Post-exposure prophylaxis with doxycycline to prevent sexually transmitted infections in men who have sex with men: an open-label randomised substudy of the ANRS IPERGAY trial

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Summary

Background Increased rates of sexually transmitted infections (STIs) have been reported among men who have sex with men. We aimed to assess whether post-exposure prophylaxis (PEP) with doxycycline could reduce the incidence of STIs.

Methods All participants attending their scheduled visit in the open-label extension of the ANRS IPERGAY trial in France (men aged 18 years or older having condomless sex with men and using pre-exposure prophylaxis for HIV with tenofovir disoproxil fumarate plus emtricitabine) were eligible for inclusion in this open-label randomised study. Participants were randomly assigned (1:1) at a central site to take a single oral dose of 200 mg doxycycline PEP within 24 h after sex or no prophylaxis. The primary endpoint was the occurrence of a first STI (gonorrhoea, chlamydia, or syphilis) during the 10-month follow-up. The cumulative probability of occurrence of the primary endpoint was estimated in each group with the Kaplan-Meier method and compared with the log-rank test. The primary efficacy analysis was done on the intention-to-treat population, comprising all randomised participants. All participants received risk-reduction counselling and condoms, and were tested regularly for HIV. This trial is registered with ClinicalTrials.gov number, NCT01473472.

Findings Between July 20, 2015, and Jan 21, 2016, we randomly assigned 232 participants (n=116 in the doxycycline PEP group and n=116 in the no-PEP group) who were followed up for a median of 8·7 months (IQR 7·8–9·7). Participants in the PEP group used a median of 680 mg doxycycline per month (IQR 280–1450). 73 participants presented with a new STI during follow-up, 28 in the PEP group (9-month probability 22%, 95% CI 15–32) and 45 in the no-PEP group (42%, 33–53; log-rank test p=0·007). The occurrence of a first STI in participants taking PEP was lower than in those not taking PEP (hazard ratio [HR] 0·53; 95% CI 0·33–0·85; p=0·008). Similar results were observed for the occurrence of a first episode of chlamydia (HR 0·30; 95% CI 0·13–0·70; p=0·006) and of syphilis (0·27; 0·07–0·98; p=0·047); for a first episode of gonorrhoea the results did not differ significantly (HR 0·83; 0·47–1·47; p=0·52). No HIV seroconversion was observed, and 72 (71%) of all 102 STIs were asymptomatic. Rates of serious adverse events were similar in the two study groups. Gastrointestinal adverse events were reported in 62 (53%) participants in the PEP group and 47 (41%) in the no-PEP group (p=0·05).

Interpretation Doxycycline PEP reduced the occurrence of a first episode of bacterial STI in high-risk men who have sex with men.

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Introduction

The global burden of sexually transmitted infections (STIs) worldwide is huge, with more than one million STIs acquired every day.[1] Increased rates of STIs have been reported in several countries, in particular among men who have sex with men (MSM).[2] In the USA, 2015 was the second year in a row with an increased incidence of all three bacterial STIs (gonorrhoea, *Chlamydia trachomatis*, and syphilis), with syphilis increasing at an alarming rate among MSM.[3] High rates of STIs have also been reported in trials of pre-exposure prophylaxis (PrEP) with oral tenofovir disoproxil fumarate plus emtricitabine among high-risk MSM and during PrEP rollout, probably because of low condom use and frequent STI testing.[4–9] Although increased STI rates were reported before PrEP was implemented, STIs represent a growing concern among PrEP users and a major public health challenge.[10] Because of the absence of effective vaccines against bacterial STIs, consistent condom use remains the cornerstone of prevention but biomedical interventions such as antibiotic prophylaxis might need to be revisited. The effectiveness of antibiotic prophylaxis for STIs has been assessed since the 1940s, with limited success so far

Research in context

Evidence before this study

Antibiotic prophylaxis has been used for decades as a biomedical intervention to contain the spread of sexually transmitted infections (STIs) in high-risk individuals. Early studies in the 1940s were done in the navy to assess the benefit of post-exposure prophylaxis (PEP) with sulfonamides or penicillin for gonorrhoea, but this approach was associated with rapid selection of antibiotic resistance. Similar results were observed in the 1980s with minocycline PEP for gonorrhoea, showing limited effectiveness in men exposed to gonococci resistant to minocycline. This strategy was subsequently abandoned. More recently, antibiotic prophylaxis for STIs has been assessed as a way to reduce the risk of HIV acquisition in female sex workers in developing countries by use of monthly periodic presumptive treatment with azithromycin. This strategy was associated with a modest reduction in the incidence of gonorrhoea and chlamydia but not of syphilis or HIV. Following the implementation of pre-exposure prophylaxis (PrEP) with oral tenofovir disoproxil fumarate plus emtricitabine to prevent HIV acquisition in men who have sex with men (MSM), high rates of STIs have been reported in this population. We searched PubMed for articles published until Sept 8, 2017, using the terms "antibiotic", "prophylaxis", "men", and "trial", along with "STIs", "gonorrhoea", "syphilis", or "chlamydia". We reviewed 60 publications and identified two studies, one reported by the US military in 1979 on the use of minocycline PEP to prevent gonorrhoea but with no data for chlamydia or syphilis and another randomised trial of 30 HIV-infected patients involving daily doxycycline prophylaxis or incentive payments, which showed decreased incidence of STIs with antibiotic prophylaxis.

Added value of this study

This study is, to our knowledge, the first large, open-label, randomised trial assessing the efficacy and safety of a novel antibiotic PEP strategy for STIs involving doxycycline (200 mg taken within 24 h after sex) in MSM taking PrEP for HIV prevention. This study showed a high rate of STIs without prophylaxis, the majority of which were asymptomatic, but this antibiotic strategy showed significant benefit, with an overall 47% relative reduction in the incidence of a new STI. Although no clear benefit was shown for gonorrhoea, probably because of the already high rate of doxycycline resistance, a significant relative reduction in the incidence of chlamydia and syphilis was observed. The median use of doxycycline was 680 mg per month, with a good safety profile apart from an increased rate of gastrointestinal adverse events compared with PrEP alone.

Implications of all the available evidence

The results of this doxycycline PEP study for STIs in high-risk MSM taking PrEP show that this strategy can reduce the incidence of chlamydia and syphilis in this population with a good safety profile. Additional studies are needed to assess the full effect of this strategy on the selection of antibiotic resistance for gonorrhoea, syphilis, and chlamydia. Selection of tetracycline resistance remains an important potential risk of doxycycline PEP; we could not assess this risk because of the sample size and the relatively short period of follow-up. Pending additional studies, the use of doxycycline as PEP should be restricted to research purposes. In the future, this strategy might become an effective addition to a combined intervention approach to reduce the high rate of STIs in PrEP users.

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See **Online** for appendix

because of the short-term benefit of antibiotics and the selection and dissemination of antibiotic resistance, in particular for gonorrhoea.[11–16] However, antibiotic resistance to *Chlamydia trachomatis* and *Treponema pallidum* remains rare, with no known resistance to doxycycline.[17,18] PrEP programmes that allow long-term follow-up and monitoring of high-risk individuals provide a unique opportunity to do research on STIs and assess new preventive strategies. Doxycycline has been used successfully for post-exposure prophylaxis (PEP) of Lyme disease and leptospirosis, two spirochaetal diseases, and its role in prevention of STIs has been investigated in a small trial of HIV-infected MSM.[19–21] We therefore aimed to assess, in the open-label phase of the France Recherche Nord & Sud Sida-HIV Hépatites (ANRS) IPERGAY trial, whether PEP with doxycycline could reduce the incidence of bacterial STIs among high-risk MSM.

Methods

Study design and participants

This open-label randomised trial was a substudy of the ANRS IPERGAY trial, which showed the efficacy of on-demand PrEP with tenofovir disoproxil fumarate plus emtricitabine in reducing HIV incidence among high-risk MSM.[6] Following this result, an open-label study extension was implemented from Nov 4, 2014, to June 30, 2016, to provide all participants with tenofovir disoproxil fumarate plus emtricitabine until PrEP approval.[22] In July, 2015, the ANRS IPERGAY protocol was again amended to implement this study of doxycycline PEP for STIs among French sites only. This amendment was approved by public health authorities and ethics committees in France (CPP Paris Saint-Louis). All participants provided written informed consent. Full details of the study design can be found in the study protocol (appendix).

Briefly, HIV-negative men or transgender women having sex with men, aged 18 years or older, and at high risk for HIV acquisition (defined as having condomless anal sex with at least two different partners during the past 6 months) were eligible for inclusion in the ANRS IPERGAY trial. All participants attending their scheduled visit in the open-label extension of the ANRS IPERGAY trial were eligible for inclusion in this study. Exclusion criteria in the doxycycline PEP study included a symptomatic bacterial

STI at the enrolment visit, doxycycline allergy, or another contraindication for doxycycline use (use of systemic retinoids or high-dose vitamin A).

Randomisation

Eligible participants were randomly assigned at the same visit. Randomisation was done centrally by means of a fixed-size block randomisation of four. Participants were assigned in a 1:1 ratio in an open-label design to receive, in addition to PrEP with tenofovir disoproxil fumarate plus emtricitabine, either doxycycline PEP or no prophylaxis.

Procedures

Doxycycline was given as 100 mg pills purchased from Arrow Laboratories (Lyon, France). For each sexual intercourse event deemed at risk (ie, condomless anal or oral sex), participants in the doxycycline PEP group were instructed to take two oral pills of doxycycline within 24 h after sex and no later than 72 h. To reduce the risk of doxycycline-related adverse events and antibiotic selective pressure, participants were also instructed to take no more than six pills of doxycycline per week.

Study visits were scheduled every 2 months after enrolment until June 30, 2016—a predefined date when approval of tenofovir disoproxil fumarate plus emtricitabine for PrEP was anticipated in France. Each scheduled visit in the PEP group included drug dispensation with enough pills to cover a weekly use of doxycycline of up to six pills (each participant received two boxes of 30 pills), a pill count, and adherence counselling. Before each visit, all participants were asked to complete a computer-assisted structured interview at home to collect information about sociodemographic characteristics, recreational drug use, sexual behaviour, and adherence to tenofovir disoproxil fumarate plus emtricitabine. Sexual behaviour assessments included the number of sexual acts in the past 4 weeks, the number of sexual partners in the past 2 months, and the use of condoms for the most recent acts of anal intercourse and receptive anal intercourse.

At every scheduled visit, all participants were offered a comprehensive package of prevention services, including patient-centred interactive risk-reduction and adherence counselling on PrEP (and on doxycycline PEP in those randomly assigned to the PEP group) done by a peer community member, and free condoms and gel.[6]

At the enrolment visit and every 2 months thereafter, participants were tested for syphilis by use of serological assays with both treponemal (*T pallidum* haemagglutination assay or enzyme immunoassays) and non-treponemal (venereal disease research laboratory or rapid plasma reagin) tests, and for chlamydial and gonorrhoeal infections with a specific PCR assay (Abbott Real-Time CT/NG Assay, Rungis, France) done on anal and throat swabs and first-void urine samples. Cultures were also tested for gonorrhoea and chlamydia when possible.

In case of symptomatic gonorrhoea and in case of a positive PCR result before treatment was initiated, culture for *Neisseria gonorrhoeae* was attempted on chocolate agar plates by use of ESwab tubes, which were centralised (Copan Diagnostics Inc, Murrieta, CA, USA). Minimal inhibitory concentrations (MICs) were ascertained with the *E*-test method (Biomerieux, Marcy l'Etoile, France). Tetracycline resistance was defined as a MIC_{tet} greater than 1 mg/L and intermediate resistance as MIC_{tet} greater than 0·5 mg/L and less than or equal to 1 mg/L. Molecular detection of tetracycline resistance was confirmed by a specific PCR test for acquisition of the *tetM* gene (associated with high levels of tetracycline resistance) and the Val57Met mutation in the *rpsJ* gene. Additionally, overexpression of the MtrCDE-encoded efflux pump was assessed by screening for mutations in the promoter of the *mtrR* gene or in the MtrR protein. Similarly, all positive PCR samples for *C trachomatis* obtained from throat and anal swabs during follow-up were centralised to do genotyping and cell cultures to assess tetracycline MICs in vitro. Genotyping was done by sequencing the *opmA* gene to identify the genovar of *C trachomatis*.[23] All tests were done in blinded groups. At each visit, patients were asked about symptoms related to a potential STI, and a physical examination of the skin, throat, and anogenital areas was done.

Syphilis was diagnosed by a positive serological assay with treponemal and non-treponemal tests. In patients with previous syphilis, an increase in non-treponemal titres of four-times or greater with the same assay in the same laboratory was required to confirm the diagnosis. In cases where serology of syphilis was difficult to interpret, sera from previous visits were centralised and retested in the same batch. Primary syphilis, secondary syphilis, and early latent syphilis were diagnosed according to the US Centers for Disease Control and Prevention (CDC) guidelines.[24] Chlamydial and gonorrhoeal infections were defined by a single positive PCR test or culture from at least one site (throat, urine, or anus). In case of a positive PCR result at multiple sites with the same organism at the same time, a single infection was counted. All cases of gonorrhoeal, chlamydial, and syphilis infections were reviewed by a blinded event review committee. STIs were treated according to protocol recommendations, which were similar to CDC guidelines.[24]

Outcomes

The primary study endpoint was the occurrence of a first STI, defined as the first evidence of syphilis, chlamydial, or gonorrhoeal infection after the enrolment visit. STIs diagnosed at the enrolment visit were not included in the assessment of the primary endpoint. Participant follow-up was right-censored at the time of the first STI. The occurrence of the first episode of each STI (gonorrhoea, chlamydia, and syphilis) was also assessed.

A planned secondary analysis was the occurrence of all episodes of STIs during the trial. All participants who were followed up were included in this analysis.

Pill count was the main measure of adherence. Participants were asked to return their study drug boxes at each visit and a pill count of unused medication was done. Stored plasma samples were tested for the presence of doxycycline at each visit by use of a validated liquid chromatography tandem mass spectrometry method with a limit of quantification of 50 ng/mL. This assay is able to detect doxycycline in plasma up to 48 h after intake. Adherence to doxycycline was also assessed through face-to-face interviews at each visit. Participants were asked about their use of doxycycline since their last visit (none, for all at-risk sexual intercourse acts, or for some at-risk sexual intercourse acts), their reasons for not using doxycycline, date of last sexual intercourse, and time (day and hour) of last drug intake.

Safety analyses included all randomised participants. Adverse events were recorded at each visit, regardless of their relation to study drugs. Toxicity was graded according to the ANRS scale of the severity of adverse events in adults.[25]

Statistical analysis

The planned primary analysis was a modified intention-to-treat analysis, including all randomised participants except for those who withdrew consent at day 0 or those who did not receive doxycycline treatment boxes. Since no participant withdrew consent at day 0 and all participants received doxycycline boxes in the PEP group, the primary analysis was done on an intention-to-treat basis.

We used the Kaplan-Meier method to estimate the cumulative probability of a first STI (syphilis, gonorrhoea, or chlamydia) in each group, which was compared by use of log-rank tests. Hazard ratios (HRs) were estimated by use of Cox proportional hazards models. We calculated that a sample size of 276 participants would be required to show a 55% relative reduction in the cumulative probability of a first STI in the doxycycline PEP group at 10 months, assuming a cumulative proportion of participants with STIs of 33% in the no-PEP group, a study discontinuation rate of 15%, study power of 80%, and a two-sided alpha level of 0·05, by use of a bilateral log-rank test (Nquery, version 7.0) . To assess changes in sexual behaviour or practices, we implemented a post-hoc linear regression analysis of each indicator commonly used in time-series analyses. A trend term and a dichotomous variable distinguishing between participants receiving PEP (=1) and those receiving no PEP (=0) were included as explanatory variables. The cross-product of these explanatory variables was also tested to verify whether a trend existed in each separate group or not (see appendix for more details). The study data were reviewed by an independent data and safety monitoring board. Analyses were done with Stata/SE 12.1 software and SAS software (version 9.3, SAS Institute). All p values and confidence intervals are two-sided.

This trial is registered with ClinicalTrials.gov number, NCT01473472.

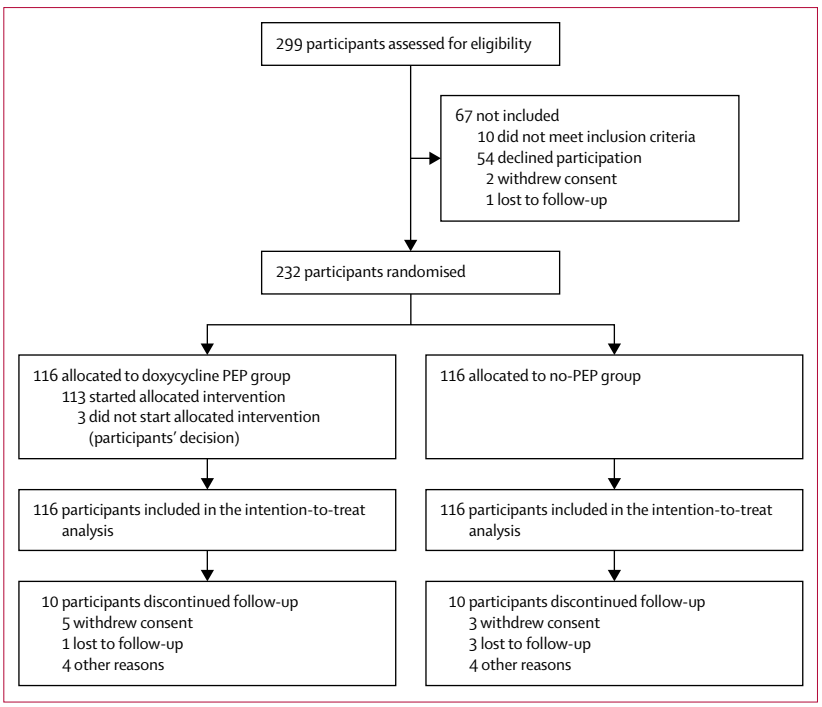

Figure 1: **Trial profile**
The most common reason for not being randomised in this study was participant refusal. Three participants were randomly assigned to the doxycycline post-exposure prophylaxis (PEP) group but did not start treatment. Their data were included in the intention-to-treat analysis.

	Doxycycline PEP	No PEP
2 months	111/116 (96%)	107/114 (94%)
4 months	112/116 (97%)	109/114 (96%)
6 months	106/114 (93%)	105/111 (95%)
8 months	99/101 (98%)	91/97 (94%)
10 months	45/46 (98%)	42/42 (100%)

PEP=post-exposure prophylaxis.

Table 1: **Bi-monthly visit attendance in both groups**

Role of the funding source

The sponsor of the study (ANRS) had no role in data collection, data analysis, data interpretation, or writing of the report, but was involved in the study design. The authors were not paid to write this article and the corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

From July 20, 2015, to Jan 21, 2016, 299 participants were screened. 232 participants were randomly assigned, 116 to the doxycycline PEP group and 116 to the no-PEP

	PEP* (n=116)	No PEP (n=116)
Age		
Median age (years)	38 (33–48)	39 (32–44)
18–24	0 (0%)	5 (4%)
25–29	12 (10%)	11 (10%)
30–39	47 (41%)	41 (35%)
40–49	31 (27%)	44 (38%)
>49	26 (22%)	15 (13%)
Ethnic origin		
White	110 (95%)	110 (95%)
Other	6 (5%)	6 (5%)
Employed	102 (88%)	98 (84%)
Not in a relationship	82 (71%)	81 (70%)
Post-secondary education	109 (94%)	103 (89%)
Use of recreational drugs†	49 (42%)	49 (42%)
Site of enrolment		
Paris, France	64 (55%)	72 (62%)
Lyon, France	25 (22%)	21 (18%)
Nice, France	9 (8%)	13 (11%)
Tourcoing, France	6 (5%)	8 (7%)
Nantes, France	12 (10%)	2 (2%)
Sexual risk factors at screening		
Number of partners in past 2 months	10 (5–15)	10 (5–20)
Number of sexual intercourse acts in past 4 weeks	10 (5–15)	10 (4–20)
Number circumcised (%)	28 (24%)	21 (18%)
STIs diagnosed at screening ‡	22 (19%)	16 (14%)

Data are n (%) and median (IQR). PEP=post-exposure prophylaxis. *PEP with doxycycline. †Recreational drugs in past 12 months included ecstasy, crack, cocaine, crystal meth (methamphetamine), speed (amphetamine), gamma butyrolactone (GHB), and gamma hydroxybutyrate (GBL). ‡Sexually transmitted infection (STI) screening included serological testing for syphilis by means of rapid plasma reagin confirmed with the use of a treponema-specific assay. *Neisseria gonorrhoeae* and *Chlamydia trachomatis* were detected by PCR on urine samples and throat and anal swabs.

Table 2: **Baseline characteristics of the study participants according to study group**

group (figure 1; table 1). Baseline characteristics of study participants are shown in table 2 and were well balanced across the two study groups. 22 participants (19%) in the doxycycline PEP group and 16 (14%) in the no-PEP group were diagnosed with a bacterial STI that was asymptomatic at the time of randomisation. One patient in the no-PEP group was diagnosed with acute asymptomatic hepatitis C virus (HCV) infection at the time of randomisation. Retention was similar in both groups during the study period, with 20 participants (9%) prematurely discontinuing the study (ten in each group), resulting in a total of 163·1 person-years of follow-up, with a median follow-up of 8·7 months (IQR 7·8–9·7).

73 participants presented with a new STI during follow-up, 28 in the PEP group (9-month probability 22%, 95% CI 15–32) and 45 in the no-PEP group (42%, 33–53; log-rank test p=0·007; figure 2A). The occurrence of a first STI in participants taking PEP was lower than in those not taking PEP (HR 0·53, 95% CI 0·33–0·85; p=0·008). The incidence of a first STI (chlamydia, gonorrhoea, or syphilis) during follow-up was 37·7 per 100 person-years in the PEP group and 69·7 per 100 person-years in the no-PEP group.

47 participants presented with a new episode of gonorrhoea during follow-up, 22 in the PEP group (9-month probability 16%, 95% CI 10–24) and 25 in the no PEP group (23%, 16–32; figure 2B). The occurrence of a first episode of gonorrhoea did not differ significantly between the PEP and no-PEP group (HR 0·83, 95% CI 0·47–1·47; p=0·52). The incidence of a first episode of gonorrhoea during follow-up was 28·7 per 100 person-years in the PEP group and 34·5 per 100 person-years in the no-PEP group.

28 participants presented with a new episode of chlamydia during follow-up, seven in the PEP group (9-month probability 6%, 95% CI 3–14) and 21 in the no-PEP group (19%, 13–28; figure 2C). The occurrence of a first episode of chlamydia in participants taking PEP was lower than in those not taking PEP (HR 0·30, 95% CI 0·13–0·70; p=0·006). The incidence of a first episode of chlamydia during follow-up was 8·7 events per 100 person-years in the PEP group and 28·6 events per 100 person-years in the no-PEP group.

13 participants presented with a new episode of syphilis during follow-up, three in the PEP group (9-month probability 3%, 95% CI 1–7) and ten in the no-PEP group (11%, 6–19; figure 2D). The occurrence of a first episode of syphilis in participants taking PEP was lower than in those not taking PEP (HR 0·27, 95% CI 0·07–0·98; p=0·047). The incidence of a first episode of syphilis during follow-up was 3·7 events per 100 person-years in the PEP group and 12·9 events per 100 person-years in the no-PEP group.

The incidence of all STIs during follow-up was 45·9 per 100 person-years in the PEP group (38 participants) and 79·6 per 100 person-years in the no-PEP group (64 participants [HR 0·57, 95% CI 0·13–0·62; p=0·014]; data not shown). The total number of gonorrhoeal infections during follow-up was 57, with 65 sites yielding a positive PCR test, mostly from anal and throat swabs (appendix). When all episodes were considered, the rate of gonorrhoea was 32·6 per 100 person-years of follow-up in the PEP group and 37·3 per 100 person-years of follow-up in the no-PEP group (p=0·63). Symptoms were reported for only 13 (20%) of 65 positive sites.

The total number of chlamydial infections during follow-up was 32, with 36 sites yielding a positive PCR test, mostly from anal swabs (appendix). The overall rate of chlamydial infection was 9·6 per 100 person-years of follow-up in the PEP group and 29·8 per 100 person-years of follow-up in the no-PEP group (p=0·008). Symptoms were reported for only seven (19%) of 36 positive sites.

13 cases of syphilis were validated during follow-up, ten (77%) with symptoms: five cases of primary syphilis

and five cases of secondary syphilis. Three cases of early latent syphilis were reported.

In the PEP group, 20 STIs were diagnosed following discontinuation of doxycycline prophylaxis but a negative PCR test or serological assay following prophylaxis discontinuation and before diagnosis was available in only seven cases (two with chlamydia, four with gonorrhoea, and one with syphilis). Overall, in this study, 72 (71%) of 102 STIs diagnosed after randomisation were asymptomatic. No HIV seroconversion was reported during the study period but two participants acquired HCV infection, one in each group.

Among the 57 gonorrhoeal infections with a positive PCR assay in 47 participants, culture was attempted in 28 (49%) cases. Only nine (32%) of 28 samples yielded a positive culture in eight participants, two in the PEP group and six in the no-PEP group. Tetracycline resistance was detected for four *N gonorrhoeae* isolates and intermediate resistance for three *N gonorrhoeae* isolates, with all fully resistant isolates from participants in the no-PEP group. Molecular detection of tetracycline resistance identified the *tetM* gene in one of those resistant isolates. All resistant strains also carried the Val57Met mutation in the *rpsJ* gene and mutations associated with overexpression of the antibiotic efflux pump MtrCDE.

Chlamydia isolation was attempted from 22 anal and two oral swabs, and a culture was positive in five (21%) samples from four participants, two in each group. All tetracycline MICs were in the normal range (0·12–0·25 mg/L). Ten of the 24 *C trachomatis*-positive specimens were successfully genotyped; five strains belonged to genovars L and five strains belonged to genovars non L. Only two of five patients infected with an L strain were symptomatic.

The median number of pills used per participant in the PEP group was 6·8 per month (IQR 2·8–14·5), representing a median of 680 mg doxycycline used per month (IQR 280–1450). Overall, participants in the PEP group reported doxycycline use in 83·7% of study visits (appendix). Individual patterns of pill use showed large inter-patient and intra-patient variability over time (figure 3). For 232 (83%) of 280 occurrences of sexual intercourse, doxycycline was taken within 24 h following sexual intercourse. Additionally, three participants in the PEP group did not start PEP and 29 (26%) of 113 discontinued PEP during follow-up for various reasons, including drug-related adverse events (all gastrointestinal adverse events) in eight (7%) participants.

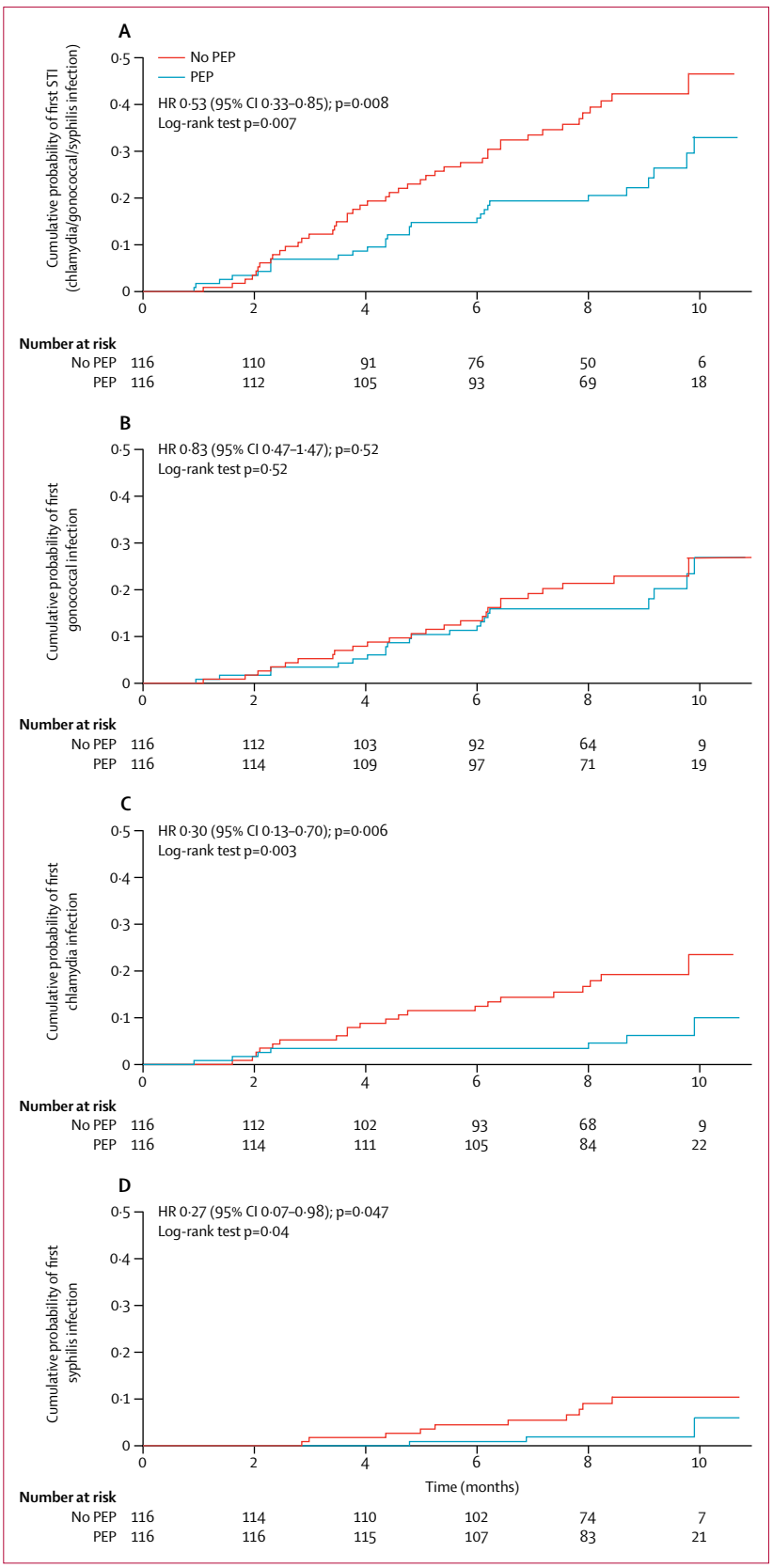

Figure 2: **Kaplan-Meier estimates of time to first STIs in the intention-to-treat analysis, according to study group**
(A) Time to first sexually transmitted infection (STI; chlamydia, gonorrhoea, or syphilis). The cumulative probability of STI acquisition is shown for the two study groups. (B) Time to first gonorrhoeal infection. The cumulative probability of gonorrhoea acquisition is shown for the two study groups. (C) Time to first chlamydial infection. The cumulative probability of chlamydia acquisition is shown for the two study groups. (D) Time to first syphilis infection. The cumulative probability of syphilis acquisition is shown for the two study groups.

Figure 3: **Patterns of doxycycline pill use per participant per month based on visits during the study period in the PEP group**
Five categories of pill use per month were defined at each visit: 0–4 pills per month, 5–11 pills per month, 12–18 pills per month, or 19–30 pills per month. Each horizontal bar represents a single patient and the duration of follow-up varies according to the time of enrolment. Missing values are left blank. PEP=post-exposure prophylaxis.

We also measured doxycycline concentrations in plasma at each visit in all participants (appendix). Overall, 141 (30%) of 465 samples from participants in the PEP group and 39 (9%) of 440 samples from participants in the no-PEP group had detectable doxycycline in plasma after enrolment, consistent with dosing within the previous 48 h. Notably, 73 (63%) participants in the PEP group and 29 (25%) in the no-PEP group had at least one plasma sample with doxycycline detected. Only five (17%) of those 29 participants in the no-PEP group reported doxycycline use for treatment or prophylaxis.

	PEP (n=116)	No PEP (n=116)	p value
Any adverse events	106 (91%)	104 (90%)	0·65
Any serious adverse events	5 (4%)	10 (9%)	0·18
Any grade 3 or 4 events	4 (3%)	8 (9%)	0·24
Treatment discontinuation because of adverse events	8 (7%)	NA	..
Gastrointestinal adverse events	62 (53%)	47 (41%)	0·05
Drug-related gastrointestinal adverse events	29 (25%)	16 (14%)	0·03
Nausea or vomiting	10 (9%)	3 (3%)	..
Abdominal pain	14 (12%)	5 (4%)	..
Diarrhoea	6 (5%)	9 (8%)	..
Other gastrointestinal disorders	5 (4%)	1 (1%)	..
Confirmed laboratory events			
Elevated plasma creatinine			
All grades	15 (13%)	15 (13%)	1·00
Grade 2	3 (3%)	0 (0%)	..
Proteinuria grade 2 or worse	4 (3%)	5 (4%)	0·73
Glycosuria grade 2 or worse	1 (<1%)	1 (<1%)	1·00
Elevated ALT concentrations			
All grades	14 (12%)	20 (17%)	0·27
Grade 4	1 (<1%)	2 (2%)	1·00

Data are n (%). Only the first occurrence of adverse events per patient was reported. ALT=alanine aminotransferase. PEP=post-exposure prophylaxis (with doxycycline).

Table 3: **Adverse events according to study group**

Sexual practices remained similar between study groups during the study period (appendix). No significant differences were observed between groups in the number of sexual intercourse acts in the 4 weeks before scheduled visits (p=1·00), the numbers of sexual partners within the past 2 months (p=0·57), the proportion of condomless receptive anal intercourse acts (p=0·26), and the proportion of condomless anal sex acts at the last sexual intercourse (p=0·23). However, a slight but significant decrease in condom use was reported during the study period in the no-PEP group, with 80% of participants reporting condomless anal sex during their last intercourse at baseline and 90% at the month 8 visit (p for trend=0·01).

The frequency of serious adverse events or of grade 3 or 4 adverse events did not differ significantly between the study groups, and no participant died during the study (table 3; appendix). Eight (7%) participants in the PEP group discontinued doxycycline because of multiple drug-related adverse events: abdominal pain (in five patients), nausea (in three), diarrhoea (in one),

bloating (in one), gastric reflux (in one), fatigue (in one), and dizziness (in one). Drug-related gastrointestinal adverse events were reported more commonly in the PEP group (29 [25%] participants) than in the no-PEP group (16 [14%] participants; p=0·03). All three patients with grade 4 alanine aminotransferase elevation had acute HCV infection (one at baseline in the no-PEP group, one during follow-up in the PEP group, and two during follow-up in the no-PEP group).

Discussion

The results of this open-label randomised trial show that, among high-risk MSM using PrEP with tenofovir disoproxil fumarate plus emtricitabine for HIV prevention, the use of doxycycline PEP following condomless sexual activity was associated with a significant decrease in the occurrence of a new bacterial STI, with an overall 47% relative reduction in the risk of acquiring a new bacterial STI (gonorrhoea, chlamydia, or syphilis). However, the short duration of follow-up in our study might have increased the likelihood of an exaggerated estimate of efficacy caused in part by the high initial adherence to PEP, which could decrease over time (appendix).

As expected, the benefit of doxycycline prophylaxis varied according to the type of STI considered. No change was observed in the occurrence of a new episode of gonorrhoea with doxycycline prophylaxis, in line with the already known high prevalence of tetracycline resistance among *N gonorrhoeae strains* in France.[26] In the USA, 25·3% of *N gonorrhoeae* strains are resistant to tetracyclines.[27] Notably, although a lower number of positive PCR tests for *N gonorrhoeae* in urine samples and anal swabs was found in the PEP group than in the no-PEP group (appendix), the number of positive PCR tests in throat swabs was similar, and represented 41·5% (27 of 65) of all positive PCR tests. This result could be the consequence of a higher proportion of gonococcal strains with tetracycline resistance in throat swabs than in urine samples or anal swabs, or it could be the consequence of a lower concentration of doxycycline in the throat than in urine or anal mucosa, since doxycycline is preferentially eliminated in urine and the gastrointestinal tract.[26,28]

We observed a significant decrease in the occurrence of a new episode of chlamydial infection and syphilis with doxycycline PEP. In the intention-to-treat analysis, we observed a 70% relative reduction in the risk of chlamydial infection and a 73% relative reduction in the risk of syphilis, which are, to our knowledge, among the highest ever reported with antibiotic prophylaxis for STIs.[14,15,29]

These results were also obtained with limited exposure to doxycycline, since participants in the PEP group used a median of only 6·8 pills of doxycycline per month. However, assessment of adherence to doxycycline PEP in this study was challenging and was based mainly on self-reported data. Measures of plasma drug concentrations revealed only a small proportion of participants who were taking doxycycline, since our assay was only able to detect doxycycline in plasma within 48 h of drug intake (appendix). Additionally, doxycycline was detected in plasma of a small number of participants in the no-PEP group, although no such use was reported. One possibility for this observation is that these participants, knowing the purpose of the study, might have used doxycycline in the no-PEP group, which might have slightly underestimated the benefit of this strategy.

Similarly to previous trials of antibiotic prophylaxis for STIs, we saw no difference in sexual behaviour between the study groups (appendix).[15] However, an overall significant decrease in condom use was seen over time during this trial, with 10% of participants reporting condom use for anal intercourse at the end of the follow-up compared with 20% at baseline. This low rate of condom use did not undermine the efficacy of PrEP, since no breakthrough HIV infection was reported. Doxycycline use was associated with self-limited gastrointestinal symptoms, consistent with previous reports, but eight (7%) participants discontinued doxycycline prophylaxis because of drug-related adverse-events.[19–21]

Our study has various limitations. First, it is an open-label study and investigators and participants knew whether or not they were receiving antibiotic prophylaxis, which could have biased assessment of the primary endpoint. However, most endpoints were based on the results of the bi-monthly PCR tests for gonorrhoea and chlamydia, and serological assays for syphilis, which were blinded to the study groups. The event review committee was also blinded to study groups, so the study design is unlikely to have had a major effect on assessment of outcomes. Second, the median duration of follow-up was short, so the long-term benefit of this strategy cannot be predicted. Additionally, since most participants used PEP within 24 h after sexual intercourse, we were unable to assess which timing was most effective for PEP. Our study also did not address the effect of increased doxycycline use on resistance to this antibiotic for non-STI organisms. Future studies should explore this issue.

Importantly, we were unable to assess the effect of this strategy on the selection and dissemination of antibiotic resistance for STIs. Few strains of *N gonorrhoeae* and *C trachomatis* were available for antibiotic susceptibility testing, probably because the majority of cases were diagnosed by PCR in asymptomatic individuals, and the inoculum was probably too low to allow strain isolation. Similarly, we did not attempt sequencing of *T pallidum* strains to detect resistance mutations.

The selection and dissemination of tetracycline resistance is particularly important for chlamydial infections and syphilis. These antibiotics represent first-line or second-line treatment options, since *C trachomatis* and *T pallidum* strains remain fully

susceptible to doxycycline, probably because these bacteria, unlike *N gonorrhoeae*, do not carry all the genetic elements allowing horizontal transfer of resistant genes.[16–18] However, under a high selective pressure with tetracycline, *Chlamydia suis* strains in pigs can acquire tetracycline resistance via an efflux pump from an aquatic bacteria found in fish that could be used to feed pigs. Therefore, the risk of selecting *C trachomatis* or *T pallidum* strains that are resistant to tetracyclines does exist, since single point mutations in the 16S rRNA gene could be theoretically sufficient to confer tetracycline resistance, as is the case for 23S rRNA mutations and azithromycin-resistant *T pallidum* strains.[17–18] Furthermore, selection of antibiotic resistance might take some time, and only long-term follow-up of this strategy can provide further information in this regard. Another concern is selection of antibiotic-resistant strains of gonorrhoea, leading to cases of untreatable gonorrhoea, so prevention of this STI is a public health priority. In the absence of a vaccine, prevention of gonorrhoea transmission relies on promotion of consistent condom use and regular testing. The results of this study should therefore be interpreted with caution, and we await the results of additional studies with longer follow-up periods and thorough analyses of resistance before recommending widespread implementation of this strategy of antibiotic PEP in high-risk individuals.

The use of doxycycline PEP could be considered as a short-term strategy included in a comprehensive prevention package for high-risk individuals with a high incidence of STIs, to be phased out once other preventive measures are in place. Results of this study also indicate that frequent testing of STIs among high-risk MSM should be mandatory, because of the high rate of asymptomatic STIs in this population. Better partner notification and early treatment should also be emphasised, as well as regular use of condoms. Altogether, these data also underscore the need to develop effective vaccines for bacterial STIs, while vaccination against hepatitis B virus and hepatitis A virus should be mandatory in susceptible individuals.[30]

In summary, our study shows a decreased occurrence of chlamydial infection and syphilis with doxycycline PEP in high-risk MSM using HIV PrEP and engaging in condomless anal sex, providing proof of concept that this strategy could be potentially useful in this population. While we await the development of effective vaccines, combining prevention tools and scaling up testing and early treatment of those infected with STIs could contain the spread of STI epidemics in these high-risk populations.

Contributors

J-MM designed and led the study and wrote the first draft of the report. IC and LM designed the analysis. IC, LM, CCa, DC, and J-MM analysed the data. CCa coordinated the study and oversaw data management with SL and VD. BS, DR-C, and LS-T designed the counselling interventions. JF did the pharmacological assays. CD, BB, and CB did the tests for STIs. J-MM, CCh, GP, EC, LC, OR, FR, PC, AA, JC, and LN did the study at their sites. All authors critically reviewed and approved the manuscript.

Declaration of interests

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