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Title: MPrEP+: Assessing the feasibility and acceptability of a combination PrEP and adherence support intervention for male clients of female sex workers in Kisumu, Kenya

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ABSTRACT

Introduction: Male clients (MC) are integral to sex work-driven HIV transmission dynamics and as sexual partners of female sex worker (FSW), contribute disproportionately to new HIV infections globally and in sub-Saharan Africa. Twenty-seven percent of new HIV infections are attributed to MC of FSW and other partners of key populations. MC with sexual partners in FSW and other social groups are central to HIV transmission networks, making them an important focus for HIV prevention interventions. Gaps in coverage of HIV testing and prevention services among men, including MC, are well-documented, yet research and innovative interventions to improve MC uptake of effective HIV prevention services, including pre-exposure prophylaxis (PrEP), are scarce.

Methods and analysis: The MPrEP+ study assesses the feasibility and acceptability of a PrEP-focused combination prevention strategy providing daily oral tenofovir/emtricitabine (TDF/FTC) in combination with three adherence self-management interventions: real-time feedback from point-of-care urine drug-level assay with tailored adherence counseling; frequent HIV self-testing (HIVST); and one-way text message reminders. These interventions were delivered to 120 MC enrolled in the study in Kisumu, Kenya, over a 6-month period. Our primary outcome is PrEP adherence at six months as measured by PrEP drug levels. Bivariate and multivariable regression models are used to identify predictors of PrEP adherence. We also explore associations of socio-demographic characteristics, PrEP beliefs and norms with PrEP adherence.

Ethics and dissemination: The study was approved by the Columbia University Irving Medical Center Institutional Review Board (Protocol# AAAT6103) and the Maseno University Ethical Review Committee (Protocol# MUERC/00932/21). Results of the main trial will be submitted for publication in peer-reviewed journals. A summary and an Infographic of study results will be developed and distributed to MC and FSW as well as stakeholders working in HIV prevention and support for workers and clients engaged in sex work, including Kenya's Ministry of Health.

Trial registration number NCT04898699; Registered on 24 May 2021

Strengths and limitations of this study

- This is the first known pre-exposure prophylaxis (PrEP) trial among male clients of female sex workers. Clients of sex workers are an understudied population at risk for HIV and other sexually transmitted infections, and tailoring prevention interventions to meet their needs can strengthen efforts to reduce HIV infections.
- Study findings will provide key information about how best to engage male clients in PrEP and support their PrEP use, to inform the design and implementation of HIV interventions.
- The use of a novel pharmacologic measure, a point-of-care urine assay, provides objective real-time feedback on PrEP adherence and may reinforce continued PrEP medication-taking.
- The study uses an observational design with no comparison group; thus, the design does not control for confounding factors that might affect study outcomes.
- The small sample size may limit ability to demonstrate statistical power.

INTRODUCTION

Globally male clients (MC) of female sex workers (FSW) experience a greater burden of HIV compared to men who do not pay for sex[1-3] due to a constellation of factors, including number of sexual partners, HIV prevalence among FSW, and patterns of condom use with FSW. A recent meta-analysis of 87 population surveys in 35 sub-Saharan African (SSA) countries between 2000 and 2020 indicated that paid sexual encounters among men are prevalent: 8% of sexually active men aged 15-54 reported they had ever paid for sex, and this proportion was even higher in East African studies (11.3%).[3] Based on 52 of these surveys, men who paid for sex were 50% more likely to be living with HIV (prevalence ratio [PR] = 1.50; 95% CI 1.31–1.72) compared to men who had not. This meta-analysis also estimated that only 67.5% of men surveyed between 2010-2020 reported using a condom during their last paid sex. A second meta-analysis of 44 studies in low- and middle-income countries conducted between 1989-2019 also found an elevated risk of HIV among men who purchased sex (5% pooled HIV prevalence; n=21 studies), and in studies conducted between 2011-2019 (2.85%), compared to men who did not purchase sex.[1] Thus, an effective response to the elevated HIV vulnerability experienced by MC is essential to controlling the HIV epidemic, particularly in East and Southern Africa, where MC and other sexual partners of key populations accounted for 15% of new infections among those aged 15-49 years in 2019.[4] However, data on factors associated with risk of HIV acquisition as well as studies of HIV prevention interventions among this population are limited, likely due to stigma, difficulty in identifying them, and varying legality of commercial sex across countries.

Interventions directed to MC are needed to strengthen the impact of combination prevention strategies.[5] Pre-exposure prophylaxis (PrEP) is an effective biomedical HIV prevention intervention[6-8] and an optimal HIV prevention strategy for MC of FSW given the multiple barriers to condom use in the sex work context.[9-11] In Kenya, the site of this study, the 2018 national guidelines recommend PrEP for individuals at substantial risk for HIV, including those whose partners engage in transactional sex.[12] HIV prevalence in Kenya in 2018 was estimated at 4.9% (males: 3.1%; females: 6.6%), with 1.3 million people living with HIV (PLWH); however, in the western Lake Victoria area that is home to this study's site in Kisumu County, the epidemic is markedly more severe, with adult prevalence of 17.5%.[13] The HIV epidemic in western Kenya is significantly impacted by HIV infection in FSW. In 2013, the most recent year in which HIV surveillance data for key populations are available, national HIV prevalence among sex workers was 29.3%.[14]

Formative research we conducted to inform the study protocol indicated that MC were supportive of and interested in PrEP, and most FSW and MC viewed PrEP as life-saving protection for both them and their non-commercial sex partners.[5] Yet, we are unaware of any published studies offering PrEP to MC of FSW. These data highlight the need for implementation science research in real-world care settings to demonstrate how to engage MC in PrEP use and to inform national programs as they expand PrEP to reach key and priority populations. Additionally, as adherence is a critical determinant of PrEP efficacy, research to guide the design and implementation of evidence-based adherence support interventions for MC is needed to realize PrEP's individual- and population-level effectiveness.

Self-management approaches offer a promising and novel framework to optimize adherence and engagement in PrEP, whereby persons at substantial risk for HIV initiate PrEP, and proactively

adopt and monitor their own behaviors to optimize PrEP effectiveness and safety. Such approaches have been used to manage chronic conditions, e.g., cardiovascular disease, creatinine monitoring post-kidney transplant, glycemic control for diabetes, body weight in obesity and HIV treatment, but are less frequently applied for HIV prevention.[15-19] Objective feedback on adherence behavior to tailor counseling and reinforce successful adherence is a critical component in self-management approaches,[20,21] and a potentially impactful support for PrEP adherence.[22,23] Therefore, we are implementing MPrEP+, to our knowledge, the first HIV combination prevention intervention that offers oral PrEP with adherence support strategies to increase PrEP use among MC.

METHODS AND ANALYSIS

Study design

MPrEP+ is a single-arm longitudinal study offering PrEP and adherence support to men who purchase sex from FSW in Kisumu County, western Kenya. The study assesses adherence, feasibility, and acceptability of PrEP-focused prevention strategy offering daily oral PrEP (tenofovir disoproxil fumarate/emtricitabine [TDF/FTC]) in combination with three adherence self-management interventions: real-time feedback from point of care (POC) urine drug-level assay, HIV self-testing (HIVST). and weekly one-way text message reminders plus standard of care HIV risk-reduction counseling over a six-month period among male clients of FSW in Kisumu, Kenya.

Eligibility criteria

Participants are HIV-negative men aged 18 and over who report having exchanged money, goods, or services for sex with a woman in the past three months, and live or work and intend to stay in Kisumu County for the next six months. Other inclusion criteria include ability to provide informed consent and complete study procedures in English, Kiswahili or Dholuo, report no current or recent (within past 3 months) PrEP use and are willing to participate and adhere to the study intervention.

Sampling and recruitment

Participants are identified and recruited by FSW who serve as mobilizers in an ongoing PrEP trial for FSW from pre-specified community-based venues (‘hotspots’) such as sex work venues, bars, and other social spaces in the Kisumu urban area. Potential participants are prescreened with a brief questionnaire to assess initial eligibility (age, residence and intent to stay in Kisumu County for study duration, and having exchanged money, goods, or services for sex with a woman in the past three months).

Mobilizers invited MC who completed pre-screening as potentially eligible to the study site to undergo the informed consent process and assessment for PrEP eligibility. The recruitment goal is for 120 HIV-negative MC to be enrolled in the cohort.

Study procedures

Baseline visit

Informed Consent and Locator Information

Prior to the initiation of any study activities, participants undergo an informed consent process. Once consented, trained study staff collect complete locator information from all participants.

Clinical and laboratory assessments

All consented participants undergo HIV rapid testing and counseling following national guidelines and are assessed for PrEP eligibility using screening procedures detailed in the 2018 Guidelines on Use of Antiretroviral Drugs for Treating and Preventing HIV Infection in Kenya.[12] Standard procedures include assessment of behavioral and medical eligibility for PrEP using national tools; symptom-driven assessment for acute HIV infection; and assessment for contraindications for use of TDF/FTC.

A 10ml blood sample is collected via venipuncture for creatinine and hepatitis B surface antigen (HBsAg) testing as required for monitoring safe PrEP use. Additionally, a 10 ml urine sample is taken for chlamydia, gonorrhea and trichomoniasis screening. If a participant is found to have one of these STIs, he is immediately referred to the study clinician for STI treatment.

Interview

At baseline, all participants complete a baseline interview administered by trained research staff in English, Kiswahili or Dholuo according to preference. Interview domains are guided by the adapted Information-Motivation-Behavioral Skills (IMB) Model (Figure 1), including demographic information; psychosocial characteristics; alcohol and drug use; sexual partnering, including relationships with FSW; sexual practices and relationship characteristics; values and norms related to gender and sex; history and current experiences of psychological, physical, and sexual abuse; social support; HIV-related stigma; HIV- and prevention-related knowledge, practices, attitudes, including those related to PrEP, and effects of the ongoing COVID-19 pandemic on their lives.[24] Details of domains included in the baseline interview are found in Table 1.

Follow-up visits

Clinical and laboratory assessments

At each follow-up visit, participants undergo HIV rapid testing and counseling following Kenya's national guidelines and a symptom-driven clinical exam including assessment of symptoms of acute HIV infection or STIs. Participants found to be HIV-positive receive confirmatory testing and appropriate post-test counseling, including assisted referral for immediate HIV treatment initiation at local health facility. There is no further study follow up for HIV-positive participants.

In addition, a 10ml blood sample is collected via venipuncture at Months 3 and 6 follow-up visits to assess PrEP drug levels.[25] Other laboratory tests are conducted when clinically indicated.

Interview

At follow-up visits, all participants complete a follow-up interview administered by trained research staff in English, Kiswahili or Dholuo according to preference. Follow-up questionnaires are 45-60 minutes in duration; see Table 1 for interview domains at 1, 3, and 6-month follow-ups. At the 6-month follow-up interview, we added a limited number of open-ended questions regarding participants' experience taking PrEP and with study participation. Participants who express a desire to end study participation at the 3-month visit will be asked to complete the module of open-ended questions during the 3-month interview. Responses to open-ended questions will be transcribed verbatim, and if needed, translated from Kiswahili or Dholuo into English, and reviewed for accuracy and completion, de-identified and entered into a Dedoose database for analysis.

MPrEP+ combination prevention intervention components and procedures

The MPrEP+ intervention includes the provision of daily oral PrEP combined with two adherence self-management interventions: (1) use of a validated point-of-care (POC) urine tenofovir (TFV) assay, UrSure, with real-time feedback and tailored self-management counseling; (2) HIV self-testing; and (3) weekly one-way text messaging.

Daily oral FTC/TDF as PrEP

At enrollment visit, participants with no contraindications for PrEP receive a one-month supply (30 pills) of FTC/TDF as daily oral PrEP and receive education and counseling about PrEP dosing, signs and symptoms of drug toxicity, acute HIV infection and STIs, importance of daily adherence, and need for frequent HIV testing. At Month 1, a two-month supply of daily oral FTC/TDF after HIV testing, assessment for acute HIV infection and review of side effects and adherence at the one-month study assessment. At Month 3, a three-month supply of oral FTC/TDF will be given. At Month 6, participants receive a referral to local PrEP providers to continue on PrEP.

Urine assay with real-time feedback

This POC assay provides an objective biomarker of recent nonadherence, which can be used to validate other measures of PrEP adherence, e,g., self-report and PrEP drug concentration in blood plasma, in real-world settings, by detecting tenofovir disoproxil fumarate with greater sensitivity than plasma-based measures, with return of results within 10 minutes.[26,27] Determining non-adherence in real time allows for immediate return of this information to the participant and providing support to improve adherence. Also, real-time feedback based on test results at study visit can assure adherent PrEP users that they are achieving the prerequisite drug level for protection. Study participants are provided with brief interactive counseling tailored to results of their urine assay at their three- and six-month visits.

The POC UrSure testing is done at Month 3 and Month 6 follow-up visits to measure PrEP drug levels for adherence in participant urine samples over the preceding seven days. At enrollment, study staff will explain the use of this UrSure kit and how it will be used to inform PrEP adherence counseling at follow-up visits. At Month 3 and Month 6 follow-up visits, participants are asked to provide a 5 ml urine sample that will be used to perform the UrSure test. Participants will receive real-time feedback and self-management counseling, tailored to the results of their urine assay.

HIV self-testing (HIVST)

The MPrEP+ intervention conceptualizes HIVST[28] as a self-management tool allowing participants control over combination HIV prevention, including regular testing. Several studies have found HIVST to be acceptable and feasible in Kenya,[29-32] including among MC.[33,34] The enormous strain on health systems wrought by the ongoing COVID-19 pandemic brought into sharp relief the potential of HIVST to ensure access to essential testing resources outside of clinical settings.[35-37] At each study visit, participants are given two HIVST kits for self-testing between study visits. They receive detailed, interactive training on HIVST with pictorial elements, including instructions in the three study languages to contact study staff immediately in event of a positive test for confirmation as per national guidelines.

Weekly SMS text messaging

Immediately following the baseline visit, all participants begin receiving discrete weekly SMS text messages (or voice message in the case of low literacy) to support PrEP adherence, encourage healthy behaviors, use of HIVST, and study engagement. Message content is selected by the

participant and does not include information identifying the participant as part of a study or study details, e.g., "Remember to look after yourself today. See you tomorrow."

Reimbursement for participant time and transport

After completion of each study visit, participants receive the equivalent of about $13 in Kenya shillings for their time and effort. This amount is specified in the consent form. Refreshments are also provided during participation in study procedures.

Retention procedures

At enrollment, participants are asked to provide detailed locator information (e.g., name, address, email or social media details, telephone number, usual hangouts, and at least one alternative contact address and phone number). This information is updated at each follow-up visit. Participants also receive reminder calls or text messages the day prior to their scheduled visit and contacted immediately in the case of missed visits.

Patient and public involvement

The study team collected extensive formative data among MCs in Kisumu, which informed the development of the existing study protocol, specifically around study design, recruitment methods and intervention components.[5] Findings were presented to national stakeholders in advance of protocol finalization.[38,39] Interview questions at the final study visit will include preferences for venues and format of conveying findings larger groups of MC in Kisumu county. The study has an active advisory group composed of local stakeholders, including advocates and representatives of FSW, and the advisory group will be involved in planning dissemination to local and national audiences.

Table 1. MPrEP+ activities and procedures by time point					
Activities and procedures	**Pre-enrollment**	**Baseline**	**Month 1**	**Month 3**	**Month 6**
Screening & Enrollment					
Eligibility screen	Eligibility checklist				
Informed consent		X			
Clinical & Laboratory					
HIV rapid testing		X	X	X	X
Venipuncture		X Monitoring Creatinine and HBsAg for PrEP safety		X Detection of PrEP drug concentration in plasma	X Detection of PrEP drug concentration in plasma
Urine assay for STIs (chlamydia, gonorrhea, & trichomoniasis)		X			
Clinical exam (symptom-driven)		X	X	X	X
MPREP+ Intervention Components					
Oral PrEP (FTC/TDF)		30-day supply	2-month supply	3-month supply	Referral for post-intervention PrEP
POC UrSure urine assay (with tailored HIV risk-reduction counseling)				X	X
HIV self-testing			X	X	X
SMS text messaging			X	X	X
Interview Domains					
Quantitative					
Demographics and mobility		X	X	X	X
HIV risk perception		X			X
Knowledge of HIV		X			

HIV testing history		X	X	X	X
STI history		X		X	X
Global social support		X			X
Experience purchasing sex		X	X	X	X
Beliefs and attitudes about sex work		X			
Stigma		X			
Violence		X		X	X
Sexual partnerships and practices		X	X	X	X
Alcohol and use of other drugs		X		X	X
Mental health (depression)			X		X
Use of STI services		X		X	X
Knowledge and attitudes about PrEP/PEP		X		X	X
Impact of COVID-19		X		X	X
PrEP adherence and discontinuation			X	X	X
Acceptability of study components			X	X	X
Adverse events screening (including social harms)			X	X	X
Qualitative					
Exploration of good and bad things about taking PrEP; reasons for wanting to continue or discontinue taking PrEP upon study completion; experience participating in the study					X

Data analysis plan

Sample size justification

The sample size for the MC cohort was determined to be 120. Given that participants will be recruited using a convenience sample, a design effect of two was applied to the sample size calculations for the MPrEP+ strategy. With 120 participants enrolled, and treating those lost to follow-up as "not adherent" (as in the primary analysis), this sample size will result in a reasonably precise estimate of adherence at 6 months. For example, assuming 70% adherence at 6 months, our powered 95% CI will be 53.6-86.4% (16.4% precision). Similarly, conducting a "complete case" analysis (as in the secondary analysis) restricted to those with complete outcome ascertainment and assuming loss-to-follow-up of 10%, our powered 95% CI will be marginally wider at 52.7-87.3% (17.3% precision).[44]

Quantitative data analysis will be conducted using SAS Version 9.4 (Cary, NC). Table 2 presents an overview of primary and secondary outcomes and their definitions.

Primary outcome

Adherence to PrEP

Our primary outcome is PrEP adherence measured at six months. To estimate this outcome, we will calculate the proportion of participants who are adherent with oral PrEP (FTC/TDF) at 6 months as measured through antiretroviral drug levels. For the primary analysis we will conservatively assume those participants lost to follow-up or discontinuing PrEP for any reason were 'non-adherent'. In a secondary analysis, a "complete case" analysis will be performed, restricted to those not lost to follow-up and otherwise adhering to the intervention protocol. Sensitivity analyses will also explore multiply imputing likely 6-month adherence status among those lost to follow-up (LTF) assuming a missing at random, conditioned on covariates, mechanism of missingness.

For both the primary and secondary measurement of PrEP adherence, bivariate and multivariable regression models will be used to identify predictors of PrEP adherence. Specifically, we will explore the association between sociodemographic factors (e.g., age, socioeconomic indicators, religious affiliation, number of children), PrEP knowledge, perception, beliefs and concerns, and adverse events during PrEP and PreP adherence at 3 and 6 months.

Secondary outcomes

Acceptability of daily oral PrEP

Participants will be asked about their satisfaction using PrEP during the 1, 3, and 6 month follow-up interviews. Similar to the analyses described for PrEP retention, bivariate analyses will examine associations between participant socio-demographic and clinical characteristics and acceptability (overall and by study arm).

Adverse events

Adverse events will be measured with two constructs: the proportion of participants who discontinue PrEP due to adverse events and the proportion of individuals reporting social harms due to adverse events (based on self-report). Overall frequency of these outcomes will be tabulated, along with bivariate comparison between treatment arms

Validity of self-report, pill count, and metabolite measures for PrEP adherence

Taking measures of PrEP drug concentration in plasma as the gold standard measure for PrEP adherence, we will compute the sensitivity, specificity, and predictive value of (a) urine metabolite classification, (b) pill count classification, and (c) self-report against classification into "adherent" or "not adherent" groupings. Additionally, we will compare the correlation between metabolite levels and pill count classification and self-reporting of days adherent using correlation coefficients.

Association of PrEP adherence with sexual risk behavior

Across and within study arms, we will compare changes in sexual risk behavior between participants classified as "adherent" and "not adherent" to PrEP. Sexual risk behavior will be operationalized as the number of paying and non-paying sexual partners over a given time period; changes in sexual risk behavior will be operationalized as the difference in number of these sexual partners from the baseline estimate provided by the participant. First, Wilcoxon rank-sum tests will be used to assess whether the median change in number of sexual partners at 6 months differs between participant classified as adherent vs. not adherent to PrEP. Second, the average change in number of sexual partners over time will be estimated using repeated measures generalized estimating equations, allowing for repeated measurements over the time period of interest.

Experience taking PrEP and study participation experience. Open-ended questions in the six-month follow-up interview will be analyzed with content analysis for categorizing and eliciting meaning from the content of the textual responses.[40]

Table 2 Study objectives and outcome definitions

Outcomes	Outcome definitions
Primary	
1. PrEP adherence at 6 months	% of participants with plasma tenofovir concentration of >40 ng/mL (consistent with daily adherence)[41]
Secondary	
2. PrEP adherence at 3 months	% of participants with plasma tenofovir concentration of >40 ng/mL
3. Detectable ARV at 3 and 6 months	% of participants with detectable ARV (i..e., plasma tenofovir concentration of >0.31 ng/ml) % of participants with inconsistent adherence (i.e., plasma tenofovir concentration between 0.31 and 40 ng/ml) at 3- and 6-month visit
4. Self-reported adherence at 1, 3 and 6 months	% who self-report daily adherence in the past 7 days (no doses missed)
5. Completion of study visits at 3 and 6 months	% who completed scheduled MPrEP+ study visits
6. Acceptability of urine drug-level assay as objective measure of recent PrEP adherence at 3 and 6 months	Scaled perceptions of acceptability of urine drug level as a measure of recent PrEP adherence
7. Acceptability of feedback and counseling based on urine drug-level assay results at 3 and 6 months	Scaled perceptions of satisfaction with feedback and counseling
8. Association of PrEP adherence with sexual risk behavior at 1, 3 and 6 months	Association of self-reported PrEP adherence with sexual risk behavior
9. Acceptability of daily oral PrEP at 3 and	MC perceptions of and experience with MPrEP+ strategy

6 months	Challenges faced
10. Feasibility of recruiting MC into MPrEP+ intervention	% of men approached accepting screening; % of those screened who are eligible; % of those eligible enrolled Ability to recruit MC for MPrEP+ intervention
11. Feasibility of retaining MCs in MPrEP+ intervention at 3 and 6 months	% of MCs retained Pre-post comparison with regard to risk behaviors # and type of retention efforts needed to support retention over study duration
12. Feasibility of MPrEP+ strategy to determine whether future testing is warranted	% of MPrEP+ intervention implemented as planned
13. Use and acceptability of HIVST to confirm HIV status while taking PrEP	% of test kits distributed used Standardized format to record HIVST use
14. N umber of new HIV infections (descriptive purposes only) at 6 months	% of participants self-reporting reactive test result via HIVST kit # of participants self-reporting reactive test result via HIVST kit with a confirmatory HIV positive test at follow-up visits
15. Social harms associated with PrEP use at 1, 3 and 6 months	Discontinuation rates of PrEP due to an AE or drug toxicity and occurrence of social harms among MC

Ethics and dissemination

The MPrEP+ study is registered at clinicaltrials.gov: NCT04898699 (24 May 2021). This study has been approved by the Columbia University Irving Medical Center Institutional Review Board (Protocol# AAAT6103) and the Maseno University Ethical Review Committee (Protocol# MUERC/00932/21). Key to our ethics approach is the monitoring of social harms related to PrEP use and trial participation at all follow-up visits. All assessments, consent forms and other relevant forms have been translated into the local languages, Dholuo and Kiswahili, and translations were verified for accuracy and received ethics approval.

Study findings and lessons learned from study implementation will be disseminated through peer-reviewed journals, national and international conference presentations to key policymakers and implementers, meetings with national and county level Ministry of Health leadership, other stakeholders and study participants, and through social and mainstream media outlets such as list-servs, websites of NGO stakeholders who work with sex workers, and local newspapers.

Conclusion

MPrEP+ addresses a social group both integral to sex work-driven HIV transmission dynamics and globally underserved by HIV prevention programs, MC. Conducted in a real-world setting, the research will contribute much needed insight and data to inform efforts to extend the coverage and potential impact of PrEP beyond key population groups like FSW. Given that it is being implemented while the global COVID-19 pandemic is affecting use of facility-based HIV prevention services, the inclusion of feasibility and acceptability of HIVST as part of a PrEP-based approach to combination HIV prevention makes the study findings particularly relevant to efforts to develop and evaluate the delivery of tailored prevention services outside of health facility settings.

Authors Contributions

JEM, JF, ML, WME and KA led the process of study conceptualization. JEM, JF, AZ, DO, ML, DN, WME and KA developed the study protocol and associated data collection tools and informed consent forms. AZ and DO facilitated receipt of all required ethics committee and IRB approvals for the protocol. KA and DO are overseeing day-to-day study implementation, including subject recruitment and enrolment and data collection activities. ML, MRL and DMR are leading the development of the statistical plan and planned data analysis. All authors reviewed and edited this manuscript. All authors read and approved the final version of the manuscript.

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Competing interests

All authors declare that they have no competing interests.

Figure 1. MPREP+ Adapted IMB Model: Determinants of PrEP Adherence, Feasibilty[24]

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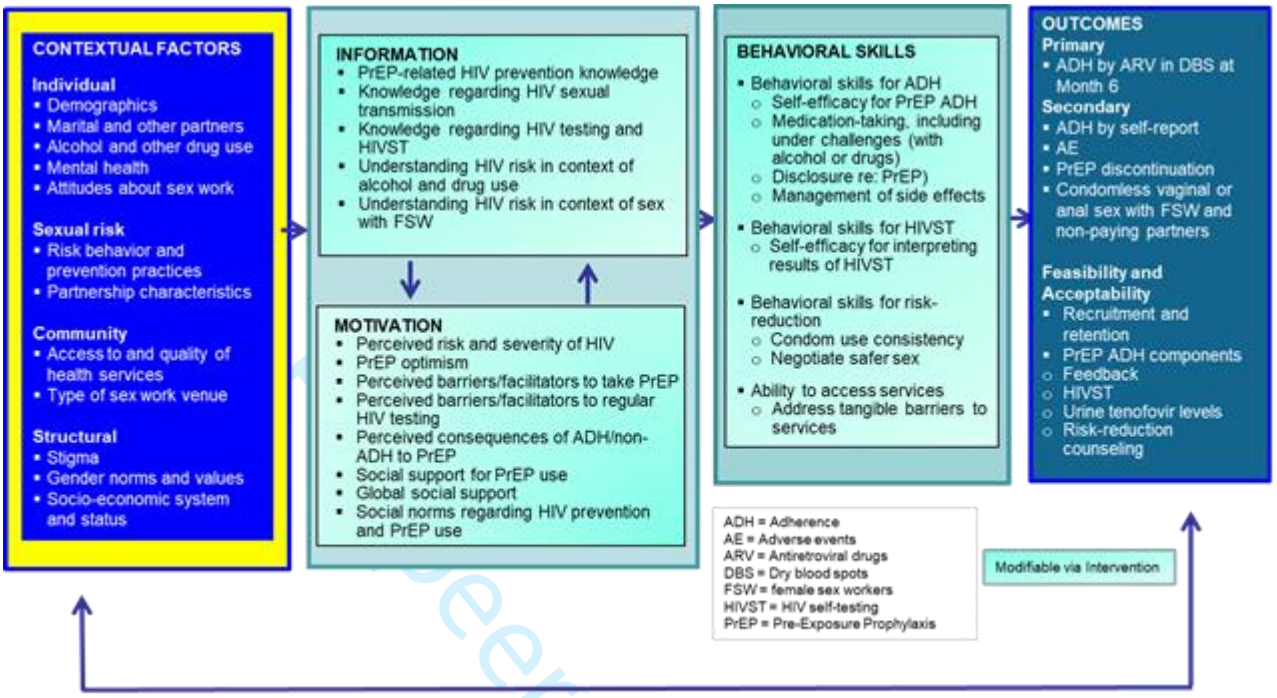

Figure 1. MPREP+ Adapted IMB Model: Determinants of PrEP Adherence, Feasibility[24]

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	5, 8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	11-13
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-10
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	11
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	11-13
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	11-13
Results			Not applicable
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	NA

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	NA
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	3
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	NA
Generalisability	21	Discuss the generalisability (external validity) of the study results	NA
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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MPrEP+ Study protocol: A prospective cohort study assessing the feasibility and acceptability of an HIV pre-exposure prophylaxis (PrEP) strategy for male clients of female sex workers in Kisumu, Kenya

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Title: MPrEP+ Study protocol: A prospective cohort study assessing the feasibility and acceptability of an HIV pre-exposure prophylaxis (PrEP) strategy for male clients of female sex workers in Kisumu, Kenya

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ABSTRACT

Introduction: Male clients **(**MC) are integral to sex work-driven HIV transmission dynamics as sexual partners of female sex worker (FSW). MC contribute disproportionately to incident HIV globally and in sub-Saharan Africa, with 27% of new infections attributed to MC of FSW and other partners of key populations. Gaps in coverage of HIV testing and prevention services for men, including MC, are well-documented, yet research and innovative interventions to improve MC uptake of effective prevention services, including pre-exposure prophylaxis (PrEP), are scarce.

Methods and analysis: MPrEP+ is a cohort study designed to assess the feasibility and acceptability of a PrEP-focused HIV prevention strategy providing daily oral tenofovir/emtricitabine (TDF/FTC) in combination with three adherence self-management interventions: (1) use of a validated point-of-care urine drug level assay with real-time feedback and tailored self-management counseling; (2) frequent HIV self-testing (HIVST); and (3) weekly one-way text messaging. This package of interventions is being delivered to 120 MC enrolled in the study in Kisumu, Kenya over a six-month period. The primary outcome is PrEP adherence at six months as measured by PrEP drug levels. Bivariate and multivariable regression models will be used to identify predictors of PrEP adherence. We will also explore associations of socio-demographic characteristics, PrEP beliefs with PrEP adherence.

Ethics and dissemination: The study was approved by the Columbia University Irving Medical Center Institutional Review Board and the Maseno University Ethical Review Committee. Study enrollment was initiated in November 2021 with participant follow-up planned through August 2022. Study results will be submitted for publication in peer-reviewed journals. Summaries and infographics of study findings will be developed and distributed to MC, FSW, and stakeholders working in HIV prevention and support for people who sell and buy sex, including Kenya's Ministry of Health.

Trial registration number NCT04898699; Registered on 24 May 2021

Strengths and limitations of this study

- The study engages an understudied population vulnerable to HIV infection in a tailored strategy delivering a highly effective biomedical prevention tool, PrEP.
- The use of a novel pharmacologic measure, a point-of-care urine assay, provides objective real-time feedback on PrEP adherence and may reinforce continued PrEP medication-taking.
- The study uses an observational design with no comparison group; thus, the design does not control for confounding factors that might affect study outcomes.
- The small sample size may limit ability to demonstrate statistical power.
- All participants enrolled in the study will receive the same package of adherence self-management interventions and thus, will not be able to determine the effect of individual intervention effects.

INTRODUCTION

Globally male clients (MC) of female sex workers (FSW) experience a greater burden of HIV compared to men who do not pay for sex[1-3] due to a constellation of factors, including number of sexual partners, elevated HIV prevalence among FSW, and patterns of condom use with FSW. A recent meta-analysis of 87 population surveys in 35 sub-Saharan African countries between 2000 and 2020 indicated that paid sexual encounters by men are prevalent: 8% of sexually active men aged 15-54 reported they had ever paid for sex, and this percent was higher in studies conducted in East Africa (11.3%).[3] Based on 52 of these surveys, men who paid for sex were 50% more likely to be living with HIV (prevalence ratio [PR] = 1.50; 95% confidence interval [CI] 1.31–1.72) compared to men who had not. This meta-analysis also estimated that only 67.5% of men surveyed between 2010-2020 reported using a condom during their last paid sex encounter. A second meta-analysis of 44 studies in low- and middle-income countries conducted between 1989-2019 also found an elevated risk of HIV among men who purchased sex (5% pooled HIV prevalence; n=21 studies), and in studies conducted between 2011-2019 (2.85%), compared to men who did not purchase sex.[1] Thus, an effective response to the elevated HIV vulnerability experienced by MC is essential to controlling the HIV epidemic, particularly in East and Southern Africa, where MC and other sexual partners of key populations, including FSW, accounted for 15% of new infections among those aged 15-49 years in 2019.[4] However, data on factors associated with risk of HIV acquisition as well as studies of HIV prevention interventions among this population are limited, likely due to stigma, difficulty in identifying them, and varying legality of commercial sex across countries.

Interventions directed to MC are needed to strengthen the impact of combination prevention strategies.[5] Pre-exposure prophylaxis (PrEP) is an efficacious biomedical HIV prevention intervention[6-8] and an optimal tool for MC of FSW, given the multiple barriers to condom use in the sex work context.[9-11] In Kenya, the site of this study, the 2018 national guidelines recommend PrEP for individuals at substantial risk for HIV, including those engaged in transactional sex.[12] HIV prevalence in Kenya in 2018 was estimated at 4.9% (males: 3.1%; females: 6.6%), with 1.3 million people living with HIV (PLWH); however, in the Lake Victoria region where this study is conducted in Kisumu County, adult prevalence is 17.5%.[13] The HIV epidemic in western Kenya is significantly impacted by HIV infection in FSW. In 2013, the most recent year in which HIV surveillance data for key populations are available, national HIV prevalence among FSW was 29.3%.[14] Under Kenya's national policy guidelines, PrEP is prioritized as part of combination HIV prevention for people who engage in sex work, including MC.[15] However, MC have not been a focus of national PrEP implementation plans.

Formative research we conducted to inform the study protocol indicated that MC were supportive of and interested in PrEP, and most FSW and MC viewed PrEP as life-saving protection for both themselves and their non-commercial sex partners.[5] Yet, we are unaware of any published studies offering PrEP to MC of FSW. This data highlights the need for implementation science research in real-world settings to demonstrate how to engage MC in PrEP use and to inform national programs as they expand PrEP to reach key and priority populations. Additionally, as adherence is a critical determinant of PrEP efficacy, research to guide the design and implementation of evidence-based adherence support interventions for MC is needed to realize PrEP's individual- and population-level effectiveness.

Self-management approaches offer a promising and novel framework to optimize adherence and engagement in PrEP, whereby persons at substantial risk for HIV initiate PrEP, and proactively adopt and monitor their own behaviors to optimize PrEP effectiveness and safety. Such approaches have been used to manage chronic conditions, e.g., cardiovascular disease, creatinine monitoring post-kidney transplant, glycemic control for diabetes, body weight in obesity and HIV treatment, but are less frequently applied for HIV prevention.[16-20] Objective feedback on adherence behavior to tailor counseling and reinforce successful adherence is a critical component in self-management approaches,[21,22] and a potentially impactful support for PrEP adherence.[23,24] Therefore, we are implementing MPrEP+, to our knowledge, the first HIV combination prevention strategy that offers oral PrEP with adherence support interventions to increase PrEP use among MC.

METHODS AND ANALYSIS

Study design

MPrEP+ is a single-arm longitudinal study offering PrEP and adherence support to MC of FSW in Kisumu County, western Kenya. The study assesses adherence, feasibility, and acceptability of PrEP-focused prevention strategy offering daily oral PrEP (tenofovir disoproxil fumarate/emtricitabine [TDF/FTC]) in combination with three adherence self-management interventions: real-time feedback from point of care (POC) urine drug-level assay, HIV self-testing (HIVST). and weekly one-way text message reminders plus standard of care HIV risk-reduction counseling over a six-month period among MC in Kisumu, Kenya. All participants receive the same intervention and attend four study visits over a six-month follow-up period.

Eligibility criteria

Participants are HIV-negative men aged 18 and older who report having exchanged money, goods, or services for sex with a woman in the past three months, and live or work and intend to stay in Kisumu County for the next six months. Other inclusion criteria include ability to provide informed consent and complete study procedures in English, Kiswahili or Dholuo, report no current or recent (within past 3 months) PrEP use and are willing to participate in study procedures, including the study intervention.

Sampling and recruitment

Recruitment is conducted by trained, supervised mobilizers connected to FSW groups active in the study catchment area. Mobilizers conduct outreach and education about the study aims and components in community-based venues such as bars and other social spaces where people sell and buy sex in the Kisumu urban area. Interested individuals are asked for verbal consent to undergo prescreening at the venues. Those providing verbal consent are prescreened with a brief questionnaire to assess initial eligibility (age, residence and intent to stay in Kisumu County for study duration, and having exchanged money, goods, or services for sex with a woman in the past three months).

Mobilizers invite MC identified in pre-screening as potentially eligible to the study site to complete an enrollment visit, beginning with the informed consent process and study eligibility assessment, including eligibility for PrEP. The recruitment goal is 120 HIV-negative MC enrolled in the cohort. Study staff document the number of individuals approached by mobilizers; number agreeing to

pre-screen; number prescreened as potentially eligible who attend scheduled enrollment visits; and number enrolled.

Study procedures

All study procedures, including baseline and follow-up visits, are conducted at the clinical research site managed by Impact Research and Development Organization. This site is located within a low-cost private hospital in Kisumu, Kenya, and has an onsite pharmacy and certified laboratory. The population being served by the hospital comprises both low- and middle-income neighborhoods.

Baseline visit

Informed consent and locator information

Prior to the initiation of any study activities, participants undergo a written informed consent process. Once consented, trained study staff collect complete locator information from all participants.

Clinical and laboratory assessments

All consented participants undergo HIV rapid testing and counseling following national guidelines and are assessed for PrEP eligibility using screening procedures detailed in the 2018 Guidelines on Use of Antiretroviral Drugs for Treating and Preventing HIV Infection in Kenya.[12] Standard procedures include assessment of behavioral and medical eligibility for PrEP using national tools; symptom-driven assessment for acute HIV infection; and assessment for contraindications for use of TDF/FTC.

A 10 milliliter (ml) blood sample is collected via venipuncture for measurement of creatinine and hepatitis B surface antigen (HBsAg) testing as required in the PrEP guidelines. Additionally, a 10 ml urine sample is taken for chlamydia, gonorrhea and trichomoniasis screening. If a participant is found to have one of these sexually transmitted infections (STIs), he is immediately referred to the study clinician for further management.

Baseline interview

At baseline, all participants complete a baseline interview administered by trained research staff in English, Kiswahili or Dholuo according to preference. Interview domains are guided by the adapted Information-Motivation-Behavioral Skills (IMB) Model (Figure 1), including demographic information; psychosocial characteristics; alcohol and drug use; sexual partnering, including relationships with FSW; sexual practices and relationship characteristics; history and current experiences of psychological, physical, and sexual abuse; social support; HIV-related stigma; HIV- and prevention-related knowledge, practices, attitudes, including those related to PrEP, and effects of the ongoing COVID-19 pandemic on their lives.[25] Details of domains included in the baseline interview are found in Table 1.

Follow-up visits

Follow-up visits are conducted at Month 1, Month 3 and Month 6 post-enrollment.

Clinical and laboratory assessments

At each follow-up visit, participants undergo HIV rapid testing and counseling following Kenya's national guidelines and a symptom-driven clinical exam including assessment of symptoms of

acute HIV infection or STIs. Participants found to be HIV-positive receive confirmatory testing and appropriate post-test counseling, including assisted referral for immediate HIV treatment initiation at local health facility. There is no further study follow-up for HIV-positive participants.

In addition, for all participants, a 10 ml blood sample is collected via venipuncture at Months 3 and 6 follow-up visits to assess metabolized tenofovir (TFV) levels.[26] Other laboratory tests are conducted when clinically indicated.

Follow-up interview

At follow-up visits, all participants complete a follow-up interview administered by trained research staff in English, Kiswahili or Dholuo according to preference. Follow-up questionnaires are 45-60 minutes in duration; see Table 1 for interview domains at 1, 3, and 6-month follow-ups. The six-month follow-up interview includes several open-ended questions regarding participants' experience taking PrEP and with study participation. Participants who express a desire to end study participation at the 3-month visit will be asked to complete the module of open-ended questions during the 3-month interview. Responses to open-ended questions will be transcribed verbatim, and if needed, translated from Kiswahili or Dholuo into English, and reviewed for accuracy and completion, de-identified and entered into a Dedoose database for analysis.

MPrEP+ adherence support intervention components and procedures

The MPrEP+ strategy includes the provision of daily oral PrEP combined with three adherence self-management interventions: (1) use of a validated point-of-care (POC) urine TFV assay, UrSure, with real-time feedback and tailored self-management counseling; (2) HIV self-testing; and (3) weekly one-way text messaging.

Daily oral FTC/TDF as PrEP

At enrollment visit, participants eligible for and willing to take PrEP receive a one-month supply (30 pills) of FTC/TDF as daily oral PrEP and education and counseling about PrEP dosing, signs and symptoms of drug toxicity, acute HIV infection and STIs, importance of daily adherence, and need for regular HIV testing. At Month 1, a two-month supply of daily oral FTC/TDF after HIV testing according to national guidelines is provided, along with assessment for acute HIV infection and review of side effects and adherence. At Month 3, oral FTC/TDF will be dispensed as a three month supply. At Month 6, participants receive a referral to local PrEP providers to continue on PrEP.

Urine assay with real-time feedback

This point-of-care (POC) assay provides a biomarker of PrEP pill-taking within the past 72 hours, with return of results provided within 15 minutes.[27,28] Sharing this objective measure of recent adherence behavior with participants during follow-up visits facilitates open discussion of recent PrEP use and allows providers to tailor counseling messages to reinforce each participant's strengths and address their challenges. Also, real-time feedback based on test results at study visit can assure adherent PrEP users that they are achieving the prerequisite drug level for protection. Study participants are provided with brief interactive counseling tailored to results of their urine assay at their three- and six-month visits.

At enrollment, study staff explain the use of this UrSure kit and how it will be used experimentally to inform PrEP adherence counseling at follow-up visits. At Month 3 and Month 6 follow-up visits, participants are asked to provide a 5 ml urine sample that will be used to perform the UrSure test.

Participants receive real-time feedback and self-management counseling, tailored to the results of their urine assay.

HIVST

The MPrEP+ intervention conceptualizes HIVST[29] as a self-management tool allowing participants control over combination HIV prevention, including regular testing. Several studies have found HIVST to be acceptable and feasible in Kenya,[30-32] including among MC.[33,34] The enormous strain on health systems wrought by the ongoing COVID-19 pandemic brought into sharp relief the potential of HIVST to ensure access to essential testing resources outside of clinical settings.[35-37] At each study visit, participants are given two HIVST kits for self-testing between study visits. They receive detailed, interactive training on HIVST with pictorial elements, including instructions in the three study languages to contact study staff immediately in event of a positive test for confirmation as per national guidelines.

Weekly SMS text messaging

Upon completion of the baseline visit, all participants begin receiving discrete weekly SMS text messages (or voice message in the case of low literacy) to support PrEP adherence, encourage healthy behaviors, use of HIVST, and study engagement. Message content is selected by the participant and does not include information identifying the participant as part of a study or study details, e.g., "Remember to look after yourself today. See you tomorrow."

Reimbursement for participant time and transport

After completion of each study visit, participants receive the equivalent of about $13 in Kenya shillings for their time and effort. This amount is specified in the consent form. Refreshments are also provided during participation in study procedures.

Retention procedures

At enrollment, participants are asked to provide detailed locator information (e.g., name, address, email or social media details, telephone number, usual hangouts, and at least one alternative contact address and phone number). This information is updated at each follow-up visit. Participants also receive reminder calls or text messages the day prior to their scheduled visit and contacted immediately in the case of missed visits.

Patient and public involvement

The study team collected extensive formative data among MCs in Kisumu, which informed the development of the study protocol, specifically in relation to the study design, recruitment methods and intervention components.[5] Findings were presented to national stakeholders in advance of protocol finalization for feedback.[38,39] We will draw on experience with previous research dissemination activities, including those related to our formative work, as well as other types of events (participant appreciation events) to inform how best to convey findings to larger groups of MC in Kisumu. The study has an active advisory group composed of local stakeholders, including advocates and representatives of FSW, and the advisory group will be involved in planning dissemination to local and national audiences.

Table 1. MPrEP+ activities and procedures by time point					
Activities and procedures	**Pre-enrollment**	**Baseline**	**Month 1**	**Month 3**	**Month 6**
Screening & Enrollment					
Eligibility screen	Pre-screen	Eligibility checklist			
Informed consent		X			
Clinical & Laboratory					
HIV rapid testing		X	X	X	X
Venipuncture		X Creatinine and HBsAg for PrEP safety		X Detection of PrEP drug concentration in plasma	X Detection of PrEP drug concentration in plasma
Urine assay for STIs (chlamydia, gonorrhea, & trichomoniasis)		X			
Clinical exam (symptom-driven)		X	X	X	X
MPrEP+ Intervention Components					
Oral PrEP (FTC/TDF)		30-day supply	2-month supply	3-month supply	Referral for post-intervention PrEP
POC UrSure urine assay (with tailored HIV risk-reduction counseling)				X	X
HIVST			X	X	X
SMS text messaging			X	X	X
Interview Domains					
Quantitative					
Demographics and mobility		X	X	X	X
HIV risk perception		X			X
Knowledge of HIV		X			
HIV testing history		X	X	X	X
STI history		X		X	X
Global social support		X			X
Experience purchasing sex		X	X	X	X
Beliefs and attitudes about sex work		X			
Stigma related to engaging with FSW[40]		X			
Violence[41,42]		X		X	X

Sexual partnerships and practices		X	X	X	X
Alcohol and use of other drugs		X		X	X
Mental health (depression)			X		X
Use of STI services		X		X	X
Knowledge and attitudes about PrEP/ post-exposure prophylaxis (PEP)		X		X	X
Impact of COVID-19		X		X	X
PrEP adherence and discontinuation			X	X	X
Acceptability of study components			X	X	X
Adverse events screening (including social harms)			X	X	X
Qualitative					
Exploration of good and bad things about taking PrEP; reasons for wanting to continue or discontinue taking PrEP upon study completion; experience participating in the study			X	X	X
*Only for those who report discontinuation of PrEP at Month 1 and Month 3 visits					

Data analysis plan

Sample size justification

The study sample size was determined to be 120 MC based on feasibility concerns for conducting a convenience sample of this population. An estimate of the precision of the 95% confidence interval estimating our primary outcome of six-month adherence (described below) was obtained using the methodology applied by Cornfield and assuming a Design Effect of 2.[43] A Design Effect is a simple number that estimates how much less efficient a non-random sample compared to a simple random sample; a Design Effect of 2 implies that a non-random sample would need twice the number of individuals as a simple random sample to obtain the same-precision estimates .[44]

With 120 participants enrolled, and treating those lost to follow-up as "not adherent" (as in the primary analysis), this sample size will result in a reasonably precise estimate of adherence at six months. For example, assuming 70% adherence at six months, our powered 95% CI will be 58.4%-81.6%% (11.6% precision). Similarly, conducting a "complete case" analysis (as in the secondary analysis) restricted to those with complete outcome ascertainment and assuming loss-to-follow-up of 10%, our powered 95% CI will be marginally wider at 57.8%-82.2% (12.2% precision).[44] With 120 participants our precision will be similar across a range of measured adherence proportions at 6 months (Table 2).

Table 2: Width of 95% CI for estimating adherence at 6 months, assuming a sample size of 120 and a design effect of 2

Proportion adherent at 6m	LCL	UCL	Precision (1/2 width of 95% CI)
30%	18.4%	41.6%	11.6%
40%	27.6%	52.4%	12.4%
50%	37.3%	62.7%	12.7%
60%	47.6%	72.4%	12.4%
70%	58.4%	81.6%	11.6%
80%	69.9%	90.1%	10.1%
90%	82.4%	97.6%	7.6%

Quantitative data analysis will be conducted using SAS Version 9.4 (Cary, NC). An overview of primary and secondary outcomes and their definitions follows:

Primary outcome

Adherence to PrEP

The primary outcome is recent PrEP adherence measured at six months. Recent adherence will be operationalized as a dichotomous variable based on measured presence of plasma TFV at or above the test level of detection of 10 ng/mL.[26] To estimate this outcome, we will calculate the proportion of participants who are adherent with daily oral PrEP (FTC/TDF) at six months as measured through plasma TFV. For the primary analysis we will conservatively assume those participants lost to follow-up or discontinuing PrEP for any reason were 'non-adherent'. In a secondary analysis, a "complete case" analysis will be performed, restricted to those not lost to follow-up and otherwise adhering to the intervention protocol. Sensitivity analyses will also explore multiply

imputing likely 6-month adherence status among those lost to follow-up assuming a missing at random, conditioned on covariates, mechanism of missingness.

For both the primary and secondary measurement of PrEP adherence, bivariate and multivariable regression models will be used to identify predictors of PrEP adherence. Specifically, we will explore the association between sociodemographic factors (e.g., age, socioeconomic indicators, religious affiliation, number of children), PrEP knowledge, perception, beliefs and concerns, and adverse events during study participation, and PrEP adherence at three and six months.

Secondary outcomes

Acceptability of daily oral PrEP

Participants will be asked about their satisfaction using PrEP during the one, three, and six- month follow-up interviews. Similar to the analyses described for PrEP retention, bivariate analyses will examine associations between participant socio-demographic and clinical characteristics and acceptability (overall and by study arm).

Acceptability of HIVST

Participants will be asked about perceived benefits and dislikes of HIVST, reasons for not self-testing, and likelihood pf recommending self-testing to a family member or a friend during the one, three, and six- month follow-up interviews. Similar to the analyses described for PrEP retention, bivariate analyses will examine associations between participant socio-demographic and clinical characteristics and acceptability (overall and by study arm).

Adverse events

Adverse events will be measured in two ways: the proportion of participants who discontinue PrEP due to adverse events and the proportion of individuals reporting social harms due to adverse events (based on self-report). Overall frequency of these outcomes will be tabulated, along with bivariate comparison between treatment arms

Validity of self-report, pill count, and metabolite measures for PrEP adherence

Taking measures of PrEP drug concentration in plasma as the objective gold standard measure for PrEP adherence, we will compute the sensitivity, specificity, and predictive value of (a) urine metabolite classification, (b) pill count classification, and (c) self-report against classification into "adherent" or "not adherent" groupings. Additionally, we will compare the correlation between metabolite levels and pill count classification and self-reporting of days adherent using correlation coefficients.

Association of PrEP adherence with sexual behavior

Across and within study arms, we will compare changes in sexual behaviors between participants classified as "adherent" and "not adherent" to PrEP. Sexual behavior will be categorized based on number of sexual partners reported during follow-up as well as self-report of condom use at last sexual encounter, separately for paying and non-paying sexual partners. Wilcoxon rank-sum tests will be used to assess whether the median change in number of sexual partners (overall and stratified by paying and non-paying partners) at six months differs between participant classified as adherent vs. not adherent to PrEP. Second, changes in the proportion reporting condom use at at last sexual encounter across follow-up time points will be estimated using repeated measures

generalized estimating equations, allowing for repeated measurements over the time period of interest.

Experience taking PrEP and study participation experience. Open-ended questions in the six-month follow-up interview will be analyzed with content analysis for categorizing and eliciting meaning from the content of the textual responses.[45]

Ethics and dissemination

The MPrEP+ study is registered at clinicaltrials.gov: NCT04898699 (24 May 2021). The study was approved by the Columbia University Irving Medical Center Institutional Review Board (Protocol# AAAT6103, approved 24 May 2021) and the Maseno University Ethical Review Committee (MUERC) (Protocol# MUERC/00932/21, approved 31 March 2021). Key to our approach is the monitoring of social harms related to PrEP use and trial participation at all follow-up visits. All assessments, consent forms and other relevant forms have been translated into the local languages, Dholuo and Kiswahili, and translations were verified for accuracy and received ethics approval.

Study findings and lessons learned from study implementation will be disseminated through peer-reviewed journals, national and international conference presentations to key policymakers and implementers, meetings with national and county level Ministry of Health leadership, other stakeholders and study participants, and through social and mainstream media outlets such as list-servs, websites of non-governmental organization stakeholders who work with sex workers, and local newspapers.

Authors Contributions

JEM, JF, ML, WME and KA led the process of study conceptualization. JEM, JF, AZ, DO, ML, DN, WME and KA developed the study protocol and associated data collection tools and informed consent forms. AZ and DO facilitated receipt of all required ethics committee and IRB approvals for the protocol. KA and DO are overseeing day-to-day study implementation, including subject recruitment and enrolment and data collection activities. ML, MRL and DMR are leading the development of the statistical plan and planned data analysis. All authors reviewed and edited this manuscript. All authors read and approved the final version of the manuscript.

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Competing interests

All authors declare that they have no competing interests.

Figure 1. MPREP+ Adapted IMB Model: Determinants of PrEP Engagement and Sexual Behavior among Male Clients in Kenya [24]

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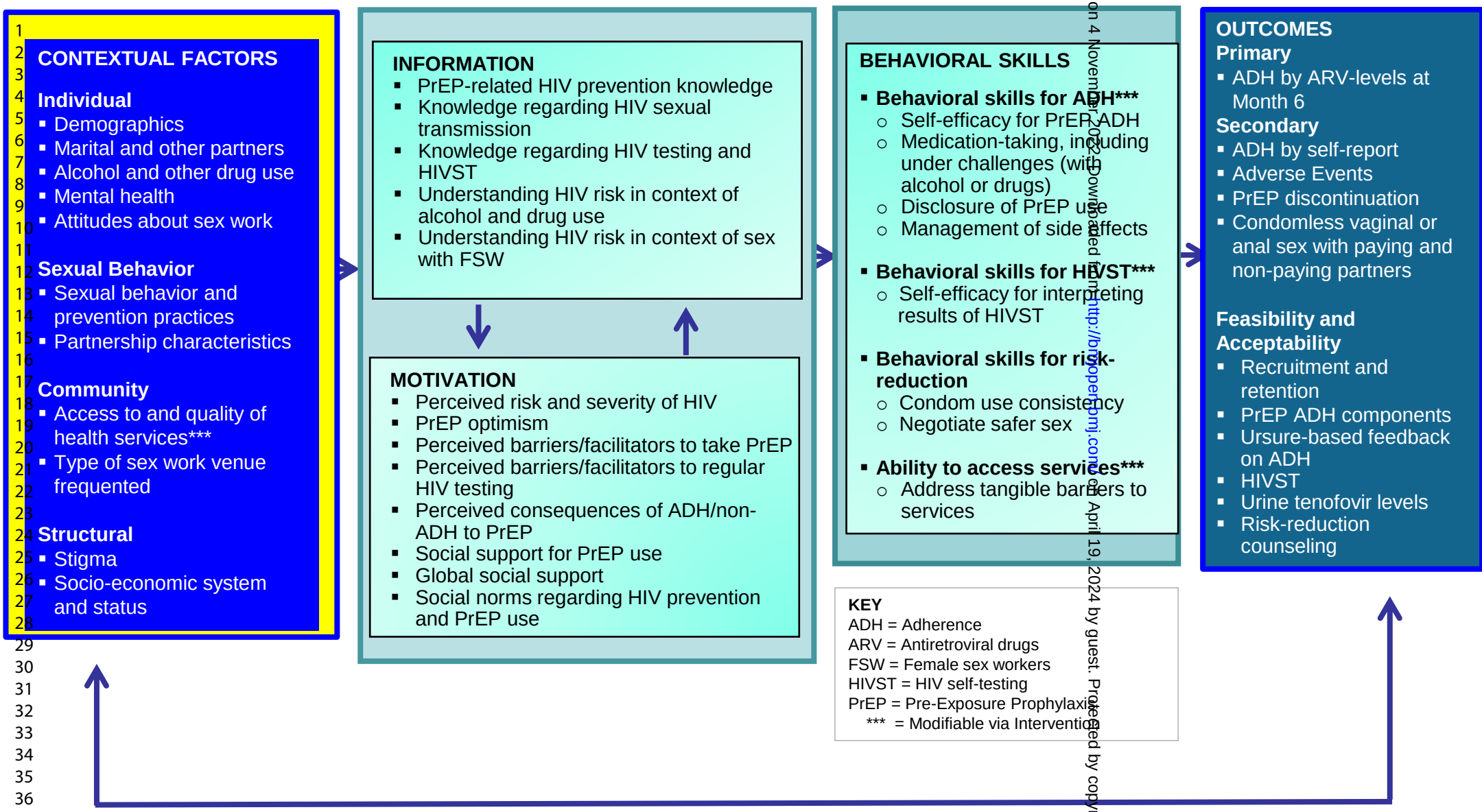
Figure 1. MPREP+ Adapted IMB Model: Determinants of PrEP Engagement and Sexual Behavior among Male Clients in Kenya



STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	5, 8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	11-13
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-10
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	11
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	11-13
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	11-13
Results			Not applicable
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	NA

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	NA
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	3
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	NA
Generalisability	21	Discuss the generalisability (external validity) of the study results	NA
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.