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A randomised placebo-controlled safety and acceptability trial of PRO 2000 vaginal microbicide gel in sexually active women in Uganda

Keywords: Vaginal microbicide, clinical trial, HIV

Authors: Anatoli Kamali^a; Helen Byomire^a; Catherine Muwonge^a; Julie Bakobaki^b; Clare Rutterford^b; Pius Okong^c; Albert Profy^d; Romano Byaruhanga^c; Stella Namukwaya^a; Sheena McCormack^b; Heiner Grosskurth^{a,f}; Andrew J Nunn^b; Charles JN Lacey^e.

^aMRC Uganda/UVRI Research Unit on AIDS, Entebbe, Uganda

^bMRC Clinical Trials Unit, London, UK

^cSt Francis' Hospital, Nsambya, Kampala, Uganda

^dIndevus Pharmaceuticals, Inc, USA

^eHull York Medical School, University of York, UK

^fLondon School of Hygiene and Tropical Medicine, UK

Correspondence to: Prof Charles JN Lacey, Hull York Medical School, University of York, York YO10 5DD, UK. **Email:** charles.lacey@hyms.ac.uk

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Abstract

Objectives

To determine the safety of 0.5% and 2% PRO 2000 gel in terms of local and systemic adverse events (AEs), and the acceptability of gel use.

Design

A randomized placebo-controlled trial among healthy, sexually active African women aged 18-45 years. Between June 2003 and September 2004, 180 consenting women were randomized to one of 4 groups: PRO 2000 gel (0.5% or 2%), placebo gel or condom use only. Participants were screened for sexually transmitted infections, with HIV counseling and testing. Women randomised to gel used this intravaginally twice daily for 28 days. Follow-up visits were fortnightly up to 6 weeks from enrolment, and comprised a physical examination including colposcopy, laboratory testing and questionnaire interviews.

Results: Ten women were lost to follow-up, none due to AEs. Adherence with total gel doses was 69%. Observed rates of the primary toxicity endpoints, ulceration >2 x 1cm and clinically relevant coagulation abnormalities were, for PRO 2000 0.5%: 1.6% (95% CIs 0.04–8.5%) & 0% (97.5% CIs 0-5.7%), and for PRO 2000 2%: 0% & 0% (97.5% CIs 0-5.9%) Women randomized to active gels did not show an increased rate of AEs. Gel use had no significant effect on haematology and biochemistry results. Women found gel use highly acceptable.

Conclusions: Both concentrations of PRO 2000 gel were found to be safe and well tolerated. These data justified testing the gels in large scale effectiveness trials. The final results of these trials are expected by end-2009.

Key messages:

- Vaginal microbicides are a potential new female-controlled HIV prevention tool
- PRO 2000 is a microbicial polyanionic naphthalene sulphonate polymer with activity *in vitro* and in animal models against HIV-1, HSV2, *N. gonorrhoeae*, and *C. Trachomatis*
- A phase 2 trial studied 180 women in an urban setting in Kampala, Uganda. 149 women used PRO 2000 0.5%, PRO 2000 2% or placebo microbicide twice a day for 4 weeks
- Both concentrations of PRO 2000 microbicide were shown to be safe and acceptable

Introduction

The HIV epidemic in sub-Saharan Africa continues relentlessly, with ~ 1.9 million new infections in 2007.¹ Over 80% of current HIV transmissions are through heterosexual intercourse, with women being more vulnerable due to transmission dynamics, socio-economic factors, and their limited control over safer sexual practices.^{1,2} Female controlled HIV prevention methods are thus urgently needed for women in the developing world. The development of vaginal microbicides offers a potential new prevention strategy, but the results of effectiveness trials with nonoxynol-9, SAVVY, cellulose sulphate, and Carraguard have been disappointing.⁴

PRO 2000 is a microbicial polyanionic naphthalene sulphonate polymer that has been formulated as a vaginal gel.⁵ *In vitro* and in animal models, PRO 2000 blocks infection by a range of HIV isolates, herpes simplex virus, *Neisseria gonorrhoeae* (NG) and *Chlamydia trachomatis* (CT)⁵⁻⁹. Early safety studies showed PRO 2000 gel to be safe, well tolerated and acceptable.¹⁰⁻¹³ We conducted a phase II trial of two concentrations of PRO 2000 gel (0.5% and 2%) among sexually active women in Uganda. The primary objectives of the trial were to investigate product safety in terms of adverse events (AEs) both local, using clinical inspection and colposcopy, and systemic, using haematology, biochemistry and coagulation parameters. Secondary objectives included detection of unexpected inter-menstrual bleeding (IMB), effects on vaginal flora, and documentation of gel acceptability and adherence.

Methods

Screening, enrolment and follow-up

The study procedures were used in a previous study at the same site, and have been described elsewhere.¹³ Briefly, we recruited asymptomatic, sexually active women aged 18-45 years at St Francis Hospital, Nsambya, Kampala. Women were eligible if they were willing to undergo HIV counselling and testing, to use condoms and able to give informed consent. Exclusion criteria included pregnancy, intending to become pregnant, being within 6 weeks postpartum, abnormal colposcopy findings, untreated sexually transmitted infections (STIs), symptomatic bacterial vaginosis (BV), abnormal grade II haematology or biochemistry findings, coagulation disorders, cervical intraepithelial neoplasia grade II/III, post-coital or IMB in the preceding 3 months, pelvic inflammatory disease, latex allergy, and persistent abnormal vaginal discharge. HIV-seropositive women were eligible if they fulfilled all other entry criteria and were in an HIV-positive concordant relationship.

The study design is shown in figure 1. Informed consent (signed or thumb-printed for illiterate participants) was obtained separately for screening and enrolment procedures. Screening tests included HIV, STIs, haematology, biochemistry, and coagulation, and general and genital examinations, including colposcopy, were performed. All women with STIs were treated according to national treatment guidelines before enrolment, with partner notification.

Randomisation was performed in two phases: the first 100 women to either 0.5% gel, placebo gel or an observation (condom only) arm (phase 1); and the last 80 women to either to 2% gel, placebo gel or the observation arm (phase 2). The allocation was weighted so that at least 60 women received active gel in each phase. In both phases we included women in observation only arms who followed the same study schedule but without gel use. Our aim was to enrol between 60 and 65 women into the 0.5% and 2% arms respectively, which allowed for some loss to follow-up, 25 women into a placebo gel control groups, and a further 30 women into observation only arms.

Participants using gel were asked to use one applicator (approximately 2g of gel) intravaginally twice daily for 28 days with interruption during menses if preferred. They were instructed on applicator insertion and provided with sufficient supplies to last two days beyond their next clinic visit. Women were advised to wash their vagina prior to inserting the gel using plain water, as this is the normal local female hygiene practice. Women were provided with condoms and encouraged to use them at all times. An interim visit was conducted after 7 days gel use with a clinical examination only if genital symptoms were reported. Further follow-up visits were performed fortnightly until 6 weeks from enrolment. Adherence with gel administration was measured by structured face-to-face interviews, counting of returned and used applicators, and examination of diary cards at 14 & 28 days follow-up.¹⁴ Between phases 1 and 2 of the study, the medical staff who conducted the interviews and examination changed, in that a male clinician left and was replaced by two female clinicians.

Laboratory methods

NG and CT detection was by polymerase chain reaction (Amplicor, Roche Diagnostics) on endocervical specimens. *Trichomonas vaginalis* (TV) was detected by culture (TV-Inpouch, Biomed Diagnostics Inc.). Bacterial vaginosis was assessed by vaginal pH and Gram stained vaginal smears using Nugent's criteria.¹⁵ HIV testing was performed using a rapid test (Capillus HIV-1/HIV-2 rapid slide agglutination assay, Trinity Biotech). Positive results were confirmed with two independent EIAs (Recombigen HIV-1/HIV-2 EIA, Trinity Biotech, and Wellcozyme HIV Recombinant EIA, Murex Biotech).

Statistical Methods

Data management: Data were double entered and verified using an Access 1997 database (Microsoft Corporation, USA). The data were exported to STATA 9 (STATA Corporation, Texas, USA) using Stat Transfer (1986-2003 Circle Systems, Seattle, USA), for statistical analysis.

Sample size: The sample size calculation was based on the procedure described by Fleming.¹⁶ The underlying assumptions were that a primary toxicity endpoint rate of 15% is unacceptable, and that a gel that results in a toxicity rate of 5% or less warrants further investigation; the study was powered to be able to distinguish between these two rates, for a type I error probability of 5% and a power of 80%, a total of 59 women would be required on active gel. The trial was not powered to make statistical comparisons between the trial arms.

Endpoints and analysis

The primary endpoints of the trial were (i) deep or extensive (>4 swab tips) ulceration of the genital mucosae, and (ii) the development of a clinically relevant coagulation abnormality. The secondary endpoints were Grade 3 clinical, laboratory, or unexpected vaginal bleeding events, Grade 1 unexpected vaginal bleeding (intermenstrual bleeding), development of abnormal vaginal flora, and acceptability of the gels.

All analyses were by intention to treat, at the 5% level of significance. The analysis of binary data was performed using chi-squared tests with the Mantel-Haenszel test controlling for possible confounders of treatment and phase where appropriate. Laboratory parameters at screening were compared with the week 4 visit results; comparisons were made using either a paired t-test or the Wilcoxon signed rank test, depending on the distribution of the data.

Ethical considerations

The Research Ethics Committees of Nsambya Hospital and the Uganda Virus Research Institute, the Uganda National Council of Science and Technology and St Mary's Hospital, London, UK, provided ethical approval of the study. The trial was overseen by a Data Monitoring Committee and a Trial Steering Committee. The participants were provided an equivalent of US\$ 7.00 per visit to compensate for the time spent at the clinic and transport costs.

Results

A total of 320 women were screened between June 2003 and September 2004. 140 women were excluded. Reasons for exclusion were HIV positive with a serodiscordant partner (30), unlikely to comply with the protocol (34), no regular sexual partner (26), pregnancy (9), significant current medical illness (8), abnormal laboratory results (18), sexually inactive (3), recent history of IMB (4) and other gynaecological abnormalities (8).

A total of 180 (107 HIV negative; 73 HIV positive) participants were randomized during the two phases. The first phase included 100 women: 63 allocated to 0.5% gel, 15 to placebo (Plac-1) and 22 to observation only (Obs-1). In the second phase 80 women were randomised, 61 allocated to 2% gel, 10 to placebo (Plac-2), and 9 to observation only (Obs-2). Ten participants (3 on 0.5% gel, 6 on 2% and 1 in the observation group) were lost to follow-up. These participants contributed to the analysis only for periods prior to loss to follow-up. The reasons for loss were: 6 relocated, 2 withdrew consent, 1 was unable to adhere to the visit schedule and 1 was withdrawn by the investigator because the participant expected material gains. No participant discontinued due to AEs.

Table 1 shows baseline demographic characteristics and menstrual history by study arm. In general the groups were similar. The overall HIV prevalence was 40%, with a somewhat lower prevalence among those on 2% gel (33%) compared to those on 0.5% gel (46%). Approximately 85% of women reported 2-3 sexual acts per week. Six (2 on 0.5%, 2 on 2% and 2 in Obs-1) women reported a previous history of IMB or post coital bleeding at screening.

Participants were tested for STIs at screening and at week 4. There were no significant differences in the frequencies of infection across different arms, or between HIV-positive and negative women. Prevalence rates at screening were NG 1.1%, CT 3.3%, TV 6.1%, active syphilis (RPR & TPHA +ve) 8.3%. Although participants were treated at screening and advised re partner notification, a similar proportion of infections were detected at 4 weeks. The frequency in the two assays that can truly detect new or ongoing infection were NG 0.6%, TV 8.1%.

Primary and secondary endpoints

Only one woman developed ulceration > 4 swab tips in area (20 x 10 mm) in the trial, who was randomised to 0.5% PRO 2000 gel (1/63 women, 1.6%, 95% CIs 0.04–8.5%). This woman had ulceration < 4 swab tips in area at visit 4, the end of dosing, which progressed to >4 swab tips at final follow-up. No woman in the trial developed a clinically relevant coagulation abnormality,

These rates are, for the 0.5% arm 0%, 97.5% CIs 0–5.7%, and for the 2% arm 0%, 97.5% CIs 0–5.9%.

Table 2 shows a summary of AEs reported. There were no clinical, laboratory, or unexpected vaginal bleeding serious (Grade 3) adverse events in the study. There were similar rates of AEs among all the study arms. During phase 1, IMB was reported by 7/63 (11.1%) women on 0.5% gel, 1/15 (6.7%) on Plac-1, and 2/22 (9.1%) in the observation arm. In phase 2 IMB was reported by 19/61 (31.1%) women on 2% gel, 2/10 (20.0%) on Plac-2 and 3/9 (33.3%) in the observation arm. All IMB episodes reported by women on active gel were mild except for one graded as moderate and all except one (from 0.5% gel group) were considered as possibly related to gel use. One participant on 2% gel reported post coital bleeding. Six participants (four on 2%, one on 0.5% and one in Obs-1) had signs of vaginal bleeding on examination; of these, 3 did not report related symptoms. In no case could a bleeding source or concurrent epithelial lesion be identified. IMB events that were not observed by a clinician resolved spontaneously, and for gel recipients they resolved without discontinuation of gel use.

There was a borderline significant association between IMB and HIV status after adjusting for treatment arm and randomisation phase (Mantel-Haenszel odds ratio=2.14, 95% CI 0.99-4.65). In addition, there was a significant positive association between an abnormal colposcopy and HIV status (P=0.01) which remained so after controlling for treatment arm and randomisation phase (Mantel-Haenszel odds ratio= 3.16, 95% CI 1.38-7.23).

Analysis of the haematology and biochemistry values at screening and week 4 visits by study arms showed no statistically or clinically significant changes. Median vaginal pH remained the same (pH=5.0) at both visits in phase 1 across all trial arms; in phase 2, pH was 6.0 in the 2% gel arm, 5.5 in the Plac-2 arm, and about 5.0 in the Observ-2 arm, all at both visits. There was no evidence that women with a Nugent score of <7 at baseline developed increased scores while using the gel (P=0.506).

Adherence with gel use

Overall gel adherence at weeks 2 & 4 was 69% (71% in the 0.5% gel, 60% in the Plac-1, 73% in the 2% gel and 50% in the Plac-2 arms, respectively). The main reasons reported for not using the gel were being away from home (11), spotting (5), forgotten (5), and ill health (3).

Six of 146 participants interviewed after 2 weeks and 5 of 144 interviewed after 4 weeks of gel use reported having found the gel difficult to apply, because the applicator was painful on insertion in the vagina. All but 1 woman reported that they would recommend the gel to others and would use it if it were effective and freely available.

Discussion

The study demonstrated that 0.5% and 2% PRO 2000 gel concentrations were acceptable and safe when applied intra-vaginally twice daily for 4 weeks by sexually active women in Uganda. Of the 180 women enrolled, only 7 missed the week 4 follow-up visit. Reasons for not using the gel were largely unavoidable: menstruation, being away from home and ill health.

There was no evidence of local or systemic toxicity related to gel use, and the gels fulfilled the protocol definitions for further study in large scale trials. Earlier studies conducted in sexually abstinent women had also demonstrated lack of systemic absorption of PRO 2000 after vaginal use.¹⁷ Approximately 60% of the AEs were genital tract related and the remainder were due to common background morbidities. None of the AEs necessitated discontinuation of gel use, or expedited reporting to ethics or regulatory authorities.

The rate of abnormal colposcopies was low in both active gel arms (about 4%). The majority of these abnormalities were small vulval superficial lesions. Overall, the rate of reported IMB in both randomisation phases was 19%. We also noted that the reported rate during the 2% phase was significantly higher than in the 0.5% phase in all the comparison arms (Mantel-Haenszel odds ratio=3.78, 95% CI 1.62-8.84). However the clinical staff conducting the interviews changed from a male clinician to 2 female clinicians between phase 1 and phase 2. We believe it likely that female participants in Africa would feel more comfortable reporting genital symptoms to female clinicians, and we feel this is a plausible explanation for the higher reported rate of IMB in all arms during the 2% gel phase. Differences in patient communication of biomedical information with female or male physicians have been previously reported.¹⁸ We found no influence of PRO 2000 on vaginal flora, whereas a reduction in BV has been reported in a phase I safety study in India.¹²

The safety and tolerability of PRO 2000 gel observed in this study are similar to findings in earlier studies in sexually abstinent European women and sexually active HIV-uninfected and abstinent HIV-infected women exposed to 2% and 4% PRO 2000 gel.^{10, 11}

We observed a high STI prevalence rate (~20%) at screening and although STIs were treated in participants and partner notification was conducted, the rate was similar at the week 4 visit. Due to

CT PCR positivity carry over, and syphilis serology dynamics it is not possible to interpret the findings for those infections. However, the GC and TV data presumably represent a mixture of re-infections, new infections and treatment failures. These observations emphasise the need for regular STI screening and health education in microbicide clinical trials. Our data also suggests that PRO 2000 gel does not significantly interfere with the STI assays we used. Indeed the Amplicor CT/NG test includes an internal positive control which detects PCR inhibition, and only about 1% of the specimens collected at the screening visit and 2% of those collected at week 4 showed inhibition. The high HIV prevalence in our study population was related to the presence of a busy HIV clinic on the hospital campus and does not reflect the background prevalence in the general population.

In summary, 0.5% and 2% concentrations of PRO 2000 gel were well tolerated in terms of both local and systemic toxicity by sexually active women both HIV negative and HIV positive when used twice daily for four weeks, and the gel was well accepted within the context of the trial. There was no evidence of systemic toxicity related to gel use. Almost all women stated that they would recommend the gel to others and would definitely use it if it became available. These results provided the justification to evaluate PRO 2000 at both concentrations in a large phase 3 trial to assess its effect on HIV transmission, the results of which will be announced in December 2009.¹⁹

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Disclaimer

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The study was conceived and designed by Charles Lacey, Sheena McCormack, Andrew Nunn, Anatoli Kamali, Pius Okong, Romano Byaruhanga, and Albert Profy. As well as the previous authors, Helen Byomire, Catherine Muwonge, Julie Bakobaki, Stella Namukwaya and Heiner Grosskurth were part of the team that conducted the trial. Clare Rutterford, Julie Bakobaki and

Andrew Nunn conducted the statistical analyses. All authors contributed to the preparation of the manuscript.

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Table 1: Baseline characteristics of participants by arm

Variable	Arm						Total
	0.5% gel N=63	Plac-1gel N=15	Obs-1 N=22	2% gel N=61	Plac-2 gel N=10	Obs-2 N=9	Randomised N=180
Demographic characteristics							
Age-median (25 th , 75 th percentiles)	30 (26, 35)	29 (24, 34)	29.5 (27.8, 36.3)	27 (24, 32)	29.5 (23.8, 30.5)	29 (26, 32)	29 (25, 33.8)
HIV positive - n (%)	29 (46%)	7 (47%)	8 (36%)	21(33%)	4 (40%)	4 (44%)	73 (40%)
Education – n (%)							
None	2 (3.2)	1 (6.7)	1 (4.6)	2 (3.3)	0 (0)	0 (0)	6 (3.3)
Primary	37 (58.7)	10 (66.7)	10 (45.5)	33 (54.1)	5 (50.0)	5 (55.6)	100 (55.6)
Secondary	23 (36.5)	3 (20.0)	9 (40.9)	25 (41.0)	5 (50.0)	4 (44.4)	69 (38.3)
Tertiary	1 (1.6)	1 (6.7)	2 (9.1)	1 (1.6)	0 (0)	0 (0)	5 (2.8)
Menstrual/sexual history							
Last menses >35 days ago	3	1	1	9	1	0	15
Due to lactation amenorrhoea	1	0	0	3	1	0	5
Due to hormonal injectables	1	1	1	6	0	0	9
Max. duration menses, days (IQR)	4 (3, 4)	4 (3, 4)	4 (3, 4)	4 (3, 4)	4 (3, 4)	4 (3, 4)	4 (3, 4)
Min. menstrual cycle- median days (IQR)	28 (28, 28)	28 (28, 28)	28 (28, 28)	28 (26, 28)	28 (27.5, 28)	28 (27, 29)	28 (28, 28)
Reported number of sex acts/week							
n (%)							
2 - 3	54 (85.7)	14 (93.3)	19 (86.4)	52 (85.3)	8 (80.0)	7 (77.8)	155 (85.6)
4 or more	9 (14.3)	1 (6.7)	3 (13.6)	9 (14.8)	2 (20.0)	2 (22.2)	26 (14.4)

Table 2: Comparison of adverse events reported during gel use (N =number of participants) by arm

Event	0.5%	Plac-1	Obs-1	2%	Plac-2	Obs-2	Total
N (%)	N=63	N=15	N=22	N=61	N=10	N=9	N=180
Spotting (IMB)	7 (11.1)	1 (6.7)	2 (9.1)	19 (31.1)	2 (20.0)	3 (33.3)	34 (18.9)
Dysuria	2 (3.1)	1 (6.7)	1 (4.5)	1 (1.6)	0 (0.0)	0 (0.0)	5 (2.7)
Itching	13 (20.6)	5 (33.3)	5 (22.7)	11 (18.0)	2 (20.0)	0 (0.0)	36 (20.0)
Burning	4 (6.3)	3 (20.0)	0 (0.0)	13 (21.3)	1 (10.0)	0 (0.0)	22 (12.2)
Dyspareunia	2 (3.2)	0 (0.0)	0 (0.0)	2 (3.3)	0 (0.0)	0 (0.0)	4 (2.2)
Other	23 (36.5)	2 (13.3)	9 (40.9)	24 (39.3)	6 (60.0)	4 (44.4)	68 (37.8)

Figure 1: Trial visits and investigations

Study design

