1. PROTOCOL TITLE: Packaging PrEP to Prevent HIV Transmission among Women who Inject Drugs (WWID)

2. IRB REVIEW HISTORY: Approved 4/25/17; Modification 7 approved 07/06/2018

3. OBJECTIVES/AIMS: This study will address the following objectives or specific aims:

Aim 1: To describe WWID's engagement in the PrEP care continuum. Using data from baseline and exit (N=200), we will quantify participant engagement including: (1) attending initial clinical appointment; (2) enrolling in health insurance or medication assistance programs for uninsured participants; (3) accepting a PrEP prescription; (4) filling the PrEP prescription; (5) adhering to PrEP, and (6) returning for follow-up care. These activities represent critical moments when women could disengage or need additional support to remain in care.

Aim 2: To assess the impact of predisposing, enabling, and need-related factors on WWID's engagement in the PrEP care continuum. We will test for associations between Behavioral Model for Vulnerable Populations (BMVP) factors and stage of engagement.

Aim 3: To explore how and why model factors are associated with WWID's decisions and ability to engage in PrEP care. A subset of WWID representing those who never initiated PrEP (n=15), those who initiate but disengage (n=15), and those who adhere/return for 3 months (n=15) will complete an in-depth qualitative interview that explores individual and structural facilitators and barriers that support or hinder engagement. Interviews will draw on quantitative findings and provide contextual accounts of how factors operate, potential modification of service delivery and targets for behavioral interventions to support engagement.

Aim 4. To describe sexual behavior and incident STI among WWID. Using data from baseline, follow-up and exit (N=200), we will describe sexual risk behavior and acquisition of incident infections of syphilis, gonorrhea, chlamydia, and trichomoniasis among WWID. We will test for differences in risk/STI between those who initiated PrEP and those who did not.

4. BACKGROUND: Pre-exposure prophylaxis (PrEP) is a promising bio-medical HIV prevention strategy that involves the use of antiretroviral medications by HIV negative individuals to reduce their risk of acquiring HIV. In 2013, the Centers for Disease Control and Prevention (CDC) recommended emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) as PrEP for people who inject drugs (PWID).[1] However, research and programs to bring PrEP to scale have yet to focus on this group. Therefore, little knowledge exists to help address PrEP implementation challenges among PWID. Research is necessary to identify strategies that successfully promote engagement in PrEP care among at-risk PWID. The proposed study will address these gaps.

Compared to men, women who inject drugs (WWID) are less likely to control drug preparation practices and more likely to share syringes, have a sex partner who also injects drugs, and to be injected by their partners.[2-5] They are also more likely to report risky sexual behavior. In our recent study 1:4 WWID tested positive for chlamydia or gonnorhea.[6] This is 4-fold the rate for men and likely corresponds to the statistically greater proportion of women reporting recent transactional sex, higher numbers of sex partners, and inconsistent condom use.[6] Research indicates that STI can be considered a biologic marker for imminent HIV infection.[7,8] These data suggest no single intervention strategy will eliminate HIV among WWID because they are at an intersection of three types of risks – those associated with drug use, those associated with high-risk sexual behavior, and those associated with belonging to high-prevalence networks. It also suggests the WWID should be prioritized for initial strategies to implement PrEP for PWID as a complement to existing interventions known to reduce HIV risk such as syringe exchange.

One concern regarding PrEP is that many WWID face a number of challenges to accessing medical care, including a lack of engagement in primary care, transiency, and opioid dependence.[9] Our research indicates they will face similar challenges to accessing PrEP.[10] Therefore, alternative care approaches based outside of traditional clinical settings are needed to increase the individual and public health benefits of PrEP. Syringe exchange programs (SEPs) are well integrated within this community and may be uniquely qualified to "seek, test, prevent and retain" WWID in PrEP services. Our rationale for this approach is that (1) SEPs may currently provide prescription medications and long-term monitoring for other conditions such as buprenorphine for opioid dependence, so PrEP is a natural extension of what is already being done with great success, (2) SEPs

are a viable access point for many HIV-uninfected WWID who would be considered eligible for PrEP under current clinical guidelines, and (3) PrEP interventions, delivered in settings already utilized by WWID, will increase uptake, adherence and retention in PrEP (hereafter called engagement in the PrEP care continuum).

5. INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria are:

1. Age of 18 years or older;
2. ability to speak and read in English;
3. engagement in high-risk behavior within 30 days including non-prescription injection drug use;
4. engagement in at least one of the following in the last 6 months: sex exchange, inconsistent condom use with partners who are HIV+, MSM, or IDU, bacterial STI, syringe sharing, or recent opioid agonist treatment;
5. HIV seronegative (documented with test results dated within 2 weeks)
6. not currently taking Truvada/PrEP;
7. able to understand informed consent documents; and
8. willing to provide informed consent.

Exclusion criteria are:

1. HIV seropositivity;
2. pregnancy, breastfeeding or intention to become pregnant within 3 months;
3. currently taking PrEP
4. previous participation in the study.

☐ *Adults unable to consent*
☐ *Individuals who are not yet adults (infants, children, teenagers)*
☐ *Pregnant women*
☐ *Prisoners*
☒ *Not Applicable*

6. STUDY-WIDE NUMBER OF PARTICIPANTS
N = 200

7. STUDY-WIDE RECRUITMENT METHODS
Recruitment materials that include study purpose, methods, and research team contact information (see study flyer) will be placed in public spaces at PPP, their outreach vans and within the harm reduction packets distributed via the secondary exchange (in which those accessing the SEP take harm reduction supplies to individuals in their social and sexual networks). To screen potential participants for eligibility we will meet with them face-to-face in a private space at PPP or speak to them by phone and complete a brief screening assessment (see Appendix 1 for Eligibility Screener). These recruitment and screening procedures will be similar to those used by Dr. Roth in other studies conducted at PPP.

Based on our pilot data and the characteristics of the target population served by PPP, we anticipate approximately 15% of women who are interested in participating will be ineligible based on their risk profile or HIV status. Thus, we anticipate screening approximately 250 women to reach our final sample of 200. While this may seem like a large N of a WWID, a very hidden population, our community partner Prevention Point Philadelphia (PPP) is the largest harm reduction agency in the mid-Atlantic. Through their main building and mobile outreach, PPP served approximately 5,700 unduplicated clients in 2015; approximately 20% were women and 10% were living with HIV. In 2015, PPP clients reported accessing supplies for an additional 48,000 PWID via the secondary exchange. Therefore, we anticipate few challenges engaging with 250 WWID in order to enroll our final sample.

8. STUDY TIMELINES

To achieve study objectives/aims, Dr. Roth will hold weekly research meetings with project staff, discuss the project on a monthly basis with co-investigators, and on a quarterly basis with consultants/collaborators and the CAB. The study timeline is: *0 to 2 months:* hire and train staff, assemble CAB and obtain IRB approval. *3 to 6 months:* pilot instruments; revise instruments based on pilot testing, initiate recruitment and data collection. *7 to 21 months:* continue enrollment and follow-up; begin analysis. *22 to 36 months:* prepare and clean data; continue analysis; present at scientific meetings; publish manuscripts; develop application for an intervention to overcome mechanisms for non-initiation or suboptimal adherence based on findings that will be evaluated in a R34/R01 controlled trial.

- The duration of an individual subject's participation in the study is approximately 7 months.
- The duration anticipated to enroll all study subjects is 21 months.
- The estimated date for the investigative team to complete preliminary analysis for this study is 24 months.
- The estimated duration for the majority of dissemination activities (publication, presentations, etc) is 36 months.

9. STUDY ENDPOINTS

Our novel structural intervention of pairing PrEP and SEP services represents a new approach for the delivery of effective biomedical HIV prevention strategies. To our knowledge, this strategy has not been previously tested. One endpoint is to determine the acceptability and feasibility of this approach. Further, we will identify the populations of WWID who need additional intervention to fully engage in PrEP and the best strategies for supporting engagement. Findings will inform a tailored intervention, delivered within the SEP, to increase engagement at each stage. While this study will be set in Philadelphia, one metropolitan area, we believe the innovative approach of packaging STI/PrEP services in a community-based SEP will be replicable in other cities. The reproducibility of this study's approach significantly increases this work's potential impact to improve outcomes among PWID in other cities and settings. Thus, the long term-impact of this project will be a reduction in HIV incidence among WWID which aligns with national HIV prevention priorities.

10. METHODS INVOLVED

This will be a mixed-methods observational study. We will recruit 200 PrEP-eligible WWID from SEPs operating in Philadelphia and follow them over three months. At baseline (T0), participants will complete a survey based on our conceptual framework, undergo STI testing and relevant testing for PrEP medical monitoring, receive a brief educational intervention, undergo a clinical consultation, be offered PrEP, and scheduled for a STI results appointment. At follow-up approximately 7 days later (T1), we will provide STI results/treatment and participants will complete a brief survey. A subset of those declining the PrEP prescription will participate in a qualitative interview exploring this decision (n=15). At follow-up (T2) approximately 90 days after T1, participants will undergo STI testing complete a semi-structured interview based on our conceptual framework to explore individual and structural factors that support or hinder engagement in the PrEP continuum and those who initiated PrEP will receive relevant tests for medical monitoring. At follow-up approximately 7 days later, we will provide STI results/treatment. A subset those who initiate but disengage (n=15) and those who remain engaged for 3 months (n=15) will complete an in-depth qualitative interview exploring how and why individual and structural factors hinder or support engagement. At exit (T3) approximately 6 months after T1, participants will undergo STI testing and complete a semi-structured interview based on our conceptual framework to explore individual and structural factors that support or hinder engagement in the PrEP continuum. Those who initiated PrEP will receive relevant tests for medical monitoring. At follow-up approximately 7 days later, we will provide STI results/treatment.

10.a Study Setting

Our study will take place in PPP's main building located in the Kensington neighborhood of Philadelphia at 2913 Kensington Ave, Philadelphia, PA 19134. We will embed PrEP services within PPP's existing clinical infrastructure that includes seven private patient rooms. As part of the informed consent and health authorization process, participants will agree to allow the study team to access their medical and case management records from PPP in order to obtain information relevant to the study, namely HIV and Hepatitis C test results and case management records regarding enrollment in health insurance (described in detail in 10.b Study Procedures).

10.b Study procedures

10.b.i Informed Consent
Prior to beginning the study, eligible participants will be given a consent form and asked to follow along while the interviewer reviews it with them. Included in the informed consent document are check boxes wherein the participant agrees to the study team accessing their PPP records. Staff will answer questions about the consent forms or research process. Before signing the consent, the interviewer will assess whether the individual comprehends the consent by asking 3 true/false questions such as "I will have the opportunity to be screened for sexually transmitted infections in my vagina, throat and rectum and if I test positive I will have access to free treatment at PPP." "Through this study, I will learn about a new medication to prevent HIV." "I can agree to participate and then change my mind at any time with no penalty.") If any of the responses to these questions are incorrect, the consent form will be re-reviewed with the individual. The individual will be given 3 chances to answer the questions correctly. After 3 failures, the individual will be considered to be unable to give voluntary, informed consent. Each participant will receive a copy of the consent form to keep for their records.

10.b.ii Baseline (T0) & Initial PrEP Visit
At T0 after providing informed consent, participants will be assigned a unique study ID number, and complete participant tracking forms and HIV test release of information (Appendix 6 and Appendix 11). Client names linked to ID number will be in a separate locked file cabinet and only the PI (and project manager) will have access to this file. Participants will undergo venipuncture to collect blood for syphilis (RPR) and hepatitis B serologies and creatinine testing utilizing PPP's staff and standard practice; participants with evidence of syphilis, active hepatitis B infection, or abnormal renal function will be referred for evaluation for treatment, and those with who are susceptible to hepatitis B will be referred for hepatitis B vaccination. Next, participants will self-obtain specimens (throat, urogenital, and rectal) for gonorrhea (GC), chlamydia (CT), trichomoniasis (TV; vaginal test only at baseline) screening as well as a urine sample for pregnancy testing. Self-collection instructions can be found in Appendix 10. Trained staff will provide verbal and written instructions regarding the self-sampling procedures and answer any questions related to this procedure. **This procedure is acceptable to participants, is of minimal discomfort, has minimal safety risks (sample collection is considered non-invasive from a regulatory perspective), and provides reliable specimens.** Women who test positive for pregnancy will be withdrawn from the study and referred to their primary care provider (PCP). If women do not have a PCP we will work with them to establish care. Participants will then compete a quantitative baseline assessment (QBA). The QBA will be scripted using Qualtrics software, pre-tested, and administered face-to-face on an iPad and will take approximately 60 minutes to administer. The QBA is available in Appendix 9. Finally, staff will conduct a brief educational intervention (~10 minutes) about PrEP. We will start the educational session with a video https://www.youtube.com/watch?v=ueKrjO6rAyE developed by Dr. Rivet Amico (co-investigator). The video includes PrEP-related information such as clinical indications for PrEP, a description of the medication and common side effects, need for adherence and ongoing clinical monitoring, how to pay for PrEP. We will also provide participants with PrEP educational materials tailored for WWID that are adapted from the CDC's PrEP information sheet (see Appendix 2).[11] We will then assess participant's insurance status and will help participants obtain health insurance coverage by working with PPP case manager to facilitate enrollment into Medicaid or prescription assistance from Gilead. Participants in need of health insurance will be asked to sign of release of information for PPP so that we verify if they were signed up for insurance (Appendix 11). Next, the clinical provider (CP) who will be either currently licensed medical doctor, nurse practitioner or physician's assistant, will meet with participants to discuss any of the patients' remaining questions or concerns about PrEP. She will obtain a medical history, provide counseling on PrEP, contraception and HIV risk-reduction as recommended by the CDC, and asses participant interest in PrEP. All participants will receive the PrEP Resource Guide (Appendix 12) which has information on the hours of operation for neighborhood pharmacies where they can fill their prescription, locations for local STI clinics and social service providers offering women-specific services, and some basic information on HIV transmission. Participants will receive $40 for this visit.

10.b.iii Follow-Up (T1): STI Results
At this visit, the CP will provide participants with test results. Those screening positive for RPR, CT or GC will receive or be referred for no-cost treatment. Finally, we will review participant contact information and schedule participants for their second follow-up appointment and participants will receive $20 for this visit.

At this visit, we will recruit a purposive sample of 15 WWID who declined the PrEP prescription. Recruitment will be done so that we elicit diverse reasons for refusal. Questions will focus on key domains from the BMVP such as how perceived HIV susceptibility and attitudes toward PrEP impacted this decision. A draft of the interview questions for those who decline a PrEP prescription is in Appendix 4. This subset of participants will receive $20 for completing the qualitative interview.

10.b.iv Provision of Prescriptions

Any insured participant who is interested in PrEP or birth control will be given 2 options for obtaining their prescriptions (should baseline tests indicate they are clinically eligible for PrEP per the CDC guidelines—Creatinine clearance ≥60mL/Min): 1) the study team will fax prescriptions to Philadelphia Pharmacy who will deliver the PrEP prescription to Prevention Point Philadelphia (Appendices 17, 18) or 2) a paper prescription that the participant will be given so that they may fill it at the pharmacy of their choice. Given the opioid crises in Philadelphia and its impact on study participants, we will also offer a prescription for Naloxone, a medication that rapidly reverses the effects of an opioid overdose which is safe, recommended for use in this population by the CDC, and has been in use in hospitals and ambulances since 1979. Participants will also have the option to receive refills for their prescriptions at PPP. Participants preferring the study team fax the prescription will complete the prescription authorization and release of information form (Appendix 17). Participants who prefer the paper prescription will complete the pharmacy release of information (Appendix 14).

10.b.v PrEP Check In: For only those who accepted a PrEP prescription If participants choose to take a prescription for PrEP, we will schedule them for a check in visit to assess tolerance and adherence for approximately two weeks after T1. The "check in" assessment is in Appendix 13. Participants will receive $5 for this visit.

10.b.vi Follow-Up Visit (T2)

T2 will occur approximately 3 months after T1. Participants will self-obtain specimens (throat, urogenital, and rectal) to monitor incident gonorrhea (GC) and chlamydia (CT). Participants will also provide urine and blood specimen to monitor PrEP adherence,[79-81] creatinine levels, syphilis, pregnancy, and HIV (provided by PPP per their standard of care). PrEP adherence, creatinine levels, and pregnancy testing will only be performed for women taking PrEP. Participants will complete a semi-structured interview to explore psycho-social factors associated with HIV/STI risk, and engagement across key transition points in the PrEP care continuum including (1) attending initial clinical appointment; (2) enrolling in health insurance or medication assistance programs for uninsured participants; (3) accepting a PrEP prescription; (4) filling the PrEP prescription; (5) adhering to PrEP using a validated three-item self-report measure for anti-retroviral therapy adherence in the last 30 days, modified for PrEP adherence;[12] (6) and returning for follow-up care. These activities represent critical moments when women could disengage or need additional support to remain in care. If participants disengage in care at any point in the PrEP continuum, we will ask about the factors motivating this decision. Then, we will assess the acceptability of receiving PrEP care at the SEP, intention to remain engaged in PrEP care, and the factors motivating them to do so (or drop out of care). A draft of the semi-structured interview is in Appendix 3. Participants will receive $25 for this visit. Any participant needing clinical follow-up after T2 will be scheduled with the CP outside of study hours. Women who test positive for pregnancy will not be eligible for follow-up PrEP care at PPP. They will be referred to their primary care provider (PCP). If women do not have a PCP we will work with them to establish care.

We will also recruit a purposive sample of WWID who initiate but disengage (n=15) and WWID who adhere/remain engaged in PrEP for 3 months (n=15) to participate in an in-depth qualitative interview. Recruitment will be done so that we elicit diversity in opinions, challenges, and successful strategies to engagement. Interviews will elicit previously unmeasured but critical factors impacting women's decisions and will also explore individual and structural facilitators and barriers that hinder or support engagement at each stage of the care continuum drawing from the BMVP. A preliminary draft of the in-depth interview is in Appendix 5. This subset of participants will receive $20 for participating in the qualitative interview.

10.b.vii T2 Follow Up For STI Results

At follow-up approximately 7 days later, we will provide STI results/treatment. Participants will receive $5 for this visit.

10.b.viii Follow-Up Visit (T3)

T3 will occur approximately 3 months after T2. Participants will self-obtain specimens (throat, urogenital, and rectal) to monitor incident gonorrhea (GC) and chlamydia (CT). Participants will also provide blood specimen to

monitor creatinine levels (if someone is taking PrEP only), syphilis and HIV (provided by PPP per their standard of care). Urine specimen will be collected to monitor pregnancy for women taking PrEP. They will also sign a release of information (Appendix 14) to allow us to contact the pharmacy where they report filling their PrEP prescription to verify fill dates. Participants will complete a semi-structured interview to explore psycho-social factors associated with HIV/STI risk and engagement across key transition points in the PrEP care continuum. If participants disengage in care at any point in the PrEP continuum, we will ask about the factors motivating this decision. Then, we will assess the acceptability of receiving PrEP care at the SEP, intention to remain engaged in PrEP care, and the factors motivating them to do so (or drop out of care). A draft of the semi-structured interview is in Appendix 15. Participants will receive $35 for this visit. Any participant needing clinical follow-up after T3 will be scheduled with the CP outside of study hours. Women who test positive for pregnancy will not be eligible for follow-up PrEP care at PPP. They will be referred to their primary care provider (PCP). If women do not have a PCP we will work with them to establish care.

We will also recruit a purposive sample of WWID who initiate but disengage (n=15) and WWID who adhere/remain engaged in PrEP for 6 months (n=15) to participate in an in-depth qualitative interview. Recruitment will be done so that we elicit diversity in opinions, challenges, and successful strategies to engagement. Interviews will elicit previously unmeasured but critical factors impacting women's decisions and will also explore individual and structural facilitators and barriers that hinder or support engagement at each stage of the care continuum drawing from the BMVP. A preliminary draft of the in-depth interview is in Appendix 5. This subset of participants will receive $20 for participating in the qualitative interview.

10.b.viv T3 Follow Up For STI Results

At follow-up approximately 7 days later, we will provide STI results/treatment. Participants will receive $5 for this visit.

10.d Continuity of Care for those who engage in PrEP

Following the T3 (last) visit we will offer participants who want to remain in PrEP, standard care using the same clinical staff and facilities for the duration of the study. At study conclusion, we will facilitate transfer of clinical care to an appropriate medical provider. We have developed a list of local PrEP providers who have expressed willingness to work with our population (see Appendix 7). Referral will include provision of the provider list and help with scheduling their first clinical appointment for those expressing this need.

10.e Retention

To decrease attrition, we will develop a tracking protocol to ensure multiple points of contact with participants. Using their preferred mode of contact, we will remind participants of study visits and follow up with those who "no show." For each "no show," we will follow up twice weekly for 3 weeks. Any participant failing to contact staff within 3 weeks will be considered lost to follow up. However, they will not be withdrawn from the study. Using these procedures, we anticipate >85% retention.

10.f Laboratory Tests

Philadelphia Department of Health will perform STI testing using the AC2 CT/GC assay on the Hologic Tigris platform, Hepatitis B testing will be performed on the Abbott Architect and creatinine testing will be performed on the Beckman Coulter DXC. Positive test results will be reported to disease control agencies per local regulations. This process is outlined in the informed consent. Philadelphia FIGHT will perform drug-level monitoring using a semi-quantitative liquid chromatography-tandem mass spectrometry urine assay with high sensitivity and specificity to monitor TFV. Specimens will be processed and confidential results returned within 7 days. Pregnancy tests will be performed by the CP using a rapid urine assay to detect human chorionic gonadotropin hormone.

10.e Procedures to lessen the probability or magnitude of risk

Free treatment for STI: Participants screening positive for STI will receive no cost treatment at their follow-up appointments T1, T2 and T3. Participants screening positive who fail to return for test results and appropriate treatment, will be referred to the Philadelphia Department of Health to arrange treatment. Participants will consent to PDH follow-up if they fail to obtain treatment from the study team during the informed consent process.

Pregnancy: We will provide patients with contraceptive counseling and prescriptions as in the current standard of care for women on PrEP per CDC PrEP clinical guidelines. Women who test positive for pregnancy will be

withdrawn from the study and referred to their primary care provider (PCP). If women do not have a PCP we will work with them to establish care.

Medication adverse effects: There is minimal risk of harms associated with the use of daily FTC/TDF as PrEP by HIV-uninfected individuals. Medication intolerance during clinical trials included nausea, vomiting, abdominal pain, and diarrhea. These effects occurred in a minority of PWID (<20%) participating in the Bangkok Tenofovir Trial and most participants reported symptoms had resolved by the 2nd month. Of these side effects, only nausea and vomiting were statistically higher among PWID on Tenofovir than those taking the placebo. Tenofovir has been linked to renal impairment when used for HIV treatment, and a meta-analysis of 3 PrEP efficacy studies found that use of TDF/FTC was associated with small but statistically significant decreases in renal function. However, increased creatinine was observed in only 3% of patients in the Bangkok Tenofovir study, and other studies have found that changes in renal function with use of PrEP are reversible upon discontinuation of TDF/FTC[13,14]. To monitor for potential medication-related renal toxicity, we will measure creatinine levels at T1 and T2 (which will be scheduled over 3 months) as is recommended in the current CDC PrEP clinical guidelines and is considered standard of care. We will also follow-up with participants accepting a PrEP prescription approximately 2 weeks after T1. During that check-in we will assess for medication intolerances, assess adherence, and provide adherence counseling. Any participant with intolerances (i.e. that do not resolve by 2 months after use of PrEP) or any abnormal renal function testing will be scheduled with the CP. Those with any persistent intolerances or abnormal renal function will be referred to their primary care provider (PCP). If women do not have a PCP we will work with them to establish care.

10.f Data Sources

☒Medical Record/Chart Review ☐Films/X-rays

☐Computer/Database ☐Hospital administrative/billing records

☐Quality Improvement Records

Other types of records please specify:

Surveys and interview data. All instruments are included as appendices.

Is data ONLY from the clinical department of the PI and sub-I's? ☐ Yes ☒ No

11. DATA AND SPECIMEN BANKING

Not applicable.

12. DATA MANAGEMENT

12a. Data analysis plan

Aim 1. Describe WWID's engagement in the PrEP care continuum among WWID. We will use summary statistics (frequency and percent with associated error terms) to describe participant engagement across key transition points in the care continuum including: (1) returning for STI results at T1; (2) enrolling in health insurance or medication assistance programs for uninsured participants between T0 and T2; (3) accepting a PrEP prescription; (4) filling the PrEP prescription or providing authorization for the PrEP prescription to be filled between T0 and T2; (5) adhering to PrEP between T1 and T3;[16] (6) and returning for follow-up care at T2 and T3. Descriptive analyses will also be used to characterize adherence in terms of perfect defined as a dose of TFV within 48 hours (>1000 ng/mL), low adherence (>10 to >100 ng/mL), and non-adherence as defined by last dose more than one week prior (<10 ng/mL).79-81 We will also compare concordance of self-reported adherence to urinalysis.

Aim 2. To assess the impact of predisposing, enabling, and need-related factors on WWID's engagement in the PrEP care continuum. We will test the association between BMVP factors and WWID's engagement at each stage outlined above using procedures that have been used previously to describe gaps in the PrEP care continuum for MSM.(9,14) Independent variables will represent each of the model's domains including: predisposing factors, enabling factors, and need (drawn from Table 1). In the case WWID do not populate each stage describe above we will collapse engagement into an ordered categorical variable similar to how we are approaching qualitative data. In this case, engagement would be treated as a 3-level variable: never initiated PrEP vs those who initiate but disengage vs those who remain engaged for 3 months. Inferential statistics will be used to identify associations between factors in the model and PrEP engagement. For

continuous variables, such as age or number of sex partners, we will provide medians with associated interquartile ranges and utilize independent samples t-tests or Mann-Whitney U tests to identify differences in medians between women who do or do engage at each stage. For categorical and binary variables, such as race/ethnicity or insured (yes/no), $\chi 2$ tests will be used to detect differences in factors that may be associated with PrEP engagement. Assessing the factors impacting engagement is critical for the design of intervention strategies, as different populations of WWID may need different cues to action or support in order to engage at each stage. These analyses will inform future study designs and sample size.

Aim 3. To explore how and why model factors are associated with WWID's decisions and ability to engage in PrEP care. One of the objectives of this study is to determine the relative importance of factors that are facilitators or barriers to PrEP engagement. This will be done using content analysis of qualitative data. To do this, we will explore the relative impact of predisposing, enabling, and need-related factors on PrEP continuum engagement. Interviews will draw on the quantitative findings and provide contextual accounts for how these factors impact decisions about and ability to engage in PrEP care. Data from WWID who never initiated PrEP, those who initiate but disengage, and those who adhere/engage for 3 and for 6 months will be analyzed separately and then compared/contrasted. To create a coding framework for analyzing interview data we will use an iterative process. First, a priori "structured codes" corresponding to the domains in the interview guide will be developed. Second, "emergent codes" that reflect unanticipated factors outside of our conceptual framework will be developed. Two analysts will code each transcript. Discrepancies in coding will be resolved by discussion until inter-rater reliability is >75%. Finally, we will triangulate data with quantitative assessments and member check findings with the CAB to increase the validity of the findings. Analyses will answer the following research questions (this list is not exhaustive): 1) What predisposing, enabling, and need-related factors influence women's decision to initiate (or decline) PrEP and how do they operate? 2) What contextual factors positively (and negatively) impact women's ability to adhere to PrEP? 3) Are there differences in the narratives told within the subpopulations of women (i.e., those with STI, those engaging in transactional sex, or by primary vs secondary exchange clients)? 4) What features of a structural or behavioral intervention could assuage barriers to care and how would they need to operate? 5) What factors are associated with risk compensatory behavior among WWID who initiate PrEP? Our team has experience with similarly structured qualitative data to understand barriers/facilitators and patient preferences for sexual health care and is well equipped to conduct these analysis.[17-19]

12b. Power analysis

Not applicable as this is an exploratory study we are not testing hypotheses because there are few data from which we can draw to estimate PrEP initiation among WWID (which highlights the gap in knowledge regarding this vulnerable population). However, we selected a target sample of 200 women based on the following data: estimating numbers from our pilot data collected from this population in which 86% of WWID expressed a willingness to use PrEP. We conservatively estimate that approximately 50% of those expressing willingness to initiate PrEP will do so. We also estimate15% attrition at each study visit (based on previous experience with this population). Thus, we expect to have a final sample of approximately 122 WWID with 61 WWID in the PrEP initiation group and 61 in the declined group.

12b. Steps to be taken to secure data

Surveys will be identified solely with a participant study ID number. Surveys will be completed in Qualtrics, an electronic survey platform available through Drexel One. In order to log into Qualtrics, users must provide a username and password. Further, the participants will complete surveys on a password protected laptop or tablet. Thus, these data are electronically secured. Access will be limited to only the study's PI and study staff. Client names linked to ID number will be in a separate locked file cabinet and only the PI and Research Coordinator will have access to this file.

Qualitative interviews will be identified using the same unique ID number that was assigned during the assessment. We will not collect participants' names or other identifying information. The unique ID that was assigned to the QBA survey we will link the qualitative interview information with the quantitative data for analyses.

The Qualitative Interviews will result in three pieces of information:

1. The digital audio recording file

2. A typed transcript of the digital recording
3. Hand- or computer-written notes from the interview

All of the information generated from the Qualitative Interview will be identified solely with the unique study ID number. Data generated from the Qualitative interviews will be maintained on password-protected Drexel University computer network server with access limited to only the study's PI and research staff using the same procedures for data security and backup outlined above.

Risks to subjects will be also minimized through staff ethics training, layered data security and by restricting access of sensitive information to staff members who have a specific need for the information.

- Training: All study staff are trained in the ethical treatment of study subjects and subject data with special emphasis on maintaining confidentiality.
- Data Security: All subjects will be assigned an identification number at the screening interview which will be used in place of names. All data files will be encrypted and password protected with passwords known only to the Principle Investigator and research staff.
- Restricted Access: Laptop computers will all be secured with password access and available only to study staff members. Laptops will be locked in cabinets in the secured study office when not in use.

Identifying information on participants will be on the consent forms and tracking forms. These forms will be kept in a locked filing cabinet in the PI or Research Coordinators office and will be separate from all other study-related data. Information from the tracking form and data relating to the management of participants will also be entered into and stored on the Drexel University College of Medicine secure, web-based solution designed to support data collection strategies for research studies — REDCap. The contact information will be stored in one study database separate from all other study-related data ((i.e., acceptance of a PrEP prescription, STI dx and related treatment, adherence call follow-up details) which will be identified with only the participant's unique study ID.

12c. Procedures to control quality of collected data

All staff will undergo extensive training on protocol. We will develop a checklist for each study visit to ensure consistency in data collection. The checklists (see Appendix 8) will detail the order of the appointment, forms to be completed, and specimen to be collected. Training will also included role-playing and mock interviewing. We will perform twice monthly review of subject files to ensure data completeness.

12.d. How data and specimens will be handled study-wide

- What information will be included in that data or associated with the specimens?
    - Urine specimens transported for Philadelphia FIGHT will be labeled only with participant unique study identifiers. Blood and swabs transported to the Philadelphia Health Department Laboratory will be labeled only with participant names per the requirements of health department and state law for reporting notifiable infections. On these specimens participant IDs will not be included; thus, linking between ID and name will be impossible.
- Where and how data or specimens will be stored?
    - Specimens will be stored in a locked case that only study personnel will have the keys to until they are transferred to an accredited laboratory for testing. Specimens going to FIGHT and to the Philadelphia public health lab will be transported in separate cases to ensure names and study ID numbers are separated.
- How long the data or specimens will be stored?
    - Specimens will be stored overnight in a locakable refrigerator and following testing the samples will be retained until the conclusion of the study. All data regarding subjects will be retained until the completion of the study and until manuscripts describing the data have been published.
- Who will have access to the data or specimens?

        - Only members of the research team will have access to subject data. Philadelphia Department of Health will perform STI, Hepatitis B and creatinine testing. They are located at 500 S. Broad Street. Philadelphia, PA 19146. Philadelphia FIGHT will perform drug-level monitoring. FIGHT is located at: located at 1207 Chestnut Street, Philadelphia, PA 19107. Research team members will transport specimens to the lab for processing within 72 hours of their collection.
- Who is responsible for receipt or transmission of the data or specimens?
    - Principal Investigator (AMR) or co-Investigators (MAF and BLP) are responsible for receipt and transmission of the data/specimens.
- Will data be sent outside of the Drexel University system? **NO** IF YES
    - Where will the data be sent?
    - Why is it necessary to send the data outside of the Drexel University system?
    - How and in what format will the data be sent? (PHI must be encrypted).
    - How data and specimens will be transported?

13. Provisions to Monitor the Data to Ensure the Safety of Subjects

This study is considered minimal risk as there is minimal risk associated with daily FTC/TDF as PrEP by HIV-uninfected individuals. Side effects during clinical trials included nausea, vomiting, abdominal pain, and diarrhea. These effects occurred in a minority of PWID (<20%) participating in the Bangkok Tenofovir Trial and most participants reported symptoms had resolved by the 2nd month. Of these side effects, only nausea and vomiting were statistically higher among PWID on Tenofovir than those taking the placebo. Tenofovir has been linked to renal impairment when used for HIV treatment, however, increased creatinine was observed in only 3% of patients in the Bangkok Tenofovir study.

Therefore a DSMB is not needed.

14. Withdrawal of Subjects

During the consent processes, potential participants will be informed that the alternative to study participation is not to participate. They will be informed that their decision regarding participation will not affect their participation in PPP or Drexel University services. If a participant screens positive for HIV during the baseline appointment, the PI will remove the participant from the study. If participants choose to withdraw, all data collection will stop. Participants will receive relevant compensation for having attended the study visit if they choose to withdrawal.

As stated above, we will follow up with participants twice weekly for 2 weeks when they “no show” for an appointment. Any participant failing to contact staff within 2 weeks will be considered lost to follow up. However, they will not be withdrawn from the study.

15. Risks to Subjects

Loss of Confidentiality: There is the possibility that participants’ confidentiality could be compromised through the inadvertent loss of confidential information. Participants may experience loss of confidentiality if participant information is inadvertently shared with individuals not authorized to view it. To minimize this risk, all data collection will occur in a private space. A unique study identification number will be assigned to each participant and will be used to link participant quantitative surveys, audio-files, and transcription of the open-ended sections of semi-structured interviews with clinical records. On these data, the participant’s identification number—not their name—will be used in the files to be analyzed.

Psychological Discomfort: There is the possibility that participants could experience psychological discomfort as a result of study questions during quantitative surveys or interviews relating to assessments of sexual behavior and drug use or if they were to receive a positive STI result during the study. We minimize the potential for psychological discomfort by informing participants that they are not required to participate in the study, that they should only share information they feel comfortable sharing, that they can refuse to answer any individual questions or withdraw from the study completely, and that there is no penalty for not participating.

We feel that these procedures will be effective in minimizing risks to the participants.

STI Testing: There is the minimal risk that participants could injure themselves through over-aggressive sample collection. We will minimize this risk by providing all participants instructions on how to collect their specimen. The literature shows that this procedure is acceptable to participants, is of minimal discomfort, has minimal safety risks (sample collection is considered non-invasive from a regulatory perspective), and provides reliable specimens.

Pregnancy: We will provide patients with contraceptive counseling and prescriptions as in the current standard of care for women per CDC PrEP clinical guidelines.

Toxicity: There is minimal risk associated with daily FTC/TDF as PrEP by HIV-uninfected individuals. Side effects during clinical trials included nausea, vomiting, abdominal pain, and diarrhea. These effects occurred in a minority of PWID (<20%) participating in the Bangkok Tenofovir Trial and most participants reported symptoms had resolved by the 2nd month. Of these side effects, only nausea and vomiting were statistically higher among PWID on Tenofovir than those taking the placebo. Tenofovir has been linked to renal impairment when used for HIV treatment, however, increased creatinine was observed in only 3% of patients in the Bangkok Tenofovir study. To monitor toxicity, we will measure creatinine levels at T1 and T2 (which will be scheduled over 3 months) as is recommended in the current CDC PrEP clinical guidelines and is considered standard of care.

16. Potential Benefits to Subjects

4.1 Benefits to Subjects

Study participants might experience direct benefits in several ways. Participants will receive free HIV, Hepatitis C, STI, pregnancy and creatinine testing. As many of these women are unlikely to receive regular preventive medical care, we detect acute infections and by treating them, prevent sequelae. They will also receive HIV risk reduction counseling and be given information about PrEP, a promising biomedical intervention to prevent HIV.

4.2 Benefits to Others

These data will be used for future public health planning in the region. Specifically, information learned from WWID about barriers and facilitators to PrEP uptake/utilization will provide insights to design relevant and culturally appropriate intervention activities to reduce their risk to HIV infection.

The proposed observational study does not constitute a clinical trial or involve the use of experimental treatments (behavioral or medical) on human subjects; thus, a Data and Safety Monitoring Plan is not required. However, we consider the security of data collected in this study to be of the utmost importance.

17. Vulnerable Populations

Not applicable

18. Multi-site Research

Not applicable

19. Community-Based Participatory Research

Since the beginning of the HIV epidemic, community engagement has been critical to understanding and meeting the needs of those most impacted by HIV.[15] We will engage and collaborate with PPP to establish a community advisory board (CAB) comprised of clients, staff, and other community advocates. The CAB will meet quarterly throughout the project period to review study instruments, protocols, and contextualize data. This will increase the reliability and validity of findings by allowing for member checking, a method for confirming the study team's interpretation and implications of the data.

20. Sharing of Results with Subjects

The results of the study will be summarized in an easy-to-read document, such as a pamphlet, that can be distributed to the CAB, PPP board of directors, PPP clients, and Drexel University School of Public Health. The pamphlet will be made available in the PPP office. In addition, a luncheon will be held at PPP detailing the results of the study to staff members.

21. Setting

Our study will take place in PPP's main building located in the Kensington neighborhood of Philadelphia where both an open air drug market and well-known sex work stroll operate.[16,17] We will embed PrEP services within PPP's existing clinical infrastructure that includes seven private patient rooms. PPP is located at 2913 Kensington Ave, Philadelphia, PA 19134. The study team has been provided with private clinic rooms to conduct study visits and a lockable file cabinet for study files. We have also obtained a lockable refrigerator to store study specimens. Only study team will have access to the keys of the cabinet and refrigerator. Informed consents and participant tracking forms will be stored in research team's main office in the Dornsife School of Public Health at 3215 Market St, 4th floor, 19104.

22. Resources Available

Feasibility of recruiting subjects: Prevention Point Philadelphia (PPP) is the largest harm reduction agency in the mid-Atlantic. Founded in 1991, PPP serves approximately 5,500 unduplicated clients each year; approximately 20% are women. Weekly PPP serves approximately 50 women during a SEP for women. We anticipate we can enroll the sample within 12-months which will require successful enrollment of ~16 women/month which will be feasible even once follow-up visits begin.

23. Prior Approvals

Original IRB Approval: 4/25/17

Approved Modification: 5/9/17

References

1. Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines MNR--. Update to Interim Guidance for Preexposure Prophylaxis (PrEP) for the Prevention of HIV Infection: PrEP for Injecting Drug Users. *MMWR 2010;.* 2013;62(23):463-465.
2. Evans JL, Hahn JA, Page-Shafer K, et al. Gender differences in sexual and injection risk behavior among active young injection drug users in San Francisco (the UFO Study). *J. Urban Health.* Mar 2003;80(1):137-146.
3. Davey-Rothwell MA, Latkin CA. Gender Differences in Social Network Influence among Injection Drug Users: Perceived Norms and Needle Sharing. *Journal of Urban Health : Bulletin of the New York Academy of Medicine.* 08/08
04/16/received
07/20/accepted 2007;84(5):691-703.
4. Syvertsen JL, Robertson AM, Strathdee SA, Martinez G, Rangel MG, Wagner KD. Rethinking risk: Gender and injection drug-related HIV risk among female sex workers and their non-commercial partners along the Mexico-U.S. border. *The International journal on drug policy.* 02/14 2014;25(5):836-844.
5. Bryant J, Brener L, Hull P, Treloar C. Needle sharing in regular sexual relationships: an examination of serodiscordance, drug using practices, and the gendered character of injecting. *Drug Alcohol Depend.* Mar 1 2010;107(2-3):182-187.
6. Roth AM, Goldshear JL, Martinez-Donate AP, Welles S, Chavis M, Van Der Pol B. Reducing Missed Opportunities: Pairing Sexually Transmitted Infection Screening With Syringe Exchange Services. *Sexually Transmitted Diseases.* 2016;43(11):706-708.
7. Marx GE, Bhatia R, Rietmeijer CA. An Opportunity Too Good to Miss: Implementing Human Immunodeficiency Virus Preexposure Prophylaxis in Sexually Transmitted Diseases Clinics. *Sex. Transm. Dis.* 2016;43(4):266-267.
8. Pathela P, Braunstein SL, Blank S, Shepard C, Schillinger JA. The High Risk of an HIV Diagnosis Following a Diagnosis of Syphilis: A Population-level Analysis of New York City Men. *Clin. Infect. Dis.* July 15, 2015 2015;61(2):281-287.
9. Kelley CF, Kahle E, Siegler A, et al. Applying a PrEP Continuum of Care for Men Who Have Sex With Men in Atlanta, Georgia. *Clin. Infect. Dis.* November 15, 2015 2015;61(10):1590-1597.
10. Aumeir B SZ, Martinez-Donate AP, Van Der Pol B, Wells S, Chavis M, Roth AM. Acceptability of pre-exposure prophylaxis (PrEP) among persons who inject drugs. Poster Presentation at: The Philadelphia HIV Research Collaboration Conference; January 2016; Philadelphia, PA.
11. Centers for Disease Control and Prevention PISP-ePPfHP, http://www.cdc.gov/hiv/pdf/prep_gl_patient_factsheet_prep_english.pdf Accessed May 2, 2016.
12. Wilson IB, Lee Y, Michaud J, Fowler Jr FJ, Rogers WH. Validation of a New Three-Item Self-Report Measure for Medication Adherence. *AIDS and Behavior.* 2016;20(11):2700-2708.
13. Solomon MM, Lama JR, Glidden DV, et al. Changes in renal function associated with oral emtricitabine/tenofovir disoproxil fumarate use for HIV pre-exposure prophylaxis. *AIDS (London, England).* 2014;28(6):851-859.
14. Yacoub RR. Elevations in Serum Creatinine With Tenofovir-Based HIV Pre-Exposure Prophylaxis: A Meta-Analysis of Randomized Placebo-Controlled Trials. *Journal of acquired immune deficiency syndromes (1999).* 2016;71(4):e115-e118.
15. Rhodes SD MR, Jolly C. Community-based participatory research (CBPR): A new and not-so-new approach to HIV/AIDS prevention, care and treatment. AIDS Education and Prevention. 2010:22(3):173-183.
16. U.S. Department of Justice. *Philadelphia/Camden High Intensity Drug Trafcking Area, Drug Market Analysis 2011.* Johnstown, PA. https://www.justice.gov/archive/ndic/dmas/Philadelphia-Camden_DMA-2011(U).pdf.: Accessed May 5, 2016;2011.
17. Deeney J. Philly's Cop-Free Heroin Zone. *The Daily Beast.* August 13, 2011, 2011.