Optimizing PrEP Uptake and Adherence among Male Sex Workers Using a Two-Stage Randomization Design
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Site Principal Investigator: Philip A. Chan, MD

OBJECTIVE

The objective of this study is to evaluate the effectiveness of the "PrEPare for Work" intervention, consisting of strength-based case management and cognitive behavioral theory-based PrEP adherence counseling, in promoting PrEP uptake and adherence among men who have sex with men (MSM) in Providence, RI.

BACKGROUND

Male sex workers (MSW), or men who exchange sex for money, goods, drugs, or other items of value with other men, are at exceptionally high risk for HIV infection. A recently published meta-analysis from the PIs for this application found an estimated HIV prevalence of 20% among men who have ever engaged in transactional sex in the United States (US) [1]. Research shows that MSW, particularly those who solicit male clients on the street, engage in frequent condomless anal sex with both paying and non-paying sexual partners [2,3]. Notably, MSW have a higher burden of psychosocial problems, such as heavy substance use, depression, and victimization, and often face unique contextual challenges such as homelessness and unemployment—all of which potentiate HIV sexual risk. Additionally, while MSW are often included as a subgroup of MSM, survey data show that a large proportion (approximately 50%) identify as heterosexual [4]. As such, behavioral interventions to decrease HIV risk specific to gay- or bisexually-identified men often do not reach MSW and do not adequately address their lived realities. Moreover, compared to cisgender and transgender women who engage in transactional sex, MSW are less likely to identify as "sex workers" [5]; as a result, even interventions or programs specific to sex workers may not be appropriate. Hence, HIV prevention interventions addressing the unique life circumstances of MSWs are needed to curb HIV spread.

A growing number of clinical trials and demonstration projects have provided strong evidence for the efficacy of a once-daily oral pill (emtricitabine/tenofovir) as pre-exposure prophylaxis (PrEP) for the prevention of HIV among uninfected, at-risk individuals, including MSM [6–8] and injection drug users [9]. However, implementation of PrEP in at-risk populations such as MSWs has been limited by several concerns including adherence to the medication. In order to be most effective, PrEP adherence must be high (four or more doses per week) [10,11]. A body of evidence regarding adherence to PrEP is just beginning to emerge, suggesting that, similar to antiretroviral therapy (ART) among HIV-infected individuals, PrEP adherence may be suboptimal among individuals with psychosocial problems (e.g., substance use, depression, violence victimization). Given the complexity of sexual decision making for MSW, a PrEP uptake and adherence package would need to be responsive and tailored to MSWs' distinct circumstances and contextual surroundings to optimize their likelihood of initiating PrEP, and sufficiently adhering to, this biomedical HIV prevention modality. Informed by our formative research (including individual qualitative interviews, focus groups, and a longitudinal epidemiological cohort study of HIV risk, in which all examined perceived PrEP acceptability) and programmatic work with US based MSWs over the past decade, we adapted the "Life-Steps" model [12,13]—a proven efficacious intervention for HIV treatment adherence among marginalized groups—for the provision of PrEP. The resulting theory-based intervention, PrEPare for Work—developed by our interdisciplinary investigator team—addresses access to and uptake of PrEP, and provides skills training to optimize adherence. As such, the PrEPare for Work intervention includes two components: 1) Strength-based case management for PrEP access and initiation, and 2) Cognitive-behavioral theory-based PrEP adherence counseling by a trained masters-level counselor—both as part of a comprehensive, context-specific approach to HIV prevention for MSW in Providence, Rhode Island. Providence, often described as the epicenter of male sex work, has one of the largest populations of street-based MSWs in the US [4].

STUDY SITES

Project Weber, a 501(c)(3) nonprofit organization serving MSWs in Rhode Island, is the primary recruitment and screening site for this study. In over seven years of service, Project Weber has reached over 800 MSWs, with 160 individuals currently accessing its drop-in center. The study team published a sexual health needs assessment of MSWs in Providence, Rhode Island in collaboration with Project Weber [4]. Most needs assessment participants reported a history of HIV testing within the past year (73%). Self-reported HIV prevalence was 6%, and 22% reported Hepatitis C infection. Most participants had been engaged in sex work for more than 3 years (70%), and more than a quarter (26%) reported unprotected anal and/or vaginal sex with sex work clients. Of 48 participants reporting drug use patterns, most (94%) had used drugs in the past, 39% had previously injected drugs (25% in the past month), and 19% reported sharing needles. Nearly half (42%) reported a previous diagnosis of depression. These results demonstrate both the study team's success in engaging this population and the ongoing and the complex HIV prevention needs experienced by this population. Project Weber staff will conduct screening assessments at the drop in center and during routine outreach services to identify potential research participants. Eligible participants will be referred to Brown research staff for eligibility confirmation. The case management visits may occur at this site and will be administered in one on one sessions. Additionally, survey and adherence counseling sessions may be conducted at Project Weber, if preferred by the participants.

Brown University is the home institution of Principal Investigators Matthew Mimiaga, ScD and Katie Biello, PhD. Brown University will act as the coordinating site for all regulatory matters (protocol and SOP authoring; IRB applications and approvals; Quality Control and Assurance; etc.). Brown University will also collaborate in the design, implementation, and analysis of the study, including primary responsibility for epidemiologic and statistical analysis of study data. Additionally, survey and adherence counseling sessions may be conducted at Brown University School of Public Health, if preferred by the participants (including collection of blood and hair for drug level testing).

The Miriam Hospital (TMH) will collaborate with Brown University for study implementation, and is the home of Principal Investigator Philip Chan, MD. The PrEP clinic at TMH will be the primary study site for clinical visits. Participants will complete an initial visit at TMH PrEP clinic during which time they will be screened for eligibility for PrEP, and this site will serve as the site for follow-up PrEP monitoring visits, including where HIV and renal function tests will occur, as well as collection of blood and hair for drug level testing. Additionally, survey and adherence counseling sessions may be conducted at The Miriam Hospital, if preferred by the participants.

RESEARCH PROTOCOL

Specific Aim 1 - Pilot RCT: To evaluate both PrEP initiation and adherence, we will use a two-stage randomization design. In Stage 1, we plan to enroll 130 MSW (65 per randomization arm to achieve N=104 completers for Stage 1; ~80% retention), who will be equally randomized to receive either the PrEPare for Work strength-based case management (SBCM) or standard of care (i.e., referrals only) to evaluate successful PrEP initiation. In Stage 2, those who initiate PrEP (n~44; ~80% in Stage 1 intervention arm and ~20% in Stage 1 comparison arm), regardless of their Stage 1 randomization condition, will then be equally randomized to the PrEPare for Work adherence intervention condition or standard of care comparison condition (22 per randomization arm to achieve N=40 completers for Stage 2; ~90% retention). While we are aware that there may be important differences that affect adherence in those who initiate PrEP without additional SBCM and those who received SBCM, we anticipate that randomization at the second stage will balance out potential confounding by level of motivation to initiate PrEP. See point of contact diagram below for specific details.

Recruitment: All participants will be identified by staff at Project Weber, our community partner organization and study site for this study, and will live in or participate in sex work in RI. In addition to identifying participants at the drop-in center, participants will be recruited from a variety of sources: (1) members of our recruitment/outreach team will actively recruit participants in the community via direct outreach at venues where we know sex workers solicit clients (such as bars, night/dance clubs, on the streets), (2) via the internet, by posting study related advertisements which may include a brief anonymous self-administered pre-eligibility assessment, (3) via direct engagement with internet escorts on the internet for which

their profiles are soliciting sex for pay, and (4) via snowball techniques. These efforts have been successful in other projects with this population, and as such, we do not anticipate having problems reaching our target sample. However, if we are not able to reach our sample size with these methods, we will also enroll MSWs in Greater Boston (<1 hour from Providence) and implement the intervention at Fenway Health—the largest provider of medical services for, and research with, MSM in New England, including PrEP (Mimiaga & Biello both have faculty appointments at Fenway Health and having ongoing research studies there). Eligibility screening may be incentivized with a $5 gift card in order to maximize recruitment in this difficult-to-reach population in particular venues (such as bathhouses). This initial screening incentive will be provided for completion of the eligibility survey, regardless of whether the participant is actually eligible after screening.

Screening and Enrollment: As part of the screening process, a brief anonymous pre-eligibility assessment may be conducted online or by phone prior to the full eligibility screening. The full eligibility screening may take place by phone, in a private room at one of the study sites (Brown University, Project Weber or The Miriam Hospital); or in a public location (coffee shop, library, etc) where the participant feels most comfortable. Participants will be asked to complete a survey assessing demographic information, sexual orientation, ethnic/racial identity, education level, history of HIV and other STDs, history of HIV testing, access to HIV and STD diagnostic and treatment services, recent sexual behavior, characteristics of recent partners, use of PEP previously and knowledge and anticipated acceptability of PrEP and other new biomedical prevention methods. The screening visit will take place in a private room at one of the study sites (Brown University, Project Weber or The Miriam Hospital); the participant can select where he feels most comfortable. Enrollment will be limited to participants who are English -speaking, HIV-uninfected, report having exchanged sex for money or drugs with another man in the past three months in RI, report at least one episode of condomless anal intercourse with an HIV-infected or unknown serostatus partner in the previous three months, who express an interest in using PrEP as an HIV prevention tool and live in the New England area. Potential participants will be asked to undergo antibody testing for HIV as well as screening for Hepatitis B infection (Hepatitis B surface antigen and antibody) and renal insufficiency (serum creatinine). Individuals will also be screened for acute HIV infection. A release of medical information will be requested upon enrollment. Only information regarding the PrEP clinic visit is requested and completion of the release is voluntary.

Research Assessments: Behavioral assessments will be conducted using ACASI at Stage 1 baseline, Stage 1 one-month follow-up, Stage 1 two-month follow-up, Stage 2 baseline, and Stage 2 three and six-month follow-up visits. It is expected that each ACASI survey will require less than 1 hour to complete. Both quantitative and qualitative assessment will collect information on the following key domains: sexual behavior; risk for HIV/STI transmission; use of alcohol and drugs; depression and anxiety; knowledge, attitudes, and beliefs related to pre-exposure prophylaxis. Exit interviews will be conducted as individual interviews and will last 15-20 minutes. Research assessments can be conducted at The Miriam Hospital, Brown University or Project Weber. Visits that include collection of blood and hair may only occur at The Miriam Hospital or Brown University. Participants who are unable to complete the Stage 2 three- or six-month follow-up visit in-person at Brown University or The Miriam Hospital may be given the option to schedule a phone interview with research staff to complete the Stage 2 follow-up assessment. This option will only be offered in extenuating circumstances (ex. participant moves out of the state). Phone interview follow-ups will be interviewer-administered. Participants who complete the phone interview will then receive instructions with a labeled, prepaid FedEx envelope to provide a self-collected hair sample. The sample will be mailed back to Brown University.

Incentives: All participants may receive up to $210. Participants will receive $30 USD compensation at each assessment visit (Stage 1 baseline, Stage 1 one-month follow up, Stage 1 two-month follow-up, Stage 2 baseline, Stage 2 three-month follow up and Stage 2 six-month follow up), individuals randomized to the strength based case management intervention condition will receive $15 USD for the first case management session and individuals randomized to the Stage 2 intervention condition will also receive $15 USD

compensation for each of the PrEPare for Work intervention sessions attended. Participants who complete a phone interview follow-up will receive a $15 gift card upon completion of the interviewer-administered assessment and an additional $15 gift card once the participant's hair sample is received via FedEx. Study staff will confirm the mailing address with participants prior to sending the gift cards.

Overview of the PrEPare for Work PrEP Initiation and Adherence Intervention Package (see appendix for manual).

1. Stage 1: Strengths-based Case Management to facilitate integration into The Miriam Hospital PrEP Clinic. Following Stage 1 randomization, participants randomized into the intervention arm will be provided a case manager to support, facilitate, and assist in linkage to our established PrEP clinic at The Miriam Hospital and to facilitate initiation of, and obtaining, PrEP medications. This is comprised of facilitated strengths-based case management to assess barriers to initiation, to help navigate the PrEP medical care system and to support the participant and health care staff in meeting the challenges faced with obtaining PrEP medication (e.g., overcoming insurance barriers, or barriers with copays). This also includes facilitated integration into the PrEP clinic and obtaining their PrEP prescription through the clinic (refilled monthly).

   A trained staff member will be based at Project Weber and will provide case management to all eligible participants interested in taking PrEP. Staff will receive training concerning the provision of case management services, including how to use past experiences with sex work as a tool for understanding, role modeling, outreach and engagement, ethical guidelines, such as confidentiality and professional boundaries, and administrative tasks (e.g., documentation).
2. Stage 2. Only participants who complete an initial visit at the PrEP clinic are clinically evaluated, receive a prescription for PrEP, and confirm their interest in using PrEP for HIV prevention will be randomized in Stage 2 to either the PrEPare for Work adherence training and counseling condition or the standard of care condition. All participants enrolled in Stage 2 will be offered a study cell phone to receive appointment reminders and, for participants randomized to the intervention, to receive daily adherence SMS text reminders (full description on page 6 under Adequacy of Protection of Risk). Participants may choose to decline the study cell phone and/or to participate in the daily adherence SMS text reminders (full description SMS text component page four Section B). For participants who decline and elect to use a personnel cell phone for study appointment reminders and/or daily adherence SMS text messages standard text messaging rates will apply and are not compensated for by the study.
   A. *Component I. Individual Adherence Counseling for PrEP adherence among MSW in Providence, RI.* Intervention participants will undergo up to three adherence training and counseling intervention sessions (once per week for 2-3 weeks) with a clinical interventionist. Intervention sessions may be scheduled once a participant is assigned to the intervention and must be completed within 12 weeks of randomization. A summary of topics to be covered is a follows:
      i. *Introduction, rapport building, education.* The initial adherence session will involve getting to know the participant, a conversation about general information about PrEP, and the rationale for the counseling. This will include a general discussion of the participant's sexual behavior, sexual history, and general patterns regarding unsafe sex.
      ii. *Educational information about PrEP and coping with side effects*
      iii. *Motivation for using PrEP, based on motivational counseling principles*
      iv. *HIV risk reduction counseling and behavioral adjustment*
      v. *PrEP adherence and problem solving barriers to adherence.* The remaining time will involve going through a list ("steps") of potential barriers to PrEP adherence. The following list of topics will be addressed, although the relative emphasis on the different topic areas will be adjusted according to the unique needs of the participants.
         a. Daily schedule and weekend schedule, for the purpose of scheduling dosing
         b. Coping with distress; mental health referrals made as necessary

c. Substance use, including possible interaction with PrEP adherence; referrals for substance treatment and support services made as necessary
d. Sex work and daily adherence
e. Other structural factors, e.g. homelessness or other barriers, as appropriate
f. Reminder strategies for taking PrEP

B. *Component II. Daily SMS text messaging of personalized reminders to take PrEP as prescribed ("reminder cues").* As an optional component, we will send daily text messages to all participants randomized to the PrEPare for Work intervention condition, as reminders to take PrEP as prescribed and as cues regarding behavioral skills gained as a result of in person adherence counseling sessions. The messages will not have any information about the participant's health, medication or any information identifying them as a MSW. Text messages will be programed to begin upon completion of the stage two baseline and to end upon the completion of the three-month follow-up visit. Participation in text message reminders will be left to the participants' discretion, may be deployed on a study cell phone or a personal cell phone, and can be stopped at any time. Text messages will be programed utilizing a web-based data management system. This system is password protected and available only to trained study personnel. Text messages are registered by participant ID and study cell phone number. Participants personal information cannot be traced back to study cell phones. Participants electing to use personal cell phones to receive text reminders will be registered by name and phone number to eliminate identifying the study ID with a personal phone number.

Data management: Demographic and behavioral assessments will be administered primarily on a tablet computer using a web-based data collection tool system. As the participant enters data points, each response will be immediately encrypted and transmitted back to a secure server. This will enhance confidentiality and minimize risks to patients. The digital data collection tool will be programmed to automatically store identifiable information and any PHI in a separate database from questions about demographics, risk behaviors, and health outcomes. No data will be stored on the tablet computer at any time.

Whenever possible, the information will be collected digitally in this manner. However, in venues with large testing volume, or when the PIs deem it safer to collect data in paper format, a paper survey will be administered. In these cases, hard copies of the survey will separate any identifying information from health outcome data. Identifying information including name, phone number and zip code will be stored with their unique identifier separately from all other responses and will serve as a linkage file. The unique identifier will be used on all other testing and data collection documents. The linkage file will be kept only on secure and encrypted Lifespan and Brown University computers.

Inclusion criteria:

- 18 years of age or older
- Assigned male at birth
- Report having exchanged sex with another man for money or drugs in the past three months
- Report behavioral risk for HIV infection, consistent with Centers for Disease Control and Prevention guidelines for prescribing PrEP: condomless anal intercourse with at least one HIV-infected or unknown serostatus partner in the past three months
- HIV-negative by antibody test *Stage 2
- Able to understand and speak English, for consenting and counseling
- Lives in the New England area
- Willing to initiate PrEP

Exclusion criteria:

- Unable to provide informed consent, including as a result of severe mental illness requiring immediate treatment or mental illness limiting the ability to participate
- HIV Positive at baseline
- Infected with Hepatitis B or diagnosed with renal insufficiency (glomerular filtration rate < 50) *Stage 2
- History of or current medical conditions that would preclude taking Truvada for PrEP *Stage 2
- Currently taking Truvada for PrEP

Sample size: We expect to recruit 130 participants for the pilot RCT (Specific Aim 1).

PROTECTION OF HUMAN SUBJECTS

Potential Risks

Protected Health Information: This study will obtain data on sexual practices, sexual partners, drug use, visitation to local sex venues and attitudes regarding aspects of STIs. During the course of the study, preservation of confidentiality and safeguarding of PHI will be a paramount concern. A potential risk is breach of confidentiality and privacy.

Psychological Consequences: Another potential risk of the study is the possibility that participants could become upset, uncomfortable, or have other serious emotional responses to discussing sexual network information and risk behaviors during the study.

Risk of loss of privacy or confidentiality: Participants in Stage 2 intervention may opt to receive a study cell phone for appointment reminders and text messages. Any communication deployed via study cell phone will not contain information about the participant's health, medication or any information identifying them as a MSW. Participants can decline this phone and stop using it at any time.

Recruitment and Informed Consent: Subjects will be recruited through Project Weber as described above. Potential participants will be offered enrollment in the study by research personnel. Participants will be told that the study is being performed to help evaluate the ways in which STIs spread through the community and how infection may be prevented. Conversations will be held in closed and private areas. Participants who agree to enter the study will sign a statement of informed consent. Participants will be informed that they do not have to answer any of the questions if they choose not to.

Certificate of Confidentiality: This research specifically targets a vulnerable population, men who have sex with men in exchange for money. We will take every available step to minimize the risk of identifying/linking data being subpoenaed, stolen, or inadvertently released. We will request a Certificate of Confidentiality from the NIH prior to enrolling participants. As noted on the NIH website (http://grants.nih.gov/grants/policy/COC/faqs.htm#187), a Certificate of Confidentiality will help the research team "...avoid compelled 'involuntary disclosure' (e.g., subpoenas) of names and other identifying information about any individual who participates as a research subject (i.e., about whom the investigator maintains identifying information) during any time the Certificate is in effect." We have applied for and received Certificates of Confidentiality for other NIH-funded research projects, and given the sensitive nature of the data collected for this project, do not foresee difficulty securing one for this study.

Adequacy of Protection against Risks

Protected Health Information: For all components of the research plan, the study team will clearly identify themselves as being research personnel from The Miriam Hospital and Brown University. During the course of informed consent, strict confidentially will be assured to all subjects and will be stated on the informed consent form. Only the PI and immediate study personnel performing the study will have access to PHI and other sensitive data. All data including names and identifying information will be kept behind locked

doors in locked cabinets or on password-protected Lifespan and Brown University computers. Data obtained over the web survey will be collected in a secure and encrypted format available only to research staff. Data emailed over the internet will be avoided, but if essential will be using standard encryption browser technology through the Lifespan VPN (encrypted using 'PHI' – personal health information - in the subject line, as per routine clinical practice). All persons involved in this research project will undergo human subjects and HIPAA training. In the event that confidentiality is breached, the PIs, mentoring team, and IRB will immediately be notified. All conversations with study subjects will be behind closed doors in confidential settings to address privacy.

Psychological Consequences: Any psychological or other mental health consequences as a result of this study will be immediately referred to the study PIs and will be addressed by the study team and by trained clinical psychologists that currently provide support services at the Immunology Center, free of charge. Participants will be able to stop the assessment or interview at any point and may discontinue their involvement in the study at any time.

Risk of loss of privacy or confidentiality: Study cell phones are issued by AT&T through Brown University. Individual study cell phones cannot be traced back to research participants by name. Study phones are registered by study ID and identified as the Center for Health Equity Research (at Brown University). Daily adherence SMS text messages are deployed utilizing a web-based data management system which is password protected and only trained study personnel can access. If participants who use study cell phone agree to receive appointment reminders via this device, the phone number is recorded the link file containing contact information. This file is password protected and can only be accessed by trained study personnel.

Additional Protections for Children

The prospective component of this proposal will only enroll individuals aged 18 years or older and is not pertinent to children.

Data and Safety Monitoring Plan

We have identified Jennifer Mitty, MD and Josiah Rich, MD as two individuals qualified to assist us in the oversight of participant safety and the monitoring of any unforeseen events during this study. Drs. Mitty and Rich are not directly involved in our study and can provide unbiased input and advice. Both are experienced in working with both HIV-infected and HIV at-risk individuals. We will provide Drs. Mitty and Rich with a status summary of research activities via email for review on at least a half-yearly basis. In addition, Drs. Mitty and Rich will be available on an ad-hoc basis as necessary for us to discuss any issues that may arise.

Potential Benefits of the Proposed Research

There will be no direct benefit from participating in this study to the participating subjects. Subjects will receive education and counseling to reduce risky behaviors. The public health benefits and knowledge gained during this study will lead to a better understanding of PrEP uptake and adherence among male sex workers.

TIMELINE

The expected timeline of the study is three years. Review and updates will be provided to the IRB as necessary.