PROTOCOL

Weekly doxycycline DOT for STI prevention among cisgender women taking HIV PrEP in Kisumu, Kenya

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GLOSSARY

AE	Adverse event
AMR	antimicrobial resistance
ART	Antiretroviral therapy
CDC	Centers for Disease Control
COVID-19	Coronavirus Disease 2019
CT	*Chlamydia trachomatis*
DAIDS	Division of AIDS
DALY	Disability-adjusted life year
DOT	Direct Observation Therapy
dPEP	Doxycycline post-exposure prophylaxis
GEE	Generalized estimating equations
HAL	Hair Analytical Laboratory
HIV	Human Immunodeficiency virus
HSV	Herpes simplex virus
IATA	International Air Transport Association
ICER	Incremental cost effectiveness ratio
IDI	In-depth interviews
IH	Intracranial hypertension
IRB	Institutional Review Board
IPV	Intimate partner violence
KEMRI	Kenya Medical Research Institute
LARC	Long acting reversible contraceptives
LMP	Last menstrual period
MOH	Ministry of Health
MSM	Men who have sex with men
NAAT	Nucleic acid amplification test
NASCOP	National AIDS & STI Control Programme
NG	*Neisseria gonorrhoeae*
PCR	Polymerase chain reaction
PEP	Post-exposure prophylaxis
PID	Pelvic inflammatory disease
PLWH	People living with HIV
PPB ECCT	Pharmacy and Poisions Board Expert Committee on Clinical Trials
PPE	Personal protective equipment
PrEP	Pre-exposure prophlaxis
RPR	Rapid Plasma Reagin
SAE	Serious Adverse Event
SMS	Short message service
SOP	Standard operating procedures
STIs	Sexually transmitted infections
TDF/FTC	Tenofovir/Emtricitabine
*tet*R	Tetracycline resistant
UCSF	University of California San Fransisco
UW	University of Washington
VCT	Voluntary counseling and testing

ABSTRACT

African women face disproportionate risk from overlapping epidemics of HIV and bacterial sexually transmitted infections (STIs). HIV pre-exposure prophylaxis (PrEP) is emerging into a global context with unprecedented rates of curable STIs. Post-exposure prophylaxis using the antibiotic doxycycline has been proposed as a novel STI prevention strategy. The first study of doxycycline postexposure prophylaxis for cisgender women did not reduce incident STIs likely due to low use of doxycycline. The overarching goal is to assess acceptability and adherence to once-weekly doxycycline dosing to prevent STIs. We will conduct a pilot study of once-weekly doxycycline to prevent bacterial STIs among Kenyan cisgender women using PrEP for HIV prevention. Approximately 50 (up to 60) sexually active, cisgender women ages 18-30 years will be enrolled in this study and followed for six months. Participants will receive doxycycline once-weekly dose as directly observed therapy (DOT). All participants will complete STI testing (chlamydia, gonorrhea, and syphilis)at enrollment, month-three and month-six. Prior to initiating treatment and at exit visit, all participants will have samples collected for future microbiome and resistance testing. Hair samples will be collected at follow-up visits for future pharmacokinetic model development. The primary endpoint is percentage of completed weekly DOT doxycycline doses. Secondary endpoint is quarterly incident rate of *Chlamydia trachomatis* compared with quarterly incidence among participants assigned to standard of care in the dPEP Kenya Study.

LAY SUMMARY

We propose to conduct research on weekly antibiotic, specifically doxyclycline, taken under the observation of trained research staff, for prevention of bacterial sexually transmitted infections (STIs) among Kenyan women. The study population will include up to sixty Kenyan women between 18 and 30 years old who are already using a medication called pre-exposure prophylaxis (PrEP) for prevention of HIV. The study will be conducted at the KEMRI-RCTP clinic at Lumumba Sub-County Hospital in Kisumu County, Kenya. The primary objectives of the study are to assess the acceptability and continued use of weekly doxycycline when given under direct observation. We will also measure rates of STIs when taking weekly doxycycline prophylaxis among HIV-uninfected Kenyan women compared with data from a similar population of participants in a recently completed study (dPEP Kenya Study) in Kisumu, Kenya. Participants will be followed for six months. Participants will receive doxycycline once-weekly dose with assistance from study staff to be taken under direct observation, and participants will have STI (chlamydia, gonorrhea, and syphilis) testing and treatment at enrollment, at month-three, and at month-six. The primary outcome is continuation of antibiotic prophylaxis, or the percentage of completed weekly doxycycline doses. Secondary outcomes include quarterly new infections with the bacterial STI, *Chlamydia trachomatis*. Before starting study medicine and at the final visit, all participants will have samples collected for future testing of bacteria that live in the reproductive and gastrointestinal tract and resistance to antibiotics. Hair samples will be collected at follow-up visits for future study of the amount of doxycycline in hair with once a week use of doxycycline.

1. BACKGROUND AND SIGNIFICANCE

1.1. Background

African women face disproportionate risk from overlapping epidemics of HIV and bacterial sexually transmitted infections (STIs). More than two million persons become newly infected with HIV each year, the majority in sub-Saharan Africa.[1] Young African women (under age 30) face disproportionate HIV risk, accounting for more than half of new infections on the continent, and with incidence rates that are often double or more than their male age-mates.[2-4] At the same time, African women also face a disproportionate burden of STIs. Globally, the World Health Organization (WHO) estimates that 358 million new cases of four curable STIs – three bacterial pathogens (*Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Treponema pallidum* [etiologic cause of syphilis]), plus the parasite *Trichomonas vaginalis* – are acquired worldwide.[5-7] Overall, the global burden of STIs is greatest in low- and middle-income countries, and the overlapping epidemics of HIV and bacterial STIs in Africa have been recognized since the earliest days of the HIV epidemic.[8-12] The consequences of bacterial STIs on sexual and reproductive health can be profound: pelvic inflammatory disease (PID), chronic pelvic pain, tubal infertility, pregnancy complications, fetal and neonatal death, and increased susceptibility to HIV.[8, 11, 13-17] These consequences are overwhelmingly borne by women.

HIV pre-exposure prophylaxis (PrEP) is emerging into a global context with unprecedented rates of curable STIs. The past decade has witnessed monumental strides in the development of highly-effective HIV prevention interventions, including antiretroviral PrEP.[18-21] PrEP reduces incident HIV but was not expected to prevent other STIs, including gonorrhea, chlamydia, or syphilis. In high-income countries, like the US, the past decade has seen an explosion in the incidence of bacterial STIs among MSM.[22-24] The scale-up of PrEP in the US and other settings with MSM-predominant epidemics is concurrent with this STI rise, although several other major transitions are also occurring, including evidence for antiretroviral treatment as prevention (and the undetectable=untransmittable [U=U] campaign)[25, 26] and changing trends in sexual mixing patterns.[27, 28] HIV and STIs overlap in transmission pathways through sexual exposure; thus, it is not surprising that high STI rates are seen among persons who use PrEP. The role of PrEP in driving changes in sexual behavior and increased risk for STI acquisition among MSM using PrEP has been a source of substantial scientific and public health debate.[24, 29, 30]

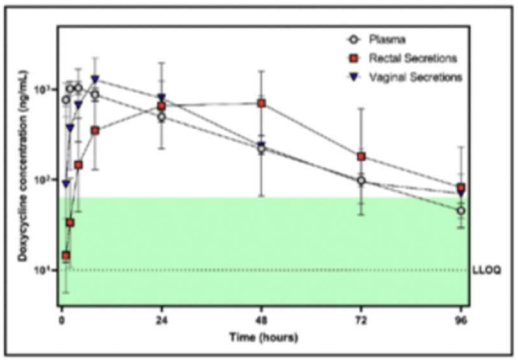
Post-exposure prophylaxis using the antibiotic doxycycline has been proposed as a novel STI prevention strategy. Several recent open-label clinical trials among MSM in France (IPERGAY followed by DOXYVAC) and the US (DoxyPEP) found a 47-70% relative reduction in new bacterial STIs (specifically, *C. trachomatis*, *N. gonorrhoeae*, or *T. pallidum*) among PrEP users who also took doxycycline hyclate 200mg following every sexual encounter.[31, 32] This reduction was driven by reductions in incident *C. trachomatis* (70% reduction) and *T. pallidum* infections (73% reduction). The use of post-exposure doxycycline to prevent infections is already standard, recommended practice – for example, after tick exposure in areas of high Lyme disease prevalence or after flooding in leptospirosis endemic areas.[33-35] The concept of STI prophylaxis has a long history,[31, 36, 37] and several studies on single dose or monthly antibiotics, among female sex workers in Asia and Africa, demonstrated reduced disease burden;[38-43] a meta-analysis showed a statistically significant impact on incidence of curable STIs in 13 of 14 studies included.[37] The IPERGAY results[31] were striking in the overall reduction in incident STIs, good tolerability and safety, high adherence, and continuation (both >90%), and without a significant change in sexual behavior in the intervention arm.[31] These results were similar to results among people assigned male sex at birth, taking HIV PrEP, and history of an STI in the prior year in the US with 70% reduction in *C. trachomatis, T. pallidum,* and *N. gonorrhoeae*.[32]

The first study of doxycycline postexposure prophylaxis for cisgender women did not reduce incident STIs likely due to low use of doxycycline. The dPEP Kenya Study enrolled 449 cisgender women taking HIV PrEP in Kisumu, Kenya. Participants were randomized 1:1 to open-label use of doxycycline hyclate 200mg within 72 hours of condomless sex compared with standard of care, or quarterly STI testing and treatment. Participants

in this study had high prevalence (18%) and annual incidence (27%) of bacterial STIs, primarily *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, with no statistical difference in frequency of quarterly incident STIs between groups. Using objective measures of doxycycline use, doxycycline was only detected in approximately 1/3 of hair samples, and low use of doxycycline PEP contributed to a null result in this trial. Qualitative data suggests that participants experienced multiple barriers to event-driven dosing.

Doxycycline was detectable in the serum and vaginal secretions at high levels for at least four days following a single oral dose of 200mg oral doxycycline hyclate per recent pharmacokinetic data (**Figure 1**).[44] Limited data on minimum inhibitory concentration (MIC) of doxycycline needed to treat a *C. trachomatis* infection suggests that these high levels of doxycycline sustained for four days are above the MIC. There is no established MIC for prevention, and due to a smaller bioburden of organisms with an initial exposure compared with an infection that has already invaded tissue, it is presumed to be less than that needed for treatment.

Figure 1. Drug concentration compared with therapeutic dose for treatment of *C. trachomatis* following a dose of doxycycline hyclate 200mg. Haaland R. et al., CROI, 2023



	Time above MIC value		
	C_{max}	MIC	4x MIC
Plasma	16x	87 hr	44 hr
Rectal Secretions	11x	97 hr	62 hr
Vaginal Secretions	20x	101 hr	45 hr

Minimum Inhibitory Concentrations (MIC):
C trachomatis MIC_{90} = 64 ng/mL Zheng *Sex Transm Dis* 2015

Doxycycline prophylaxis could be especially impactful for African women using PrEP. Essentially all global conversation about doxycycline for STI prevention has been directed towards MSM in high-income settings, but the benefits might be especially great for women in Africa. Due to limited availability of etiologic STI testing in Africa, few studies have assessed STI risk among PrEP-using women in Africa, but we have led several studies among young African women that also contribute some of the only information about both STI prevalence and incidence in that population (**Table 1**).[45-48] In those studies, we are seeing very high STI rates, already comparable to those seen among PrEP-using MSM in high income countries. Thus, African women already carry a striking burden of STIs, reflecting likely high rates in male partners as well, low ability to negotiate condom use, and great need for prevention. PrEP roll-out provides an opportunity to impact both HIV and STI rates in African women. First, the consequences of STIs (PID, tubal infertility, complications of pregnancy) are arguably substantially greater than those faced by MSM with pharyngeal or rectal STIs. Second, the current standard of care in Africa for STI diagnosis is syndromic management, which has very poor sensitivity (<20%) compared to etiologic testing[47] and low positive predictive value (approx. 50%);[49, 50] Doxycycline prophylaxis could be an inexpensive intervention in settings where testing is unavailable or unaffordable. Third, doxycycline is affordable and accessible in Africa. Fourth, weekly doxycycline does not rely on partner participation.

Table 1. High STI rates among young African women in three vanguard PrEP cohorts

	Chlamydia trachomatis	*Neisseria gonorrhoeae*
MTN-020/ASPIRE (phase III dapivirine ring trial) [Baeten, protocol chair]	Prevalence = 12% Incidence = 27% per year	Prevalence = 4% Incidence = 11% per year
HPTN 082 (PrEP demonstration project) [Baeten, co-I]	Prevalence = 29% Incidence = 33% per year	Prevalence = 8% Incidence = 14% per year
POWER (PrEP implementation project) [Baeten, protocol chairs, Bukusi, co-I]	Prevalence = 26% Incidence = 53% per year	Prevalence = 10% Incidence = 20% per year
dPEP Kenya (doxycycline for STI prevention) [Stewart, protocol chair, Baeten/Bukusi, MPI]	Prevalence = 14% Incidence = 21% per year	Prevalence = 4% Incidence = 8% per year

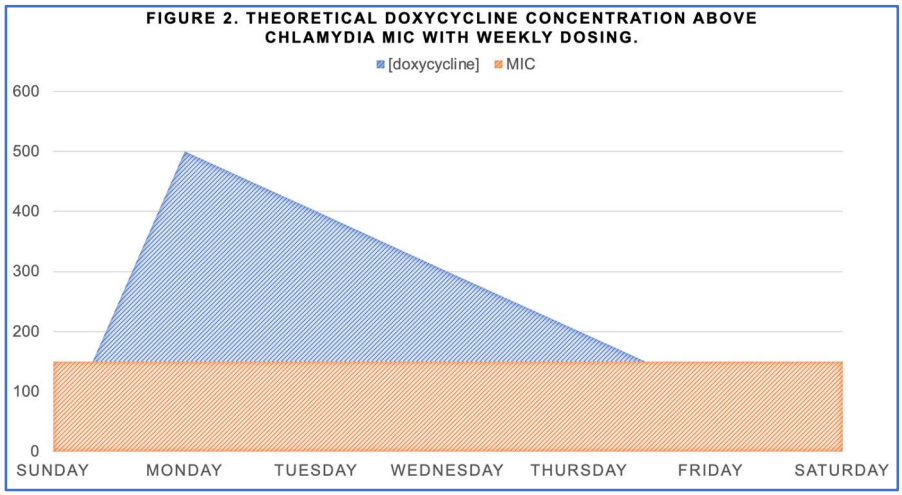
Note: Syphilis prevalence was <2% in these studies, with incidence <5% per year – emphasizing that the burden of STIs in this population is cervical infections. HSV-2 seroprevalence was ~50%.

1.2. Rationale

Rationale for evaluation of Kenyan women

Prior work on doxycycline post-exposure prophylaxis against bacterial STIs in Kisusmu, Kenya, demonstrated high rates of STIs among cisgender women taking HIV PrEP and low use of doxycycline as an event-driven post-exposure prophylaxis. The proposed study will focus on enrolling women, who far disproportionately bear the global burden of morbidity and mortality from sexually transmitted infections. Thus, this work will ensure that this potential prevention strategy is justly studied in women, and a specific focus on women is justified.

Rationale for weekly doxycycline dosing



Given low rates of use with event-driven doxycycline PEP along with high rates of STIs and extremely low rates of condom use indicate a need for alternative strategies for STI prevention and recent pharmacokinetic data suggests that one 200mg dose a week results in four days of doxycycline drug level above the treatment MIC, which may be sufficient for prevention of bacterial STIs regardless of timing of exposure each week, allowing for an opportunity for supported dosing with Direct Observed Therapy (DOT). Participants receiving a weekly dose would have inhibitory concentrations in vaginal secretions for four days of each week and then the following dose would be within 72 hours of the prior dose allowing for a pre-exposure and post-exposure combination approach to dosing that would minimize pill burden and allow for added adherence support with directly observed dosing (**Figure 2**). DOT in this study offers numerous advantages. By monitoring patients as they take their medication, DOT ensures that any treatment failure detected is not due to missed doses of treatment[51], leading to more accurate data on treatment effectiveness. It also allows research staff to promptly identify and address potential side effects or adverse reactions to medications. Furthermore, DOT contributes to better overall health outcomes by reducing the likelihood of developing antibiotic resistance, as patients are more likely to complete their prescribed treatment course. A standardized weekly DOT will also allow for crucial data collection needed to build a pharmacokinetic model for interpreting quantitative concentrations of doxycycline in hair samples.

Doxycycline safety

Safety was a key consideration for the development and evaluation of PrEP, and similarly should be part of STI PEP assessment. Data evaluating PrEP use in women at all stages of reproductive planning (desiring pregnancy, achieving pregnancy, and in combination with hormonal contraceptives) have demonstrated safety, many of the studies by our team.[52-57] Doxycycline is well-tolerated and recent data show strong safety when used by women, including in early pregnancy.[34] Early data on tetracycline found bone and tooth effects when used in late pregnancy, and cautions were extended to the entire tetracycline class, including doxycycline, despite lack of drug-specific data.[58] Tetracyclines are safe for use in lactating women but are not recommended at high doses or extended courses due to theoretical risk of infant tooth discoloration.[59, 60] Expert opinion is now calling for reconsideration of doxycycline use in pregnant and lactating populations given significant differences between doxycycline and tetracycline and lack of evidence showing adverse events with doxycycline exposure in pregnant women.[61] For women who do not desire pregnancy, there are no estrogen/progesterone and doxycycline drug-drug interactions, so doxycycline use will not alter hormonal contraceptive effectiveness.[57]

Potential for drug resistance

The potential for inducing drug-resistant STIs is an important concern for doxycycline prophylaxis. On one hand, antibiotic resistance to tetracycline-class drugs is selected relatively easily in some bacteria (e.g., *N. gonorrhoeae*); on the other hand, resistance for *N. gonorrhoeae* is common globally, making additional resistance selection unlikely, but other organisms (e.g., *C. trachomatis*) have never demonstrated resistance. Syphilis (*Treponema pallidum*) is at risk of developing tetracycline resistance; however, we anticipate very low rates (<2%) of syphilis and thus in this population the risk of developing resistance is very low. In the dPEP

Kenya study, there was only 1 *T.pallidum* infection among 109 incident STIs reported. The dPEP Kenya Study also revealed that 100% (n=48) of all *N. gonorrhoeae* infections were associated with a high level tetracycline resistance molecular mutation, *tet*M, including at baseline and participants assigned to standard of care indicating that further exposures to doxycycline could not increase the prevalence of resistance in Kisumu, Kenya.[62] In general, if weekly doxycycline is successful in preventing STIs, this dramatically reduces the risk of resistance, as selection should only happen if infection is established and replication occurs despite antibiotic pressure. Overall, we feel there are both important knowns and unknowns that define equipoise for this question, and we have put strong strategies in place to measure and mitigate potential resistance risks.

2. OBJECTIVES

2.1. Primary Study Objectives:

1. Assess the acceptability of once weekly doxycycline prophylaxis
2. Assess persistence in once weekly doxycycline DOT

2.2. Secondary Study Objectives:

1. Evaluate incidence rate of STIs in women given once-weekly doxycycline DOT
2. Assess the safety and tolerability of once weekly doxycycline prophylaxis
3. Collect samples for future doxycycline hair drug level pharmacokinetic drug testing, rectal swabs and endocervical swabs for resistance testing, and rectal and vaginal swabs for microbiome evaluation.

3. METHODOLOGY

3.1. Design

Overview: The overarching goal is to assess acceptability and adherence to once-weekly doxycycline dosing to prevent STIs through a pilot study.

Enrollment: Eligible participants will be assigned to doxycycline and will be given doxycycline 200 mg orally, once weekly at the study clinic or within the community with a trained study staff as DOT. Study staff will record confirmation of each dose taken. Enrollment visit will take place in the clinic to allow for provider collected sample collection and delivery of first DOT.

Study visits: All participants will attend the clinic for quarterly visits after enrollment (Month 3 and Month 6). Participants will provide provider-collected genital swab for STI testing. Treatment will be provided for any positive test result. Hair samples (50-100 strands) will be collected at Month 3 and Month 6 from all participants with sufficient (>1cm) hair. Month 6 exit visit will also include collection of samples for future microbiome and resistance testing).

Study population: This study will enroll approximately 50 Kenyan women (maximum of 60) aged ≥18 and ≤30 years who are sexually active and using PrEP for HIV prevention. Participants must be willing to adhere to DOT visits for the six month course of the study.

3.2. Selection and enrollment of participants

Potential participants will be screened for eligibility prior to enrollment in the study. The eligibility criteria are as follows:

3.2.1. Inclusion criteria

1) Willing and able to give written informed consent
2) Age 18-30 years
3) Female sex at birth
4) HIV-seronegative, according to national HIV testing algorithm

5) Has a current prescription for PrEP, according to the national guidelines of Kenya
6) Able and willing to adhere to DOT dosing schedules

3.2.2. Exclusion criteria

1) Pregnant
2) Breastfeeding a child
3) Allergy to tetracycline class
4) Current medications which may impact doxycycline metabolism or that are contraindicated with doxycycline, as per the prescribing information. These include systemic retinoids, barbiturates, carbamazepine, phenytoin, and warfarin.
5) Active, clinically significant medical or psychiatric conditions that would interfere with study participation, at the discretion of the site investigator or designee.
6) Prior enrollment in The dPEP Kenya Study

3.2.3. Recruitment

The study team will employ a variety of methods to recruit and screen potential participants in the Kisumu, Kenya region and will use the same strategies as the dPEP Kenya Study to improve likelihood of enrolling a similar cohort. The experienced community outreach team at the study site in Kisumu employs community-based mobilization strategies, including engaging community health volunteers, gate keepers, peer-to-peer mobilization, youth peer providers and ambassador models, use of printed and electronic IEC materials, social media (WhatsApp and Facebook), radio talk shows in English, *Kiswahili*, and the local *DhoLuo* dialects, active participation in local social events for information sharing, and partnering with learning institutions to give health talks and to provide study related information. Careful attention to confidentiality is made in the recruitment process and potential participants are never approached individually in group settings or public messaging. Recruitment messaging is screened for cultural and community acceptability to reduce risk of stigma for study participants. Potential participants who are not interested in the study or do not meet study eligibility criteria, may be notified of alternative studies that they may be eligible for, or provided information about where to access standard of care for HIV prevention and STI services.

3.3. Study treatment

3.3.1. Study product

Generic immediate release doxycycline hyclate 100 mg capsules will be provided by the study to participants randomized to doxycycline DOT and will take two capsules once weekly for six months. Doxycycline hyclate is a standard formulation of doxycycline that is widely available internationally and FDA approved for the treatment of a number of infectious conditions. Doxycycline hyclate will be purchased from a quality-controlled supplier in Kenya and with consultation by the Kenya National AIDS and STI Control Programme. Product suppliers will be able to provide evidence of good manufacturing practices.

3.3.2. Safety

Doxycycline is widely used for the treatment of chlamydia and other infections. Serious side effects are extremely rare.

The possible side effects of doxycycline are[63, 64]

- Gastrointestinal upset: nausea, diarrhea, epigastric pain, and candidiasis
- Esophageal disorders: dysphagia, pill esophagitis, and rarely esophageal ulceration. Risk for esophageal irritation can be reduced by taking doxycycline capsules at least one hour before bedtime (to avoid being lying down with doxycycline intake) at a meal with a glass of water (100 ml).
- Skin reactions including maculopapular, erythematous, and photosensitivity skin reactions.

3.3.3. Dispensing and administration

Doxycycline will be stored at the Kisumu site pharmacy at room temperature (59-86° F). Study pharmacists will be responsible for dispensing and accountability of all study product.

Participants randomized to receive doxycycline will be advised on potential side effects and their management. Participants will take their first dose of doxycycline at the study clinic. Thereafter, each dose will be provided either at the study clinic, at a community location agreed upon by the participant and study staff, or at a community pharmacy where study staff are available to provide DOT. Study staff carrying doxycycline outside of the study clinic will keep the drug secure and within temperature range to the extent possible. Accountability logs and study case report forms will document the administration of doxycycline. Doxycycline may be taken on an empty stomach or with food, and it is advised to take with a large glass of water to reduce risk of esophageal irritation and with food to reduce nausea.

3.3.4. Concomitant Medications

Participants should report current and new medications to the study team to ensure no concern for drug interactions. The prescribing information for doxycycline hyclate and azithromycin should be reviewed to ensure no potential for drug interactions. Medications that interact with doxycycline include barbiturates, carbamazepine, phenytoin, methoxyflurane, acitretin, isotretinoin, and warfarin.

3.4. Study procedures

An overview of study procedures is provided in Table 2. Participants will also have weekly visits as described below.

Table 2. Schedule of study procedures.

Study Visit	S	E	3	6
Administrative				
Obtain informed consent	X			
Screen for inclusion/exclusion	X	X		
Collect updated contact information	X	X	X	X
Reimbursement	X	X	X	X
Surveys				
Demographic information	X	X		
Acceptability		X	X	X
Sexual behavior		X	X	X
Clinical care				
Medication review	X	X	X	X
General symptom assessment		X	X	X
WHO pregnancy checklist	X		X	X
STI symptom assessment	X	X	X	X
Counseling				
STI/HIV risk reduction counseling	X	X	X	X
Condom provision	X	X	X	X
Clinical Testing				
HIV testing (rapid test)	X		X	X
Urine pregnancy testing	(X)	X	(X)	(X)
CT/NG testing Xpert (endocervical swab)		X	X	X
Syphlis testing (serum RPR)		X	X	X
Archived Sample Collection				
Hair collection for drug level testing (stored)			X	X
Aptima CT/NG endocervical swab (stored)		X	X	X
Endocervical swabs for resistance (stored)		X		X
Rectal swabs for resistance (stored)		X		X

	Vaginal swabs for microbiome (stored)		X		X

3.5. Study visits

Specific study procedures are detailed in Table 2.0. Study visits will take place at screening/enrollment, Month 3, and Month 6 with additional weekly DOT delivery of doxycycline. We will conduct tracing in the case of missed visits to ensure that missed visits are minimized regardless of whether or not doxycycline is continued. All participants will provide clinical and behavioral data. We will use electronic data capture for surveys and case report forms. All participants will receive reimbursement for their time and effort for each visit, in accordance with local regulatory and ethics approvals.

3.5.1. Screening Visit:

Potential participants will be screened for inclusion and exclusion criteria, and those eligible will be invited to enroll. Potential participants will provide written informed consent before any research procedures are completed. Participants will be screened for symptoms of STIs, and treated empirically if symptomatic (per Kenyan National Guidelines). Pregnancy will be assessed using the WHO pregnancy check list and a pregnancy test. If the woman is pregnant, she will not be eligible for enrollment and will be referred for antenatal services.

3.5.2. Enrollment Visit:

The enrollment visit will be as soon as the following day after screening visit and as late as 28 days following the screening visit. Demographic, behavioral, and medical information will be collected. Prior to administration of doxycycline, providers will complete a pelvic exam and genital sample collection for CT/NG testing (NAAT Xpert), and future resistance and microbiome testing. Additionally, two rectal swabs will be collected: one for future resistance testing and one for future Aptima testing. Participants with an STI at enrollment will complete treatment. Women will be tested for pregnancy with urine rapid pregnancy test at enrollment regardless of contraceptive use, and may also receive a referral for contraception, if desired. All potential participants will be screened for HIV, following national HIV testing guidelines. Women who have a positive HIV test will be referred for HIV care and treatment and counseled on discontinuation of HIV PrEP.

3.5.3. Follow-up clinic visit (Month 3):

All participants will visit the study clinic at three months (+/- two weeks) after enrollment. Participants will be tested for STIs using provider collected endocervical swab (CT/NG) and blood (syphilis) as well as blood for HIV testing. An additional endocervical Aptima swab will be collected for future testing if needed. If a participant has signs or symptoms of an STI, she will be provided with syndromic management and treatment or following receipt of the STI results if willing to wait for same day results. Participants will also be asked to provide a hair sample (50-100 strands) to be used for drug-level testing in the future. Behavioral questionnaires will be administered, including sexual behavior and acceptability. Participants will be asked about adverse events and any changes to their medical history or concomitant medication use.

3.5.4. Exit clinic visit (Month 6):

All participants will visit the study clinic at six months (+/- two weeks) after enrollment. Participants will be tested for STIs using provider collected endocervical swab (CT/NG) and blood (syphilis) as well as blood for HIV testing. An additional endocervical Aptima swab will be collected as well as endocervical and rectal swab for resistance testing in the future and vaginal swab for microbiome testing in the future, which will all be stored and archived. If a participant has signs or symptoms of an STI, she will be provided with syndromic management and treatment or following receipt of the STI results if willing to wait for same day results. Participants will also be asked to provide a hair sample (50-100 strands) to be used for drug-level testing in the future. Behavioral questionnaires will be administered, including sexual behavior and acceptability. Participants will be asked about adverse events and any changes to their medical history or concomitant medication use.

3.5.5. Doxycycline DOT visits:

Participants will have once-weekly visits (every 7 days +/- 1 day) to receive doxycycline for up to six months of follow-up. Participants may meet with study staff at the clinic, outside of the clinic at an agreed upon place with a trained peer-navigator, or at pre-specified community pharmacies where KEMRI staff are located.

Participants will be provided with 200mg doxycycline hyclate each week as DOT and study staff will record observation of dosing or reason for missed dose on study CRFs.

3.5.6. ***Unscheduled interim visits*****:**

Women may return to the study clinic for interim visits for any reason and can undergo STI testing and treatment if STI symptoms are present. Additionally, participants concerned about any adverse event from the study drug are invited to return to study provider evaluation and management.

3.5.7. Sample collection and outcome measures:

Primary study outcome: Confirmation of DOT dosing each week will be recorded on weekly CRFs and quarterly surveys on acceptability will be completed.

STI testing: Provider collected endocervical swabs will be used for STI (CT/NG) testing as well as blood testing for syphilis at Months 3 and 6. An additional Aptima swab will be collected for CT/NG testing.

Doxycycline drug level testing: As an objective measure of doxycycline use, hair samples will be tested for doxycycline drug levels. The weekly doxycycline dosing will be used to develop and validate a standardized pharmacokinetic model for doxycycline hair concentrations that will also be used to interpret results of hair samples collected from from the The dPEP Kenya Study that was carried out by our team in Kisumu Kenya.

Resistance testing: Providers will collect endocervical and rectal swabs at enrollment and Month 6, to be stored for future NG and enteric organism resistance testing.

Microbiome testing: Providers will collect vaginal swabs at enrollment and Month 6, to be stored for future microbiome testing.

3.5.8. Laboratory Procedures:

Samples will be tested within Kenya where feasible. All diagnostic tests will be done at our laboratory in Kisumu. Any samples that require specialized testing will be shipped to the University of Washington (UW) and/or other laboratories described below. For hair samples doxycycline testing, we have no laboratory with capacity to test this in Kenya and the only laboratory that specializes in this analysis is at the University of California, San Francisco, where we will be sending the hair samples for analysis. Resistance and microbiome swabs for future will be stored and tested at Dr. Soge's lab at the University of Washington.

3.5.8.1. STI testing:

All STI screening will be completed with same day testing in Kisumu, Kenya (Cepheid GeneXpert) or in the laboratory of Dr. McClelland in Mombasa, Kenya, operating with external quality assurance for >10 years (Aptima Combo 2). Vaginal swabs will be tested for *C. trachomatis* and *N. gonorrhoeae* by nucleic acid amplification testing (NAAT). Syphilis will be tested by rapid plasma reagin (RPR) titers (BD Macro-Vue) with *Treponema pallidum* hemagglutination assay (TPHA) confirmatory testing (Fortress Diagnostics) using plasma samples in the Kisumu KEMRI-RCTP lab.

3.5.8.2. Resistance testing:

Endocervical samples will be shipped to the University of Washington laboratory of Dr. Soge for possible future molecular testing of *N. gonorrhoeae* for high-level tetracycline resistance (tetM). DNA will be purified from residual endocervical NAAT samples and endocervical swabs using the *High Pure* DNA *Kit* (Roche Diagnostics, Indianapolis, IN). Swabs containing organisms will similarly be archived at University of Washington for future evaluation of doxycycline resistant enteric commensals (e.g., *Eschericia coli, Enterococcus spp., Enterobacter spp.,* and *Shigella spp.)*

3.5.8.3. Drug-level testing:

Hair sample will be collected for future testing of drug levels for a more objective assessment of exposure to doxycycline. Hair samples (50-100 strands) will be collected following consent to collection and confirmed eligibility for hair collection (occipital hair >1cm in length with absence of bleaching) from all participants at each follow-up visit (Months 3 and 6). In the future, hair samples will be shipped to Dr. Monica Gandhi's UCSF Hair Analytical Laboratory (HAL).

3.5.8.4. Microbiome testing:

We will archive vaginally collected foam tip swabs at -80C for potential future testing to evaluating potential changes in microbiome following initiation and continuation of weekly doxycycline.

3.5.9. Management and treatment of STIs

Participants found to have a diagnosis of gonorrhea, chlamydia, or syphilis will be contacted by study staff or provider regarding their new diagnosis. Participants will be offered prompt treatment (single dose azithromycin tablets, ceftriaxone intramuscularly (IM) once or benzathine penicillin G intramuscularly once) at the study clinic. If there is a delay in treatment, participants with known STIs will have doxycycline DOT held until the day after they complete their single dose treatments. Participants with clinical concern for complicated STI (i.e., PID) will be offered prolonged treatment (single dose IM ceftriaxone and 2 week course of azithromycin and metronidazole) and doxycycline DOT will be held for the duration of treatment. Participants will be encouraged to tell partners to also be treated per Kenya guidelines and offered expedited partner therapy (EPT). Counselling on STI prevention strategies will be provided to all participants during treatment.

3.5.10. Risk compensation counselling

To mitigate against potential risk compensation arising from sense of safety due to use of doxycycline for prevention of STIs, participants will receive specific counselling emphasizing on the unknown efficacy of the study medication as used in the study. Participants will also be provided with condoms for free should they need them. At each study visit, participants will receive general counselling on STI and HIV prevention strategies.

3.5.11. Management of HIV-seroconversion

If a participant tests HIV positive, following national testing algorithms, study clinicians will follow national guidelines for discontinuing PrEP. Women will be referred to the nearest HIV care clinic for initiation of antiretroviral therapy. Women who seroconvert will remain in the study through the end of their scheduled follow-up and will be permitted to continue taking doxycycline.

3.5.12. Management of doxycycline with contraceptives and pregnancy

Contraceptives will be offered on-site but will not be required for study participation. The effectiveness of contraceptives or doxycycline will not change with concomitant use. Women will be counseled on current Kenyan guidelines, which do not recommend use of doxycycline in pregnant women, due to lack of safety data, and participants will stop doxycycline should pregnancy occur. Women, who are not using LARC, will be screened for possible pregnancy at each quarterly visit using the WHO pregnancy checklist and if

needed a urine pregnancy test will be conducted. Women can resume weekly doxycycline when no longer pregnant or breastfeeding. Pregnancies will be followed to completion. Any babies born to participants during the trial period will be passively followed and asked about the health of their baby. Breastfeeding will be an exclusion criterion for the trial, to limit exposure prior to demonstration of effectiveness; doxycycline is generally felt to be safe at standard doses in lactating women, although no formal declaration of safety exists for this population. Doxycycline is well-tolerated and recent data emphasize a strong safety profile when used by women, including in early pregnancy, and children. Early data on safety of tetracycline found potential adverse effects when used in late pregnancy (specifically, bone and tooth effects), and cautions were extended to the entire tetracycline class, including doxycycline, despite lack of drug-specific data.[133,136] Expert opinion is now calling for reconsideration of doxycycline use in pregnancy given significant differences between doxycycline and tetracycline and lack of evidence showing adverse events with doxycycline exposure in pregnant women.

3.6. Adverse Events (AE) And Study Monitoring

3.6.1. Adverse Event Collection Requirements

3.6.1.1. Adverse Events (AEs)

The following AEs will be recorded on data collection forms:

- All AEs that are attributed to study product in the opinion of the site investigator
- All AEs meeting SAE definition

3.6.1.2. Serious Adverse Events (SAEs)

An SAE is defined as any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above

All AEs that are recorded must have their severity graded. To grade AEs, sites should refer to the most recent version of Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table).

3.6.2. Study Monitoring

The study team will monitor the conduct of the study through summary reports of accrual, baseline characteristics and reports of data pooled over treatment arms of data completeness, specimen collection, and AEs. The study team will review individual participant-level safety data frequently to assess the relation of all reported AEs to study treatment. The study team will review premature study discontinuations or premature study treatment discontinuations on a case-by-case basis.

3.7. Medical Monitoring Committee

We will constitute an independent medical monitoring committee composed of a variety of experts on doxycycline prophylaxis and sexual and reproductive health research, drawn from Kenya and internationally. The committee membership will be restricted to individuals free of significant conflicts of interest. This committee will meet prior to enrollment, 33% completion of study follow up time, and 66% completion of study follow up time. The committee will track side effects, potential safety concerns

associated with study participation, and fidelity to this open-label, single study arm, pilot study protocol. Open study reports containing enrollment and retention rates, participant characteristics, adverse events, and social harms, will be sent to the committee members at least one week prior to each meeting. All medical monitoring meeting reports will be shared with the overseeing ethics review committee within two weeks of each meeting or earlier per requirements of each ethics committee.

3.8. Criteria for discontinuation

Participants will continue in the study, regardless of medication or study visit adherence, with the exceptions listed below.

3.8.1. Premature Study Treatment Discontinuation

- Requirement for prohibited concomitant medications or other contraindication to doxycycline
- Occurrence of an AE requiring discontinuation of study product
- Request by participant to terminate study treatment
- Clinical reasons believed life threatening by the physician, even if not addressed in the toxicity section of the protocol

Participants who stop study treatment should be continued on study, with continued evaluations. The reason for treatment discontinuation should be recorded.

3.8.2. Premature Study Discontinuation

- Request by the participant to withdraw
- Participant judged by the investigator to be at significant risk of failing to comply with the provisions of the protocol as to cause harm to self or seriously interfere with the validity of the study results
- At the discretion of the IRB/EC, funder, or Office for Human Research Protections (OHRP)

3.9. Statistical Considerations

3.9.1. Outcome measures

***3.7.1.2. Primary outcome*:**
Percentage of completed doses of weekly doxycycline DOT

***3.7.1.3. Secondary outcomes*:**

- Safety: Safety assessment will be measured in both arms: serious adverse events (SAEs), related all AEs and discontinuations (in the dPEP arm only), and a standardized symptom assessment for doxycycline-specific side effects (e.g., nausea, pill esophagitis, photosensitivity, vaginal candidiasis).
- Acceptability: Longitudinal change in survey responses
- Incidence of *C. trachomatis* based on NAAT

3.9.2. Statistical power and analysis

3.9.2.1. Primary Analysis:

We will describe the percentage of completed doses of weekly doxycycline DOT of the 26 anticipated doses per participant, and evaluate measured rate of completion with anticipated adherence of greater than 80% of planned weekly doxycycline DOT doses completed, excluding any dose held for clinical reason (e.g., pregnancy, severe adverse reaction, etc).

3.9.2.2. Secondary Analysis:

We propose comparing weekly doxycycline DOT with being assigned to standard of care in recently completed dPEP Kenya Study. The dPEP Kenya Study was a randomized controlled trial in which participants were assigned in a 1:1 ratio to doxycycline post-exposure prophylaxis (doxycycline hyclate 200mg) along with quarterly STI testing or to standard of care, defined as quarterly STI testing and treatment alone among whom baseline rates of STIs were high at 17.9% with 14.1% prevalence of chlamydia, 3.8% with gonorrhea, and 0.4% with syphilis.

The secondary trial outcome will be the combined incidence of incident *C. trachomatis*, *N. gonorrhoeae*, and syphilis, compared between the weekly doxycycline DOT and SOC from dPEP Kenya Study, analyses will also test *C. trachomatis* alone.

Analyses for this pilot study will be descriptive among all women and among those who achieve perfect DOT dosing. STI incidence will be compared between groups using time to first event cox proportional hazard analysis. Additional comparisons will be done using repeated measures analysis of proportions (e.g., generalized estimating equations [GEE]), given possibility of repeat infection within individuals. Adjusted analyses will be done as needed, controlling for potential confounders: demographics (e.g., age, education), sexual behavior (e.g., condom use, # partnerships), and acceptability. SAS or R will be used.

3.10. Biohazard Containment

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the CDC and the National Institutes of Health. All non-blood biological samples will also be handeled by study team with appropriate precautions per standard clinical and laboratory guidelines.

All dangerous goods and materials, including diagnostic specimens and infectious substances, will be transported using packaging mandated by CFR 42 Part 72. Please refer to instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations.

4. ETHICAL CONSIDERATION

4.1. Institutional Review Board (IRB) Review

The study protocol, informed consent forms, participant education and recruitment materials, and other requested documents—including any subsequent modifications—will be reviewed and approved by the UW IRB, KEMRI SERU, and PPB ECCT in accordance with their requirements; they will be responsible for oversight of research conducted at the study site. Subsequent to initial review and approval, the UW IRB and KEMRI SERU will review the study at least annually.

4.2. Informed Consent

Written informed consent will be obtained from all study participants prior to any research procedures. Participants will be offered copies of the informed consent forms. Forms will be translated into local languages and verified by performing an independent back-translation. Informed consent forms will be kept in a secure and locked location for a period of at least 3 years following completion of the trial, longer if required by local regulations or requirements of overseeing IRBs/ECs.

4.3. Study records

The study site will establish a standard operating procedure for confidentiality protection. Each site will ensure that study records including administrative documentation and regulatory documentation as well as documentation related to each participant enrolled in the study, including informed consent forms, locator forms,

case report forms, notations of all contacts with the participant, and all other source documents are stored in a secure manner.

4.4. Confidentiality

Every effort will be made to protect participant privacy and confidentiality to the extent possible. Personal identifying information will be retained at the Kisumu study site and not forwarded to any collaborating institutions or labs; instead, all information will be identified only by a study ID number. The site will use their standard operating procedure for confidentiality protection that reflects the input of study staff and community representatives to identify potential confidentiality issues and strategies to address them.

All study-related information will be stored securely at the study sites. All participant information will be stored in areas with limited access. Data collection, administrative forms, laboratory specimens, and other reports will be identified only by the study ID number to maintain participant confidentiality. All local databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link participant ID numbers to other identifying information will be stored in a separate, locked file in an area with limited access.

4.5. Participants' rights under data protection laws

Participants have the right to access, correct, and restrict the use of their data at any time during the study. Participants also have the right to report a complaint to the local data protection authority: Data Protection Commissioner, Ministry of ICT, Innovation and Youth Affairs, Teleposta Towers, Kenyatta Avenue off Koinange Street, P.O Box 30025-00100, Nairobi – Kenya, Telephone: (+254) 020 4920000 / 1. Email: info@information.go.ke. Participants can object at any time to their data being used for the study, however, in that case, participants will also have to stop participation in the study. Participants can exercise these rights through the study staff. These details will be included in the informed consent forms, a copy of which will be given to all participants.

4.6. Risks/Benefits

Participants may experience pain or discomfort during blood draws and pelvic exams. They may be embarrassed or worried about the STI and HIV testing conducted during the study. Study questionnaires asking information about sexual behavior or partners may also make the participant uncomfortable or embarrassed. All study staff are trained to provide professional care in both clinical sample collection and counseling and administering study questionnaires.

There are known side effects to doxycycline, as listed in protocol section X.X. Participants will be counseled on the side effects and ways to take the medication in order to minimize the impact of any side effects. Participants will be encouraged to come to the study clinic if they have any concerns about the medication or side effects they are experiencing.

Study staff will make every effort to protect participants' privacy and confidentiality. It is possible that participants' involvement in the study could become known to others, and that social harms may result (i.e., because participants could become known as participating in a trial involving sexually active women or persons using PrEP). For example, participants could be treated unfairly or discriminated against, or could have problems being accepted by their families and/or communities. It is possible that participants may have problems with their partner or experience intimate partner violence. Counseling and referrals will be available, if needed. To mitigate against social harms from study participation, participants will have the opportunity to attend their weekly visits at safe spaces and to bring their partners to the research clinic for explanation of the study, for STI treatment and for counselling in case of positive STI results, alongside partner notification letters with contact information of the study doctor and expedited partner treatment.

Participants may benefit from their study participation as they will be receiving free STI testing and treatment that is not readily available in public clinics. Prompt treatment of STIs, including asymptotic STIs, is beneficial

to women in order to reduce the risk of pelvic pain, infertility, or other problems with future pregnancies that can develop when STIs go untreated.

4.7. Reimbursement

Participants will be provided reimbursement for their travel costs and compensation of time spent during study visits, in accordance with local guidelines and regulatory approvals.

4.8. COVID-19 safety measures

The Coronavirus Disease 2019 (COVID-19) pandemic continues to evolve and participant safety will remain a top priority in all study procedures. Study staff will follow all relevant local, national and WHO guidelines for minimizing exposure risk to participants, including but not limited to safety training, wearing appropriate personal protective equipment (PPE), and enforcing social distancing. Specific procedures will be documented in a standard operating procedures (SOP) and updated as needed, particularly as more information about best practices for reducing COVID-19 transmission becomes available. During the consenting process, participants will be advised of the potential COVID-19 transmission risks related to in-person study procedures and the site procedures in place to minimize this risk.

4.9. Dissemination and utilization of study findings

Our findings will be disseminated at the County, National and International level in the form of presentations and policy briefs to the Kisumu County Health Management Teams, relevant National AIDS and STIs Control Program (NASCOP) technical working groups, relevant stakeholder organizations, and at regional and international scientific conferences. Our manuscripts will also be published as open access articles available to the public free of charge.

Findings from this study will provide key evidence to policymakers to support the implementation of STI prevention within PrEP delivery programs in Kenya. The results will also be useful to other researchers considering similar studies in other populations / countries.

5. TIMELINE

Table 3. Study timeline.

Table 3. Timeline				
	Q3 2023	**Q1 2024**	**Q2 2024**	**Q3 2024**
IRB and Ethics approval				
Research staff training				
Data collection - Aims 1 and 2				
Data analysis, dissemination, and manuscript development				

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