Dextrin Sulfate as a Vaginal Microbicide: Randomized, Double-Blind, Placebo-Controlled Trial Including Healthy Female Volunteers and Their Male Partners

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Summary: This randomized, placebo-controlled trial assessed the safety and acceptability of vaginally administered 0.125% dextrin sulfate (DS) gel in sexually active women and their male partners. A single 2-mL dose of study gel was self-administered every night over two 14-day periods separated by a 7-day interval, during which menses was expected to occur. Up to two supplementary doses per 24 hours were provided for use before sexual intercourse. Semistructured interview, colposcopy, and laboratory safety studies were used to assess adverse events. Male partners who agreed to participate in a substudy were exposed to gel through sexual intercourse during the second 14-day exposure period. Seventy-three women (36 DS recipients and 37 placebo recipients) used at least one application of gel, of whom 66 (33 DS recipients and 33 placebo recipients) completed follow-up. Eleven women (5 DS recipients and 6 placebo recipients) reported intermenstrual bleeding during gel use, which in most cases was light and resolved within 24 hours. Ten male partners (4 with DS exposure and 6 with placebo exposure) were enrolled in the study and all completed follow-up. There was no evidence of systemic toxicity or genital epithelial disruption attributable to DS gel. Key Words: Dextrin sulfate—Microbicide—HIV—Prevention—Female-controlled methods—Virucide.

An estimated 40 million people worldwide are infected with HIV, of whom >70% live in sub-Saharan Africa—where most acquired their infection through heterosexual intercourse (1). Although consistent and correct use of condoms by men remains the most effective form of protection from heterosexually acquired HIV infection, women are not always able to negotiate condom use. An effective prophylactic vaccine remains a key objective, but development is complex because of virus variability and difficulty in determining the immunologic correlates of protection. Vaginal microbicides are being developed in response to the urgent need for an HIV prevention method that women themselves can control. Licensed spermicides containing nonoxynol-9 (N-9), which has potent anti-HIV activity in vitro, were the first products to be investigated as potential microbicides in clinical trials. However, the association of N-9 products with genital epithelial disruption (2–5), histologically determined genital inflammation (6), and reduction in populations of vaginal lactobacilli (7) led to concerns that their use could enhance the risk of HIV transmission. Early phase 3 studies of N-9 products yielded conflicting results (2,8–10), but more recently, a multicenter, randomized, placebo-controlled trial of COL-1492, a low-dose N-9 formulation, demonstrated an increased incidence of HIV infection among N-9 recipients compared with placebo recipients (11). These findings have intensified efforts to develop agents with a more favorable toxicity profile.
Dextrin sulfate (DS) gel is a candidate vaginal microbicide at an advanced stage of development that is likely to be tested in phase 3 efficacy trials in the future. DS is a sulfated polysaccharide with in vitro activity against HIV, which acts at the cell surface to block entry of the virus (12). It is a potent inhibitor of the growth of diverse laboratory strains of HIV-1 in a variety of human cell lines and peripheral blood lymphocytes (13,14), with inhibition of 50% of virus at 2–6 µg/mL, as determined by established assays. It has a high selectivity index and is nontoxic in cell culture (15). Although DS has marked anticoagulant activity (16), its large average molecular weight of 20 kd makes systemic absorption across the vaginal mucosa unlikely.

Macaque challenge experiments provided some data supporting the efficacy of DS gel (15). Two of four rhesus macaques pretreated with vaginally administered DS gel at a concentration of 1% were uninfected following vaginal challenge with SHIV89.6 pd (10^4 TCID in 0.87 mL given twice 3 hours apart). DS gel can be manufactured relatively cheaply and is highly stable, compatible with latex condoms, and nonspermicidal.

In an initial phase 1 clinical trial of DS gel, 36 healthy sexually abstinent female volunteers were randomized to receive 5 mL of DS gel at 30 µg/mL (0.003%), DS gel at 100 µg/mL (0.01%), or matched placebo (17). These gels were found to be safe and well tolerated, although women in all study arms complained of excessive vaginal discharge, without microscopic or microbiologic evidence of genital infection. This discharge was attributed to leakage of the gel from the vagina. Colposcopy revealed mild erythema in five of 24 subjects receiving active gel and in none of the 12 placebo recipients. No evidence of inflammation by histologic analysis, no change in numbers of vaginal lactobacilli, and no abnormalities revealed by laboratory safety studies were found. Using the same methodology, a subsequent safety study including 18 participants (10 DS recipients and 8 placebo recipients) demonstrated a similarly favorable toxicity profile for DS gel at 0.5 mg/mL (0.05%) (18).

The present study explored the safety and acceptability of a higher dose of DS gel (0.125%) in a smaller volume (2 mL) over a longer exposure period (28 days) in sexually active women. In a substudy, the safety and acceptability in male partners exposed to the gel through sexual intercourse was also explored.

**METHODS**

**Study Design**

This double-blind, placebo-controlled trial was conducted at the Clinical Trials Centre, St. Mary’s Hospital (London, United Kingdom); the trial was approved by the local ethics committee. Participants were randomized to receive DS gel or placebo gel in a ratio of 1:1. Healthy female volunteers aged 18–45 years were recruited via advertising in the local press and the environs of the hospital. Participants were required to be sexually active with a regular male partner and to have no history of genital ulceration or bleeding diathesis.

**Study Gels**

The DS gel consisted of DS at 1.25 mg/mL (0.125%; total dose, 2.5 mg) in a gel base composed of lactic acid (500 µg/mL), carbopol 974-P (10 mg/g), sodium hydroxide (for pH adjustment to 4.5), and purified water. The placebo gel consisted of this base alone.

There were two 14-day periods of gel administration—referred to as parts 1 and 2 of the study—separated by a 7-day break, during which menses were expected to occur (see Table 1). During each part of the study, the female volunteers were asked to insert 2 mL of the allocated gel every night. A supplementary dose of the study gel was administered before sexual intercourse, if the last dose of gel had been applied >1 hour previously. A maximum of three doses of study gel could be applied in any 24-hour period. During part 1, female participants were provided with spermicide-free male latex condoms to prevent exposure of their male partners to the study gel. In part 2, male partners eligible for participation in a substudy agreed not to use condoms and were exposed to the study gel during sexual intercourse. Female participants whose partners were not enrolled in the substudy were asked to ensure that their partners continued to use condoms in part 2.

**TABLE 1. Study schedule**

<table>
<thead>
<tr>
<th>Study phase</th>
<th>Part 1</th>
<th>Part 2</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Screen</td>
<td>Baseline</td>
</tr>
<tr>
<td>Visit number</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>HIV risk assessment</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Pregnancy test</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Colposcopy</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Sexually transmitted infection screen</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Laboratory safety studies</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Questionnaire</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Evaluation of Female Participants**

The study schedule is shown in Table 1. There were five scheduled study visits: visit 1 (screening), visit 2 (baseline), visit 3 (after 14 days
use of study gel), visit 4 (after a further 14 days of study gel), and visit 5 (7 days after discontinuing use of the study gel). However, if for any reason the visit 3 or 4 appointment times were delayed, participants were asked to continue gel use until the night before their rescheduled appointment, potentially prolonging their period of gel exposure. At the screening visit (visit 1), participants underwent general medical examination and were screened for sexually transmitted infections (STIs). An HIV risk assessment questionnaire was completed, and a pregnancy test was performed. At the baseline visit (visit 2), participants assessed to be at low risk of HIV infection who tested negative for STIs were enrolled in the study and were randomized to receive either DS or placebo gel. All participants whose male partners were enrolled in the study were required to have an HIV test to confirm that they were HIV negative. Participants were questioned at each follow-up visit with regard to dysuria, genital itching, burning, irritation, and dyspareunia. Product acceptability with respect to ease of use, smell, sensation, and lubricating qualities was also assessed. Diary cards were provided for each 2-week period of gel use, and women were requested to record details of gel administration, coital frequency, and genital symptoms.

Laboratory safety studies—including complete blood cell count, determination of urea, electrolyte, and glucose levels, and liver function tests—were performed at screening and at visits 3, 4, and 5. Coagulation studies, consisting of determination of international normalized ratio, activated partial thromboplastin time, and prothrombin time, were performed at the same time points. These findings provided a surrogate marker for systemic absorption of the gel.

Colposcopy

Colposcopy was performed at each study visit according to modified WHO guidelines (19). Findings were recorded on a standardized diagram.

Microbiology

An STI screen was performed at each study visit, which consisted of sampling from the endocervix for diagnosis of *Chlamydia trachomatis* infection (by ligase chain reaction analysis), sampling from the urethra and endocervix for diagnosis of *Neisseria gonorrhoeae* infection (by microscopy and culture), and sampling of vaginal fluid from the posterior vaginal fornix for diagnosis of *Trichomonas vaginalis* infection (by microscopy of a wet preparation specimen). Further samples were obtained for diagnosis of bacterial vaginosis (BV) by vaginal pH assessment and microscopic detection of clue cells and for diagnosis of *Candida albicans* infection by microscopy. Blood specimens were collected for syphilis serology at visits 1 and 5.

Male Substudy

Eligible and willing partners of female participants were enrolled in a male substudy. These men were exposed to study gel through sexual intercourse over a 14-day period (part 2). Eligibility criteria included a negative HIV antibody test (see above) and no history of genital ulceration or bleeding diathesis. Only men who were not reliant on condom use for contraception were considered for recruitment to the male substudy.

Evaluation of Male Participants

Male participants enrolled in the substudy were exposed to the gel through sexual intercourse over a 14-day period (part 2). There were four scheduled study visits: visit 1 (screening), visit 2 (baseline), visit 3 (after partner had used study gel for 14 days), and visit 4 (7 days after discontinuation of study gel by partner). At the screening visit, all participants underwent general medical examination and were screened for STIs. An HIV risk assessment questionnaire was completed, and all male participants were required to have an HIV antibody test to confirm that they were HIV negative. Participants were questioned at each visit with regard to dysuria, genital itching, burning, or irritation or pain during sexual intercourse. The acceptability of the gel with respect to smell, sensation, and lubricating qualities was also assessed. Diary cards were provided for the 2-week period of gel exposure, and men were requested to record coital frequency and any symptoms attributed to gel exposure. Coagulation studies and laboratory safety studies were performed at visits 1, 3, and 4.

Genital Examination

A genital examination was performed at each study visit. Findings were recorded on a standardized diagram of the genital area.

Microbiology

An STI screen was performed at each study visit, consisting of sampling from the urethra and microscopy of a gram-stained preparation for diagnosis of *N. gonorrhoeae* infection (by microscopy and culture), diagnosis of *C. trachomatis* infection (by ligase chain reaction analysis), and quantification of neutrophils (by microscopy). Blood specimens were collected for syphilis serology at visits 1 and 4.

RESULTS

Study Population

Seventy-seven of the 87 women who attended an initial screening visit were randomized (39 allocated to DS arm and 38 allocated to placebo arm). Of the 10 women not randomized, two were excluded because they reported dyspareunia, and eight withdrew from the study. Four women who were randomized did not receive gel; three had abnormal results of coagulation studies, and one withdrew from the study. The flow of participants through the study, including those who withdrew and those lost to follow-up, is shown in Figure 1. The following analysis comparing the safety of the DS and placebo gels was conducted for the 73 women who used at least one application of gel.

Baseline Characteristics

Baseline characteristics of women in both study groups are shown in Table 2; these characteristics were similar except for the number of genital infections diagnosed at baseline, which occurred more frequently in the placebo group. One woman coinfected with *C. trachomatis* and *T. vaginalis* was enrolled in the study after completion of treatment of these infections. Three
women enrolled in the study following an enzyme-linked immunoassay negative for *Chlamydia* at screening (this test was used because the ligase chain reaction machine was temporarily out of service) interrupted gel use after a sample taken at baseline tested positive for *Chlamydia* by ligase chain reaction analysis: one of these women did not recommence gel administration after treatment due to difficulty in maintaining consistent condom use.

**Gel Use and Sexual Activity**

Gel use and sexual activity were determined from data recorded in the diary cards in parts 1 and 2 of the study. Eleven women used gel for >28 days, and the maximum period of gel exposure was 32 days. As the total period of gel exposure was variable, the frequency of gel use and sexual intercourse was expressed as a percentage of the total number of days over which gel was applied. The median percentage of days that gel was applied in part 1 was 93% (interquartile range [IQR], 86–100) for DS and 94% (IQR, 86–100) for placebo, compared with 93% (IQR, 79–100) for DS and 100% (IQR, 86–100) for placebo in part 2.

**Adverse Events**

**Systemic Toxicity**

Changes in coagulation parameters and platelet counts did not suggest systemic toxicity of DS gel. A total of three women (2 DS recipients and 1 placebo recipient) were found to have a raised activated partial thromboplastin time (>43 seconds) following exposure to gel, but the elevation was transient in both women receiving DS. Three women with normal platelet counts at baseline were found to have values below the lower limit of the normal range (<169 $\times 10^9$/L) at follow-up. Two of these women were in the DS group, but in both cases, the abnormalities were transient and no lower than 155 $\times 10^9$/L.

**Colposcopy**

Cervicovaginal findings are shown in Table 3. There were no cases of ulceration of the cervix or vagina throughout the study, and no new abrasions occurred during gel use, although one woman in the DS group was observed to have a cervical abrasion at the final follow-up.
up visit. Four women (2 DS recipients and 2 placebo recipients) with no erythema at baseline were observed to have erythema at one or more follow-up visits, and all tested negative for genital infections. Sixteen women (7 DS recipients and 9 placebo recipients) with no vascular lesions (petechiae or ecchymoses) at baseline were observed to have vascular lesions during the course of follow-up.

Vulval findings are shown in Table 4. There were no cases of vulval ulceration during exposure to study gel. However, one woman (DS group) presented with vulval ulceration at the final follow-up visit (1 week after discontinuation of gel use) that was clinically consistent with a herpes simplex virus lesion, although culture was negative for herpes simplex virus. There were no cases of vulval abrasions or vascular lesions. Three women (all DS recipients) with no vulval erythema at baseline were observed to have erythema following exposure to study gel. In one of these cases, this finding was associated with vaginal candidiasis.

**STIs and Vaginal Infections**

No women developed a STI during the course of the study. However, six women were diagnosed with vaginal infections at one or more follow-up visits; three women developed infection with *Candida* (1 DS recipient and 2 placebo recipients), and three developed BV (1 DS recipient and 2 placebo recipients). In one of the women with BV (DS group), the infection was recurrent, as she had already been treated for this condition at baseline.

**Genital Symptoms**

Genital irritation, defined as pain passing urine or itching or burning in the genital area, was reported by 26 (14 DS recipients and 12 placebo recipients) of 67 women at one or more follow-up visits. Five of these women had a demonstrable genital infection that may have explained their symptoms: two (1 DS recipient and 1 placebo recipient) had vaginal candidiasis, and three (1 DS recipient and 2 placebo recipients) had BV. Another woman reporting genital irritation (placebo group) was diagnosed with a urinary tract infection, and her symptoms resolved once she received antibiotic treatment. Most women with genital irritation had mild symptoms that were transient and resolved without interruption of gel use. Only two women (1 DS recipient and 1 placebo recipient) with genital irritation interrupted gel use. Eight women (3 DS recipients and 5 placebo recipients) had discomfort during sexual intercourse in the absence of genital irritation, but none interrupted gel use.

Forty-five (23 DS recipients and 22 placebo recipients) of 67 women reported vaginal discharge different from usual during one or both periods of gel use. This discharge was typically described as thick white discharge occurring intermittently that was attributed to leakage of gel. In five women, the discharge was associated with an infection; three women (1 DS recipient and 2 placebo recipients) had vaginal candidiasis, and two (1 DS recipient and 1 placebo recipient) had BV. Twenty-two (12 DS recipients and 10 placebo recipients) of the 45 women with discharge reported genital irritation, the severity of which was mild or moderate in all cases.

### TABLE 3. Cervicovaginal findings at colposcopy

<table>
<thead>
<tr>
<th></th>
<th>Abrasion</th>
<th>Vascular lesions</th>
<th>Erythema</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dextrin sulfate</td>
<td>Placebo</td>
<td>Dextrin sulfate</td>
</tr>
<tr>
<td>Baseline</td>
<td>1</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Follow-up after 1st 2-week gel exposure (visit 3)</td>
<td>0</td>
<td>1 (0)</td>
<td>9 (5)</td>
</tr>
<tr>
<td>Follow-up after 2nd 2-week gel exposure (visit 4)</td>
<td>0</td>
<td>0</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Final follow-up (visit 5)</td>
<td>1 (1)</td>
<td>0</td>
<td>2 (0)</td>
</tr>
<tr>
<td>Total women with findings</td>
<td>2 (1)</td>
<td>1 (0)</td>
<td>13 (7)</td>
</tr>
</tbody>
</table>

New cases arising after baseline are shown in parentheses. There were no cervicovaginal ulcerations.

### TABLE 4. Vulval findings at colposcopy

<table>
<thead>
<tr>
<th></th>
<th>Ulceration</th>
<th>Erythema</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dextrin sulfate</td>
<td>Placebo</td>
</tr>
<tr>
<td>Baseline</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Follow-up after 1st 2-week gel exposure (visit 3)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Follow-up after 2nd 2-week gel exposure (visit 4)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Final follow-up (visit 5)</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Total women with findings</td>
<td>1 (1)</td>
<td>0</td>
</tr>
</tbody>
</table>

New cases arising after baseline are shown in parentheses. There were no vulval abrasions or vascular lesions.
Intermenstrual Bleeding

Women were not routinely questioned with respect to intermenstrual bleeding (IMB), but the characteristics of women who reported IMB are shown in Table 5. Eleven (5 DS recipients and 6 placebo recipients) of 73 women reported IMB, of whom eight (4 DS recipients and 4 placebo recipients) had a single episode of bleeding and three (1 DS recipient and 2 placebo recipients) had two episodes. For 10 of the 14 episodes, there was a delay of ≥4 days between the last day of bleeding and examination at follow-up. Eleven of the IMB episodes lasted either 1 day (n = 8) or 2 days (n = 3) and constituted pink/brown discharge, spotting, or, in one case, bloody mucus on the tip of the applicator. None of these 11 episodes caused sufficient concern for the women to seek the advice of the study investigators before their routine follow-up visit; in two of these 11 episodes, bleeding was confirmed at examination, and in none of them was a source of bleeding identified. Three episodes of IMB progressed to more prolonged blood loss, constituting a pink discharge lasting 3 days (n = 1) or fresh blood loss lasting 3 days (n = 1) or 5 days (n = 1). Only the latter two episodes caused sufficient concern for the women to call the study investigators and present for examination before their scheduled follow-up visit. In both cases, results of coagulation studies were normal, and bleeding was confirmed at examination. In one case, blood was seen to be originating from the cervical os, suggesting that the endometrium was the probable source of bleeding. Of the 11 women who had IMB, seven (64%) were known to have had one or more risk factors for IMB (large cervical ectropion, hormonal contraception, and/or endocervical polyp) compared with 29 (47%) of 62 women who did not have IMB (p > .25).

Acceptability

Application of the gel was easy for most women. None of the women receiving DS reported difficulties in applying gel, compared with 10 of the 36 women receiving placebo (p < .01). Most women who commented on the reasons for these difficulties described leakage of gel from the vagina during and/or after application. Of the 66 women assessed at the final visit, 76% of DS users (n = 25) and 70% of placebo users (n = 23) said that they would be prepared to use the gel on a long-term basis.

Male Partner Substudy

Of the 73 female participants, 28 were reliant on the use of the male latex condom for contraception. Therefore, only 45 male partners were considered for recruitment to the male partner substudy, of whom 10 (4 with DS exposure and 6 with placebo exposure) were willing to take part in the substudy and attended an initial screening visit. All 10 male partners tested negative for HIV antibody and had negative results of screening for genital infections. All 10 men were enrolled in the study and completed all study visits. The mean age of male participants was 28 years (range, 21–48 years) and all were white. There were no cases of genital epithelial disruption, and results of laboratory safety studies remained normal for all participants. At follow-up, four men (1 with DS exposure and 3 with placebo exposure) reported transient genital burning or soreness during gel exposure, and in two cases (both with placebo exposure), this condition was associated with localized erythema. Neutrophils were found on a urethral smear specimen from one of these men, and a urethral swab taken at this time was positive for C. trachomatis. His screening tests, includ-

<table>
<thead>
<tr>
<th>Gel</th>
<th>Case</th>
<th>Part 1 or 2</th>
<th>Day of gel use</th>
<th>Colposcopy findings</th>
<th>Description</th>
<th>Risk factors for intermenstrual bleeding*</th>
</tr>
</thead>
<tbody>
<tr>
<td>DS</td>
<td>A</td>
<td>2</td>
<td>11</td>
<td>No bleeding</td>
<td>Spotting</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>1</td>
<td>2–4</td>
<td>Slight blood loss in vagina</td>
<td>Fresh bleeding</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>1</td>
<td>2–6</td>
<td>Moderate bleeding from cervical os</td>
<td>Fresh bleeding</td>
<td>Large cervical ectropion</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>2</td>
<td>8</td>
<td>No bleeding</td>
<td>Pink discharge</td>
<td></td>
</tr>
<tr>
<td></td>
<td>E</td>
<td>1</td>
<td>9</td>
<td>Menses</td>
<td>Spotting</td>
<td>OCP</td>
</tr>
<tr>
<td>Placebo</td>
<td>F</td>
<td>2</td>
<td>16</td>
<td>Slight blood loss in vagina, vaginal ecchymosis</td>
<td>Brown discharge</td>
<td>OCP</td>
</tr>
<tr>
<td></td>
<td>G</td>
<td>1</td>
<td>4</td>
<td>No bleeding</td>
<td>Spotting</td>
<td>Large cervical ectropion</td>
</tr>
<tr>
<td></td>
<td>H</td>
<td>2</td>
<td>1</td>
<td>Slight blood loss in vagina</td>
<td>Blood on tip of applicator</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>I</td>
<td>2</td>
<td>3</td>
<td>Menses</td>
<td>Pink discharge</td>
<td>OCP</td>
</tr>
<tr>
<td></td>
<td>J</td>
<td>2</td>
<td>10–11</td>
<td>Menses</td>
<td>Brown discharge</td>
<td>Large cervical ectropion</td>
</tr>
</tbody>
</table>

* Defined as oral contraceptive pill (OCP), large cervical ectropion (>50% of cervical diameter), or endocervical polyp.
ing analysis of a urethral swab for *C. trachomatis*, had been negative. He was given appropriate antibiotic treatment. His regular partner who was enrolled in the study tested negative for *C. trachomatis* infection but was given antibiotic treatment.

Most male partners participating in the substudy had a favorable view of DS gel use, and eight men (3 with DS exposure and 5 with placebo exposure) indicated that they would find it acceptable for their partners to use the gel on a long-term basis.

**DISCUSSION**

This study suggests that DS gel at a concentration of 0.125% administered in a 2-mL volume (total dose, 2.5 mg) at least once daily had an acceptable toxicity profile compared with placebo gel in our population of sexually active women and their male partners. Minor abnormalities revealed by coagulation studies and platelet counts occurred in both treatment groups and were not suggestive of systemic absorption. No women were observed to have new lesions of genital epithelial disruption at their first or second follow-up visit. Cervicovaginal erythema and vascular lesions occurred at a similar frequency in both groups. These findings are comparable with the results of safety studies of other novel microbicidal agents for low-risk populations, including BufferGel (20), carrageenan (21), and PRO 2000 (22), and contrast with reports of significant epithelial toxicity observed in some studies of N-9 (2–4).

Although the women in our study were not routinely questioned about IMB, this was reported by 15% of women (5 DS recipients and 6 placebo recipients). IMB was confirmed at examination in only four women, and a likely source of bleeding was identified in only one woman, in whom blood was seen to be coming from the cervical os and was assumed to be endometrial in origin. In most cases, these women did not perceive the bleeding to be a health concern, as it was slight and lasted no longer than 24 to 48 hours, and only two women (1 DS recipient and 1 placebo recipient) contacted the study investigators to report this problem. One (DS group) of these two women had a history of gynecologic problems, used only one application of gel, and had bleeding the following day; results of colposcopy were normal. The second woman (placebo group) had bleeding during both phases of gel exposure that was accompanied by symptoms of genital irritation and was found to have diffuse cervical erythema at all follow-up visits. One further woman (placebo group) who had bleeding had a small cervical abrasion that was noted to be present at the baseline visit, did not worsen after exposure to the gel, and was not considered to be an adequate explanation of IMB.

IMB can occur as a physiologic event. In otherwise healthy women, it is usually assessed only in the context of hormonal contraception or where symptoms are severe and/or recurrent. For most women who had IMB in this study, the bleeding took the form of the loss of small amounts of blood from the vagina, and a likely source of bleeding was identified in only one woman. As the incidence of IMB was similar in the DS and placebo groups and as a raised activated thromboplastin time occurred in only two (1 DS recipient and 1 placebo recipient) of the 11 women who had IMB, it is unlikely that IMB occurred as a specific adverse effect of DS. There are a number of possible causes for IMB. First, it may have occurred as part of the background rate of IMB in this study population; risk factors for IMB include hormonal contraception, endometrial or endocervical polyps, and cervical ectropia. We were not able to assess for the presence of endometrial polyps in this study. However, although not statistically significant, the percentage of women known to have a large cervical ectropion or endocervical polyp and/or who were using hormonal contraception was greater among those with IMB (64%) than among those without IMB (50%). Second, the gel base may have adversely affected the cervicovaginal epithelium or endometrium. This base consisted of lactic acid, water, and carbopol, but there are no data to suggest toxicity of these agents. Finally, IMB may have occurred as a result of applicator trauma causing either disruption of the ectocervical or vaginal epithelium or bleeding from a cervical ectropion. Although it would be expected that any disruption of the ectocervical or vaginal epithelium would be visualized at colposcopy, for 10 of the 14 episodes of bleeding there was a delay of ≥4 days between the last day of bleeding and examination at follow-up, which may have allowed small lesions to heal. The impact of intermenstrual spotting on the effectiveness of a candidate vaginal microbicide in high-risk populations is unknown, but there are two concerns: first, that it may increase the risk of HIV transmission (23), and second, that it may adversely affect the acceptability of the product, although this was not the experience of our study population.

Twenty-one women (12 DS recipients and 9 placebo recipients) reported unexplained irritative genitourinary symptoms. Symptoms were generally mild, were of short duration, and resolved without intervention or discontinuation of product use. Use of DS was not associated with an increased incidence of BV or vaginal candidiasis in this study population.
The strengths of this study were its size, the randomized, double-blind, single-center design, and the relatively long exposure period. The assessment of the exposure of male partners to DS gel through sexual intercourse is novel. Although these preliminary data on the safety of DS gel for men are encouraging, studies involving larger numbers are required. This study demonstrated an unexpectedly high frequency of IMB among both DS and placebo recipients, which was usually not of clinical significance. However, interpretation of these data is limited by the lack of a “no gel” observation group.

In conclusion, compared with placebo gel, DS gel at a concentration of 0.125% was not associated with disruption of the genital epithelium or systemic toxicity in this population of low-risk women. Future microbicide studies should assess the safety and acceptability of DS gel in both HIV-negative and HIV-positive women.

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