Feasibility of Short-Term PrEP Uptake for MSM With Episodic High-Risk for HIV

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# Epi-PrEP: Detailed Protocol

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## 1. BACKGROUND AND SIGNIFICANCE

### 1.1 ABSTRACT

This proposed study is designed to investigate the acceptability, perceived need and uptake of short-term episodic Pre-Exposure Prophylaxis (PrEP) for HIV prevention among men who have sex with men (MSM). Long-term PrEP may be unnecessary for the majority of HIV-negative men who do not have sustained periods of high-risk sex, but rather episodic, contextually defined, high-risk periods, particularly when away from their home setting. Alternative dosing strategies, such as short-term fixed-interval episodic PrEP (Epi-PrEP), may be a more realistic, feasible, acceptable and useful option with high public health impact for the majority of high-risk MSM whose risk behaviors may be best described as occasional, episodic, but non-random.

### 1.2 BACKGROUND

Current approaches to HIV prevention are not controlling the HIV/AIDS epidemic among MSM. After 30 years of experience in fielding behaviorally-based interventions, high HIV incidence rates among MSM continue to be reported, a situation that is attributable to limited HIV prevention impact. Of the 1.2 million people living with HIV in the U.S., MSM continue to be disproportionately impacted accounting for 61% of all incident U.S. HIV infections in 2009 [2, 3]. Stall, et. al., in a systematic review of HIV incidence rates among MSM in the post-HAART era calculated an overall community-based HIV incidence rate of 2.4% among MSM (with 4% for Black MSM). Assuming an annual incidence rate of 2.4%, prevalence rates in a cohort of 18 year-old HIV-negative men would increase to 41% by age 40 [4], thereby reproducing the AIDS epidemic across generations. Combined, these findings highlight both the contributions and shortcomings of current HIV prevention practice: although behavioral interventions reduce risk, they are unable in and of themselves to achieve the sustainable risk reductions necessary to control the HIV epidemic among MSM.

PrEP, in combination with behavioral interventions, is a promising approach to increasing the effectiveness of HIV prevention efforts. Biomedical advances have created the opportunity to increase the effectiveness of biobehavioral HIV interventions. According to one model, with sufficient coverage, available biobehavioral interventions could prevent a quarter of new infections [5]. For example, combination prevention [6, 7] approaches attempt to reduce HIV transmission through multiple methods including ARV treatment to decrease individual and community viral load (CVL), structural change, and behavioral interventions. ARV treatment has proven effective in decreasing individual plasma HIV RNA (viral load) thereby reducing the risk of sexual transmission of HIV [8]. Furthermore, reductions in plasma HIV RNA at the individual level have resulted in reducing levels of viral load at the community level [9-11]. PrEP is the next step in the use of ARVs to both prevent HIV and be part of combination packages to reduce CVL. Daily tenofovir-emtricitabine (TDF/FTC) use among at risk HIV-uninfected individuals in decreased HIV transmission by 44% in an RCT in MSM (iPrEX) and retrospective analyses found that participants who had blood levels consistent with daily use achieved a 99% level of protection [12] and was recently FDA approved for use as PrEP [13].

PrEP can be taken on a short-term basis to achieve optimal protection. The overall intent-to-treat protective effect of TDF/FTC for MSM was 44% in iPrEX [1], but drug was detected in only about 50% of the samples tested among participants randomized to receive the active medication. In the post-hoc analysis of the iPrEX data [12] although blood levels consistent with daily PrEP use were associated with a greater than 99% protection rate, drug levels consistent with every-other-day usage (i.e. 4 times a week) were associated with 96% protection, and studies of intermittent PrEP are underway. TDF/FTC needs to be phosphorylated intracellularly to inhibit HIV reverse transcriptase and it is estimated that at least 4 daily doses are needed to begin to achieve steady state concentrations consistent with 90% protection [12, 14-16]. The iPERGAY study of French and Quebecois MSM is evaluating peri-event dosing, and HPTN 067 (Project Adapt) which is comparing peri-event dosing, fixed interval (e.g. weekend focused) dosing, and daily dosing among MSM in Bangkok and Harlem and women in South Africa. However, neither of these trials are focused on a population of individuals who may have discrete but intense periods of risk, in which daily dosing would be preferable.

Risk among MSM is often episodic, contextual and predictable [17, 18]. We have known for a quarter of a century that few MSM report consistent high-risk sex over time [4]. Sexual risk reductions among most MSM are unlikely to be permanent, but rather characterized by episodic lapses [4]. Evidence of increased behavioral risk associated with travel/vacation has been found in studies of circuit parties. In two recent studies, circuit party-goers reported increased substance use, condomless sex anal sex with more partners and more serodiscordant condomless sex anal sex during party weekends away from home compared to MSM attending circuit parties at home and MSM during typical home weekends. This suggests an increased risk both from the party atmosphere and from being away from home [17, 19]. Benotsch, et al., found that vacation risk behaviors significantly contributed to HIV acquisition among MSM vacationers in Key West [20]. More recently, our group completed a survey on a sexual networking site, with more than 9,000 respondents, and found that 76% went on a vacation in the prior year; and 19.4% of those who vacationed anticipated UAS while away. The median duration of vacations was 7 days (IQR: 4-10), with 69% reported going on vacation more than once per year. Only 1.9% of those who planned UAS during vacation had ever used PrEP. MSM who reported increased UAS on vacation had greater odds of indicating that they would take PrEP if it were helpful for short periods (aOR=1.83, 95% CI 1.49-2.25) [21]. These data support our approach of investigating the feasibility of developing protective strategies for one particular time-limited period of episodic risk and that HIV-negative men who take vacations in high-risk settings might be a particularly promising group for whom Epi-PrEP is indicated and for whom data on Epi-PrEP adherence would prove valuable to guide future combination prevention practice.

Risk is also influenced by environmental/structural factors. Millett's findings that African-American MSM experience disproportionate HIV burden not due to individual risk behaviors but because of the epidemiological context within which they find sexual partners [22, 23] may be germane to considering the consequences of episodic risks among MSM in new contexts. Millett's analyses highlight the importance of the prevalence of uncontrolled HIV replication among the members of a network (CVL) in explaining excess HIV burden among African-American MSM, and show that it is the social network in which men meet partners that contributes to high HIV infection rates. Several other recent studies also suggest complex interactions between neighborhood environments and individual-level identity expression and behavior [24-30] that function to raise levels of risk. Sexual scripting (finding sex partners/behavior during sex) is also greatly impacted by environment (e.g. space/place, socio-sexual networks, perceived norms).

There is evidence suggesting that some MSM may already be identifying periods of risk and self-initiating context-specific risk reduction including PrEP. For example, 76% of men in iPrEx who reported URA sex had detectable drug levels compared to 36% who had not [31], possibly suggesting a link between self-identified need (i.e. risk) and use (i.e. adherence) of PrEP. Others have documented PrEP self-initiation and ARV sharing [32-36]. Providers in both Pittsburgh and Boston have reported men requesting PrEP to use during upcoming vacations [37]. These observations suggest that a program of education about how to optimally use episodic PrEP might result in optimal uptake and adherence at a time when chemoprophylaxis is most needed.

While promising, there are many barriers and unanswered questions to Epi-PrEP uptake among MSM. For Epi-PrEP to succeed, MSM must successfully navigate a set of barriers [38] for which there are no intervention protocols. These barriers include: 1) Risk Identification: Men must be able to accurately self-identify when they are appropriate candidates for Epi-PrEP and then be willing and able and to access it through their provider. There are likely several individual (e.g., self-awareness of and stigma associated with high-risk behavior, being 'out' to providers) and structural (e.g. non-HIV provider awareness of PrEP and sexual risk behavior) barriers to achieving this goal. 2) Acceptability/Uptake: Much remains unknown about how MSM will respond to Epi-PrEP as a prevention option. The few studies that have been conducted have found low levels of PrEP awareness [32-36] and initiation [33, 35]. The limited number of studies that have examined interest in PrEP as a prevention option cite affordability [32] and effectiveness [36] as major barriers to uptake. Even less is known of attitudes about medication-taking (e.g. unwillingness to take any medicine, stigma associated with having "HIV medication") and dosing preferences (e.g. everyday vs. event-based) among high-risk MSM. 3) Cost: Yearly HIV treatment with TDF/FTC is costly (≈$1000/month) [39]. PrEP also incurs additional costs such as safety lab monitoring (i.e. renal function), HIV/STI testing, adherence/risk counseling and other ancillary services. Current cost/effectiveness data suggest that without increased efficacy or a reduction of medication cost, PrEP is unlikely to be a cost neutral intervention [40] and is likely to be beyond the means of men who would have to cover these costs without insurance. 4) Adherence: Adherence is a key predictor of developing successful protection [8, 11, 41] and likely to be one of the largest barriers to effective implementation. For community-level PrEP dissemination to have a significant impact on decreasing HIV incidence among MSM, an efficacious bio-behavioral intervention will need to address adherence-related issues. Without a combined bio-behavioral approach to uptake and adherent use, PrEP will be unable to achieve its full promise as an effective tool for HIV prevention.

Several of these challenges may be addressed by shorter-term episodic PrEP. Epi-PrEP could be highly effective for HIV prevention [42, 43] while also decreasing medication burden and costs [44], avoiding long term drug side effects and adherence fatigue. Furthermore, understanding how to get Epi-PrEP to effectively work among MSM will likely have implications on how to better implement PrEP for other key populations. A contextually specific frame may help to introduce MSM and the larger community to this new prevention technology in a tangible fashion thereby creating a bridge to longer-term interventions for those with greater need. The proposed project represents one of the steps on the behavioral PrEP agenda.

The Need for Epi-PrEP Biobehavioral HIV Prevention Interventions: PrEP cannot achieve its promise as a HIV prevention tool if MSM do not access it or are insufficiently adherent while using it. For some, PrEP may be unsuitable for use as a long-term prevention strategy, not only because of the episodic nature of risk, but also because of cost issues and concerns about the biological consequences of long-term medication use. Thus the development of protocols to support effective PrEP use should begin by developing interventions to support appropriate uptake and adherence to Epi-PrEP among men entering a temporary period of their life in which their risks for HIV infection are increased. Studying the facilitators and barriers to Epi-PrEP use among high-risk MSM is a necessary first step to understanding how to support Epi-PrEP uptake. Similarly, MSM who are entering high-risk episodes are an appropriate population to study short-term barriers and facilitators to adherent use of Epi-PrEP. By basing the creation of new intervention strategies on data that measure both Epi-PrEP uptake and adherence among high-risk MSM, we can help ensure that PrEP strategies will reduce HIV transmission among the risk group that accounts for nearly two-thirds of all new HIV infections in the U.S.

### 1.3 SIGNIFICANCE

This study proposes one of the first attempts to measure the feasibility of episodic context-specific PrEP to reduce HIV transmission among MSM. Long term PrEP regimens may be untenable for most MSM, the largest (by far) risk group for HIV in the U.S., for reasons having to do with cost, possible drug side effects and the fact that many MSM have recurrent but short-term periods in their lives when they are at high-risk. Relatively few MSM manifest patterns of very high-risk for long periods of time, thereby making long-term

PrEP unnecessary. Shorter-term dosing for those periods when men are likely to be at high-risk will help control toxicity and costs and so be more appealing to MSM. However, whether high-risk MSM are able to achieve high-level adherence to medications during periods in their lives when their normal routines are disrupted remains unknown. This study will pave the way for the development of an intervention combining both pharmacological and behavioral components that would work to lower risk of HIV infection for men who are entering a time-limited high-risk period in their lives.

This proposal suggests a novel study to identify the psychosocial characteristics of MSM who report episodic high-risk sexual behavior and the likely barriers they will experience to achieve appropriate Epi-PrEP presentation. For Epi-PrEP to succeed as an effective public health tool, high-risk MSM will need to do more than adhere to the regimen. They will need to be able to self-diagnose the need for Epi-PrEP and to present for treatment before entering into a high-risk period. Currently we know surprisingly little about the characteristics of men who report episodic risk. This gap in our knowledge also extends to the barriers that high-risk men are likely to experience in presenting for Epi-PrEP. This study will pave the way for public health campaigns that will help men understand how to appropriately determine when they might use episodic PrEP and address barriers they may experience accessing it from health care providers.

HIV behavioral literature has largely emphasized variables at the individual level. This study proposes an emphasis on the context within which individuals operate, how a change in context increases levels of risk and how episodic PrEP could be used to make movement to unknown or known-risky contexts less risky. Although increasing evidence is being produced to highlight the importance of contexts as drivers of HIV risk [22, 23], the study of how to intervene in high-risk contexts remains underdeveloped in the HIV prevention literature. The use of a combination prevention approach to intervene at the contextual level to lower HIV risk adds to the innovation of this research design. By studying whether men can achieve the necessary levels of adherence to TDF/FTC during contextually driven high-risk episodes, we will learn a great deal about how to field efficacious combination prevention interventions in high-risk contexts. To the best of our knowledge, this will be the first study of HIV risk and Epi-PrEP adherence defined to highlight context-specific drivers of risk behaviors and drug adherence.

Creating biobehavioral combination prevention approaches may lower HIV incidence among high-risk MSM. We have seen that, while effective, behavioral intervention potency may be limited in reducing HIV incidents thereby creating demand for additional tools to significantly control the epidemic among MSM. Epi-PrEP offers an exciting new tool to reduce HIV infections within the risk group that accounts for nearly two out of every three new infections in the U.S. However, Epi-PrEP cannot achieve its promise if men who need to use it don't present for treatment and if they don't adhere to TDF/FTC during high-risk phases of their lives. Unfortunately, our knowledge about how to achieve these necessary goals with this new biomedical innovation is limited. This proposed study represents a first step in developing a new bio-behavioral innovation to support this new technology in a way that combines clinical (effects of short course medical regimens), behavioral (how to optimize short-term adherence), community (assessment of norms related to acceptability and patterns of uptake), and cost-effectiveness (optimum length of treatment dependent on risk) considerations.

## 2. SPECIFIC AIMS

The specify aims and hypotheses to be tested in this research project include:

**2.1 Epi-PrEP Trial:** Determine the feasibility of clinic-based Epi-PrEP implementation pilot project for up to 50 MSM (approximately 25 at each of the two study sites) who report occasional condomless sex and who anticipate that they will have a period of high-risk while away from home (e.g. vacation) during the study period. To accomplish this we will assess adherence to Epi-PrEP via self-report and drug level assessments for the entire period they are prescribed PrEP. *Hypothesis*: *MSM who use Epi-PrEP will have varying levels of adherence as measured by self-report and drug levels, and those who are not adherent to Epi-PrEP will have multiple psychosocial health problems that will warrant additional adherence support.*

**2.2 Qualitative**. Identify specific adherence-related contexts and problems, as well as resiliencies that will inform the intervention design of a larger scale trial of the efficacy of Epi-PrEP. To do this we will conduct qualitative interviews to compare perspectives and experiences of Epi-PrEP adherent (n≈10) and non-adherent (n≈10) MSM from the implementation pilot. *Hypothesis*: *Adherent and non-adherent men will report different themes regarding adherence vulnerabilities (e.g. substance use, lack of schedule).*

## 3. SUBJECT SELECTION

### 3.1 Inclusion/Exclusion Criteria

#### 3.1.1 Epi-PrEP Trial

INCLUSION CRITERIA

1. Self-identify as MSM: (1) born male who (2) has sex with men
2. Age: 18 or older
3. Sexual Risk: has had condomless anal sex with 2 or more men or any transactional sex with a man within the past 12-months.
4. Vacation: identified an upcoming period of episodic risk away (i.e. vacation) from their home city that will last at least 7 but not more than 14 days during which they anticipate having at least one high-risk sexual event.
5. Able and willing to provide informed consent

EXCLUSION CRITERIA

1. HIV positive
2. Glomerular filtration rate < 60 mL/min (calculated using the Cockcroft-Gault formula)
3. Hepatitis B surface antigen positive
4. Symptoms suggestive of acute HIV seroconversion at screening or enrollment
5. Have used PrEP or PEP within the previous 3 months
6. Currently enrolled in another study involving medications, investigational drug, or medical device
7. Has other conditions (based on opinion of investigator or designee) that would preclude informed consent, make the study unsafe, complicate interpretation of study outcome data, or otherwise interfere with study procedures

#### 3.1.2 Qualitative Interviews

All participants for the qualitative interviews will be recruited from men who enrolled in the Epi-PrEP trail.

### 3.2 Source of Subjects and Recruitment Methods

#### 3.2.1 Recruitment.

##### 3.2.1.1 Epi-PrEP Trial

Participants will be recruited through 1) research assistants (RAs) and study coordinators working with treatment providers and 2) advertisements. We will use recruitment techniques previously employed in Fenway and University of Pittsburgh studies, including venue outreach (bar, club, cruising areas), community outreach, word of mouth from past or present participants in studies, and advertising (print, clinic flyers and electronic media). Recruitment for the present study will be done in conjunction with recruitment for other, ongoing studies and health promotion activities. Our recruitment efforts, in line with our previous recruitment initiatives, will include targeted recruitment of people of color, by adapting our recruitment materials, and conducting recruitment drives in minority communities. We have budgeted time for study staff to encourage and insure adequate recruitment.

##### 3.2.1.2 Qualitative

Participants will be recruited from the men enrolled in the Epi-PrEP trial and will be purposively sampled based on self-report or biological adherence outcomes. Men will be equally enrolled into a balanced design as adherent

(n≈10) or non-adherent (n≈10). Our goal is to divide interviews as equally as possible between University of Pittsburgh and Fenway Health.

### 3.2.2 Retention.

The study coordinators will track participant retention, which will be reviewed weekly by the PI or co-PI. As has been successful in previous trials with this population, we will collect extensive locator information (such as information regarding at least two significant others with whom the participant is in regular contact and involvement with AIDS service organizations) for participants. To facilitate retention, if necessary we will meet with participants at their homes or any confidential location that is comfortable for them for study assessment visits. Additionally, we have budgeted for appropriate financial incentives for participants which correspond to clinical visits.

To reduce non-response to the follow-up assessments, we will send text messages and emails, and make phone calls prior to the scheduled assessment. At enrollment, participants will be asked to identify individuals to serve as locators. Participants will be asked to sign a form letter addressed to each of the locators, which explains that the participant is participating in a research project with Fenway Health or the University of Pittsburgh and that they have named this person as a locator. Locators will be contacted only if all efforts to reach the participant with the provided information failed. Weekly case review meetings will be held among investigators to discuss ways to complete contact with the participants when necessary.

## 4 Subject Enrollment

**4.1 Referral** is described above under section 3.2.1.

**4.2 Screening**. Initial screening will be done by the research assistants or other study administrative staff. The initial screening will occur either over the telephone or in person using attached phone screen. If the participant appears to be eligible and is interested, he will be scheduled for an informed consent and screening visit.

**4.3 Informed Consent.** Informed consent will be obtained by the interventionist or other study staff. Every participant will read or have read to them a statement of informed consent which includes all of the study procedures, information about potential risks and benefits of participation, and information regarding who they can contact for further questions. Before any other study procedures take place, each participant will read and review the Informed consent with study staff and allowed time to ask any questions they have before signing the form. After completion of the informed consent form, the participant undergoes the screening diagnostic evaluation. At the end of the diagnostic assessment, the participant is asked again about study participation.

## 5.0 Study Procedures

### 5.1 Study Visits

| Schedule of Study Visits | | | |
|---|---|---|---|
| **Time Period** | **Type of Visit** | **Assessment** | **Compensation** |
| **Pre-Trip** | | | |
| 2+ weeks pre-trip | Phone Screening | Establish basic eligibility requirements | NA |
| At least 2 weeks pre-trip | Clinical Baseline | Full assessment battery, safety labs, STI screening. Online behavioral interview | $25 |
| At least 1 week pre-trip | Epi-PrEP enrollment | Review labs, dispense Epi-PrEP, counseling | $25 |

| | | | |
|---|---|---|---|
| **Trip** | | | |
| 7-14 days away | NA | NA | NA |
| **Post-Trip** | | | |
| 1-3 days post-trip | Clinical Post-Trip Follow-up | TFV concentrations, STI screening, safety labs, online behavioral interview. | $25 |
| 3 months post-trip | Final Clinical | Safety labs, STI testing if symptomatic, online behavioral interview. | $25 |
| 6 months post-trip | Final Survey | Online behavioral interview emailed to participant to be completed outside the context of an office visit. | NA |

### 5.1.1 Phone Screening

Phone screening to determine eligibility will be completed by study coordinator or recruiter.

**FORMS TO COMPLETE**

1. Phone screener

### 5.1.2 Visit 1: Clinical Screening

1. Informed Consent: prior to any research-related activities, subjects must read or have read to them a statement of informed consent. Subjects must understand and sign this statement.
2. Medical History: general medical history including pre-existing medical conditions, prior hospitalizations, current medications (including over-the-counter medications and nutritional supplements), any known medication allergies or intolerances.
3. Physical examination: this will include: vital signs (temperature, blood pressure, pulse rate and respiration rate) and a symptom-directed examination, i.e., examination of body systems in which the subject reports active symptoms.
4. Questionnaire: See **Section 8** for more detail.
5. HIV risk reduction counseling: will include a discussion of how HIV antibody and antigen testing is conducted, the "window period" of seronegativity following HIV exposure, methods of HIV transmission and means for avoiding exposure and/or transmission ("safer sex").
6. Laboratory Testing:
   a. Mandatory:
      - 4th generation HIV-1 ELISA
      - Hepatitis B Panel: Hepatitis B surface antigen (only if not done within the past month)
      - Creatinine (calculate creatinine clearance estimated by Cockcroft-Gault equation)
      - STI Testing
        - Syphilis serology
        - CT/GC Urine NAAT
        - CT/GC Cx - Anal
7. Refer to Mental Health provider on call if appropriate (e.g. suicidality, severe depression)
8. Make appointment for Visit 2
9. Obtain Locator Information

**FORMS TO COMPLETE**

1. Consent Form
2. Locator Form
3. Medical Release Form
4. Medical History Form
5. ROS/Physical Exam Form(s)
6. Con Medication Log

7. Eligibility Checklist
8. Creatinine clearance log
9. Clinical Screening Checklists: RA and clinician

### 5.1.3 Visit 2: Epi-PrEP Enrollment

1. Disclosure of results from Visit 1; exclusion from study if HIV-infected and referral to primary care/infectious diseases
2. Review of systems (symptom-directed physical exam if indicated)
3. Review concomitant medications
4. Medications dispensed. Participants will receive TDF 300 mg/FTC 200 mg in fixed dose combination (Truvada®), to be taken once daily. Subjects will be given 30 tabs in the original bottle and will be asked to return any unused tabs to study staff at their 3 month visit.
5. Refer for Hepatitis B Vaccination if seronegative; excluded from study if there is evidence of current Hepatitis B infection
6. If participant consents, send provider letter indicating TDF/FTC prescription.
7. Adherence intervention session
8. Make appointment for Visit 3.

**FORMS TO COMPLETE**

1. ROS
2. Update Con Med log
3. Dispensation log
4. Enrollment Visit Checklists: RA and Clinician

### 5.1.4 Visit 3: Clinical Post-Trip Follow-up

1. Recording of adverse events and concomitant medications
2. Review of systems (symptom-directed physical exam if indicated)
3. Questionnaire: See **Section 8** for more detail.
4. Laboratory Testing:
   a. Mandatory:
      i. Kinetic drug level assay
         1. Collect samples for both PBMC and plasma analyses
      ii. 4th generation HIV-1 ELISA
      iii. Creatinine (calculate creatinine clearance estimated by Cockcroft-Gault equation)
5. Make appointment for visit 4.
6. Refer to Medical Department for STD testing if symptomatic

**FORMS TO COMPLETE**

1. ROS
2. Update Con Med log
3. Update AE log
4. Update creatinine clearance log
5. Visit 3 Checklists: RA and Clinician

### 5.1.5 Visit 4: 3 Month Follow-up study visit

1 Recording of adverse events and concomitant medications
2 Review of systems (symptom-directed physical exam if indicated)
3 Questionnaire: See **Section 8** for more detail.
4 Laboratory Testing:
   a. Mandatory:
      - 4th generation HIV-1 ELISA
      - Creatinine (calculate creatinine clearance estimated by Cockcroft-Gault equation)
5 –Refer to Medical Department for STD testing if symptomatic
   a.

**FORMS TO COMPLETE**

1. ROS
2. Update Con Med log
3. Update AE log
4. Update creatinine clearance log
5. Visit 4 Checklists: RA and clinician

### 5.1.6 6 Month: Final Online Survey

Participants will be emailed a link to complete a final online survey. This survey will be implemented using the Qualtrics system allowing participants to log in and complete the survey from anywhere with Internet connectivity, including desktop and laptop computers and mobile devices. The electronic survey will be designed to take approximately 20 minutes. Data will be submitted anonymously through a secure system developed for previous collaborations accessible only to the PIs and study staff. Participants will be given a unique link which will allow us to link responses to study PTID.

### 5.1.7 Qualitative interview Visit

To minimize participant burden, the qualitative interview visit can be either a standalone visit or added to the three month study visit. This in-depth qualitative interview will last approximately 90 min. For information on selection of participants for the qualitative interview see **Section 3.2.1.2.** For detail on content see attached interview guide as well as **Section 8.2**.

### 5.1.8 Interim Visits

Interim visits may occur at any time during the study. Interim visits may occur for the following reasons: (1) for operational reasons, e.g., a participant may request to reschedule, or to ask questions; (2) for product-related reasons, e.g., a participant may need additional study product or want to discuss problems with adherence to product use; (3) for AE-related reasons. When interim contacts or visits are completed in response to participant reports of AEs, study staff will assess the reported event clinically and provide appropriate medical care or make appropriate referrals; (4) for interim STI counseling and testing in response to STI symptoms. (5) if a participant presents to the study site after having missed a scheduled visit (e.g., in response to locator/tracing efforts) on a day that does not fall within a scheduled visit window; (6) if a participant is experiencing symptoms suggestive of acute HIV infection; or, (7) for other reasons at participant request. Subjects with symptoms consistent with acute HIV infection syndrome will receive diagnostic testing to attempt to elucidate the cause of the syndrome, including rapid testing for HIV RNA and additional tests as medically indicated. Subjects will be taken off of study drug if they have any reactive rapid HIV antibody test. All interim contacts and visits will be documented in participants' study records and on applicable CRFs.

### 5.1.9 HIV Seropositive Visits

Men who are found to have a reactive HIV antibody test during the study will be instructed to stop the study drug immediately. After confirmatory HIV serology, individuals with confirmed HIV infection will be referred for HIV care.

### 5.1.10 Participant Replacement policy

If a participant does not complete the post-vacation visit (within 7 days of returning from vacation), they will be considered lost to follow up and may be replaced in the study with another participant. Those who enroll but do not go on vacation may also be replaced. Participants who are unable to attend an enrollment visit and acquire study product at least 7 days prior to their vacation will be excluded and replaced.

### 5.1.11 Reimbursements

Participants will receive a monetary remuneration in the amount of $25 at the end of each scheduled office visit including: Visit 1: Clinical Baseline; visit 2: Epi-PrEP Enrollment; visit 3: Post Trip; and visit 4: 3 Month Follow-up. A light snack and refreshment may be provided. Participants will not be compensated for completing the online survey emailed to them at the 6 month time point (see **Section 5.3.6**). To

encourage participants to take this survey, we will enter all participants who complete this survey in a drawing to win a $50 Amazon.com gift card. The drawing will take place at least 7 months after the last active participant's enrollment date. Each site will have its own drawing for participants who completed study visits at that site; two drawings in total will occur.

Participants who are selected for the qualitative interview and complete that interview will be compensated $50 for their time. If the qualitative interview occurs the same day as an existing visit, this compensation will be in addition to the compensation the participant was otherwise entitled to.

#### 5.1.12 Interface with Electronic Medical Record – Fenway only

For participants who are seen at Fenway Health, after obtaining bi-directional Medical Record release, study staff will interface with the Electronic Medical Record. Study staff will review the participant's EMR at screening to obtain concomitant medications and pre-existing conditions. Study staff will alert the participant's provider of participation and that the patient has been prescribed Truvada. Study staff will also notify the participant's provider of laboratory results.

#### 5.1.13 Interface with outside providers

With their consent and a signed medical release, patients will have a letter sent to their primary care provider discussing their involvement in the study. The letter to providers will alert the physician to their patient's new prescription: Truvada™. The letter will state that involvement does not preclude any regular HIV risk reduction strategies they may have been working on. In our prior work, sending this letter has not adversely affected study outcomes. Study staff will notify the participant's provider of clinically relevant laboratory results.

## 6.0 Study Agents and Pharmacy

### 6.1 Truvada™

Emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) is a fixed-dose co-formulation of FTC and TDF prescribed for daily administration. Each FTC/TDF tablet contains of 200 mg of FTC and 300 mg of TDF (equivalent to 245 mg of tenofovir disoproxil). All study products will be supplied by Gilead Sciences (Foster City, Ca). More detail about Truvada provided in the most recent package insert for the drug, attached.

### 6.2 Pharmacy Facility

Fenway Health: The pharmacy facilities will be located at the study site and staffed by credentialed pharmacists. The pharmacy will have adequate space to store sufficient quantities of study agent to assure access to all study participants. The study drug will be stored in accordance with the drug manufacturer's recommendations. The study pharmacy will be locked by a secure door and will be accessed only by the pharmacy staff. The pharmacy is a climate-controlled environment, with temperature controlled to remain within limits allowed by the manufacturer for drug storage.

University of Pittsburgh: Investigational Drug Service Pharmacy (IDS): The main IDS pharmacy, used primarily for ACTG studies, is located in UPMC Presbyterian University Hospital (PUH), approximately one block from the research clinic, connected by an interior walkway. The IDS has two offices for staff, each with computers, printers, desks, shelves, and a fax machine for IDS employees. The main pharmacy room is approximately 22 X 17 feet. An additional pharmacy room and storage space are located at Montefiore University Hospital Pharmacy, located one block from UPMC-PUH and connected by an interior walkway. The investigational drug storage area is maintained at a temperature of 72°F. A continuous temperature monitoring system for the ambient temperature and relative humidity is in operation at all times. The unit is on battery back-up. All refrigerators and freezers have temperature sensor alarms that are monitored 24 hours daily.

### 6.3 Study Drug Accountability

The site pharmacist is required to maintain complete records of all study products received from Gilead Sciences and subsequently dispensed to study participants. The pharmacist at the study site will receive the study agent and store it in the pharmacy. Access will be restricted to pharmacy personnel authorized

by the pharmacist of record. The pharmacist will be responsible for keeping accurate records of the material received. At the end of the study, the pharmacist will perform the final drug accounting of unused study material on the proper log documents. Unused study agent will be disposed of as instructed by the Principal Investigator and by study agent manufacturer.

### 6.4 Study Drug Dispensing

A study nurse will be responsible for dispensing the drug to each study participant. The pharmacist will receive the prescription that includes the participant's ID number. For each bottle dispensed, the pharmacist will enter the bottle label information and date in a Drug Dispensation Log. Dispensation of all study products to study staff and distribution to participants will follow the institutions SOP on Study Product Chain of Custody.

### 6.5 Replacing Study Drug

Lost or misplaced study drug will be replaced at the discretion of the site PI after the study team has reviewed the case with him.

### 6.6 Toxicity

Per the inclusion/exclusion criteria, individuals with pre-existing renal disease (GFR <60) will not be enrolled in the study. Those who are hepatitis B seronegative will be referred to receive vaccination. Participants with chronic hepatitis B (Hepatitis B surface antigen) will be excluded from the study for their own safety. Any participant who develops a Grade III toxicity per the DAIDS Adverse Event Tables will have medication held, and only restarted after a full clinical assessment, including consultation of the study clinicians with the principal investigator. Participants with Grade IV or recurrent Grade III toxicities will have medication discontinued, and referred to primary care for follow up.

## 7.0 Adherence Intervention

**7.1 Nurse-administered adherence and sexual risk CBT.** Intervention participants will undergo a single session CBT-based intervention at visit 2: enrollment (guide attached). The intervention will involve a series of cognitive-behavioral and problem-solving steps. Including the following sections:

1. Psychosocial assessment (10 minutes)
2. PrEP psychoeducation (10 minutes)
3. Brief motivational interviewing (5-10 minutes)
4. Making a plan for adherence/forgetting (5 minutes)
5. Barriers to adherence (5-10 minutes)
6. Closing

This adherence intervention is designed to first get to know the participant through a conversation about general information about PrEP and the rationale for the counseling including:

- *Daily routine.* This will include a general discussion of the participant's sexual behavior, sexual history, and general patterns regarding unsafe sex.
- *Educational information about PrEP, coping with side effects*. The counselor will go over a "fact sheet" regarding PrEP and the rationale behind adherence to PrEP. This will be basic educational information about PrEP adherence and will serve as a basis for motivational interviewing and problem solving. It will also include a discussion about taking PrEP daily versus intermittently. Additionally, tips for coping with side effects and information about their expected course of medication will be discussed.

We will then turn to motivational interviewing about staying PrEP adherent. Accordingly, the nurse interventionist will ask about PrEP motivations, as well as complete a pros and cons exercise about PrEP adherence. Following motivational interviewing guidelines, the nurse will ask about the advantages and disadvantages of both "not adhering" as well as adhering to PrEP. The interventionist will then ask the participant to rate how motivated they are to be adherent to PrEP and will subsequently have a discussion about why the participant made the rating, and a discussion about what it would take for them to be even more motivated. Again, this will be a basis for the problem-solving steps to come, and the

interventionist will be particularly sensitive to issues regarding social capital or social roles. This step will address the issue of taking medication for preventative as opposed to treatment purposes, which may play a role in PrEP adherence for men in the study.

Next, the conversation changes to focus on making a plan for adherence/forgetting. The counselor will work with the patient to establish a daily dosing time based on the patient's preferences (keeping in mind the relationship between dosing time & side effect management), and when it can be linked to a daily-occurring behavior.

The counselor will then focus on barriers to PrEP adherence and problem solving. They will review a list of potential barriers to PrEP adherence. For each issue, following principles of CBT problem-solving, the counselor will assess what potential problems could emerge with each issue, and discuss whether the participant has a current plan and backup plan for each.

The following preliminary list of topics will be addressed, although the relative emphasis on the different topic areas will be adjusted accordingly:

- **Daily schedule and weekend schedule**. This discussion will involve reviewing with the participant the times when PrEP can be most reliably taken, and will include a discussion, again, of the timing of PrEP in relation to potential sexual risk episodes.
- **Substance use**. This will involve learning about the participant's current substance use patterns and how that will interact with taking PrEP. As needed, additional referrals will be made for detoxification or other substance abuse services. Potentially, motivational interviewing will be used regarding assessing the participant's readiness to use specific services.
- **Meeting sexual partners and pill taking**. This will involve a discussion of how the participant meets sexual partners in general, and how to continue daily PrEP use within the context of sexual episodes.
- **Reminder strategies**. This will involve having a reminder strategy for PrEP, such as programming a reminder on a cell phone alarm, which will be based on the preference of the participant.
- **Need to take PrEP even if not currently sexually active**. One potential problem may occur if participants decide that they are not going to be sexually active and thus do not need PrEP, but then have episodic risky sex during a period when they have discontinued PrEP or are non-adherent. Given that data demonstrating the efficacy of intermittent PrEP are unlikely to emerge for several years, in the current study, we will work with participants to make a plan for using PrEP on a daily basis using strategies such as motivational interviewing and planning for unforeseen sexual experiences.
- **Generation of a list of potential barriers, and problem solving to overcome each barrier.** The interventionist will query the participant for additional potential barriers to PrEP. Similar to steps above, a plan and backup plan will be generated for each.

Finally, the counselor will: summarize the content of the session; review the adherence plan(s); review back-up plan(s); and review the plan should side effects emerge. The session will end with time for the participant to ask any further questions.

## 8.0 Data Sources

### 8.1 Epi-PrEP Trial

#### 8.1.1 Adherence

Adherence will be measured both by self-report and from biological assays.

#### 8.1.2 Behavioral assessments

| TABLE 3: Proposed Constructs, Domains, and Scales of Clinical Visit and Surveys for Implementation Pilot | | |
|---|---|---|
| **Construct** | **Study Visit** | **Description** |

| | | |
|---|---|---|
| **SURVEYS** | | |
| Demographics | Baseline | Data to characterize the sample (e.g. ethnicity, age, sexual orientation) |
| Implementation | Final | Extent to which part. received and satisfaction with key study elements |
| **Theory of Planned Behavior Variables** | | |
| PrEP Knowledge & Perceptions | Baseline, 3M, final | Knowledge of PrEP, how it works, how to take it, community perceptions |
| PrEP Uptake Barriers | Baseline, 3M, Final | Willingness (e.g. stigma of HIV medication, slut stigma), Access (e.g. availability, cost, not out to MD, unwilling/unknowledgeable MD) |
| PrEP uptake | Baseline, post-trip | Baseline = perceptions about using PrEP, Post-Trip = experience with PrEP |
| PrEP Intentions | Baseline, post-trip,3M, final | Bridge to Successive and/or Longer Term PrEP, perceptions of future use |
| **Syndemics Variables** | | |
| Psychosocial | Baseline | Syndemics and resiliency production, planned behavior and other psychosocial measures |
| Sexual Risk Behaviors | Baseline, post-trip | Freq. of sex and URAI/UIAI: substance use during UAI: Sexual Partners: No. of partners by partner type (main, casual, trading) & perceived HIV status. Serosorting. Condom use and self-efficacy scale (CUSES). Past 6 mos/on vacation. |
| Substance Use | Baseline, post-trip, | Type, frequency, and self-perceived problem use. Type and frequency of substance and alcohol use. Past 6 months and on vacation. |
| **Dependent Variable** | | |
| Adherence | Post-trip | Self-reported number of missed doses. |

### 8.1.3 Clinical symptoms

Clinical symptoms will be systematically assessed in a structured medical history at every in-person study visit. Clinical side effects of FTC/TDF that have been reported are primarily gastrointestinal, including nausea, vomiting, and flatulence. The severity of clinical symptoms will be scored using the DAIDS Table for Grading the Severity of Adult and Pediatric AEs, Version 2.0, November, 2014 (DAIDS AE Grading Table which can be found at http://rsc.tech-res.com/safetyandpharmacovigilance/gradingtables.aspx).

### 8.1.4 HIV-1 Antibody Testing and STI Testing

Participants will be tested for HIV using a 4th generation HIV-1 ELISA test at Visits 1, 3, and 4. Frequent HIV testing is an important part of safety monitoring because the medications prescribed for PrEP would not be sufficient compared to the usual three-drug regimens prescribed for treatment, and the potential for medication resistance could emerge.

### 8.1.7 Creatinine

Blood for creatinine clearance will be drawn at major study visits (visit 1, 3, and 4) to determine eligibility and monitor for safety.

### 8.1.8 Hepatitis testing and HBV management

All participants will undergo testing for HBV virus (HBV) at the screening visit. This will include tests for HBV surface antigen (HBsAg). Those who are hepatitis B seronegative will receive referral to be vaccinated as indicated. Participants with chronic hepatitis B (HBsAg positive) will be excluded from the study.

### 8.1.9 Study agent drug level assay

To better understand patterns of pill taking, PMBC samples will be collected at visit 3 for assays for intracellular levels of tenofovir. PBMC will be processed and stored off site and will be batch shipped to Hopkins lab for analysis. Blood serum samples will also be collected at visit 3 and frozen. These frozen serum samples will be stored for consideration for other drug level detection assays in the future.

These samples will not be analyzed until all active study participants have concluded visit 3.

## 8.2 Qualitative Interviews

Domains to be included in the qualitative interviews are outlined below. The full interview protocol is attached.

**TABLE 4: Qualitative Interviews: Proposed Constructs and Sample Questions**

| Construct | Description | Example Questions |
|---|---|---|
| PrEP attitudes | Pre-post individual attitudes and community norms about PrEP and Epi-PrEP | In what ways has your view of PrEP changed or remained the same? How does Epi-PrEP impact your overall opinion of PrEP? What do your friends think of PrEP? What will you tell them about your experience? |
| PrEP uptake | Epi-PrEP experience and pre-post barriers and facilitators to uptake (e.g. stigma, vacation activities, only long term option) | What were your attitudes to using PrEP/Epi-PrEP before you enrolled? What were the attitudes about using PrEP/Epi-PrEP among your friends? What are some of the barriers to deciding to use PrEP (probe: only long term option, HIV medication stigma, slut stigma, vacation activities)? How have your attitudes changed since using Epi-PrEP? What would increase the likelihood that you – or your friends – would be more willing to use PrEP? |
| Adherence | Barriers and facilitators to adherence, explore any inconsistencies between self-report and biomarkers | What made it easy or difficult to take the pill everyday (probe: familiarity with daily medications, context)? How was it different taking the medication before your trip, during, after? What did/would have helped you maintain better adherence (probe: what kinds of support, technology?). Your perceived adherence was different than what we found in your blood, can you tell me more about what you self-reported (probe: real perception, wanted to look good)? |
| Episodic Risk Behavior | Behaviors at home and on vacation (e.g. substance use, partner selection, condom use, serosorting) impact of Epi-PrEP) | Tell me about your vacation (probe: where, with whom, activities). More specifically now, lets talk about sex, alcohol/drugs, and HIV risk (probe: partners, activities, condoms). How was sex different on vacation vs. how it usually is at home (probe: people, places, activities)? How did being on Epi-PrEP influence your behaviors? How did your behaviors influence your Epi-PrEP adherence? |
| Future PrEP intention | Bridge to successive and/or longer term PrEP, other episodic risk periods | How do you imagine using PrEP in the future? In what contexts would you/would you not? Other than vacations, tell me about other episodic risk periods that you or your friends have experienced where Epi-PrEP may have been an appropriate HIV prevention tool. |
| Intervention design | Perception/satisfaction with current key study elements. Thoughts on intervention design, components, dissemination. | Thinking back to what you said about adherence, what thoughts do you have on designing an Epi-PrEP adherence intervention (probe: components, format, length, think about guys who may get this from their PCP – what would they need to know)? |

### 8.3 Audio Recordings

All counseling and qualitative interview sessions will be audio-recorded and may be reviewed by study staff, such as, therapists who assist with the development of the intervention, or therapists who are learning to deliver the interventions. This is to help insure that the interventions are designed well and improved upon as needed, and to insure that the each participant receives the same level of care. Recordings may also be transcribed onto paper and reviewed to look at potential themes or concerns among participants, further helping to shape future interventions. Names mentioned on the tape will be removed prior to analysis. Recordings will be identified by a study identification number only, and will be stored at The Fenway Institute in a secure, locked file cabinet and/or a password-protected folder on an electronic server. Recordings will be retained for seven years and then destroyed. Participants may elect not to have their sessions audio-recorded and still participate in the study. Additionally, they may ask to turn off the recorder at any point during the sessions.

## 9 Biostatistical Analysis

### 9.1 Overview

The primary analysis will be an assessment of feasibility as measured by self-reported and biological markers of adherence. While biomarkers will give a more accurate measure, the self-reported data will provide insight on participant perception of adherence. Inconsistencies will be followed up on during the qualitative interviews. Primary analysis will again begin with describing the characteristics of the men in the sample. The appropriate parametric or nonparametric test will then be used to compare groups. To the extent possible logistic regression will be used to look at predictors of adherence including the impact of psychosocial burden (e.g. substance use, depression) on being able to remain adherent. While the limited sample size will limit our ability to determine significant effect sizes, it will allow for exploratory analysis of trends to explore in more depth in the qualitative interviews.

### 9.2 Adherence outcomes

As determined from biomarkers, adherence will be defined either a dichotomously including: Determined protective drug level (previous studies determined this to be 90% adherence) during episodic period or determined non-protective drug level). Or, categorically as follows: 1) Good adherence: detection of normal drug levels, indicating protective level of drug taken in the prior week. 2) Poor adherence: detection of below normal tenofivir diphosphate (TFV-DP) in PMBC. 3) No adherence: no detection of drug, indicating no drug taken in the prior week.

### 9.3 Qualitative Interviews

Transcripts and notes will be analyzed using NVivo (v.11) to explore preexisting based on the theoretical contexts from which the interview guides will be developed and emergent themes. Content areas that we propose to address include: 1) general thoughts and feelings about PrEP and Epi-PrEP (before/after use); 2) an in-depth exploration of the Epi-PrEP; 3) adherence barriers/facilitators; 4) risk behaviors related to vacation and PrEP; 5) future PrEP intentions; 5) thoughts on intervention design/components. Once the interviews are transcribed, we will use two strategies, contextualizing and categorizing, to analyze the data [69-71]. First, the interviews will be summarized in a “digest” that identifies the major themes of the interview. Next, we will conduct coding, a categorizing strategy that facilitates comparisons within and between analytic categories that describe the data, in three steps. First, based on the summaries and recordings read and listened to by Stall (PI) and Egan (PD) will compose a list of analytic areas (code list). Second, Stall and Egan will reread the summaries and listen to the recordings and identify chunks of text to be given a descriptive label (either a label from the closed code list or an original one). Where necessary, summaries will be expanded to include data related to new codes; expansion of summaries may involve selective verbatim transcription of additional key segments of interviews. Next, the open-coded data will be organized under and integrated into the closed code list. Third, the data under the codes of particular interest will be re-read and recoded into sub-categories in order to refine the analytic categories [70]. Based on these results, we will develop a number of items, not already reflected in our current battery of measures. A minimum of 5 transcripts will be coded by 2 coders and compared for consistency. Results will be discussed with the research team and community volunteers to triangulate and validate the findings.

### 9.5 Sample Size and Power.

The primary focus of Aim 2 is the feasibility of providing short-term fixed interval episodic PrEP (Epi-PrEP) as measured by adherence. With the small sample size, power is limited. To find statistical significance, the effect sizes would need to be large. As such, we will focus on descriptive characteristics of different adherence groups and predictive trends, rather than significant effect sizes, which will be explored in greater depth in the qualitative interviews.

While there is no way to determine the necessary sample size for qualitative analysis, we feel that with N=20 (40% of pilot sample) we will be able to reach saturation on the key questions. As is the power of qualitative work, we also believe that important findings can be gained from the insight and/or disagreement of a small number of men.

## 10 Risks and Discomforts

### 10.1 Complications of Surgical and Non-surgical Procedures, etc.

**Not taking the study drug as prescribed.** Because the only FDA approved indication for the use of TDF/FTC as PrEP is by oral daily administration, participants will be instructed to take the study drug daily. However, it is unclear how suboptimal adherence will affect the effectiveness of the drug. Participants will be told that in the iPrEx study, less adherent participants had a greater risk of becoming infected.

**Mistakenly believing that the study drug may confer complete protection against HIV/STI**: As a result, participants could increase their sexual risk behaviors while in the study.

### 10.2 Drug Side-effects and Toxicities

As a result of taking the FTC/TDF regimen, some of the participants could experience transient nausea (which may last a few weeks), loss of appetite, renal dysfunction (which is almost always reversible when the product is stopped), accelerated bone loss after long term use, or a flare up of chronic hepatitis B infection when medication is suddenly discontinued. Laboratory monitoring and symptom-directed physical exams will detect major adverse events. Drug will be held for drug related Grade II or any new Grade III or IV events, and referral will be made to PCP for ongoing monitoring.

### 10.3 Device Complications/Malfunctions

There are no biomedical devices used.

Participants will be asked to use either their own or a provided computer to answer surveys. Reminders of scheduled visits will be sent both via phone and/or email.

### 10.4 Psychosocial (non-medical) Risks

The interviews and assessments will involve discussions on personal matters, such as sexual behavior, and talking about these matters may make participants feel uncomfortable, embarrassed, upset, tired, or anxious. Furthermore, there is a risk of violation of confidentiality. Participants who are enrolled in the study will be evaluated for level of sexual risk. Those enrolled will be determined to be at higher risk for acquisition of HIV (i.e., have engaged in condomless sex anal intercourse receptive or insertive in the three months prior to enrollment). There is a potential that enrolled subjects will be stigmatized if they reveal their involvement with the study or in some other way become associated with the study (e.g., social harm).

Participating in a counseling study for adherence can be difficult, because it may involve discussing personal matters. Another focus of the study is sexual risk-taking, which may be a difficult or uncomfortable topic at times. It is possible that participants will feel embarrassed or uncomfortable, particularly while discussing issues of a personal or sexual nature. In addition, a participant may become worried or uncomfortable from thinking about their non-adherent or sexual behaviors, and it is possible that participants may find some of the questions asked in the risk assessment to be emotionally upsetting. Likewise, the behavioral intervention may involve discussion of other emotionally upsetting topics. However, the risk to the participant is no greater than other standard counseling relationships. Participants are free to refuse to answer any question and may terminate participation in the study at any time. All information disclosed to the researcher will remain confidential if the participant chooses not to complete the study. Moreover, the participant can ask study staff to provide him with referrals to counselors or other means of support. Participants will have access to a licensed clinical psychologist and other Masters-level counselors who can help them deal with any feelings and/or questions they have which arise.

With their consent and a signed medical release, patients will have a letter sent to their primary care physician discussing their involvement in the study. The letter will state that involvement does not preclude any regular HIV risk reduction strategies they may have been working on. In our previous studies, sending this letter to providers has not adversely affected study outcomes; however, whenever participant information is shared there is a risk of loss of confidentiality.

As in any study, there is always risk of an inadvertent breach of confidentiality. Fenway and Pitt have been involved with numerous local, national, and international studies of persons with and without HIV and have considerable experience implementing measures to protect confidentiality. Some of these steps include signed confidentiality agreements, in-service trainings on confidentiality, and the assignment of study ID numbers. Staff at Fenway and Pitt who conduct participant recruitment, screening, enrollment, HIV testing, and assessments will have been trained in ethical human subjects research and screening and interviewing techniques to minimize participant risk as much as possible.

### 10.5 Radiation Risks (statement provided by Radiation Safety Committee)
Not applicable.

## 11 POTENTIAL BENEFITS

### 11.1 Potential Benefits to Participating Individuals
All participants will receive the study drug, which, if taken as prescribed, has been shown to reduce the risk of acquiring HIV among high-risk MSM. In addition, some participants may have the opportunity to access expedient treatment and decreased morbidity due to early diagnosis and treatment of abnormalities in biological tests. Finally, participants may appreciate the opportunity to contribute to the body of knowledge in the field of PrEP research.

Previous interventions using behavioral skills enhancement for adherence that are individualized to participants' needs have shown success in helping patients increase their adherence to medication. All participants will be actively tracking their adherence to the study drug, sexual behavior, substance use, and mental health needs by completing major assessments at visits 1,3,4, and 5.

PrEP has been shown to decrease incident HIV infections, but adherence has been suboptimal, impeding the full benefit of the medication. This project is innovative because by combining an evidence-based behavioral intervention with the provision of PrEP in clinical settings, a combined biobehavioral intervention that targets adherence is likely to be an effective strategy to reduce new HIV infections among MSM, which can have public health implications insofar as it may help to curb new HIV infection rates among MSM. Thus, the anticipated benefits have been determined to outweigh the minimal risks involved with participation in this study.

### 11.2 Potential Benefits to Society
HIV is a serious, incurable disease that can be spread, among other behaviors, through condomless insertive and receptive anal sex. PrEP has been shown to reduce the risk of HIV acquisition among high-risk MSM. However, low rates of adherence have hampered the protective effects of the medication. Further understanding the reasons behind low adherence rates for PrEP among high-risk MSM and addressing them in a tailored intervention may positively impact the rates of PrEP adherence and ultimately reduce the number of new HIV infections.

## 12 Quality Assurance

### 12.1 Overview of study design
Up to 50 participants in total will be enrolled in the Epi-PrEP trial and offered PrEP for the duration of their upcoming vacation. All participants will complete an informed consent process before entry into the study. This will include completing the informed consent form and reviewing all study procedures verbally with the investigator or designee. During future study visits, participants will be asked about any further questions or concerns about informed consent. An administrative record of any informed consent issues that occur after the initial informed consent procedure will be maintained, and the PI or designee will review all informed consents within one week of their completion. Participants are provided compensation for all scheduled in-office visits.

Because the use of TDF/FTC as PrEP has been FDA approved since July 2012, and subsequent studies have monitored patients for long periods of time, we do not feel a data safety and monitoring board necessary for this project. As outlined in this protocol, we will follow standard of care in prescribing PrEP and monitoring safety.

### 12.2 Data monitoring
Data collection will occur in the form of: (1) diagnostic and clinical assessments, (2) self-report assessments administered by computer, and 3) biological tests. A quality management plan will be developed to specify daily quality control and monthly quality assurance measures. This will also ensure

the usability of the data. The principal investigators on the project (Drs. Mayer and Stall), working closely with the other investigators, will oversee all data management and analysis issues. A quality management plan will be developed to specify daily quality control and monthly quality assurance measures. The Fenway Health and University of Pittsburgh IRBs will review the data-monitoring plan along with the full study protocol, which will be reviewed at least annually by the IRBs. Study progress, including accrual, attrition and data acquisition, will be monitored regularly throughout the course of the study. Case report form (CRF) completion will specifically be reviewed, especially in the initial months of study implementation. Every effort will be made to minimize attrition, and participants who miss visits will be contacted using primary and secondary contact information collected at screening and confirmed at each follow-up visit.

### 12.3 Project organization

To ensure consistency in study operations, the investigative team will have weekly team meetings to discuss and review study policies and procedures. During these contacts, they will address issues related to study recruitment, interventions, outcomes, measurement, retention and attrition, data management and quality control, and data analysis. There will be a study coordinator at Fenway Health and University of Pittsburgh that will supervise the project staff. This individual will also participate in the weekly team meetings and monthly protocol team meetings with both study sites.

### 12.4 Training of study interventionists

Nurse-interventionists will undergo study-specific training. The training will be led by a certified clinical psychologist, who has considerable experience in the delivery of behavioral adherence interventions. The intervention will be manualized and the nurse-interventionists will receive intensive training in the correct dissemination of the intervention content.

### 12.5 Data analysis

For the analyses, first, all forms will be checked for any missing data following interviews and prior to data entry. Attrition effects will be evaluated by testing whether systematic differences exist between participants who complete the research versus those who drop out, as well as between the intervention and comparison conditions. Multiple imputation techniques will be utilized to protect against the bias that can occur with missing data. We will initially inspect distributions for outliers and deviations from normality and will perform the necessary modifications to adjust for these issues.

## 13. Safety and Monitoring

Data and safety Monitoring Plan: The conduct of this study and the protection of the enrolled subjects are the responsibility of the principal investigator (PI). Accrual, confidentiality, subject complaints, subject withdrawals, adverse events, and safety laboratories will be reviewed on an ongoing basis by the study nurse and by the PI and co-investigators (Co-Is) at least weekly. All local serious, expected adverse events; unexpected adverse events of moderate or greater intensity; or > grade 2 laboratory abnormalities occurring during the study will be brought to the immediate attention of the investigators and to the IRB. The PI will be responsible for reporting aggregate data and risk/benefit summaries to the IRB at the time of annual renewal unless the information contained in these reports changes the benefit-to-risk ratio of study participation as defined in the currently approved research protocol and consent form, in which case a modification will be immediately submitted to the IRB. During monthly full protocol team calls aggregate AE will be reviewed by the respective site safety officers (Drs. Ho and Mayer).Concerning trends in AE will be reported to the IRB.

### 13.1 Definition of an Adverse Event and Serious Adverse Events:

An adverse event (AE) is defined as any untoward medical occurrence in a clinical research participant who has been administered an investigational product, and that does not necessarily have a causal relationship with the investigational product. An AE can, therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. All grades of AEs must be recorded in the participant record for all study participants throughout study participation. Study participants

will be provided instructions for contacting the study site to report any untoward medical occurrences they may experience, except for possible life-threatening events, for which they will be instructed to seek immediate emergency care.

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose:

1) Results in death
2) Is life threatening (i.e., the subject was, in the opinion of the Investigator, at immediate risk of death from the event as it occurred)
3) Requires or prolongs inpatient hospitalization or prolongs hospitalization[1].
4) Results in persistent or significant disability/incapacity (i.e., the event causes a substantial disruption of a person's ability to conduct normal life functions)
5) Results in a congenital anomaly/birth defect
6) Is an important medical event that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or require intervention to avoid outcomes listed above.

Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Note: Overdose and cancer are classified as Serious for data collection purposes. HIV-1 infection occurring during the study will not be considered as an SAE, but will be reported to sponsor within 24 hours of diagnosis.

The following types of hospitalizations do not meet the SAE definition:

- Any admission unrelated to an AE (administrative or social admission for temporary shelter placement).
- Protocol specified admission.
- Admission for a diagnosis or therapy of a pre-existing condition that has not increased in severity or frequency.

### 13.2 Grading of Adverse Events

Local and systemic signs and symptoms are assessed and graded based on *The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events* (DAIDS AE Grading Table), Version 2.0, November, 2014 (available at http://rsc.tech-res.com/safetyandpharmacovigilance/gradingtables.aspx), except that unintentional weight loss of less than 10% in body weight from baseline is not required to be reported as an AE.

### 13.3 Assessment of Relationship to Study Agent

The relationship of study drug to AEs will be determined by the primary investigator or designee (M.D., N.P., P.A.) and will be based on the following definitions:

- **Not Related:** The AE is not related if exposure to study drugs has not occurred, OR the occurrence of the AE is not reasonably related in time, OR the AE is considered unlikely to be related to use of the study drugs.
- **Related:** The AE is possibly, probably or absolutely related to the study drug.

The study agents that must be considered in determining relationships of AEs are emtricitabine and tenofovir disoproxil fumarate.

### 13.4 AE and SAE follow-up and reporting:

Each study site will be responsible for the management of safety data, reporting of safety information and any associated regulatory reporting obligations in compliance with all applicable laws, rules and regulations.

This protocol will record all adverse events on a cumulatively AE log from the period of study drug dispensation till participant termination from the study. All AEs will be followed until resolution, stabilization or participant termination from study.

SAE collection begins once patient signs the informed consent and ends 30 days after discontinuation of dosing or completion of the patient's participation in the Project if the last scheduled visit occurs at a later time.

### 13.5 Gilead SAE Reporting:

All SAEs including any deaths, product complaints with an associated SAE or reports of medication error or overdose regardless of an associated SAE occurring during the study will be reported to Gilead Drug Safety and Public Health (DSPH) within 15 calendar days of site awareness and in accordance with applicable laws, rules, regulations and guidance. All reports to Gilead will be sent to the attention of:

Gilead Sciences, Inc.
Drug Safety & Public Health
333 Lakeside Dr. Foster City, CA 94404
Fax: 650-522-5477 Tel: 650.522.5114 E-mail: Safety_FC@gilead.com

Upon Gilead's request the investigator will provide any additional information related to any SAEs including any deaths, product complaints with an associated SAE or reports of pregnancy, medication error or overdose regardless of an associated SAE occurring during the study.

### 13.6 Discontinuation of study agent due to an AE

An MD investigator has the authority to stop study agent for any participant due to clinical or laboratory AEs or at any time if it their opinion it would be in the best interest of the participant. Study product will be discontinued for participants with a Grade 3 or higher AE deemed related to study agent. Participants withdrawn from taking study product due to an AE (or for other reasons), will be followed by the investigator at least until a final outcome is determined (i.e., AE resolves or sequelae are considered permanent) and reported to BMS, Abbott and Gilead, and if possible until the study is completed.

### 13.7 Review of participant safety data

Routine participant safety review occurs at the start of enrollment and then throughout the study. The investigator is responsible for providing periodic updates on safety information to the Fenway IRB and BMS.

## 14 Participant Confidentiality

In order to strictly protect participant confidentiality all study data will be identified by a coded number not participant name. The coded information will be kept in a locked file and separate from any documents that include participant's name. Number coded information may become part of an electronic database, which is password-protected and only accessible to study staff. A list, which links participant code number and name, will be stored separately from both participant personally identifiable information and participant number coded information.

**Participant name will not be publicly disclosed at any time**, and the records will be strictly maintained according to current legal requirements. This applies to any written records, visit documentation, or interviews.

Participant records or any part thereof can only be legally obtained with written permission of the participant specifying what exact information is to be released or if subpoenaed by law. However, the

investigators will report cases of child or elder abuse or neglect to the authorities. Furthermore, if participant indicates that they are in imminent danger of hurting themselves or others, the investigators will need to reveal this information in order to protect the participant or that person.

The University of Pittsburgh, Fenway Community Health and affiliated hospitals, researchers, health care providers, and physician network will make all reasonable efforts to protect the privacy of information that identifies the participant and relates to participant past, present, and future physical and mental health conditions. This is referred to as "protected health information" throughout the rest of this section.

Health Information that does not contain any identifying information and cannot be connected to the participant is referred to as "study information".

Who may study information (which does **NOT** contain identifying information) be shared with?

- The Fenway Community Health IRB
- Fenway Community Health Research Staff
- University of Pittsburgh IRB
- University of Pittsburgh Research Staff
- Office of Human Research Protection
- National Institute of Mental Health
- National Institutes of Health

This study information (**which does not contain participant identity**) may also be published.

## 15 Regulatory Authority Approval:

This study will be conducted in accordance with Good Clinical Practice (GCP) and all applicable regulations, including the Declaration of Helsinki, June 1964, as modified by the 48th World Medical Association, Republic of South Africa, October 1996.

## 16 Institutional Review Board Approval

The Investigator will ensure that this protocol is reviewed and approved by the Fenway Community Health and University of Pittsburgh IRBs.

The Fenway and Pittsburgh IRBs will also review and approve the informed consent form (ICF) and any other written information provided to the subject prior to any enrollment of subjects, and any advertisement or public announcement that will be used for subject recruitment. The Investigator or his designee will forward to Gilead copies of the IRB approval and the approved informed consent materials, prior to the start of the study.

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