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A Phase 1 trial to assess the safety, acceptability, pharmacokinetics and pharmacodynamics of a novel dapivirine vaginal film

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Abstract

Background—Films may deliver antiretroviral drugs efficiently to mucosal tissues. In this first in-human trial of a vaginal film for delivering the non-nucleoside reverse transcriptase inhibitor dapivirine, safety, pharmacokinetics, and pharmacodynamics of film and gel formulations were compared to placebo.

Methods—61 healthy HIV negative women were randomized to daily dapivirine (0.05%) or placebo gel, or dapivirine (1.25mg) or placebo film for seven days. The proportion of participants experiencing Grade 2 and higher adverse events related to study product were compared. Plasma dapivirine concentrations were quantified. Paired cervical and vaginal tissue biopsies obtained ~2 hours following the last dose were measured for tissue drug concentration and exposed to HIV in an *ex vivo* challenge assay.

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Results—Two Grade 2 related AEs occurred in the placebo film group. Women randomized to gel and film products had 4 $\log_{10}$ higher of dapivirine in cervical and vaginal tissues than plasma. While gel and film users had comparable plasma dapivirine concentrations, tissue concentrations of dapivirine were 3 to 5 times higher in the gel users when compared to film users. HIV replication in the *ex vivo* challenge assay was significantly reduced in vaginal tissues from women randomized to dapivirine film or gel; furthermore, tissue drug concentrations were highly correlated with HIV protection. Women rated the film more comfortable with less leakage, but found it more difficult to insert than gel.

Discussion—Both film and gel delivered dapivirine at concentrations sufficient to block HIV *ex vivo.* This proof of concept study suggests film formulations for microbicides merit further investigation.

Keywords

Microbicide; Vaginal film; Dapivirine; HIV prevention

Background

The highest priority in the field of microbicide research is the development of safe and effective topical products which reduce HIV transmission. While establishing the safety and efficacy of products in development is of utmost importance, participant adherence to product use is also critical to their success. Randomized placebo controlled trials of pre-exposure prophylaxis (PrEP) using oral tenofovir/emtricitabine and 1% tenofovir gel demonstrated that moderate to high participant adherence coupled with highly effective antiretroviral (ARV) products led to a reduction in HIV acquisition.[1-4] However, other trials evaluating these same drugs in daily dosing regimens did not find these products to be efficacious due to low participant adherence.[5,6] This has led to the recognition that microbicide products which do not require daily use, deserve prioritization. Sustained delivery products such as vaginal rings or long acting injectable formulations represent alternative options to enhance product adherence. Phase 2 and 3 studies evaluating the safety of injectable long-acting forms of rilpivirine (a non-nucleoside reverse transcriptase inhibitor [NNRTI]) or cabotegravir (an integrase inhibitor) (NCT02165202 and NCT02178800, clinicaltrials.gov), as well as two Phase 3 studies trials assessing efficacy of a silicone vaginal ring containing 25 mg of the NNRTI dapivirine, are ongoing (NCT01617096 and NCT01539226, clinicaltrials.gov). These studies are also evaluating the emergence of NNRTI resistance mutations in the HIV isolates for people who seroconvert in these studies.

Not all women who would potentially use an HIV prevention product would choose a sustained delivery product due to prolonged drug exposure. Some women may have infrequent sexual exposures and may desire HIV protection only during times of sexual activity. Therefore, there is still a recognized need for on-demand microbicide products. Most on demand microbicide products evaluated for effectiveness to date have been aqueous-based gels applied peri-coitally.[2,7-13] Quick dissolving films may be a suitable and inexpensive alternative vaginal dosage form for delivery of ARV microbicides. The Listerine® breath mint strips have familiarized many people already with quick dissolving film technology, and marketing has revealed that these films are an acceptable dosage form

for oral use. However, aside from the contraceptive film containing nonoxynol-9,[14] consumers have limited experience with films for vaginal use. Because films are thin and dry, they have relatively small volume and weight when compared to aqueous-based gels. This has two distinct advantages: firstly, films are more discreet because the packaging is smaller and, in use, the product is associated with less leakage than gels. Indeed, in acceptability studies comparing vaginal contraceptive films to gels, films have performed well.[15,16] Secondly, because films are dissolved in physiologic fluids, they should not dilute the endogenous antibacterial and antiviral properties of vaginal fluid in the same manner as gel formulations, and hence should only minimally impact innate immunity. There are other potential advantages of films related to logistics and manufacturing. Films can be manufactured to deliver fixed dosages without the need for an applicator. This substantially reduces the associated environmental impact and costs when compared to vaginal gels.

Dapivirine has been evaluated in various gel formulations and in a silicone vaginal ring. Though not effective against other sexually transmitted infections, dapivirine is an attractive ARV for use in prevention of HIV due to its high potency and its effectiveness in the humanized mouse model. Studies of the dapivirine ring and gel have found the product to be very well tolerated.[17,18] For the present study, a polyvinyl alcohol (PVA) based vaginal film was developed.[19] The target loading dose for the film was 1.25 mg of dapivirine, based on phase 1 studies using dapivirine gels at concentrations of 0.05% with administration of 2.5 mL.[17,20-22] Dapivirine films are soft, flexible and translucent. Individual film units were made 1” × 2” in size and 70 μm thick; they weighed 110 mg on average. The films were designed to dissolve rapidly upon exposure to an aqueous environment. Greater than 50% of the loaded dapivirine was released from the film within 10 minutes in *in vitro* release studies.[19] In this first in-human, placebo-controlled trial of this quick dissolving film for delivery of dapivirine (NCT01548560, clinicaltrials.gov), we compared the safety, pharmacokinetics, and pharmacodynamics of film versus gel formulations.

Methods

This was a phase 1, four arm, single-site, double blind, randomized placebo-controlled trial comparing the safety, pharmacokinetics, and pharmacodynamics of two formulations of dapivirine: gel and film. The protocol was approved by the University of Pittsburgh Institutional Review Board.

Sixty-one HIV-negative women were enrolled between September 2012 and July 2013; women were recruited from gynecology clinics at Magee-Womens Hospital at the University of Pittsburgh Medical Center and the surrounding community. All participants provided written informed consent for screening and study procedures. Participants were 18–45 years of age and agreed to be sexually abstinent from the screening visit through one week post study product exposure. Exclusion criteria included pregnancy, hysterectomy, active sexually transmitted infection, active vaginal infection, abnormal complete blood count or complete metabolic panel, anticipated vaginal bleeding during the first week after enrollment, and the use of antibiotics or antifungals in the 14 days preceding enrollment.

Women were randomized with equal frequency to one of four arms using a permuted block design with block sizes of 4 and 8. The groups included universal placebo gel (HEC gel), dapivirine (0.05%) gel, placebo film, and dapivirine (1.25 mg) film. The primary objective was to assess safety with the primary endpoint of Grade 2 or higher adverse events deemed related to study product. One secondary objective was to assess the impact of formulation type on the vaginal ecology. Another secondary objective was to delineate the pharmacokinetic parameters of dapivirine film and gel; endpoints included dapivirine concentration in plasma, vaginal fluid, cervicovaginal lavage (CVL), and genital tissues. For the pharmacokinetic (PK) analyses and the exploratory objective using an *ex vivo* challenge assay as a pharmacodynamic (PD) measure, only women who were deemed evaluable and had used the product as instructed were included. Evaluable participants reported using their product at home for 5 out of 6 doses including the day prior to the biopsy visit. This population was also used to evaluate anti-HIV activity in the CVL.

There were four study visits in total. Eligibility was initially assessed at the screening visit (V1) during which a baseline CVL was collected using 10 ml of sterile normal saline. After the screening visit, eligible participants presented for enrollment within 56 days. At the enrollment visit (V2), participants were uniformly counseled on product use by site staff, and after baseline samples were collected, participants self-inserted the first dose of study product while in the clinic. Site staff was readily available for assistance. Participants were provided with five additional doses of study product to use daily at home. One to three days after the enrollment visit, participants were contacted to assess challenges with study product use and adverse events. One week after enrollment, participants presented for the third clinic visit (V3) at which point they inserted the last dose of study product. Two to four hours later, participants underwent specimen collection, including plasma, CVL and genital tissue biopsies (two cervical and two vaginal). Participants returned for a final safety visit (V4) one month after enrollment. This included a final CVL collection.

Participants were instructed to use the product daily for one week to allow sufficient exposure to assess the safety of the product, though in real world use, the drug would be used peri-coitally. For this reason, tissue for the *ex vivo* challenge assay and drug concentration were obtained shortly after drug delivery, in an effort to mimic peri-coital use.

Local and systemic safety was assessed by eliciting Adverse Events (AEs) through history, physical exam, and laboratory evaluation. AEs were defined and graded according to the Division of AIDS Table for Grading Severity of Adult and Pediatric AEs, Version 1.0, December 2004 and the Female Genital Grading Table for Use in Microbicide Studies (Addendum 1 to the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004). The number of AEs by body system and relationship to study product was tabulated; individual participants contributed only once to the calculation of event rates. The proportion of participants experiencing Grade 2 and higher AEs deemed related to study product was compared across treatment arms using Fisher's exact tests. To compare the effects of gel and film formulations of dapivirine on vaginal ecology, Nugent scores and quantitative vaginal cultures were compared between groups. Participant opinions on product and acceptability were collected via questionnaires at the end of the biopsy visit (V3).

Dapivirine concentrations in plasma and CVL were quantified via ultra-performance liquid chromatographic-tandem mass spectrometric (LC-MS/MS) validated methods as previously described.[23,24] The lower limits of quantification (LLOQ) for dapivirine in plasma and CVL were 0.02 ng/mL and 2 ng/mL, respectively. One set of tissue biopsies intended for drug concentration was weighed, snap frozen, and stored at -80°C prior to drug quantification. Tissue dapivirine quantification was performed using calibrators prepared in human plasma and matrix-specific tissue quality control samples. Following homogenization and protein precipitation, tissue dapivirine concentrations were determined via LC-MS/MS with a LLOQ of 0.05 ng/sample.

PK / PD relationships were evaluated in tissue and CVL. The second set of biopsies was used fresh for the *ex vivo* challenge assay. As previously described, the tissue biopsies were briefly exposed to HIV-1_{BaL} in the laboratory.[25] HIV infection was measured over the culture period by HIV-1 p24 ELISA (Alliance, Perkin Elmer). A log-log, linear least-squared model with a subject covariate was used to test for the significance of the slope estimate, difference from zero, where a statistically significant negative slope indicated drug mediated virus suppression in the *ex vivo* challenge assay. For CVL PD activity, testing was done using an in vitro TZM-bI assay with the CVL diluted to a final concentration of 1:125. The linear association between PD activity and DPV concentration in the CVL was assessed using Pearson's correlation coefficient. The effect of formulation type (film versus gel) on innate antiviral activity was assessed by comparing the innate anti-HIV activity in the CVL collected at V1,V3, and V4. CVL with a final dilution of 1:5 was evaluated for anti-HIV activity using a TZM-bl assay.[26]

Sample size was based on the assumption that for a given arm, if the true rate of a given toxicity endpoint was 5%, 14 women per arm provide 85% power to exclude toxicity endpoint rates greater than 30% (the probability of observing zero or one event is less than 0.05 when the true rate was 30%). Fourteen women per arm would assure that a 95% confidence interval for the difference between the placebo and dapivirine toxicity rates had an upper limit no more than 16% when the true toxicity rates for placebo and active gel were both 5%. Participants were replaced if they reported missing two or more home doses or if the dose the day prior to the biopsy visit was missed.

Results

One hundred and twenty one women were screened, and 61 women enrolled. The primary reasons for screen failure are outlined in the CONSORT diagram (see Figure, Supplemental Digital Content 1, which demonstrates the distribution of participants). Fifteen women were randomized to dapivirine film, 15 to placebo film, 15 to dapivirine gel and 16 to placebo gel. One participant in the placebo film group was deemed unevaluable as she conceded that she had missed two doses of study product; she was replaced. Of 183 scheduled clinic visits, 180 (98%) were completed. The median collection time for specimen collection after the final study product use was 2.4 hours (range 2.2- 3.6). No differences with respect to demographic characteristics, sexual behavior, and familiarity with vaginal products and microbicides were noted between study arms (see Table, Supplemental Digital Content 2, which shows the demographics of the study population).

Seventy-one percent of participants reported at least 1 AE during the course of study follow-up (Table 1). There were a total of 81 AEs reported, including two Grade 2 related AEs. Both of these AEs occurred in the placebo arms. Most AEs were Grade 1 (81%) and unrelated (70%). No laboratory abnormalities were noted in follow-up. The most commonly reported AEs were vaginal discharge (n=11) and vaginal odor (n=5). All four groups had a similar distribution of mild and moderate genitourinary events. Based on cultivation methods, neither gel nor film impacted the microbiota, nor was there a shift in the Nugent Gram stain pattern associated with product use (data not shown).

At the first post-randomization visit, five participants were noted to have visible film outside of the vaginal introitus at the time of the biopsies. Additionally, one participant was noted to have no evidence of gel product in her vagina at the time of biopsies. After unblinding, it was revealed that the five film and one gel participants had been randomized to the dapivirine active groups. These six participants with poor product placement (visible film outside of the vaginal introitus or no evidence of gel within the vagina) were removed from the PK/PD analyses.

Among women with appropriate product placement, those randomized to film and gel products had similar plasma dapivirine concentrations after one week of use (median 0.22 ng/ml [0.09–0.63] and 0.31 ng/ml [0.14–0.56] respectively). As shown in Table 2, tissue concentrations of dapivirine were 3-5 times higher in the gel users when compared to film users. Dapivirine concentrations in CVL were comparable between groups.

Both active products, when placed correctly, were protective against HIV infection when biopsy tissues were challenged in the *ex vivo* challenge assay. However, in the cervical tissues, only dapivirine gel had a statistically significant protective effect against HIV infection (Figure 1A). Vaginal biopsies showed a strong correlation between the dapivirine concentration and inhibition of HIV infection for both film and gel users ($P = 0.01$, $P < 0.001$, respectively) (Figure 1A). Luminal antiviral activity was evaluated using the TZM-bl assay with CVL collected at V3. Strong anti-HIV activity was noted for both film and gel users and was correlated with drug concentration ($P < 0.001$ for both products) (Figure 1B).

One of the hypothesized advantages of film formulations was that they would not dilute the innate antiviral activity of vaginal fluid. To evaluate the impact of gel and film use on the innate anti-HIV activity, the CVL from placebo users was compared across the three study visits, using each woman as her own control (Figure 2). As measured over time, film users showed no change in innate anti-HIV activity. However, gel users showed a significant loss of innate anti-HIV activity after the final product application compared to baseline ($P = 0.0085$) which persisted to V4, one month after enrollment (Figure 2). The loss of anti-HIV activity was not attributable to changes in cell line viability.

Overall, study participants reported that both film and gel formulations were acceptable (Table 3). Eighty percent of film users and 68% of gel users reported that they would likely use the product should it be found to be effective against HIV. Acceptability characteristics did not differ significantly between active and placebo product within each formulation group, however they did differ between formulation types. Compared to the film group, gel

users were more likely to report product leakage (84% vs 30%, P<0.001) and to describe the product as very, moderately or minimally uncomfortable (39% vs 13%, P=0.04). In contrast, film users were more likely to describe product insertion as very or moderately difficult compared to gel users (40% vs 0%, P<0.001).

In order to explore the characteristics associated with poor product placement, the five women with poor film placement and the ten women within the same active dapivirine film group who had good film placement were compared. While the two groups did not differ with respect to demographics (data not shown), a higher percentage of participants with good placement reported previous use of tampons (100% vs 60%, p=0.10) and lubricants (50% vs 20%, p=0.58) prior to enrollment than the participants with poor placement. In addition, further comparisons between placebo and active product films were conducted including disintegration time, burst strength, and water activity. Ultimately, the two products were nearly identical with respect to these characteristics, as well as appearance, mass, thickness and length.

Discussion

In this first in-human assessment of a vaginal film containing dapivirine, daily use of films and gels had comparable safety and tolerability. The rate of AEs, including that of genitourinary irritation, was similar between dapivirine and placebo arms and similar to rates of AEs published for other microbicide trials.[5]

The results from this study suggest that film and gel formulations release dapivirine into the vaginal fluid, tissues and plasma at similar levels. While tissue dapivirine concentrations were significantly higher in the gel group as compared to the film group, nearly identical plasma drug concentrations support similar release profiles. Dapivirine tissue concentrations were likely inflated secondary to residual drug adherent to tissue surfaces following gel dosing despite tissue collection after a one minute lavage of the vaginal vault for all study groups. Importantly, cervical and vaginal tissue concentrations of dapivirine after one week of film use were comparable to cervical tissue concentrations achieved after 1 month of vaginal ring use (0.6×10^6 pg/mL) in the MTN-013 study.[27] As in MTN-013, tissue DPV concentrations were roughly 4 $\log_{10}$ greater than plasma. The present proof of concept study demonstrates that quick dissolving films can effectively deliver ARVs to genital tissue at concentrations similar to sustained delivery systems and that tissue drug concentrations are sufficient to prevent HIV infection in an *ex vivo* challenge assay.

While no differences were noted for reported AEs for women using either films or gels, there were noted differences in their vaginal innate anti-HIV activity. We have previously shown that healthy women have substantial innate anti-HIV activity in CVL.[26] While the level of antiviral activity was similar between groups at baseline, there was a significant decrease in innate anti-HIV activity after gel use, but not film use (Figure 2). The reduction in antiviral activity among gel users could be due to dilution since the volume of gel was greater than the volume of the film (4 grams vs 110 mg). However, because loss of innate anti-HIV activity was still observed even 3 weeks after the last application of gel, additional factors may have contributed to the decrease in innate antiviral activity in gel users. Changes

in antiviral activity could be associated with product associated binding of mucins in the vaginal fluid. The placebo gel differs from the film in it is polymer content, with the gel being hydroxyethyl cellulose[28] and the film being polyvinyl alcohol.[19] Further work is underway to define changes in glycoprotein content of the cervicovaginal fluid of gel and film users which could account for the apparent disruption in innate anti-HIV activity.

Our study substantiated previous research that found film products to be more acceptable than gel products in young sexually active women, although in this trial women used the product only for 7 days which limits the generalizability of this finding. In an earlier side-by-side acceptability study of different formulations of nonoxynol-9, women found film to be more acceptable and cited “messiness” as the main drawback to gel formulations. Coggins et al asked women in Thailand, Zambia, the Ivory Coast, and the United States to use film to suppositories, gel, and foam dosage forms.[15] Participants used each product for four weeks and then were asked to assess the relative acceptability of each product. Most participants preferred the film and gel to suppository. In a study of 1536 US women using a nonoxynol-9 film for contraception over 6 months, 42-51% of women using gels reported messiness with product use as compared to 13% of film users, a finding which is similar to the findings of our study regarding product leakage. In that same study, difficulty with insertion was noted by 40-60% of women, which is similar to our findings in the present study.[14] In one study which found a preference for gel over film, participants cited distrust of the film as significant concern. Hardy et al asked Brazilian participants to handle cream, gel, film, foam and tablet formulations. The film formulation was the least popular method based on the participant's suspicion that the film would be less efficacious than gel formulation. [29]

The main drawback of the current dapivirine film formulation used in this study was the difficulty five participants experienced placing the film correctly inside the vagina. Surprisingly, none of these participants was aware of the misplacement and only two described film placement as moderately or very difficult, although the women with poor product placement tended to have less experience with the use of tampons and vaginal lubricants. Though there was no obvious difference between placebo and dapivirine film characteristics to explain why application difficulties were limited to the dapivirine group, ongoing studies are evaluating how film size, polymer type, and tactile properties impact placebo film application.

Prior microbicide clinical trial experience has demonstrated that adherence to a daily use vaginal product is low in a study population at high risk of HIV.[5] Adherence was slightly improved with peri-coital administration in one study,[2] but not in a second study evaluating this approach.[30] While the focus of vaginal microbicide research has shifted to sustained delivery formulations such as vaginal rings, long-acting injectables and possibly implants, the evaluation of a variety of formulations that address personal preferences, and dosage options remains a priority. As the field of contraception has demonstrated, providing choices for women is important as it increases uptake and use. The film dosage form could provide a lower cost on-demand microbicide product for women that may be more acceptable than gels. Film formulation for the delivery of drugs to the vagina is still early in the drug development process. However, the data derived from this proof of concept study suggest

that the development of films for delivery of antiretroviral drugs as microbicides merits further investigation. Modification of the films and the use of potent, long acting ARVs may allow for the development of slow release films that could provide several days of protection from a single application.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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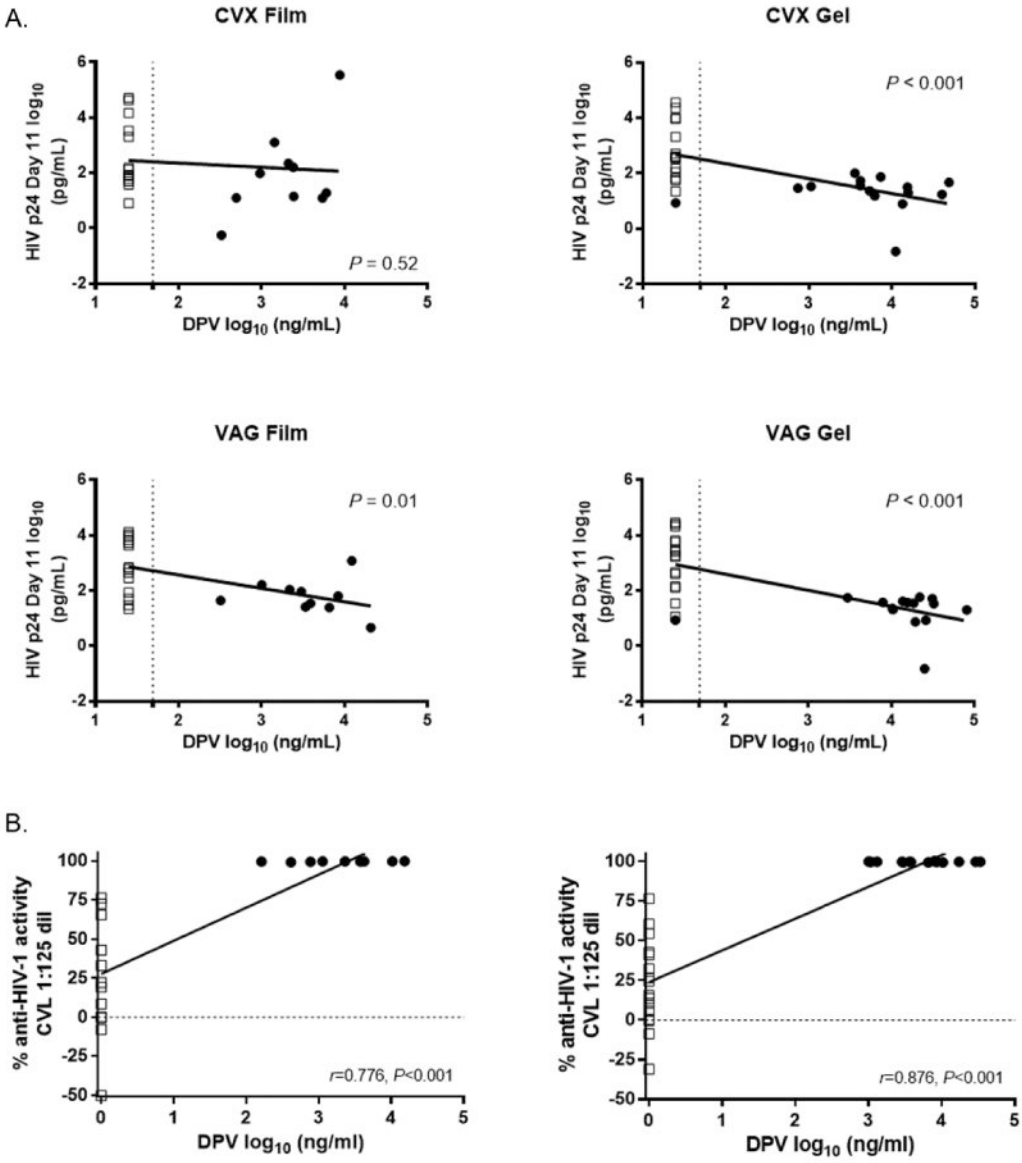

Figure 1.

Pharmacokinetic and pharmacodynamic correlations were defined between dapivirine (DPV) film and gel users in (A) tissue and (B) cervicovaginal lavage (CVL) compartments. A) Paired cervical (CVX) and vaginal (VAG) tissue were collected from participants 2-4 hours after their last dose of film or gel. In one set of biopsies, DPV was quantified by LC-MS/MS and expressed as ng/mL. In the other set of biopsies, DPV activity was evaluated using an *ex vivo* challenge assay and expressed as pg/mL of HIV p24gag. The dotted vertical line represents the lower limit of quantification (LLOQ) for DPV in tissue. Values below the LLOQ were imputed as ½ the LLOQ. B) CVL was collected 2-4 hours after the last dose of film (left) or gel (right) and DPV was quantified by LC-MS/MS and expressed as ng/mL and DPV activity was evaluated using a TZM-bl assay and expressed as %anti-HIV activity. The LLOQ for DPV in CVL was 2 ng/mL; ½ the LLOQ was imputed from CVL that was below the LLOQ. DPV product users are represented by a solid circle while

placebo product users are represented by an open square. Solid lines represent linear least squared regression with a P value test for zero slope using subject as a covariate

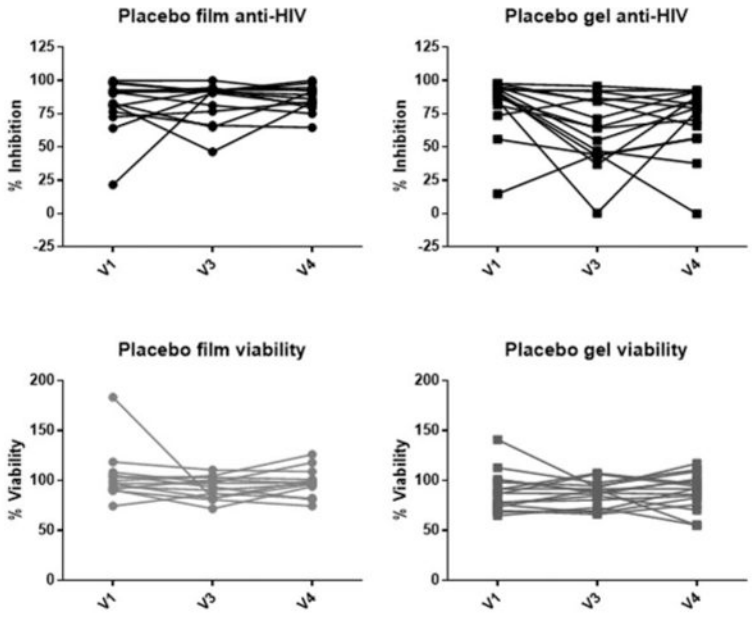

Figure 2.

Cervicovaginal lavage (CVL) innate anti-HIV activity in placebo film (left panels) and gel (right panels) users. Innate anti-HIV activity was quantified from CVL collected at visits 1, 3 (after product use), and 4 from placebo users using a TZM-bl assay. Viability was measured in lower panels to ensure changes in anti-HIV activity were not associated with deviations in cell line viability.

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Table 1

Incidence of adverse events (AEs) by study arm

	Total (N=61)	Placebo Gel (n=16)	Dapivirine Gel (n=15)	Placebo Film (n=15)	Dapivirine Film (n=15)	P-value*
Participants with at least one AE	43 (70.5%)	11 (68.8%)	10 (66.7%)	11 (73.3%)	11 (73.3%)	>0.999
Gastrointestinal complaint	6 (9.8%)	2 (12.5%)	2 (13.3%)	2 (13.3%)	0	0.581
Abdominal discomfort	1 (1.6%)	1 (6.3%)	0	0	0	
Nausea/Emesis	3 (4.9%)	2 (12.5%)	1 (6.7%)	0	0	
Bowel dysfunction	3 (4.9%)	0	1 (6.7%)	2 (13.3%)	0	
Genitourinary complaint	32 (52.5%)	9 (56.3%)	7 (46.7%)	9 (60.0%)	7 (46.7%)	0.869
Pelvic pain	4 (6.6%)	2 (12.5%)	1 (6.7%)	0	1 (6.7%)	
Genital itching	6 (9.8%)	3 (18.8%)	1 (6.7%)	2 (13.3%)	0	
Genital irritation	3 (4.9%)	0	1 (6.7%)	1 (6.7%)	1 (6.7%)	
Vaginal discharge	11 (18.0%)	2 (12.5%)	1 (6.7%)	5 (33.3%)	3 (20.0%)	
Vaginal odor	5 (8.2%)	2 (12.5%)	3 (20.0%)	0	0	
Vaginal infection	2 (3.3%)	0	0	1 (6.7%)	1 (6.7%)	
Bleeding abnormality	8 (13.1%)	3 (18.8%)	2 (13.3%)	2 (13.3%)	1 (6.7%)	
Urinary irritation	2 (3.3%)	1 (6.3%)	1 (6.7%)	0	0	
AE Severity (any body system)						
Grade 1	36 (59.0%)	11 (68.8%)	9 (60.0%)	8 (53.3%)	8 (53.3%)	0.797
Grade 2	12 (19.7%)	2 (12.5%)	2 (13.3%)	5 (33.3%)	3 (20.0%)	0.560
Grade 3	0	0	0	0	0	
AE Relatedness to study product (any body system)						
Related	20 (32.8%)	6 (37.5%)	5 (33.3%)	6 (40.0%)	3 (20.0%)	0.711
Not Related	31 (50.8%)	7 (43.8%)	8 (53.3%)	7 (46.7%)	9 (60.0%)	0.869

Each participant contributes only one observation per category

*P-value from Fisher's exact test

Table 2
Median dapivirine concentrations in biologic matrices

	Dapivirine film (n=10)	Dapivirine gel (n=14)	P-value*
Plasma (ng/ml)	0.22 (0.09–0.63)	0.31 (0.14–0.56)	0.192
Tissue- Cervical (ng/g)	2.25×10^3 (0.33×10^3–8.72×10^3)	6.79×10^3 (0.74×10^3–48.85×10^3)	0.016
Tissue- Vaginal (ng/g)	3.61×10^3 (0.32×10^3–20.64×10^3)	18.96×10^3 (2.97×10^3–80.97×10^3)	0.001
CVL (ng/ml)	2.30×10^3 (0.16×10^3–15.30×10^3)	5.18×10^3 (1.01×10^3–33.60×10^3)	0.141

Data presented as median (range). Women with poor placement were excluded. This included five women with visible film external to the vaginal introitus at the time of biopsy and one woman randomized to gel with no visible product in her vagina at the time of biopsies.

*P-value from Mann-Whitney U test

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Table 3

Acceptability

Characteristic	Total (N=61)	Placebo Gel (n=16)	Dapivirine Gel (n=15)	Placebo Film (n=15)	Dapivirine Film (n=15)	P-value*
How difficult was the product to insert						<0.001
Difficult	12 (19.7%)	0	0	6 (40.0%)	6 (40.0%)	
Not difficult	49 (80.3%)	16 (100%)	15 (100%)	9 (60.0%)	9 (60.0%)	
How did the study product feel once inserted						<0.001
Uncomfortable	16 (26.2%)	10 (62.5%)	2 (13.4%)	2 (13.3%)	2 (13.3%)	
Not uncomfortable at all	45 (73.8%)	6 (37.5%)	13 (86.7%)	13 (86.7%)	13 (86.7%)	
Did you experience product leakage						<0.001
No leakage	26 (42.6%)	1 (6.3%)	4 (26.7%)	10 (66.7%)	11 (73.3%)	
Some leakage	35 (57.4%)	15 (93.8%)	11 (73.3%)	5 (33.3%)	4 (26.7%)	
How likely would you be to use this product if it were found to protect users from getting HIV?						0.924
Unlikely	16 (26.2%)	6 (37.5%)	4 (26.6%)	3 (20.0%)	3 (20.0%)	
Likely	45 (73.8%)	10 (62.5%)	11 (73.4%)	12 (80.0%)	12(80.0%)	

*P-value from Fisher's exact test