PROTOCOL

PrEP and dPEP: Doxycycline post-exposure prophylaxis for prevention of sexually transmitted infections among Kenyan women using HIV pre-exposure prophylaxis

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STUDY TEAM

Kenya Medical Research Institute, Kisumu, Kenya

Elizabeth Bukusi, MBChB, PhD, Co-Principal Investigator
Josephine Odoyo, KRCHN, MPH
Zachary Kwena, PhD
Kevin Oware, MA

University of Washington, Seattle, WA

Jared Baeten, MD, PhD, Co-Principal Investigator
Jane Simoni, PhD
Olusegun Soge, MSc, PhD
Connie Celum, MD, MPH
Ruanne Barnabas, MBChB, DPhil
Deborah Donnell, PhD
Jenell Stewart, DO, MPH
Scott McClelland, MD, MPH
Caitlin Scoville, MPH
Lauren Violette, MPH

University of California San Francisco, San Francisco, CA

Monica Gandhi, MD, MPH

National AIDS & STI Control Programme, Kenya Ministry of Health, Nairobi, Kenya

Catherine Ngugi, MBChB

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
dPEP	Doxycycline post-exposure prophylaxis
DSMB	Data safety and monitoring board
FGD	Focus group discussion
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

SUMMARY

PrEP and dPEP: Doxycycline post-exposure prophylaxis for prevention of sexually transmitted infections among Kenyan women using HIV pre-exposure prophylaxis

Design: Open-label 1:1 randomized clinical trial of doxycyline PEP to reduce bacterial STIs – *Neisseria gonorrhoeae, Chlamydia trachomatis, and T. pallidum* (syphilis) – among Kenyan women taking PrEP. We will also use quantitative questionnaires, focus group discussions, SMS, and in-depth interviews to study acceptability and changes in sexual behavior due to dPEP.

Study Population: 550 Kenyan women aged ≥18 and ≤30 years old taking PrEP randomized to dPEP and standard of care vs. standard of care alone

Study Sites: KEMRI RCTP – Lumumba clinic

Primary Study Objectives:

1. Evaluate the effectiveness of doxycycline post-exposure prophylaxis (PEP) to reduce STI infections in HIV-uninfected Kenyan women taking HIV PrEP
2. Assess the safety, tolerability, and acceptability of dPEP
3. Assess adherence to dPEP
4. Investigate the impact of dPEP on tetracycline resistance in *N. gonorrhoeae* and *C. trachomatis*
5. Measure the cost of dPEP and estimate the cost per case averted, budget impact, and affordability.

Approach: We will conduct an open-label randomized trial of dPEP versus standard of care (STI screening and treatment and risk-reduction counseling without dPEP) among 550 women taking PrEP (1:1 allocation, 223 per arm). Women will be followed for 12 months, with quarterly STI testing, treatment, and adherence counseling. STI testing will be blinded. The trial will have >80% power to detect a 50% reduction in curable STI incidence, overall and for *C. trachomatis* alone, the most common curable STI. We will use multidisciplinary science to measure a) tolerability and safety of dPEP (including effects on sexual behavior), b) acceptability, including challenges and motivators, of dPEP use, c) self-reported and objective measures of adherence to dPEP and PrEP, and d) occurrence of antimicrobial resistance in *N. gonorrhoeae* and *C. trachomatis* isolates using rigorous molecular methods. Finally, we will estimate cost per incident STI case and complications averted taking into account nonadherence and antimicrobial resistance.

1.0 BACKGROUND AND SIGNIFICANCE

Background

African women face disproportionate risk from overlapping epidemics of HIV and bacterial 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 that 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 sexually transmitted infections (STIs). Globally, the World Health Organization (WHO) estimates that 358 million new cases of four curable sexually transmitted infections – 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.

PrEP is an effective, recommended, and impactful strategy for HIV prevention. The past decade has witnessed monumental strides in the development of highly-effective HIV prevention interventions, including antiretroviral pre-exposure prophylaxis (PrEP).[18-21] In 2015, WHO issued guidance recommending TDF-containing PrEP as a prevention option for all persons at high risk for acquiring HIV.[22] At the individual level, HIV protection is on the order of 90-100% in both women and men when adherence is high, as demonstrated by studies measuring tenofovir in blood samples.[18,19,23] PrEP adherence and HIV prevention effectiveness have been high in open-label demonstration projects among serodiscordant couples, men who have sex with men (MSM), and African women (the last a notable contrast to results seen in clinical trials),[24-28] hypothesized to be a result of offering a strategy with demonstrated safety and effectiveness, and without a placebo.[28-32]

PrEP is emerging into a global context with unprecedented rates of curable STIs. 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.[33-35] 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)[36,37] and changing trends in sexual mixing patterns.[38,39] 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.[35,40,41]

Post-exposure prophylaxis using the antibiotic doxycycline (dPEP) has been proposed as a novel STI prevention strategy. A recent open-label clinical trial among MSM in France (IPERGAY) found a 47% relative reduction in new bacterial STIs (specifically, either *C. trachomatis*, *N. gonorrhoeae*, or *T. pallidum*) among PrEP users who also took doxycycline following every sexual encounter.[42] 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; doxycycline is also used as malaria pre-exposure prophylaxis for travelers.[43-45] The concept of STI prophylaxis has a long history (**Table 1**).[42,46,47] Several studies on single dose or monthly antibiotics, among female sex workers in Asia and Africa, demonstrated reduced disease burden;[48-53] a meta-analysis showed a statistically significant impact on incidence of curable STIs in 13 of 14 studies included.[47] The IPERGAY results[42] were striking in the overall reduction in incident STIs, good tolerability and safety, high adherence to dPEP, and continuation (both >90%), and without a significant change in sexual behavior in the intervention arm.[42] We,

like the IPERGAY investigators, think an open-label design among PrEP users (who have already made one prevention-oriented decision by taking PrEP) is scientifically most appropriate for this evaluation. Moreover, while dPEP may be able to prevent STIs, it carries important risks that could counter its benefits; global debate about the balance of these potential risks and benefits requires data to inform policy and implementation.[54]

Table 1. Evidence base for antibiotic prophylaxis for STI prevention

Study	Population	Intervention	Results
Molina et al.	MSM taking PrEP, France (n=232)	Single-dose 200 mg doxycycline after condomless sex vs. no medication (open label)	47% reduction in curable STIs, with greatest reductions for chlamydia (70%) and syphilis (73%). Medication was well-tolerated & highly acceptable. Limited assessment of resistance in STIs.
Bolan et al.	HIV+ MSM with history of syphilis, US (n=30)	100 mg doxycycline daily vs. no medication (open label)	73% reduction in STIs. No self-reported behavior change.
Steen et al.	Female sex workers, multinational (meta-analysis of 14 studies)	Single dose or monthly antibiotic treatment (most used azithromycin with ciprofloxacin or cefixime)	40-60% reduction in *Neisseria gonorrhoeae* & 47-62% reduction in *Chlamydia trachomatis*. No evidence of risk compensation. Few studies assessed STI antibiotic resistance.

The potential emergence of antimicrobial resistance selected by intermittent antibiotic use is an important concern for STI PEP. Following the initial study of empiric single-dose antibiotics to reduce gonorrhea among sex workers in the Philippines, follow-on studies showed some women (12%) reported self-prescribing antibiotics for empiric treatment, and high rates of penicillin-resistant *N. gonorrhoeae* were associated with self-prescription.[55] Today, multi-drug resistant *N. gonorrhoeae* is a growing international public health issue.[56-61] Notably, the IPERGAY results found no reduction in gonorrhea, which was expected given the high percentage (56%) of *N. gonorrhoeae* in Europe are already resistant to tetracyclines.[42,62] In Africa, antimicrobial resistance data are more sparse, but high prevalence (73-97%) detection of plasmid mediated tetracycline-resistant *N. gonorrhoeae* has been seen, including in our preliminary results from Kenya.[56,57,63,64] Importantly, and in contrast, *C. trachomatis* has never been reported to express resistance to doxycycline worldwide, although *Chlamydia suis* with tetracycline resistance has been documented in pigs.[65-67] Rigorous studies are needed to quantify resistance in populations exposed to dPEP and whether dPEP use results in additional resistance.

Doxycycline PEP could be especially impactful for African women using PrEP. Essentially all global conversation about dPEP for STI prevention has been directed towards MSM in high-income settings, but the benefits might be especially great for women in Africa (**Table 2**). 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 three pivotal PrEP projects among young African women that also contribute some of the only information about both STI prevalence and incidence that population (**Table 3**).[27,68-70] In those studies, we are seeing very high STI rates, already comparable to those seen among PrEP-using MSM in the US. 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[69] and low positive predictive value (approx. 50%);[71,72] STI PEP could be an inexpensive intervention in settings where testing is unavailable or unaffordable. Third, STI prevention is valued – women in PrEP trials report that a prime motivation for their participation was access to STI services.[73,74] Fourth, doxycycline is affordable and accessible in Africa. Fifth, dPEP would be woman-

Table 2. Potential benefits of dPEP for African women

Benefit	Rationale
High need	High burden of STIs and their consequences
Bypass unavailable diagnostics	Syndromic assessment is standard; etiologic testing is rarely done; dPEP could prevent STIs that would otherwise go undetected
Valued	Women report high value to quality STI services
Affordable	Doxycycline available in Africa, at a price that is affordable, even for women to self-pay
Woman-controlled	Women control their own STI prevention

Table 3. 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) [Celum protocol chair, Baeten, co-I]	Prevalence = 29% Incidence = 33% per year	Prevalence = 8% Incidence = 14% per year
POWER (PrEP implementation project) [Baeten/Celum, protocol chairs, Bukusi, co-I]	Prevalence = 26% Incidence = 53% per year	Prevalence = 10% Incidence = 20% 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%.

controlled, in contrast to other STI prevention strategies like male condoms and partner notification which rely on partner participation.

Novel hair testing to assess adherence. Prior work by Dr. Gandhi's UCSF Hair Analytical Laboratory (HAL), has shown that hair antiretroviral levels are a robust biomarker of adherence to treatment and prevention,[75-108] hair levels of TFV and FTC are a long-term metric of exposure to PrEP drugs,[76,78,86,96,97,107-110] and doxycycline hair level similarly measure exposure over time.[111] The HAL uses liquid chromatography-tandem mass spectrometry (LC-MS/MS) for testing. The HAL has found high rates of acceptability and feasibility (>95%) of collecting hair samples in African and Asian settings,[79,80,85,90,103,108] and among U.S. adolescents[87] and women.[100,101,108] Our group has had extensive experience with hair collection across several studies and have found it acceptable. In this study, participants will have a hair sample (50-100 strands) collected at each follow up.

State-of-the-art assessment of antimicrobial resistance. Over the past 14 years, Dr. Soge has worked extensively in the field of gonococcal antimicrobial resistance (AMR). Dr. Soge's laboratory characterizes molecular mechanisms of AMR in N. gonorrhoeae isolates and is a core laboratory for CDC's national gonococcal AMR surveillance project,[59,112-114] and he has identified isolates with unique AMR profiles.[115-117] Preliminary results from frozen STI+ endocervical swab samples from Kenyan women in our Partners PrEP Study[19] (i.e., *not* using dPEP) were tested for tetracycline resistance using the molecular methods: 50 with *N. gonorrhoeae* and 10 with *C. trachomatis*. Detection of tetracycline-resistance was high for *N. gonorrhoeae* (*tet*(M)=48/50, 96%), suggesting resistance may be at a ceiling in the community already, prior to dPEP use, but also that dPEP may not be effective against *N. gonorrhoeae*. No *C. trachomatis* organisms had resistance (*tet*(C)=0/10, 0%).

Mathematical modeling and costing studies help to define optimal models for PrEP delivery. Led by Dr. Barnabas, we have used costing methods and mathematical modeling to address key questions related to how to best deliver PrEP. For serodiscordant couples.[118] we found the cost of PrEP per infection averted is significantly offset by future savings in ART costs, especially time-limited PrEP – used prior to and early after ART initiation by an HIV infected partner, when risk is highest.[119] These results were a key basis for designing our "PrEP as a bridge to ART" strategy in the Partners Demonstration Project. Second, we used methods for development of clinical prediction rules to derive a risk scoring tool for couples.[120] Our work has been a model for risk scores for other populations[121] – for example, the VOICE score for women at risk[121] – and for programmatic prioritization of subpopulations for PrEP.[28,122,123] Third, micro-costing, time and motion work, and mathematical modeling have helped define the annual cost of PrEP (~US$100) for the Kenya Ministry of Health.[124,125]

PrEP scale-up among African women is expanding rapidly. In 2017, Kenya was one of the first countries in the world to launch a national PrEP program, making PrEP available through the Kenya Ministry of Health to all populations at risk for HIV. Early data, including our own, show that there is substantial demand and many women are able to adhere to and persist with PrEP. We hypothesize that women engaging in PrEP are a priority population for prevention of curable STIs, given high incidence, interest in longitudinal preventative services, and willingness to take pills for prevention. Nesting into Kenya's national PrEP services, we propose an evaluation of the benefits, risks, and costs of dPEP among women, in the first trial of this intervention for this population. While dPEP has potential as a novel prevention strategy, we recognize important potential risks, including safety, acceptability, adherence, and selection of antibiotic resistance, any/all of which may overwhelm its benefits. The results of this work will have immediate implications for the global epidemic of STIs and for PrEP programs.

Rationale

Rationale for a randomized trial

We posit that there is equipoise to conduct a randomized evaluation at this time: while dPEP has demonstrated efficacy in one trial, it was relatively small in size and limited to MSM in France. Data specific to women are needed to know if dPEP is effective and safe. Additionally, the potential disadvantages of dPEP, such as

antibiotic resistance, tolerability, and low adherence, have not been studied in women and justify the use of a control arm. Randomization in 1:1 allocation will be the most efficient for evaluating efficacy of dPEP and balancing unknown acceptability. Like IPERGAY, we propose that an open-label design allows for optimal evaluation of effectiveness. First, the open-label model directly addresses questions about acceptability, as participants will react to dPEP itself, not a blinded, potentially placebo version. Second, an open-label design is likely to result in greater (and more realistic) adherence – in placebo-controlled trials of PrEP among African women, adherence was very low, and subsequent qualitative studies found concerns about receiving a placebo as a principal reason, with greater adherence in recent open-label studies.[122,126-128] Third, the design will directly allow assessment of sexual behavior changes (i.e., disinhibition) related to STI PEP, which could overwhelm dPEP's benefits and is only assessable if subjects know if they are actually taking active dPEP.

Rationale for evaluation of Kenyan women
Prior work on doxycycline post-exposure prophylaxis against bacterial STIs has only been studied in men having sex with men in France. 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.

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, much of it from our team.[28,31,129-132] Doxycycline is well-tolerated and recent data show strong safety when used by women, including in early pregnancy.[44] 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.[133] 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.[134,135] 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.[136] 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.[132]

Potential for drug resistance
The potential for inducing drug-resistant STIs is an important concern for dPEP. 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. Moreover, if dPEP is successful in preventing STIs, resistance may not occur, 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 manage and mitigate potential resistance risks.

2.0 STUDY DESIGN

Overview: The overarching goal is to assess the effectiveness of dPEP on incidence of STIs while also balancing acceptability, cost, and impact on tetracycline resistance to inform public health policy. Participants will be randomized 1:1, and will receive dPEP and standard of care or the standard of care only. Participants will be counseled about the preliminary effectiveness data from IPERGAY, and the potential for resistance in STIs or other bacteria.

Randomization and follow-up: Participants will be randomized 1:1 to dPEP versus standard of care; randomization will be done in variable-sized blocks and using an online randomization system. Participants assigned to dPEP will be instructed to take doxycycline 200 mg (two 100mg capsules) orally within 24 hours and up to 72 hours after each condomless sex act (consistent with IPERGAY) as frequently as daily if indicated but not more than once daily. At Months 0/3/6/9, women randomized to dPEP will receive doxycycline, sufficient for nearly daily use for 3 months (i.e., 100 capsules). Unused capsules will be counted at each follow-up visit (Months 3/6/9/12) and additional doxycycline will be given to total 180 capsules if needed. The medication, doxycycline hyclate, will be purchased from a quality-controlled supplier and with consultation by the Kenya National AIDS and STI Control Programme. Participants will also be offered single- or multi-dose pill carriers for ease of dosing dPEP following exposures. All participants will receive quarterly visits for standard of care prevention services and collection of clinical and behavioral data, for a total of 12 months of follow-up.

Study visits: Every 3 months, study visits will include STI screening, behavioral questionnaires, hair sample collection, and swab collection for archived samples. Women may return to the study clinic for interim visits for any reason and will undergo STI testing and treatment if STI symptoms are present. Participants with a new STI diagnosis will return for prompt treatment, provided on-site. Laboratory testing will be conducted by staff blinded to randomization assignment, and STIs will be reviewed by an Endpoint Adjudication Committee blinded to treatment arm. All participants diagnosed with an STI will either receive same day treatment or return to the research clinic for treatment, using WHO/Kenya standard therapies, avoiding doxycycline options, and a second visit two weeks following completion of STI treatment will be done for test of cure; this mitigates potential risk to participants and the community if resistance is selected.

Study population: This study will enroll approximately 550 Kenyan women aged ≥18 and ≤30 years old taking PrEP. PrEP use is an eligibility criterion for enrollment because we hypothesize that women engaging in PrEP are a priority population for prevention of curable STIs, given high incidence, interest in longitudinal preventative services, and willingness to take pills for prevention. Aligning with Kenya's national PrEP services, we propose an evaluation of the benefits, risks, and costs of dPEP among women, in the first trial of this intervention for this population. However, participants may opt to stop PrEP use at any time during the study without affecting their involvement in the study. Any HIV-uninfected participants who subsequently seroconvert will be managed clinically by the study site according to local practice (appropriate counseling, clinical evaluation and immediate linkage to clinical and psychosocial services). These participants will also be retained in the study unless they choose to discontinue study participation.

3.0 OBJECTIVES

Primary Study Objectives:

1) Evaluate the effectiveness of doxycycline post-exposure prophylaxis (dPEP) to reduce STI infections in HIV-uninfected Kenyan women taking HIV PrEP.
2) Assess the safety, tolerability, and acceptability of dPEP.
3) Assess adherence to dPEP.
4) Investigate the impact of dPEP on development of tetracycline resistance in *N. gonorrheae* and *C. trachomatis.*
5) Measure the cost of dPEP and estimate the cost per case averted, budget impact, and affordability.

Secondary Study Objectives:

1) Investigate the impact of dPEP on development molecular markers of tetracycline resistance (tetR) in *Mycoplasma genitalium* and nasopharyngeal carriers of *S. aureus* and other commensal organisms from swabs from all participants, stored for future evaluation.
2) Assess the effect of dPEP on the vaginal microbiome through quantitative polymerase chain reaction (PCR) and *Lactobacillus* and other flora resistance to doxycycline from vaginal swabs from all participants, stored for future evaluation.

3) Assess the effect of indole producing organisms in the vaginal microbiome on the effect of dPEP from quarterly vaginal swabs from all participants, stored for future evaluation.

4.0 SELECTION AND ENROLLMENT OF PARTICIPANTS

Inclusion criteria

1) Willing and able to give written informed consent
2) Age ≥18 years and 30 years old
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.

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) Recent use of prolonged (more than 14 day course) antibiotics in the month prior to enrollment
6) Active, clinically significant medical or psychiatric conditions that would interfere with study participation, at the discretion of the site investigator or designee.

Recruitment

We will be recruiting from clinics providing PrEP in Kisumu. 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 particiapants who are not interested in the study or do not meet study eligibility crtieria, may be notified of alternative studies that they may be elgibile for, or provided information about where to access standard of care for HIV prevention and STI services.

5.0 STUDY TREATMENT

Study product

Generic immediate release doxcycyline hyclate 100 mg capsules will be provided by the study to participants randomized to open-label dPEP. Doxycycline hyclate is a standard formulation of doxycycline that is widely avaible 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. To ensure consistency and quality of the doxycycline, we will use the same formulation of drug for the duration of the trial and work with suppliers able to provide evidence of following good manufacturing practices.

Safety of doxycycline

Doxycycline is an antibiotic that can be used for prolonged periods of several months in the treatment of acne or in the prevention of malaria. The tolerance of repeated-dose of doxycycline in this 12-month study should therefore be acceptable.

The possible side effects of doxycycline are[137,138]

- Gastrointestinal: 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.

Doxycline dispensing and administration

Doxycycline will be dispensed at each 3 month visit or in shorter intervals per patient prefence, with additional dispensation as needed to replace lost medication or provide additional medication when needed. Capsules should be stored at room temperature (59-86^{o} F) to the extent feasible. Participants will be instructed to take 2 pills of 100 mg doxycycline as soon as possible after condomless sexual contact, ideally within 24 hours but no later than 72 hours after sex. Participants will be instructed to take a maximum of 200 mg in a 24 hour period. For particiants reporting sexual encounters on consecutive days, 200 mg of doxycycline will be recommended to be taken until within 24 (and up to 72) hours after the last sexual encounter. Study staff will instruct participants on procedures for replacement of lost medication. Doxycycline may be taken on an empty stomach or with food, and it is advised to take with a large glass of water and to taking at least 60 minutes before bed to reduce risk of esophageal irritation. All participants randomized to dPEP will be advised on potential side effects and their management.

Concomitant Medications

Participants randomized to dPEP should report current and new medications to the study team to ensure no concern for drug interactions with doxycycline. The prescribing information for doxycycline hyclate should be reviewed to ensure no potential for drug interactions. Medications that interact with doxycycline include barbiturates, carbamazapine, phenytoin, methoxyflurane, acitretin, isotretinoin, and warfarin. Additionally, medications that interact with doxycycline when taken at the same time include medictions that contain cations (iron, aluminum, calcium, or magnesium) and ideally should be separated 2 hours before or after doxycycline.

HIV pre-exposure prophylaxis (PrEP), STI treatment, and contraceptives

PrEP, STI treatment, and contraceptives will be provided by the study and will be accessible through the study clinic or local MOH following the standard of care. All participants diagnosed with an STI will return to the research clinic for treatment, using WHO/Kenya standard therapies, avoiding doxycycline options (i.e. azithromycin, ceftritriaxone, penicillin G benzathine, and metronidazole as needed by pathogen diagnosed) and a second visit two weeks following completion of STI treatment will be done for test of cure; this mitigates potential risk to participants and the community if resistance is selected. The study site will provide contraceptives and PrEP.

6.0 STUDY PROCEDURES

Study Visit Month	S	0	3	6	9	12
Study coordination						
Obtain informed consent	X					
Screen for inclusion/exclusion	X	X				
Randomization		X				
Collect updated contact information	X	X	X	X	X	X
Reimbursement	X	X	X	X	X	X
Questionnaires						
Demographic information	X	X				
Behavioral questionnaire		X		X		X
HIV risk perception		X	X	X	X	X
Social Harms and IPV		X	X	X	X	X
Sexual behavior and exposure history		X	X	X	X	X
PrEP adherence		X	X	X	X	X
dPEP adherence (timeline follow-back calendar)			X[a]	X[a]	X[a]	X[a]
Fertility intention		X	X	X	X	X
Quality of Life		X	X	X	X	X
Clinical Study Care						
Medication review	X	X	X	X	X	X
General symptom assessment		X	X	X	X	X
WHO pregnancy checklist	X		X	X	X	X
STI symptom assessment	X	X	X	X	X	X
Supply condoms	X	X	X	X	X	X
Contraception counseling and provision/referral	X	X	X	X	X	X
Risk reduction counseling	X	X	X	X	X	X
dPEP pill count and refill			X[a]	X[a]	X[a]	X[a]
Sample collection						
HIV testing (rapid test)	X		X	X	X	X
Urine pregnancy testing (rapid test)	X[b]	X	X[b]	X[b]	X[b]	X[b]
Syphilis testing (serum RPR)		X	X	X	X	X
Creatinine (serum)		X[b]	X[b]	X[b]	X[b]	X[b]
CT/NG testing and resistance (endocervical swabs)[c]		X	X	X	X	X
Hair PrEP and doxycycline drug levels		X	X	X	X	X
Trichomonas screening (vaginal swab)		X	X	X	X	X
Archive						
Microbiome testing (vaginal swab)		X	X	X	X	X
BV testing (vaginal swab)		X	X	X	X	X
M. genitalium screening and resistance (endocervical swab)		X	X	X	X	X
Pharyngeal microbiome and resistance (pharyngeal swab)		X				X
Rectal microbiome and resistance (rectal swab)						X
Rectal CT screening (rectal swab)						X
HSV-2 testing (serum)		X				X
Y chromosome DNA testing (vaginal swab)		X	X	X	X	X
S. aureus resistance screening (nasal swab)		X	X	X	X	X

S = screening visit
[a]intervention arm only
[b]if clinically indicated
[c]Participants diagnosed with an STI will return 2 weeks following treatment for test of cure

Study visits

Figure 1. Study visit protocol

Specific study procedures are detailed in Table 6.0. Visits will take place at enrollment and quarterly thereafter, up to 12 months; we will conduct tracing in the case of missed visits to ensure high retention. Interim visits may take place if participants present for diagnosis and treatment of STI, 2 weeks following treatment of STI for test of cure, for subgroup of participants completing in-depth interviews or focus group discussions, or for evaluation of possible doxycycline associated adverse events. All participants will receive quarterly visits for standard of care prevention services and collection of clinical and behavioral data, for a total of 12 months of follow-up. We will use electronic data capture (CommCare or REDCap).

Screening Visit:

Potential participants will be screened for inclusion and exclusion criteria, and those eligible will be invited to enroll. Oral and written informed consent will be obtained for screening and enrollment. Participants will be screened for symptoms of STIs, and treated empirically if symptomatic (per Kenyan National Guidelines). Participants will also be screened for HIV, following national HIV testing guidelines, at the screening visit; pregnancy will be assessed using the WHO pregnancy checklist and a pregnancy test will be done if indicated by the checklist.

Enrollment Visit:

The enrollment visit will be as soon as the following day after the screening visit and as late as 28 days following the screening visit. Demographic, behavioral, and facilitators/barriers information will be collected at enrollment. Pelvic exam for baseline STI testing and sample storage will be done at enrollment and prevalent STIs will be treated. Full medical review of symptoms and medications, blood testing (up to 20mL of blood drawn), hair sample, and nasal and pharyngeal swabs will be collected at enrollment. Pregnancy testing will be completed for all women at enrollment.

Randomization :

Participants will be randomized 1:1 to dPEP versus standard of care; randomization will be done in variable-sized blocks and using a computer based randomization system, following consent and eligibility confirmation.

Quarterly visits after enrollment :

dPEP (intervention) group: Study visits, every 3 months, will include questionnaires, risk reduction counseling, PrEP and dPEP adherence counseling (including dPEP dosing information), pill count and refill, a blood draw (up to 10mL), HIV testing, a hair clipping, a nasal swab, a pharyngeal swab, (rectal swabs at the final visit only), WHO pregnancy check list (with possible urine pregnancy test), and vaginal and endocervical swabs. All participants will receive reimbursement for attending quarterly study visits.

Standard of care (control) group: Study visits, every 3 months, will include questionnaires, risk reduction counseling, PrEP adherence counseling, a blood draw (up to 10mL), HIV testing, a hair clipping, a nasal swab, a pharyngeal swab, (rectal swabs at the final visit only), WHO pregnancy check list (with possible urine pregnancy test), and vaginal and endocervical swabs. All participants will receive reimbursement for attending quarterly study visits.

Any participant with a positive STI result will be asked to return two weeks after treatment for a test of cure visit, which will include STI testing.

Unscheduled interim visits:

Women may return to the study clinic for interim visits for any reason and will 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.

Mobile phone SMS (optional – for participants with a phone and who agree to optional SMS component):

Participants who consent to SMS will receive weekly SMS sent in English, *Kiswahili,* or *DhoLuo* as part of a momentary ecological assessment of adherence and exposure. Exposure, i.e. have penatrative sex without a condom, will be referred to by a code word for added privacy: for example, "How many times did you dance this week?" If a participant is in the dPEP arm, they will receive a second SMS, "How many times did you take dPEP this week?" Encrypted transmission, password protection to open the surveys, and immediate deletion permit sensitive data to be collected safely.

Time and motion observations (length of quarterly visit):

A small random subset of participants in the dPEP group will be asked to give verbal consent to have their study visit observed by a study team member to record time needed to provide this intervention.

Instructions for evaluations

Questionnaires and Interviews:

Quantitative data: Demographic and behavioral surveys will be administered at each visit, using questions we have used extensively in our prior trials (**Table 4**). All participants will complete questionnaires each study visit on faciliators and barriers to STI prevention and dPEP.

Table 4. Data collection on facilitators of and barriers to STI prevention and dPEP: all have been used in our prior work (Table 5)

Structural	E=enrollment, Q=quarterly, 6=Month 6 visit, 12=Month 12 visit
Socioeconomic status	employment (E), income (E), presence of running water/electricity/metal roof/TV/phone at home (WAMI) (E)
Individual	
Demographic factors	age (E), race/ethnicity/tribe (E), educational level (E), time spent traveling for clinic visit (E, 6, 12)
Alcohol use	# days in last week consumed, rapid alcohol problems screen–quantity frequency (RAPS4-QF) (E, 6, 12)
Depression	somatization, obsessive-compulsive, interpersonal sensitivity, anxiety and depression (HSCL-D) (E, 6, 12)
HIV risk perception	what do you think is your risk of getting (giving) HIV and STIs from (to) your partner? (4 item Likert scale) (E, Q)
Prevention strategies	perceived dPEP efficacy for STI prevention, perceived PrEP efficacy for HIV prevention (E, Q)
Social Harms	physical, social and economic social harms (E, Q)
Dyadic	
Relationship	partnership status (E, Q), social support (Modified UNC-Duke) (E, 6, 12), partner violence (E, Q)
Sexual behavior	sex frequency (E, Q), condom use (E, Q), sexual power (E, 6, 12)
Fertility intention	# of children (E), current pregnancy (E, Q), goal # of children and fertility intentions (E, Q)
HIV stigma	scale plus disclosure (e.g., serodiscordant status) to family/friends/religious leaders & adverse effects (E, 6, 12)

Sexual behavior questionnaire: Participants will be asked to complete a sexual behavior questionnaire using timeline follow-back calendar to record number and type of sexual contacts (including condom use) in the past 3 months at each study visit.

Fertility intention survey and counseling*:* All participants will receive quarterly evaluation of fertility intention by survey with counseling on contraceptive options and supply contraceptives if desired by participant. For participants not using long acting reversible contraceptives (LARC), we will use the WHO pregnancy checklist to screen for possible pregnancy, and if pregnancy can not be ruled out with the pregnancy checklist, a urine pregnancy test will be completed.

Qualitative work: Qualitative data collection will include serial in-depth individual interviews (n=40) and focus group discussions (n=4 focus groups; approximately 48 participants) in the dPEP arm. Semi-structured qualitative interview guides will provide a general structure for discussion.[139] The serial IDI will be conducted soon after enrollment to get information on early experiences and at Months 6 and 12 after participants have experienced dPEP; focus group discussions will be conducted at study exit. Interviews will be conducted using the participants' preferred language (English, *Dholuo*, or *Kiswahili*). Participants will be sampled for the qualitative interviews to include diversity in relationship status, adherence level, and participation in transactional sex (stratified-purposive sampling).

Clinical study care

Review of current medications*:* All participants will have current medications reviewed at screening for possible drug interaction with doxycycline. At subsequent quarterly visits, participants randomized to dPEP will have current medications reviewed and any new medications will be assessed for possible drug interactions.

STI symptom screen: Participants will be asked about current STI symptoms including vaginal discomfort, dysuria, rash, vaginal discharge, rectal pain, pelvic pain, and genital lesions.

General symptom assessement: At each visit, participants in both study arms will be asked about possible doxycycline side effects, including esophagitis, rash, gastrointestinal symptoms, photosensitivity, headache, and vaginal yeast infection. Control arm participants will be asked about these symptoms to establish a comparator for non-specific symptoms which can occur in the absence of doxycycline.

Risk reduction counseling*:* At each visit, staff will counsel participants about risk reduction and HIV and STI prevention and will receive condoms.

Pill count and dPEP adherence assessment*:* Participants assigned to dPEP will be asked to bring their doxycycline blister packs in at each visit for a pill count. While completing the timeline follow-back calendar to record sexual exposures will be asked when dPEP was taken and if each sex act were covered by dPEP in the past 3 months.

PrEP adherence assessment and counseling: All participants will receive quarterly PrEP adherence assessment (Likert scale) and adherence counseling.

Sample collection and outcome measures:

Primary study outcome STI testing: A pelvic exam will be performed at enrollment and all quarterly study visits for all participants. Participants will be encouraged to coordinate study visits prior to or following menstration and participants presenting during menstration will be rescheduled to return the following week.

N. gonorrhoeae/C. trachomatis: The enrollment visit and quarterly follow-up visits, every 3 months, will include a provider-collected endocervical swab to test for STIs. We have focused on cervical STIs since they are the source of morbidity in women and rectal/pharyngeal STI testing is not standard of care in Africa. We will collect a rectal swab on the final visit to further open inquiry into the theoretical role of rectal STIs among the participants. Women may return to the study clinic for interim visits for any reason and will undergo STI testing and treatment if STI symptoms are present. Participants with a new STI diagnosis will return for prompt treatment, provided on-site. Testing will be conducted by staff blinded to randomization assignment, and STIs will be reviewed by an Endpoint Adjudication Committee blinded to treatment arm. All participants diagnosed with an STI will be treated same day or return to the research clinic for treatment, using WHO/Kenya standard therapies, avoiding doxycycline

options, and a second visit two weeks following completion of STI treatment will be done for test of cure; this mitigates potential risk to participants and the community if resistance is selected.

RPR: The enrollment visit and quarterly follow-up visits, every 3 months, will include blood sample collection for syphilis serology testing (incident infection=4-fold rise in non-treponemal RPR titer). RPR should be conducted at least 30 days after last syphilis treatment and must be interpreted in the context of prior test results and current symptoms and exposure history. The need for treatment will be based on the clinical assessment of the site investigator based on the serological data and clinical findings. All syphilis endpoints will determined by the Endpoint Adjucation committee.

Adherence: All participants will receive 1:1 adherence counselling for PrEP with individualized barrier identification and problem-solving assistance. Participants in the dPEP arm will receive 1:1 adherence counselling as well as reminders on their daily PrEP tablet bottle as a reminder to assess personal need for dPEP on that day.[140,141] A number of measures will be used to determine adherence:

Self-reported measures: Sexual behavior and, for those assigned to the dPEP arm, pill-taking behavior, will be measured by timeline follow-back calendar[142] at each follow-up visit to assess exposures and dPEP use. Because dPEP is an exposure-driven medication, adherence is dependent on use of dPEP following each exposure.

Real-time behavioral measurement (optional): Weekly SMS will be sent in English, *KiSwahili* or *DhoLuo* as part of a momentary ecological assessment of adherence and exposure. Exposure (i.e., condomless sex) will be referred to by a code word for added privacy: for example, "How many times did you dance [have sex without a condom] this week?" [If in the dPEP arm] "How many times did you take dPEP this week?" We have used real-time SMS data collection in multiple prior PrEP studies in Kenya;[32,143,144] cell phones are very common in Kenya (outnumbering citizens). Encrypted transmission, password protection to open the surveys, and immediate deletion permit sensitive data to be collected safely. Studies of PrEP demonstrated that there was improved comfort with reporting sexual behavior via SMS, though objective adherence measures were far superior to self-report.[144]

Objective measures: Hair drug levels will be measured to more objectively assess quantitative exposures to dPEP, for several analyses. Hair samples (50-100 strands) will be collected following consent to collection and confirmed eligibility for hair collection (occipital hair >0.5cm in length with absence of bleaching) from all participants at each visit (Months 0/3/6/9/12). Hair samples will be shipped to Dr. Monica Gandhi's UCSF Hair Analytical Laboratory (HAL).

Costing*:* We will estimate incremental costs, incurred and averted, of adding dPEP to PrEP. Activity-based micro-costing studies will be conducted to estimate costs incurred (e.g., start-up activities, training, and dPEP) and costs averted (diagnosis and treatment of symptomatic STIs, infertility, and adverse pregnancy outcomes). Also, cost data will be collected from the study budget, published reports, and the literature. Time and motion studies will be conducted by observing visits and staff time spent on dPEP initiation and adherence counseling, and clinical procedures. The total time required for the intervention will be estimated, adjusting for time spent on research activities. Using these data, the time and costs for dPEP will be estimated. We will adapt compartmental, dynamic models to simulate STI transmission in Kisumu; and capture the movement of individuals from the susceptible state/compartment to infected, treated, and return to the susceptible compartment as well as capturing the proportion of individuals moving from infected to PID and further possible complications (infertility, ectopic pregnancy, and fetal complications).[8,13,145-148] The model is stratified for age, sexual activity, marital status, and adherence to dPEP. The model is continuous for age and time and can capture trends in time (e.g., changes in STI testing) and age (e.g., behavior change with age). Each STI (chlamydia, gonorrhea, and syphilis) will be modeled separately with STI specific parameters and a model structure to capture the distinct epidemiology and biology of that specific STI. STI acquisition is a

function of dPEP use by susceptible individuals who are taking PrEP, contact with an infectious partner(s), coital frequency, STI transmission probability, and condom use. dPEP impacts the force of infection (λ), thus modifying STI incidence. The model will be parameterized using demographic, behavioral, intervention uptake, and mobility data collected during the study and from the literature. The model will be validated using independent estimates of STI/HIV prevalence and incidence from these populations. To estimate DALYs associated with STIs, we will use the 2013 Global Burden of Diseases estimates for infectious diseases and abdominopelvic complications, including female infertility in a low-and-middle-income setting.[149,150] The model is programmed in Matlab (MathWorks, Natick, MA).

Archived Samples:

Stored Nasal and pharyngeal swabs: We will archive (at -80C) samples at each visit for potential future testing, including for studies of commensal *Staphylococcus aureus* and other organisms detection and resistance.

Stored vaginal swabs: We will archive (at -80C) samples at each visit for potential future testing, including vaginal Gram stain and vaginal swabs for studies of bacterial vaginosis, vaginal microbiome and detection of Y chromosome DNA (as a biologic marker of unprotected intercourse for sensitivity analysis of exposure in adherence and objective marker of potential change in sexual behavior).

Stored endocervical swabs: We will archive (at -80C) samples at each visit for potential future testing, including residual sample from NAAT testing (for testing for *Mycoplasma genitalium*, an emerging STI, which should not be prevented by dPEP.

Stored rectal swabs: We will archive (at -80C) samples at the final visit for potential future testing, including *C. trachomatis* infection or colonization of the rectum from NAAT testing and microbiome resistance patterns.

Stored serum*:* We will archive (at -80C) samples at Enrollment and Month 12 for potential future testing, including HSV-2 testing.

Laboratory Procedures:

Samples will be tested within Kenya where feasible. Any samples that require specialized testing will be shipped to the University of Washington (UW) or the University of California San Fransisco (UCSF) as described below.

STI testing:
All STI screening will be completed with point-of-care 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). Endocervical swabs will be tested for *C. trachomatis* and *N. gonorrhoeae* by nucleic acid amplification testing (NAAT). Vaginal swabs will be tested for *Trichomonas vaginalis* by NAAT (Cepheid GeneXpert).

Hair testing:
Hair samples from all participants will be collected. A subset will be shipped from University of Washington to Dr. Monica Gandhi's University of California San Francisco Hair Analytical Laboratory (HAL), which uniquely is able to do the required testing. Samples from three groups of participants will be analyzed: 1) 50 participants in the dPEP arm for dPEP and PrEP drug levels at each follow-up visit (Months 3/6/9/12), 2) any dPEP arm participant with incident STI, and 3) 10% all-comers (n=50) at enrollment (Month 0) and 5% of control arm at follow up visits (Months 3/6/9/12). Samples will be analyzed using liquid chromatography-tandem mass spectrometry (LC-MS/MS) testing for doxycycline hair level exposure over time (by hair segments representing weekly exposures) and hair levels of TFV

and FTC are a long-term metric of exposure to PrEP. Testing of additional samples may be done if the results of this pre-defined sample warrant.

Resistance testing:
Endocervical samples – baseline and follow-up, from both arms – with a positive NAAT result for *C. trachomatis* and/or *N. gonorrhoeae*, will be shipped to the University of Washington laboratory of Dr. Soge for molecular testing. DNA will be purified from residual endocervical NAAT samples and endocervical swabs using the *High Pure* DNA *Kit* (Roche Diagnostics, Indianapolis, IN). The impact of dPEP on *C. trachomatis* and *N. gonorrhoeae* resistance will be measured by comparing the overall rates of doxycycline-resistant events occurring in the dPEP arm to rates in the control arm, at baseline and separately during follow-up adjusted for medical factors that confound the dPEP-resistance risk relationship.

Testing for tetracycline resistance among N. gonorrheae
Molecular characterization of *N. gonorrhoeae* will include strain typing using the internationally frequently used *N. gonorrhoeae* multiantigen sequencing typing (NG-MAST) system;[151] and detection of *tet*R including plasmid-mediated *tet*(M); and chromosomally-mediated resistance determinants: mtrR (A39T, G45D, G45S, −35delA and −10insTT), rpsJ (V57M), porB (G120K, A121D/N), and pilQ (E666K) by PCR and sequencing.[152] Well-characterized positive control strains and negative controls will be included in all PCR assays.[153] The detection of the plasmid-encoded *tet*(M) gene and/or *tet*R genetic resistance determinants is indicative of phenotypic resistance to tetracycline, doxycycline, and minocycline.[153] All samples with the same NG-MAST sequence types will be further differentiated by multilocus sequence typing. Whole genome sequencing will be conducted on endocervical swabs from patients with the same strain types and *tet*R genotypes and rigorous investigation of single nucleotide polymorphisms associated with novel resistance mechanisms will be performed.[154]

Molecular testing for tetracycline resistance genes in C. trachomatis
The horizontally acquired genomic island which *encodes* the tetracycline efflux pump *tet*(C), found in *Chlamydia suis* strains from pig,[155] is the only reported *tet*R determinant in the genus *Chlamydia.*[156] Therefore, we will screen for the presence of *tet*(C) in all samples found to be positive for *C. trachomatis;* and use real-time PCR assays for genotyping of *C. trachomatis* including *Lymphogranuloma venereum* (LGV) associated L-serovars L1, L2, or L3.[157-159]

Management and treatment of gonorrhea, chlamydia, and syphilis
Participants found to have a diagnosis of chlamydia, gonorrhea, 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 + single dose azithromycin tablets, benzathine penicillin G intramuscularly once) at the study clinic. 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). All participants treated for a bacterial STI will then return to the study clinic two weeks following STI treatment for test of cure. Participants will be encouraged to tell partners to also be treated per Kenya guidelines. Should patients develop signs or symptoms of an STI at any point in the study they may come to the study clinic for additional testing (including for trichomonas, BV, or candida infections) and treatment if needed. Study visits will include testing for *Trichomonas vaginalis* for prompt treatment with Metronidazole if detected. Flexible clinic scheduling is available to promote high rates of follow-up. We will make efforts to retain all subjects at their final visit to meet standard of care in addition to ensuring complete information is available for the entire population and to ensure all have a final STI assessment.

Pregnancy, breastfeeding, and HIV seroconversion

Management of dPEP with contraceptives and pregnancy:
Contraception will be offered on-site but will not be required for study participation. The effectiveness of contraceptives or dPEP will not change with concomitant use. Women will be counseled on current Kenyan guidelines, which do not recommend use of doxycycline in pregnant women and participants

will stop dPEP 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 will be counseled on current Kenyan guidelines, which do not recommend use of doxycycline in pregnant women and participants will stop dPEP should pregnancy occur; women can resume dPEP 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 for 1 year following their birth. Participants who deliver a baby during the trial will be asked to return for scheduled, quarterly study visits for a total of up to 12 months even though dPEP will be stopped if they are in the dPEP group. Additionally, they will be asked about the health of their baby at each study visit with continuation of questionnaire on health of their infant for first 12 months of infant's life. 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. 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.

Management of PrEP with contraceptives and pregnancy:
PrEP and contraception have no adverse drug-drug interactions. If an HIV negative woman becomes pregnant while taking PrEP, careful consideration should be given to whether use of PrEP should be continued, taking into account the potential increased risk of HIV infection during pregnancy and post-partum period. Available human and animal data suggest that tenofovir-based PrEP does not increase the risk of major birth defects overall compared to the background rate, although well-controlled data are limited. Current US FDA and Kenya labeling for tenofovir disoproxil fumarate/emtricitabine is permissive to the use of PrEP in pregnancy. If a woman becomes pregnant or breastfeeding during the proposed study, PrEP will continue to be offered, as is consistent with Kenya national guidelines.

Management of HIV-seroconversion:
If a participant tests HIV positive, 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 dPEP, if they are assigned to the intervention group.

6.0 ADVERSE EVENTS (AE) AND STUDY MONITORING

Adverse Event Collection Requirements
The following AEs will be recorded on data collection forms:

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

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).

Study Monitoring

Study Team Monitoring
The study team will monitor the conduct of the study through monthly summary reports of arms of accrual, and baseline characteristics and quarterly 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. On a monthly basis, the study team will review by-arm summaries of premature study discontinuations and premature study treatment discontinuations (and reasons) and AEs.

DSMB
An independent data safety and monitoring board (DSMB) will be convened for this study with expertise, from US and Kenya, in STIs, PrEP, and antimicrobial resistance and a biostatistician. The purpose of the DSMB is to monitor the study for operational futility, social harms, and efficacy. The DSMB will evaluate the progress of the project, including periodic assessments of accrual, retention, safety, performance and variation of the project sites, and other factors that can affect project implementation. The DSMB will review the study after approximately 1/3 and 2/3 of follow-up time with pre-specified stopping rules for efficacy and futility in terms of the efficacy of dPEP in reducing the incidence of gonorrhea, chlamydia, and syphilis overall, and the ability of the study to meet its objectives. The DSMB will be charged with the decision to recommend stopping the study early if interim analyses demonstrate emergent differences between the trial arms meeting pre-defined levels of significance, significant change in rate of doxycycline-resistant STIs, or significant safety concerns. At a minimum, a DSMB meeting must have a quorum of the chair and 2 other members. One or more Formal Interim Analysis meetings will be held to review data relating to relative effects of treatment on the trial outcomes. Patient safety and quality of trial conduct will also be reviewed at these meetings. The study team will carefully document any participants who become excluded from intervention arm due to pregnancy or are breastfeeding for careful review by DSMB for any adverse events to pregnant women or infants. Discussion of formal interim monitoring guidelines will be discussed at the Organizational Meeting prior to trial initiation. The DMSB will also consider factors external to the project when relevant information becomes available, such as policy changes or scientific developments that may have an impact on project implementation, safety, and integration of dPEP in the STI and HIV care clinics.

The DSMB will conduct reviews every six month and convene by teleconference. Open reports containing accrual and retention rates, participant characteristics, serious adverse events, and social harms, will be sent to the protocol team and DSMB members the week prior to the DSMB meeting. Only the DSMB members and the unblinded biostatistician will receive password-protected closed reports of STI endpoints by randomization arm. The DSMB membership will be restricted to individuals free of apparent significant conflicts of interest. The source of these conflicts may be financial, scientific or regulatory in nature. Reports from all reviews will be provided for submission to overseeing IRBs/ECs.

8.0 CLINICAL MANAGEMENT ISSUES

Toxicity

Only toxicities related to study medications provided through the study will be considered in the toxicity management section.

Grade 1 or 2
Participants who develop Grade 1 or 2 toxicity (per DAIDS toxicity table) felt to be related to doxycycyline may continue study treatment at the discretion of the site investigator with close follow-up. If a participant chooses to discontinue study treatment, the site should notify the study protocol team within 7 days.These participants will remain on study, off study treatment and have all evaluations performed per current clinical guidelines.

Grade 3
- Participants who develop a Grade 3 toxicity thought by the site investigator to be related to study drug should have study drug held. The participant should be reevaluated weekly until the AE returns to Grade ≤2, at which time study drug may be reintroduced at the discretion of the site investigator in consultation with the protocol team.
- Participants experiencing Grade 3 toxicity requiring permanent discontinuation of study drug should be followed weekly until resolution of the toxicity. Participants will have premature study treatment discontinuation evaluations performed as noted in most up to date clinical evidence. These participants will remain on study, off study treatment and have all evaluations performed per current clinical guidelines.

Grade 4
- Participants who develop a Grade 4 symptomatic toxicity felt to be related to the study drug will have study drug permanently discontinued.
- Participants experiencing Grade 4 toxicity requiring permanent discontinuation of study drug should be followed weekly until resolution of the AE or return to baseline. These participants will remain on study, off study treatment and have all evaluations performed per current clinical guidelines.

Specific Management of Toxicities Related to Study-Provided Drugs

Possible intracranial hypertension (IH)
Participants taking doxycycline who report new or worsening headaches, visual changes or vision loss should have doxycycline temporarily discontinued and an evaluated for IH, including a fundoscopic exam to look for papilledema. If IH is rule out or an alternate etiology identified, doxycycline may be restarted, at the discretion of the site investigator.

Skin erythema
Increased photosensivity is a known possible side effect of doxycycline. Doxycycline should be discontinued if skin erythema develops and may reinstituted when resolved at the discretion of the site investigation. Any SAE should lead to permanent discontinuation of doxycycline.

Fixed drug eruption
Suspected fixed drug eruption should be evaluated for possible etiologies – if a doxycycline fixed drug eruption is suspected, doxycycline should be stopped.

Allergic reactions
Doxycycline should be discontinued permanently if an allergic reaction is suspected. These participants will remain on study, off study treatment and have all evaluations performed per current clinical guidelines.

9.0 CRITERIA FOR DISCONTINUATION

Premature Study Treatment Discontinuation

- Requirement for prohibited concomitant medications or other contraindication to doxycycline
- Occurrence of an AE requiring discontinuation of doxycycline
- 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
- Requirement for chronic tetracycline use (>14 days)
- Pregnancy
- Breastfeeding

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

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)

10.0 STATISTICAL CONSIDERATIONS

Outcome measures

Primary outcome: Combined incidence of *N. gonorrhoeae, C. trachomatis*, or early syphilis infection by by laboratory-based diagnosis (e.g., positive *N. gonorrhoeae* or *C. trachomatis* based on NAAT or syphilis based on four-fold increase in non-treponemal titers).

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 qualitative themes and associated barriers and facilitators
- Adherence: We will explore the self-reported measures and SMS data, defining adherence as the percentage of times that dPEP was taken following an episode of condomless intercourse. Stored vaginal swabs for Y chromosome testing can be available for later validation.
- Resistance: The detection of the plasmid-encoded *tet*(M) gene and/or *tet*R genetic resistance determinants is indicative of phenotypic resistance to tetracycline
- Cost: The incremental cost effectiveness ratio (ICER) per incident STI case averted and DALY averted

Statistical power and analysis

We propose a standard randomized superiority design, comparing dPEP to standard of care. The primary trial outcome will be the combined incidence of incident *C. trachomatis*, *N. gonorrhoeae*, and syphilis, compared between the randomization arms, to mirror the IPERGAY approach; analyses will also test each pathogen alone. We have been conservative in planning: first, we have planned for an STI incidence of 22% per year in the standard of care arm, which is less than the *C. trachomatis* incidence seen in our recent studies **(Table 3)** and second, we will calculate based on time to first incident STI alone, although we anticipate that some women will have repeat STIs contributing additional events and additional statistical power. We have planned for a 50% effect, comparable to the IPERGAY results and sufficiently great for public health benefit, but we anticipate that the *C. trachomatis* effect could be >50%, given universal susceptibility to doxycycline and

IPERGAY findings. With 80% power, 10% loss-to-follow-up, incidence of 22% vs. 11% (n=44 vs. 22 cases), and a two-sided alpha of 0.05, a sample size of n=550 is needed (n=275 per arm).

Primary Analysis:
We will analyze the composite endpoint of any of the three STIs as well as for *C. trachomatis* alone, and we will continue until there are sufficient *C. trachomatis* events (n=66) given the high incidence of this pathogen and its importance for reproductive morbidity (the consequence of which will be that the total number of events in the composite of *C. trachomatis*, *N. gonorrhoeae*, and syphilis will be greater than n=66). Analyses will be intention-to-treat, including women whether or not they continue dPEP (as well as whether or not they continue PrEP). STI incidence will be compared between arms using repeated measures analysis of proportions (e.g., generalized estimating equations [GEE]), given possibility of repeat infection within individuals. Per-protocol and adjusted analyses will be done as needed, controlling for potential confounders: demographics (e.g., age, education), sexual behavior (e.g., condom use, # partnerships), and beliefs (e.g., risk perception, dPEP/PrEP efficacy). SAS or R will be used.

Secondary Analyses:

Safety: Safety outcomes (i.e., AEs, tolerability, pregnancy, behavior) will be compared between arms using repeated measures analyses.

Adherence: We will explore the self-reported measures and SMS data, defining adherence as the percentage of times that dPEP was taken following an episode of condomless intercourse. Stored vaginal swabs for Y chromosome testing can be available for later validation, as noted in Aim 1 above. For hair, we plan three analyses, focused on 1) describing overall adherence in the population, 2) understanding the relationship between adherence and STI protection, and 3) exploring for cross-over (contamination between arms) that could occur since doxycycline is available in the community. We will complete a descriptive analysis of nonadherence events (defined as self-report of unprotected sex in last 3 months corresponding with elevated pill count or undetectable hair drug level), both for dPEP (dPEP arm only) and for PrEP, with log binomial regression with GEE to account for repeat measures of adherence over time. Adjusted analyses will control for potential confounders as in Aim 1.

Acceptability: Quantitative analysis will be completed using GEE to test associations between facilitators/barriers and randomization arm, dPEP adherence, and STI outcomes. Data will be analyzed to understand factors impacting acceptability of dPEP, including demographics, stigma, fertility desire, dPEP effect on sexual and preventative decision making. Qualitative analysis will take a longitudinal approach. Interview discussions will be recorded, transcribed, and translated into English. Transcripts will be reviewed separately by two investigators for completeness and initial theme generation. We routinely use rapid debriefing reports to obtain real-time information;[160] formal coding and analysis will be performed with Atlas.ti, using inductive approach informed by theoretical framework of acceptability (TFA), a recently developed approach to acceptability research of medical interventions.[161] The components of TFA are affective attitude, burden, ethicality, intervention coherence, opportunity costs, perceived effectiveness, and self-efficacy. Initial code generation of the transcript themes will capture experiences and context of dPEP use. Codes will be reviewed for consistency and inter-coder agreement with consensus code generation by themes. Following a similar process, transcripts from Months 6 and 12 will be coded with reference to the baseline codes to capture temporality of experiences and contexts within each participant. Codes generated from transcripts at Months 6 and 12 will be compared across participants to establish differences and similarities across the sample. The code will reflect the longitudinal data and emergence of new codes. Descriptive thematic analyses will be done at baseline and over time.

Resistance: The impact of dPEP on *C. trachomatis* and *N. gonorrhoeae* resistance will be measured by comparing the overall rates of doxycycline-resistant events occurring in the dPEP arm to rates in the

control arm, at baseline and separately during follow-up adjusted for medical factors that confound the dPEP-resistance risk relationship.

Cost: Using the effectiveness estimated through Aim 1 and the costing and modeling from this study, the incremental cost effectiveness ratio (ICER) per incident STI case averted, and disability-adjusted life year (DALY) averted will be estimated for dPEP compared to the control arm. Sensitivity analyses will address adherence, risk compensation, and programmatic issues (e.g., medication stock-outs). The primary analysis will be from a programmatic perspective, the purview of decision makers. Following suggested update to cost effectiveness definition for low-income countries, interventions will be considered cost-effective if the ICER is 500 USD per DALY averted.[162,163] In the budget impact analysis, we will consider direct program costs, and ensure that measurements of programmatic costs reflect the opportunity cost of the resources used in delivering services.[164] We will report on all costs using a recommended discount rate of 3% per year, as well as an alternative 5% discount rate and undiscounted inputs.[162] This will facilitate comparison to other strategies and help decision makers to define priorities and allocate resources.

Endpoint adjudication
All STI endpoints will be reviewed by a blinded, independent Endpoint Adjudication Committee, following CDC guidelines for the diagnosis of STIs.[165] Incidence of individual STIs and tetracycline resistance will also be evaluated.

12.0 PARTICIPANTS

Institutional Review Board (IRB) Review
The study protocol, site-specific 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 will review the study at least annually.

Informed Consent
Written informed consent will be obtained from all study participants prior to enrollment in any study-related activities. 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.

Study records
Each 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.

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 the labs in Mombasa, San Francisco, or Seattle, or to the University of Washington team; instead, all information will be identified only by 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 records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored separately from study records identified by study ID number. 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.

Risks/Benefits

Participants may experience pain or discomfort during blood draws pelvic exams, and rectal and nasal swab collection. They may be embarrassed or worried about the STI and HIV testing conducted during the study. Participants may also have some anxiety or worry about providing a hair sample, though the technique is optimized to minimize visible hair removal. 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. Counseling will be available to participants who feel they would benefit based on their experiences in the study.

Weekly SMS will be received outside of the study clinic and thus study staff cannot guarantee that someone other than the participant will see the message. The SMS will be coded so that if another person sees the message, it will not indicate the nature of the question or reveal that it is part of a research study. The participant may respond to the message at anytime she feels comfortable to do so, i.e. it does not require an immediate response. Additionally, if ever she would like to stop receiving the weekly SMS, she may request this from the study staff and she will be removed from the list of participants receiving the SMS.

For women assigned to the dPEP group, there are known side effects, as listed in protocol section 5.0. Participants will be counseled on the side effcts 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.

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.

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.

Participants who complete SMS surveys will receive airtime after 6 months of survey completion. Participants who continue to attend their follow-up visits may receive tokens of appreciation, for example study related gifts such as t-shirts or bags.

COVID-19 safety measures

The Coronavirus Disease 2019 (COVID-19) pandemic is rapidly evolving 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.

13.0 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 dangerous goods and materials, including diagnostic specimens and infectious substances, must 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.

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