A randomized controlled safety and acceptability trial of dextrin sulphate vaginal microbicide gel in sexually active women in Uganda

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Objective: To assess the safety of dextrin sulphate (DS) gel compared to placebo gel in terms of local and systemic adverse events, and to determine the acceptability of dextrin sulphate gel.

Design: A 4-week randomized trial of DS intra-vaginal gel, partially blinded, with placebo and observation control arms. Participants were randomized to use DS gel twice daily, placebo gel twice daily, DS gel pre-sex, or into an observation only arm.

Methods: Sexually active women were recruited from post natal and HIV clinics at Nsambya Hospital, Kampala, Uganda. Screening, enrolment and follow-up visits took place every 1 or 2 weeks over an 8-week period and consisted of questionnaire interviews, colposcopy examinations, sexually transmitted infection screen and routine laboratory testing.

Results: Out of a total of 172 women screened, 109 were randomized to use DS gel twice daily (65 women), placebo gel twice daily (15 women), DS gel pre-sex (nine women) or into an observation only arm (20 women). Two individuals had abnormal colposcopy findings in the DS twice daily gel use arm. Vaginal bleeding was reported as frequently by participants in the active gel arm as by participants in the placebo and observation only arms. No clinically significant difference was observed between arms in terms of vaginal flora, *Candida*, haemoglobin, white cell count, platelets, thrombin time, activated partial thromboplastin time, creatinine and aspartate aminotransferase results after 4 weeks of gel use. DS gel appeared to be acceptable to over 95% of the users.

Conclusions: Results show a satisfactory safety and acceptability profile of dextrin sulphate gel.

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Introduction

The majority of adult human immunodeficiency virus (HIV) infections are acquired through heterosexual intercourse. Previous sexually transmitted HIV prevention efforts have targeted consistent condom use, abstention from sex and delay of sexual debut. However, these assume that women are in a position to make

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empowered choices, abstain from sex, live within monogamous sexual relationships or consistently use condoms. To quote the AIDS Epidemic Update 2004: 'HIV prevention efforts do not take into account the gender and other inequalities that shape people's behaviours and limit their choices' (UNAIDS, 2004, p. 9). This is particularly true of women living in sub-Saharan Africa and other developing countries, and more so of women living there in poverty. More than 60% of people living with HIV in the world live in sub-Saharan Africa (around 25.4 million people), and statistics show around 11.5 million women in 2004 in this part of the world were infected compared with around 10 million men [1]. There is still an urgent need for additional methods to prevent the heterosexual transmission of HIV, and vaginal microbicides, which would remain under the control of women, are being developed as part of the global response to this need [2,3].

A 'microbicide' is a topically applied chemical agent (formulated as gels, creams, films, pessaries or suppositories) that could prevent HIV and sexually transmitted infection (STI) transmission in a number of ways: disrupting or disabling organisms, or interfering with cell surface receptors to block entry into host cells. For HIV-1 such inhibition of sexual transmission could be mediated via the viral membrane, envelope glycoproteins, reverse transcriptase, or cellular receptors such as CD4, co-receptors, or C-type lectin receptors [4]. The first microbicide to reach human trials was Nonoxynol-9 (N-9) in the late 1980s. N-9 was available for many years as a contraceptive and was shown to be effective against HIV *in vitro* [5]. However, a recent technical consultation reviewing the evidence from studies conducted on N-9 recommended N-9 is no longer used for STD or HIV prevention. The report concluded that N-9 may increase the risk of HIV infection through cytotoxicity to the cervico-vaginal mucosae [6].

More recently, new microbicides have been under development. Dextrin sulphate (DS) has been shown to inhibit HIV infection in a variety of cell lines by blocking viral entry into susceptible cells [7]. Phase I trials using DS microbicide gel were still being completed in the United Kingdom and Belgium around the start of the present study but available data showed that the product had no serious side effects and was not systemically absorbed [8,9]. As a result of its promising safety profile and in-vitro activity, a phase II safety and acceptability study of 4% DS gel was carried out in Uganda.

Methods

Women were recruited from the post-natal clinic and outreach clinics in the surrounding area of Nsambya Hospital, Kampala, Uganda. The study clinic was located in the hospital grounds. Laboratory testing was performed at the Medical Research Council/Uganda Virus Research Institute in Entebbe, around 30 km away. Participants were healthy, sexually active females aged between 18 and 45, willing to undergo HIV testing, genital infection screens and examinations, reported willingness to use condoms for the duration of the study and able to give informed consent. Sexual activity was defined as having sexual intercourse at least twice a week. Exclusion criteria included being pregnant or within 6 weeks postpartum, untreated gonorrhoea, *Chlamydia, trichomonas*, syphilis or symptomatic bacterial vaginosis, abnormal grade II haematology or biochemistry observations, clinical coagulation disorder, cervical intraepithelial neoplasia (CIN) greater than or equal to CIN II within the preceding 3 months, acute or subacute pelvic inflammatory disease, latex allergy, post-coital or intermenstrual bleeding in the previous 3 months and persistent abnormal vaginal discharge.

Around the time the Ugandan trial was due to start, data from the European phase I studies of DS showed an unexpectedly high number of instances of intermenstrual bleeding in participants using DS gel and placebo in comparison with those using no gel [10]. The Ugandan trial design was amended from the original 80 participants randomized to receive DS gel ($n = 65$) or placebo gel ($n = 15$), to include a no gel group and a group randomized to use DS gel prior to sex only. The pre-sex group was chosen to explore the theory that cumulative gel may precipitate an increased awareness of intermenstrual bleeding. It was also decided to restrict the population to HIV-negative women and to review safety data after the first 35 women had completed follow up.

Following this early data review, the DMC recommended the trial continue in Uganda and the trial steering group made the decision to amend the study design to a double-blind, placebo-controlled, twice daily gel trial, including an additional group of women under observation only. Since the proportion of women reporting intermenstrual bleeding in the pre-sex arm was similar to that in the twice daily arm, the trial proceeded to randomize another 54 participants to use active or placebo gel twice daily and a further 10 into the observation arm. The second part of the trial included HIV-positive women recruited from the HIV clinic within the hospital grounds, providing they brought their partner for HIV testing and the couple were shown to be concordantly HIV positive.

The sequence of trial visits and investigations are shown in Fig. 1. At the recruitment interview volunteers were given verbal and written information about the trial. Those interested in participating were given a screening appointment. Women found to have STIs were treated according to national syndromic treatment guidelines and enrolment was deferred until after treatment. Participants were given 12 000 Uganda shillings (equivalent to approximately £4.50) at each scheduled visit to cover

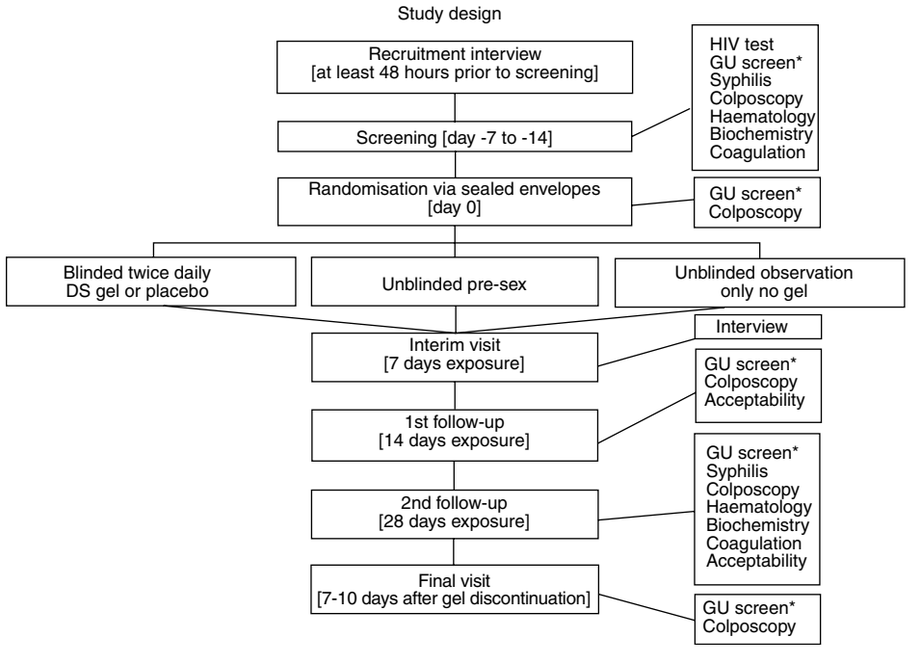

Fig. 1. Trial visits and investigations. *Genito urinary (GU) screen comprising microscopy of vaginal smear (neutrophils, *Candida* clue cells and Nugent score), urine sample for culture of Trichomonas vaginalis and ligase chain reaction testing for *Neisseria gonorrhoea* and *Chlamydia trachomatis*.

transport costs and a meal and drink while at the clinic. The trial included six scheduled visits spanning a period of approximately 8 weeks. Participants were given diary cards to complete while they used the gel to help them remember when they had used it and any symptoms they noted. Illiterate participants were advised to mark the cards in any way they felt comfortable to indicate they had used the gel, and to remind them to discuss any symptoms with the trial team.

Each participant in the trial signed or gave a thumb-printed consent to participate before screening and prior to enrolment in the trial. Ethics committee approval was obtained from Nsambya Hospital Research Committee, Uganda Virus Research Institute Science and Ethics Committee, Uganda National Council of Science and Technology and St Mary's Hospital Ethics Committee, London, UK. Volunteers were given pre- and post- HIV-test counselling in a private, supportive environment.

The primary objective of the trial was to determine the safety of DS gel in terms of local and systemic adverse events. Secondary objectives were to determine all other severe adverse events (clinical and laboratory) deemed possibly or probably related to gel, unexpected vaginal bleeding, acceptability of the study gels, and the effects of the study gel on vaginal flora.

Trial intervention

Study product was supplied in cardboard cartons containing 16 single-use tubes. Each of these tubes contained 2 g of gel and a single-use two-part plastic vaginal applicator. Participants were shown how to fill the applicator and instructed on how to insert the gel. They were asked to insert the study product into their vagina either before sex only, or twice a day, depending on the randomization outcome. Those randomized to the twice-a-day arm were instructed to time one of the applications to allow prolonged exposure, anticipated to be prior to the longest period of sleep, and the other 12 h later.

Laboratory assessments

A blood sample was taken from each woman for rapid HIV testing (Capillus HIV-1/HIV-2 rapid slide agglutination assay; Trinity Biotech Plc, Bray, County Wicklow, Ireland) and serum was transported to the MRC laboratories in Entebbe for confirmatory enzyme-linked immunosorbent assay (ELISA) testing of all specimens (Recombigen HIV-1/HIV-2 EIA; Trinity Biotech Ltd, and Wellcozyme HIV Recombinant EIA; Murex Biotech Ltd, Dartford, Kent, UK). Samples with discrepant results on ELISA were further tested by western blot (Cambridge Biotech, Calypte Biomedical Corporation, Rockville, Maryland, USA).

Neisseria gonorrhoea and *Chlamydia trachomatis* detection was performed by Ligase Chain Reaction (Abbott Laboratories, Abbott Park, Illinois, USA) on an endocervical swab. Bacterial vaginosis was assessed by microscopy of a Gram-stained vaginal smear to give a Nugent's score [11]. The presence or absence of *Candida*, clue cells and neutrophils was also assessed from the smear. *Trichomonas vaginalis* was detected by TV-Inpouch cultures

(Biomed Diagnostics Inc, San Jose, California, USA) from a high vaginal swab.

The vaginal pH was assessed at examination. Thrombin time and activated partial thromboplastin time (APTT) ratio coagulation measurements were assayed in Entebbe. Specimens were transported in a cool box and tested within 4 h of the specimen being taken. The reagents were supplied by Sigma (Poole, Dorset, England) and the test was performed using a KC 1A micro-coagulation analyser. Tests and controls were performed in duplicate.

Haemoglobin, white blood cell and platelet haematology were read at Nsambya hospital from 5 ml of blood collected from the ante-cubital fossa using a sterile needle. Aspartate aminotransferase (AST) and creatinine biochemistry measurements were also read at Nsambya hospital from another 5 ml of blood collected in a similar way.

Haematology and chemical pathology specimens were taken to the hospital laboratories regularly during the day. Coagulation specimens were kept on ice and transported with the HIV and syphilis specimens in the afternoons to MRC laboratories in Entebbe. Coagulation specimens were frozen and analysed in batches.

Pregnancy tests were performed by analysis of a urine sample for human chorionic gonadotrophin (HCG) by immunoassay at both enrolment and week 4 follow-up visits in the clinic laboratory.

Data management

Data were recorded at each visit on duplicate carbonized case record forms (CRFs) by the study clinician or social scientist. The CRFs were stored in individual participant folders in the clinic office. Once all laboratory results were available from a particular visit the duplicate forms were separated and one copy was sent to the data management department of the Medical Research Council offices in Entebbe. The CRFs were double-data entered and verified in an Access 1997 database (Microsoft Corporation, Redmond, Washington, USA) and statistical analyses were performed in STATA 6 (STATA Corporation, College Station, Texas, USA) after data cleaning.

Results

Sixty-one volunteers were screened between April and August 2001 to enrol 35 participants into the first stage of the trial. These 35 participants were randomized to receive DS gel or placebo twice daily for 28 days (16 participants), DS gel before sex only for 28 days (nine participants) or into an observation arm where participants followed the protocol apart from using the study product (10 participants). The remainder of the participants were screened and followed between March and November 2002. In total 172 women were screened and 59 were excluded for a number of reasons including being HIV positive when screened during the first part of the trial (18), having abnormal laboratory results at screening (four), being in an HIV discordant relationship (12) or having sex less than twice a week (two). In all, 65 women were randomized to use DS gel twice daily (38 HIV negative and 27 HIV positive), 15 to use placebo gel twice daily (nine HIV negative and six HIV positive), nine to use DS gel before sex (all HIV negative in the first part of the trial), and 20 to the observation arm (15 HIV negative and five HIV positive). Four enrolled participants were lost to follow-up: one in the DS twice daily and one in the observation arm could not be traced after their enrolment visits, one in the placebo arm started a new business and failed to come to the clinic for her final follow up visit, and one in the pre-sex arm withdrew consent on the advice of her partner after her enrolment visit.

Baseline characteristics (age, education, religion, menstrual cycle, and the number of sex acts per week), past medical histories, STI results at screening and after follow-up were very similar across the four study arms (Table 1).

Two participants in the active DS twice daily arm had abnormal colposcopic findings that had not been observed on examination at the two visits prior to randomization. In the first a single, small, superficial vulval epithelial disruption was recorded at the final follow up visit, noted as being a possible herpetic ulcer. The second had a single, small, superficial cervico-vaginal cystic swelling observed after both 4 weeks of gel use and at the final follow-up visit. Seven other individuals also had vulval or cervico-vaginal epithelial disruptions or other abnormalities observed on colposcopy examination (one in the twice daily DS arm, three in the placebo arm, one in the pre-sex DS arm and two in the observation arm), all noted before gel administration.

Participants were asked to report non-menstrual spotting at each follow-up visit after enrolment in the trial. Eleven participants reported spotting: six of 65 (9.2%) in the twice daily DS arm, two of 15 (13.3%) in the placebo twice daily arm, one of nine (11.1%) in the pre-sex DS arm, and two of 20 (10%) in the observation arm. The participant reporting non-menstrual spotting in the pre-sex arm reported it occurring before she started using the gel, and one of the participants in the observation arm and two in the active gel twice daily arm reported using hormonal contraceptives.

Table 2 shows the laboratory results by arm after 4 weeks of gel use. There was no evidence to suggest differences between the active gel, placebo gel and observation arms in terms of Candida, haemoglobin, white cell count,

Table 1. Baseline characteristics of participants by arm of trial.

	BD DS gel $N = 65$	BD Placebo gel $N = 15$	Pre-sex gel $N = 9$	Observation $N = 20$	Total $N = 109$
Age median (range)	28 (22.5, 34.5)	28 (24, 30)	26 (19, 31)	27 (22.8, 34.8)	28 (22.5, 33.5)
Religion *n* (%)					
Anglican	22 (33.9)	8 (53.3)	3 (33.3)	3 (15.0)	36 (33.0
Catholic	24 (36.9)	6 (40.0)	4 (44.4)	12 (60.0)	46 (42.2)
Muslim	16 (24.6)	1 (6.7)	2 (22.2)	3 (15.0)	22 (20.2)
Other[a]	3 (4.6)	0	0	2 (10.0)	5 (4.6)
Education *n* (%)					
None	5 (7.7)	0	1 (11.1)	1 (5.0)	7 (6.4)
Primary	34 (52.3)	9 (60.0)	7 (77.8)	10 (50.0)	60 (55.1)
Secondary	26 (40.0)	6 (40.0)	1 (11.1)	9 (45.0)	42 (38.5)
No. days since last menses (participants were asked this question if they had not had menses in the last 3 months) median (IQR)	55 responses 10 (4, 20)	14 responses 14 (4, 21)	6 responses 12 (2.3, 28)	16 responses 8 (3.3, 18.8)	91 responses 10 (4, 20)
If last menses > 3 months:					
Lactation amenorrhoea – Yes *n* (%)	7 (70.0)	1 (100)	2 (66.7)	3 (75.0)	13 (76.5)
Lactation amenorrhoea – No *n* (%)	3 (30.0)[b]	0	1 (33.3)[c]	1 (25.0)[b]	5 (27.8)
Max. duration menses, median days (range)	4 (3, 4.5)	4 (3, 4)	4 (3.5, 4.5)	4 (4, 5.8)	4 (3, 5)
Min. menstrual cycle, median days (range)	28 (28, 28)	28 (28, 28)	28 (28, 28)	28 (28, 28)	28 (28, 28)
Average number of sex acts per week *n* (%)					
Two or three	62 (95.4)	15 (100)	8 (88.9)	19 (95.0)	104 (95.4)
Four or more	3 (4.6)	0	1 (11.1)	1 (5.0)	5 (4.6)
Negative STD screen	44 (67.7)	10 (66.7)	7 (77.8)	16 (80.0)	77 (70.6)

[a]Adventist, Pentecostal; [b]Hormonal induced amenorrhoea, using injectable contraceptives; [c]Had abortion 6 weeks previously. BD, twice daily; DS, dextrin sulphate; IQR, interquartile range; STD, sexually transmitted diseases.

platelets, thrombin time, APTT, creatinine and AST results after 4 weeks of gel use.

A positive pregnancy result was reported in a 31-year-old HIV-negative participant in the DS gel twice daily arm at her final follow-up visit, 16 days after completing gel use. She had a spontaneous abortion 42 days after completing gel use. Investigation found the woman to have had four previous live births and two other pregnancies that did not run to term. The clinical decision was that this event was highly unlikely to have been related to gel use.

Sixty-one participants reported other adverse events which included dysuria, itching, burning and dyspareunia (Table 3). Most of these events were mild (57 of 61), lasted 2 or 3 days, and in most cases were observed in similar proportions in each of the arms. Moderate events were reported in two cases of malaria, both in the DS twice daily gel arm, one case of dyspareunia in the DS twice daily gel arm, and one case of eczema in the DS twice daily gel arm. Eight of the 65 (12.3%) women in the DS twice a day arm and one of nine (11.1%) in the DS pre-sex arm spontaneously reported excessive thirst on the diary cards (Fisher's exact test *P*-value 0.4 comparing frequency of reports in women using DS twice daily with women in the placebo group). This symptom was unsolicited and not reported in the placebo or observation arms. All the women reporting thirst described it lasting between 2 and 6 days in the first week of gel use.

All 64 participants followed up to visit 3 in the DS twice daily gel arm, and 14 of 15 in the placebo arm, reported using condoms before participating in the trial. When asked how frequently they used condoms before enrolling in the trial five of 64 (7.8%) women in the DS gel twice a day arm answered 'always', three of 64 (4.5%) 'mostly' and 55 of 64 (85.9%) 'sometimes', compared with one of 14 (7.1%) answering 'always', one of 14 (7.1%) 'mostly' and 13 of 15 (86.7%) 'sometimes' in the placebo arm. The number of participants who claimed to use condoms every time they had sex in the previous week increased marginally from 75 to 79% during the course of the 4 weeks in the trial. Only one participant in the DS pre-sex arm reported a drop in 'always' use of a condom in the previous week from visit 3 to visit 4.

None of the participants using either active or placebo gel reported finding it difficult to insert. Compliance with gel use was good with 70 of 79 (88.6%) participants reporting using it twice a day every day for the follow-up period (this includes 26 participants who reported taking a break from using the gel while they had their menses, which was not considered a protocol deviation). Eleven women reported the gel interfered with sex due to too much lubrication. All of these women were in the active DS

Table 2. Comparison of laboratory results by arm at baseline (screening) and after 4 weeks of follow-up.

Results, median (IQR)	DS gel twice daily $N = 65$ at baseline, 64 at week 4	Placebo gel twice daily $N = 15$	DS gel pre-sex $N = 9$ at baseline, 8 at week 4	Observation $N = 20$ at baseline, 19 at week 4
Haemoglobin (g/dl)				
baseline	13.2 (12, 13.8)	12.7 (12, 13.7)	12.8 (11.6, 13.9)	12.6 (12, 13.6)
week 4	12.9 (12, 13.8)	13.1 (12.3, 13.3)	12.6 (12, 13.2)	12.5 (11.8, 13.4)
White cell count (10^9/l)				
baseline	5 (4.3, 5.9)	5.2 (3.5,5.8)	6.1 (4.9, 6.9)	4.7 (3.8, 6.4)
week 4	4.8 (4, 5.7)	4.1 (3.3, 6.3)	5.6 (4.6, 6.4)	5.3 (4.2, 5.9)
Platelet count (10^9/l)				
baseline	253 (219, 303)	264 (203, 329)	334 (261, 365)	258 (210, 298)
week 4	259 (211, 302)	284 (222, 362)	314 (297, 368)	272 (185, 307)
Creatinine (μmol/l)				
baseline	0.4 (0.2, 0.7)	0.5 (0.3, 0.8)	0.5 (0.3, 0.8)	0.5 (0.2, 0.7)
week 4	0.5 (0.3, 0.8)	0.4 (0.3, 0.5)	0.5 (0.3, 0.7)	0.4 (0.3, 0.5)
AST (IU/l)				
baseline	19 (14.5, 22)	21 (17, 23)	14 (12, 18)	21 (16, 26)
week 4	19 (16.8, 23)	23 (20, 35)	22.5 (17, 26.8)	21 (19.8, 28)
APTT ratio				
baseline	1.0 (0.9, 1.1)	1.0 (1.0, 1.1)	1.1 (0.9, 1.2)	1.0 (1.0, 1.1)
week 4	1.0 (0.9, 1.1)	1.0 (0.9, 1.2)	1.0 (0.9, 1.1)	1.1 (1.0, 1.2)
Thrombin time (s)				
baseline	15.4 (14.4, 16.6)	15.6 (14.2, 16.4)	14.2 (13.8, 16.3)	15.0 (14.0, 16.3)
week 4	14.9 (13.8, 16.1)	14.7 (13.8, 15.9)	14.3 (12.6, 15.9)	15.3 (13.5, 16.2)
Candida, number positive (%)				
baseline	5 (7.7)	1 (6.7)	2 (22.2)	2 (10.0)
week 4	8 (12.5)	3 (20.0)	1 (12.5)	1 (5.3)
Nugent score N > 7 (%)				
baseline	21 (47.7)	3 (33.3)	1 (11.1)	9 (45.0)
week 4	23 (52.3)	6 (66.7)	1 (12.5)	12 (63.2)

N, number of participants. IQR, interquartile range; DS, dextrin sulphate; AST, aspartate aminotransferase; APTT, activated partial thromboplastin time.

Table 3. Comparison of adverse events reported during follow-up.

Symptom *n* (%)	DS gel twice daily $N = 65$ (%)	Placebo gel twice daily $N = 15$ (%)	DS gel pre-sex $N = 9$ (%)	Observation $N = 20$ (%)	Total $N = 109$ (%)
Dysuria	3 (4.6)	0	2 (22.2)	1 (5.0)	6 (5.5)
Itching	10 (15.4)	3 (20.0)	0	4 (20.0)	17 (15.6)
Burning	2 (3.1)	0	1 (11.1)	1 (5.0)	4 (3.7)
Dyspareunia	1 (1.5)	0	0	0	1 (0.9)
Thirst	8 (12.3)	0	1 (11.1)	0	9 (8.3)
Other[a]	16 (24.6)	5 (33.3)	2 (22.2)	1 (5.0)	24 (22.0)

[a]Other reported events included malaria, fever, joint pains, diarrhoea, tonsilitis, eczema and conjunctivitis. *N*, number of participants. DS, dextrin sulphate.

twice a day arm. Sixty-three of 65 (98%) women in the active gel twice daily arm reported they would recommend the gel to others, and the same number (63 of 65, 98%) reported they would definitely or probably continue using the gel if it was available for free.

Discussion

The findings from this study indicate a satisfactory safety and acceptability profile of dextrin sulphate gel given for 4 weeks in a peri-urban Ugandan population. Minimal adverse events were reported with no significant differences between the trial arms. These are important findings that would lend support to proceeding to a phase III efficacy trial.

Genital examination identified a low frequency of epithelial disruption in the population. Abnormalities observed on colposcopy were largely thought to be unrelated to gel and were often present before the onset of gel application. The majority of these findings were vulval warts, herpetic ulcers, polyps and Candida.

The frequency of inter-menstrual bleeding observed in this study population was lower than that observed in similar studies conducted in Europe, where it was reported in up to 25% of participants [10]. Inter-menstrual bleeding reported during this trial occurred in

only six (9.2%) of 65 women using DS gel twice daily, it was mild, lasted 1 to 2 days and did not warrant interrupting or discontinuing gel application. The frequency of reports of inter-menstrual bleeding reported in women under observation only was similar to the frequency in those using gel. A recent community-based study in the UK has suggested that irregular inter-menstrual loss in healthy women may be much more frequent than previously thought [12]. The reasons for the difference in frequency of inter-menstrual bleeding in different populations is unclear but a number of clinical and behavioural differences exist between these European and African populations such as differences in contraceptive use, smoking and vaginal hygiene practices.

Most other adverse events were mild (64 of 68) and were similarly distributed across the trial arms. Although all the women reporting excessive thirst whilst using the gel were in the active DS gel arms, there is no obvious explanation for this finding. One would expect that thirst could be a problem if the DS gel was absorbed into the blood stream, yet after 4 weeks of gel use each of the participants reporting the finding had normal AST and thrombin time measurements, and only one had a mild APTT abnormality of 1.3 (the normal range defined in the protocol is 0.8–1.2). Haematology, coagulation and biochemistry assessments remained essentially unchanged during the course of the trial.

The woman who had the spontaneous abortion subsequent to completing follow-up in the trial had had two previous spontaneous abortions. The clinical opinion was that this event was highly unlikely to be related to the woman's use of the study product but the protocol definitions allowed only for a 'possible' relationship to gel use being assigned to the event due to its 'reasonable temporal relationship' with study product use.

There was very little evidence of reported change in condom use while women were participating in the trial. Most participants said they used condoms during the trial because they were instructed to do so by study staff. Women were advised that they would be required to use condoms consistently for the duration of the trial at their recruitment visit, and it was one of the inclusion criteria that they were willing to receive condoms and health education about condoms during the trial. This may have meant that women who thought their partners would not be willing to use condoms did not volunteer to participate. While recruiting women to participate in the first part of the trial it became apparent that they were seeking partner approval before choosing to participate. As a result the team designed an information sheet for the male partners of women wishing to participate in the trial. This may also have helped the number of women who were able to report a consistent or increased use of condoms during their time in the trial.

The gel was well tolerated by the participants, who appeared to have few problems using it, and there was a high compliance rate of gel use.

In conclusion, the results of the trial in terms of both local and systemic toxicity, and acceptability of the gel, have proved favourable. Few abnormal colposcopy findings and a low frequency of inter-menstrual bleeding were observed. No significant changes in vaginal flora or evidence of systemic toxicity related to gel use were observed. Other adverse events were reported with a similar or lower frequency in the twice-daily active DS gel arm, apart from the finding of 'excessive thirst' which needs further investigation.

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Addendum

The MRC/DfID funded Microbicides Development Programme (MDP) began in October 2001, and this Ugandan Microbicides Initiative in Africa (MIA) phase II dextrin sulphate trial ended in November 2002. Subsequently, additional *in vitro* and *in vivo* data have emerged and the MDP Programme Management Board reviewed all of the data on dextrin sulphate and other similar compounds in August 2004. Although it was recognized that dextrin sulphate had a favourable safety profile it was also noted that it had significantly lower activity against R5 viruses (the type of virus now recognized as the dominant type in mucosal transmission) in comparison with the other polyanions. For this reason the MDP decided not to proceed with dextrin sulphate in the planned Phase III effectiveness trial. This decision was documented in a press release on the MDP website with http reference http://www.mdp.mrc.ac.uk/downloads/Statement_2409.doc.