

A CONTROLLED TRIAL OF NONOXYNOL 9 FILM TO REDUCE MALE-TO-FEMALE TRANSMISSION OF SEXUALLY TRANSMITTED DISEASES

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ABSTRACT

Background Nonoxynol 9 is a proved spermicide, but whether it is also a microbicide is uncertain. A truly effective vaginal microbicide would reduce the susceptibility of women to sexually transmitted diseases, including infection with the human immunodeficiency virus (HIV).

Methods We enrolled 1292 HIV-negative female sex workers in Cameroon in a double-blind, placebo-controlled study in which the participants were randomly assigned to use either a film containing 70 mg of nonoxynol 9 or a placebo film, inserted into the vagina before intercourse. All of the women were provided with latex condoms and were instructed to have their male sexual partners use them. At monthly follow-up visits, we examined the women with a colposcope for genital lesions, tested endocervical specimens for gonorrhea and chlamydia infection with DNA probes, tested for HIV infection, and treated the women for curable sexually transmitted diseases.

Results The rates of HIV infection (cases per 100 woman-years) were 6.7 in the nonoxynol 9 group and 6.6 in the placebo group (rate ratio, 1.0; 95 percent confidence interval, 0.7 to 1.5). The rates of genital lesions were 42.2 cases per 100 woman-years in the nonoxynol 9 group and 33.5 in the placebo group (rate ratio, 1.3; 95 percent confidence interval, 1.0 to 1.6). The rates of gonorrhea were 33.3 and 31.1 cases per 100 woman-years in the nonoxynol 9 and placebo groups, respectively (rate ratio, 1.1; 95 percent confidence interval, 0.8 to 1.4). The corresponding rates of chlamydia infection in the nonoxynol 9 group and the placebo group were 20.6 and 22.2 cases per 100 woman-years (rate ratio, 0.9; 95 percent confidence interval, 0.7 to 1.3). The women reported that condoms were used during 90 percent of sexual acts.

Conclusions The use of a nonoxynol 9 vaginal film did not reduce the rate of new HIV, gonorrhea, or chlamydia infection in this group of sex workers who used condoms and received treatment for sexually transmitted diseases. (N Engl J Med 1998;339:504-10.)

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NONOXYNOL 9 is a nonionic detergent that has been used as a spermicide since the 1950s. By disrupting the membranes of epithelial cells, bacteria, and viruses, nonoxynol 9 inactivates many sexually transmitted pathogens in vitro, including *Neisseria gonorrhoeae*,^{1,2} *Chlamydia trachomatis*,³⁻⁵ *Haemophilus ducreyi*,⁶ *Treponema pallidum*,¹ *Trichomonas vaginalis*,² and the herpes simplex virus.^{5,7,8} Nonoxynol 9 appears to be moderately effective in vivo as prophylaxis against cervical infection by *N. gonorrhoeae* and *C. trachomatis*⁹⁻¹² and vaginal infection by *T. vaginalis* and the bacteria associated with bacterial vaginosis,¹³ providing a 25 percent reduction in the rate of infection.

Evidence from in vitro studies¹⁴⁻¹⁷ and animal models^{18,19} shows that nonoxynol 9 can inactivate the human immunodeficiency virus (HIV), but three clinical studies^{12,20,21} have had conflicting results. A randomized, controlled trial of the 1000-mg nonoxynol 9 vaginal sponge, conducted among 138 female sex workers in Kenya, was stopped early because of an increase in HIV infection among the users of the sponge (rate ratio, 1.6; 95 percent confidence interval, 0.8 to 2.8).¹² This same study reported an increase in genital lesions and a decrease in cervical gonorrhea. A cohort study conducted among 273 female sex workers in Cameroon reported a lower rate of HIV infection among women who consistently used suppositories containing 100 mg of nonoxynol 9 than among those who used the suppositories less consistently (rate ratio, 0.1; 95 percent confidence interval, 0.1 to 0.6).²⁰ A cohort study conducted among 110 couples in Zambia in which only the man was HIV-positive reported a crude rate ratio for HIV transmission of 0.5 (95 percent confidence interval, 0.1 to 3.8) among women who reported 100 percent use of nonoxynol 9 as compared with those who reported less than perfect use.²¹

We conducted a randomized, controlled trial to determine the effect of a film containing 70 mg of nonoxynol 9, inserted vaginally before intercourse, on the rate of sexually transmitted diseases, including HIV type 1, among women. This study was performed in the context of the current recommen-

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dations for prophylaxis against HIV infection: promotion of condom use by men and treatment of curable sexually transmitted diseases.

METHODS

Study Participants

All participants were HIV-seronegative female sex workers residing in Yaoundé or Douala, Cameroon, who averaged at least four sexual partners per month; were between the ages of 18 and 45 years; were not known to be allergic to latex or nonoxynol 9; were not pregnant or desiring to become pregnant in the next year; and were willing to learn their HIV-test results. We asked each woman to return monthly for follow-up visits for at least one year.

Study Size

We anticipated an incidence of HIV of 10 cases per 100 woman-years in the placebo group after the promotion of condom use, on the basis of the previous cohort study in Cameroon.²⁰ We estimated that 1000 women would need to be enrolled, given our assumptions of a rate ratio of 0.5 for HIV, 90 percent power to detect a 50 percent reduction in the rate of HIV infection, an alpha level of 0.05, a 20 percent loss to follow-up per year, a period of one year to recruit the cohort, and a period of at least one year of follow-up. For the study to have 90 percent power, 88 seroconversions would have to occur.

Study Procedures

Study recruiters invited potential participants to attend a session at the study clinic, during which the staff described the study requirements, conducted the HIV-testing consent process, gave pretest counseling, tested for HIV infection, and asked interested women to return in one month for study enrollment. At the return visit, each woman was given the results of her HIV test and post-test counseling. The HIV-negative women who consented to participate in the study proceeded to the base-line phase. The protocol and consent process were approved by the national ethics committee, the University of Yaoundé School of Medicine board in Cameroon, and an institutional review board at Family Health International; we obtained written informed consent from all the women for the initial determination of HIV serostatus and again one month later at enrollment.

Randomization

Family Health International produced randomization schedules, stratified according to clinic, using a computerized random-number generator to select permuted blocks of eight. The treatment-group assignments were concealed in sequentially numbered, sealed opaque envelopes. The envelopes were opened only after enrollment. The clerk at each clinic gave the assignment envelopes to the interviewer, who made the assignments. This method of randomization prevents bias in randomized, controlled trials.²²

Blinding and Study Products

The study was double-blinded — that is, neither the women nor the study staff, including the biostatisticians from Family Health International, knew which group was using the nonoxynol 9 film. The nonoxynol 9 film contained 28 percent nonoxynol 9 (70 mg), glycerin, and polyvinyl alcohol. The placebo film contained glycerin, polyvinyl alcohol, and less than 2 percent polysorbate 60. The two films were identical in appearance, packaging, and labeling.

We chose film as the vehicle for nonoxynol 9 because it has characteristics that are likely to make it acceptable for widespread use — i.e., it is small (5 cm by 5 cm and paper thin), requires no applicator, is easy to use, dissolves in two to five minutes, and is not messy or affected by heat. The nonoxynol 9 film has been used as a spermicidal product for more than 15 years. We tested

both films for in vitro inactivation of HIV. The nonoxynol 9 film inactivated HIV at a dilution of 0.035 percent but did not inactivate all the virus at 0.0035 percent. We do not know the concentration of nonoxynol 9 achieved in vaginal fluids when film is used during coitus; however, one study has found a concentration of 7 to 11 percent in vaginal fluid after application.²³ The placebo film had no cell toxicity and did not inactivate HIV.

The condoms provided were made of latex, were not lubricated with spermicide, and were 52 mm wide and 180 mm long. We urged all the women to use a film and have their male partners use a condom with each coital act. If a condom could not be used, the women were instructed to use the film alone.

Data Collection

We collected information on demographic characteristics and base-line sexual behavior during the screening visit to the clinic. Information needed to assess the randomization process and potential confounders was collected one month later when the women were enrolled. This information included data on the women's history of sexually transmitted diseases, the frequency of intercourse according to type (oral, anal, or vaginal), condom and film use during vaginal intercourse, antibiotic use, method of contraception, blood transfusions, receipt of injections, and use of other vaginal agents (e.g., douches).

Questions about the women's sexual networks were designed to obtain information about types of sexual partners, such as new clients, regular clients, and nonclients, and about the use of condoms and nonoxynol 9 with these various types of partners. To enhance recall, the women were interviewed monthly. Pictorial coital logs recorded information on each episode of vaginal intercourse, including the type of sexual partner (client or nonclient), whether a condom or a film was used (or both), and whether the condom broke. An interviewer tallied the coital log monthly. The logs served as a counseling tool for condom and film use and indicated whether the use of condoms and film was similar in the two study groups. The logs were not reliable enough to be used to assess compliance with recommendations for the use of film and condoms.

We conducted an examination for genital ulcers, signs of genital irritation, and infections at the time of enrollment and at each monthly follow-up visit. We used colposcopes to examine the vulva, vagina, and cervix at each visit as a means of locating micro-ulcerations. We focused on the areas of the vagina that were exposed to the highest concentrations of nonoxynol 9. We palpated the inguinal lymph nodes, inspected the vulva and perineum for lesions, and inspected the introitus, vagina, and cervix. We placed a swab from the vaginal pool in a test tube with a few drops of normal saline for preparation of a wet mount (saline and potassium hydroxide). We took a specimen from the endocervix for the gonorrhea and chlamydia DNA-probe tests and performed a bimanual pelvic examination.

The PACE 2 assay (Gen-Probe, San Diego, Calif.) was used to test for *N. gonorrhoeae* and *C. trachomatis* (sensitivity, 92 percent; specificity, 98 percent, as compared with culture for both organisms) and provided the information required for a diagnosis of cervical infection. A supplemental test to detect nonspecific signal was used to confirm positive results. The manufacturer of the PACE assay states that spermicide does not interfere with the assay.

We determined HIV serologic status by the sequential method (in which positive status requires two positive enzyme immunoassays followed by positive Western blot analysis).

Outcome Measures

The primary objectives of this clinical trial were to determine the effect of the nonoxynol 9 vaginal film on the rate of HIV infection, to measure its effect on the rate of genital ulcers, and to measure its effect on the rate of cervical gonorrhea and chlamydia infection. The measures used for determining the occurrence of infection were the crude incidence-density rates and the

Kaplan–Meier estimates of the cumulative probability of the detection of HIV and other sexually transmitted diseases. All measures of effectiveness considered the time to the first evidence of infection.

Safety

The main issues of safety associated with the use of nonoxynol 9 are whether it increases the risk of HIV infection and, secondarily, whether it increases the incidence of breaks in the genital epithelium. The measures for determining the incidence of breaks in the genital epithelium were the crude incidence-density rates and the cumulative probability of lesions on the vulva, vagina, cervix, or any of the three sites.

Statistical Analysis

We used prevalence ratios to compare the base-line characteristics of the two groups. We used the log-rank statistic to test differences between the groups in Kaplan–Meier estimates of survival for the variables of time to a first event and study discontinuation. We calculated rate ratios using Cox proportional-hazards regression models, with the clinic site as a covariate. We performed all analyses on an intention-to-treat basis.

The population included in the primary analysis with respect to HIV consisted of all the HIV-negative women enrolled in the study who were randomly assigned to a treatment group and who had at least one additional HIV test. To be included in the gonorrhea, chlamydia, or genital-lesion analysis, a woman had to have been in the population included in the HIV primary analysis, not to have had the disease being analyzed at the time of her initial physical examination, and to have had a follow-up examination.

Interim Analysis

One interim analysis was conducted, and the results were presented to an independent data and safety monitoring board organized by the National Institute of Allergy and Infectious Diseases after one third of the total expected events had occurred. A two-sided log-rank test gave a critical value of 1.76 with a P value of 0.54. The Lan–DeMets²⁴ spending function was used to determine that 0.004 of the type I error of 0.05 was spent on the interim analysis. The board recommended that the study continue.

RESULTS

Randomization began in March 1994, and the last follow-up visits were conducted in December 1996. Of the 2290 women initially tested for HIV infection and interviewed, 1317 enrolled in the trial and received nonoxynol 9 or placebo film. Of the women not enrolled, 40 percent were HIV-positive, 51 percent did not return after screening, and 9 percent were excluded for other reasons. Among the randomized women, 25 were not clearly HIV-negative at enrollment, including 8 who were seropositive at screening, 15 who had seroconversion in the month between screening and enrollment, 1 who was not screened but was seropositive at enrollment, and 1 who was never tested. Of the 1292 women eligible for the study, 69 in the placebo group and 53 in the nonoxynol 9 group never returned for a follow-up HIV test. The remaining 1170 women (575 in the placebo group and 595 in the nonoxynol 9 group), who were HIV-negative at screening and enrollment and had at least one HIV test after enrollment, constituted the population for the primary analysis with respect to HIV.

TABLE 1. SELECTED BASE-LINE CHARACTERISTICS USED TO ASSESS RANDOMIZATION IN THE PRIMARY-ANALYSIS POPULATION.*

CHARACTERISTIC	PLACEBO GROUP (N=575)	NONOXYNOL 9 GROUP (N=595)
Age (yr)	25.5±5.7	26.0±5.6
Able to read (%)	99	99
No. of living children	1.4±1.5	1.4±1.4
Contraceptive method (%)		
None	87	86
Hormonal	5	5
Other	8	8
Use of douching (%)	25	27
Use of another vaginal substance (%)	43	47
Sexually transmitted disease in past 3 mo (%)	8	10
Years as sex worker	3.7±3.5	4.5±4.1
Use of condom with last client (%)	48	49
Vulvar ulcers present (%)	15	15
Current gonorrhea infection (%)	10	13
Current chlamydia infection (%)	12	11

*Plus–minus values are means ±SD.

Characteristics of the Study Participants at Base Line

Base-line characteristics were similar in the two groups (Table 1). Other variables that were similar in the two groups included marital status (95 percent were unmarried in the nonoxynol 9 group, and 97 percent in the placebo group), whether the woman was living with a man (2 percent and 1 percent), use of medicine in the previous 30 days (12 percent and 11 percent), whether the woman ever practiced oral sex (24 and 27 percent) or anal sex (16 percent and 17 percent), whether the woman's male partners used a condom, and the numbers and types of sexual partners the woman had.

The prevalence of sexually transmitted diseases at base line was similar in the nonoxynol 9 and placebo groups, and the percentage of women with genital ulcers at the time of physical examination in the two groups was similar. Eight percent of the women in the placebo group and 10 percent of those in the nonoxynol 9 group reported that they had contracted a sexually transmitted disease in the previous three months. No evidence suggests that the women excluded from the primary-analysis population or the women who withdrew from the study early were significantly different from those included in the HIV primary-analysis population.

Disposition of Study Participants

There were no differences according to treatment group in the number of women who completed follow-up or withdrew from the study. Withdrawal curves for the two treatment groups were similar (P=0.39), with about 73 percent of each group

continuing in the study at 1 year and with a mean follow-up period of approximately 14 months. The number of women who withdrew from the study and the reasons for withdrawal from the study were similar in the two treatment groups (Fig. 1). There were three deaths, which were not related to study participation — one in the placebo group and two in the nonoxynol 9 group.

Prospectively Measured Potential Confounding Factors

The women in the two groups were involved in about the same total number of coital acts during the course of the study (Table 2). Condom use was reported for 90 percent of vaginal sexual acts and was slightly less common in the nonoxynol 9 group than in the placebo group. Condom and film use varied according to type of sexual partner. Film use without a condom was more likely to occur with nonclients (16 percent) than with clients (3 percent). The use of neither condoms nor film was more likely to occur with nonclients (6 percent) than with clients (1 percent).

Nonvaginal Sexual Acts

The prevalence of oral and anal sex was similar in the two treatment groups. Eleven percent of the

women in the placebo group reported ever having had oral sex, as compared with 10 percent of the women in the nonoxynol 9 group (one seroconversion was detected in each group among the women who had had oral sex). Six percent of the women in the placebo group and 5 percent of those in the nonoxynol 9 group reported ever having had anal sex (two seroconversions were detected in each group among these women). The number of seroconversions among the women reporting nonvaginal sex was small, as compared with the total number of seroconversions (6 of 94).

Effect on HIV, Gonorrhea, and Chlamydia

There were a total of 94 HIV seroconversions — 48 in the nonoxynol 9 group and 46 in the placebo group. The event rates in the two groups were almost identical (Table 3). The curves for HIV seroconversion for the two groups showed no divergence ($P=0.85$). Similar results were noted for gonorrhea and chlamydia, with virtually identical event rates in the two groups.

Effect on Genital Lesions

The women in the nonoxynol 9 group were more likely to have genital lesions than those in the placebo

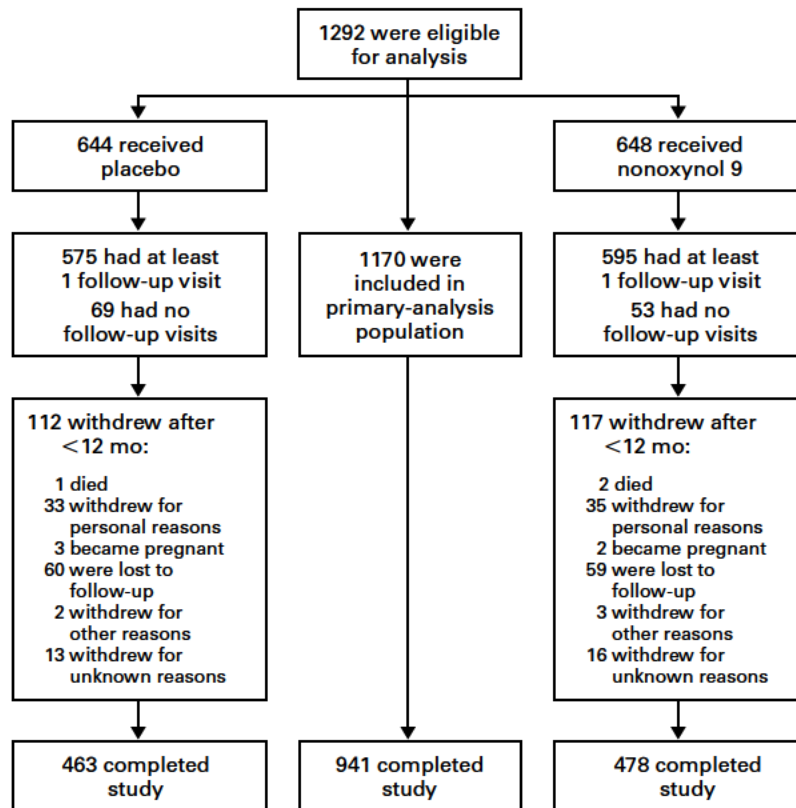


Figure 1. Progress of Women through the Study and Reasons for Discontinuation.

TABLE 2. REPORTED USE OF CONDOMS AND FILMS FOR VAGINAL SEXUAL ACTS DURING THE STUDY, ACCORDING TO TYPE OF SEXUAL PARTNER.

VARIABLE	PLACEBO GROUP		NONOXYNOL 9 GROUP	
	CLIENT	NONCLIENT	CLIENT	NONCLIENT
	number (percent)			
Use of film only	3,465 (4)	9,270 (18)	2,792 (3)	7,446 (15)
Use of condom only	11,530 (12)	6,891 (13)	9,967 (10)	5,808 (11)
Use of film and condom	77,830 (83)	33,442 (63)	83,146 (86)	35,305 (69)
Use of neither film nor condom	1,267 (1)	3,247 (6)	956 (1)	2,576 (5)
Total no. of coital acts	94,092	52,850	96,861	51,135

TABLE 3. RATES OF HIV, GONORRHEA, AND CHLAMYDIA INFECTION IN THE PLACEBO AND NONOXYNOL 9 GROUPS.

INFECTION AND TREATMENT GROUP	NO. OF WOMEN	WOMAN-YEARS	NO. OF EVENTS	EVENT RATE*	RATE RATIO (95% CI)†
HIV					
Placebo	575	698	46	6.6	
Nonoxynol 9	595	720	48	6.7	1.0 (0.7–1.5)
Gonorrhea					
Placebo	435	357	111	31.1	
Nonoxynol 9	441	342	114	33.3	1.1 (0.8–1.4)
Chlamydia					
Placebo	420	365	81	22.2	
Nonoxynol 9	451	384	79	20.6	0.9 (0.7–1.3)

*The event rate is the rate per 100 woman-years.

†The placebo group served as the reference category. CI denotes confidence interval.

bo group, although this difference was not significant (Table 4). Most lesions were on the vulva and included excoriations, fissures, and ulcers. Genital lesions did not predict HIV seroconversion in this study. The HIV-infection rate per 100 woman-years in the placebo group was 5.9 among those with lesions and 5.0 among those without lesions. The HIV-infection rate for women in the nonoxynol 9 group was 5.0 among those with lesions and 5.3 among those without lesions.

Blinding

We asked 126 staff members their opinions of which film was the placebo. Eighteen percent thought film A (the placebo) was the placebo, 13 percent thought film B (nonoxynol 9) was the placebo, and 69 percent had no opinion about which film was the placebo. Of the 68 peer educators (the staff members most likely to reflect the opinion of the participants), 16 percent thought film A was the placebo, 13 percent thought film B was the placebo, and 71 percent had no opinion.

DISCUSSION

Nonoxynol 9 film did not give the women in this study any additional protection against infection with HIV, gonorrhea, or chlamydia beyond that provided by condoms and treatment for sexually transmitted diseases. Our instructions to the women were that the vaginal film should be used in addition to condoms for greater protection against sexually transmitted diseases; if a condom could not be used, the film should be used alone.²⁵

Our results with respect to HIV infection are consistent with the findings of the only other randomized, controlled trial.¹² However, we did not find that nonoxynol 9 provided protection against gonorrhea, as found in the earlier study. The previous study used the ratio of the number of events to the number of visits for each treatment group as the measure of effect. The number of events and person-years were not reported, so we cannot make a direct comparison with our results. This difference in outcome measures could account for some of the difference in the two findings regarding gonorrhea. The nonoxynol 9 sponge used in the earlier study may also act as a physical barrier that prevents *N. gonorrhoeae* from infecting the endocervix.

As expected, there was an increase in genital ulcers in the nonoxynol 9 group. As was the case in the sponge study,¹² the majority of lesions were external rather than internal; the highest concentration of nonoxynol 9 is internal. However, in our study, the women who had genital ulcers did not have a higher rate of HIV infection, and there was no difference in the rate of infection between the women who had genital ulcers and used nonoxynol 9 and those who had genital ulcers and used placebo.

There are many possible reasons for the fact that the nonoxynol 9 film did not prevent sexually transmitted diseases. The film may not be the optimal formulation; nonoxynol 9 may not be an adequate microbicide; the women may not have used the product correctly or as frequently as necessary (every time as opposed to most of the time); or condoms may have

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