ORIGINAL ARTICLE

Doxycycline Prophylaxis to Prevent Sexually Transmitted Infections in Women

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ABSTRACT

BACKGROUND

Doxycycline postexposure prophylaxis (PEP) has been shown to prevent sexually transmitted infections (STIs) among cisgender men and transgender women, but data from trials involving cisgender women are lacking.

METHODS

We conducted a randomized, open-label trial comparing doxycycline PEP (doxycycline hyclate, 200 mg taken within 72 hours after condomless sex) with standard care among Kenyan women 18 to 30 years of age who were receiving preexposure prophylaxis against human immunodeficiency virus (HIV). The primary end point was any incident infection with *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, or *Treponema pallidum*. Hair samples were collected quarterly for objective assessment of doxycycline use.

RESULTS

A total of 449 participants underwent randomization; 224 were assigned to the doxycycline-PEP group and 225 to the standard-care group. Participants were followed quarterly over 12 months. A total of 109 incident STIs occurred (50 in the doxycycline-PEP group [25.1 per 100 person-years] and 59 in the standard-care group [29.0 per 100 person-years]), with no significant between-group difference in incidence (relative risk, 0.88; 95% confidence interval [CI], 0.60 to 1.29; P=0.51). Among the 109 incident STIs, chlamydia accounted for 85 (78.0%) (35 in the doxycycline-PEP group and 50 in the standard-care group; relative risk, 0.73; 95% CI, 0.47 to 1.13). No serious adverse events were considered by the trial investigators to be related to doxycycline, and there were no incident HIV infections. Among 50 randomly selected participants in the doxycycline-PEP group, doxycycline was detected in 58 of 200 hair samples (29.0%). All *N. gonorrhoeae*–positive isolates were resistant to doxycycline.

CONCLUSIONS

Among cisgender women, the incidence of STIs was not significantly lower with doxycycline PEP than with standard care. According to hair-sample analysis, the use of doxycycline PEP among those assigned to receive it was low. (Funded by the National Institutes of Health; dPEP ClinicalTrials.gov number, NCT04050540.)

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A Quick Take is available at NEJM.org

The global incidence of bacterial sexually transmitted infections (STIs), specifically *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and *Treponema pallidum*, are rising, with 374 million infections estimated to occur annually.[1] Women are disproportionately burdened by STI sequelae, including pelvic inflammatory disease, chronic pain, infertility, ectopic pregnancy, increased risk of human immunodeficiency virus (HIV) acquisition, and pregnancy and fetal complications.[2,3] Strategies for the prevention of STIs traditionally rely on abstinence, condom use, and, in some settings, screening and treatment as well as partner therapy.[4,5] These tools, which in many cases require the cooperation of partners, have not curbed the rise of STIs at the population level.[6]

The prevalence and incidence of bacterial STIs are frequently high among persons receiving HIV preexposure prophylaxis (PrEP) worldwide.[7-10] The World Health Organization recently called for integration of STI prevention and care into PrEP care.[11] Doxycycline postexposure prophylaxis (PEP) effectively reduced the incidence of STIs (chlamydia, gonorrhea, and syphilis) among cisgender men and transgender women in France and the United States.[12-14] We report the results of a trial of doxycycline PEP for the prevention of STIs in cisgender women.

Methods

Trial Population

Between February 5, 2020, and October 30, 2022, we enrolled and followed women 18 to 30 years of age in Kisumu, Kenya, who were not pregnant and were receiving HIV PrEP (tenofovir disoproxil fumarate [300 mg once daily]–emtricitabine [200 mg once daily], as provided in Kenya by the Ministry of Health). The authors vouch for the completeness and accuracy of the reported data and for the fidelity of the trial to the protocol, which is available with the full text of this article at NEJM.org. The trial protocol[15] was approved by the Kenya Medical Research Institute Scientific and Ethics Review Unit and the institutional review board at the University of Washington. All the participants provided written informed consent.

Randomization and Trial Procedures

Participants were assigned in a 1:1 ratio to receive doxycycline PEP along with quarterly STI testing and treatment or standard care, defined as quarterly STI testing and treatment alone. Randomization was performed by means of a computer-based system (www.randomize.net) with the use of blocks of varying sizes. Participants in the doxycycline-PEP group were instructed to take 200 mg of doxycycline hyclate within 72 hours after condomless sexual intercourse, with a maximum dose of 200 mg daily regardless of the number of exposures in the previous day.

At enrollment and quarterly follow-up visits over 12 months, the participants completed questionnaires regarding behavior and symptoms and provided clinician-collected samples (blood for HIV and syphilis testing, endocervical swabs for bacterial STI and tetracycline-class resistance testing, and hair [50 to 100 strands] for objective measurement of doxycycline use). Doxycycline (100 capsules) and a discrete pill carrier were dispensed at enrollment, followed by 100-capsule refills at each quarterly visit; an additional supply was available if needed between visits. HIV PrEP refills were available to all participants at the trial site, and participants could discontinue HIV PrEP and still continue doxycycline PEP. All the participants were offered contraception and condoms at each visit; use of contraception was not required. Participants who became pregnant during the treatment period were retained in the trial and were referred to clinical care; HIV PrEP was continued and doxycycline was discontinued for the duration of pregnancy and breast-feeding.

Participants received weekly short message service (SMS)–based surveys on sexual exposure; those assigned to receive doxycycline PEP also reported doxycycline use. At every quarterly visit, the participants in the doxycycline-PEP group filled out timeline follow-back calendars to report sexual activity, condom use, and use of doxycycline PEP in the previous 2 weeks. Safety was evaluated according to standardized symptom assessment, and serious adverse events in both groups and all doxycycline-related adverse events and discontinuations were recorded.

STI Testing

The primary efficacy end point was any incident infection with *C. trachomatis*, *N. gonorrhoeae*, or *T. pallidum*. Endocervical swabs were evaluated for *C. trachomatis* and *N. gonorrhoeae* by means of nucleic acid amplification testing (NAAT) (Cepheid

or Aptima). After treatment of chlamydia or gonorrhea infections, participants returned for a test-of-cure assessment with a repeat NAAT after 2 to 4 weeks to ensure clearance of infection; retreatment and a repeat test-of-cure were performed in the case of any positive test. Incident infections were preceded by a negative test.

Participants were evaluated for infections quarterly and could contribute data on up to one incident infection per quarter. Plasma samples were tested quarterly for rapid plasma reagin titers with the BD Macro-Vue test. An incident syphilis infection was defined as a newly positive rapid plasma reagin titer, as confirmed by a positive *T. pallidum* hemagglutination assay (Fortress Diagnostics), or as a rapid plasma reagin titer that had increased by at least two dilutions (i.e., quadrupled). Chlamydia was treated with 1 g of oral azithromycin, gonorrhea was treated with 500 mg of ceftriaxone (intramuscular injection) or 400 mg of oral cefixime, and syphilis was treated with 2.4 million units of penicillin G benzathine (intramuscular injection). Expedited partner therapy was offered for all the participants who were receiving treatment for an STI. All incident STIs were reviewed by an end-point adjudication committee, the members of which were unaware of the trial-group assignments.

HAIR TESTING FOR DOXYCYCLINE USE

Hair (50 to 100 strands) was collected by means of well-described methods.[16] The 1-cm segment closest to the root, representing approximately 1 month of exposure, was cut, and doxycycline was extracted from the sample with the use of methanol. The resultant liquid was tested for doxycycline at a concentration of greater than 0.020 ng per milligram by means of liquid chromatography–tandem mass spectrometry. In a randomly selected 10% sample of enrollment visits, the hair samples that had been collected were tested, and in a randomly selected 22% sample of participants in the doxycycline-PEP group, the hair samples that had been collected at all the follow-up visits were tested; in the standard-care group, hair samples were tested in a randomly selected 5% sample of follow-up visits.

MOLECULAR RESISTANCE TESTING

The endocervical swabs that had been obtained from the participants in whom *N. gonorrhoeae* was detected at a follow-up visit were purified, and the bacterial DNA was extracted. The DNA samples were used as templates for the detection of the tetracycline resistance gene *tet*(M) of the American- and Dutch-type plasmids, as performed under previously described polymerase-chain-reaction and cycling conditions and with standard controls.[17] In addition, DNA from endocervical swabs that had tested positive for *C. trachomatis* on NAAT were tested for the *tet*(C) gene cassette.[18]

STATISTICAL ANALYSIS

The trial was designed to have 80% power to detect a 50% decrease with doxycycline PEP in the risk of the combined STI primary end point; a total of 66 *C. trachomatis* infections was estimated to be the minimum required for this analysis. The incidence of an STI was compared between trial groups by estimating the relative risk of at least one STI per quarter at each quarterly visit with the use of a modified Poisson model fitted according to generalized-estimating-equation methods to account for repeated observations within individual participants, with the assumption of an independent covariance structure, with the trial group as the only covariate. The same analysis was repeated for the individual STIs, and an analysis was conducted in which data were censored in the follow-up time after a participant had become pregnant (because doxycycline was withdrawn in the event of pregnancy). A two-sided alpha level of 0.05 was considered to indicate statistical significance, and 95% confidence intervals were computed with the use of robust standard errors. No adjustments were made for multiple testing, and the widths of the confidence intervals were not adjusted for multiplicity and may not be used in place of hypothesis testing. We conducted subgroup analyses defined according to the presence of an STI at baseline, history of transactional sex, use of contraception, parity, and age. Subgroup analyses were not completed for gonorrhea or syphilis individually owing to the small sample size. Time-to-event analyses of the first incident STI and incident *C. trachomatis* infection were conducted with the use of Kaplan–Meier curves and Cox proportional-hazards regression models. Proportional hazards were confirmed by including an interaction term between (log) time and randomization assignment in the Cox model and testing for statistical significance. An independent data and safety monitoring board reviewed the trial for operational futility, safety, and efficacy after one

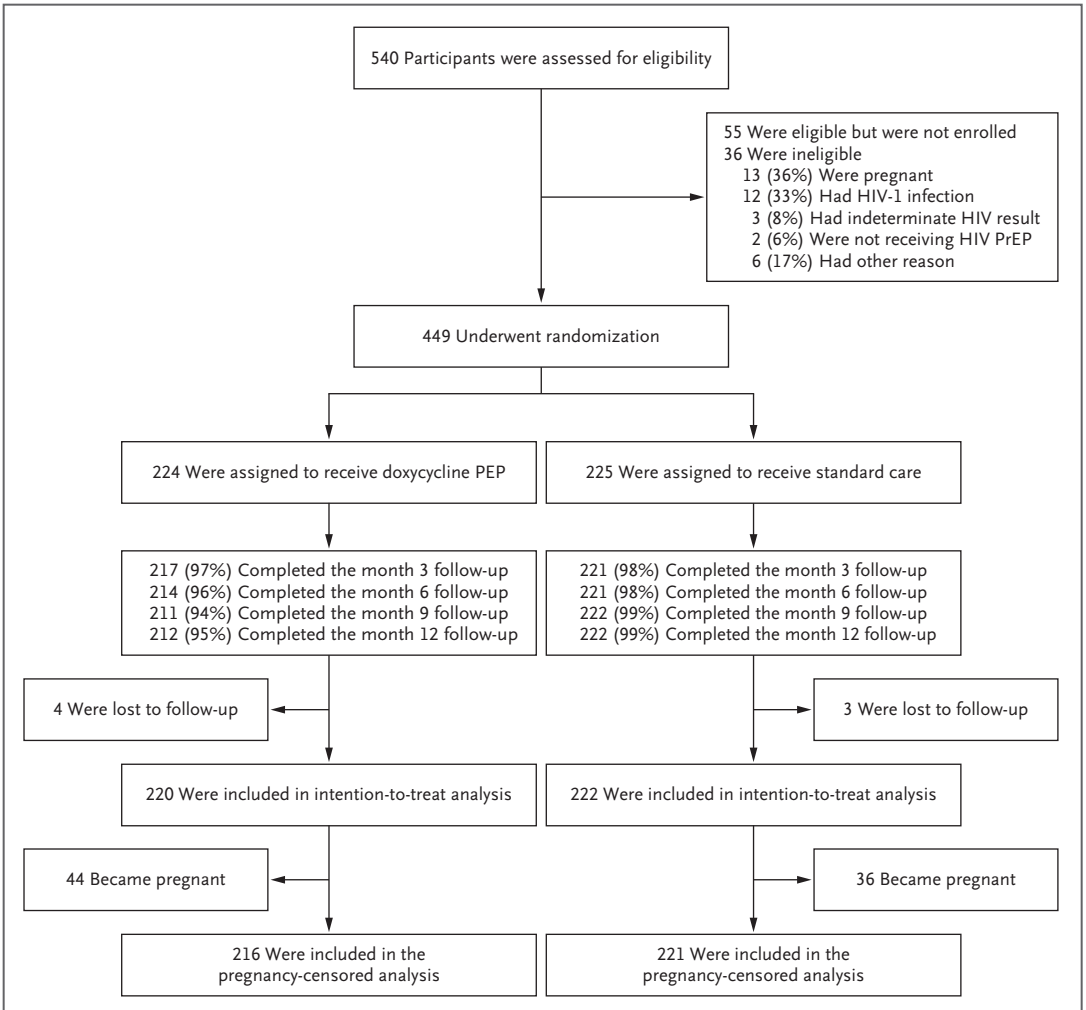

Figure 1. Screening, Randomization, and Follow-up.
HIV denotes human immunodeficiency virus, PEP postexposure prophylaxis, and PrEP preexposure prophylaxis.

third and two thirds of the total expected follow-up time were completed. Statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

TRIAL PARTICIPANTS

Of 540 women who underwent screening, 449 were randomly assigned to a trial group (224 to the doxycycline-PEP group and 225 to the standard-care group) (Fig. 1). The median age of the cohort was 24.3 years (interquartile range, 21.8 to 27.0) (Table 1). At enrollment, 80 participants (17.9%) received a diagnosis of an STI (*C. trachomatis* infection in 63, *N. gonorrhoeae* infection in 17, and *T. pallidum* infection in 2). The baseline characteristics were similar in the two trial groups, except for a higher number of women who had never been married in the doxycycline-PEP group than in the standard-care group (158 vs. 139).

RETENTION, SEXUAL BEHAVIOR, AND ADHERENCE

Enrolled participants completed 96.9% of quarterly follow-up visits; the percentage of participants who completed the final follow-up visit at 12 months was similar in the two trial groups (95.1% in doxycycline-PEP group and 98.7% in the standard-care group). A total of 80 women became pregnant (44 in the doxycycline-PEP group and 36 in the standard-care group). Holds on doxycycline use during pregnancy accounted for

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.*

Characteristic	Doxycycline PEP (N=224)	Standard Care (N=225)
Median age (IQR) — yr	24 (22–27)	24 (22–27)
Highest level of education — no. (%)		
No schooling	1 (0.4)	0
Primary school	48 (21.4)	55 (24.4)
Secondary school	135 (60.3)	128 (56.9)
Postsecondary school	40 (17.9)	42 (18.7)
Earns own income — no. (%)	137 (61.2)	143 (63.6)
Marital status — no. (%)		
Never married	158 (70.5)	139 (61.8)
Married	39 (17.4)	53 (23.6)
Previously married	27 (12.1)	33 (14.7)
Has a primary sex partner — no. (%)	186 (83.0)	184 (81.8)
New sex partner in the previous 3 mo — no. (%)	77 (34.4)	72 (32.0)
Median no. of partners in the previous 3 mo (IQR)	2 (1–5)	2 (1–4)
History of transactional sex in the previous 3 mo — no. (%)	89 (39.7)	76 (33.8)
Condom use at last vaginal sex act — no./total no. (%)†	62/199 (31.2)	67/199 (33.7)
History of anal sex in the previous 3 mo — no. (%)	4 (1.8)	7 (3.1)
Median duration of HIV PrEP (IQR) — mo	7.5 (4.1–14.9)	7.2 (3.7–13.8)
Use of contraception — no. (%)‡	143 (63.8)	135 (60.0)
Parity — no. (%)		
None	72 (32.1)	65 (28.9)
1 live birth	89 (39.7)	83 (36.9)
≥2 live births	63 (28.1)	77 (34.2)
Presence of STI — no. (%)		
Chlamydia trachomatis§	30 (13.4)	33 (14.7)
Neisseria gonorrhoeae§	10 (4.5)	7 (3.1)
Treponema pallidum	0	2 (0.9)
Any STI§	40 (17.9)	40 (17.9)

* Percentages may not total 100 because of rounding. HIV PrEP denotes preexposure prophylaxis against human immunodeficiency virus, IQR denotes interquartile range, PEP postexposure prophylaxis, and STI sexually transmitted infection.
† A total of 51 participants did not have vaginal sex in the 3 months before enrollment.
‡ Contraception includes intrauterine device, implant, depot medroxyprogesterone acetate, and oral contraceptive pills.
§ One participant without an endocervical swab collected at baseline was enrolled.

10.1% of follow-up visits; in the standard-care group, pregnancy accounted for 6.0% of the follow-up visits. Additional holds on doxycycline use accounted for 5.0% of the follow-up visits by the 224 participants in the doxycycline-PEP group, with doxycycline being discontinued by 10 participants (4.5%) because of a change in sexual partnership, by 6 participants (2.7%) because of adverse effects, and by 3 participants (1.3%) because of social harms (i.e., verbal and physical violence).

The median number of doxycycline doses taken per month was four (interquartile range, zero to eight), and the median number of sex acts per month was four (interquartile range, two to eight). The median number of partners during the past quarter was one (interquartile range, zero to two). Having more than one sexual partner

in the past quarter was reported at 794 of 1740 follow-up visits (45.6%): having two sexual partners was reported at 305 visits (17.5%) and having three or more sexual partners was reported at 489 visits (28.1%). The participants in the doxycycline-PEP group reported zero sexual exposures in the past week in 2222 of 7818 weekly SMS-based surveys (28.4%).

A majority (91.1% [468 of 514]) of quarterly timeline follow-back calendars that had been filled out by the participants showed that there was at least 80% coverage with respect to doxycycline use after exposure to condomless sex in the previous 2 weeks. At 176 of 755 visits (23.3%), participants reported not taking doxycycline after the last sexual intercourse. Nearly all of the last doxycycline doses that were reported to have been taken were within 24 hours after sexual intercourse (reported at 575 of 579 visits). The participants in the doxycycline-PEP group completed 7818 of 10,051 weekly SMS-based surveys (77.8%). In more than 90% of the weekly SMS-based surveys, 116 of 211 participants (55.0%) in the doxycycline-PEP group reported taking doxycycline at least as many days as they had sex.

Among the 50 participants in the doxycycline-PEP group who had been randomly selected for evaluation of doxycycline concentrations in hair, doxycycline was detected in at least one visit in 28 (56%). Across all quarterly visits, doxycycline was detected in 58 of 200 visits (29.0%). With the exclusion of visits in which doxycycline was on hold, doxycycline was detected in 58 of 178 visits (32.6%). Among the participants at enrollment with tested hair samples, doxycycline was detected in 3 of 45 samples (6.7%). Among the participants in the standard-care group with tested hair samples, doxycycline was detected in 2 of 39 samples (5.1%).

EFFECT OF DOXYCYCLINE PEP ON INCIDENT STIS

A total of 109 incident STIs were detected — 50 cases (25.1 per 100 person-years) occurred in the doxycycline-PEP group and 59 cases (29.0 per 100 person-years) occurred in the standard-care group (Table 2). The 109 incident STIs included 85 infections with *C. trachomatis*, 31 infections with *N. gonorrhoeae*, and 1 infection with *T. pallidum*, with 8 instances of dual infection with *C. trachomatis* and *N. gonorrhoeae*. A total of 12 participants had more than one incident infection — 9 had multiple *C. trachomatis* infections, 2 had multiple *N. gonorrhoeae* infections, and 1 had both *C. trachomatis* and *N. gonorrhoeae* infections. The overall quarterly incidence of STIs was not significantly lower with doxycycline PEP than with standard care (relative risk, 0.88; 95% confidence interval [CI], 0.60 to 1.29; P=0.51). The time to the first incident STI or time to the first incident *C. trachomatis* infection also did not differ significantly between the trial groups (Fig. 2). In the analysis in which data were censored in the follow-up time after a participant had become pregnant, the incidence of STIs was not substantially lower with doxycycline PEP than with standard care (relative risk, 0.91; 95% CI, 0.62 to 1.35) (Table S1 in the Supplementary Appendix, available at NEJM.org). Subgroup analyses of the incidence of STIs according to age, use of contraception, history of transactional sex, and STI detection at baseline showed results similar to those of the primary and other analyses. Participants accepted expedited partner therapy at approximately two thirds of the visits during which an STI was diagnosed and treatment administered (67 of 100 participants [67.0%] in the doxycycline-PEP group and 64 of 110 participants [58.2%] in the standard-care group).

PREP USE AND HIV INCIDENCE

Participants had received HIV PrEP for a median of 7 months before trial enrollment. No participants had received a diagnosis of HIV during the 12 months of follow-up. Discontinuation of PrEP was reported by 59 participants (13.1%) during the trial. Of the 381 participants who were receiving PrEP at month 12, consistent daily use was reported by 311 (81.6%).

RESISTANCE

Prevalence of the *tet*(M) gene, which confers high-level tetracycline-resistant *N. gonorrhoeae*, was 100% at baseline (in 16 enrollment visits in which DNA samples were tested) and 100% at the follow-up visits in the doxycycline-PEP group (in 20 visits) and standard-care group (in 12 visits). Of 76 *C. trachomatis* samples tested (20 at baseline, 25 during follow-up in the doxycycline-PEP group, and 31 during follow-up in the standard-care group), none had *tet*(C) gene cassette detected.

Table 2. Intention-to-Treat and Subgroup Analyses of Incident STIs.

Analysis and End Point	Doxycycline PEP (N=224)	Standard Care (N=225)	Relative Risk (95% CI)*
	no. of events/no. of trial visits		
Intention to treat			
Any STI (primary end point)	50/854	59/886	0.88 (0.60–1.29)†
Chlamydia	35/854	50/886	0.73 (0.47–1.13)
Gonorrhea	19/854	12/886	1.64 (0.78–3.47)
STI at baseline			
Any STI			
No STI at baseline	34/697	39/730	0.91 (0.57–1.47)
STI at baseline	16/157	20/156	0.79 (0.44–1.45)
Chlamydia			
No STI at baseline	25/697	32/730	0.82 (0.47–1.42)
STI at baseline	10/157	18/156	0.55 (0.27–1.13)
Transactional sex			
Any STI			
No history of transactional sex	32/515	42/586	0.87 (0.54–1.39)
History of transactional sex	18/339	17/300	0.94 (0.50–1.76)
Chlamydia			
No history of transactional sex	22/515	38/586	0.66 (0.38–1.15)
History of transactional sex	13/339	12/300	0.96 (0.47–1.97)
Use of contraception			
Any STI			
No use of contraception	18/291	29/356	0.76 (0.41–1.39)
Use of contraception	32/563	30/530	1.00 (0.62–1.62)
Chlamydia			
No use of contraception	16/291	25/356	0.78 (0.40–1.53)
Use of contraception	19/563	25/630	0.72 (0.40–1.27)
Parity			
Any STI			
Nulliparous	18/262	26/256	0.68 (0.36–1.26)
Multiparous	32/592	33/630	1.03 (0.64–1.67)
Chlamydia			
Nulliparous	16/262	22/256	0.71 (0.35–1.43)
Multiparous	19/592	28/630	0.72 (0.41–1.27)
Age			
Any STI			
≤24 yr	35/517	38/496	0.88 (0.56–1.40)
>24 yr	15/337	21/390	0.83 (0.42–1.63)
Chlamydia			
≤24 yr	29/517	33/496	0.84 (0.50–1.41)
>24 yr	6/337	17/390	0.41 (0.16–1.03)

* The widths of the 95% confidence intervals have not been adjusted for multiplicity and may not be used in place of hypothesis testing.
† P=0.51, as calculated with the generalized-estimating-equation test.

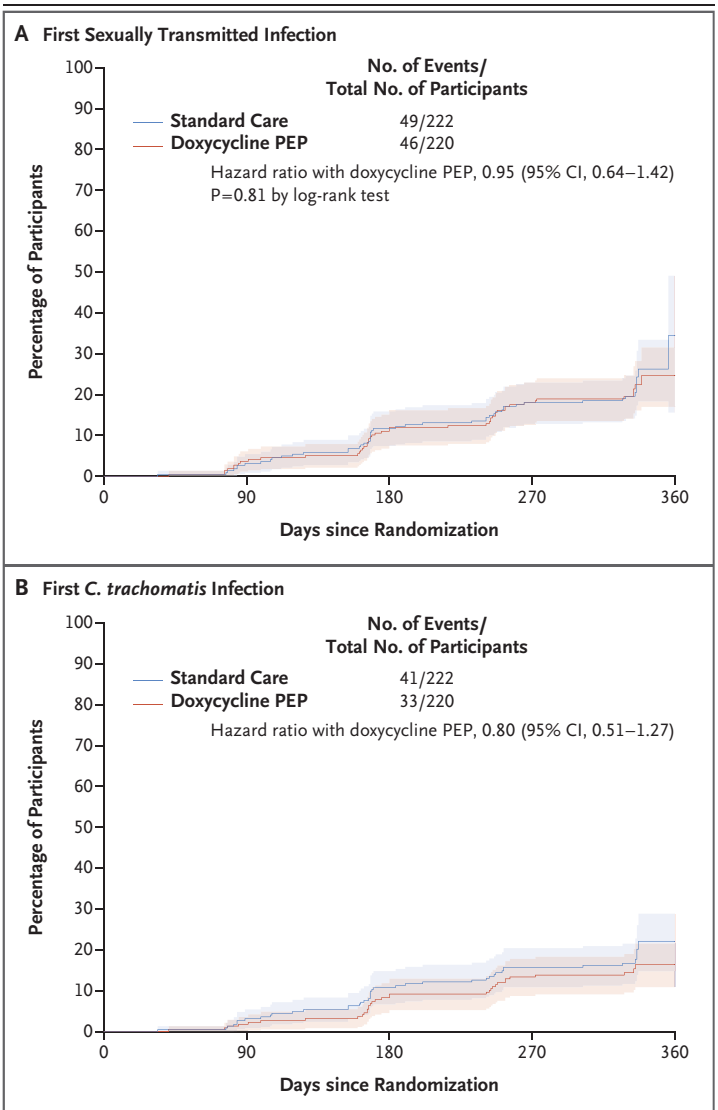

Figure 2. Time to the First Sexually Transmitted Infection and the First *Chlamydia trachomatis* Infection.

Panel A shows the time to the first sexually transmitted infection, and Panel B shows the time to the first *Chlamydia trachomatis* infection. The widths of the confidence intervals (shaded areas) have not been adjusted for multiplicity and may not be used in place of hypothesis testing.

SAFETY

No serious adverse events that were related to doxycycline use, as determined by trial investigators, occurred. Nausea was the most frequent doxycycline-related adverse effect and was reported at 7.2% of the follow-up visits in the doxycycline-PEP group and at 4.6% of the follow-up visits in the standard-care group (Table 3). In addition, social harms were reported four times among three participants in the doxycycline-PEP group because of unintentional disclosure of the use of doxycycline PEP.

DISCUSSION

Among women receiving HIV PrEP in Kenya, the incidence of bacterial STIs was not significantly lower with doxycycline PEP than with standard care. These data on the efficacy of doxycycline PEP as prevention against STIs among cisgender women differ from the results of trials involving cisgender men and transgender women, among whom doxycycline PEP was shown to confer a high level of protection against STIs. Objective assessment of hair samples for doxycycline use suggested that doxycycline was not taken during the majority of months, which is discordant with participant-reported use.

Low detection of doxycycline among participants assigned to receive doxycycline PEP offers a primary explanation for the differing results between this trial and other studies of doxycycline PEP. Adherence is a necessary component of effective medical interventions when under individual control. Pill taking is a challenge for many people, and low adherence to HIV PrEP resulted in null results among women in two previous trials of HIV PrEP.[19,20] The current trial was designed to maximize adherence by enrolling women who were already taking a preventive medication (i.e., PrEP), by having an open-label design without a placebo to ensure that participants knew they had received an active medication with a well-established safety profile, and by offering adherence support with weekly text messages and discrete pill carriers. The assessment of adherence to an event-driven intervention is limited by participant-reported exposures. Participant-reported adherence was moderately high; however, the results of doxycycline testing in hair suggests that 44% of the participants assigned to receive doxycycline PEP may not have taken any doxycycline. No incident HIV infections were diagnosed over 12 months, a finding that suggests effective use of HIV PrEP. Differences between doxycycline PEP and HIV PrEP, including dose and administration, motivation, familiarity, and adverse effects, could contribute to differences in use. Aside from the doxycycline holds during pregnancy, HIV PrEP was reported to have been discontinued more frequently than doxycycline PEP.

Table 3. Reported Adverse Effects.

Event	Doxycycline PEP*				Standard Care†			
	Month 3	Month 6	Month 9	Month 12	Month 3	Month 6	Month 9	Month 12
	number of participants (percent)							
Nausea	27 (12.4)	13 (6.1)	12 (5.7)	10 (4.7)	9 (4.1)	14 (6.3)	11 (5.0)	7 (3.2)
Vomiting	18 (8.3)	8 (3.7)	10 (4.7)	8 (3.8)	10 (4.6)	12 (5.4)	11 (5.0)	4 (1.8)
Diarrhea	9 (4.1)	8 (3.7)	3 (1.4)	1 (0.5)	8 (3.7)	5 (2.3)	6 (2.7)	6 (2.7)
Rash	8 (3.7)	5 (2.3)	6 (2.8)	8 (3.8)	13 (5.9)	13 (5.9)	13 (5.9)	8 (3.6)
Acne	1 (0.5)	0	1 (0.5)	0	0	1 (0.5)	0	1 (0.5)

* Among the participants in the doxycycline-PEP group, surveys were completed at the quarterly follow-up visit by 217 at month 3, by 214 at month 6, by 212 at month 9, and by 213 at month 12.
† Among the participants in the standard-care group, surveys were completed at the quarterly follow-up visit by 219 at month 3, by 221 at month 6, by 222 at month 9, and by 222 at month 12.

Sexual network dynamics, including the number of partners, frequency of sexual exposures, and services for testing and treatment for partners, could contribute to differences between trials. A previous diagnosis of an STI was required for enrollment in other trials of doxycycline PEP; however, women enrolled in the current trial did not have access to STI testing, and their medical history regarding STIs was unknown. Direct data on individual partners were not available.

Differences in primary infection sites are an important consideration for doxycycline prophylaxis; cisgender women more commonly have endocervical infections than rectal or pharyngeal infections. Recent evidence suggests that drug concentrations of doxycycline in the vagina are sufficient to prevent *C. trachomatis*, *N. gonorrhoeae*, and *T. pallidum*; peak concentrations were higher in vaginal mucosa, but time above the minimum inhibitory concentration was higher in rectal tissue.[21] In the current trial, the presence of rectal or pharyngeal STIs was not measured, and thus it cannot be inferred whether doxycycline is protective at those sites in women.

Lack of efficacy for doxycycline to prevent *N. gonorrhoeae* infection is probably due in part to a high prevalence of high-level tetracycline-resistant (*tet*[M]) *N. gonorrhoeae*, an observation that is consistent with findings from previous studies conducted in Kenya.[22] Tetracycline-resistant *C. trachomatis* was not detected in the current trial. This trial was not powered to assess the effect of doxycycline PEP on prevention of syphilis, and the low incidence of *T. pallidum* infection was consistent with the findings from other studies conducted in western Kenya.[23,24] Among the participants who were assigned to receive standard care, doxycycline was detected in 6.6% of the hair samples that were collected at the time of enrollment and during follow-up, a finding that indicates the background frequency of doxycycline use in the population.

Prevention of STIs among cisgender women has the potential to reduce the disproportionate burden of complications from STIs,[3] and prevention interventions are needed. The participants in this trial are representative of a key population affected by STIs (Table S2). The high frequency of pregnancy in the trial cohort indicates the need for integration of comprehensive sexual health with PrEP care.

Our findings emphasize the need for preventive options for STIs that are effective and acceptable among women. Research on doxycycline PEP is needed across a spectrum of populations; the primary focus has been on cisgender men, among whom three trials have been completed and three more are in process[25]; however, no additional trials are in process for cisgender women, who bear the highest global burden of complications from STIs. Further trials investigating doxycycline PEP among persons who had been assigned a female sex at birth are warranted. Adherence to preventive medicines needs to be better understood and supported for biomedical prevention to be effective.

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