WHO-Recommended Periodic Presumptive Treatment versus Doxycycline Post-Exposure Prophylaxis for STI Control among Cisgender Men Who Have Sex with Men in Kenya

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Abbreviations

ACASI	Audio computer-assisted self interview
AMR	Antimicrobial resistance
ART	Antiretroviral therapy
AST	Antimicrobial sensitivity testing
CAPI	Computer assisted personal interview
CT	Chlamydia trachomatis
doxyPEP	Doxycycline post-exposure prophylaxis
HIV	Human immunodeficiency virus
LGBT	Lesbian, gay, bisexual and transgender
MHRC	MSM health research consortium
MPI	Multiple principal investigators
MoH	Ministry of Health
MSM	Men who have sex with men
NAAT	Nucleic acid amplification testing
NASCOP	National AIDS & STI Control Programme
NG	Neisseria gonorrhoeae
NRHS	Nyanza Reproductive Health Society
POC	Point-of-care
PPT	Periodic presumptive treatment
PrEP	Pre-exposure prophylaxis
RAI	Receptive anal intercourse
RPR	Rapid plasma reagin
sSA	sub-Saharan Africa
STI	Sexually transmitted infections
SWOP	Sex Worker Outreach Program
TGW	Transgender women
UW	University of Washington
WHO	World Health Organization

1. Title of the Project

WHO-Recommended Periodic Presumptive Treatment versus Doxycycline Post-Exposure Prophylaxis for STI Control among Cisgender Men Who Have Sex with Men in Kenya

[Protocol Number] **SERU**

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N.B. Investigator CVs are included in the appendices.

Sponsoring Institution/Clinical Research Centre:

University of Washington/Pwani Research Centre at the Ganjoni Municipal Clinic, Mombasa

3. Abstract

Men who have sex with men (MSM) are at high risk for gonorrhoea and chlamydia in Kenya, where nucleic acid amplification testing (NAAT) is not feasible, and most infections therefore go undiagnosed. In 2011, the WHO recommended periodic presumptive treatment (PPT) of *Neisseria gonorrhoeae* (NG) and *Chlamydia trachomatis* (CT) infections for MSM at high risk for HIV acquisition due to condomless anal intercourse with multiple sex partners or a recent STI exposure. More recently, trials in well-resourced settings have demonstrated the efficacy of doxycycline post-exposure prophylaxis (doxyPEP) for reducing NG, CT, and syphilis infections among high-risk MSM. The goal of this study is to evaluate the impact and cost-effectiveness of WHO-recommended PPT versus doxyPEP compared to standard syndromic treatment among Kenyan MSM. This study aims to (1) evaluate the effectiveness and impact on antimicrobial resistance in NG of WHO-recommended PPT given every 3 months and of doxy-PEP taken 24-72 hours after condomless sex for reducing STI burden among Kenyan MSM; (2) assess the acceptability, feasibility, and safety of implementing WHO-recommended PPT and doxy-PEP compared to standard care among providers and patients; and (3) model the health and economic impact of scaling up WHO-recommended STI PPT and doxyPEP compared to standard of care on STI control among MSM and their partners in Kenya. We will conduct an open-label randomized trial with 2900 participants to evaluate these two interventions versus standard care assigned in a 2:2:1 ratio, with 18 months of follow-up at three MSM-friendly research clinics in Kenya. Results will inform parameters to update a stochastic model of STI transmission and cost-effectiveness analysis to project the impact of scaled-up STI PPT and doxyPEP in Kenya. This work will provide the critical data needed to inform guidelines and improve STI control among this key population in sub-Saharan Africa and other resource-limited settings.

4. Lay Summary

1. Why should you do this study?

   We are conducting this study to test two different interventions to improve sexually transmitted infection (STI) control among gay, bisexual, and other men who have sex with men (GBMSM) in Kenya. GBMSM have a high burden of STI that mostly are detected by expensive laborotory tests that are not available in public hospitals.

2. What questions are we trying to answer?

   One intervention that may reduce STIs among GBMSM is periodic presumptive treatment (PPT), in which one is treated every 3 months for STI regardless of symptoms. STI PPT has been recommended by the World Health Organization for GBMSM but never tested in a randomized trial. The other intervention is called doxyPEP, which consists of taking a medication called doxycycline 24-72 hours after you have condomless sex, as post-exposure prophylaxis (PEP) to prevent STI. DoxyPEP has been found to reduce STI among GBMSM in the United States and France but has not been tested among GBMSM in sub-Saharan Africa. No one knows if STI PPT or DoxyPEP is better at reducing STI among GBMSM in Kenya and similar settings.

3. Where is the study taking place?

   In 3 friendly GBMSM study sites in Kisumu, Nairobi, and Mombasa.

4. How many participants does it involve?

   We will enroll 2900 GBMSM participants. In addition up to 60 study staff will provide feedback on the two interventions.

5. How will they be selected?

   GBMSM participants will be engaged and screened for eligibility at community-based organizations at each of the three study sites. Participants need to be between 18-29 years, report condomless anal intercourse with a man in the past 6 months, multiple partners or a partner with a STI. They need to be willing to follow study procedures and remain in the study area for 18 months. GBMSM will be excluded if they are unable to understand the study purpose and procedures despite a thorough explanation by and discussion with the study team, are allergic to any of the antibiotics used, have used antibiotics for 14 days or more in the month before enrolment, or are taking medications that impact any of the antibiotics used.

6. What does the study involve for those taking part?

   Participants will be randomised to one of the following three groups: PPT, doxyPEP or standard of care. They will make seven quarterly research visits during the study, for 18 months from enrolment.

   At each visit, a clinician will collect 2 throat swabs, 2 rectal swabs, urine, and blood from each participant. Blood will be tested for syphilis and, if there is an infection, participants will be treated according to standard of care as soon as results are available. The swab and urine samples will be tested for gonorrhea and chlamydia at the end of the study, to determine which intervention worked best to reduce STI. At each visit a small hair sample will also be collected to measure antibiotic use in all participants.

   Additionally, a digital fingerprint will be taken to allow us to confirm participant's identity at study visits without using a name or other identifiers. We will also collect a brief survey lasting 50-60 minutes on a tablet computer. This survey will include questions about sexual behavior, STI symptoms, antibiotic use, substance use, and mental health.

7. What are the risks and benefits of taking part?

There is a small risk of loss of privacy. For participants assigned to the intervention groups there is risk of medication side effects. Participants may benefit from regular physical exams, free syphilis testing, and counselling about STI prevention.

8. How will the study benefit society?

   The burden of STI among GBMSM and their sexual partners in Kenya may be reduced through the outcomes of this study. This is a contribution to science and will help inform health policy for GBMSM in Kenya and similar resource-limited settings.

9. When does the study start and finish?

   The study will likely start in the second half of 2024 and follow patients over 3 years (through June 2027), followed by testing of samples for chlamydia and gonorrhea and for antibiotic resistance in gonorrhea, as well as modeling and cost-effectiveness evaluations to inform scale-up, should either intervention prove to be more effective than standard care.

5. Introduction/Background

Bacterial sexually transmitted infections (STI) caused by *Neisseria gonorrhoeae* (NG), *Chlamydia trachomatis* (CT), and *Treponema pallidum* (syphilis) are highly prevalent and a major cause of morbidity among gay, bisexual, and other men who have sex with men (MSM) and their sexual partners. In sub-Saharan Africa (sSA), published prevalence estimates among MSM range from 3.0%–11.5% for NG and 10.0%–14.5% for CT and 1.1%–5.7% for early syphilis. [1-7] Without timely screening and treatment, these STIs lead to a range of complications and increase HIV acquisition risk. [8] Indeed, modelling studies estimate that 10.2% of all HIV infections among MSM are attributable to NG and CT infections alone. [9] While laboratory-based or point-of-care (POC) nucleic acid amplification testing (NAAT) for NG and CT are widely used in well-resourced settings, [10,11] NAAT for NG and CT is prohibitively expensive in African settings, at approximately $97 per infection diagnosed, even if urethral, rectal, and pharyngeal samples are pooled. [1] As a result, most resource-limited settings rely on syndromic treatment, which misses over 90% of STI among MSM because they are asymptomatic. [2,12]

While development of low-cost POC diagnostics is an urgent priority, [12] low-cost and feasible interventions to control STI among MSM are needed now, as we await technology advances. In 2011, the WHO recommended periodic presumptive treatment (PPT) to eradicate asymptomatic NG and CT infections for MSM who report condomless receptive anal intercourse (RAI) and either multiple sex partners or a sex partner with an STI in the past 6 months. [13] More recently, clinical trials among MSM in France and the United States have reported good safety and high adherence to doxycycline post-exposure prophylaxis (doxyPEP), which led to a 47%-70% reduction in NG, CT, and syphilis. [14-16] Evidence is lacking regarding acceptability, feasibility, safety, and effectiveness of PPT and of doxyPEP for MSM in settings such as sSA where the standard of care is syndromic treatment. These strategies each have potential drawbacks, such as increased antimicrobial resistance (AMR) in NG – a major public health concern globally. [17] Research to evaluate the efficacy, long-term safety, impact on AMR, and cost-effectiveness of these STI control strategies among MSM in resource-limited settings is urgently needed. [18-20]

6. Problem Statement

MSM face disproportionate risk for STIs, especially in resource-limited settings. A recent meta-analysis of 2016 data estimated the global burden of bacterial STIs at 376.4 million infections, including 127.2 million chlamydia cases, 86.9 million gonorrhoea cases, and 6.3 million syphilis cases.[1] The burden of STIs is greatest in low- and middle-income countries, and overlapping, synergistic epidemics of HIV and bacterial STIs in Africa have been recognized since the earliest

days of the HIV epidemic.[1-3] Among MSM and their male sexual partners, STI caused by NG and CT are a significant cause of morbidity, ranging from urethritis, epididymitis and proctitis to disseminated gonococcal infection.[4] Bacterial STI can also lead to reproductive health problems among cisgender female partners of MSM, including pelvic inflammatory disease, chronic pelvic pain, tubal infertility, pregnancy complications, and foetal and neonatal death.[2,5-10] Of note, 56% of MSM in our ongoing cohorts report a cisgender female partner in the past 3 months (unpublished data). NG and CT increase the risk of HIV-1 transmission,[11] with estimates from modelling studies suggesting that 10.2% of all HIV infections among MSM are attributable to NG and CT.[12] In sSA, published prevalence estimates among MSM have ranged from 3.0%–11.5% for NG and 10.0%–14.5% for CT and 1.1%–5.7% for early syphilis.[13-19]

Syndromic treatment, the current standard of care in Kenya, misses the majority of infections, but current diagnostic assays are too costly for most resource-limited settings. Syndromic treatment is standard care for STI management in most of sSA, is less costly than etiologic testing,[3] and has relatively good sensitivity for male urethritis (87%-99%) and high cure rates when administered.[20] Unfortunately, syndromic treatment misses over 90% of STIs among MSM because they are asymptomatic, especially rectal and pharyngeal infections.[14,21] While laboratory-based or POC NAAT for NG and CT are widely used in well-resourced settings,[22,23] NAAT for NG and CT is prohibitively expensive in African settings, at approximately $19 per test conducted and $97 per infection diagnosed, even if urethral, rectal, and pharyngeal samples are pooled.[13] In contrast, the estimated health expenditure per capita in Kenya in 2018 was $88.39.[24] The challenges with funding STI diagnostic tests is explicitly acknowledged in the 2022 WHO Implementation Tool for PrEP for HIV Infection, which recommends a stepwise approach to integration of STI services with PrEP services, starting with syndromic management and integrating rapid diagnostic tests and eventually molecular tests depending on resource availability, among other considerations.[25] While the development of low-cost POC diagnostics is an urgent priority,[21,26] low-cost and feasible interventions to control STI among MSM are needed now, as we await technology advances.

DoxyPEP as an STI control strategy for MSM has been evaluated in well-resourced settings, but not in settings without access to periodic NAAT screening. The Intervention Préventive de l'Exposition aux Risques avec et pour les Gays (IPERGAY) sub-study, a randomized open-label clinical trial of doxycycline 200 mg within 24-72 hours after condomless sex ("doxyPEP") among MSM in France, reported a good safety profile, high levels of adherence and a 47% relative reduction in new bacterial STIs among HIV pre-exposure prophylaxis (PrEP) users who also took 200 mg of doxycycline following every sexual encounter.[27] This reduction was driven by decreases in incident CT (70% reduction) and *T. pallidum* infections (73% reduction); there was no significant impact on NG.[27] Since that time, the DoxyPEP study (PI Celum, NIH R01 AI143439), a randomized open-label trial among MSM and transgender women (TGW) people with HIV or taking HIV PrEP in Seattle and San Francisco randomized participants in a 2:1 ratio to 200 mg doxycycline hyclate within 72 hours of condomless sex or to a control arm, with STI testing at quarterly visits and when symptomatic.[28] A single interim analysis after ~50% of follow-up time had accrued led to stopping of the control arm by an independent data and safety monitoring board. Among 360 participants on PrEP, 65 STI endpoints (29.5%) occurred in controls and 47 (9.6%) in doxyPEP participants (RR 0.33; 95% confidence interval [CI] 0.23–0.47; p<0.0001). Among 194 participants with HIV, 30 STI endpoints (27.8%) occurred in controls and 31 (11.7%)

in doxyPEP participants (RR 0.42; 95% CI 0.25–0.75). NG, CT, and syphilis were each reduced in the doxyPEP arm, with only 8.1% of DoxyPEP participants having NG diagnoses, compared to 19.8% in the control arm.[28] More recently, the DOXYVAC study in France reported a significant reduction in all three STI (i.e., GC, CT, and syphilis) in the doxyPEP group with early termination of the control arm; these results will be presented at CROI 2023.[29] The patient-controlled doxyPEP intervention could be effective in resource-limited settings, although the lack of quarterly NAAT to identify and treat "breakthrough" NG infections could limit effectiveness of this strategy. Because NG is the only STI that has been associated with increased HIV acquisition among MSM in Kenya,[30] its effective control should be a priority. *Further research to evaluate the overall risk-benefit ratio of doxyPEP, in terms of efficacy, long-term safety, impact on AMR, and cost-effectiveness among MSM in resource-limited settings is needed, especially as tetracycline resistance is common globally.*[31-34]

STI PPT has been proposed as a novel STI prevention strategy for MSM and TGW at risk for bacterial STI. In 2011, the WHO recommended PPT to eradicate asymptomatic NG and CT infections for MSM and TGW who report condomless RAI and either multiple sex partners or a sex partner with an STI in the past 6 months.[4] Although targeting criteria for this recommendation have been evaluated by our research in Kenya,[35,36] evidence of the efficacy of STI PPT is lacking, as is an evaluation of its potential downsides. Several studies on single-dose or monthly antibiotics among female sex workers in Asia and Africa demonstrated reduced disease burden using various PPT strategies.[37-42] Moreover, a meta-analysis of PPT intervention effects showed a statistically significant impact on the incidence of curable STIs in 13 of 14 studies included.[43] The premise that STI PPT could help reduce STI burden among MSM in resource-limited settings is supported by this evidence, yet an investigation of the potential impact, risks and benefits of STI PPT for MSM and TGW in a randomized controlled trial has not been conducted. Since MSM are the larger population, and TGW may have different needs and perceptions of STI interventions than MSM, we focus on MSM in this application. *As a provider-delivered strategy that can be directly observed, STI PPT could prove more effective than doxyPEP if doxyPEP adherence is suboptimal or AMR limits the impact of doxyPEP on NG control.*

The potential emergence of AMR is an important concern for both doxyPEP and STI PPT. Following early studies of empiric single-dose antibiotics to reduce NG burden among female sex workers in the Philippines, some women (12%) reported self-prescribing antibiotics for empiric treatment, and high rates of penicillin-resistant NG were associated with self-prescription.[44] Today, multi-drug resistant NG is a growing international public health issue.[45-50] In sSA, reports of cephalosporin resistance in NG have been relatively rare (<1%) to date; however, high levels of tetracycline and quinolone resistance have been reported, with detection of plasmid-mediated tetracycline-resistant NG estimated at 73%–97%.[45,46,51-53] In Kenya specifically, no confirmed cephalosporin resistance has been reported,[45,54,55] although one study reported increasing minimum inhibitory concentrations for ceftriaxone in isolates collected between 2002 and 2009.[51] Of note, doxycycline resistance in NG is estimated at 56% in France,[56,57] where doxyPEP had unclear efficacy against NG in the IPERGAY study, compared to 20%–30% in the US, where the doxyPEP study demonstrated a significant decrease in NG.[28] *Rigorous studies are needed to quantify the scope of potential resistance that might accompany doxyPEP or STI PPT in resource-limited settings with high levels of tetracycline resistance, to mitigate this critical problem.*

STI control for African MSM: balancing benefits, risks, and costs. The potential benefits of implementing either doxyPEP or STI PPT for the control of CT, NG, and syphilis among MSM in African settings are substantial; at the same time, these strategies are untested, and potential risks – including adverse events, increased AMR, risk compensation impacting sexual behavior, and increased costs – could counteract these benefits. Only a well-designed randomized trial comparing these two interventions to standard care can help address these questions and determine whether the benefits outweigh risks for each strategy, compared to standard care.

Experience conducting research on sexual health for MSM in Kenya. In the past 15 years, we have conducted numerous studies with MSM in coastal Kenya and Kisumu on sexual risk behavior,[30,58-61] CT and NG prevalence and incidence,[16,62] AMR,[45 49 51 55] HIV incidence,[30] partner notification services,[63] risk factors for loss to follow up,[64,65] PrEP uptake and adherence,[59,66] ART adherence promotion,[67-69] and mental health and substance use.[70,71 72] In 2014, we formed a sexual and gender minority health research consortium with representatives from the three major population centers in Kenya (Kisumu, Nairobi and Mombasa) and designed a multi-site demonstration cohort study of HIV-negative MSM participants at high risk for HIV acquisition. This demonstration cohort was launched in 2019 with a small grant from the International AIDS Vaccine Initiative (IAVI) and programmatic funding from PEPFAR, successfully recruiting 850 participants aged 18-29 years, 300 in Kisumu, 300 in Nairobi, and 250 in the Kenyan coast, for quarterly follow-up visits. Important features of this cohort include regular investigator meetings, common visit procedures, a common sociobehavioral questionnaire designed for audio computer-assisted self-interviewing (ACASI), and fingerprint scanning at each visit, with real-time checks of digital fingerprint data to prevent co-enrolment. X-pert CT/NG testing of urine, rectal, and pharyngeal specimens has been conducted among participants who remained in follow-up after the COVID-19 pandemic (approximately 67% of the pre-COVID-19 sample), demonstrating a combined CT/NG point prevalence of 17.3% at baseline and 15.0% at month 6. Retention in studies completed before the COVID-19 pandemic ranged from 82%–94%,[61,64,69] and is expected to be similar or higher in this trial, given adequate funding for rigorous retention support.

Evaluation of the WHO PPT targeting criteria and number needed to treat at two sites in Kenya. In 2013, we assessed the prevalence of genitourinary and rectal symptoms among HIV-negative and -positive MSM followed in the coastal Kenya cohorts, to estimate the number of men meeting WHO criteria for presumptive STI treatment, as well as the prevalence and 3-month incidence of rectal NG and CT infections.[35] Among 244 MSM screened, of whom 147 (61.3%) reported any RAI in the past 6 months, 240 (98.4%) were asymptomatic. Among 85 asymptomatic MSM meeting criteria for WHO-recommended STI PPT, 20 (23.5%) had rectal infections. Among 62 asymptomatic MSM who did not meet criteria, 7 (11.3%) had rectal infections. Sensitivity and specificity of the WHO algorithm were 74.1% (95% CI, 53.7%–88.9%) and 45.8% (95% CI, 36.7%–55.2%), respectively. Among MSM who would qualify for STI PPT, the number needed to treat (NNT) to treat one infection was four. In a 2016 follow-up study of MSM from the same coastal Kenya cohorts who reported RAI, the combined prevalence of rectal NG and CT by NAAT in 104 MSM was 21.2% at baseline. Over 6 months of follow-up, the combined incidence of rectal NG and CT was 53.0 (95% CI, 34.5–81.3) per 100 PY, with 12 cases of each for an incidence of 30.0 (95% CI, 17.2–53.3) per 100 PY for each infection.[62]

In 2016, among 698 MSM tested at baseline in the Anza Mapema study in Kisumu, overall anorectal NG/CT prevalence by NAAT was 5.2% (n=36), of which 58.3% (n=21) were asymptomatic infections.[36] Factors associated with anorectal NG/CT in asymptomatic men were age 18-24 years (aOR 7.6, 95% CI 1.7–33.2, relative to older men), HIV-positive status (adjusted odds ratio [aOR] 6.9, 95% CI 2.2–21.6) and condomless anal sex in the past 3 months (aOR 3.8, 95% CI 1.2–11.9). In a model-derived risk score developed to identify NG/CT cases in asymptomatic men, with 2 points each for age 18-24 and HIV-positive serostatus, and 1 point for any condomless anal sex in the past 3 months, sensitivity and specificity were optimal (81.0% and 66.1%, respectively) at a risk score cut-point ≥3, and the NNT was 12.[36]

7. Justification for the study

Feasible, scalable, cost-effective strategies to control bacterial STI among MSM in low-resource settings are urgently needed to reduce STI burden and decrease HIV transmission risk. *STI PPT has been recommended by the WHO for MSM in settings in which NAAT are unavailable, and doxyPEP is a promising STI control strategy for MSM, yet there are no data on its health and economic impact relative to standard syndromic treatment in settings in which NAAT use is prohibitively expensive.*

We posit that there is equipoise to conduct a randomized trial, since while doxyPEP has demonstrated efficacy in studies of MSM in well-resourced settings in which NAAT-guided treatment are widely available, none of these studies was conducted in a resource-limited setting in which syndromic treatment is the norm. In addition, there have been no clinical trials of WHO-recommended STI PPT for MSM, which could have similar or greater efficacy, especially if doxycycline resistance in NG or poor adherence limit the efficacy of doxyPEP. Randomization in a 2:2:1 allocation with a common control arm will allow evaluation of both interventions in the same trial, and an open-label design allows for optimal evaluation of effectiveness and robust evaluation of acceptability, feasibility, and safety in practice, as well as adherence and sexual behaviour among participants who are aware of their assignment.

8. Hypotheses

Hypothesis 1: Both STI PPT and doxyPEP will decrease the burden of bacterial STI among Kenyan MSM, but doxyPEP will lead to more NG AMR than STI PPT, which may exert less pressure to select for mutations.

Hypothesis 2: STI PPT and doxyPEP will each have high acceptability and feasibility among providers and patients, with minimal increases in adverse events relative to standard care.

Hypothesis 3: Both interventions will lead to improved STI control in the target population relative to standard care, but STI PPT will be more cost-effective compared to doxyPEP.

9. Objectives

Objective 1. To evaluate the effectiveness and impact on AMR in NG of two interventions: WHO-recommended PPT given every 3 months and doxy-PEP taken 24-72 hours after condomless sex, compared to standard syndromic treatment, for reducing STI burden among Kenyan MSM.

Objective 2. To assess the acceptability, feasibility, and safety of implementing WHO-recommended PPT and doxy-PEP compared to standard care among providers and patients.

Objective 3. To model the health and economic impact of scaling up WHO-recommended STI PPT and doxyPEP compared to standard of care on STI control among MSM and their partners in Kenya.

10. Methodology

a. Study sites

Kisumu: The study will be conducted at the Anza Mapema clinic in Kisumu, which is presently serving MSM in research or prevention and care programmes. This site will be overseen by the Nyanza Reproductive Health Society and led by Dr. Fred Otieno.

Nairobi: The study will be conducted at a Sex Worker Outreach Programme clinic in Nairobi, which is presently serving MSM and male sex workers. This site will be overseen by Partners for Health & Development in Africa and led by Dr. Joshua Kimani.

Mombasa: The study will be conducted at the Pwani Research Centre at the Ganjoni Municipal Clinic site, in collaboration with two local community-based organisations (the HIV and AIDS People Alliance of Kenya [HAPA Kenya] and the International Centre for Reproductive Health [ICRH]) located in the Mombasa area. This site will be overseen by the University of Washington (UW) and led by Dr. Eduard Sanders, assisted by Dr. Scott McClelland, the lead researcher at Pwani Research Centre.

b. Study design

The proposed study is an open-label randomized controlled trial with a hybrid type 1 implementation-effectiveness component comparing each intervention (i.e., STI PPT, doxyPEP) to a common control in a 2:2:1 ratio.

Approach for objective 1: We will conduct an open-label randomized clinical trial with 2900 participants to evaluate these two interventions versus the standard of care assigned in a 2:2:1 ratio, with 18 months of follow-up and rigorous culture-based and molecular analysis of AMR in NG at three MSM-friendly research clinics in Kenya.

Approach for objective 2: We will use multidisciplinary science to measure the acceptability, feasibility, and safety of these two interventions, using a conceptual model based on Proctor's Implementation Science Framework. [21,22]

Approach for objective 3: Aim 1 and 2 results will inform parameters to update a stochastic model of STI transmission and cost-effectiveness analysis to project the impact of scaled-up STI PPT and doxyPEP in Kenya.

c. Study populations

Trial participants

Inclusion criteria

1. 18-29 years old
2. Assigned male sex at birth
3. Identifies as male (cis-gender)
4. Reports condomless anal intercourse with a man in the past 6 months
5. Reports multiple male sex partners OR a male sex partner with a syndromic (urethritis, proctitis, or genital ulcer disease) or laboratory-diagnosed sexually transmitted infection in the past 6 months
6. Willing and able to provide written informed consent and participate in all study procedures
7. Planning to remain in the study area for 18 months

Exclusion criteria

1. Unable to understand the study purpose and procedures
2. Allergy to cephalosporin (cefixime), macrolide (erythromycin or azithromycin), or tetracycline (doxycycline) class antibiotics
3. Recent use of prolonged antibiotics (≥14-day course in the month before enrolment)

Use of medications that impact cefixime, azithromycin, or doxycycline metabolism (check versus list in screening SOP)

Study staff: Research staff will participate in minuted staff meetings, provide feedback on the interventions tested, and contribute to the collection of data for cost analysis.

Inclusion criteria

1. 18 years of age or older
2. Employed at one of the study sites as research staff contributing to this study

Exclusion criteria

1. None

d. Sample size determination

Power and sample size.

The trial will have >80% power to detect a 33% reduction in a combined bacterial STI prevalence outcome, the optimal estimate of overall burden in a setting in which syndromic treatment is standard of care.

We propose a standard randomized superiority design, comparing each intervention separately to the standard of care arm. The primary trial outcome will be the combined prevalence of NG, CT, and early syphilis ascertained by laboratory diagnosis (e.g., positive NAAT for NG or CT or new syphilis diagnosis, based on first positive rapid plasma reagin [RPR] or a fourfold increase in non-treponemal titres); the prevalence of each pathogen individually will be secondary outcomes. Outcomes will be assessed at baseline and every 3 months for 18 months. We have selected prevalence instead of incidence as our outcome of interest, because a major drawback of syndromic treatment is its failure to identify and treat asymptomatic infections that can therefore persist as a reservoir for transmission, despite spontaneous clearance of some infections.[46] To detect a 33% reduction in STI prevalence (from 16.0% to 10.8%) for each intervention compared to standard care, we will need 2,465

participants total: 986 participants in each intervention group and 493 in the control group (α=0.05, β=0.20). Accounting for 15% attrition after randomization, we will need 2,900 participants: 1,160 participants in each intervention group and 580 in the control group. We will target enrolment of ≈967 participants at each of our three research sites to attain the required sample size. For analysis of AMR rates, our power will be limited for very rare outcomes (e.g., cefixime resistance), but we will have 80% power to detect an increase in tetracycline resistance from 80% to 86.7% or from 85% to 90.8% in each intervention arm compared to the control arm.

e. Stakeholder engagement and recruitment procedures

Drs. Graham, Sanders, Otieno, and Kimani and their teams have a strong history of recruiting and retaining MSM in prospective studies. We will plan for multilevel engagement at each site during the protocol approval process, including input from our site-specific community advisory boards, local MSM community leaders, and NASCOP, building on strong existing relationships with these entities.

Recruitment and retention. We will enrol 2900 MSM age 18-29 in this randomized controlled trial (1160 to each intervention arm and 580 in the control arm, with approximately 967 per site) and follow participants quarterly for 18 months.

Our three research sites are in the three largest cities in Kenya (estimated populations 4,400,000 in Nairobi, 1,440,000 in Mombasa, and 610,000 in Kisumu). We estimate that at least 2,000 MSM age 18-29 are active with the largest MSM community-based organization (CBO) in Mombasa (HAPA Kenya), and additional CBOs serving sexual minority men are in the study area. In Kisumu, NRHS serves approximately 2,000 MSM of whom 68% (1,340) are aged 18-29 years, and there are several vibrant CBOs serving MSM (MAAYGO, NYARWEK, etc.) in the study area. Finally, through the SWOP clinics, PHDA serves at least 7000 MSM, of whom approximately half are aged 18- 29. There are several active CBOs serving MSM in the Nairobi area, including HOYMAS, Ishtar, and GALCK+.

Recruitment will be conducted by fliers, information sessions, word of mouth, and social media apps (Facebook, WhatsApp) to increase awareness of the study at the three research clinics and at local CBO partner sites in each site's catchment area. In addition, we will recruit participants through experienced peer outreach workers affiliated with each site at previously mapped MSM hotspots, including bars, discos, restaurants, and social halls, and through moonlight outreaches. Recruitment will be done primarily through word of mouth and in-person outreach by our community outreach team to eligible participants in the study area, so as to minimize stigma surrounding male-male sex in Kenya. Any printed recruitment materials or flyers to be used on-site at our research clinic will be developed in collaboration with our CBO partners at each site and will be submitted to the IRB for review and approval before use.

f. Study procedures

A brief screening form will be used to evaluate whether an individual is eligible for study participation. This form will include a study ID that will be assigned sequentially at each site (KIS0001 for the first patient in Kisumu, etc.). For persons who do not enrol, we will collect

no identifiable information; data collection for these individuals will be limited to the screening form responses. For persons who enrol in the trial, the study ID will be matched to subject identifiers that will be collected after informed consent is given.

Recruitment will begin in the second half of year 1, after a period of preparation involving staff hiring, training, and community engagement meetings. Participants will have their fingerprint scanned at enrolment and subsequent visits in a cloud-based database accessible to all three sites. Biometric identification allows for prevention of co-enrolment, as participation will be verified at each visit at each of the three sites. We have experience with fingerprint scanning from a previous study involving these 3 sites. Given our extensive experience recruiting MSM for a number of studies, assistance from our community partners, and ongoing work with the target population, we expect to meet this target with no problems.

Retention efforts will be supported by ensuring that the trial sites offer high-quality MSM-friendly services, offer flexible hours, monitor clinic flow and wait times, and provide HIV and STI treatment free of charge. In addition, we use SMS reminders 3 days and 1 day before a scheduled visit to promote timeline attendance. Tracing of participants who miss visits will be the responsibility of the outreach teams at each research site. These teams have many years' experience tracing patients who miss visits or have laboratory results needing follow-up. Because residential locations are very difficult to find due to poor maps and the lack of a formal numbering system, the team has used GPS mapping to locate a participant's home or workplace for future contacts; this service is provided to participants who agree to show the home or workplace to the study team member after a clinic visit. In addition, we collect tracking information that includes participant cell phone numbers, home location and nearby landmarks. The outreach team will use SMS reminders before visits, cell phone calls in the event of missed visits, and home visits as needed to encourage retention and complete follow-up. These methods have led to successful retention of ≈85% participants on average in completed trials we have conducted and will be bolstered for this trial.

Regardless of the participant retention methods described above, participants may voluntarily withdraw from the study for any reason at any time. Should a participant indicate that he would like to withdraw, study staff will request completion of a short assessment survey characterizing reasons for withdrawal. The MPIs may withdraw participants from the study in order to protect their safety and/or if they are unwilling or unable to comply with required study procedures, after consultation with rest of the research team. Participants also may be withdrawn if the study sponsor, government or regulatory authorities, or IRBs/ECs terminate the study prior to its planned end date. Trial participants who decide to withdraw from the study prior to the last follow-up visit will be asked if they will complete the procedures that would have been completed at this visit, but they will not be required to do so. Additionally, study staff will invite such participants for brief exit interviews and record the reason(s) for all withdrawals from the study in participants' study records (regardless of whether participants complete an exit interview), to further understand reasons for withdrawal. The brief exit interviews will be recorded if the participant consents to this.

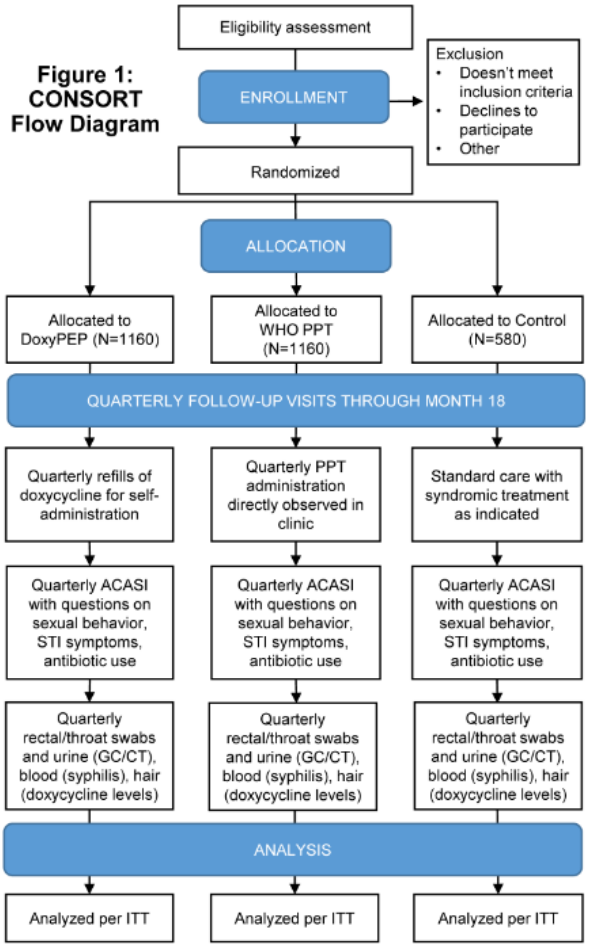
Population and procedures (Table 1, Figure 1). Interested individuals will be provided information on the study intervention and randomization, then screened for eligibility. Sociodemographic data will be collected for all individuals screened, whether or not they are determined eligible or choose to enrol. Those who are eligible and choose to enrol will provide written informed consent.

Table 1. Operational components of Aim 1

Inclusion/ exclusion criteria	Inclusion criteria: 18-29 years of age; assigned male sex at birth; identifies as male; reports condomless anal intercourse and either multiple male sex partners or a male sex partner with a syndromic (urethritis, proctitis, or genital ulcer disease) or laboratory-diagnosed STI (NG, CT or syphilis) in the past 6 months; willing and able to give written informed consent. Exclusion criteria: allergy to cephalosporin, macrolide, or tetracycline class antibiotics; recent use of prolonged antibiotics (≥14-day course) in the month before enrollment; use of medications that impact cefixime, azithromycin, or doxycycline metabolism; receipt of Bexero meningococcal group B vaccine; ongoing participation in another clinical trial; or active, clinically significant medical or psychiatric conditions that would interfere with study participation, at the discretion of the site investigator.
Sample size	2900 MSM; randomized 2:2:1 to directly observed STI PPT or doxyPEP vs. standard care syndromic STI treatment
Visit schedule	Screening, enrollment, quarterly for 18 months; reminders and tracing in case of missed visits to ensure high retention
Standard of care package	All participants: Syndromic STI treatment and partner notification per current guidelines as indicated, risk reduction counseling, condoms, lubricants, and standard HIV prevention or care services according to HIV status

Subjects will then be randomized in variable-sized blocks stratified by site, using opaque envelopes opened at randomization. Participants will attend quarterly visits, which are standard of care for HIV prevention and care services, for 18 months of follow-up. At each visit, we will collect participant data via Audio Computer-Assisted Self Interview (ACASI) software (Questionnaire Development System™, Nova Research Company, Silver Springs, MD, USA) that we have used for many of our studies in Kenya. Clinic data will be entered in REDCap, a secure web application for building and managing online surveys and databases which is freely available through the UW or in Computer Assisted Personal Interview (CAPI) software (Questionnaire Development System™, Nova Research Company, Silver Springs, MD, USA).

Figure 1: CONSORT Flow Diagram



- Rectal/throat swabs and urine for GC/CT will be collected at unscheduled interim visits for any reason. In addition, swabs of urethral discharge will be collected from participants in each arm who present with symptomatic urethritis at scheduled or interim visits.

Study arms. The three medications to be used in the interventions we propose have been used safely for STI treatment for decades. In addition, doxyPEP has not led to significant safety concerns in the two trials with available results to date.[15,23] All study medications will be obtained from a quality-controlled pharmacy used by the ongoing Kenya "dPEP" trial of doxyPEP for adolescent girls and young women (MPI Bukusi and Baeten, R01 AI145971): Goodman Agencies, Limited in Nairobi. Our study arms will be as follows:

- *STI PPT intervention.* Participants assigned to the STI PPT arm will be evaluated at baseline and every 3 months thereafter for STI PPT eligibility based on having had condomless anal sex and either multiple sex partners or a sex partner with an STI in the past 6 months.[24] If eligible, they will be offered 400 mg po cefixime plus 1 gram azithromycin po under direct observation, using the same regimen as for syndromic treatment per the latest WHO recommendations.[25]
- *DoxyPEP intervention.* Participants assigned to the doxyPEP arm will be provided with a 30-day supply of doxycycline hyclate at each quarterly visit and given 1:1 counselling on the self-administration of 200 mg po doxycycline within 24-72 hours after condomless anal or vaginal sex as frequently as daily if indicated but not more than once daily, in accordance with the doxyPEP trial in the United States.[15] Refills will be provided as needed. Since doxyPEP is only indicated after condomless sex, some participants will use this less than daily and so will not need monthly refills. We will instruct participants very clearly that no more than two 100-mg tablets should be taken on a given day, to avoid overuse. When refills are needed, participants will have the option to pick these up at the clinic where they are enrolled or to request delivery from an outreach worker trained by the study team. Participants will not be reimbursed for refill pick-up at the clinic, since we assume those who come for these refills will be attending the clinic for other purposes (e.g., social activities, other events at the site). Refill provision will be carefully documented at the clinic and when delivery is provided in the field by outreach workers.
- *Standard care.* Participants assigned to the standard care arm will receive screening for STI symptoms at every scheduled visit and syndromic treatment with cefixime 400 mg po stat plus azithromycin 1 gram po stat under direct observation, in accordance with current Kenyan recommendations for genital and anorectal infections.[26] This regimen will be updated if Kenyan recommendations change. Standard care also includes notification of partners who may have been exposed, with expedited partner treatment to those in ongoing relationships with the index patient.[26]

Participants may return to the study clinic for interim visits at any time STI symptoms are present, regardless of study arm. Intervention participants who report genitourinary or rectal symptoms compatible with urethritis or proctitis at scheduled visits will also receive syndromic treatment. All treatment will be documented, whether at a scheduled quarterly or interim visit. Fidelity of delivery of each intervention will be closely monitored and documented, using a detailed implementation SOP with a checklist of steps completed.

Procedures at study visits. At each quarterly study visit beginning with the enrolment visit, the following procedures will be carried out:

- Before each scheduled study visit, we will contact participants by SMS with a visit reminder. If participants miss a scheduled visit, we will contact them by phone or SMS asking them to reschedule. If we cannot reach them, we will send a peer education worker to find them at the address provided to us upon enrolment.
- At each scheduled visit, participants will be asked to complete a brief survey lasting 30-45 minutes on a tablet computer with questions about their sexual behaviour, STI symptoms, antibiotic use, substance use, and mental health since the last visit.
- At each scheduled visit, participants will see a clinician, who will do the following:

    - Ask if the participant has any symptoms of an STI, such as pain or discharge with urination, throat pain, rectal pain or discharge, genital lesions, or a rash.
    - Perform a focused physical examination depending on the participant's symptoms.
    - Ask if the participant has any side effects that can be associated with taking cefixime, azithromycin, or doxycycline.
    - Collect two swabs of the participant's throat, two swabs of their rectum, and a small sample of hair (approximately 20 hairs from the back of the head).
    - Ask the participant to provide a urine sample.
    - Draw the participant's blood, collecting 1 tube of blood for syphilis testing.
    - Provide treatment according to Kenyan guidelines for any STI symptoms the participant has (part of standard care).
    - Provide HIV testing and prevention services if the participant is HIV negative and HIV care if the participant is HIV positive, according to Kenyan guidelines (part of standard care).
    - Offer the participant condoms, lubricants and counseling about how to reduce their STI risk.
    - Give the participant a survey asking their opinion about the STI control intervention they are assigned to.
- If a participant has STI symptoms between scheduled visits, such as a sore throat, discharge from their penis, burning when they urinate, or rectal pain or discharge, they will be asked to come to the research site for sample collection to test for possible STI.
- If a participant's blood test is positive for syphilis, they will be contacted so they can come to the clinic and receive treatment.
- After each scheduled research visit, participants will receive 1000 Kenya shillings (approximately $7.00) to compensate for their time and participation. This is in line with our most recent research studies with this population in Kenya.
- Text reminders will be sent for scheduled study visits and exit interviews. Participants who miss a scheduled visit or exit interview, and those with lab results indicating a need for syphilis treatment, will be traced and invited to return to the clinic where they enrolled.
- Participants who move to a different study site (e.g., from Nairobi to Kisumu) will have the option to complete follow-up at the new location. Those who are unable to complete participation will be invited to an exit interview for their feedback before being withdrawn from the study.

Timing of study visits and procedures:

- The initial enrolment visit will take approximately 90 minutes.
- Scheduled follow-up visits every 3 months will take approximately 60 minutes.
- Interim visits for symptom evaluation or for treatment of syphilis, when needed, will take approximately 30 minutes.

Study medications

All study medications will be obtained from a quality-controlled pharmacy used by the ongoing Kenya dPEP trial of doxyPEP for adolescent girls and young women (MPI Bukusi and Baeten, R01 AI145971): Goodman Agencies or a quality-controlled pharmacy with similar degree of quality

assurance and oversight. A licensed clinical trials pharmacist will provide oversight to pharmacy technicians based at each site. As described above, our study arms will be as follows:

- **STI PPT intervention.** Participants assigned to the STI PPT arm will be evaluated at baseline and every 3 months thereafter for STI PPT eligibility based on having had condomless anal sex and either multiple sex partners or a sex partner with an STI in the past 6 months. [24] If eligible, they will be offered 400 mg po cefixime plus 1 gram azithromycin po under direct observation, using the same regimen as for syndromic treatment per the latest WHO recommendations. [25]
- **DoxyPEP intervention.** Participants assigned to the doxyPEP arm will be provided with a 30-day supply of doxycycline hyclate at each quarterly visit and given 1:1 counseling on the self-administration of 200 mg po doxycycline within 24-72 hours after condomless anal or vaginal sex as frequently as daily if indicated but not more than once daily, in accordance with the doxyPEP trial in the United States. [15]
- **Standard care.** Participants assigned to the standard care arm will receive screening for STI symptoms at every scheduled visit and syndromic treatment with cefixime 400 mg po stat plus azithromycin 1 gram po stat under direct observation, in accordance with current Kenyan recommendations for genital and anorectal infections. [26] This regimen will be updated if Kenyan recommendations change.

Specimens, Testing and Shipment within and outside Kenya:
As described above in the procedures section, the following specimens will be subject to shipment:

- **All NG/CT samples for NAAT.** These samples will be transferred (from Ganjoni Clinic) or shipped (from Kisumu or Nairobi) for storage at -80^{o}C in the **UW/University of Nairobi East Africa STI Laboratory in Mombasa**, which has operated with external quality assurance for >10 years. At the end of study follow-up, Aptima Combo 2 testing for NG and CT will be conducted in Mombasa on a Hologic Panther platform by experienced laboratory staff blinded to randomization assignment. To reduce testing costs, we will pool the 3 samples from each participant for initial testing following published protocols. [28,29] All NG-positive pools will be broken down and individually tested to identify the infected site or sites. [28]
- **NG AMR testing in Seattle.** We will perform culture and susceptibility testing of urethral swabs from symptomatic urethritis cases in Kenya, due to the high yield of these specimens on culture. [34] We will supplement this testing with rigorous molecular methods using residual NAAT samples and non-cultured swab or urine specimens to identify well-characterized genetic AMR determinants conferring cefixime, azithromycin or tetracycline resistance in NG. Of note, we have validated and successfully used these methods for strain typing and characterization of resistance determinants in NG. [33,35,36] We will select a **random sample of 25% of all NG-positive specimens (≈761 samples) from each intervention arm** (50% at baseline and 50% at follow-up) for shipment to the laboratory of Dr. Soge at the UW for molecular testing. Of note, Dr. Soge has begun a collaboration to transfer this technology to the UW/University of Nairobi East Africa STI Laboratory at the Coast General Hospital in Mombasa, which will be used as our primary AMR testing site once capacity is fully established and rigorous quality control and quality assurance measures are in place.

- **Hair samples for doxycycline levels.** We will collect hair samples from all participants at all visits, but do not have enough in the budget to test them all. Therefore, we plan to ship a random sample of 10% of all hair samples collected (≈812 samples) from the month 6 and month 18 visits in the doxyPEP arm to the UW in Seattle for testing for doxycycline levels; [30] this testing will be done through the Hair Analytical Lab at UCSF or another vendor, depending on costs and availability at the time of testing. The rest of the samples will be stored and if funding permits and the science warrants it, we might test additional samples.

Specimen collection, testing and storage. HIV testing and counseling will be conducted for previously HIV-negative participants at each quarterly visit, per Kenyan guidelines for key populations. At each quarterly visit, participants will undergo hair collection for testing of doxycycline levels and three-site screening for NG and CT, with provider-collected pharyngeal and rectal swabs (2 of each) and a clean-catch urine. Participants who return to the study clinic for interim STI symptoms will undergo collection of the same pharyngeal, rectal, and urine samples. We will not diagnose and treat infections other than syphilis in real time. Syphilis serology including RPR (Becton Dickinson) and, if reactive, TPHA (Biotec) will be tested at quarterly visits, with treatment provided to participants with a new syphilis diagnosis as soon as results are available. Samples for NG and CT NAAT will be stored for batch testing at the study's end. Participants who have symptomatic urethritis at any study visit (estimated at 5% of visits or ≈1,015 visits) will undergo swab collection of urethral discharge for Gram staining and NG culture using modified Thayer-Martin Agar, a selective medium supplemented with nystatin, colistin, vancomycin, and trimethoprim that favours growth of *Neisseria gonorrhoeae* while suppressing genital and extragenital commensal microbial flora growth. Antimicrobial susceptibility testing (AST) will be performed using disk diffusion for penicillin and tetracycline and Etest for cefixime, azithromycin, and doxycycline, using WHO control strains for quality assurance of AST at each of the site's microbiology labs. [27]

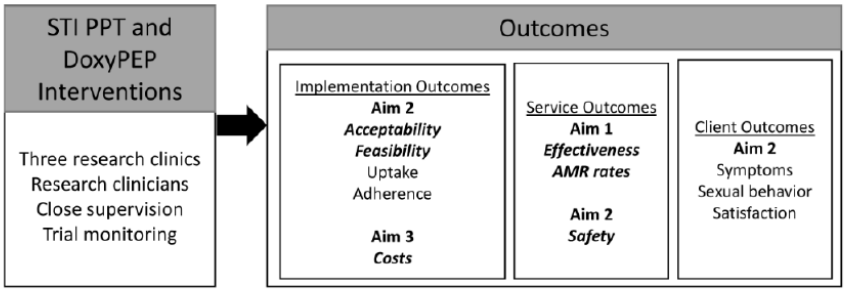
All NG/CT samples for NAAT will be transferred (from Ganjoni Clinic) or shipped (from Kisumu or Nairobi) for storage at -80^{o}C in the UW/University of Nairobi East Africa STI Laboratory in Mombasa, which has operated with external quality assurance for >10 years. At the end of study follow-up, Aptima Combo 2 testing for NG and CT will be conducted on a Hologic Panther platform by experienced laboratory staff blinded to randomization assignment. To reduce testing costs, we will pool the 3 samples from each participant for initial testing following published protocols. [28,29] All NG-positive pools will be broken down and individually tested to identify the infected site or sites. [28] All NG, CT, and early syphilis diagnoses will be reviewed by an Endpoint Adjudication Committee blinded to treatment arm. We will collect hair samples from all participants at all visits, but do not have enough in the budget to test them all. Therefore, we plan to ship a random sample of 10% of all hair samples collected (≈812 samples) from the month 6 and month 18 visits in the doxyPEP arm to Seattle for testing for doxycycline levels; [30] this testing will be done through the Hair Analytical Lab at UCSF or another vendor, depending on costs and availability at the time of testing. The rest of the samples will be stored and if funding permits and the science warrants it, we might test additional samples.

NG AMR testing in Seattle. The potential for selection of AMR by STI PPT or doxyPEP is one of the greatest risks to the success of these strategies; however, the magnitude of this risk cannot be known without empiric data. Cephalosporin resistance in *N. gonorrhoeae* is happily still rare in Kenya. Azithromycin resistance in *N. gonorrhoeae* is uncommon in Kenya (0%-8.3% in recent

studies), [31,32] and STI PPT may not increase it substantially given co-coverage with cefixime. Resistance to azithromycin in *C. trachomatis* has not been seen. Plasma-mediated doxycycline resistance in NG is common and may impact the efficacy of doxyPEP. [33] We will perform culture and susceptibility testing of urethral swabs from symptomatic urethritis cases due to the high yield of these specimens on culture, [34] but will supplement this testing with rigorous molecular methods using residual NAAT samples and non-cultured swab or urine specimens to identify well-characterized genetic AMR determinants conferring cefixime, azithromycin or tetracycline resistance in NG. Of note, we have validated and successfully used these methods for strain typing and characterization of resistance determinants in NG. [33,35,36] We will select a random sample of 25% of all NG-positive specimens (≈761 samples) from each intervention arm (50% at baseline and 50% at follow-up) for shipment to the laboratory of Dr. Soge at UW for molecular testing. DNA will be purified and extracted from residual NAAT samples, swabs, and/or urine using the Total Nucleic Acid Isolation Kit on the Roche MagNA Pure 24 System (Roche Diagnostics, Indianapolis, IN), an automated nucleic acid purification system that has been validated by Soge Lab to yield high-quality DNA from NAAT and clinical specimens. [37] Molecular characterization of NG will include strain typing using the internationally used *N. gonorrhoeae* multiantigen sequencing typing (NG-MAST) system; [38] detection of plasmid-mediated *tet*(M), which confers high-level tetracycline resistance (tetR), and the chromosomally-mediated mutation rpsJ V57M, which confers low-level tetR; [39] detection of single-nucleotide polymorphisms (SNPs) associated with reduced cephalosporin (cefixime/ceftriaxone) susceptibility and resistance (mosaic *penA* allele*s, penA* A311V, *penA* N513Y, *ponA* L421P, *mtrR* −35delA, and *porB* G120K/A121D/N), [40-43] and detection of azithromycin resistance (23S rRNA A2059G, C2611T) [41,44] by PCR and sequencing. Well-characterized positive control strains and negative controls will be included in all PCR assays. [45] Of note, Dr. Soge has begun a collaboration to transfer this technology to the UW/University of Nairobi East Africa STI Laboratory at the Coast General Hospital in Mombasa, which will be used as our primary AMR testing site once capacity is fully established and rigorous quality control and quality assurance measures are in place.

Aim 2. To assess the acceptability, feasibility, and safety of implementing WHO-recommended STI PPT and doxy-PEP compared to standard care among providers and patients. Approach: We will use multidisciplinary science to measure acceptability, feasibility, and safety of these interventions, using a conceptual model based on Proctor's Implementation Science Framework[21,22] (Figure 2, with primary outcomes related to each aim in ***bold italic***.)

Figure 2. Conceptual Model



Considering the unique needs of Kenyan MSM with respect to sexual health will be essential to developing effective strategies to address their STI burden. In addition, any STI control intervention must be acceptable, feasible, and safe for the

patient. We will prioritize these three outcomes for our Aim 2 work and capture acceptability and feasibility data from both providers and participants. We note that Aim 1 will focus on two service outcomes (effectiveness, AMR rates) and Aim 3 will include analysis of an implementation outcome (costs). Secondary outcomes related to the STI PPT and doxyPEP interventions that we will assess include the implementation outcomes of uptake and adherence (related to acceptability and sustainability of the interventions) and client outcomes including satisfaction, symptoms, and sexual behaviour. The quantitative and qualitative measures we will use to assess these outcomes are presented in Table 2. [22]

Table 2. Aim 2 intervention outcomes, by type

Outcome type	Specific outcome	Approach	Outcomes
Implementation	Acceptability	Brief questionnaire for eligible individuals who decline to enroll; ACASI questions (Table 3); brief exit interviews; staff meeting minutes and questionnaire	Understanding how well STI PPT and doxyPEP are received by and are perceived to meets the needs of the target population
	Feasibility	ACASI questions (Table 3), staff meeting minutes and questionnaire	Understanding how easily STI PPT and doxyPEP can be carried out
	Uptake	Acceptance of directly observed STI PPT or of doxycycline tablets at baseline	Estimate STI PPT and doxyPEP acceptance at baseline documented in clinic records
	Adherence	Administration records for STI PPT participants, doxycycline levels in hair for doxyPEP participants	Estimate STI PPT and doxyPEP acceptance over time documented in clinic records
	Costs	Microcosting, time motion surveys (aim 3)	Cost to system, cost to patient
Service	Effectiveness	Impact on NG and CT incidence and on AMR (aim 1)	Reduction in NG and CT incidence without increased AMR
	Safety	Rigorous monitoring of safety, including social harms	Adverse events (AE) attributed to STI PPT or doxyPEP, discontinuation due to AE
Client	Symptoms	Quantitative measures of symptoms (Table 3)	Understanding how symptoms differ by arm
	Sexual behavior	Measurement of sexual behavior and antiretroviral use in all arms, brief exit interviews	Understanding of any behavioral disinhibition with STI PPT or doxyPEP
	Satisfaction	Brief exit interviews	Understanding how well STI PPT and doxyPEP met the needs of the target population

Data collection. Due to its enhanced privacy, ACASI will be the main method of data collection, in English, Dholuo, or Kiswahili. We have successfully used ACASI to capture data in multiple projects at our research sites. [48-52] Because participants occasionally have difficulties using ACASI, a research assistant will be available to assist participants if needed. Our initial selection of measures to evaluate draws from our conceptual model for the Aim 2 work, extensive experience conducting research among Kenyan MSM and published literature on correlates of sexual behaviour, HIV/STI incidence, and medication adherence. Table 3 presents an overview of data elements, content, tools for assessment, frequency of assessment, and applicable study arm. Of note, this list will be updated and finalized before study launch.

Table 3. Quantitative Data Elements Collected from Participants: Content, Collection Method, Frequency and Arm

Data Element	Method and Content	Frequency and Arm
Aim 1 Outcome Variables		
NG, CT, or early infection (primary outcome)	Aptima NAAT: Pooled specimen (throat, rectal, and urine) positive for NG or CT; first positive rapid plasma reagin [RPR] or a fourfold increase in non-treponemal titres) for early syphilis	All arms: Quarterly and at interim visits for STI symptoms
Each infection individually	Same as above	All arms: Quarterly and at interim visits for STI symptoms
AMR	Resistance to penicillin, tetracycline, cefixime, azithromycin, or doxycycline by culture of urethral discharge (symptomatic urethritis cases) or molecular testing (25% of all NG-positive samples	All arms: Quarterly and at interim visits for STI symptoms
Aim 2 Outcome Variables		
Acceptability	ACASI: Acceptability of Intervention Measure (AIM), [53] Likert-scale questions on each intervention adapted from the	Intervention arms: Quarterly

	doxyPEP study[15]	
Feasibility	ACASI: Feasibility of Intervention Measure (FIM) [53]	Intervention arms: Quarterly
Uptake	Direct observation: Administration of cefixime and azithromycin, receipt of doxycycline	Intervention arms: Quarterly
Adherence	ACASI: Self-report questions on interventions adapted from the doxyPEP study; [15] counts of returned doxycycline tablets; hair doxycycline levels; directly observed PPT	Intervention arms: Quarterly
Safety including social harms	ACASI questions plus study monitoring: adverse events and social harms reported by participants or study staff	All arms: Quarterly
Symptoms	ACASI: Modified SAFTEE scale: 26-item scale rating symptoms and their attribution to medications; [54] pharyngeal, urethral, or rectal symptoms since past visit and whether treatment was sought outside the study	All arms: Quarterly
Sexual risk behaviour	ACASI: Condomless anal sex, anal intercourse, vaginal intercourse, condom use, partner numbers, partner HIV status, concurrency, sexual networks, sexual violence	All arms: Quarterly
PrEP or ART use and adherence	ACASI: Use of PrEP (if HIV-negative) or ART (if HIV-positive), visual analog scale, [55,56] self-rating scale, [57] pill counts, [58] medication possession ratio[59]	All arms: Quarterly
Study retention	Study records: Scheduled visits completed within 1-month window	All arms: Quarterly
Potential Correlates of Study Outcomes		
Demographics	ACASI: Age, education, religion, marital status, gender identity, [60] sexual orientation, transactional sex, employment, income	Both arms: Baseline
Clinic access	ACASI: Transportation costs, wait times, problems with clinic hours or staffing, experienced discrimination[61]	Both arms: Quarterly
STI knowledge	ACASI: Questions will be based on ongoing work in the *Shauriana* project (R34 MH118950-01)	Both arms: Quarterly
STI risk perception	ACASI: Two questions "What do you think is your risk of getting (giving) STIs from (to) your partner?" (4 item Likert scale) [62,63]	Both arms: Quarterly
HIV status	Laboratory testing according to Kenyan guidelines at each study visit, with quarterly rapid tests if previously seronegative and every 6 month viral load monitoring if seropositive[64]	Both arms: Quarterly or every 6 months, depending on HIV status
Antibiotic use	ACASI: Trimethoprim-sulfamethoxazole prophylaxis, [33] report of any antibiotic use outside the study in the past 30 days	Both arms: Quarterly
Substance use	ACASI: Alcohol Use Disorders Identification Test (AUDIT), [65-67] Drug Abuse Screening Test (DAST) [68]	Both arms: Quarterly
Sexual stigma	ACASI: Sexual stigma as used in our previous work. [69]	Both arms: Every 6 months
HIV stigma	HIV/AIDS Stigma Instrument – PLWH[70]	Both arms: Every 6 months if HIV positive
Depressive symptoms	ACASI: Patient Health Questionnaire-9 (PHQ-9): a validated Swahili version is available. [71,72]	Both arms: Quarterly

Qualitative Data Collection. During study screening, a brief questionnaire with 2-3 open-ended questions will be used to capture reasons for declining to enrol, including poor individual-level acceptability of STI PPT, doxyPEP or randomization. During the trial, qualitative data collection will include brief exit interviews with a subset of 30 participants in each intervention arm (10 at each site), to understand participant-level acceptability and satisfaction with the interventions. Interviews will be conducted using participants' preferred language (English, Dholuo, or Kiswahili). Participants will be sampled for these interviews to include a range of ages and reported risk

behaviours (e.g., transactional sex), using a stratified-purposive sampling approach. At any visit on which a participant withdraws, a similar exit interview will be conducted to obtain feedback on the intervention received. Interviews will be recorded if permission is granted; detailed notes will also be taken to document participant feedback. Minutes will be taken at monthly staff meetings at each site to document any challenges arising. At each staff meeting, we will let staff know that we are taking notes for the research and that staff can let us know if they have any questions or concerns about this. At the end of the study, acceptability and feasibility for providers will also be assessed using the 4-item AIM and 4-item FIM tools in a questionnaire administered to research staff. [53] Examples of AIM items tailored for the STI PPT intervention include: "STI PPT meets my approval" and "STI PPT is appealing to me." Example of FIM items tailored for the doxyPEP intervention include "DoxyPEP seems implementable" and "DoxyPEP seems easy to use." Responses include 1 = completely disagree, 2 = disagree, 3 = neither agree nor disagree, 4 = agree, and 5 = completely agree.

Microcosting. We will conduct microcosting, semi-structured interviews or focus group discussions with staff regarding time spent on different work activities, and time and motion observation of the intervention and standard of care treatments within the RCT. Costs will be divided into diagnostic evaluation or testing and NG and CT treatment. Direct medical costs of standard syndromic treatment, STI PPT, and doxyPEP will include costs of personnel, transportation, and communication. Direct medical costs of NAAT-guided treatment will include these costs, plus the costs of testing supplies, which are a factor of resource use for testing and unit costs for NAAT supplies. Costs of personnel are a factor of wages for clinical, counselling, field workers, and laboratory testing (NAAT scenario only), and the time spent performing different activities. Communication cost will be obtained by estimating the number of minutes per call, the mean number of calls, and costs per call-minute. Costs of NG and CT treatment include the costs of medications used for treatment and the cost of partner treatment under each scenario. Indirect costs will be estimated using data from patient exit interviews and publicly available data. Questions about patient transport costs, transport time, and upkeep costs will be added to data collection forms and subsequently combined with data on patient waiting and patient contact time with health workers to estimate indirect costs. Wages will be estimated based on Kenya's gross domestic product per capita. We will conduct semi-structured interviews or focus group discussions with up to 5 research staff at each site, to assess daily responsibilities associated with the interventions and standard syndromic treatment. Time and motion observation of intervention activities for 50 patient/provider interactions per intervention arm will be conducted to inform staff time costs and productivity assumptions. Research time (e.g., informed consent) will be removed from programmatic costs. These procedures will also be used to elicit qualitative information from staff on the feasibility of intervention delivery. If staff agree, these sessions will be audio-recorded for ease of analysing the data. Participants present during time and motion observation will not be audio-recorded without participants' verbal agreement.

g. Limitations and Alternative Approaches

We have carefully considered our study design and approach to optimize feasibility, while maintaining high rigor and ensuring that results will be reproducible.

Feasibility. Kenya is an ideal setting for evaluating STI PPT and doxyPEP among MSM, as the Government of Kenya's visionary 20-year plan for evidence-based HIV and STI prevention, the *Kenya HIV Prevention Revolution Road Map: Count Down to 2030,* aims to drive new HIV infections towards zero between 2013 and 2030 using effective HIV and STI prevention initiatives.[83] As HIV transmission decreases, risk has become more concentrated in key populations such as MSM, who also experience high rates of bacterial STI. The Kenyan Ministry of Health endorses STI control in key populations, has worked to address health disparities among MSM, and supports this proposal, ensuring that our trial results will be linked to policy. In addition, each research site has collaborative relationships with MSM-led community-based organizations with large membership rosters, laying the groundwork for community feedback on the proposed work and its implementation, and for successful outreach, recruitment, and retention.

PPT regimen selection. We debated using the CDC's currently recommended STI treatment regimen consisting of IM ceftriaxone and PO doxycycline. However, we decided against this because of concerns about low acceptability of injections and the advice of Dr. Teodora Wi, the WHO Medical Officer in charge of STI Programs. Most low- and middle-income countries still using cefixime and azithromycin have not seen the same levels of AMR as in high-income countries, likely due in large part to lack of NAAT screening to guide treatment.[84,85] Azithromycin provides both CT coverage and dual coverage of most NG. Although azithromycin resistance can emerge in NG due to the long half-life of this drug,[86,87] data from the CDC's NG surveillance program suggest that cefixime resistance decreased after the addition of azithromycin to the NG treatment regimen.[88,89] In contrast, a recent study of our isolates in Kenya suggested that doxycycline can select for plasmid-mediated penicillin resistance and therefore could potentially increase the risk of cephalosporin resistance.[31] Therefore it is critical to evaluate NG AMR to all three antibiotics in all study arms.

Timing of STI PPT administration. The WHO did not specify a frequency for STI PPT assessment and delivery in their recommendations.[13] We debated offering this intervention on a 6-monthly basis, but felt this might weaken the intervention's efficacy. We will be able to explore the potential efficacy of different frequencies of PPT administration in our modelling work.

Treatment of uninfected individuals. We have estimated a NNT with STI PPT to treat one infection ranging from 4-12 (***Preliminary Results***). In the doxyPEP study in United States settings with similar STI incidence as in Kenya, the NNT was estimated at 5.[15] Treatment of uninfected individuals occurs in the setting of epidemiologic treatment of partners; for example, a recent study estimated that 65% of individuals receiving expedited partner treatment (often with po cefixime) are asymptomatic and NAAT negative.[90] An important aspect of the proposed research is delivery of STI PPT or doxyPEP in a setting in which the vast majority of bacterial STI are currently undiagnosed and therefore left untreated.

Low STI rates in the control condition. Given high rates of STIs in our MSM cohorts and service disruptions that resulted from COVID-19, it is unlikely that STI rates will be low. Our data safety and monitoring board will monitor STI rates in the control condition and on STI treatment received outside the research clinics and will inform the team if assumptions regarding STI rates should be revisited to ensure adequate power.

Selection bias: This study depends on participation by MSM who live in the catchment areas of the three research clinics, accept research screening, and agree to enrol in the study. As detailed in the approach, we will collect data on characteristics of the MSM who decline trial participation.

Generalizability. While the three research sites selected do not represent all geographic areas and CT/NG prevalence conditions in Kenya, data from the MHRC suggests that the behaviour risk profiles, sexual networks, and social interactions of MSM across the three sites are similar. Evaluating these interventions at sites with adequate research capacity is important for practical reasons related to feasibility, budget, and experience.

Contamination and period effects: We will collect data on receipt of syndromic treatment and of other antibiotics in the past 30 days during follow-up, to monitor for contamination in the standard care arm. Providing STI PPT or doxyPEP to intervention arm participants may reduce STI rates in the control arms by reducing NG and CT prevalence within sexual networks.

Reliability of participant self-report: An important limitation is the potential for underreporting of stigmatized behaviours, such as condomless RAI and substance use. Our experience with ACASI in prior studies suggests that this method of data collection may yield more frank responses to questions on sensitive topics. [48,91]

Differential retention given the open-label design. At enrolment, we will describe the equipoise to evaluate the effectiveness of STI PPT and doxyPEP in the Kenyan setting. After enrolment, we will try to address attrition bias by minimizing the burden of study visits and each intervention on participants, keeping procedures within a reasonable timeframe and monitoring clinic flow. The research team has decades of experience conducting trials with retention averaging ≈85% in prior studies (see ***Preliminary Results***), and we will carefully monitor enrolment and visit attendance to identify any potential impact on study power.

Resistance in organisms other than NG. To have ample power for evaluating the effect of our two interventions on AMR in NG, we prioritized site support for trial implementation and the NAAT and AMR testing required for Aim 1. We recognize that we have not included testing for resistance in other organisms such as *Staphylococcus aureus* or *Streptococcus pneumoniae* due to a ceiling on our allowed budget. If our funding application is successful, we will seek additional funding for additional testing of stored swabs and hair samples to explore the relationship between STI PPT and doxyPEP and AMR in additional organisms.

11. Data Management and Analysis

a. Data Collection

Data collection procedures and variables to be collected were described in the study procedures, detailed above. Data collection procedures that will be used include electronic data capture with audio computer-assisted self interviews (ACASI) or computer-assisted personal interviews (CAPI) for study participants, case report forms (CRF) for staff to complete documenting study visits, recording of interviews with participants and staff, and minuting of staff meetings. Draft study tools are included in the appendices; any updates before study launch will be submitted as a modification.

b. Data Storage

All study data will be stored securely and password security-protected on a Sharepoint site accessible only to the data managers and study PIs. The data collected on desk top computers/ laptops/ tablets using ACASI or CAPI programmed in QDS software (Questionnaire Development System™, Nova Research Company, Silver Springs, MD, USA) will be encrypted such that only password-authorized study staff can access the data. CRF data will be entered after each visit using REDCap, a secure web application for building and managing online surveys and databases which is freely available through the UW. All participant study files including hard copy CRFs will be retained at the study sites for a minimum of 10 years after study completion. Measures taken to protect confidentiality will include:

i. **De-identified data:** The use of participant names to identify study related documents will be minimized to the extent possible. All documents bearing participant names will be stored apart from documents bearing PTID or Screening ID or barcode numbers. In lieu of names, the study ID will be used so that the names will not appear on study documents. Data collected from the fingerprint scan will translate into a unique identification number that will be accessible only to study staff, at the primary site and collaborating sites. No other data than the unique 12-digit number will be stored in the shared database.
ii. **Locked Cabinets:** All files will be stored in locked cabinets in the MHRC sites, with access limited to study staff.

c. Data analysis

Data cleaning, recoding and analysis will be conducted using Stata® (StataCorp, College Station, Texas) or similar software. Entered data will be checked against the source through line listing and all data entry errors corrected. Data will then be checked for logic and consistency using Stata do-files and all discrepancies reconciled with the source before locking the database.

Aim 1 data analyses will be intention-to-treat, including participants whether or not they accept or continue STI PPT or doxyPEP. Of note, in a small sample (≈80) of MSM attending the Mtwapa clinic in 2018-2019, acceptability of STI PPT at quarterly visits in the KWRTP cohort was over 90%; COVID-19 led to the discontinuation of this pilot program. Bacterial STI diagnoses (GC, CT, and early syphilis) will be reported at baseline and each follow-up visit by arm and by study site. The combined STI outcome will be compared between each intervention and the common control arm by estimating the relative risks of any STI over follow-up (months 3-18) using a modified Poisson model fitted with generalized estimating equations (GEE) methods to account for repeated observations for each participant, assuming an independent covariance structure, with site and study arm as the only covariates. 47 The test for significance will use a two-sided α=0.05, and 95% confidence intervals will be calculated using robust standard errors. The same approach will be used for each STI individually. Complete case analysis will be used for the primary efficacy analysis, unless substantial imbalance (>8%) in missing primary endpoints by arm occurs. Appropriate missing data methods (e.g., imputation) or causal estimation of direct effects will be conducted to assess the potential influence of differential missingness by arm. Syndromic infections diagnosed and treated at interim visits after 28 days will be defined as infections for the current quarter and handled in the analysis as if they were present at the next scheduled visit. Per-protocol analyses will also be conducted, as well as analyses controlling for potential confounders such as HIV status

if they are unbalanced across arms. Resistance to each antibiotic assessed (i.e., penicillin, tetracycline, cefixime, azithromycin, and doxycycline) among NG cases will be tabulated by study arm, research site, site of infection, and AMR assessment method. The odds of resistance among NG cases with resistance results will be compared between each intervention and the common control arm using logistic regression, with repeated measures GEE if repeat infections occur. We will also analyse nonparametric trends over time in the proportion of NG isolates demonstrating resistance to each antibiotic in the study overall and by study arm. Additional analyses with adjustment for baseline STI, sexual risk behavior, and HIV status will also be performed.

Aim 2 Data Analysis. GEE with appropriate links and robust standard errors will be used to test retention across all study arms and to evaluate associations between study arm and the aim 2 quantitative outcomes collected for both interventions (e.g., AIM, FIM, uptake, AE, symptoms, sexual risk behaviour). Factors associated with adherence to doxyPEP will be analysed in the population for whom hair samples are tested, based on semiquantitative assessment of high vs. low doxycycline concentrations. [30] For all quantitative analyses, patterns of missing data will be evaluated, and multiple imputation will be used where appropriate.

Exit interview notes and transcripts and staff meeting minutes will be translated into English if necessary and imported into Dedoose qualitative analysis software. These documents will be reviewed separately by two investigators for completeness and initial theme generation. Coding and analysis will focusing on participant-level acceptability and satisfaction and on staff-level acceptability and feasibility, starting with a deductive approach informed by the theoretical framework of acceptability (TFA), a recently-developed approach to acceptability research of medical interventions. [73] The components of TFA are affective attitude, burden, ethicality, intervention coherence, opportunity costs, perceived effectiveness, and self-efficacy. Additional codes emerging from an inductive process will be added as they arise. Codes will be reviewed for consistency and inter-coder agreement with consensus code generation by themes. Descriptive thematic analyses will be done separately for individuals who refuse participation, trial participants (including those who withdraw) and staff. Within these groupings, results will be triangulated with relevant quantitative data using joint displays.

Aim 3 data analysis. Modelling and cost-effectiveness analyses (CEA) overview. After the trial is completed, mathematical models will be used to simulate long-term health and cost outcomes based on study data and to consider clinical outcomes beyond the scope and time horizon of the Aim 1 and Aim 2 work. Using cost and effectiveness outcomes estimated by the model, we will calculate the cost-effectiveness of STI PPT and of doxyPEP as interventions. The CEA will follow WHO guidelines and Cost of Implementing New Strategies (COINS) recommendations, [74,75] and report summary estimates which allow comparison to standard-care syndromic management. In addition, a comparison to NAAT-guided treatment (as done in well-resourced settings) will be made. CEA results will provide important information to decision makers charged with defining priorities and allocating resources.

Model Design. We will develop a stochastic, network-based model of NG, CT and HIV transmission in Kenya. Because syphilis is uncommon among Kenyan MSM and its transmission has not yet been extensively modelled, our model will not include syphilis. The general modelling approach will follow that developed by Jenness et al for modelling NG, CT, and HIV transmission among MSM in the United States. [76] As the model contains more forms of individual heterogeneity and

types of transitions than a standard compartmental model, we cannot easily depict it with a traditional flow diagram. The model will simulate a population of 100K individuals distinguished by the following attributes: age; gender identity; sexual role preference (insertive, receptive, versatile); relationship status; NG, CT and HIV status; diagnosis status; time since infection; treatment status; and HIV viral load, among possible relevant others revealed by our fieldwork. Individuals can undergo any or all of the following transitions: enter the sexually active population; age; form or dissolve relationships of different types; become infected with NG, CT, or HIV; experience STI and/or HIV symptoms; test; become diagnosed; undergo treatment; discontinue ART treatment; re-initiate ART treatment; age out of the population; or die due background age-specific mortality or HIV-related mortality. Within each partnership, individuals will engage in anal intercourse with coital frequency based on a Poisson model fit to study participant data; use condoms based on a binomial model also fit to study participant data; choose a sexual role (insertive, receptive) for each act of anal intercourse based on individual preferences; and disclose STI or HIV status.

The network dynamics will be modelled using Exponential-family random graph models (ERGMs) and their dynamic extension temporal ERGMs (TERGMs) which provide a foundation for statistically principled simulation of local and global network structure given a set of target statistics from empirical data. The network models will be estimated using the *statnet* suite of R packages that Dr. Goodreau has co-developed; [77] A range of partnership types is common in some parts of Eastern Africa, and likely maintains the persistence of transmission at observed levels. A unique network model (ERGM or TERGM) will be estimated for each relationship type and then used to simultaneously simulate the different types of relationships dynamically on a common set of nodes (individuals). The epidemic model will be coded in R and use the EpiModel platform for simulating epidemics. [78] We will develop unique modules for vital dynamics, transmission, testing, disclosure, treatment, coital acts and condom use based off of code from the Jenness model, [76] but highly revised to deal with the specifics of the study population and our research data.

Data Sources, Parameters, and Validation. Population-specific birth and death rates, including general mortality and survival trajectories, will be used to parameterize vital dynamics. Data on population structure will be drawn from the 2022 Kenya Demographic and Health Survey[79] or more recent surveys when available. Existing rates of standard care syndromic treatment, NG and CT prevalence and morbidity will be estimated from the latest available literature for Kenya at the time of model-building. Parameters for sexual network modules will be derived from Aim 2 sexual network data for MSM and other recent data from Kenya (i.e., the most recent Kenya Demographic Survey and Kenya AIDS Indicators Surveys). The efficacy of the WHO-recommended PPT and doxyPEP interventions and their impact on NG and CT diagnosis and treatment for index cases and their partners will be estimated from study data; our model will then layer these onto the baseline model to estimate potential population-level impact. Sensitivity analyses will be conducted, especially around key parameters of the individual-level intervention efficacy. Comparison will also be made to NAAT-guided treatment as done in well-resourced settings. Model outcomes will include life-years lived with untreated NG or CT, incident NG and CT cases averted, and DALYs averted. We will validate the model using available Kenyan surveillance data. [80]

Modeling and CEA Outcomes. The model will be used to project the potential impact of each STI control strategy on NG and CT incidence, HIV incidence, and morbidity. Four scenarios will be modelled:

1. Baseline model (current guidelines and practice): standard syndromic treatment for all symptomatic individuals
2. STI PPT intervention: STI PPT delivered in clinic every 3 months to eligible MSM, overlaid on standard syndromic treatment
3. DoxyPEP intervention: self-administration of doxycycline within 24-72 hours after condomless anal or vaginal sex, overlaid on standard syndromic treatment and with adherence estimates from trial data
4. NAAT-guided treatment: NAAT screening for eligible MSM every 3 months with treatment of laboratory-diagnosed infections, overlaid on standard syndromic treatment

Cost-effectiveness analysis. We will combine effectiveness estimates from the updated stochastic model with the cost estimates from each intervention to calculate cost per NG or CT case identified and treated, and the incremental cost-effectiveness ratio (ICER) measured as cost per incident NG or CT case averted and cost per DALY averted. Disability weights for calculation of DALYs will be obtained from the latest global burden of disease study. [81] We will calculate the ICER associated with STI PPT and with doxyPEP as the ratio of difference in costs divided by difference in DALYs compared to the next most costly strategy over a 10-year horizon. Following updated guidelines recommending use of a supply-side threshold to reflect the opportunity cost of additional health investment, STI PPT and/or doxyPEP will be considered cost-effective if the ICER is ≤USD 500 per DALY averted. [82] We will utilize both the governmental and societal perspectives. Univariate and probabilistic sensitivity analyses will be performed to determine model robustness and the impact of varying different parameters through their plausible ranges on the estimate of cost-effectiveness.

12. Ethical Considerations

Ethical approval will be sought from KEMRI Scientific and Ethics Review Unit (SERU). The study involves human subjects and the principles below will be observed.

a. Risks to Human Subjects

The potential risks of study participation can be divided into risks specifically related to the study and, for those participants who are randomized to the STI PPT or doxyPEP arms, the risks inherent in taking prophylactic antibiotics.

<u>Risks and Inconveniences Related to Trial Participation</u>

- There is a small risk of loss of privacy or confidentiality for participants related to study visits, in-depth or exit interviews, or contacts by staff, peers, or field workers. This study will include questionnaires and counselling on sensitive topics including sexual risk behavior.
- Participants may also experience psychological discomfort during discussion and disclosure about stigma, mental health symptoms, and substance use.
- Participants may experience stigma or discrimination if stigmatized sexual risk behavior (e.g., male-male sex) is revealed.

- Participants may feel some discomfort when blood is drawn or when throat or rectal swabs are collected. After a blood draw, participants may have a small bruise or swelling where the blood was drawn.

Potential inconveniences include:

- Intensive monitoring during the 18 months of study follow-up, and
- Collection of hair, urine, throat swabs, rectal swabs, and blood specimens according to the study protocol.

Risks and Inconveniences Inherent to Use of STI PPT or DoxyPEP

Medical risks associated with STI PPT include those associated with the two medications that will be used in the STI PPT regimen, namely cefixime and azithromycin. Medical risks associated with doxyPEP include those associated with doxycycline. Potential adverse reactions to each of the three medications are summarized below:

- *Doxycycline:* gastrointestinal symptoms, photosensitivity, yeast infections, increased lactate dehydrogenase (LDH), increased serum glucose (1%-10%); esophagitis, rash, headache, skin hyperpigmentation (<1%)
- *Cefixime:* gastrointestinal symptoms (2%->10%); allergic reactions, acute renal failure, dizziness, headache, drug fever, hepatitis, hyperbilirubinemia, jaundice, cytopenias, seizures, and pseudomembranous colitis (<2%)
- *Azithromycin:* gastrointestinal symptoms (>10%); pruritus, increased LDH, increased creatine phosphokinase (1%-10%); rash, photosensitivity, chest pain, palpitations, angioedema, bronchospasm, headache, fatigue, agitation, vertigo, hepatitis, pseudomembranous colitis, genital candidiasis (<1%)

Most medication-related adverse effects should be mild to moderate and resolve within weeks at most. Rarely, severe side effects including allergic reactions can occur, and may be life threatening. In addition, there is a risk that STI PPT or doxyPEP will increase resistance to cefixime, azithromycin, and/or doxycycline. Quantifying this risk is an important focus of the proposed work. Of note, medications including injectable ceftriaxone and spectinomycin are available for cases of urethritis, pharyngitis, or proctitis that do not respond to first-line treatment. Other potential risks and inconveniences related to STI PPT administration or doxyPEP use include loss of privacy due to the need for eligibility checking and the inconvenience of medication use. Participants who experience persistent or serious adverse effects of STI PPT or doxyPEP will be advised to stop this intervention and focus on behavioral risk reduction instead.

b. Adequacy of Protection from Risks

Every effort will be made to minimize the risks associated with study participation. Experienced research staff will counsel participants prior to enrolment, so that they are aware of the risks described above. We will have strict guidelines and procedures in order to minimize the potential for emotional distress due to questions asked in the ACASI, to physical exams, to in-depth interviews for the subset of intervention participants selected, or to exit interviews for individuals who withdraw. Participants will be told during the informed consent procedures that some of the questions asked may cause discomfort or distress. Participants will be assured of their right to refuse to answer any questions they do not wish to answer. Participants will be assured of their

right to end an interview prior to completion. To minimize the risk of discomfort, assessments and all interviews will be conducted in private areas. If during the course of an ACASI or an in-depth or exit interview, the participant demonstrates or articulates signs of distress, the research staff will be trained to immediately stop the activity taking place. Referral to mental health and other support services will be available onsite or through referrals to local community providers. Research staff members will receive initial and ongoing training in ethics and confidentiality, study protocols, emergency procedures, mandated reporting procedures, general interviewing skills and data management.

The risk for loss of privacy will be minimized by strict confidentiality procedures. Identifying information collected for tracing purposes will be kept in an encrypted contact information file on a password-protected laptop computer with an encrypted hard drive. A master electronic file including the linkage of names to numbers (used to identify participants who return without a numbered study card) will be encrypted and retained on a single computer at each research site in a secure location. This master file will be checked each day for duplicates. Consents will be stored in a separate area in a locked file cabinet. All personal identifying information will be destroyed immediately after the study is completed. In addition, privacy will be protected by ensuring that CAPI administration and physical examinations take place in private rooms. Recordings from participant interviews will be transcribed and stored on a password-protected personal computer. Interviews conducted in Swahili or Dholuo will be simultaneously translated into English and transcribed, with back-translation and verification by a different person to ensure accuracy.

Participants will not be identified by name in the interview transcripts, rather by study ID. We will also protect privacy by developing individualized procedures for study-related contacts in collaboration with each participant. Research staff and peer outreach workers at our three research clinics already have 2-10 years of experience maintaining confidentiality and privacy with MSM research participants, and are either from the LGBTQ+ community or face social challenges due to secondary stigma. Community partners and all newly hired staff and peers will undergo rigorous training on the protection of confidentiality and particular need for discretion in working with this population, whether in the clinic or community.

All study procedures will be conducted according to detailed standard operating procedures that emphasize participant protections and the voluntary nature of participation. In addition, experienced research staff will oversee all ACASI assessments, conduct interviews, and perform physical examinations and blood collection. Appropriate clinical monitoring will minimize the risk of severe adverse events related to STI PPT or doxyPEP during clinic follow-up. Participants will be assured that their non-research care will not be affected by their participation status in this study, nor by their responses in questionnaires. Participants will be informed that they have the right to withdraw or refuse an examination or sample collection at any point. All study staff involved in research procedures will be required to undergo training in Human Subjects protection certification and in Good Clinical Practice (GCP), and all laboratory staff will be required to undergo periodic training in Good Clinical Laboratory Practice (GCLP).

Of note, the County Commissioner, Officer Commanding Police Division, the County Health Director and the County Medical Officer of Health in each location are aware of our MSM research activities, and they support non-discrimination based on sexual orientation. While homosexuality

is illegal in Kenya, there are strong passages in the constitution protecting human rights, and judicial, police and health authorities have chosen to emphasize human rights as protecting LGBTQ+ individuals. This does not mean, however, that there are no risks to disclosure of same-sex sexual behaviour, and this study will do everything possible to maintain confidentiality and anonymity of study participants. At each site, we have established a community advisory board (CAB) to advise us on risks to participants related to study procedures and to assist in monitoring social and psychological harm resulting from study participation. These CABs are each currently composed of MSM community representatives and local stakeholders at each site, such as lawyers with experience in defending LGBTQ+ individuals in the courts, religious leaders, and the local County AIDS and STD Control Officer (CASCO) or other Ministry of Health representatives.

c. Potential Benefits to the Subjects and Others

All participating individuals will receive risk reduction counselling, condoms and lubricants, and screening and treatment for syndromic STI, regardless of their study arm. Standard HIV care or prevention will be provided per ongoing procedures at the research clinic, which are updated as Kenyan MoH guidelines change. All care provided at the study clinics is free of charge. Of note, HIV care and prevention services are available in a non-research (program) context in these clinics and at several sites in Nairobi, Kisumu and Mombasa, should individuals not want to participate in this research study.

In summary, potential benefits to the subjects include:

1. All trial participants may benefit in terms of access to risk reduction counselling and screening for syndromic STI, with syndromic management and partner notification services available onsite.
2. For intervention arm participants who receive STI PPT or doxyPEP during follow-up, there is the potential to reduce STI acquisition.
3. All participants will contribute to a study that will evaluate ways of improving STI control among Kenyan MSM.

Potential benefits to others include:

1. From the perspective of the population from which participants be recruited, this study offers the potential for MSM to benefit from the testing and evaluation of two STI control interventions which have the potential to improve STI control over the standard of care, syndromic treatment.
2. This study has the potential to reduce STI transmission in the study population and their sexual networks, which could in turn reduce HIV transmission in a key population that is estimated to account for 15% of new HIV infections in Kenya.

Given the low likelihood of significant risks to participants, the risks seem reasonable in relation to anticipated benefits.

d. Informed consent

Written informed consent will be obtained by trained study staff fluent in Dholuo, English and Kiswahili in a private counselling room at a participating research clinic. Staff will provide information on the study, screen individuals for eligibility after asking oral permission, and offer participation to individuals who are eligible. The informed consent document will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation.

During the consent process, staff will explain the study procedures, with an emphasis on features that differ from routine programmatic services, highlighting the risks and benefits of study participation.

Participants will be able to discuss their research participation with study staff at any time, and to ask any questions they may have. If participants change their minds about continuing and wish to withdraw, they may do so at any time. Our informed consent documents stress that all participation is voluntary, and they provide contacts should participants have any questions about the study or their rights.

Consent documents will be available in Dholuo, English and Kiswahili. Written informed consent will be obtained from all participants; persons incapable of consenting are excluded. Potential participants who would like to take additional time to consider their enrolment will be encouraged to do so. Staff will emphasize that participation is voluntary, and that participants can refuse to answer any question or undergo any procedure or can discontinue participation at any time without penalty.

If an individual is illiterate, all procedures, risks and benefits will be explained and the individual will be given the option of having a friend or family member or a trained consultant who is not a member of the research staff to be present to further explain the study. In these cases, the friend, family member, or trained consultant will be asked to sign the informed consent document as a witness.

Research staff will be trained in assessing subjects' understanding of the information presented, by asking the participant to describe the purpose of the research and his understanding of procedures, and by using additional probes if needed to ensure adequate comprehension. If it is determined that a participant is unable to understand and therefore not able to provide informed consent, that individual will be excluded from the research.

Participants will be informed of the procedures for ensuring confidentiality, including use of unique non-personally identifying ID numbers instead of names on research materials, and the maintenance of data in encrypted computer databases and locked filing cabinets in locked rooms. Enrolled participants will be provided with a signed and dated copy of the informed consent document before they leave the study site.

Withdrawal of participants. Participants will be assured that their non-research care will not be affected by their participation status in this study, nor by their responses in questionnaires. Participants will be informed that they have the right to withdraw or refuse an examination or sample collection at any point. At the time of withdrawal for any reason (e.g., a move from the study area), a semi-structured exit interview will be conducted regarding experiences, including any social harms of study participation. Consent will be obtained for these interviews, and permission will be asked for digital recording. The only other circumstances in which we would withdraw a participant from the study without their consent would be due to demonstrated inability or unwillingness to participate in study visits; this decision will be made by the entire team after documentation of multiple events of failure to participate.

e. Confidentiality of information obtained

Study team members will have access to participant names and contact information, which is needed for scheduling and sending reminders about clinic visits and exit interviews and for

contacting patients in the event of a test result needing action. These participant identifiers will not be recorded in the study database but will be included in a link log at each site. The link log will be used to record participant names, contact information, and study ID numbers, and will be maintained until participant enrolment and follow-up are complete, for the purposes of avoiding duplicate enrolments and assisting with retention. During the trial, contact information will be retained in order to reach out to any participants who have abnormal laboratory results or miss study visits. We may also use this information to follow up with any participant who experiences an adverse event or social harm, in order to provide support and ascertain the status of the event or harm after interventions by the study team or outside providers. This link log will be accessed for visit tracking, scheduling, and tracking purposes, and will be destroyed after participant enrolment and follow-up are completed. If participants consent to this, we may also use this information to contact participants about future studies that build on this work.

Fingerprint scanning technology, which we have used successfully in the past, will also be used to avoid duplicate enrolment if resources permit. This technology would link the participant's unique fingerprint pattern to the participant's study ID number; no participant name or contact information would be recorded in the fingerprint scanning database. In accordance with the Kenya Data Protection Act, all fingerprint scanning data will be stored locally in Kenya only. Fingerprint scanning data will be destroyed after the study is completed, along with other personal identifying data.

Data will be obtained directly from the subjects (ACASI, intervention feedback, exit interview) or subjects' specimens (blood, urine, swabs, hair), from clinic records (attendance, services rendered, intervention delivery), and from observations made for cost analysis (clinic flow, staff time spent on various activities, costs of equipment and supplies). All participant data, including exit interview transcripts, will be stored for future use in de-identified form. Participant ID numbers will be used, and no direct identifiers will be stored in relation to these data. Biologic specimens will be stored for testing for the purposes detailed above in the procedures section. All de-identified data produced in the course of the project will be preserved. The final dataset will include self-reported demographic and behavioral data from ACASI surveys, clinical data from participant symptoms and focused physical exams, and laboratory data from blood and genitourinary specimens provided.

To summarize our procedures related to confidentiality:

- **De-identified data:** All documents bearing participant names (e.g., consent documents) will be stored apart from documents bearing screening or participant ID numbers. In lieu of names, the study ID will be used on the screening questionnaires and interview transcripts.
- **Locked Cabinets:** All files will be stored in locked cabinets in the research data office at each clinical site, with access limited to study staff. These office are accessible only to the site PI and data management staff, who have keys for access. Non staff members who may need to perform tasks in the data office, such as carpentry or repairs, are allowed into the room only when the site PI or Data Manager is present, and care will be taken to ensure that participant records are not in view.
- **Access to the Link Log file**, which will contain names, contact information, and participant IDs, will be limited to authorized study staff members through the use of password protections.

No participant identifiers other than the participant ID will be recorded on any data collection form or interview transcript.

f. Data sharing

We will share de-identified individual-participant level data, in accordance with an open data approach, taking appropriate measures such as expert determination to identify for removal any specific variables that could potentially lead to identification of individuals. Plans for data de-identification and sharing are reflected in the informed consent forms. To facilitate interpretation of the data, a data dictionary describing all variables in the dataset, the study protocol, and all data collection instruments will be created, shared, and associated with the relevant datasets. Documentation and support materials will be compatible with the clinicaltrials.gov Protocol Registration Data Elements.

De-identified datasets will be made available at the trial's completion, and datasets used for statistical analysis will be made available in the UW Research Works Archive as manuscripts are published. Dr. Graham, as the principal investigator, will oversee and manage data sharing, assisted by the lead investigator at each site (Dr. Otieno in Kisumu, Dr. Kimani in Nairobi, and Dr. Sanders in Mombasa).

We will ask permission in our consent for possible future use of the data in related studies. Possible future uses of study data will be related to secondary analyses to investigate factors influencing the physical, mental, and sexual health of gay, bisexual and other men who have sex with men in Kenya.

g. Data safety and monitoring plan

Overall framework for safety monitoring and what will be monitored: The MPIs will take overall responsibility for making sure that the trial is conducted according to the approved protocol. Specifically, Dr. Sanders will be responsible for all elements of the field work conducted in Kenya, and Dr. Graham will be responsible for all elements of the work conducted in Seattle. Both MPIs will be supported by the two site PIs, Dr. Otieno and Dr. Kimani. Adverse events (AEs), including severe adverse events (SAEs), will be reported to SERU, the UW Human Subjects Division (HSD), and a Data Safety and Monitoring Board (DSMB; see below for details). Specific parameters that will be monitored will include:

- Signs and symptoms of systemic effects that could be related to exposure to the sexually transmitted infection (STI) periodic presumptive treatment (PPT) regimen (i.e., oral cefixime and azithromycin) or to doxycycline post-exposure prophylaxis (doxyPEP)
- Adverse events related to study procedures, including social harms

Because cefixime, azithromycin, and doxycycline are already approved treatments for gonorrhea and chlamydia, and STI prophylaxis is currently recommended by the WHO for MSM, we believe that an investigational new drug (IND) application is not needed for this study. Nonetheless, if funded, we will bring this question to NIAID program staff and the Kenya Poisons Board, and would prepare an investigator-initiated IND application if needed. Of note, there is an ongoing trial of doxyPEP for adolescent girls and young women in Kenya (NCT04050540) led by a UW-affiliated MPI (Dr. Jared Baeten); Dr. Celum is a collaborator on this trial and is available to help guide regulatory applications as needed.

Frequency of monitoring: Interim analyses will be presented to a DSMB when enrolment reaches 50%, and quarterly thereafter until follow-up is completed. The purpose of these reviews will be to assess recruitment, retention, and safety. Laboratory testing for study endpoints will not be completed until after participant follow-up has ended.

Process for reporting adverse events: Adverse events will be reported on a case report form (CRF) developed for this purpose. This will include an assessment of the severity of the event (which influences the timeline for reporting). The following guidelines will be used to quantify severity:

- Mild: events require minimal or no treatment and do not interfere with the patient's daily activities.
- Moderate: events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe: events interrupt a patient's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.
- Life threatening: any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

We will also document changes in the severity of adverse events, to allow assessment of the duration of the event at each level of intensity. Adverse events characterized as intermittent will require documentation of onset and duration of each episode.

Serious Adverse Events will be defined as AEs that meet one or more of the following conditions:

- Death during the period of protocol-defined surveillance
- Life-threatening event (defined as a subject at immediate risk of death at the time of the event)
- An event requiring inpatient hospitalization or prolongation of existing hospitalization during the period of protocol-defined surveillance
- Results in a persistent or significant disability/incapacity
- Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All SAEs will be recorded on the appropriate AE CRF, followed through resolution by a study clinician, and reviewed and evaluated by the MPI team and the Site PI responsible for the participant. The specific procedures for reporting of AEs depend on their severity, as detailed above. The MPI team will be responsible for reporting all AEs that are observed or reported during the study. Information to be collected includes event description, time of onset, investigator assessment of severity, relationship to study product, and time of resolution/stabilization of the event. All adverse events occurring while in study will be documented appropriately regardless of relationship.

Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an AE. However, if the condition deteriorates at any time during

the study, it will be recorded as an AE. Study staff will document AEs and SAEs from the Enrollment Visit through the End of Study Evaluation at month 18. We will follow NIAID guidelines for reporting of adverse events; SAEs will be reported to the SERU and the UW HSD within 72 hours. Non-severe AEs will be reported in regular scheduled reports to SERU and the UW HSD. In addition, the summary of all AEs (including SAEs) will be presented to the DSMB in an interim report.

h. Data safety and monitoring board

Safety oversight will be under the direction of a DSMB composed of several independent experts in infectious diseases and STI control. This will include at least one Kenyan medical professional and at least one independent statistician from the UW. The DSMB will review the protocol and a detailed monitoring plan including dummy tables for enrolment and retention data and adverse events prior to study initiation. Interim analyses will be presented to the DSMB at the frequency described above to assess recruitment, retention, and safety. In addition, the MPI team will request a safety review by the DSMB if there is more than one unexpected SAE that is attributable to the study product or procedures. No interim analysis of outcomes is planned, as lab testing for the primary and exploratory endpoints will be completed after participant involvement has been completed. Dr. Graham is currently serving on a DSMB for an NIH-funded trial of an HIV treatment support intervention (NCT05046392, PI Ramsey) and therefore has experience with trial monitoring by a DSMB.

i. Handling adverse events

Each research site has clinical staff on hand to assist in the event of bruising or bleeding after phlebotomy and counselling staff available to support participants with addressing social harms or discomfort with questions. Most mild or moderate adverse events, such as rash or nausea, can be managed by the clinical officers at each site, with oversight by licensed physicians as needed. Participants with severe or life-threatening adverse events such as anaphylaxis will be stabilized at the study site and emergently transferred to a local medical facility for treatment. Of note, we expect severe or life-threatening reactions to the commonly used antibiotics that will be provided in our two interventions to be very rare. Each participating clinic also has counselling staff and support for persons with depressive symptoms, stigma, or substance abuse problems. We will conduct no medical diagnostic or genetic testing in this study other than the STI testing described in the protocol.

Adverse Events Facilities: Our research clinics will have all the facilities and equipment necessary to handle mild or moderate adverse events. Participants with severe or life-threatening adverse events such as anaphylaxis will be stabilized at the study site and emergently transferred to a local medical facility for treatment. While exclusion of patients with prior allergic reactions will help safeguard against such events, we will ensure that each clinic team has up-to-date first aid training and supplies in the event of such an emergency.

Financial Responsibilities: The study team will provide treatment for physical injuries that are mild or moderate on site, free of charge. We are obtaining quotes for trial insurance and will have this in place prior to enrolment. The NRHS team has had a good experience working with Takaful Insurance Company, and we are comparing a quote from Takaful with quotes from other similar companies.

13. Expected application of the results

The findings of this study will be relevant to participants, community organizations serving cisgender MSM, policy makers, and agencies considering at-risk populations for efficacy trial evaluation of new products. The findings will be published in relevant peer reviewed journals and presented at national and international conferences, such as the STI/HIV collaborative meeting in Nairobi, and the biannual International Society for Sexually Transmitted Diseases Conference.

14. Time Frame/Duration of the Project

	2024		2025		2026		2027		2028	
ACTIVITY	**Q 1-2**	**Q 3-4**	**Q 1-2**	**Q 3-4**	**Q 1-2**	**Q 3-4**	**Q 1-2**	**Q 3-4**	**Q 1-2**	**Q 3-4**
1) Protocol development, review and approval	x									
2) Training of study staff		x								
3) Engagement of stakeholders		x								
4) Enrolment and quarterly visits		x	x	x	x	x	x			
5) NAAT CT/NG analysis						x	x			
6) Data analysis (interim report)						x	x			
7) Modelling and cost-effectiveness analysis						x	x	x		
8) Results write up and dissemination									x	x

15. Budget

Budget (Year 1)	**US$**	**Ksh**
Personnel	779,007	124,641,120
Ethical/scientific review and translations	8,000	1,280,000
Office supplies	21,600	3,456,000
Clinical supplies	12,711	2,033,760
Medications for interventions	56,948	9,111,680
Laboratory supplies	19,148	3,063,680
Participant reimbursement	25,000	4,000,000
Shipping within Kenya	4,000	640,000
Overhead 8%	74,113	11,858,080
Total Year 1	1,000,527	160,084,320
Total Over 5 Years	5,000,000	800,000,000

Exchange rate: $1.00 = 160 KSh

16. Budget Justification

Cost categories are provided for Year 1 (total US$ 1,000,527), which is currently awarded. The total budget for the 5 study years is US$ 5 million, with funding for years after Year 1 to be awarded contingent upon study progress.

Personnel. This line item includes salaries and fringe benefits for the site PIs and staff at the 3 study sites (Kisumu, Nairobi, and Mombasa), for Dr. Sanders at the Aurum Institute, and for Dr. Graham and co-investigators, consultants and grant administrators at the University of Washington.

Ethical/scientific review and translations. This line item includes payment of KEMRI ERC fees for non-KEMRI investigators, payment of NACOSTI registration, and payment for review by the Kenya Pharmacy and Poisons Board. Translation will be done for informed consent documents (submitted in English, Kiswahili, and Dholuo) and for case report forms after approval.

Office supplies. This line item covers the cost of office supplies at the 3 sites, including stationary, telephone and internet support, printing and photocopying.

Clinical supplies. This line item includes medical supplies such as exam gloves and lights, sterile urine collection cups, alcohol swabs, vacutainers, needles, and biohazard bags.

Medication for interventions. This line item includes purchase and storage costs for the three study drugs: doxycycline, cefixime, azithromycin.

Laboratory supplies. This line item includes supplies for syphilis testing, collection kits for CT and NG testing, and supplies for Gram stain, culture, and sensitivity of urethral discharge. CT/NG NAAT testing will be done from year 4 onward in bulk in Mombasa.

Participant reimbursements. Enrolment of the 2900 participants will start in second half of year 1, and will continue through year 3. Participants will make 7 visits in total and be reimbursed at 1000 KSh per visit.

Shipping within Kenya. Medications and laboratory supplies will be shipped to all three sites after purchase centrally. Samples will be shipped from Kisumu and Nairobi to the University of Washington/University of Nairobi laboratory in Mombasa in batches.

Overhead on grants from the United States NIH is allowed at 8% of direct costs.

17. Role of Investigators

Name	Roles	Responsibilities
Susan M. Graham	PI	Protocol development, questionnaire design, data analysis, study oversight
Eduard J. Sanders	Co-PI	Protocol development, questionnaire design, data analysis, study oversight
Joshua Kimani	Site PI	Protocol development, questionnaire design, study oversight
Fred Otieno	Site PI	Protocol development, questionnaire design, study oversight
Deven Hamilton	Co-I	Modelling the impact of intervention scale up (Aim 3)
R. Scott McClelland	Co-I	Study oversight Ganjoni, implementation science expertise
Monisha Sharma	Co-I	Cost effectiveness analysis

Olusegun O Soge	Co-I	Testing of gonorrhoea samples for resistance mutations of clinical importance
Robert C. Bailey	Consultant	Technical assistance and administrative support at the Kisumu site as needed
Connie Celum	Consultant	Expertise in doxyPEP and clinical trials, support to the Leadership team as needed
Steven Goodreau	Consultant	Support to Dr. Hamilton and the leadership team on modelling as needed

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19. Appendices

1) Informed Consent Documents
    a) English version 1.0, dated 20 February 2024
    b) Kiswahili version 1.0, dated 20 February 2024
    c) Dholuo version 1.0, dated 20 February 2024
    d) Translation certificates
2) Draft study tools
    a) Screening form
    b) Participant questionnaire
    c) Exit interview topic guide
    d) Staff questionnaire
    e) Staff interview topic guide
3) Investigator curriculum vitae
4) Investigator ethics certificates
5) Investigator practicing licenses
6) Case report form
7) UW ethical approval
8) Insurance quotation