants that all information obtained during assessments is confidential.

(b) Procedures to guarantee the accuracy and completeness of the data during data collection, transmission, and analysis. First, the Data Coordinator will review each file within 2 weeks of data collection for completeness, accuracy, and validity of responses. All scanned data will be verified by the Data Coordinator using a computerized verification program. Data files are accessible only to project personnel and are password protected. The Data Coordinator will review the distributions of all raw data to ensure that data are within range and to check missing data with the hard copy of the data. The project database (including uploaded data files from the computer (CASI), text messaging database and

scanner machine) is password protected and accessible only to the project's Data Coordinator, staff members on the project, and members of the Biostatistics Core.
(c) Procedures to maintain confidentiality. Study staff will maintain strict confidentiality regarding all aspects of a subject's participation in this study. Any individual information gathered in the course of the study will not be discussed with anyone who is not directly involved with this study. For each stage of the research, participant names and contact information will be maintained in a recruitment/enrollment database during the course of the study. Once individuals enroll in the study, names will be linked to participant ID number in this database, which will be kept in a restricted access folder on a secure server. This file will be assigned a code name unrelated to the name of the study. Signed consent forms will be kept in a locked file cabinet, separate from any other project data. Once data collection is completed, the corresponding recruitment/enrollment database will be deleted as it is unnecessary to maintain the link between participant identity and study data. All information collected as part of this study will be accessible only to research staff who have completed mandatory training in the protection of human subjects.

Potential Risks to Participants

Potential risks in the study are considered low and include: (1) potential discomfort related to completing questionnaires about sensitive information such as sexual behavior and alcohol/drug problems, (2) potential discomfort during blood draws for viral load, CD4, and liver function tests, (3) potential breach of confidentiality and/or privacy; (4) symptoms of alcohol withdrawal.

Protection against Risks

Potential risks of the study are considered low. For the possibility of subjective discomfort from answering questions, any distress will be minimized by assurance that participants can refuse to answer any question that they do not feel comfortable addressing and may withdraw at any time without penalty. Interviewers are skilled in talking about sensitive information with subjects, and subjects may decide to end an interview at any time. In the unlikely event that a participant experiences considerable distress we will make a referral (if needed) for clinical assessment and/or counseling provided onsite. Subjects will be asked to provide urine and blood samples for testing. Potential discomfort during the blood draw and urine collection will be explained during informed consent. Subjects can choose to withdraw from the study without penalty.

Confidentiality is maintained as follows. Data files recorded with a participant identification number will be stored at their respective clinics; Fenway Health in Boston and JMHMC in Miami. These files are accessed only by project staff, who will be either Fenway Health, JMHMC, or Brown University employees. All project staff are knowledgeable about confidentiality and human subjects protection. Follow-up contact forms that require identifying information are stored separately from data files and are accessed only by those staff conducting follow-up interviews. Information about participants that is needed for intervention delivery will be collected by staff at Fenway Health or JMHMC and uploaded without identifying information to a secure Brown folder. Brown staff conducting videoconferences with participants will do so in room that is private from other Brown staff. The videoconference software used is HIPAA compliant. During follow-up telephone calls to the participants' homes, no information is provided to others in the household. All blood samples are identified by subject ID number only before being sent to the Virology Core for testing. Data files contain no identifying information, including date of birth and town of residence. Data are transmitted to the Data Core at the Center for Statistical Sciences in encrypted format.

All text messages sent from subjects to our phone number will be catalogued and encrypted, stored per Brown University security standards. Once received the responses from each participants will be separated from the cell phone number and identified only by ID number. All participants will be advised to set up password protection on their cell phones and to erase messages after responding to

minimize the chance of loss of private information. We state explicitly in the consent that we will not be able to respond in real-time to any concern a participant has that is outside the expected responses that is sent to our phone number, nor any text message outside the scope of the question we ask.

Breach of confidentiality is highly unlikely because all information will be identified with a numeric code only and stored in a locked file cabinet. An enrollment database linking names and study identification numbers will be kept in a secure folder separate from other subject data sources and will be used to facilitate the collection of follow-up data. Only grant staff will have access to this database. All staff are or will be fully trained in relevant ethical principles and procedures, including confidentiality. All assessment and treatment procedures will be closely supervised by the PI. All audiotapes will be erased upon completion of data analysis.

Some subjects may experience mild to moderate symptoms of alcohol withdrawal such as insomnia, psychomotor agitation, or hand tremor if they choose to stop or substantially reduce drinking; however, more significant withdrawal symptoms will be unlikely given our exclusion criteria. Specifically, we will exclude individuals who show clinically significant alcohol withdrawal at baseline after abstaining from alcohol for 24 hours. Given our exclusion criteria, any alcohol withdrawal symptoms are likely to be mild to moderate in intensity and transient.

During this clinical trial, we will notify officials, as mandated by law, if a participant reports intentions to harm him/herself or others, or reports child abuse or abuse of an elder. If a participant reports current suicidal ideation when completing the MINI, the participant will be evaluated by Dr. Pantalone (or another licensed clinical professional) at Fenway Health or a licensed clinical professional at JMHMC before being ruled out of the study.

Our rigorous screening procedures will help to ensure that consenting volunteers are recruited who do not report significant psychiatric disturbance. However, in the event a participant were to report a need or interest in treatment for substance dependence, psychiatric disorder, or distress, an appropriate referral to resources will be provided. We have included a description of the plan for data and safety monitoring of the research and adverse event reporting to ensure the safety of participants.

Potential Benefits of the Proposed Research to the Subjects and Others

As part of their participation in the study, participants will receive a brief intervention which could lead to reduced hazardous drinking. Furthermore, subjects will be participating in a study that may provide knowledge to guide the future treatment of HIV-infected patients who drink heavily. Given that the risks to subjects are considered to be minimal, the risk-benefit ratio is deemed favorable.

In addition, this study has the potential to contribute valuable information about the potential for brief alcohol interventions to reduce drinking in patients in HIV primary care and about the effects of reducing drinking on a range of important HIV-related biomedical and behavioral outcomes. Developing effective interventions that address alcohol use in HIV patients can make a major public health impact by reducing the morbidity, mortality, and transmission risk associated with heavy alcohol use. Given the substantial health risks associated with heavy drinking in HIV patients and the relatively minor risks to subjects, the importance of the potential knowledge to be gained relative to the subject risk is favorable.

Alternative treatments. Participants will be randomized to receive a brief alcohol intervention in addition to their standard HIV care. Alternative alcohol treatments are available in the Boston and Miami areas, including specialized addictions treatment services housed within Fenway Health and JMHMC. Individuals desiring additional treatment for alcohol problems will be given appropriate referrals.

Informed Consent

All participants will be fully informed of the purposes and procedures of the study. Research interviewers will describe the screening and the study to potential participants, including that if they are eligible and then agree to participate, they will be re-contacted over the following twelve months, that

they are paid for completing the follow-up interviews, that the information they provide is kept confidential, and that they may withdraw at any time without penalty. If an individual wishes to participate, he will be asked to sign an informed consent form prior to completing the baseline assessment. Participants are provided with a copy of the consent forms, and the originals are kept in locked files at Fenway Health and JMHMC.

Statistical Analysis Plan

For primary outcomes—(a) drinks per week and (b) number of heavy drinking at 6- and 12-months follow-ups—we fit marginalized zero-inflated negative binomial (MZI-NB) models to test the main and interactive effects of each of the three factors in the study design:
$log\ \{E(Y)\} = \beta_0 + \beta_1 A + \beta_2 B + \beta_3 C + \beta_{12} AB + \beta_{23} BC + \beta_{13} AC + \beta_{123} ABC + \gamma X.$ (Eq1)
with a similar logit model describing the excess zeros as in the traditional zero-inflation model. The terms A, B, and C in Eq1 are dummy variables for BI vs. MI, no ITM vs. ITM, and no EI vs. EI; and coded orthogonally so they can be evaluated concurrently with the three 2-way interactions and one 3-way interaction among these factors. The model parameters β_1, β_2 and β_3 capture the main effects, and $\beta_{13}, \ldots, \beta_{123}$ capture the two- and three-way interaction effects. The models are adjusted for baseline covariates X, including the baseline value of the dependent variable, recruitment site, and indicators for interventionists. Following intention-to-treat principles, we conduct regression analyses on all participants who were randomized to an intervention condition regardless of the number of sessions of intervention they completed.

Secondary outcomes for this study are: (1) the number of days engaging in condomless sex with a non-steady partner in the past 30 days at 6 and 12 months, (2) percentage of the past 30 days taking all prescribed ART doses at 6 and 12 months, and (3) HIV viral suppression (i.e., <20 copies/ml) at 12 months. Due to limited variation in condomless sex and ART adherence outcomes, we dichotomize these, respectively, as: (a) 0 day vs ≥ 1 day of condomless sex with non-steady partner and (b) ≥ 95% ART adherent [i.e., perfect or near-perfect adherence] vs < 95% ART adherence. For secondary outcomes, logistic regression models, similar to the model above but replacing the left-hand side of Eq1 by $h\{E(Y)\}$ with $h(.)$ being the logit link function, were used to test the main and interactive effects of the three study factors.

Missing data. We conducted our primary analyses using complete data. We also used re-ran analyses with imputed data as a sensitivity analysis. Imputation of missing data was carried out using the chained-equation method (R MICE package) assuming that data were missing at random. We maintained the longitudinal structure of the data and built imputation models that imputed missing values at 6 months only using baseline data and observed 6-month data, and imputed the missing values at the 12 months using baseline and imputed 6-month data and observed 12-month data. Imputations were iterated until the distribution of imputed values stabilized. Five complete datasets were created and used for regression analyses. The results were then pooled using Rubin's method[56,57].

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