

Roddy et al. (Ref. 22) followed up with a study in 175 women to evaluate effects of dosing on vaginal and cervical irritation using a vaginal suppository with 150 mg of nonoxynol 9 at various dosing frequencies for 2 weeks. The women agreed to refrain from sexual intercourse and douching during the study period. Clinical signs of genital irritation included erythema and epithelial disruption. Erythema in the vagina was the major clinical sign noted. Epithelial disruption was defined as a break in the epithelium lining of the vulva, vagina, or cervix. Women with vulvar irritation also had vaginal and cervical irritation. The symptoms that were attributed to genital irritation included dysuria, genital itching, and burning. The irritation from using nonoxynol 9 every other day was no different than using the placebo. Use of nonoxynol 9 once or twice a day increased the rate of epithelial disruption. Use of nonoxynol 9 four times a day increased the rate of epithelial disruption about five times that of the placebo. However, the authors noted that having symptoms was not predictive of clinical signs and women with obvious clinical signs did not always report symptoms. The authors stated that there is no conclusive evidence of a dose response, but the data suggest a stepwise increase in signs of irritation with an increasing number of doses per day.

Van Damme et al. (Ref. 23) conducted a multicenter, randomized, double-blind, controlled trial with three groups (52.5-mg nonoxynol 9 gel, placebo gel, and a no-treatment control), examining the use of a lower dose of nonoxynol 9 in 534 women at low risk of HIV infection. The subjects were healthy women with no evidence of STDs and no clinical or colposcopic abnormalities. The subjects were to apply the study products once daily at the same time each day for 14 days and were allowed to have sexual intercourse. Incidences of genital symptoms such as vaginal discharge, erythema, lesions, and petechial hemorrhage (the most frequent abnormality reported) were significantly greater in the group using the nonoxynol 9 gel than the other groups. Women in the group using the nonoxynol 9 gel were significantly more likely to develop a lesion than those in either the placebo or no-treatment group. The authors noted that the clinical significance is unclear with regard to the excess incidence of petechial hemorrhage in the nonoxynol 9 group and of other types of lesions that were not associated with epithelial

disruption. The authors stated that, in theory, it is possible that any type of genital lesion may increase a woman's risk of becoming infected with HIV, especially if it serves as a focus for the recruitment of HIV-infectable inflammatory cells. However, they stated that whether this is of significance will need to be ascertained by large-scale intervention trials in populations at high risk of HIV infection.

The incidence of ulceration, abrasion, and STD or other genital infections was low for all three treatment groups. The authors suggested that these findings were the result of the once a day application of the nonoxynol 9 and that at this frequency of use the nonoxynol 9 gel can be considered safe. The authors also stated that having established the safety of a single application, it was important to evaluate the effects of multiple doses. They noted that a study, which was not cited, involving the application of the same nonoxynol 9 gel four times daily had recently been completed.

Kreiss et al. (Ref. 24) studied 138 HIV seronegative female sex workers at very high risk of HIV seroconversion who were randomly assigned to a nonoxynol 9 (1,000 mg) containing vaginal sponge or placebo (glycerin vaginal suppository containing mineral oil, subsequently a water-based vaginal cream was used). Subjects were instructed to insert a sponge before the first sex partner each day, replace the sponge after every two to three partners, and remove the sponge 6 hours after the last sex partner. All subjects were intensively counseled and urged to have each sexual partner use condoms. Women in the study used the sponge an average of 14 times per week. Women were asked to return for followup at monthly intervals or more frequently if needed. The duration range for followups was between 1 and 46 months. The mean (average) duration period of followup was 14 months for the nonoxynol 9 group and 17 months for the placebo group. Spermicide-attributed complaints, mostly vulvar irritation, burning, and ulceration, were reported in 47 percent of the nonoxynol 9 users and 7 percent of the placebo users. There was a higher seroconversion (i.e., testing showing conversion from HIV negative to HIV positive) in women using the nonoxynol 9 containing sponge than the placebo product. Because of concern regarding the adverse local effects of the nonoxynol 9 (1,000 mg) containing sponge, and its potential for increasing the risk of HIV transmission, rather than being protective, the study was prematurely terminated.

Martin et al. (Ref. 25) studied the use of a nonoxynol 9 gel (52.5 mg) in 52 HIV seronegative female sex workers. Subjects had to be free of STDs and any evidence of genital epithelial disruption, and had to report 100 percent compliance with condom use. Subjects were randomized to the nonoxynol 9 gel or to a placebo group and used one applicatorful per day. After a 14-day washout period, the subjects used the other treatment for 14 days. Subjects were evaluated by a questionnaire and physical examinations, including colposcopy. The authors concluded that daily application of the 52.5-mg nonoxynol 9 gel was safe, but they made no extrapolations to more frequent use. However, the authors acknowledged the shortness of the duration of use and that the power of this study to detect a small increase in epithelial toxicity might be limited.

Roddy et al. (Ref. 26) studied the use of a nonoxynol 9 containing film as a vaginal microbicide in 1,295 HIV-negative female sex workers. In a double-blind, placebo-controlled study, the subjects were instructed to have their male sexual partners use latex condoms and were randomly assigned to use either the nonoxynol 9 film or a placebo film. At monthly followup visits, the women were examined with a colposcope for genital lesions and were tested for gonorrhea, chlamydia, and HIV infection. Seventy-three percent of the women remained in the study for 12 months with a mean followup period of approximately 14 months. The authors concluded that the use of the nonoxynol 9 vaginal film did not reduce the rate of new HIV, gonorrhea, or chlamydia infection even in those that used latex condoms and who received treatment for STDs.

Van Damme et al. (Ref. 27) looked at more frequent use of the nonoxynol 9 (52.5 mg) gel among 320 HIV-seronegative female sex workers who did not have clinical STDs, genital ulcers, or abrasions, did not use illicit drugs, and participated in a 100 percent condom-use program. The study was designed as a randomized, placebo-controlled, triple-blind trial to assess the effect of nonoxynol 9 gel in the prevention of HIV/STD infection. Subjects were instructed to apply the test product or the placebo (gel vehicle without the nonoxynol 9) and to have their male sexual partners use a condom for every sex act. There were major differences in condom use between the study centers. The mean number of applicators of the daily gel use was 1.2 and 1.3, respectively, in the treatment and placebo groups. Colposcopy