ACCEPTABILITY OF A VAGINAL MICROBICIDE AMONG FEMALE SEX WORKERS

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Objectives. A short study was undertaken to assess the acceptability and short-term safety of a vaginal microbicide (COL-1492) and its compatibility with the preference for dry sex among sex workers at truck stops in KwaZulu-Natal.

Design. A randomised double-blind placebo-controlled trial was conducted from March to July 1996.

Setting. Truckstops in KwaZulu-Natal, South Africa.

Participants. Twenty sex workers. The participants were assigned to either COL-1492 (which contains 52.5 mg of nonoxynol 9) or a placebo. The first month of use was followed by a 1-month washout period; thereafter the women who had used the COL-1492 used the placebo (and vice versa) during the third month. Baseline and fortnightly assessment included microbiology and serology for sexually transmitted diseases, questionnaires to assess acceptability of COL-1492, and a clinical examination by colposcopy.

Outcome measures. Acceptability of the product/placebo and short-term safety of the product.

Results and conclusion. Our study revealed that while on COL-1492, 19 of the 20 women found the product to be entirely satisfactory. On colposcopy, similar lesions were found in the women who were using COL-1492 and those using placebo. This study has shown that COL-1492 was found to be acceptable by sex workers. COL-1492 was not associated with more colposcopic changes in the vagina and cervix compared with placebo. It was concluded that conditions are conducive within this cohort of sex workers for a COL-1492 efficacy trial.

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With the expanding AIDS epidemic worldwide it has become increasingly important to develop and provide a wider range of contraceptive methods that will also protect against sexually transmitted diseases (STDs). Recent developments have focused on vaginal microbicides, which have the advantage of being female-controlled and have been shown to provide significant protection against STD.[1,2] At this time, the most intensively studied vaginal microbicide is nonoxynol 9 (N9), a non-ionic detergent that has been used as spermicide for more than 30 years. It acts by disrupting cell membranes, and is active *in vitro* against *Neisseria gonorrhoeae, Chlamydia trachomatis, Trichomonas vaginalis,* and herpes simplex virus.[3,4] It has also been shown to cause irritation of the epithelial cells. Documented side-effects include itching, although serious adverse events such as teratogenicity or carcinogenicity have not been observed.[4]

Studies assessing the protective effect of the vaginal application of N9 on HIV infection have been inconsistent. In Zambia a study conducted among discordant couples[5] reported a decreased incidence of HIV among women using N9 vaginal film (70 mg). Zekeng *et al.*[6] reported a decrease in the rate of HIV seroconversion among sex workers using N9 (70 mg) in Cameroon. Both studies were neither controlled nor randomised. Kreiss *et al.*[7] reported an increase in seroconversion in an N9 group using a high dose (1 000 mg) in a vaginal sponge. Although the study[7] was randomised, there was a high proportion of women with ulceration on the external genitalia in the N9 group at admission.

COL-1492 (Advantage 24) is a vaginal gel containing 52.5 mg of N9 in a neatly developed bio-adhesive carrier. Prior to participation in a large multicentre efficacy trial of the vaginal microbicide COL-1492, a short study of the acceptability of the product was undertaken. This was done in order to address a concern that a product that causes wetness in the vagina may interfere with the local preference for 'dry sex' reported among South African sex workers.[8] The safety of the product, as assessed by colposcopy, was also studied.

METHODS

Twenty female sex workers from truckstops in the KwaZulu-Natal midlands with a median age of 27 years (range 19 - 44 years) were approached to participate in the study. This study population comprised a small community of women selling beers and sex to truck drivers and local men at a major truckstop almost midway between Johannesburg and Durban. All sex workers approached were willing to participate in the study. Ethical approval was granted by the ethical review board of the University of Natal Medical School, Durban.

Those women who were under the legal age of 18, who had fewer than 5 partners per week, who wished to become pregnant, who were allergic to latex or who were on long-term

treatment for a defined disease (e.g. tuberculosis), were excluded from the study. As this was an acceptability study, HIV seropositivity was not an exclusion criterion. Day-long workshops were held during which the women were given pre-test counselling, and issues relating to AIDS, HIV and STD infection were discussed. The research team emphasised the need for condom use. Post-test counselling was provided and condoms were distributed.

Written informed consent was obtained from each participant. Women were reimbursed for transportation, given a free meal and free medical examination, and treated for STDs during the study period.

A randomised double-blind placebo-controlled cross-over trial was conducted over a period of 12 weeks from April to July 1996.

Twenty eligible sex workers were randomised and assigned to one of the two arms of the trial. During the first 4 weeks the participants used the product to which they were assigned (COL-1492 or placebo). During the second 4 weeks the participants did not use any product; this constituted the wash-out period. During the final 4 weeks, the participants who had used the COL-1492 in the first 4 weeks now used the placebo, and those who had used the placebo now used COL-1492.

Participants were enrolled in the study only when clinical examination revealed no abnormal vaginal or cervical discharge, ulceration or other abnormality. During each visit (every 2 weeks) a behavioural and an acceptability questionnaire was administered that included information on intravaginal insertion practices. In addition, short-term safety of the product was assessed by examination of the lower genital tract by colposcopy, as per the World Health Organisation *Manual for the Standardisation of Colposcopy.*[9]

A gynaecological examination, including a speculum examination, was performed. The amount, type and consistency of the vaginal secretions was assessed. Vaginal secretions were obtained for Gram stain smears and the amine test. Vaginal pH estimations were made using a narrow range pH paper, while the remaining secretions were mixed with saline for wet smear microscopy and inoculated into modified Diamond's medium for culture of *T. vaginalis* and *Candida albicans.*

Wet preparations were examined at the patient's side for yeasts and bacteria and motile trichomonads. All bacterial and yeast isolates were identified by conventional laboratory methods. A diagnosis of bacterial vaginosis was based on raised vaginal pH (> 4.5), presence of amines and presence of 'clue' cells.

One endocervical swab was taken for inoculation into modified New York City medium for isolation of *N. gonorrhoeae*, and another was rolled onto a glass slide for direct immunofluorescent staining for the detection of *C. trachomatis* antigens.

Venous blood was collected. Syphilis serology was performed using the rapid plasma reagin test (RPR) and the specific *Treponema pallidum* haemagglutination assay (TPHA). A subject was regarded as having active syphilis if the TPHA was reactive and the RPR was reactive at a titre 1 in 8 or greater.

Antibody to human immunodeficiency virus (HIV) was detected by Abbott recombinant HIV-1/HIV-2 enzyme-linked immunosorbent assay (ELISA). The second ELISA was the Vironostika HIV Uniform II micro-ELISA system (Omnimed). All evaluations were performed at every follow-up visit.

During the study period participants were requested to keep accurate coital log charts measuring frequency of coitus, application of the trial product and condom use. In order to monitor compliance with the study products (placebo and COL-1492), women were requested to return all used and unused applicators. The number of used applicators was compared with the number of coital acts protected by the products.

Participants were told to insert the product after routine cleansing in the morning. A second dose of the product was applied only if the women douched in between clients.

Statistical analysis

The number of participants presenting with colposcopic lesions in the placebo and COL-1492 groups was compared using McNemar's chi-square test.

RESULTS

The sociodemographic features of all 20 participants were evaluated. The mean age of participants was 27 years (range 18 - 40 years). They had spent a mean of 65 months as sex workers (range 3 months - 20 years). The majority of participants had at least 4 sexual partners a day and 17 per week. Injectable contraception was commonly used (38.8%) and very few women used oral contraception (19.2%). Baseline investigation revealed that the group as a whole had an average of 442 coital acts per week and that the rate of condom use was less than 25%.

Nineteen of the 20 women (95%) indicated approval for COL-1492. Some of the reasons given for acceptability of the product were 'protection from STDs' and that 'clients do not know that the gel is inside'. When asked about any discomfort they experienced, 2 participants complained of itching. Increased discharge was experienced by 1 participant in each of the COL-1492 and placebo groups. Only 1 participant felt that the vagina was too tight after application of the product during the first 2 weeks of follow-up. More than a quarter of the participants in the placebo and COL-1492 groups informed their steady partner of the gel. Only 1 partner in both groups complained, although the reason for dissatisfaction was not given. Overall satisfaction was high among all participants

Table I. Acceptability (20 subjects)

	COL-1492		Placebo	
	2 weeks	4 weeks	2 weeks	4 weeks
Difficulty inserting	3	0	0	0
Discomfort				
Itching	2	2	1	1
Discharge	2	0	1	0
Vagina too tight	2	0	0	0
Partner informed	5	5	6	7
Partner dissatisfied	2	0	0	2
Gel leaks				
While inserting	3	2	2	1
Before intercourse	1	2	2	4
After intercourse	3	2	2	1
Lubrication				
Too little	0	1	0	0
Appropriate	18	17	19	19
Too much	1	1	1	1
Satisfied	20	19	19	19

irrespective of placebo or product use. Lubrication with the gel was found to be appropriate by a majority of the participants (Table I).

Baseline data indicated that a total of 12 participants (60%) were HIV-positive. Of the 20 participants, 7 (35%) were infected with *T. vaginalis*, 11 (56%) had syphilis, 4 (20%) were infected with *N. gonorrhoeae* and 5 (25%) were positive for *C. trachomatis*. Bacterial vaginosis and *C. albicans* was detected in 17 (85%) and 5 (25%) of the participants, respectively.

The average number of coital acts in the placebo and COL-1492 groups over 4 weeks was 551 and 419, respectively. The number of coital acts in both the placebo and COL-1492 arms protected by the drug and condom, respectively, is shown in Table II.

The short-term safety of the product, assessed by colposcopy, revealed lesions of ulceration, abrasions and petechial haemorrhage in both the placebo and COL-1492 groups. During the 4 weeks of follow-up while on COL-1492, the colposcopic lesions included 5% ulcers, 10% petechial haemorrhage, 5% oedema and 10% abrasions. During the 4 weeks of placebo use, the colposcopic lesions included 20% ulcers, 5% oedema, and 5% petechial haemorrhage. No significant differences were noted between the two groups with regard to number of lesions observed.

Table II. Product/placebo compliance in the two study groups

	Placebo	COL-1492
Average No. of coital acts/4 weeks	551	419
Condom + product	382 (69%)*	299 (71%)*
Condom only	34 (6%)*	45 (11%)*
Product only	110 (20%)*	69.5 (16%)*
Nothing	26	4

* Protection offered by condom/product.

Other lesions observed on colposcopy were evidence of human papillomavirus (HPV) infection in 6 women, 5 of whom also had evidence of cervical intraepithelial neoplasia (CIN I).

DISCUSSION

This study, in spite of its small sample size, shows that sex workers in KwaZulu-Natal accept COL-1492 and are willing to use the product on a regular basis. When available, the gels were used by 87% of the women, most commonly in conjunction with condoms. The product did not cause lesions that were significantly different from those observed in the placebo group.

The short-term safety of COL-1492 as assessed by colposcopy revealed no difference in the rates of lesions in the two groups. A previous study of the same product (52.5 mg N9) by Stevens *et al.* (reported at the International Conference on AIDS held in Vancouver on 7 - 12 July 1996 — abstract 233) conducted in a much larger group of 60 women in Mombasa revealed no differences in the incidence of epithelial disruption between the placebo and the N9 group. In addition, as in the present study, the authors reported other signs of epithelial disruption, e.g. erythema, petechiae, ecchymosis, etc. that were not different in the N9 and placebo groups. Although the above study by Stevens *et al.* involved a once-daily dose of the N9 formulation, the results are similar to those reported here with a multiple dose of N9 per day. A recent study[10] on the safety of a nonoxynol-9 vaginal gel in Kenyan sex workers for a period of 14 days revealed no genital toxicity of vaginal gel containing 52.5 mg of nonoxynol-9.

The use of vaginally inserted substances to create a 'dry and tight' vagina was common among all the participants. The sex workers participating in this study used herbs and chemicals that have a desiccant effect on the vaginal mucosa.[11] The small volume of COL-1492 delivery (1.5 ml) and the vehicle polymer that is not entirely water-soluble may explain the sensation of 'dryness' among users. A study conducted by Brown *et al.*[11] in Zaire revealed that some substances intended to cause a 'tight and dry' vagina caused an irritation of the vaginal and cervical mucosa. Such irritation may facilitate the transmission of pathogenic micro-organisms.[12] In their Zambian study Hira *et al.*[5] reported that women who practise dry sex were more likely to become HIV-seropositive than women who do not. However, the author did not report on insertion of any intravaginal substances. Because these practices are so widespread in Africa, it is imperative that HIV and STD prevention programmes take them fully into account.

The high observed prevalence of HIV/STD co-infection is troublesome in light of infrequent barrier use, although participants did report a twofold increase in the rate of condom use from 25% to 50% during the study period. Nevertheless, the large number of clients served each week and the continuing low level of condom use contribute to this large burden of sexually transmitted infections.

Overall, the findings from this acceptability study reveal that the product was acceptable and did not compromise the traditional practices of the women. Moreover, an effective microbicide that does not moisten the vagina to a great extent may act as a substitute for other harmful traditional practices. The microbicide appears to be associated with observable colposcopic changes, but not more so than with placebo use. Finally, it is concluded that conditions within this cohort were conducive for a large phase III efficacy trial.

In sum, the sexual behaviours and prevalence of STDs among this cohort, along with the demonstrated safety and acceptability of COL-1492, indicate the appropriateness of a large phase III efficacy trial.

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