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Improving Vaginal Health in Women at Risk for HIV-1: Results of a Randomized Trial

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Abstract

Background—Vaginal infections are common and have been associated with increased HIV-1 risk.

Methods—We conducted a randomized trial of monthly oral directly observed treatment for reducing vaginal infections in Kenyan women at risk for HIV-1. Trial interventions included metronidazole 2 grams plus fluconazole 150 milligrams versus identical metronidazole and fluconazole placebos. The primary endpoints were bacterial vaginosis (BV), vaginal candidiasis, trichomoniasis, and colonization with *Lactobacillus* (ClinicalTrials.gov, NCT00170430).

Results—Of 310 HIV-1-seronegative female sex workers enrolled (155 per arm), 303 were included in the primary endpoints analysis. Median follow-up was 12 visits in both study arms ($p=0.8$). Compared to controls, women receiving the intervention had fewer episodes of BV (hazard ratio [HR] 0.55, 95% confidence interval [CI] 0.49-0.63), and more frequent vaginal colonization with *Lactobacillus* species (HR 1.47, 95% CI 1.19-1.80) and hydrogen peroxide-producing *Lactobacillus* species (HR 1.63, 95% CI 1.16-2.27). Vaginal candidiasis (HR 0.84, 95% CI 0.67-1.04) and trichomoniasis (HR 0.55, 95% CI 0.27-1.12) were reduced in treated women compared to controls, although not significantly.

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Conclusions—Periodic presumptive treatment reduced BV and promoted normal vaginal flora. Vaginal health interventions have the potential to provide simple, female-controlled approaches for reducing HIV-1 risk.

Keywords

Bacterial vaginosis; vaginal candidiasis; *Trichomonas vaginalis*; *Lactobacillus*; HIV-1; randomized trial; women; Africa

Introduction

Women account for the majority of new HIV-1 infections in Africa, the region most affected by the HIV-1 pandemic [1]. Biological, behavioral, and socioeconomic factors all contribute to HIV-1 risk in women. Abstinence, mutual monogamy, and consistent condom use have been widely promoted for preventing HIV-1 transmission, but may be difficult for women to implement in some settings. Additional strategies are needed to reduce women's HIV-1 risk.

Disturbances of the normal vaginal flora may contribute substantially to the population-level risk of HIV-1 [2]. Bacterial vaginosis (BV), vaginal candidiasis, and infection with *Trichomonas vaginalis* are common in Africa [3], and each has been associated with increased risk for HIV-1 acquisition in multiple prospective studies [4]. Additionally, normal vaginal flora, characterized by a predominance of *Lactobacillus* species, has been associated with reduced HIV-1 risk [5]. Vaginal infections can be challenging to treat successfully, and frequently recur [6, 7]. Simple, safe, and inexpensive interventions that effectively reduce vaginal infections and promote normal vaginal flora could provide important female-controlled, non-coitally dependent strategies for reducing HIV-1 risk in African women.

Methods

We conducted a randomized, double-blind, placebo controlled trial to test the efficacy of monthly periodic presumptive oral treatment with metronidazole 2 grams combined with fluconazole 150 mg to reduce the incidence of BV, vaginal candidiasis, and *T. vaginalis* infection, and to promote vaginal colonization with *Lactobacillus* species among women at risk for HIV-1.

Participants

Participants were female sex workers from Mombasa, Kenya, followed monthly as part of an open cohort study of risk factors for HIV-1 [8]. Most worked in bars or nightclubs, supplementing their income with transactional sex. Trial inclusion criteria included HIV-1 seronegative status, age 18 to 45 years, not pregnant or planning to become pregnant in the next year, and without symptoms of abnormal vaginal discharge or vulvovaginal pruritis. Exclusion criteria included history of intolerance to either study drug, anticipating travel outside of the Mombasa area, and inability to abstain from alcohol for 48 hours after each dose of study drug. HIV-1-seropositive women identified through screening could access free comprehensive care including antiretroviral therapy. The study was approved by the

Human Subjects Research Committees at Kenyatta National Hospital and the University of Washington. All participants provided written informed consent.

Procedures

At enrollment, standardized questionnaires were completed in a face-to-face interview to collect information on demographic, medical, and sexual history. A physical examination including a speculum pelvic examination was performed. Vaginal and cervical swabs were collected for laboratory diagnosis of genital tract infections. Vaginal fluid pH was measured using a test strip (ColorpHast 4.0-7.0, EM Reagents), and vaginal secretions were tested for the release of an amine odor after addition of a drop of 10% potassium hydroxide. Blood was collected for HIV-1 serological testing, and a urine pregnancy test was performed.

Women were randomized to the intervention and control arms, with participants and investigators remaining blinded to the allocation until after completion of all participant involvement. The study product and computer-generated randomization scheme were prepared by the Harborview Medical Center Investigational Drug Services Pharmacy in Seattle. Women were block-randomized in groups of 10 to receive either eight capsules containing metronidazole 250 mg each plus one capsule containing fluconazole 150 mg or eight identical placebo metronidazole capsules plus one identical placebo fluconazole capsule. Individual study drug packets were prepared and identified using sequential numbers. Trained study staff in Mombasa used the packets in numerical order. All study drugs were administered orally as directly observed treatment (DOT) in the clinic.

Women were scheduled to return for monthly follow-up visits. At each monthly visit, they completed a brief interview, physical examination, collection of genital specimens, HIV-1 serological testing, urine pregnancy testing, and DOT administration of study drug. Participants could complete up to 12 follow-up visits. Those who became pregnant were excluded from further participation. Data on adverse events were sought and recorded at each visit.

Women reporting abnormal vaginal discharge or vulvovaginal itching were treated syndromically with open-label metronidazole 2 grams as a single dose plus clotrimazole 200 mg vaginal suppositories nightly for 3 nights. When this treatment was provided, the study metronidazole/metronidazole placebo was withheld.

Because of the time required to process laboratory specimens, participants were invited to return one week after each examination to receive their test results. At enrollment and monthly follow-up visits, sexually transmitted infections (STIs) including gonorrhea, microscopic cervicitis, and trichomoniasis were treated according to WHO and Kenya Ministry of Health guidelines [9]. Treatment included open-label single-dose therapy with 2 grams of metronidazole for all diagnosed cases of trichomoniasis. Asymptomatic women with a laboratory diagnosis of BV or vaginal candidiasis were not treated, as there is currently no indication for treatment of these conditions in non-pregnant women without symptoms.

Laboratory Methods

All laboratory assays were performed in Mombasa. Serological testing for HIV-1 was performed using an enzyme-linked immunosorbent assay (ELISA; Detect-HIV; BioChem ImmunoSystems), and positive samples were confirmed using a second ELISA (Recombigen; Cambridge Biotech or Vironostika; Biomeriux) [10]. Testing for HSV-2 was also by ELISA (HerpeSelect, Focus Technologies). Pregnancy testing was performed using a rapid β -hCG test (Plasmatec Laboratory Products).

Vaginal secretions were Gram-stained and evaluated according to standardized criteria that assign a score of 0-10 based on the presence of *Lactobacillus*, *Gardnerella*, *Bacteroides*, and *Mobiluncus* morphotypes (Nugent criteria) [11]. Vaginal Gram stains were evaluated by a laboratory technician who had more than eight years of experience with this technique and had received a refresher course prior to study initiation. A vaginal saline wet mount was examined microscopically under 40X power for the presence of motile *T. vaginalis*, fungal elements, and clue cells. A drop of 10% potassium hydroxide was added to the slide, which was then examined a second time for the presence of budding yeast or hyphae. Culture for *T. vaginalis* was performed in Diamond's modified medium.

In our primary endpoints analysis, we defined BV as a Gram stain score of 7-10 [11]. In secondary analyses, we also defined BV according to clinical criteria, which require the presence of at least 3 of the following 4 clinical signs (Amsel criteria): homogeneous vaginal discharge, vaginal pH >4.5, amine odor, and clue cells [12]. *Trichomonas vaginalis* infection was defined by the presence of motile trichomonads on examination of the wet mount or a positive culture. Vaginal candidiasis was defined by the presence of budding yeast or hyphae on the vaginal wet mount.

Culture for *Lactobacillus* was performed on Rogosa agar (Difco TM, Becton Dickinson) [5], and H₂O₂ production was evaluated by subculturing on tetramethylbenzidine (TMB) agar containing horseradish peroxidase [13]. The presence of *Lactobacillus* was defined on the basis of colonial morphology and Gram stain appearance. Isolates were classified as H₂O₂-producing if blue pigment was detectable by the naked eye after growth of colonies on TMB agar.

Endocervical secretions were Gram stained and examined microscopically under 100X power. The number of polymorphonuclear leukocytes (PMN) was counted in three non-adjacent fields. Cervicitis was defined by the presence of an average cervical PMN count >30. Culture for *Neisseria gonorrhoeae* was performed on modified Thayer-Martin medium.

Sample Size and Statistical Methods

The primary outcomes in the trial were the incidence of BV, vaginal candidiasis, *T. vaginalis* infection, the presence of *Lactobacillus* by culture, and the presence of H₂O₂-producing *Lactobacillus*. We calculated that 88 events for each outcome were needed to have 90% power to detect a two-fold difference in event rates between the two study arms using $\alpha=0.05$ in survival analysis [14]. Based on the anticipated number of events from previous rates in the cohort, the trial was designed to enroll 400 women in order to have

>90% power to detect a 2-fold difference in event rates for all five primary outcomes, provided that participants followed up for an average of seven visits.

After the first 2 years of the trial, it was evident that the number of episodes of *T. vaginalis* was substantially lower than expected. The number of events would not approach 88 even with enrollment of 400 women, and we determined that the available resources would not allow us to enroll enough participants to achieve 90% power for the *T. vaginalis* endpoint. These data were provided to the Data Safety and Monitoring Board, which concurred with our assessment that a sample size of 310 would provide >90% power to detect 2-fold differences in the other four endpoints. Thus, the final enrollment in the trial was 310 participants.

Characteristics of the women enrolled in the active and placebo arms were compared using Chi square tests for bivariate data and Wilcoxon Rank-Sum tests for continuous data. Loss to follow-up was compared between the study arms using Kaplan-Meier analysis and log-rank tests. Participants were considered to be lost if they were more than 6 weeks late for a scheduled follow-up visit, and were censored before 12 months of follow-up if they seroconverted for antibodies to HIV-1, became pregnant, or remained in active follow-up at the completion of the trial in December 2006.

Because study medication was dispensed as DOT at clinic visits, adherence was closely related to follow-up, and participants were considered to be non-adherent when more than two weeks late for a scheduled visit. We compared the median adherence in each study arm by Wilcoxon Rank Sums test, and compared the proportion of visits at which the study drugs were not given using generalized estimating equations with binomial link and exchangeable correlation structure. The protocol required that study metronidazole/metronidazole placebo be withheld when open-label metronidazole was provided.

Rates of primary and secondary endpoints and of reported adverse events in the two study arms were compared using Andersen-Gill proportional hazards models with robust variance estimates to allow for multiple events per woman. The incidence of HIV-1 seroconversion in the two study arms was compared using a Cox proportional hazards model. All analyses were conducted according to the intention to treat principle. This study is registered with [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00170430) (NCT00170430).

Results

Between May 2003 and November 2005, 378 women were screened for eligibility, of whom 310 were enrolled; 155 were assigned to the active treatment arm and 155 to the placebo arm (Figure 1). Of these, 151 (97.4%) women in the treatment arm and 152 (98.1%) in the placebo arm returned for at least one follow-up visit, and were included in primary analyses ($P = 1.0$). Median numbers of follow-up visits did not differ significantly in the treatment versus placebo arm (12, interquartile range [IQR] 8-12 versus 12, IQR 9-12; $p=0.8$). Using Kaplan-Meier analysis, follow-up was 87% in the treatment arm and 92% in the placebo arm at six months, 79% in the treatment arm and 85% in the placebo arm at 12 months, and did

not differ significantly between the two arms ($p=0.2$). Follow-up was concluded in December 2006.

Participants in the two study arms did not differ significantly with respect to demographic, obstetrical, behavioral, or laboratory characteristics (Table 1). Median age was 32 (IQR 27-38) years, and most participants had no secondary education. They reported a median of one sex partner and one sex act in the prior week, and over half reported 100% condom use. While the protocol required that women did not have abnormal vaginal discharge or vulvovaginal pruritis at enrollment, over 40% had vaginal infections based on laboratory results. Mixed vaginal infections were present in 6 (2%) women (3 BV/vaginal candidiasis, 3 BV/*T. vaginalis*). Vaginal *Lactobacillus* depletion was common, consistent with prior studies in this population [3, 5].

Compared to the 56 (18%) women lost before completing 12 follow-up visits, those who completed the study were slightly older (median age 32.2 years, IQR 27.2-38.2 versus 30.1 years, IQR 26.1-34.8 years; $p=0.04$), and reported a longer duration of sex work (4.5 years, IQR 1.8-9.1 versus 2.3 years, IQR 0.7-6.3; $p=0.008$), more pregnancies (2, IQR 1-3 vs. 1, IQR 1-2), and a lower prevalence of vaginal washing (221/254, 87% versus 55/56, 98%; $p=0.02$). Women who remained in the study were more likely to have vaginal candidiasis at the baseline visit compared to women lost to follow-up (32/254, 13% versus 1/56, 2%; $p=0.02$). There were no other significant differences between the women retained versus those lost to follow-up (Table 1).

Medication was dispensed as DOT at monthly clinic visits, so women were defined as non-adherent if more than two weeks late for a follow-up visit. Using this definition, median adherence to the study regimen was 92% (IQR 83%-100%) in the treatment arm and 92% (IQR 83%-100%) in the placebo arm ($p=0.8$). Study metronidazole/metronidazole placebo was not given at 51/1,565 (3.3%) visits in the treatment arm and at 44/1,614 (2.7%) visits in the placebo arm ($p=0.5$). Study fluconazole/fluconazole placebo was not given at 7/1,565 (0.4%) visits in the treatment arm and at 19/1,614 (1.2%) visits in the placebo arm ($p=0.03$).

Primary endpoints in the intervention and placebo arms of the trial are compared in Table 2. Monthly metronidazole plus fluconazole reduced the number of episodes of BV by nearly half, and produced similar increases in the frequency of colonization with *Lactobacillus*, including H_2O_2 -producing lactobacilli. There were fewer episodes of vaginal candidiasis and trichomoniasis in active treatment recipients compared to those receiving placebo, but these did not reach statistical significance.

While the primary BV endpoint was based on microscopic criteria [11], we also evaluated the effect of the intervention on the incidence of BV as defined by clinical criteria [12]. At the enrollment visit, 24 (16%) women in the treatment arm and 20 (13%) in the placebo arm had BV by clinical criteria ($p=0.5$). During follow-up, BV was identified by clinical criteria at 150 visits (incidence 99 per 100 person-years) in the treatment arm versus 300 visits (incidence 196.6 per 100 person-years) in the placebo arm (HR 0.51, 95% confidence interval [CI] 0.42-0.62, $p<0.001$).

Five women in the treatment arm and seven in the placebo arm seroconverted to HIV-1 (HR 0.6, 95% CI 0.2-2.3, $p=0.6$). Six women in each study arm acquired gonorrhea (HR 1.0, 95% CI 0.6-1.7, $p=1.0$). No severe adverse events occurred in either study arm (Grading Severity of Adult Adverse Experiences from the Division of AIDS, NIAID). Nausea was reported at 36 visits (incidence 23.7 per 100 person-years) in the active treatment arm compared to 21 visits (incidence 13.7 per 100 person-years) in the placebo arm (HR 1.7, 95% CI 1.0-2.9, $p=0.05$; Table 3). There were no other significant differences in adverse events.

Discussion

In this randomized trial of an intervention strategy for improving vaginal health in women at risk for HIV-1, monthly DOT with metronidazole plus fluconazole significantly decreased the number of episodes of BV and increased vaginal colonization with *Lactobacillus* species. There were decreases in the incidence of vaginal candidiasis and *T. vaginalis* infection, although these were not statistically significant. By addressing vaginal health in the broad context of both normal flora and the three major infectious causes of vaginitis, these data were intended to provide insight into a novel approach that could reduce HIV-1 risk in women. This study was not specifically directed at modifying clinical symptoms.

The results of our trial add to the limited data available on regimens for reducing the frequency of BV. A recent study of US women showed that following successful treatment of symptomatic BV, suppressive therapy with metronidazole 0.75% gel on two non-consecutive nights each week reduced recurrences by clinical (relative risk [RR] 0.43, 95% CI 0.25-0.73) and microscopic (RR 0.66, 95% CI 0.39-1.12) criteria [7]. Less frequent administration (five consecutive nights every three months) of metronidazole 0.75% gel for prevention of BV was evaluated in Malawi [15]. Among HIV-1 seronegative women, this regimen resulted in a modest reduction in BV by Gram stain criteria compared to placebo buffered gel (adjusted RR 0.90, 95% CI 0.83-0.97). Overall, these data reinforce the persistent nature of BV, confirm that intermittent suppressive therapy increases the likelihood of sustained cure, and suggest that higher doses and more frequent administration of metronidazole may be more effective.

Like BV, vulvovaginal candidiasis frequently recurs [16]. A clinical trial published in 2004 demonstrated that in women with prior vaginal candidiasis, weekly oral fluconazole 150 mg was effective at reducing recurrences [6]. The median time to clinical recurrence of candidiasis was 10.2 months in the fluconazole arm versus 4.0 months in the placebo arm ($p<0.001$). In the trial presented here, monthly administration of fluconazole 150 mg led to only a small reduction in episodes of vaginal candidiasis identified by microscopy. Studies of women with recurrent vulvovaginal candidiasis have shown that weekly administration is more effective than monthly administration of fluconazole for reducing recurrences [17]. Considered together with our present findings, the data suggest that monthly dosing may have been insufficient to substantially reduce vaginal re-colonization with *Candida* in this population of female sex workers. The effect of fluconazole may also have been counter-balanced by an increased risk of vaginal candidiasis following treatment of BV with metronidazole [7, 18, 19]. Because yeast cultures were not performed, it was not possible to

evaluate rates of antifungal resistance and recolonization with non-*albicans* species in this study.

Trichomonas vaginalis is sexually transmitted, and efforts to reduce recurrences have generally focused on treatment of sexual partners and promotion of safer sex [20]. In a community randomized trial of periodic mass treatment of STIs, metronidazole, azithromycin, and ciprofloxacin were provided every 10 months [21]. This strategy significantly reduced the incidence of trichomoniasis in intervention communities compared with control communities (adjusted RR 0.52, 95% CI 0.35-0.79). In the present trial, monthly metronidazole reduced *T. vaginalis* incidence to a similar extent, but the number of infections was fewer than expected based upon prior data from the parent cohort [22], and the difference between study arms was not statistically significant. The low incidence may reflect lower risk among women who met trial inclusion criteria and the fact that all participants received monthly risk reduction counseling, free condoms, and directed treatment for *T. vaginalis*.

Studies evaluating the efficacy of metronidazole for treatment of symptomatic BV have demonstrated resolution in 47-90% of women at four or more weeks [23-28], with seven-day regimens generally producing higher rates of resolution compared to single dose treatment. For *T. vaginalis* infection, a single 2 gram dose of metronidazole is the treatment of choice, and has provided cure rates of 82-88% [29-32]. Single dose oral fluconazole 150 mg for vulvovaginal candidiasis has produced cure rates of 56-70% at follow-up a month or more after treatment [33-35]. Few trials for treatment of vaginal infections have been conducted in African women or in sex workers, so the cure rates for these populations are not well defined.

Unblinding due to side effects has been suggested as a potential limitation in randomized trials using oral metronidazole [15]. In this study, we observed only a modest increase in nausea, with no other significant differences in adverse events between active treatment and control recipients. Moreover, laboratory technicians evaluating the endpoints were blinded with respect to participants' clinical data. Thus, unblinding is unlikely to have influenced the results.

Overall, data from 98% of participants were included in analyses of the primary endpoints, and the average number of visits in both study arms substantially exceeded the pre-defined criteria for successful follow-up. The proportion of women included in the primary analyses and overall retention rate compared favorably to recent HIV-1 prevention trials in female sex workers [36, 37]. The sample size for this study provided excellent power for examining differences in the rates of BV, vaginal candidiasis, and *Lactobacillus* colonization (including the subset of H₂O₂ producing strains) between the two study arms. The final sample size provided less power for identifying differences in *T. vaginalis* incidence.

We used microscopic scoring criteria for the diagnosis of BV in our primary analyses [11]. Additional analyses demonstrated that the intervention produced similar reductions in episodes of BV by clinical criteria [12]. Microscopic criteria were selected for defining the primary BV endpoint for two reasons. First, nearly 90% of these women reported vaginal

washing, raising concern about whether the clinical criteria would produce reliable results in this population. Second, the presence of BV by Gram stain criteria has been associated with increased risk for HIV-1 acquisition in this population [3] and in a general population cohort of South African women [38]. Thus, resolution of BV by Gram stain criteria is a potentially important outcome for these women.

It is likely that these findings are generalizable to other populations of African women at risk for HIV-1. Nonetheless, it should be noted that the efficacy of this regimen could vary in relation to population characteristics including age, condom use, intravaginal practices, and prevalence of vaginal *Lactobacillus* colonization.

Vaginal infections are common, and have been associated with increased risk for HIV-1 [2]. Given the high prevalence of these infections, interventions to reduce their frequency could have a major impact on HIV-1 incidence in African women. This trial demonstrated that periodic presumptive treatment with oral metronidazole and fluconazole reduced BV and increased vaginal colonization with *Lactobacillus*. Approaches that have a greater impact on vaginal infections are needed to maximize the potential usefulness of vaginal health interventions for HIV-1 risk reduction.

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Figure 1.
Trial Profile

Table 1

Baseline Characteristics of Study Participants

Variable	Treatment Arm Number (%) or Median (IQR) N = 155	Placebo Arm Number (%) or Median (IQR) N = 155
Age (range)	31 (26-38)	32 (27-38)
Education (years)	8 (7-10)	8 (7-11)
Parity	1 (1-2)	1 (1-2)
Contraception		
OCP	13 (8%)	9 (6%)
DMPA	29 (19%)	39 (25%)
Norplant	3 (2%)	3 (2%)
IUD	3 (2%)	2 (1%)
Tubal ligation	5 (3%)	4 (3%)
Vaginal washing in past week	138 (89%)	138 (89%)
Finger for vaginal washing ^a	132 (96%)	133 (96%)
Cloth for vaginal washing ^a	6 (4%)	5 (4%)
Frequency (per week) ^a	21 (14-21)	21 (14-21)
Age at first intercourse	17 (16-19)	17 (16-18)
Duration of sex work (years)	4 (1-9)	4 (2-8)
New sex partner in past month	62 (40%)	67 (43%)
Sex partners in last week	1 (0-1)	1 (0-1)
Sex frequency in last week	1 (0-2)	1 (0-2)
Percent condom use	100 (100-100)	100 (100-100)
Lubricant used for sex		
Vaseline	43 (28%)	43 (28%)
Saliva	32 (21%)	34 (22%)
Bacterial vaginosis	48 (31%)	58 (37%)
Vaginal candidiasis	14 (9%)	19 (12%)
<i>Trichomonas vaginalis</i>	2 (1%)	2 (1%)
<i>Lactobacillus</i> (any)	13 (8%)	8 (5%)
<i>Lactobacillus</i> (H ₂ O ₂ producing)	7 (5%)	2 (1%)
<i>Neisseria gonorrhoeae</i>	1 (1%)	0 (0%)
Cervicitis ^b	0 (0%)	2 (1%)
HSV-2 seropositive	113 (73%)	115 (74%)

IQR, interquartile range; OCP, oral contraceptive pills; DMPA, depot medroxyprogesterone acetate; IUD, intrauterine device

^a N = 138 in treatment arm and N = 138 in placebo arm

^b Defined by the presence of an average of 30 polymorphonuclear leukocytes per high-power field (100X magnification) on microscopic examination of Gram stained cervical secretions.

Table 2
Cumulative Episodes of Vaginal Infections and Vaginal Lactobacillus Colonization by Study Arm

Outcome	Treatment Arm ^a Incidence per 100 person years (number of episodes ^c)	Placebo Arm ^b Incidence per 100 person years (number of episodes ^c)	Hazard Ratio Treatment/Placebo (95% CI)	p value
Bacterial vaginosis	198.6 (301)	326.4 (553)	0.55 (0.49-0.63)	<0.001
Vaginal candidiasis	87.8 (133)	106.2 (162)	0.84 (0.67-1.04)	0.1
<i>Trichomonas vaginalis</i>	7.9 (12)	14.2 (22)	0.55 (0.27-1.12)	0.1
<i>Lactobacillus</i> (any)	140.5 (213)	97.0 (148)	1.47 (1.19-1.80)	<0.001
<i>Lactobacillus</i> (H ₂ O ₂ producing)	56.7 (86)	35.4 (54)	1.63 (1.16-2.27)	0.005

CI, confidence interval

^a 152 person-years of follow-up

^b 153 person-years of follow-up

^c Participants could contribute multiple episodes for each endpoint

Table 3

Comparison of Adverse Events by Study Arm

Outcome	Treatment Arm ^a Incidence per 100 person years (number of episodes ^c)	Placebo Arm ^b Incidence per 100 person years (number of episodes ^c)	Hazard Ratio Treatment/Placebo (95% CI)	p value
Nausea	23.7 (36)	13.7 (21)	1.7 (1.0-2.9)	0.05
Vomiting	13.8 (21)	13.7 (21)	1.0 (0.6-1.9)	1.0
Diarrhea	15.8 (24)	17.0 (26)	0.9 (0.5-1.6)	0.8
Abdominal pain	16.4 (25)	15.7 (24)	1.1 (0.6-1.9)	0.8
Fever	99.3 (151)	110.5 (169)	0.9 (0.7-1.1)	0.4
Rash	2.6 (4)	1.3 (2)	1.8 (0.3-10.8)	0.5
Fatigue	29.6 (44)	21.6 (33)	1.4 (0.9-2.2)	0.1
Headache	123.0 (187)	109.8 (168)	1.1 (0.9-1.4)	0.3
Myalgia	21.0 (32)	17.0 (26)	1.3 (0.8-2.1)	0.4
Arthralgia	44.0 (67)	35.3 (54)	1.3 (0.9-1.8)	0.2
Numbness/tingling	5.9 (9)	5.2 (8)	1.1 (0.4-2.9)	0.8
Too sick to work	25.7 (39)	24.2 (37)	1.1 (0.7-1.7)	0.8

CI, confidence interval

^a 152 person-years of follow-up

^b 153 person-years of follow-up

^c Participants could contribute multiple episodes for each adverse event