ORIGINAL ARTICLE

Lack of Effectiveness of Cellulose Sulfate Gel for the Prevention of Vaginal HIV Transmission

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ABSTRACT

BACKGROUND

Women make up more than 50% of adults living with human immunodeficiency virus (HIV) infection or the acquired immunodeficiency syndrome (AIDS) in sub-Saharan Africa. Thus, female-initiated HIV prevention methods are urgently needed.

METHODS

We performed a randomized, double-blind, placebo-controlled trial of cellulose sulfate, an HIV-entry inhibitor formulated as a vaginal gel, involving women at high risk for HIV infection at three African and two Indian sites. The primary end point was newly acquired infection with HIV type 1 or 2. The secondary end point was newly acquired gonococcal or chlamydial infection. The primary analysis was based on a log-rank test of no difference in the distribution of time to HIV infection, stratified according to site.

RESULTS

A total of 1398 women were enrolled and randomly assigned to receive cellulose sulfate gel (706 participants) or placebo (692 participants) and had follow-up HIV test data. There were 41 newly acquired HIV infections, 25 in the cellulose sulfate group and 16 in the placebo group, with an estimated hazard ratio of infection for the cellulose sulfate group of 1.61 (P=0.13). This result, which is not significant, is in contrast to the interim finding that led to the trial being stopped prematurely (hazard ratio, 2.23; P=0.02) and the suggestive result of a preplanned secondary (adherence-based) analysis (hazard ratio, 2.02; P=0.05). No significant effect of cellulose sulfate as compared with placebo was found on the risk of gonorrheal infection (hazard ratio, 1.10; 95% confidence interval [CI], 0.74 to 1.62) or chlamydial infection (hazard ratio, 0.71; 95% CI, 0.47 to 1.08).

CONCLUSIONS

Cellulose sulfate did not prevent HIV infection and may have increased the risk of HIV acquisition. (ClinicalTrials.gov number, NCT00153777; and Current Controlled Trials number, ISRCTN95638385.)

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The Joint United Nations Programme on HIV/AIDS estimates that there were 33.2 million people living with infection with human immunodeficiency virus (HIV) or the acquired immunodeficiency syndrome (AIDS) in 2007; 15.4 million of these were women.[1] In sub-Saharan Africa, women make up more than 50% of the people living with HIV infection or AIDS. Sociocultural norms often make negotiating about condom use impossible for women. Male circumcision has recently been proven effective in preventing HIV infection[2-4] but is under men's control.

Topical microbicides are being investigated for HIV prevention. One such microbicide is cellulose sulfate, an entry inhibitor with in vitro activity against multiple clades of HIV type 1 (HIV-1) and HIV type 2 (HIV-2) as well as *Neisseria gonorrhoeae* and *Chlamydia trachomatis*[5] and which prevents simian–human HIV infection in macaques.[6] Several studies of women[7-11] have shown similar safety profiles between participants using a cellulose sulfate gel formulation and a control group. A tolerance study conducted in HIV-negative men found no difference in safety and tolerability between cellulose sulfate gel and a placebo gel,[12] although in another study of HIV-positive men, more penile tingling was reported in the cellulose sulfate group than in the placebo group.[13] In a noncomparative trial, the pregnancy rate among women using cellulose sulfate gel was similar to those found in historical studies of nonoxynol 9.[14]

We report the results of a randomized, double-blind, placebo-controlled HIV prevention trial that was stopped prematurely after the independent data monitoring committee determined that cellulose sulfate gel may have increased the risk of HIV infection, as compared with placebo.

Methods

Participants

Women were recruited at five sites: a community clinic and a clinic for sexually transmitted infections in Cotonou, Benin; the Y.R. Gaitonde Center for AIDS Research and Education (Y.R.G. CARE) in Chennai, India; the Medical Research Council in Durban, South Africa; the Mulago Hospital (Makarere University) in Kampala, Uganda; and in clinics in Mudhol and Jhamkandi in Karnataka, India (in collaboration with the Karnataka Health Promotion Trust, Bangalore).

To be enrolled in the study, a woman needed to provide written informed consent, have a negative HIV-antibody test, be at least 18 years old, have an average of at least three acts of vaginal intercourse per week, have had at least three different partners in the previous 3 months, and agree to come to the clinic for 12 monthly follow-up visits. A woman could not be enrolled if she had an allergy to latex or spermicides, was pregnant or wanted to become pregnant in the next year, used intravenous drugs, was participating in another trial, had already been screened for this trial, or had any condition that made her participation unsafe or that the investigator believed could complicate interpretation of the data. At each visit, women received counseling about reducing the risk of HIV infection, free condoms, and treatment for curable sexually transmitted infections according to local guidelines.

Study Intervention

Eligible women were randomly assigned to receive either 6% cellulose sulfate gel or placebo gel in a 1:1 ratio. The placebo used in the study was specifically designed to have no effect on vaginal flora or pathogens (including HIV) and was identical in appearance to the cellulose sulfate gel.[15] The gels differed in one respect: the active gel had a pH of 7.5, whereas the placebo gel had a pH of 4.4.

Gel was delivered in 3.5-ml single-use opaque applicators. Women were asked to insert the gel into their vagina within 1 hour before each act of vaginal intercourse, during a period of 1 year. Women testing positive for pregnancy at one of their monthly visits had the product withdrawn until the pregnancy resolved but did not discontinue the trial.

Data were analyzed at Family Health International (Research Triangle Park, NC). The study was approved by the Institutional Review Board of the Eastern Virginia Medical School and by local ethics committees at the sites where women were recruited. All existing local regulatory bodies approved the study before it began. The trial was conducted under the Food and Drug Administration's Investigational New Drug application number 69,107.

Objectives and Outcomes

The primary objective of the trial was to assess the effectiveness of 6% cellulose sulfate gel in preventing male-to-female vaginal transmission of HIV.

The secondary objective was to assess the effectiveness of 6% cellulose sulfate gel in preventing male-to-female vaginal transmission of *N. gonorrhoeae* and *C. trachomatis*.

The primary outcome was newly acquired HIV-1 and HIV-2 infection, as determined by the presence of HIV antibodies in blood samples collected at months 1, 3, 6, 9, or 12 or at any visit at which the product was withdrawn. If a scheduled HIV test was missed, the woman was tested at her subsequent visit. For participants in whom seroconversion occurred within 3 months after enrollment, a polymerase-chain-reaction (PCR) test for HIV RNA was performed on an enrollment sample to confirm HIV-1–negative status at baseline; women found to be infected at enrollment were excluded from the analysis. A participant was considered to be infected if two of three rapid tests (Determine HIV-1/2, Abbott Laboratories; SD Bioline HIV 1/2, Standard Diagnostics; Uni-Gold HIV Recombinant, Trinity Biotech) performed consecutively on the same blood sample were positive or if there was a positive PCR result at her final visit. Patients in whom seroconversion occurred were referred for care either within the study clinic or to an outside hospital, with funding provided by CONRAD.

The secondary outcome was newly acquired genital gonococcal or chlamydial infection, as determined by a positive test for strand-displacement amplification (SDA, Becton Dickinson) in a cervical swab from one of the quarterly visits.

METHODS TO ENHANCE THE QUALITY OF MEASUREMENTS

Laboratory staff were trained in the performance of testing for HIV and for strand-displacement-amplification by the central laboratory (Institute of Tropical Medicine, Antwerp, Belgium). Quality-assurance measures were also implemented: all HIV infections (except four, in patients for whom blood samples were not available), all positive strand-displacement-amplification results, and 10% of all negative strand-displacement-amplification results were verified at the Institute of Tropical Medicine. There were no equivocal results of HIV-antibody testing in the final database.

NUMBER OF PARTICIPANTS

The study was designed to have a statistical power of 80% to conclude that cellulose sulfate is effective, on the basis of a one-sided test and a significance level of 0.025. Enrollment of 2574 participants (1287 in each group) was planned, to achieve the 66 newly acquired infections required for the study to have a statistical power of 80%. This calculation assumed that the 12-month cumulative probability of HIV infection would be 4% in the placebo group, the cellulose sulfate regimen would reduce the risk of acquiring HIV by 50%, and at least 80% of participants would complete the study.

INTERIM ANALYSIS AND STOPPING RULES

The study protocol specified that the independent data monitoring committee would evaluate the data for the primary HIV end point for early signs of product effectiveness or potential harm after approximately half of the targeted number of HIV infections had occurred. The Lan–DeMets spending function[16] with O'Brien–Fleming boundaries[17] was to be used to preserve the type I error of concluding effectiveness with the use of a one-sided alpha level of 0.025. No attempt was made to control for the type I error for a test of harm. Instead, the independent data monitoring committee was asked to provide guidance if the interim one-sided P value was less than 0.10 in the direction of increased risk of HIV infection with the use of cellulose sulfate gel as compared with placebo.

RANDOMIZATION, CONCEALMENT, AND BLINDING OF GROUP ASSIGNMENT

The cellulose sulfate and placebo gels were each divided into three groups designated by color names to help maintain blinding (i.e., revealing one subgroup would not lead to the unblinding of all the data). The colors associated with each gel group were randomly assigned by a person not otherwise involved in the study, using a validated SAS software program (SAS Institute). Participants were assigned to the six color groups in equal ratios on the basis of a permuted-block randomization scheme with stratification according to clinic, with random block sizes of 12, 18, and 24. To conceal the group assignments, they were contained within sequentially numbered, sealed opaque envelopes that were kept in a secure office at each site. Participants who qualified for the study were assigned the next available randomization envelope. No envelopes were reused.

All participants, monitors, site staff, and central study staff were unaware of the group assignments. After the independent data monitoring

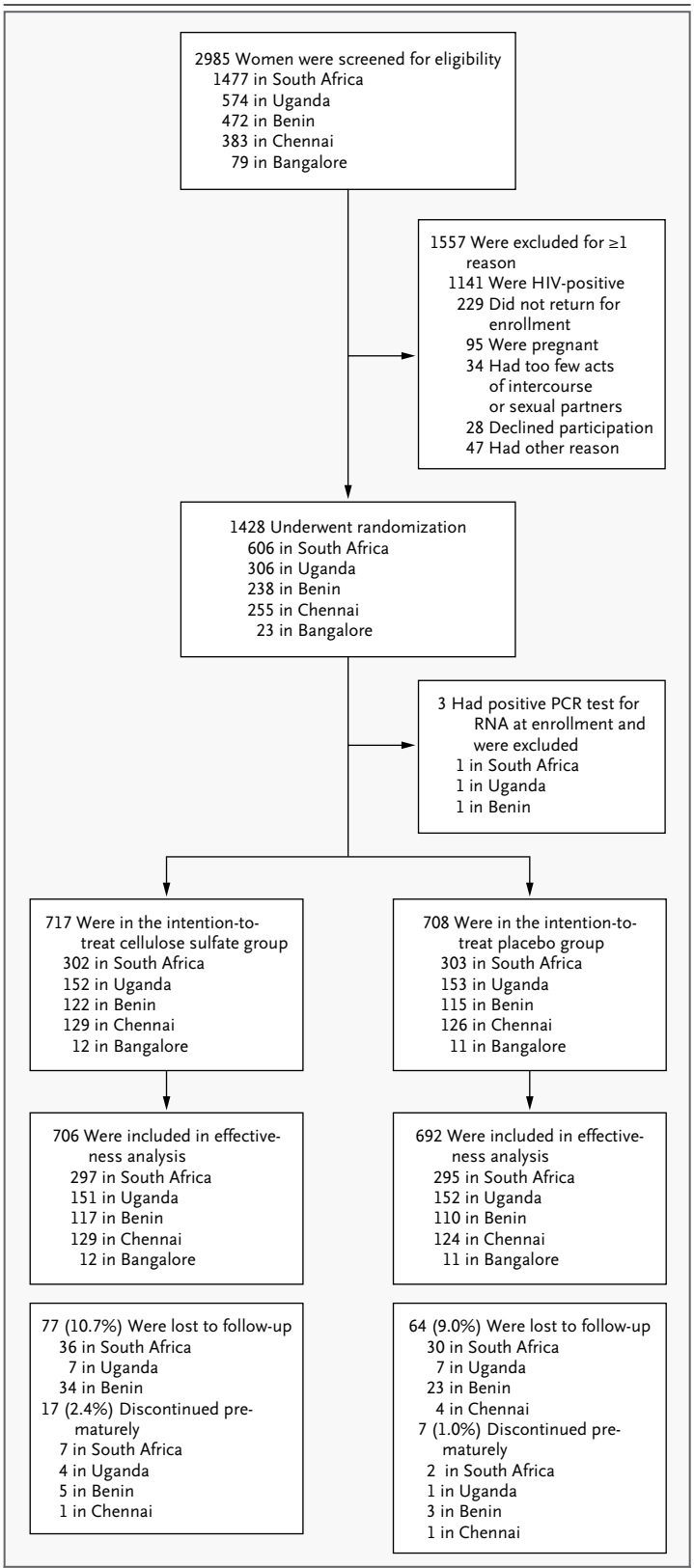

Figure 1. Screening, Randomization, and Follow-up of the Study Participants.

committee recommended that the trial be stopped, the lead statistician was made aware of the assignments to verify randomization procedures and interim analyses that had been conducted by an independent statistician. Once these were verified, the lead principal investigator was also made aware of the assignments. All participants, laboratory staff, site investigators, and other study staff remained unaware of the assignments until all final follow-up visits and HIV testing were completed.

STATISTICAL ANALYSIS

The primary effectiveness analysis was based on a log-rank test of no difference between the cellulose sulfate group and the placebo group in the distributions of time to HIV infection, stratified according to site. For both primary and secondary outcomes, estimated hazard ratios and 95% confidence intervals were computed with the use of proportional-hazards regression models, stratified according to site. Cumulative probabilities of infection were estimated on the basis of the Kaplan–Meier method, and crude incidence rates were computed by dividing the number of events by the person-years of follow-up. All reported P values are two-sided. For the secondary outcomes, P values less than 0.05 were considered to indicate statistical significance. Owing to the asymmetric interim stopping boundaries used for the primary HIV outcome, however, only an effect in the direction of protection can be considered to be tightly controlled at the corresponding one-sided 0.025 significance level.

Only women without a postrandomization HIV-test result or women who were found to be infected with HIV at enrollment were excluded from effectiveness analyses. Estimated dates of infection were computed as the midpoint between the dates of a woman's first positive HIV test and her previous negative test. Data from women completing the study without acquiring an infection were censored 380 days after enrollment (1 year of follow-up plus a 2-week period during which the final visit could occur) or on the date of the final negative test result, whichever came first. Data from women who prematurely withdrew from the study or who were lost to follow-up were censored on the date of the last test result. A prespecified, secondary subgroup analysis permanently censored data from women at the time of the first documented interruption of product use. Numerous additional, unplanned subgroup analyses based on self-reported adherence and prod-

Table 1. Baseline Characteristics of Study Participants.*

Characteristic	Cellulose Sulfate (N=717)	Placebo (N=708)	Total (N=1425)
Age — yr			
Median	28	29	29
Interquartile range	23–36	23–38	23–37
Education — yr			
Median	8	8	8
Interquartile range	5–11	5–11	5–11
Married — no. (%)	163 (22.7)	164 (23.2)	327 (22.9)
No. of partners in the 3 mo before screening			
Median	10	10	10
Interquartile range	3–90	3–96	3–94
No. of acts of vaginal intercourse in the 7 days before screening			
Median	4	4	4
Interquartile range	3–10	3–10	3–10
Anal intercourse in the month before screening — no. (%)	30 (4.2)	23 (3.2)	53 (3.7)
Condom used for last act of vaginal intercourse before screening — no. (%)	435 (60.7)	434 (61.3)	869 (61.0)
Hormonal contraception, IUD, or female sterilization — no. (%)	323 (45.0)	309 (43.6)	632 (44.4)
History of irregular menses — no. (%)	142 (19.8)	125 (17.7)	267 (18.7)
History of pregnancy — no. (%)	645 (90.0)	655 (92.5)	1300 (91.2)
Positive STI test at screening — no. (%)			
Gonorrhea	29 (4.0)	27 (3.8)	56 (3.9)
Chlamydia	41 (5.7)	48 (6.8)	89 (6.2)
Trichomoniasis	34 (4.7)	45 (6.4)	79 (5.5)
Syphilis	31 (4.3)	40 (5.6)	71 (5.0)

* Data from three participants are not shown here; after enrollment, they were found to have been infected with HIV at the time of enrollment. IUD denotes intrauterine device, and STI sexually transmitted infection.

uct-exposure data were conducted, but no adjustment for multiple testing was made.

RESULTS

RECRUITMENT AND FOLLOW-UP

Each participant came to the clinic for screening, enrollment (within 28 days after screening), and up to 12 monthly follow-up visits. The first participant enrolled on July 20, 2005, in Uganda, and the last participant enrolled on January 25, 2007, in Bangalore. The last follow-up visit occurred on March 31, 2007.

A total of 2985 women were screened, of whom 1428 were enrolled and randomly assigned to a study group (Fig. 1). Three women who tested negative for HIV at enrollment and tested positive by month 3 were excluded from all analyses because their blood samples obtained at enrollment were positive for HIV-1 RNA on PCR testing. Another 27 women had no HIV results after enrollment, leaving 1398 women (706 receiving cellulose sulfate gel and 692 receiving placebo) whose data were included in the primary effectiveness analysis. A total of 141 of the 1428 women (9.9%) were lost to follow-up and another 24 (1.7%) discontinued the study prematurely.

BASELINE CHARACTERISTICS AND PRODUCT USE

The two groups were similar with respect to demographic characteristics, medical history, and self-reported sexual behavior at baseline (Table 1). Self-reported sexual activity was considerably higher in Benin and Uganda than in South Africa, Chennai, or Bangalore (Table 2).

The reported rates of condom and gel use were

Table 2. Sexual Behavior and Product Use Reported in the 7 Days before Each Follow-up Visit.

Site and Group	No. of Participants	Median No. of Sexual Partners	Median No. of Sexual Acts	Gel Use	Condom Use	Gel Use When Condoms Not Used
				% of all sexual acts		*% of sexual acts without condom*
Benin						
Cellulose sulfate	117	17.9	20.1	94.1	96.2	32.0
Placebo	110	21.2	23.5	95.2	97.7	40.4
South Africa						
Cellulose sulfate	297	1.6	4.0	92.4	92.1	80.4
Placebo	295	1.8	4.2	93.9	94.3	70.6
Uganda						
Cellulose sulfate	151	17.5	19.8	83.8	97.5	53.2
Placebo	152	19.1	21.3	80.8	97.5	55.3
Chennai						
Cellulose sulfate	129	4.2	6.2	78.3	82.7	17.7
Placebo	124	4.0	5.4	75.5	79.1	22.3
Bangalore						
Cellulose sulfate	8	4.7	5.8	94.5	100	
Placebo	10	5.7	8.0	98.6	100	
All						
Cellulose sulfate	702	3.5	6.7	87.4	95.3	45.9
Placebo*	691	3.3	6.5	86.7	96.1	45.7

* Data were missing for one participant in the placebo group.

high overall (95.7% and 87.0% of all sexual acts, respectively) (Table 2) but were lower when only acts with primary partners were considered (74.9% and 78.0%) (data not shown). Reported gel use among acts in which a condom was not used was only 45.8% (ranging from 20.0% in Chennai to 76.2% in South Africa).

EFFECTIVENESS

A meeting of the independent data monitoring committee was convened on January 26, 2007, to review interim data collected through December 18, 2006 — the date of the interim lock on the database. There were 35 HIV infections in the interim database (24 in the cellulose sulfate group and 11 in the placebo group), with an estimated hazard ratio of 2.23 (P=0.02). The committee recommended that the trial be halted, and on January 29, 2007, sites were instructed to withdraw the product as soon as possible.

The final effectiveness analysis included six additional infections during the study not recorded in the interim database (for details, see the Supplementary Appendix, available with the full text of this article at www.nejm.org). Among the 41 newly acquired infections, 25 were in the cellulose sulfate group (incidence rate, 5.29 per 100 person-years) and 16 were in the placebo group (incidence rate, 3.33), yielding an estimated hazard ratio of 1.61 (95% confidence interval [CI], 0.86 to 3.01; P=0.13) (Table 3). The estimated cumulative probabilities of infection at 12 months were 0.50 and 0.36 in the cellulose sulfate and placebo groups, respectively (Fig. 2). There were more infections in the cellulose sulfate group than the placebo group in each site that had events (Benin, 7 vs. 2; Uganda, 3 vs. 2; South Africa, 15 vs. 12).

A preplanned per-protocol analysis censored data from participants at the time of their first documented interruption of product use (in 68.3% of women, due to positive pregnancy tests of urine samples), resulting in an estimated hazard ratio of 2.02 (95% CI, 0.97 to 4.18; P=0.05). There probably were a substantial number of acts without gel

Table 3. Results of Primary and Secondary Analyses.

Event or Analysis	Cellulose Sulfate (N=706)		Placebo (N=692)		Hazard Ratio for Cellulose Sulfate (95% CI)	P Value
	no. with event	*rate*	*no. with event*	*rate*		
HIV						
Primary	25	5.29	16	3.33	1.61 (0.86–3.01)	0.13
Per protocol	21	5.11	11	2.59	2.02 (0.97–4.18)	0.05
Interim*	24	6.75	11	3.03	2.23 (1.05–5.03)	0.02
STI†						
Gonorrhea	53	12.26	49	11.08	1.10 (0.74–1.62)	0.63
Chlamydia	37	8.47	52	11.86	0.71 (0.47–1.08)	0.11
Pregnancy†	96	21.84	103	23.13	0.95 (0.72–1.26)	0.74

* The interim analysis of data for HIV infection was based on 648 participants in the cellulose sulfate group and 638 participants in the placebo group. The rate of events is the number per 100 person-years.
† Incidence data were based on the time to the first event.

use included in this analysis, however, since a reported compliance of less than 100% was not grounds for exclusion.

The rate of gonococcal infection was similar in the two groups (hazard ratio for cellulose sulfate, 1.10; 95% CI, 0.74 to 1.62). The rate of chlamydial infection was lower in the cellulose sulfate group than in the placebo group (hazard ratio, 0.71; 95% CI, 0.47 to 1.08), but this result was not significant (P=0.11) (Table 3). Further exploratory analyses found no obvious differences between the two groups in pregnancy rates (incidence rates, 21.8 in the cellulose sulfate group and 23.1 in the placebo group; P=0.74), in findings on examination, or in patterns of self-reported sexual acts, condom use, or gel use that would explain the results of potential increased risk found in the interim and per-protocol analyses. Adjustment for prespecified baseline covariates (including the presence or absence of a sexually transmitted infection detected at screening, previous pregnancy, anal sexual intercourse, condom use, and previous spermicide use, as well as the number of sexual partners) had a negligible effect on the estimate of effectiveness (hazard ratio, 1.64).

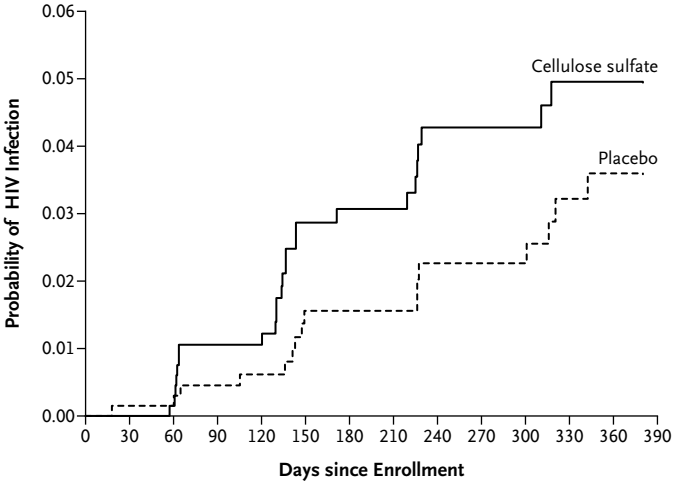

Figure 2. Kaplan–Meier Estimates of the Cumulative Probability of HIV Infection.

ADVERSE EVENTS

All adverse events were coded on the basis of the *Medical Dictionary for Regulatory Activities* (MedDRA), version 6.1. In total, 86.0% of women had one or more adverse events during follow-up, with no clinically important differences between the two groups. The most common adverse events were infections and infestations, including bacterial vaginitis (46.8% of women), candidiasis (38.3%), respiratory tract infection (20.2%), malaria (14.1%), and genital infections (11.4%). Common noninfectious reproductive-system events included pruritus (8.4%), metrorrhagia (6.0%), and vaginal discharge (5.1%). The frequency of adverse events of the reproductive tract occurring in more than 1% of women are reported in Table 4.

There were 68 serious adverse events with onset on or before January 30, 2007 (none considered related to product use), with more events in the

Table 4. Adverse Events of the Reproductive Tract That Occurred in at Least 1% of Participants.*

Event	Cellulose Sulfate (N=706)		Placebo (N=692)	
	no. of events	*no. of women with event (%)*	*no. of events*	*no. of women with event (%)*
Infection or infestation				
Vaginitis, bacterial	496	316 (44.8)	543	339 (49.0)
Genital candidiasis	424	259 (36.7)	438	276 (39.9)
Genital infection†	103	83 (11.8)	101	77 (11.1)
Cervicitis†	67	39 (5.5)	83	52 (7.5)
Pelvic inflammatory disease	49	42 (5.9)	49	39 (5.6)
Urinary tract infection	48	39 (5.5)	52	40 (5.8)
Trichomoniasis	38	35 (5.0)	39	34 (4.9)
Syphilis	7	7 (1.0)	10	10 (1.4)
Herpes simplex	8	8 (1.1)	8	8 (1.2)
Condyloma acuminatum	9	7 (1.0)	2	2 (0.3)
Other events				
Genital pruritus, female	67	62 (8.8)	60	56 (8.1)
Metrorrhagia	46	41 (5.8)	46	43 (6.2)
Vaginal discharge	46	41 (5.8)	33	30 (4.3)
Pelvic pain	17	17 (2.4)	17	15 (2.2)
Genital ulceration	11	10 (1.4)	9	8 (1.2)
Menorrhagia	8	8 (1.1)	13	10 (1.4)

* Event categories are named with the preferred term of the *Medical Dictionary for Regulatory Activities,* version 6.1.
† Diagnoses were based on a clinical examination (syndromic approach).

placebo group than in the cellulose sulfate group (40 vs. 28). The most common serious adverse events were abortion or abortion-related events (15 events) and pyrexia (11 events). There were three deaths, all in the cellulose sulfate group: one suicide, one homicide, and one death due to complications of uncontrolled hypertension.

DISCUSSION

On the basis of these results, cellulose sulfate gel has no role as an HIV prevention method. There was a higher rate of HIV acquisition in the cellulose sulfate group, although the result did not achieve statistical significance in the primary analysis. The suggestion of increased risk observed in a secondary per-protocol analysis must be viewed with caution, since data were censored on the basis of a postrandomization factor (product withdrawal) that could have been confounded with group assignment.

Given the contraceptive profile of cellulose sulfate,[14] the nondifferential pregnancy rates imply that adherence to gel use may have been low during sexual acts without condoms. This finding is in agreement with self-reported data indicating low rates of gel use (45.8%) for these high-risk acts, even though overall adherence was excellent (87.0%). Such a pattern of low adherence when condoms are not used would make it unlikely that an act-specific effect of cellulose sulfate gel (either harmful or protective) could have been detected, even if the trial had gone to completion. However, it does not preclude the possibility of an increased risk of HIV based on cumulative exposure to the product. On average, women in Benin and Uganda reported using gel two to three times per day for the duration of the study. This raises the question of whether effectiveness trials of coitally dependent microbicides should be done in two cohorts of women: one with a high coital frequency, to assess potential negative effects of high product exposure, and one with low coital frequency, to assess effectiveness in less–sexually-active populations.

Low adherence has been identified as a prob-

lem in several HIV prevention trials. The Population Council could not rule out the possibility that the lack of a protective effect in their trial was due to poor adherence.[18] The investigators of a recent trial assessing the effect of suppression of herpes simplex virus on HIV transmission also concluded that the lack of an effect may have been due to low adherence.[19] A standard for assessing adherence has not yet been identified. Some advocate the use of directly observed therapy or related high-intensity adherence monitoring, whereas others are wary of the potential problems and limitations associated with such designs (e.g., confidentiality, participant travel, and increased trial costs). The Institute of Medicine's conclusion that directly observed therapy is not advisable in this context[20] raises additional doubts about the approach. Alternative vaginal delivery systems (e.g., antiretroviral drugs released from vaginal rings) may prove more beneficial in terms of monitoring and increasing adherence.

Neurath et al.[21] found decreased anti-HIV activity of polyanions in the presence of semen, but this does not explain the suggestion of increased risk that led to premature closure of the reported trial. Balzarini et al.[22] found that PRO2000 (another polyanion) may stimulate HIV capture, but it is not known whether this finding can be extrapolated to cellulose sulfate. A parallel phase 3 trial in Nigeria[23] among women using cellulose sulfate gel approximately once per day found a slightly higher infection rate in the placebo group, although the result was not significant.

Despite the disappointing outcome of this study and recently halted vaccine trials,[24] as well as the lack of a protective effect in other recently completed HIV prevention trials,[18,25,26] the search for HIV prevention methods that can be initiated by women must continue to help stem the tide of infection in highly vulnerable populations.

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APPENDIX

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