PROTOCOL:

Alignment of PrEP use with HIV risk in young women and men

Aligning PrEP and HIV Exposure

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CONTENTS

I. ACRONYMS

AGYW	Adolescent girls and young women
ART	Antiretroviral Treatment
CT	*Chlamydia trachomatis*
DAIDS	Division of AIDS
DMPA	Depo medroxyprogesterone acetate
EC	Ethics Committee
EIA	Enzyme-linked immunosorbent assay
HBV	Hepatitis B virus
HIV	Human Immunodeficiency Virus
HIVST	HIV self-test
IDI	Infectious Disease Institute
IPV	Intimate Partner Violence
IRB	Institutional Review Board
KWBS	Kampala Women's Bone Study
NG	*Neisseria gonorrhoeae*
PrEP	Pre-exposure prophylaxis
RNA	Ribonucleic acid
STI	Sexually Transmitted Infection
TFV	Tenofovir
WHO	World Health Organization

II. STUDY TEAM

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III. SUMMARY

Oral pre-exposure prophylaxis (PrEP) is a recommended component of combination HIV prevention and its availability is rising through demonstration projects and full-scale national programs. In sub-Saharan Africa, young women are a priority population for HIV prevention and targeted to initiate PrEP, given their high HIV incidence rates and promising success from a strategy that can be used without the engagement of male partners. A key question in the field is whether young women using PrEP have ongoing HIV risk and adhere to PrEP sufficiently to have protection from HIV when they have condomless sex with HIV-infected partners. The only true way to know whether a heterosexual woman is sexually exposed to HIV or has a partner with high HIV risk is to test for HIV and STIs in her male partner(s) and quantify HIV viral levels, if any are detected. Yet engaging men in clinic-based HIV testing is challenging. More recent efforts have focused on using HIV self-testing kits to respond to demands on men's time and reluctance to seeking preventive healthcare. The availability of PrEP also provides a new incentive for men to test.

By leveraging an ongoing study of bone health with concurrent use of PrEP and injectable DMPA (often known as Depo Provera® or depot medroxyprogesterone acetate), we have opportunity to engage a new cohort of young men and objectively measure HIV and common STIs in these young men and link the results to women's use of PrEP. The primary objective of this study is to determine whether young women's adherence to PrEP aligns with the HIV status and risk of their male partners. To address its primary objectives, this study will leverage: 1) an ongoing study among young women and 2) a novel cohort of young men who are current sexual partners of the young women in the ongoing study to objectively measure PrEP use, HIV, and HIV factors related to HIV risk. This study will provide a framework for understanding how and when young women and men decide to take PrEP, estimate the proportion of women that are benefitting from HIV protection when they have male partners with or at high risk of acquiring HIV, and provide a novel opportunity to engage young men in PrEP delivery and as supporters of women's PrEP use.

IV. BACKGROUND

Oral PrEP is the latest biomedical intervention to be added to a growing of body of proven HIV prevention strategies. Oral PrEP is recommended by the World Health Organization and many Ministries of Health worldwide, including in Uganda, where HIV incidence is often greatest among young women [1-3]. In Uganda, clinical guidelines for PrEP became available in 2016 and the Ministry of Health is coordinating targeted scale up of PrEP for people with greatest HIV risk [2]. In Kampala, the capital city, PrEP is accessible through programs for key populations (e.g. sex workers, men who have sex with men, adolescent girls and young women (AGYW) and negative members of HIV serodiscordant couples, as well as through demonstration projects and clinical research.

As with any newly adopted intervention, there are key delivery questions that need to be understood to ensure efficient and effective scale up of PrEP on a population level. A large unanswered question for PrEP delivery is how well PrEP users execute daily pill taking and whether persistent PrEP use aligns with HIV exposure and risk. Initial demonstration projects among young women have found high degrees of PrEP uptake, with >80% of women offered in our ongoing program in western Kenya and South Africa [4]. However, programs are beginning to report high levels of client drop-off. Daily adherence is especially important for women to achieve tissue concentrations commensurate with HIV protection from PrEP [5]. Adherence may be greater among women who use PrEP for ≥3 months but it is not clear if adherence patterns and persistence align with HIV risk. Persistence with PrEP is important to provide protection during periods of oscillating HIV risk but PrEP could be discontinued when risk is no longer present (e.g. when a stable partner living with HIV is virally suppressed), thereby removing the low risk of medication toxicities [6].

PrEP adherence aligning with risk

A large unanswered question for PrEP delivery is how well PrEP users comply with daily pill taking and whether PrEP use aligns with HIV exposure and risk. Daily compliance with pill-taking is especially important for women to achieve tissue concentrations commensurate with protection

Table 1. **Scenarios of PrEP adherence and HIV risk in 7 days prior to sample/data collection.** Green boxes indicate scenarios where PrEP use aligns with HIV risk.

	Protection from PrEP (defined as TFV >40ng/ml or Wisepill data indicates 6-7 openings in the week prior to sampling)	**Low/no protection from PrEP** (defined as TFV <40ng/ml or Wisepill data indicates <6 openings in the week prior to sampling)
No sexual HIV risk: No sex in the past week	PrEP not necessarily needed if sex is not occurring and is not expected to occur soon	Lack of sufficient PrEP use aligns with lack of sex
Low/No sexual HIV risk	PrEP aligns with HIV risk if condomless sex is anticipated in the near future	PrEP aligns with HIV risk if condomless sex is not anticipated in the coming week
High sexual HIV risk	Possible sexual exposure to HIV aligns with PrEP adherence sufficient to provide protection from HIV infection	Possible sexual exposure to HIV and PrEP adherence insufficient to provide HIV protection

TFV: tenofovir, the circulating metabolite of TDF-based medication that can be used as a marker of short-term adherence

from PrEP.[5] Initial demonstration projects of PrEP focusing on young women have found high degrees of uptake, estimated above 80% of women offered in our ongoing program in western Kenya and South Africa [4]. However, a number of programs are also beginning to report high levels of client drop-off. Adherence may be greater among women who use PrEP for ≥3 months but it is not clear if adherence patterns align with HIV risk. Continuous PrEP use is important to provide protection during periods of oscillating HIV risk but PrEP could be discontinued when risk is no longer present (e.g. when a partner living with HIV is virally suppressed, when a partnership is stably monogamous and both partners are HIV-negative), thereby removing side effects and the low risk of medication toxicities (Table 1 shows how PrEP use could overlay with HIV risk) [6].

Delivering PrEP to young women

Young women are a focus of HIV prevention programs in many settings due to their high HIV incidence rates and unique vulnerability. For young people, preventive health services are viewed as "user-friendly" when they are efficient and offer convenient solutions to sexual and reproductive health problems including confidential HIV testing, contraception (including condoms), and self-care when available [7]. In settings that follow guidelines for syndromic management of STI, diagnostic STI testing and treatment can be a demand-creation approach [8]. When STI testing is part of PrEP delivery, young people have been motivated to attend refill visits in order to receive STI testing and treatment and receive PrEP adherence counseling at that time [9]. Recent estimates of asymptomatic curable bacterial STIs – *Neisseria gonorrhea* (NG) and *Chlamydia trachomatis* (CT) – have been alarmingly high with prevalence estimates of 30-40% in Western Kenya and South Africa [9, 10] indicating high rates of condomless sex and often the presence of untreated infection that can compromise immune function and ease entry of HIV and other pathogens [9-11].

Delivering PrEP to young men

Momentum for the delivery of comprehensive preventive health services to young men, who are typically isolated from preventive health care, is growing and can be leveraged to introduce PrEP [12, 13]. Young men value health care services that do not interfere with paid work or compromise confidentiality [14]. Interventions that meet men outside of traditional facility settings and integrate HIV prevention with full service preventive health care, such as care for hypertension and diabetes, offers convenience and may increase salience of preventive behaviors yielding greater recruitment of young men for clinical services [15]. HIV self-testing (HIVST) is another approach being tested as a strategy to engage young men to know their HIV status and link them to services whether HIV-negative (e.g. PrEP initiation) or HIV-positive (e.g. ART initiation). Studies among pregnant women, men who have sex with men, and female sex workers have found that secondary distribution of HIVST kits can increase frequency of HIV testing among male partners and HIVST kits yield accurate results [16-18]. In these studies, reports of partner-perpetrated violence were rare, indicating that people potentially used discretion when choosing partners to whom to offer HIVST [17].

Factors influencing PrEP adherence among adolescents

A key developmental feature of adolescence is a decreased ability to appraise risk and this may influence adolescent PrEP use [19]. For adolescents, risk taking provides high-level stimulation yielding a satisfying experience and often occurs in the presence of friends [20]. In later adolescence (ages 20-24 years) when self-regulatory abilities are more fully developed, risk appraisal and avoidance behavior emerges alongside choices and behaviors that minimize risk [21]. With regards to sexual behavior, adolescents may exude optimistic bias and invulnerability to unintended pregnancy or STIs, including HIV and often cite the pressure of social norms that dissuade use of condoms, especially in the context of trusting a partner [22]. With PrEP, adherence can be impacted by individual feelings of optimism and invulnerability which are often

positioned within the broader context of family/peer, community and structural factors outlined in the social-ecological model [23]. This framework has been applied in numerous studies seeking to identify novel delivery approaches for HIV prevention interventions for young women and has drawn attention to the role that male partners may play to support or undermine PrEP use by young women [8, 24-26].

Summary of unaddressed questions

In summary, PrEP is being scaled up nationally in Uganda and young people are an important target when they have substantial HIV risk. The question of whether young people align PrEP use and high adherence to PrEP with actual HIV risk and exposure is not yet fully addressed. We hypothesize that this alignment in the context of oscillating HIV risk may be challenging for young people and counselors can assist if we gain better understanding of the underlying alignment of risk and PrEP use and reasons for mal-alignment.

Overall goal for this protocol

This protocol describes methods and procedures for enrolling a new cohort of young men in order to provide testing for HIV and common curable STIs and offer men PrEP. Data from

Figure 1. The social-ecological model that can be applied to understand factors influencing adolescent PrEP use

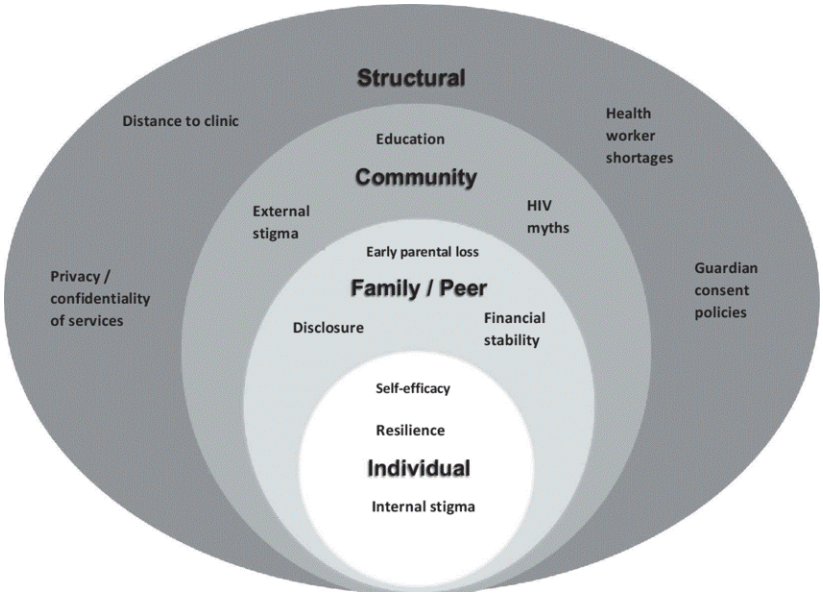

Table 2. Objective measures of HIV risk and PrEP use collected through the parent Kampala Women's Bone Study and Kampala Men's Study

Kampala Women's Bone Study (KWBS)	• HIV
	• PrEP execution:
	  ○ Tenofovir concentration in blood/urine
	  ○ Daily pillbox openings (Wisepill™)
	  ○ Self-report
	• PrEP persistence:
	  ○ Pharmacy dispensation records
	• HIV risk
	  ○ Yc DNA (marker of semen exposure/condomless sex)
	  ○ *C. trachomatis*
	  ○ *N. gonorrhoeae*

Young male partners of KWBS women joining the novel cohort established by the "Aligning PrEP and HIV exposure" protocol	• HIV
	• HIV risk
	  ○ *C. trachomatis*
	  ○ *N. gonorrhoeae*
	• PrEP execution:
	  ○ Tenofovir concentration in urine
	  • Self-report

the men enrolling will be linked to data being collected among their young female sex partners in the Kampala Women's Bone Study, including women's adherence to PrEP, HIV status and STI diagnoses. The anonymous linkage of data between male and female sex partners will permit us to answer questions about HIV risk and exposure and how this aligns with PrEP use by each sexual partner.

Our parent study, the Kampala Women's Bone Study (KWBS)

We are currently conducting a longitudinal observational study of bone health among 500 women ages 16-25 who initiate PrEP concurrently with the common injectable contraceptive, depot medroxyprogesterone acetate (DMPA, R01HD089843 PI: Heffron). In this study, we aim to determine whether young women using DMPA and PrEP will experience greater decreases in bone mineral density and markers of bone turnover and resorption relative to women using only one of the products (i.e. DMPA but not PrEP, PrEP but not DMPA) or neither. This clinically-driven parent study objectively measures bone health, PrEP adherence, and infection common curable STIs (Table 2). By anonymously linking data from the women in KWBS with data from their male partners, we can objectively measure alignment of PrEP use and HIV risk and exposure.

Recruitment for KWBS began in May 2018, 304 (60%) have been enrolled as of July 2019, and retention is high: only 5.2% of expected month-1, 2.2% of month-3, and 3.3% of month-6 visits have been missed to date. The cohort has self-reported high behavioral risk for HIV (**Table 3**), 22% were treated for a genital infection at enrollment (syndromically diagnosed), and 91% initiated PrEP at enrollment. Through our counseling, women are encouraged to use PrEP with high adherence and to discontinue PrEP during sustained periods with little risk. We are beginning to observe some PrEP discontinuations and some early decliners have initiated PrEP, indicating the potential for fluctuating risk and desire for PrEP.

Table 3. Characteristics of young women ages 16-25 enrolled in KWBS

Number enrolled (as of 15 April 2019)	240
Initiating PrEP at enrollment	91%
% expected M6 study visits not attended	3.3%
% accrued person time among women initiating PrEP at enrollment when PrEP was not dispensed (women switching on→off PrEP)	10%
% accrued person time among women non initiating PrEP at enrollment when PrEP was dispensed (women switching off→ on PrEP)	17%
% aged 16-20	61%
Number of sex acts, past 3 months, median (IQR)	24 (9-72)
% sex acts, past 3 months, that were condomless	35%
Number of male sex partners, past 3 months, median (IQR)	2 (1-5)
% male partners that were new, past 3 months	40%
Treated for syndromically-diagnosed STI at enrollment visit*	22%

**Primary STI symptom was vaginitis or vaginal discharge.*

Impact

By leveraging data already collected from young women in our ongoing study, the Kampala Women's Bone Study, and engaging a new cohort of young men for this protocol, we have an ideal platform to study whether PrEP use aligns with HIV exposure and sexual HIV risk among young women and their male sex partners, using objective measurement of HIV risk, PrEP adherence, and sexual behavior. An additional high impact result is an opportunity to identify strategies to engage young men in HIV prevention services through a novel cohort study. Findings demonstrating alignment of PrEP use and HIV risk will strengthen

confidence in programmatic PrEP delivery to young people. Findings demonstrating mis-alignment will be dissected to understand circumstances leading to over- or under-use of PrEP and opportunities for PrEP programs to improve alignment. All findings will be relevant for oral PrEP programs as well as novel PrEP strategies that are in the development pipeline, such as intravaginal rings and injectable PrEP.

V. METHODS

A. Overall Design

The proposed research will engage a new cohort of young men, whose female partners are already engaged in the Kampala Women's Bone Study. Women in the Kampala Women's Bone Study will be invited to engage in this novel study to recruit their male partners. Women's HIV risk is directly related to the HIV status and risk of their male sexual partners and thus, we will leverage our ongoing cohort of KWBS young women to recruit their male sexual partners for a new men's study. Men will be offered PrEP, diagnostic STI testing and treatment, and followed for 6 months to assess PrEP continuation and STIs. Men's data will be linked to data from their female sex partners in the parallel KWBS study to determine whether women's PrEP use aligns with HIV risk and exposure.

B. Study Aims

Aim 1. To determine whether young women's adherence to PrEP aligns with the HIV status of their male partners

Men engaging in this study will have HIV testing at enrollment, month 1 and quarterly for up to 6 months. Results from this testing will be linked to data from the participant's female sex partner that characterize her PrEP use to determine whether her PrEP use aligns with his HIV status.

Aim 2. To determine whether young women's adherence to PrEP aligns with the HIV risk of their male partners

Men engaging in this study will have testing for common curable STIs (*Chlamydia trachomatis and Neisseria gonorrhoeae)* at enrollment, month 1 and quarterly for up to 6 months. Results from this testing will be linked to data from the participant's female sex partner that characterize her PrEP use to determine whether her PrEP use aligns with his HIV risk (defined by the results from his STI testing).

Aim 3. To determine whether young men's adherence to PrEP aligns with the HIV status and risk of their female partners

We will offer PrEP to HIV-negative men enrolled in this study and track PrEP initiation, refills, and adherence to PrEP (based on self-report and drug levels). The frequency of high PrEP adherence will be compared among men with female partners infected and uninfected with HIV or another STI.

C. Primary exposure

The primary exposure is male infection with HIV (Aim 1), NG or CT (Aim 2) and female infection with HIV, NG, or CT (Aim 3).

D. Primary outcomes

The primary outcome will be PrEP used by women with sufficient daily adherence to confer HIV

protection (6-7 doses in the past week or TFV ≥40ng/mL) for periods when women are dispensed PrEP. When PrEP is not dispensed, the TFV level will be assigned as 0 ng/mL.

For Aim 3, the primary outcome will be PrEP used by men with sufficient daily adherence to confer HIV protection (4 doses in the past week), measured by self-report or objective measures (daily monitoring or drug levels).

E. Hypothesis

Women and men will continue to use PrEP when their partners refuse HIV testing or disclose STI infections.

F. Location

This study will take place at the Infectious Diseases Institute (IDI)-Kasangati research clinic, located in the Kasangati area of Kampala in close proximity of several public health care facilities.

G. *Population*

The proposed study will enroll 200 young men who are male sexual partners of women in the current KWBS parent study. This demographic has a high risk for HIV acquisition thus it is ideal to provide them with diagnostic testing, prevention and treatment services for HIV and STIs, and prevent transmission to their female partners. Women from KWBS will also be engaged to discuss the study with their male partners and to have their data anonymously linked to their male partners who join this study.

H. Eligibility for men

Inclusion criteria:

- Men ages ≥18
- Has a female sexual partner enrolled in the Kampala Women's Bone Study
- Willing and able to provide informed consent

Exclusion criteria:

- Has any other condition that would preclude the ability to provide informed consent, make study participation unsafe, complicate the interpretation of study findings or otherwise interfere with achievement of the study objectives, in the investigator's discretion.

I. Eligibility for women

Inclusion criteria:

- Participating in the Kampala Women's Bone Study
- Willing to talk with male sex partners about the new study for men and refer men for study recruitment

Exclusion criteria:

- Has concerns about potential social harm stemming from anticipated conversations with male sex partners about the new study for men such that study staff would discourage the women from participation
- Investigator discretion

J. Sample size

We will enroll approximately 200 male and 300 female participants into this study

K. Study power

Power calculations are based on the primary aim to determine alignment of women's PrEP use with male sex partner's STI infection status. Using an estimate that 20% of men will be infected with STI/HIV at any visit and 50% of their female partners will have protective PrEP levels, we estimate that we will have ≥80% power to detect a relative risk of ≥2.00 and ≥90% power to detect a relative risk of ≥2.30 in comparisons of the proportion of female visits with PrEP protection between visits when male partners had HIV risk or no HIV risk (assuming that α=0.05). If 70% of their female partners have protective PrEP levels, power will be 80% for a RR of 1.57 and 90% for a RR of 1.72 (Table 4).

Table 4. Aim 2 power: Proportion of women with PrEP at protective level needed to see significant differences by male partner HIV risk, with ≥80% or ≥90% power.

Male partner HIV risk (HIV or STI infection)	PrEP at protective level, % (RR)	
Yes, exposed, N=40	50%	70%
Unexposed, N=160		
For 80% power	24.6% (RR=2.0)	44.6% (RR=1.5)
For 90% power	21.5% (RR=2.3)	40.8% (RR=1.7)

Power calculated by nQuery Advisor using power for Chisquared test comparing two

L. Recruitment

Overall

Women will be recruited to join this study by outreach staff at the IDI-Kasangati facility at the end of routine study visits for the KWBS.

For young men who are sex partners of women in KWBS, we will leverage women participating in KWBS to recruit 200 of their current male sex partners. Women will be asked to consent to participate in recruitment of their male sex partners and to have their data anonymously linked to their male partner data. This will be a separate consent form and women may decline this component without any change to their participation in KWBS. Women with concerns about potentially experiencing violence from their male partner will be discouraged from recruiting this or any other male partners for the study and we will have staff trained in violence prevention available to counsel these women. The IDIK research clinic has established relationships with well-known organizations that specialize in IPV prevention and counseling in the event that a KWBS woman needs to be referred for more in-depth care. Ultimately, each woman's participation will be at her own discretion. Women engaging in this new study will be provided with multiple strategies to talk with male sex partners about the new study: talking points, recruitment brochures, HIV self-testing kits, and contact information for study recruitment staff.

Talking points

Women enrolled in KWBS will be provided talking points to guide them to think about how to recruit male partners. Talking points will include benign messages about a new research study for men and provide ideas about how to promote the men's study without disclosing information about their own recent HIV test/status or PrEP use (see Appendix for draft talking points).

Recruitment brochures

Women will also be given recruitment materials such as brochures, to give to their male partners that feature information on the benefits of STI testing and treatment, an introduction to PrEP and its availability for HIV-negative men through the study clinic. Recruitment materials will encourage men to call study recruitment officers or come to the IDIK research clinic. Draft brochures and other recruitment materials will be submitted to the research ethic committee for approval.

HIV self-test kits

HIV self-testing is being rolled out in Kampala by The President's Emergency Plan for AIDS Relief (PEPFAR) partners coordinated by the Ministry of Health. To align with this strategy, the study will also have HIVST in stock that will be available for women to take to male partners, should they desire. The IDIK research clinic is already using HIVST in a number of ongoing PrEP studies, including with pregnant women living with HIV and women engaging in transactional sex (NCT03484533, NCT03426670). HIVST are accompanied by written instructions in English and Luganda with pictures and diagrams that explain how to use them and provide a 24-hour phone number in case of reactive results, questions or help with the kit. Anyone reporting reactive results to study staff will be encouraged to come to the research clinic and anyone who does not come within one week will be traced via phone or an in-person visit if possible. We will follow good clinical practice guidelines to ensure that all people with a reactive result are supported and provided with confirmatory testing, treatment and care.

Contact with study recruitment team

Once women have initiated conversation with their male partner, they will be encouraged to let the recruitment team know and arrange a time for their male partner to talk with a member of the recruitment team. This will be done by having the recruitment officer call the woman at a mutually-agreeable time when she can offer her phone to her male partner, facilitating a one-on-one conversation with the recruitment officer. This method will maintain anonymity of the potential male participant and permits contact without the woman providing her partner's phone number to the recruitment officer. This recruitment strategy has worked well for our ongoing study that recruits male partners of HIV-infected pregnant women (NCT03484533). Women can also bring male partners to the study clinic for him to meet a recruitment officer in person or make other arrangements to introduce her partner to the recruitment officer.

M. Retention

We will leverage the long-established retention strategies of the community outreach team at the IDIK research clinic to ensure high rates of retention among male participants. Retention strategies include sending participants reminders before their upcoming target visit date (via SMS or phone call), calling participants the first day after a missed visit date, 3 days later, 1 week later, and 1 month later, and visiting participants in their home or place of work, when given permission, to offer them a free ride to the research clinic. In addition, a recruitment/retention officer will coordinate with the study team to ensure that study visits can be conducted on weekends and evenings and that men can be given expedited services, as necessary to align with work schedules and other obligations.

N. General study procedures

Informed consent

Written informed consent will be obtained from each female participant in the KWBS, and each male study participant prior to conducting any research procedures. Participants agreeing to participate will sign the informed consent form and be offered copies of the informed consent

forms to take home. The informed consent forms will describe the purpose of the study, the procedures to be followed, the voluntary nature of the study, and the risks and benefits of participation, in accordance with all applicable regulations. The forms will be translated into Luganda and participants will select the language of their choice (either Luganda or English) for the informed consent process. Informed consent will be conducted in a quite space in the research clinic by a study staff member trained in human subjects and good clinical practice.

Procedures for women

Women enrolled in the KWBS will be asked by the study recruitment officers if they would be interested in recruiting their male partner for this new study. Recruitment officers will ensure that women understand fully their role, discuss and consider potential benefits and risks, such as inadvertent disclosure of HIV status, PrEP use, study participation, and intimate partner violence (IPV) and how to avoid them. Women with concerns about IPV will be discouraged from recruiting potential male perpetrators for the study and we will have staff trained in IPV prevention available to counsel these women. Women who are interested in recruiting their male partners will sign an informed consent form specific to partner recruitment and linkage of their male partners data, to their KWBS data.

Following informed consent, the study staff will provide counseling messages and talking points for women to help them with the recruitment process and initiate the discussion with their male partner.

Women will receive a recruitment brochure to give to their male partners. These brochures will include benign information on STI testing and health services available at the clinic, as well as contact information of study staff, whom they can call if they are interested in joining the study or have additional questions.

Study staff will also provide women an HIVST kit, if they choose to deliver one to their male partner. To ensure that women feel comfortable with the recruitment process, study staff may also assist with role playing to act out talking points and delivery of the recruitment brochure and/or HIVST kit.

Procedures for men

Screening and Enrollment

Following informed consent, men will be screened for their willingness to comply with study procedures, complete locator information, and assigned a unique ID. Eligible men will be enrolled into the study, on the same day if possible. Procedures on the day of enrollment will include: 1) HIV testing with PrEP dispensation or active referral to ART and HIV care depending on the results, 3) Hepatitis B and creatinine testing for men starting PrEP, 2) completion of questionnaires to assess demographic information, recent sexual behavior, partnership status, HIV risk perception, alcohol and drug use, mental health, and adherence to ART/PrEP, 4) diagnostic testing for *N. gonorrhoeae* and *C. trachomatis* using rapid tests with real time results. Results from creatinine testing will be available within 3-5 days from the laboratory. Any participants with abnormal creatinine/creatinine clearance will be contacted by the study clinician and asked to return for confirmatory testing. PrEP will be discontinued for any men with confirmed abnormal creatinine/creatinine clearance levels according to national guidelines.

Follow up

Follow up visits will be conducted 1, 3 and 6 months after enrollment. Procedures at each visit will include: 1) HIV testing with PrEP dispensation or referral to ART and HIV care depending on the results, 2) completion of questionnaires to assess recent sexual behavior, partnership status, HIV risk perception, and adherence to ART/PrEP, and 3) diagnostic testing and treatment for *N.*

gonorrhoeae and *C. trachomatis*. PrEP use will be objectively measured by point-of-care urine tests, if kits become available during the study, and real time monitoring of PrEP adherence will be conducted using an electronic monitoring system that captures a date-time stamp each time the pill container is opened, if devices become available.[27] Participants using PrEP will have a creatinine test at the 6-month/study exit visit which aligns with Uganda national PrEP guidelines. For men who test HIV-positive, confirmatory HIV testing will be conducted according to Uganda national guidelines and PrEP will be discontinued. HIV-positive men will continue to be engaged until the end of their follow up time to collect sexual behavior data, but HIV testing will not be conducted once HIV-positive status is confirmed. Men will be counseled about ART initiation and ART adherence and HIV viral load testing will be conducted when HIV is first detected and 3 months after ART initiation. IDIK is situated next to a public health facility that provides ART and is often a close collaborator to receive referred research participants for HIV care.

Visit-specific procedural tables

	SCR	ENR	M1	M3	M6 & EXIT
ADMINISTRATIVE & REGULATORY PROCEDURES					
Obtain informed consent	X	X			
Collect/update locator information	X	X	X	X	X
Collect/update demographic information	X	X			
CLINICAL & COUNSELING PROCEDURES					
HIV pre and post-test counseling	X	X	X	X	X
Risk reduction counseling & condom provision	X	X	X	X	X
If HIV negative: PrEP counseling, including adherence counseling	X	X	X	X	X
If HIV negative: PrEP provision, if desired	X	X	X	X	X
If HIV negative: PrEP pill count, if using PrEP			X	X	X
If HIV negative: Urine TFV testing (when kits are available), download of electronic monitoring data (if devices are available)			X	X	X
If HIV positive: ART referral	X	X	X	X	X
If HIV positive: ART counseling	X	X	X	X	X
Diagnostic testing and/or syndromic management of STIs	X	X	X	X	X
STI treatment	[X]	[X]	[X]	[X]	[X]
LABORATORY PROCEDURES					
If HIV negative: Creatinine testing when using PrEP	X				X
If HIV negative: HBV surface antigen	X				
HIV rapid test	X	X	X	X	X

If rapid test positive: Confirmatory HIV testing and RNA quantification	[X]	[X]	[X]	[X]	[X]
BEHAVIORAL DATA COLLECTION					
Questionnaire completion		X	X	X	X
Medical History questionnaire	X	X	X	X	X
X required procedure; [X] if clinically indicated					

Study exit

Approximately 6 months after enrolling, men will complete their last study visit. At this visit, men will be provided with referrals to clinics of their choice to continue receiving PrEP and any other clinical services needed.

O. Special circumstances

HIV seroconversion

HIV rapid testing will be conducted quarterly during follow up. We expect the rate of HIV seroconversion to be very low, due to the use of PrEP and repeated counseling about HIV prevention and PrEP. However, in the event of HIV positive rapid test results, PrEP will be stopped immediately, and additional blood samples will be drawn for confirmatory HIV testing according to national guidelines. Men with confirmed HIV seroconversion will be extensively counseled and referred to local clinics providing antiretroviral medications and HIV care. Seroconverting men will remain in the study until their follow up period has ended and can continue to receive counseling services from study counselors as part of good clinical care.

Partner Notification

Research staff will follow national guidelines for assisted partner notification (APN) in the event of positive HIV diagnostic tests and take precautions to avoid safety problems. Modalities in the existing programmatic approach of APN include self-disclosure, assisted disclosure, or facilitated disclosure. Staff are well trained in counseling messages regarding the benefits of APN and are able to conduct APN activities depending on the participant's preferences. Staff are also very experienced with counseling couples' on issues of sexual health if couples choose to attend visits together.

P. Safety monitoring

Kidney function will be monitored at PrEP initiation and 6 months later, in accordance with Ugandan guidelines, using creatinine clearance calculated by Cockroft–Gault equation. The investigators will be responsible for continuous close monitoring of all adverse events that occur among study participants. For the purposes of this study, only serious adverse events (SAEs) and adverse events felt related to PrEP will be documented on case report forms. Adverse events and the severity of clinical symptoms will be scored using the DAIDS Table for Grading the Severity of Adult and Pediatric AEs.[28] The study safety monitor will review clinical and laboratory SAEs in real time as they are reported by the site clinicians on CRFs and through email within 48 hours of occurrence. As needed, the safety monitor will work to provide rapid consultation with clinicians regarding the management of toxicities. A Safety Review Team comprised of the study investigators and lead clinicians will review clinical and laboratory safety reports summarizing SAEs via conference call on an approximately quarterly basis.

VI. DATA COLLECTION

Demographic, behavioral and clinical data including STIs symptoms, sexual activity and PrEP adherence will be recorded electronically on case report forms (CRFs) directly entered by research staff into a secure web-based data management program. Results from off-site laboratory testing will be returned to the IDI research clinic and also entered into this system. Automated legal range checks will be programmed to reduce data entry errors and internal quality control reports will be run on a monthly basis. Paper backup forms will be available in the case of power or internet outages with online data entry once restored. On a weekly basis, the University of Washington data manager will archive a backup copy of the master dataset on secure servers at the University of Washington.

VII. LINKAGE WITH DATA FROM WOMEN IN THE EXISTING KWBS COHORT

Men in this study will receive a study brochure from their female partner who is participating in the KWBS study. The brochure will have a label affixed to it with a code that is anonymously linked to the study ID of the woman recruiting him. At the time of presenting to the IDIK research clinic, potential male participants will be asked to bring their brochure so that the code can be scanned, and a male ID can also be linked to the same code. Using the code will enable women's ID to be linked to men's ID(s). If an enrolling participant does not have a coded brochure, we will create a link to a woman's ID by asking for the name of the woman who recruited him and accessing our link logs that are stored in a secure room with biometric access control.

VIII. DATA ANALYSIS

Data from each man and his female KWBS partner who recruits him will be longitudinally aligned using study visit dates. The primary exposure is male infection with HIV (Aim 1), NG, or CT (Aim 2), or female infection with HIV, NG, or CT (Aim 3) and the primary outcome will be PrEP used by women/men with sufficient daily adherence to confer HIV protection for periods when PrEP is dispensed. When PrEP is not dispensed, we will assign a TFV level of 0 ng/mL. We will estimate the association between HIV risk and use of PrEP using GEE to account for repeated measurements. Models will adjust for key confounding factors (demographic, sexual behavior, clinical).

IX. HUMAN SUBJECTS CONSIDERATIONS

The protocol, informed consent forms (for cohort participation and for interviews of providers), and patient education and recruitment materials will be reviewed and approved by the IRBs/ECs responsible for oversight. Subsequent to initial review and approval, the responsible IRBs/ECs will review the study at least annually.

A. Study oversight

The protocol study team will review a comprehensive set of safety and study operational data every 6 months to ensure that timelines are being met and the study will be able to answer its primary research questions.

B. Informed consent

We will perform paper-based consenting of participants in their preferred language. After we have ensured that participants have read and understood the consent forms, we will ask them to

append their signature on paper. Any participant who wants their consent form to take home will be given a copy.

C. Risks

Risks for this cohort include side effects from PrEP provided to the young men through the study clinic, and discomfort associated with blood draws, interviews, and STI and HIV counseling and testing. Intensive and ongoing counseling and monitoring of side effects and adverse events limit the risk for participants from the direct study procedures.

For clinical data collection, standardized surveys will be used that will include questions on sensitive topics, such as sexual behavior. All participants will be extensively counseled about the risk and prevention of STIs, as well as the risk for HIV transmission with sex unprotected by a condom and/or PrEP and the importance of using condoms consistently and correctly. We expect that the risk of HIV transmission will actually be lower in this cohort than the general population of young men due to the careful attention that will be given to counseling about HIV risk and the provision of PrEP. Study staff will be aware of the potential for confidentiality issues with regards to test results from HIV testing that are part of a participant's study documents.

There is the potential for confidentiality issues with regards to study data. Although the study site will make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others, and that social harms may result. However, the research staff has extensive experience in both individual and couples counseling, particularly on the topics of serodiscordance and HIV status disclosure. The research staff will provide couples counseling if the male participant chooses to involve their study partner, or individual counseling if the male participant chooses to keep his STI/HIV results confidential.

D. Benefits

Participants will receive individualized HIV and STI risk-reduction counseling and testing, access to PrEP medication, and free condoms. In addition, participants may benefit in the future from information learned from this study.

E. Care for persons identified as HIV positive

Men who test positive for HIV at enrollment or become infected with HIV later in the study will be referred immediately to HIV care centers and encouraged to initiate antiretrovirals in line with Ugandan national antiretroviral guidelines.

F. Treatment for injury

Participants will be asked to inform the clinic staff if they feel they have been injured because of taking part in the study. Injuries may also be identified during laboratory testing, and medical histories. Treatment for adverse events related to study participation will be provided by the research clinic. If treatment is required that is beyond the capacity of the clinic, the clinic staff will refer the participant to appropriate services or organizations that can provide care for the injury. The study based at IDI will cover the costs of the referral and treatment costs up to the time the participant is stable, or injury is resolved.

F. Study records

Complete, accurate, and current study records will be maintained and stored in a secure manner throughout the study. Study records include administrative documentation and regulatory documentation as well as documentation related to each participant enrolled in the cohort, including informed consent forms, chart notes, case report forms, laboratory requisitions, notations of all contacts with the participant, and all other source documents.

G. Confidentiality

Every effort will be made to protect participant privacy and confidentiality to the extent possible. Personal identifying information will be retained at the local study site.

X. CLINICAL RESEARCH SITE

A. Site location

The Infectious Diseases Institute (IDI)-Kasangati research clinic is part of the Infectious Diseases Institute, Makerere University College of Health Sciences. The facility is located next to Kasangati Health Center IV and has adequate space and equipment for ongoing and planned research studies. The Infectious Diseases Institute training team offers specialized courses in HIV management for health providers in Africa. For this study the focus of the training will be combination HIV prevention services including PrEP as well as STI prevention and treatment.

B. Clinical facilities

The site has a large training room that can accommodate up to 50 people, 3 clinical rooms, 6 counseling rooms, a pharmacy, a phlebotomy room, a side lab, secure data room with data archive, administrative office space, wireless internet, telephone intercom system, community education offices, and a large waiting area which provide sufficient space for the execution of this study.

C. Staff

The Principal Investigator is a seasoned HIV/AIDS researcher and trainer, of local and international repute. He will lead the study team to maximize the scientific, ethical integrity of the study and ensure the training provided is of high quality. The study employs in total doctors, nurse counselors, a pharmacy technician, laboratory staff and community educators/counselors, data personnel, qualitative research associates as well as support and administrative staff. The respective staff are overseen by a site coordinator, training coordinator and administrator. The study site previously implemented the Partners PrEP Study and the Partners Demonstration Project and is currently implementing the KWBS. The staff have substantial experience in the use of PrEP and its accompanying supportive services. The staff have been involved in the conduct of protocol specific training, development of outreach materials, and have skills in training of adult learners.

D. Administrative procedures

All administrative procedures regarding protocol compliance, study coordination, study activation, study monitoring, study records, and use of information and publications will be done according to good clinical practice.

E. Laboratory considerations

We will as much as possible use the public health laboratory facilities for routine laboratory monitoring. In situations where this is not possible, specimens will be collected and transported to the study collaborating laboratories. All specimen collection, transport, processing, testing, archiving, and results reporting will be conducted in accordance with good clinical and laboratory practice standards. The collaborating laboratories for the research clinic are the IDI Core Laboratory and the Immunology Laboratory in the Department of Medical Microbiology at Makerere College of Health Sciences. These are well-established labs with extensive experience in supporting clinical trials. External Quality Assurance (EQA) procedures will be followed

throughout the study and are overseen by the University of Washington International Clinical Research Center.

XI. DATA SHARING AND OWNERSHIP

During the conduct of the trial, the study database will remain confidential. After study completion, access to data will follow requirements of the Infectious Diseases Institute, National Institutes of Health and the University of Washington. The University of Washington International Clinical Research Center has a Manuscripts and Ancillary Studies Committee established to enable data and specimen collaborative work from studies conducted through the research group. Intellectual property and data generated under the proposed project will be administered in accordance with Uganda, University of Washington and NIH policies, including the National Guidelines for Research involving Humans as Research Participants (2014) [113] and the NIH Data Sharing Policy and Implementation Guidance of March 5, 2003.

Materials generated under the project will be disseminated in accordance with University/participating institutional and NIH policies. Depending on such policies, materials may be transferred to others under the terms of a material transfer agreement. Access to databases generated under the project will be available for educational, research and non-profit purposes as approved by the relevant IRBs. Publication of data shall occur during the project, if appropriate, or at the end of the project, consistent with normal scientific practices. We will publish our findings in a timely fashion and will present unpublished data at appropriate research conferences. We are committed to collaboration in complex disease research and will participate in data-pooling studies as allowed by our currently established consent forms and IRBs.

Data obtained from this research study are the property of the Infectious Diseases Institute of Makerere University and the University of Washington International Clinical Research Center. Local researchers shall have unrestricted access rights to datasets collected through this collaborative research project in accordance with Uganda guidelines.

XII. DISSEMINATION PLAN

Dissemination of study results will follow principles of good participatory practice. Study results will be disseminated through presentations to study participants, stakeholders and policy makers, and published in conference abstracts and peer-reviewed journals. Participants will be informed that if they so desire, they will be contacted at the end of the study for the purpose of informing them about study results. Trial results will also be shared with the community advisory board, the Ministry of Health, implementing partners and civil society groups with interest in reproductive health.

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