A Randomized Male Tolerance Study of Dapivirine Gel Following Multiple Topical Penile Exposures (MTN 012/IPM 010)

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Abstract

Dapivirine (DPV) is a nonnucleoside reverse transcriptase inhibitor with a favorable safety profile following vaginal application. A penile tolerance study was conducted prior to further development of DPV as a candidate vaginal microbicide. Twenty-four circumcised and 24 uncircumcised ($N=48$) healthy HIV-negative male participants aged 18 years or older were randomized 2:1:1 to apply DPV 0.05% gel, matched placebo gel, or universal placebo gel, respectively, to their penis once daily for 7 sequential days. The safety, acceptability, and pharmacokinetic profile of DPV 0.05% gel were assessed by the presence of Grade 2 or higher genitourinary adverse events (AEs) and systemic AEs, a behavioral questionnaire, and pharmacokinetic plasma blood draw, respectively, at the final clinic visit (FCV). There were no Grade 2 genitourinary AEs in 47 participants completing the FCV. One participant in the DPV arm failed to attend the FCV. There were 13 AEs reported; all were Grade 1 except one Grade 2 corneal laceration unrelated to study product. Participants liked the gel to a moderate extent, yet 72% reported they would be “very likely” to use a gel like the one they used in the study every time they have intercourse. DPV was detectable in plasma in all 23 DPV arm study participants at the FCV. On average, the circumcised participants’ DPV concentrations were 54% of those in uncircumcised participants ($p=0.07$). Topical seven-day penile application of DPV 0.05% gel was locally and systemically safe, was acceptable to male participants, and resulted in systemic exposure to the drug.

Introduction

DAPIVIRINE (DPV) IS BEING EVALUATED as a candidate microbicide in both vaginal gel and ring formulations for the prevention of male to female transmission of HIV-1.^{1–4} In previous clinical studies, the antiretroviral DPV demonstrated no safety concerns after topical application to the female genital tract. As part of the further evaluation of the safety and tolerability of DPV, a male tolerance study of DPV 0.05% gel was conducted. Male tolerance studies play an important role in the clinical trials portfolio of vaginal microbicides, as in long-term efficacy studies the male partners of study participants may knowingly or unknowingly be ex-

posed to drug through sexual intercourse. Additionally, there is evidence that many women prefer to have partner support for microbicide use and that men favor involvement in the decision-making process on HIV prevention methods.⁵

This study was carried out to ensure that male partners of female participants in trials of DPV will not be placed at undue risk of genital irritation due to DPV exposure.

Materials and Methods

This Phase 1, randomized, double-blind, two-site, placebo-controlled trial enrolled a total of 48 healthy, English-speaking HIV-negative men, 24 of whom were circumcised and 24

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uncircumcised, at the University of Pittsburgh, Pennsylvania and the University of Alabama, Birmingham clinical research sites. Ethics approval was sought and obtained from the University of Pittsburgh and Alabama, Birmingham Institutional Review Boards prior to the study commencing.

Calculation of sample size was based upon the size of similar Phase 1 studies of topical microbicide products.^{6–10} Study participants were willing to abstain from vaginal, oral, and anal intercourse (including receptive anal intercourse), masturbation, and other activities that may cause irritation or injury to the penis during study participation.

The main study aims were to determine the genitourinary and systemic safety, acceptability, and pharmacokinetics (PK) of DPV 0.05% gel compared to matched placebo gel and universal placebo gel following seven sequential daily penile applications. The 2.5 g gel dose ingredients and percent composition were dapivirine (0.05%), purified water (90.99%), hydroxyethyl cellulose (3.50%), polycarbophil (0.20%), propylene glycol (5.00%), methylparaben (0.20%), propylparaben (0.05%), and sodium hydroxide (0.01%). The matched placebo gel consisted of the same ingredients as the corresponding DPV 0.05% gel formulation, but without the active ingredient (DPV). The universal placebo gel was a hydroxyethyl cellulose-based gel that was developed for use in clinical trials involving other investigational microbicides and in addition to purified water contains sodium chloride, sorbic acid, and sodium hydroxide.¹¹

Study endpoints were evidence of Grade 2 or higher male genitourinary and systemic adverse events (AEs) as defined by the DAIDS AE Grading Table version 1.0, December 2004 (clarification dated August 2009), Addendum 2 (Male Genital Toxicity Table for Use in Topical Microbicide Studies), the proportion of participants who at their final clinic visit (FCV) reported via the acceptability questionnaire that they would be “very likely” to use a microbicide gel in the future every time they have intercourse (vaginal and/or anal), “if it looked like the one that was used in the study and provided some protection against HIV,” with different partner types, and when condoms are not used. Quantification of DPV in plasma was also assessed at the FCV that was targeted to occur within 24 h of final application of study product and between days 7 and 8.

Participants in the circumcised and uncircumcised groups were randomized in a 2:1:1 ratio to receive DPV gel 0.05%, matched placebo gel, or universal placebo gel, respectively (see Fig. 1). The randomization scheme was generated and maintained by the statistical data management center (SDMC). The SDMC provided each study site with two sets of randomization envelopes (for circumcised and uncircumcised) to be stored and used in the study clinic. Clinic staff assigned these envelopes in sequential order, by envelope number, to eligible participants. Study staff and participants were blinded to the random assignments of all study participants. All study gels were supplied in identical, single-use applicators packaged in individual wrappers.

The study design called for seven daily applications of gel, which is a dosing regimen similar to that used in previous Phase 1 male tolerance studies of topical formulations of cellulose sulfate, C31G, BufferGel, PRO2000, and tenofovir.^{6–10} Participants were instructed to apply one applicator dose of approximately 2.5 g onto the glans penis and then spread it to cover the meatus and shaft on day 0 (Enrollment Visit) and continue daily through day 6. Additionally, uncircumcised

FIG. 1. Participant disposition. *24 circumcised and 24 uncircumcised; Acc. = acceptability; PK = pharmacokinetic. #plasma samples for participants on all arms of the study were assessed for the presence of dapivirine; as expected, no dapivirine was found in the samples of the participants in the placebo arms.

men were instructed to retract the foreskin, coat the glans and internal foreskin, and replace the foreskin. All participants were instructed to apply the gel at night before retiring or before their longest period of rest. The gel should have remained in place for 6–10 h.

All participants completed a Baseline Behavioral Questionnaire (BBQ) via web-based computer assisted self-interview (CASI) at the Enrollment Visit. In addition to demographics, this questionnaire assessed participants' sexual behavior with men and women, frequency of condom use, history of lubricant use, whether participants believe lubricant use interrupts sex, and if so, whether that bothers them. This BBQ allowed a contextualization of the participants' acceptability attitudes in relation to their sexual history.

A Product Acceptability and Adherence Questionnaire was completed by participants at the FCV. This assessment has been used in several prior microbicide trials and was adapted to measure acceptability of a gel applied to the penis rather than inside the vagina or rectum.^{7–9} It included structured and semistructured questions about liking the gel overall and at various time intervals following gel application and the overall likelihood of using a microbicide gel in the future every time they have intercourse (vaginal and/or anal), “if it looked like the one that was used in the study and provided some protection against HIV,” with different partner types, and when condoms are not used. Responses to acceptability and likelihood of use questions were measured on a 10-point Likert scale, with 1 being “disliked very much/very unlikely to use” and 10 being “liked very much/very likely to use.” Participants also indicated whether they would be in favor of or against a partner using a microbicide during sexual intercourse, by partner type (main partner, one-night stand, other

partners) on a 10-point Likert scale, with 1 being "very much against it" and 10 being "very much in favor."

This questionnaire also assessed adherence, as participants were asked to report the number of times the study gel was applied to the penis during the trial, whether they ever used less than the specified amount of gel, and if so why they used less, and how often they waited for the study product to dry before putting on clothes or going to bed. In addition, participants were asked to return both used and unused gel applicators to the clinic, which were counted and documented by study staff. Eight applicators were dispensed to each participant to allow for an extra applicator in case any applicator was rendered unusable.

Plasma DPV levels for pharmacokinetic analyses were taken at the FCV. The bioanalysis of DPV in plasma was performed by PRA International, Assen, The Netherlands. Plasma concentrations of DPV were determined using a lower limit of quantification of 3.00 pg/ml.

The full protocol is available at www.mtnstopshiv.org.

Statistical analysis

The primary analysis of safety endpoints was conducted to assess the genitourinary safety of DPV 0.05% gel following seven daily penile applications. One participant randomized to the DPV arm did not complete his FCV and was considered lost to follow-up. This participant was not replaced and was included in the safety analysis based on the principle of intent-to-treat as was outlined *a priori* in the statistical analysis plan. No adverse events were reported by this participant. For analyses comparing DPV 0.05% gel to each of the matched placebo gel and universal placebo gel, data from 18 males were included (12 participants in the DPV arm and 6 in the placebo arms) for the uncircumcised and circumcised male participants separately. To assess genitourinary safety, the number and the percentage of participants experiencing at least one Grade 2 or higher male genitourinary AE were tabulated by trial arm using MedDRA preferred terms. Each participant contributed once in each category (i.e., only for highest severity AE for each participant) for the calculation of event rates. The number and percentage of participants experiencing each type of genitourinary AE were tabulated by severity and relationship to treatment for each treatment group. Systemic AEs during 7 days of once daily penile application of DPV 0.05% gel were assessed using similar methods.

The proportion of participants with DPV detected in the blood at their FCV was assessed. DPV concentrations were plotted versus hours postdosing time for all participants and by circumcision group to explore temporal trends among the participants.

To evaluate acceptability, mean scores were calculated for liking the gel overall and at different time intervals after applying it, likelihood of use overall and with different partner types, and acceptance of partner use of a microbicide gel. In addition, the proportion of participants who at their FCV reported that they would be "very likely" to use a microbicide gel like the one they used in the study during sexual intercourse in the future was calculated by treatment arm. "Very likely" was operationalized as having a rating in the upper one-third of the 10-point scale (score of 7 or above). To describe the sexual behavior of the participants, we calculated

the percentage of participants with male and female partners, the percentage of vaginal and insertive anal sex occasions unprotected by condoms, and the percentage of participants reporting a history of lubricant use. The DPV group was compared to the two placebo groups by a series of two-group comparisons (DPV vs. matched placebo and DPV vs. universal placebo). Student's *t*-test was used to compare the two groups on continuous variables and Pearson's Chi-square test was used for dichotomous variables. Since each hypothesis was tested by two separate statistical tests, a *p*-value of 0.025 (0.05/2) was required in order to consider a result statistically significant. Similar two-group comparisons were made for circumcised vs. uncircumcised participants, using a conventional significance level of 0.05.

Results

The first study participant was recruited on March 31, 2011 and the study finished with the last participant's FCV on July 18, 2011. The sample characteristics, including age, race/ethnicity, sexual orientation, history of unprotected sexual behavior, and history of lubricant use of the 48 study participants in MTN 012/IPM 010 are shown in Table 1. The majority of the participants were white. The DPV group did not differ from the two placebo groups on any of the variables tested. Forty-seven of the 48 enrolled participants completed the FCV and 46 completed the acceptability and adherence questionnaire. In the 47 participants who completed the FCV, there were no Grade 2 or higher genitourinary AEs reported. A total of 13 AEs were reported, 12 of which were Grade 1 in addition to one Grade 2 corneal laceration (see Table 2).

Overall, the three gel formulations were well tolerated. There were no deaths or serious AEs reported in this clinical trial. Five (5/23; 21.7%) participants using DPV gel, one (1/12; 8.3%) participant using matched placebo gel, and four (4/12; 33.3%) participants using universal placebo gel experienced one or more AEs. Six participants, three (3/23; 13.0%) using DPV gel, one (1/12; 8.3%) using matched placebo gel, and two (2/12; 16.7%) using universal placebo gel, experienced eight AEs that were regarded by the investigator as "related" to gel use, all of which were Grade 1. Four events were in the DPV 0.05% gel arm (increased alanine aminotransferase, increased aspartate aminotransferase, application site paresthesia, and inflamed sebaceous gland), one in the matched placebo gel arm (application site pain) and three in the universal placebo gel arm (application site swelling, application site pruritus, and application site erythema) (see Table 2).

Five participants (including one participant in the DPV gel arm who also reported an AE deemed "related" to investigational product) reported five AEs deemed "unrelated" to investigational product: three events were in the DPV gel arm and two were in the universal placebo gel arm. Of these five AEs, two were from uncircumcised participants and three were from circumcised participants. One of these "unrelated" AEs was a Grade 2 AE that involved a corneal laceration of the participant's left eye. This was the only Grade 2 or higher AE reported in the trial.

When examining AEs by circumcision status, eight were in circumcised participants and five were in uncircumcised participants. Of the eight AEs reported to be related to investigational product, five of these were in circumcised participants and three in uncircumcised participants.

TABLE 1. SAMPLE DESCRIPTION OF RANDOMIZED PARTICIPANTS

Sample description	All arms	DPV 0.05% gel	Matched placebo gel	Universal placebo gel
Participants enrolled	48	24	12	12
Age (years)				
N	48	24	12	12
Mean (SD)	32.6 (11.2)	31.0 (9.4)	32.3 (8.1)	35.8 (16.3)
Median	30.5	28.5	32.5	32
Race/ethnicity	N (%)			
White	29 (60%)	13 (54%)	8 (67%)	8 (67%)
Black/African-American	9 (19%)	5 (21%)	2 (17%)	2 (17%)
Latino/Hispanic	5 (10%)	3 (13%)	1 (8%)	1 (8%)
Asian	4 (8%)	3 (13%)	1 (8%)	0 (0%)
Other	1 (2%)	0 (0%)	0 (0%)	1 (8%)
Sexual orientation	N (%)			
Straight/heterosexual	30 (64%)	14 (61%)	9 (75%)	7 (58%)
Gay/homosexual	16 (34%)	8 (35%)	3 (25%)	5 (42%)
Bisexual	1 (2%)	1 (4%)	0 (0%)	0 (0%)
Sexual behavior (past 3 months)	Mean (SD)			
No. times unprotected vaginal sex	5.4 (10.4)	5.1 (10.1)	5.2 (10.3)	6.0 (11.8)
No. times unprotected insertive anal sex	0.5 (1.4)	0.7 (1.7)	0.0 (0.0)	0.5 (1.4)
No. times unprotected receptive anal sex	0.4 (1.4)	0.7 (1.9)	0.1 (0.3)	0.1 (0.3)
Lubricant use	N (%)			
Ever used	29 (60%)	16 (67%)	7 (58%)	6 (50%)
Never used	17 (35%)	6 (25%)	5 (42%)	6 (50%)
I don't know	2 (4%)	2 (8%)	0 (0%)	0 (0%)

DPV, dapivirine.

Based on returned applicator counts, of the 47 participants who completed their FCV, 46 used the expected dose of seven applicators and one participant in the universal placebo gel arm from the Birmingham site used eight applicators. Yet the information reported in the Acceptability and Adherence Questionnaire was somewhat different: of the 46 participants who completed the questionnaire, two circumcised participants, one in the matched placebo gel arm and one in the DPV gel arm, reported using the gel only 1 day during the trial; neither had a genitourinary AE and the ppt in the DPV gel arm had detectable DPV at the FCV. The two other uncircumcised participants, one in the DPV gel arm and one in the universal placebo gel arm, reported using half of the dose of gel on all or most days of the study, stating that there was too much gel in the applicator. The ppt in the DPV gel arm had a genitourinary AE of "application site paresthesia," and had a

DPV concentration level exceeding the mean and upper bound of the 95% CI for levels among uncircumcised men, circumcised men, and all men combined. The time from last gel dose in both the DPV gel arm ppts was similar. Overall, 11% of men reported always waiting until the product was completely dry before putting clothes on or going to bed; 30% reported most of the time, 22% reported some of the time, and 37% reported never waiting until the product was completely dry before putting clothes on or going to bed. There were no significant differences between participants in any of the study arms.

Overall, 63% of men had ever used a commercial sexual lubricant. Of them, 62% said that application of lubricant interrupts sex but does not bother them, and 38% said it does not interrupt sex. Experience with sexual lubricants was more common among gay/bisexual identified men compared to

TABLE 2. CUMULATIVE ADVERSE EVENTS BY TRIAL ARM AND CIRCUMCISION STATUS

Dapivirine 0.05% gel (N=24)						Matched placebo gel (N=12)					Universal placebo gel (N=12)				
Circumcised		Uncircumcised		Total		Circumcised		Uncircumcised		Total	Circumcised		Uncircumcised		Total
No. of men	No. of events	No. of men	No. of events	No. of men		No. of men	No. of events	No. of men	No. of events	No. of men	No. of men	No. of events	No. of men	No. of events	No. of men
All	3 ^a	5	2	2	5 (20.8%)	1	1	0 (0%)	0	1 (8.3%)	2	2	2	3	4 (33.3%)
Related	2	3 ^b	1	1 ^c	3 (12.5%)	1	1	0 (0%)	0	1 (8.3%)	1	1	1	2	2 (16.7%)
Unrelated	2	2	1	1	3 (12.5%)	0	0	0 (0%)	0	0 (0%)	1	1	1	1*	2 (16.7%)

^aOne participant in the DPV gel arm reported both related and unrelated AEs.^bIncreased alanine aminotransferase, increased aspartate aminotransferase, and inflamed sebaceous gland.^cApplication site paresthesia.

All AEs were reported as Grade 1—mild except for one (cornea laceration—left eye) that was reported as Grade 2—moderate and is denoted by asterisk (*) in the table.

DPV, dapivirine; AEs, adverse events.

TABLE 3. PRODUCT ACCEPTABILITY BY TRIAL ARM

Response	DPV 0.05% gel (N=23) mean (SD)	Matched placebo gel (N=12) mean (SD)	Universal placebo gel (N=11) mean (SD)
Overall liking the product	6.30 (1.89)	5.92 (1.78)	6.00 (2.24)
Feeling immediately after applying	6.30 (2.55)	6.58 (2.64)	6.91 (2.34)
Feeling 30 min after applying	6.87 (2.34)	6.58 (2.31)	6.64 (1.86)
Feeling after dried out	6.09 (2.56)	6.83 (2.17)	6.73 (2.41)
Overall likelihood of use	8.22 (2.09)	7.17 (2.55)	6.64 (3.38)
Likelihood of use with steady partner	4.78 (3.45)	5.67 (3.87)	5.45 (4.23)
Likelihood of use with one-night stand	8.95 (2.17)	9.20 (2.20)	7.55 (3.17)
Likelihood of use with other sexual partners	8.83 (2.08)	8.20 (2.86)	7.36 (2.98)
Likelihood of use if no condoms	8.43 (2.54)	8.33 (2.87)	7.73 (2.87)
Acceptance of steady partner using microbicide	7.74 (2.58)	7.67 (2.90)	7.27 (3.00)
Acceptance of one-night-stand using microbicide	9.00 (2.47)	9.82 (0.60)	9.30 (1.57)
Acceptance of other partners using microbicide	9.00 (2.36)	9.55 (0.82)	8.91 (1.70)
Very likely to use ^a	87.0%	66.7%	45.5%

^aRating of 7 or higher on a 10-point scale.
SD, standard deviation.

straight identified men (82% vs. 52%, Chi square = 4.32, $df=1$, $p=0.038$).

Overall, participants in the DPV gel arm rated the gel acceptability as 6.30 (SD=1.89) compared to 5.92 (SD=1.78) in the matched placebo arm and 6.00 (SD=2.24) in the universal placebo arm (see Table 3). Those who had ever used lubricant did not significantly differ from those who had not on their liking of the gel. Seventy-two percent of the 46 participants completing the acceptability questionnaire reported that they would be "very likely" to use gel as a topical microbicide in the future if proven to be effective in preventing HIV transmission. Likelihood of use was higher among the DPV group (87%) than both placebo groups (67% and 46%), but neither comparison was statistically significant. Participants in the DPV gel arm gave a mean likelihood of use rating of 8.22 (SD=2.09), compared with 7.17 (SD=2.55) in the matched placebo arm and 6.64 (SD=3.38) in the universal placebo arm. None of the two-group comparisons (DPV vs. matched placebo and DPV vs. universal placebo) of the ratings reported in Table 3 was statistically significant.

We also examined the likelihood of use by partner type among the full sample. Likelihood of use with a steady partner was significantly lower (5.16) than with a one-night-stand (8.65; $t = -6.60$, $df=42$, $p < 0.001$) and with other partners (8.32; $t = -6.11$, $df=43$, $p < 0.001$). Similarly, among the full sample, acceptance of a steady partner using a microbicide gel was significantly lower (7.61) than acceptance of a one-night-stand (9.27; $t = -4.18$, $df=43$, $p < 0.001$) or other partner (9.11; $t = -4.09$, $df=44$, $p < 0.001$) using a microbicide gel.

Of the 24 participants randomly assigned to DPV 0.05% gel, 23 completed the FCV. All 23 participants had measurable DPV concentrations in plasma. The mean DPV concentration was 343 pg/ml (95% CI: 229; 458 pg/ml). Following 10 sequential daily vaginal applications of two formulations of 0.05% DPV gel, the mean plasma concentrations were 581.5 ± 132.8 and 621.8 ± 221.8 pg/ml.⁴ The *in vitro* IC₅₀ (50% inhibitory concentration for virus replication) of DPV is 0.3 ng/ml. On average, circumcised participants' DPV concentrations were approximately half (54%) those of uncircumcised participants. This difference was not statistically significant ($p=0.066$) (see Table 4). The mean collection times

following participants' last dose were not statistically significantly different between circumcision groups ($p=0.68$). The mean collection time after the last gel application for participants in the DPV 0.05% arm was 12.2 h (95% CI: 9.0; 15.43 h) and DPV concentration was poorly and negatively correlated with time elapsed ($r = -0.39$; $p=0.07$).

Discussion

All gel products in this study were well tolerated with a low frequency of Grade 1 genitourinary AEs reported that were similar in nature and frequency to those reported in other penile tolerance studies of both antiretroviral and non-antiretroviral drugs.^{6,7,9,10}

The DPV gel used in this study is not primarily intended for use in men by application to the penis; nevertheless, male participants reported liking the gel moderately. Although ratings for liking the gel were on average toward the positive side of the 1–10 scale, ratings were not particularly high, being on average around 6. Participants indicated that they would be very likely to use the gel in the future if it conferred protection against HIV. Risk perception appears to influence likelihood of use and acceptance of partner using a microbicide gel, given that participants reported being more likely to use the gel if it provides protection with a one-night stand or other partner than with a main partner. As with other studies that have measured participant adherence using different methods, there is conflict noted between the applicator returns and participant report of gel use. In this study the conflict occurred in a small number of participants, but emphasizes the importance of objective measures of adherence such as PK monitoring and the need to use event-related

TABLE 4. DAPIVIRINE CONCENTRATION BY CIRCUMCISION STATUS

Circumcision status	Mean (pg/ml)	95% CI (pg/ml)
All DPV participants ($n=23$)	343	229; 458
Circumcised ($n=11$)	238	97; 378
Uncircumcised ($n=12$)	440	261; 619

reports to decrease recall bias and provide investigators with an opportunity for corrective interventions.

The plasma PK assessment was undertaken at the FCV following seven sequential daily applications and showed detectable levels in both circumcised and uncircumcised participants. As may be expected, the uncircumcised group had higher DPV plasma levels, likely relating to an increased length of gel exposure by gel being held in the prepuce as well as the presence of a thinner layer of glans penis and inner foreskin stratified squamous epithelium that may have facilitated absorption when compared to the circumcised group. However, this difference did not reach statistical significance in this small study.

In this current study the mean plasma concentration after seven daily penile applications approximated that following vaginal exposure.²⁻⁴ The proximity of this plasma level in men to the inhibitory concentration of DPV *in vitro* does raise the question of the potential for resistance developing should an untreated or viremic HIV-positive male be exposed to DPV gel during sexual intercourse. However, there are several mitigating factors that make this scenario less likely and will result in reduced penile DPV exposure such as the reduced contact time during intercourse than in this study, the presence of vaginal fluid and semen diluting DPV, and activities such as penile washing that may occur following intercourse. As such, measuring plasma DPV levels in male sex partners of female DPV vaginal product users is unlikely to be clinically significant or operationally feasible.

Following completion of this study two pivotal Phase 3 clinical trials are currently investigating a vaginal matrix ring formulation of DPV for the prevention of HIV-1 infection in approximately 5,125 women at clinical research sites in sub-Saharan Africa.

Acknowledgments

The study team gratefully acknowledges the participants of MTN 012/IPM 010, the International Partnership for Microbicides for providing the study product, and both Rebecca Giguere, MPH, and Curtis Dolezal, PhD, for their work on the behavioral data analysis. Funding was provided by the National Institutes of Health Grants 5U01AI068633 and UM1AI068615. Presented in abstract: Microbicides 2012, abstract number 542, April 15–18 2012, Sydney, Australia.

Author Disclosure Statement

Dr. Cranston has received research grant funding from Merck and Co. and royalties from UpToDate online medical encyclopedia. Dr. Nel has received honoraria for lectures at the University of Stellenbosch. Dr. Carballo-Diéguez has received

grant funding from the Research Foundation for Mental Hygiene. Dr. Hendrix has received grant funding from the Bill and Melinda Gates Foundation and Gilead Sciences.

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