Effect of Nonoxynol-9 Gel on Urogenital Gonorrhea and Chlamydial Infection
A Randomized Controlled Trial

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SEXUALLY TRANSMITTED INFECTIONS (STIs) have important repercussions on reproductive health and are a major cause of morbidity and mortality worldwide. Both Neisseria gonorrhoeae and Chlamydia trachomatis are common STIs in sub-Saharan Africa.1 Primary STI prevention strategies include abstinence, mutually exclusive sexual relationships with an STI-negative partner, and the use of male or female condoms. All of these strategies require male consent and cooperation.

Nonoxynol-9 was chosen for study because it is the most commonly used spermicide worldwide and is 1 of only 2 spermicides marketed in the United States. Although data are limited, the other major spermicides available outside the United States do not appear to have a more favorable safety profile, little is known about their in vivo effectiveness with regard to STI prevention, and no data are available regarding clinical activity against human immunodeficiency virus (HIV).

Nonoxynol-9 is a nonionic detergent that has been used as a spermicide for more than 50 years. It can inactivate many sexually transmitted pathogens in vitro, including N gonorrhoeae, C trachomatis, Haemophilus ducreyi, Treponema pallidum, Trichomonas vaginalis, and herpes simplex virus.2-4 Both in vitro and animal data support the hypothesis that intravaginal application of nonoxynol-9 may help protect women from HIV and other STIs.5-8

Five randomized placebo-controlled trials of nonoxynol-9 for STI prevention have compared 4 products: 2 gels,9,10 a sponge,11 and a film.12,13 The incidence of STI was reduced anywhere from 0% to 40% in these studies (rate ratios [RRs], 1.0-0.6); however, the 95% con-
confidence intervals (CIs) for the RRs included 1, indicating possibly no protective effect. One study using the film did not find any effect of nonoxynol-9 on the rate of disease incidence for HIV, N gonorrhoae, or Chlamydia trachomatis.13 One study found a marginally significant increase in the rate for gonorrhea, but the authors did not adjust for the multiple comparisons made in the analysis. A meta-analysis of these studies would be difficult to interpret because different formulations have been assessed and the sponge study used a different measure of effect.

We studied Conceptrol Contraceptive Gel with 4% nonoxynol-9 (Advanced Care Products, Raritan, NJ). Its moderate dose, small (3.5 mL total) amount of product inserted vaginally, and single-use applicators make it an attractive product. A gel theoretically might be more readily available for protection than a film. The gel contains a lower dose of nonoxynol-9 than a sponge and may cause less epithelial irritation. A criticism of many of the previous nonoxynol-9 studies is that they were conducted among sex workers who had intercourse many times daily and with multiple partners. We chose a high-risk population but excluded sex workers.

Although not widely used, spermicides are available in Cameroon. Pharmacies carry a variety of nonoxynol-9 products, including gels, suppositories, and foaming tablets. The Cameroon National Association of Family Planning and Well-being also distributes nonoxynol-9 spermicides to clients.

Condoms are the standard of care for STI/HIV prophylaxis. A placebo gel without preservatives and without some antibacterial effect in vitro could not be manufactured. This study was designed to compare nonoxynol-9 gel and condom use with condom use alone for the prevention of male-to-female transmission of genitourinary gonorrhea and chlamydial infection.

METHODS
Study Participants and Procedures
The National Ethics Review Committee, Ministry of Public Health, Yaoundé (Cameroon), and the Protection of Human Subjects Committee, Family Health International, Durham, NC, approved the research. Each participant was required to give written consent twice: once to be screened for the study and again to enroll.

The target population was sexually active women who were not sex workers but were at risk for gonorrhea and chlamydial infection, as indicated by having symptoms of STIs immediately before contact with our study referral staff. The participants were at least 18 years of age, had at least 1 coital act weekly, were willing to learn the results of the HIV tests, and were willing not to self-medicate with antibiotics during study participation. The participants could not have a history of an adverse reaction to products containing latex or nonoxynol-9, be using a spermicide, be pregnant, or have a sebropositive HIV test result.

Study Referral
We stationed referral staff at 10 clinics and 10 pharmacies. Women receiving STI treatment at these sites were asked to speak to referral staff. Many clinics do not conduct laboratory tests for STIs but treat according to symptoms. Many women do not visit clinics but visit only the pharmacies to get treatment for symptoms, which made the pharmacies a good site for contacting potential participants. The staff explained the general purpose of the study and the eligibility requirements and referred appropriate women to the study clinic for screening after they had completed their treatment.

Study Screening
At the clinic, the staff gave another brief study explanation, and the woman entered the consent process for screening. Each woman was given a detailed study explanation by face-to-face counseling and the counselor’s reading the consent form to the woman and addressing her questions, which generally took 45 minutes to 1 hour to complete. Each woman received HIV pretest and condom counseling. Participants received a gynecological examination and had specimens collected for ligase chain reaction testing for N gonorrhoeae and Chlamydia trachomatis from the uterine cervix (Abbott LDCx Probe System, Abbott Laboratories, Abbott Park, Ill) and a saline and potassium hydroxide wet mount for bacterial vaginosis and T vaginalis. They also provided a blood sample for HIV testing (Enzygnost Anti-HIV 1/2 Plus, Aventis Bhering, King of Prussia, Pa; Multisport HIV 1/HIV 2, Bio-Rad Laboratories, Hercules, Calif; and Novopath HIV-1 Immunoblot Kit, Bio-Rad Laboratories). Two independent laboratories examined the LDCx N gonorrhoeae and C trachomatis tests for possible inhibition by nonoxynol-9. There were no false-positive or false-negative results. All women who had a curable STI were treated at no charge and invited to return for rescreening 2 weeks after they had completed treatment. Women who did not have N gonorrhoeae, C trachomatis, or HIV infection were permitted to enter the study enrollment consent process within 30 days of screening.

Study Enrollment
At enrollment, potential participants received posttest counseling, were tested for pregnancy with a urine test, were informed further about the nonoxynol-9 gel study, gave a second consent, provided an oral mucosal transudate specimen (OraSure, Epitope Inc, Beaverton, Ore) for HIV testing (Wellcozyme HIV 1 and 2 GACELISA [gamma antibody capture enzyme-linked immunosorbet assay], Murex, Oxford, England), and gave a urine specimen for testing for N gonorrhoeae and C trachomatis by ligase chain reaction. After the enrollment interview, the counselor received the randomization assignment from the clinic coordinator, told participants their assigned group, and provided condom counseling to both groups and gel use instructions to the gel group. Participants chose 1 of 10 pharmacies for their follow-up visits. All participants were asked to use condoms as often as possible, and those in the gel group were...
asked to apply 1 applicator of gel up to 1 hour before each coital act. Free condoms and gel were provided to participants.

A statistician who was not otherwise involved with the study developed the allocation sequence by using a random-number generator and randomly varied permuted blocks of 4, 8, and 12. Group assignments were concealed in sequentially numbered, sealed, opaque envelopes. Trained staff opened the envelopes only after participants were properly enrolled. The clinic coordinator maintained the envelopes in a secure office, and they were unavailable to the study counselors until randomization.

Masking participants or clinic staff to treatment assignment was impossible. However, assignments were not known by the laboratory staff and were revealed to Family Health International study investigators and analysts only after all data were entered in the study database and final-analysis programs had been verified using dummy treatment codes.

Study Follow-up
Participants made monthly follow-up visits for up to 6 months at their chosen pharmacy. Pharmacies were chosen as follow-up sites because they were located closer to the study participants, making follow-up visits easier, provided a secure place for storage of study materials, and were capable of providing a discreet area for study procedures. The staff interviewed participants about sexual behavior and product use and collected a urine specimen for N gonorrhoeae and C trachomatis testing by ligase chain reaction. At the 3- and 6-month visits, participants gave an oral mucosal transudate specimen for HIV testing. Participants visited the study clinic when they experienced adverse events or when STIs were detected. If a participant required a gynecological examination, a cervical swab was taken for N gonorrhoeae and C trachomatis testing.

Adverse events were asked about at the monthly follow-up visits. If an adverse event was reported, the participant was referred to the study clinic for examination. If the adverse event was gynecological, the study clinicians conducted a standardized pelvic examination that was identical to the examination at screening.

Gel and condom use was assessed by interview. We asked the number of vaginal sex acts the woman had had in the 7 days before the interview, and among those acts, the number of times gels, condoms, and condoms and gel together were used. From these data, we were able to calculate how many coital acts were with gel or condom use alone and how many were without gel or condom use.

Our primary end point was the occurrence of a positive ligase chain reaction test (urine or cervical swab) for either N gonorrhoeae or C trachomatis after the subject had had a negative test result for these organisms. Our secondary end point was the occurrence of HIV (defined as 2 different positive enzyme-linked immunosorbent assay [ELISA] results or a positive ELISA and a positive Western blot, after a negative HIV test result). We collected a cervical swab whenever a pelvic examination occurred (screening and gynecological adverse events) and collected urine samples at the enrollment visit and normal follow-up visits. This approach allowed us to reduce the number of pelvic examinations, reduce the inconvenience to the study participants, decentralize the follow-up process, and reduce loss to follow-up.

Statistical Analysis
This trial was designed to have at least 90% power to reject a null hypothesis of no difference in infection rates (at the .05 significance level), assuming the gel was 50% effective in preventing infection with N gonorrhoeae or C trachomatis. Nearly 90 infections (total in both groups) would be needed to achieve the desired power according to a 2-sided log-rank test. Achieving this power required enrolling approximately 1200 women for 6 months of follow-up each, assuming an incidence of infection in the condom group of 20 cases for every 100 person-years and a loss to follow-up of 10% at 6 months.

A preplanned interim analysis was conducted on data collected through the first 53 study infections. We intended to stop the trial if a significant treatment effect was observed, an independent data and safety monitoring board decided on ethical grounds to discontinue the study, or Family Health International decided to stop the study on administrative grounds. Dummy treatment indicators were used to mask data analysts, study investigators, and data and safety monitoring board members to group assignments. The Lan-DeMets spending function with O’Brien-Fleming boundaries was used to account for multiple looks at the data, resulting in a nominal significance level of .00006 (corresponding to a z score of 4.01) for a test of the primary outcome. Our primary end point was the occurrence of infection. We used a nominal significance level of .04997 to account for this interim look.

Differences in infection rates between the 2 treatment groups were assessed with 2-sided log-rank tests on an intent-to-treat basis. The event time was defined as the midpoint of the follow-up of the first follow-up visit at which an incident infection was detected and the time of the previous visit at which the participant was determined to be free from infection. Women who either did not test positive or first tested positive more than 7 months after enrollment were considered censored at either 7 months or the time of the last visit at which they were free from infection, whichever was first. Cumulative infection probabilities were based on the Kaplan-Meier method and Greenwood formula for SEs. Crude incidence rates, RRs, and 95% CIs were based on the ratio of the number of new
cases to the total length of treatment exposure in the interval. All calculations were based on time to first infection. Baseline factors were identified as potential confounders before analysis of the data: age, marital status, whether the participant was living with a partner, number of children, number of coital acts in the 7 days before enrollment, number of sex partners in the 30 days before enrollment, whether condoms were used during the last coital act, gonorrhea or chlamydia at screening, history of spermicide use, history of contraceptive use (oral contraceptives, injectables, or intrauterine device), history of douching, history of STI before the one that made the participant eligible for the study, and whether previous condom use caused irritation. Cox proportional hazards regression models were used to evaluate the effect of baseline factors on time to first infection as well as potential interaction effects with the study gel.

RESULTS

Screening for the study began in October 1998, and the first participant was enrolled in November 1998. Enrollment continued until June 2000, and the study was stopped in September 2000. The Figure shows the participant flow from first contact with study referral staff until completion of the study.

We excluded 3 participants in the gel group and 7 in the condom-only group from the effectiveness analysis because they had no follow-up data. Only HIV-seronegative women were to be enrolled in the study; however, 4 women who were HIV seropositive at either screening or enrollment were enrolled and later discontinued from the study. These women are included in the intent-to-treat analysis. We had no reports of women in the condom-only group receiving or using nonoxynol-9 gel during the study.

Participants in the 2 groups were similar in all clinical and demographic respects (Table 1). The majority of the women were single and had high educational attainment. Additionally, the majority of participants had had sex with 1 or 2 partners in the 30 days before enrollment, and most averaged 3 coital acts weekly. Women in both groups (2.5%; 17 in the gel and condom group and 14 in the condom-
only group) had a confirmed positive serology test result for syphilis.

From baseline, no changes in the reported number of coital acts weekly, the number of partners, or the number of new partners occurred during the study. Reported condom use during follow-up was 81.4% of coital acts in the gel group and 86.9% for the condom group. Condoms reportedly broke or slipped off about 4.5% of the time in both groups. Among the gel group, gel use was reported for 76.3% of the acts, both gel and condoms were used for 63.0%, and only gel was used for 13%. No gel or condoms were used 5.6% of the time in the gel group.

The rate of new urogenital infections was slightly higher in the gel group (RR, 1.2; 95% CI, 0.9-1.6; P = .21) (TABLE 2). There were 15 swab events and 101 urine events in the gel group. There were 7 swab events and 93 urine events in the condom group. Adjusting for significant covariate effects and stratifying on history of STI before the episode that made the women eligible for enrollment, the estimated Cox proportional hazards model RR for gel use vs condom use alone was no different from the crude estimate. The N gonorrhoeae RR was 1.5 (95% CI, 1.0-2.3), and chlamydial infection RR was 1.0 (95% CI, 0.7-1.4) for gel vs condom group. Only 5 HIV infections were detected in the gel group and 4 in the condom group, making a meaningful comparison impossible because of small numbers and low statistical power.

A total of 214 women in the gel group and 215 in the condom group had at least 1 adverse event. There were 292 examinations in the gel group and 296 in the condom group for adverse events. The type and frequency of adverse events were similar in both groups. Reported symptoms were also similar in both groups. Three women in each group became pregnant during the study follow-up. No differences occurred between the groups for bacterial vaginosis, yeast infections, trichomoniasis, pelvic inflammatory disease, or genital ulcers that were identified at clinic visits for adverse event.

**COMMENT**

Self-reported condom use was frequent but inconsistent in both randomized groups. Reported gel use was less consistent than condom use in the gel group. The gel group reported more coital acts with no or incomplete condom protection (23.2% vs 17.6% for the condom-only group). However, the gel group had fewer coital acts with no gel or condom use (5.6% vs 13.1%). These numbers suggest that the gel group substituted gel use for condom use. A similar pattern of behavior was reported among sex workers in Colombia.13

Two laboratories assessed whether the gel inhibited the ligase chain reaction tests for N gonorrhoeae and C trachomatis and found no problems. If the nonoxynol-9 gel had inhibited our assay, we would have expected detection of fewer infections in the gel group. We do not believe the nonoxynol-9 gel interfered with the testing, since there were more infections in the gel group.

The excessive number of gonorrheal infections among the gel group may have several explanations. First, gonorrhea may have a higher transmissibility than chlamydia, estimated at 50% vs 20%,16 which would make inconsistent condom use less forgiving for gonorrhea than for chlamydial infection. Second, nonoxynol-9 may make the epithelial cells more receptive to bacterial attachment by organisms with fimbriae, such as Escherichia coli, or pili, such as N gonorrhoeae.11 Finally, at screening, slightly more participants were infected with gonorrhea in the gel group than the condom group (5% vs 3%); therefore, the gel group may have had more exposure to infection.

A major concern when we designed this study was that loss to follow-up for the condom-only group would be much higher than for the gel group. We feared that women who did not get the study product would be upset or discouraged and not return for follow-up. However, differential loss to follow-up did not occur, and total loss to follow-up was quite low, thus not affecting the results.

The findings of this study are consistent with the findings from an earlier study conducted in Cameroon among sex workers using the nonoxynol-9 film.13 The film study used a 70-mg product, and the findings may have resulted from the smaller amount of nonoxynol-9 and possible problems with the nonoxynol-9 distribution from the film. In this study, we sought to address both these potential problems by using a higher dose of nonoxynol-9 and a formulation that was perhaps more readily available. Initially, the findings of this study appear to be at odds with those from another 100-mg gel study conducted in Alabama among a non–sex-worker population.9 That study found a statistically significant decrease in infections, but only at the 90% level, not the 95% level. It is difficult to compare this study with the nonoxynol-9 sponge study conducted among sex workers.11 The sponge contains both barrier and chemical characteristics that are impossible to separate, and the investigators chose to use the number of infections over the number of examinations (because the number of examinations was different between the 2 experimental groups) instead of the usual number of events over time.

This nonoxynol-9 gel, although safe to use, did not protect against gonorrheal and chlamydial infection.

**Table 2. Gonorrhea and Chlamydial Infection Outcome Summary**

<table>
<thead>
<tr>
<th></th>
<th>Gel and Cond</th>
<th>Condom Only</th>
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</thead>
<tbody>
<tr>
<td>No. of women</td>
<td>622</td>
<td>619</td>
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<tr>
<td>Person-years</td>
<td>266.1</td>
<td>273.3</td>
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<tr>
<td>No. who had event</td>
<td>116</td>
<td>100</td>
</tr>
<tr>
<td>Event rate per 100 person-years</td>
<td>43.6</td>
<td>36.6</td>
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<tr>
<td>Rate ratio (95% confidence interval)</td>
<td>1.2 (0.9-1.6)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

**Author Contributions:** Study concept and design: Roddy, Zekeng, Tamoufe. Acquisition of data: Zekeng, Ryan, Tamoufe. Analysis and interpretation of data: Roddy, Tweedy. Drafting of the manuscript: Roddy, Ryan. Critical revision of the manuscript for important intellectual content: Roddy, Zekeng, Tamoufe, Tweedy. Statistical expertise: Tweedy. Obtained funding: Roddy. Administrative, technical, or material support: Roddy, Zekeng, Ryan, Tamoufe. Study supervision: Roddy, Zekeng, Tamoufe.

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REFERENCES


The strongest desire known to human life is to continue living. The next strongest is to use the instruments by which life is generated for its own rewards, not for the sake of generations. The third potent desire is to excel and be acknowledged.
—Dorothy Dudley (1884-1962)