Safety of multiple daily applications of COL-1492, a nonoxynol-9 vaginal gel, among female sex workers

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Rationale: COL-1492 is a nonoxynol-9 (N-9)-containing vaginal gel and may be a potential microbicide. As part of an effectiveness trial, an initial toxicity study was conducted.

Objectives: The main objective of the reported study was the assessment of the toxicity of a 52.5 mg N-9 gel, COL-1492, when used a number of times each day by female sex workers.

Methods: This was a randomized, placebo-controlled triple-blinded trial among female sex workers. The participants were asked to use the product for each vaginal sexual act. At each monthly visit a gynaecological examination with sexually transmitted disease sampling and colposcopy was performed. Venous blood was drawn for syphilis and HIV serology. All women received intensive counselling on condom use. Male condoms and sexually transmitted disease treatment were given free of charge.

Results: Only blinded results on the colposcopic examinations are reported. The incidence of lesions with or without an epithelial disruption was low: 0.06 and 0.29, respectively, per 100 woman–days in group A; 0.09 and 0.26 respectively per 100 woman–days in group B. There was no significant difference between the two arms.

Conclusion: The multiple daily use of COL-1492 by female sex workers did not show an increase of local toxicity over that of a placebo. Colposcopy was discontinued in the autumn of 1997 in accordance with a Data Safety Monitoring Board decision. In the currently ongoing effectiveness trial the assessment of the product's toxicity continues to be monitored by simple visual examination.

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Introduction

For several years nonoxynol-9 (N-9) has received a lot of attention as a potential microbicide. It acts by disrupting the membranes of cells, viruses and bacteria. N-9 has an *in vitro* activity against HIV and other sexually transmitted disease (STD) pathogens [1–6]. Although most *in vivo* data show a protective effect against *Neisseria gonorrhoeae* and *Chlamydia trachomatis* [7–11], the data on *in vivo* anti-HIV effectiveness are

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not conclusive. Two cohort studies showed a protective effect of N-9 among consistent users [12,13]. One randomized controlled trial among female sex workers in Kenya showed an increased HIV incidence among women using a 1000 mg N-9 sponge compared with placebo users [14]. However this study has been criticized for methodological reasons [15]. A randomized controlled trial with a vaginal film containing 70 mg N-9 among Cameroonian female sex workers showed no effect, either harmful or beneficial, on HIV, *N. gonorrhoeae* or *C. trachomatis* [16]. Despite these results, an effectiveness trial with COL-1492, using a 52.5 mg N-9-containing vaginal gel, is continuing with the justification that a different formulation may give a better availability of N-9 in the vagina and that a lower N-9 concentration may be associatied with less toxicity. The trial started with an intensive toxicity monitoring phase using colposcopy. The results of these colposopic evaluations are reported here.

Methods

The reported study is part of a larger randomized, placebo-controlled, triple-blind trial among female sex workers to assess the product's effect in the prevention of heterosexual vaginal HIV infection and other STDs. Participants were recruited through the Venereal Disease Unit of the Ministry of Public Health, Bangkok, Thailand; the Prince of Songkla University, Hat Yai, Thailand; the Centre for Epidemiological Research (CERSA), Durban, South Africa and the Reproductive Health Research Unit, Johannesburg, South Africa. The technical coordination was carried out by the Institute of Tropical Medicine, Antwerp, Belgium. The main trial sponsor was UNAIDS, Geneva, Switzerland. The study was approved by all local and national ethical review boards.

HIV-seronegative female sex workers who volunteered could be enrolled if they had at least five partners per week; were participating in a 100% condom-use programme; were above the local legal adult age and were willing and able to comply with the study protocol. They were excluded if they had a genital ulcer, abrasion or clinical STD; required any long-term treatment; used intravenous drugs, crack or cocaine; were pregnant or wished to become pregnant; were allergic to latex or nonoxynol-9 or were using a vaginal spermicide. A separate randomization was carried out for each centre.

COL-1492 gel (marketed in the United States as the spermicidal gel Advantage S®, Columbia Laboratories, New York, New York, USA) contains 3.5% (52.5 mg) nonoxynol-9; other constituents include polycarbophil, a polymer with bio-adhesive properties. The placebo gel contained the same ingredients with the exception of nonoxynol-9. Both were packed in single-dose, disposable plastic applicators designed to deliver 1.5 g gel. COL-1492 and the placebo were provided by Columbia Laboratories (Paris, France).

At each visit a gynaecological examination with STD sampling and a colposcopic evaluation were carried out. Blood was drawn for HIV and syphilis serology. Participants were counselled on HIV testing and safe sex. At screening concise information on the study was given. Oral informed consent for the screening procedures was obtained. Eligible women were enrolled within 28 days after their screening. At the enrolment visit comprehensive information was given and written informed consent obtained. Whenever an STD was diagnosed, treatment was given free of charge. Women received the required quantity of study product and male condoms. They were asked to use the male condom for every sexual act and to apply the gel for every vaginal act if they had cleaned their vagina after the last intercourse.

The main outcomes of the reported sub-study were lesions revealed by colposcopy performed according to the modified WHO manual on colposcopy (i.e. no acetic acid, iodine or green filter were used) [17].

To have an 80% chance of detecting a difference of 15% in incidence of colposcopic findings between the two groups, a sample size of 150 subjects was needed ($\alpha = 0.05$, one-sided), or 75 subjects in each treatment group. An intention-to-treat analysis was performed on data of women with at least one colposcopic examination. The analysis was focused on the first five visits. For each of these visits the sample size was sufficient. A preliminary investigation to study the relationship between presence of a lesion and study drug was done by construction of 2×2 tables for each of these five visits. In order to control for confounding, logistic regression was performed comparing the treatment groups with respect to the presence of colposcopic lesions at these visits. Finally, a Cox's proportional hazards model was used to compare the incidence of lesions in each treatment group. A *P*-value of 0.05 was regarded as statistically significant.

Only the blinded results on colposcopy will be presented, because the other outcomes (gynaecological signs, visual pelvic examination, STDs and acceptability) are part of the phase III endpoints.

Results

Study population

A total of 320 women had at least one colposcopic evaluation: 158 in group A, 162 in group B. At

baseline all characteristics were similar in both arms as summarized in Table 1. Women in Hat Yai had on average fewer clients (mean of 1.6) than women in the other centres. There was a major difference between the centres with regard to condom use. In Bangkok all women reported more than 75% condom use, in Durban 63% used condoms for less than 25% of their sexual acts and 91% for less than 50%, whereas in Hat Yai and Johannesburg almost all women (98 and 91% respectively) used condoms for more than half of their sexual acts.

The mean daily gel use was 1.2 (range, 0–9.9) and 1.3 applicators (range, 0–5.9) in groups A and B respectively.

Colposcopy results

At baseline around 10% of participants in both groups had an abnormality on colposcopy. These women were excluded from the survival analysis.

During product use few lesions as described in the WHO manual were observed. In group A five ulcers occurred in the vagina and on the external genitalia. In group B seven ulcers were diagnosed. All ulcerations had disappeared at the next visit. Abrasions were diagnosed on the cervix and the external genitalia. These had also healed at the next visit. In lesions without epithelial disruption, erythema occurred most frequently and was mostly observed on the cervix. In logistic regression, controlling for centre, there was no difference at any visit (up to week 12) between the treatment groups for the probability of having a lesion.

The incidence of colposcopic lesions was low with no difference between group A and B (Table 2), and this for lesions with or without epithelial disruption. In both groups, the chance of having a lesion increased with an increase in the mean daily use of the product ($P < 0.001$). No other factors could be associated with the observation of lesions.

Table 2. Absolute number and incidence of colposcopic lesions (per 100 woman–days).

	Treatment group		
	A	B	*P*
Total follow-up time (woman–days)	15974	16246	
Ulcer	5	7	
	0.03	0.04	0.60
Abrasion	4	8	
	0.03	0.05	0.28
Ulcer and abrasion	9	15	
	0.06	0.09	0.25
Lesions without epithelial disruption	47	42	
	0.29	0.26	0.54

Discussion

The reported data show that the multiple daily use of COL-1492, a 52.5 mg N-9 gel, by female sex workers is non-toxic. The incidence of lesions with epithelial disruption was low, 0.06 and 0.09/100 woman–days in groups A and B, respectively. Lesions without an epithelial disruption occurred at similar rates in both groups.

At the present time there is some hesitation and doubt about the role of colposcopy in microbicide trials. Researchers were concerned about the potential toxicity of spermicides, and as a consequence a possible increased risk of HIV infection [14,18]. A consensus was reached that before effectiveness trials could start,

Table 1. Description of the study population.

	Treatment group	
	A	B
Number of women with at least one colposcopic examination per centre	158	162
Bangkok	27	31
Durban	44	42
Hat Yai	30	34
Johannesburg	57	55
Age (years)	26.8 ± 0.5[a]	27.1 ± 0.51
	16–44[b]	15–46
Duration as FSW (years) (SD)	2.5 ± 0.24[a]	2.9 ± 0.32
	0–20[b]	0–30
Number of daily partners	3[c]	3
	1–7[b]	1–8
Condom use		
<25%	31 (19.6%)	26 (16.0%)
>75%	69 (43.7%)	79 (48.8%)
Use of hormonal contraception	79 (50%)	92 (56.8%)

[a] Mean ± SD; [b]Range; [c]Median.

the safety of a product should be established. One tool for monitoring vaginal toxicity is colposcopy. It is a good light source, gives an enlarged view, the vascular pattern can be assessed and photographs can be taken. An international team developed the WHO manual with a primary objective of defining the standardization of colposcopy in the evaluation of vaginal products [17]. However, researchers are now aware of some limitations to colposcopy. Firstly, it is not clear how one should interpret lesions without an epithelial disruption. Do they enhance HIV infectivity and/or infectiousness? Therefore the relevance of recording them has been questioned. Secondly, lesions with an epithelial disruption, which are likely to enhance HIV transmission in analogy with ulcerative STDs [19,20] can be seen with the naked eye. Thirdly, implementing and standardizing colposcopy in the field is difficult. Fourthly, no association between colposcopic and histologic findings has been established so far [21]. In January 1999 the Contraceptive Research and Development Program (CONRAD) organized a meeting on colposcopy in microbicide trials. Among other subjects, a revision of the WHO manual was discussed. The main changes proposed were dropping the use of acetic acid, a green filter and a high magnification. Colposcopy was defined as 'a magnified visualization of the cervix and vagina' for which the use of a colposcope is not necessary as long as there is an ability to magnify between 4× and 10×, a self-contained light source and a bi- or monocular visual tool.

In the trial presented here, colposcopy was discontinued in the autumn of 1997. Together with the effect on HIV infection and other STDs, the toxicity of the product continues to be assessed through simple visual examination.

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Appendix

The COL-1492 phase II study group

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