AIDS RESEARCH AND HUMAN RETROVIRUSES
Volume 36, Number 12, 2020

DOI: 10.1089/aid.2020.0138

The Role of Volume in the Perceptibility of Topical Vaginal Formulations: User Sensory Perceptions and Experiences of Heterosexual Couples During Vaginal Sex

Kate M. Guthrie,[1–3] Joseph L. Fava,[1] Sara E. Vargas,[1,2] Rochelle K. Rosen,[1,3] Julia G. Shaw,[1] Erna M. Kojic,[4,*] Anthony S. Ham,[5,†] Lisa C. Rohan,[6,7] David Katz,[8,9] Anacecilia Panameño,[1,‡] Christopher Colleran,[1,§] David F. Friend,[10,**] Karen W. Buckheit,[5] and Robert W. Buckheit, Jr.[5]

Abstract

Users' sensory perceptions and experiences (USPEs; perceptibility) of drug formulations can critically impact product adoption and adherence, especially when products rely on appropriate user behaviors (timing of administration, dosing measurement) for effectiveness. The use of topical gel formulations for effective anti-human immunodeficiency virus/sexually transmitted infection (HIV/STI) vaginal microbicides has been associated with messiness and other use-associated challenges, resulting in low adherence. Nonetheless, such formulations remain attractive due to good pharmacokinetics and resulting pharmacodynamics through their volume and surface contact for drug delivery into luminal fluids and mucosa. Consequently, advocates and scientists continue to pursue topical forms [semisolid (e.g., gel, suppository); solid (e.g., film)] to deliver select drugs and offer user choice in HIV/STI prevention. The current data build on previously validated USPE scales evaluating perceptibility of gels with various biophysical/rheological properties. Specifically, increased formulation parameter space adds a new set of properties inherent in quick-dissolving film. We compared film, a product adding no discernable volume to the vaginal environment, to 2 and 3.5 mL hydroxyethyl cellulose gel to consider the impact of volume on user experience. We also examined the USPE scales for evaluation of male sexual partners' experiences. The original USPE scales functioned as expected. Additionally, six new USPE scales were identified in this enhanced parameter space. Significant differences were noted between USPEs in pairwise comparisons, with largest differences between film and high-volume gel. Product developers and behavioral scientists can use these scales to design products, optimizing user experience and maximizing adherence and delivery of efficacious anti-HIV/STI pharmaceuticals. They can be extended to evaluation of additional formulations, devices, and compartments, as well as single- and multipurpose pharmaceuticals. In broader contexts, USPEs could be of value in evaluating formulations and devices to prevent/treat other diseases (e.g., ophthalmologic, dermatologic). Steadfast attention should be given to patient experience, and, where applicable, experiences of partners and/or caregivers.

[1]Center for Behavioral & Preventive Medicine, The Miriam Hospital, Providence, Rhode Island, USA.
[2]Department of Psychiatry & Human Behavior, Alpert Medical School of Brown University, Providence, Rhode Island, USA.
[3]Department of Behavioral & Social Sciences, Brown University School of Public Health, Providence, Rhode Island, USA.
[4]Division of Infectious Disease, Department of Medicine, Alpert Medical School of Brown University, Providence, Rhode Island, USA.
[5]ImQuest BioSciences, Inc., Frederick, Maryland, USA.
[6]Magee-Womens Research Institute, Pittsburgh, Pennsylvania, USA.
[7]Department of Pharmaceutical Sciences, University of Pittsburgh, Pittsburgh, Pennsylvania, USA.
[8]Department of Bioengineering, Duke University, Durham, North Carolina, USA
[9]Department of Obstetrics & Gynecology, Duke University, Durham, North Carolina, USA
[10]CONRAD, Arlington, Virginia, USA.
*Current affiliation: Icahn School of Medicine at Mount Sinai, Division of Infectious Diseases, Mount Sinai St. Luke's and Mount Sinai West, New York, New York, USA.
**Current affiliation: Daré Bioscience, Inc., San Diego, California, USA.
†Current affiliation: Prometic BioTherapeutics, Rockville, Maryland, USA.
‡Current affiliation: Boston Public School System, Boston, Massachusetts, USA.
§Current affiliation: Safe Harbor Cohasset Coalition, Cohasset, Massachusetts, USA.

Keywords: microbicides, user experience, adherence, formulation design, HIV prevention

Introduction

NEGATIVE REPRODUCTIVE HEALTH outcomes (e.g., sexually transmitted infections (STIs), human immunodeficiency virus (HIV), unintended pregnancy) are major public health concerns. There are 2.5 million incident STIs annually in the United States,[1] and nearly 40,000 incident HIV infections.[2] Most U.S. women (85%) contract HIV by heterosexual contact.[3] Nearly half of U.S. pregnancies are unintended.[4,5] Condoms are the only inexpensive widely available prevention method against multiple STI/HIV and pregnancy. However, condom rates remain low[6] and condom use typically requires cooperation by male partners.[7] Topical product development continues, including on-demand prevention methods for both vaginal and rectal use.[8,9]

In penile/vaginal sex, for topical formulations to be efficacious, spreading and distribution throughout the vaginal canal, and coating and retention on the vaginal epithelium, may be critical.[10–13] Successful delivery of some pharmaceuticals acting within the vaginal mucosa requires a coated surface area across which agents exit the formulation and enter the mucosa, assuming permeability. Some formulations deliver agents that act within fluids in the vaginal lumen and on luminal mucosal surfaces.[14] In this context, broad distribution throughout the lumen along the canal is likely essential. These considerations are also of import in rectal formulations.[15–18]

Multiple formulation factors contribute to adequate epithelial coverage, including physicochemical parameters and applied volume.[14,19] These not only govern drug delivery, but also undoubtedly affect product use experience.[20,21] Greater volumes of administered product should correlate with greater spread and surface coverage. However, volume alone does not predict such metrics: other factors include formulation components, viscosity, osmolarity, temperature, surface tension, and miscibility. Increased volume applied may lead to more leakage/messiness, which is considered bothersome[22] by some users. The role of these so-called ''nuisance factors'' may be critical to use. Collectively, interdependent relationships between topical formulations, endogenous vaginal fluids, vaginal anatomy, and user behaviors impact users' sensory perceptions and experiences (USPEs) and the meanings users make of those experiences with respect to perceived product efficacy and willingness to use.[20,21,23–25] Historically, anti-HIV topical gel microbicide trials were challenged by poor adherence, hindering evaluation of product efficacy.[26–29] Volume, along with rheological changes inherent in dilution and mixing with endogenous fluids, may increase product awareness by users or sexual partners. This has implications for both overall user experience and specific circumstances, including discreet/covert use.[30–34] Adherence to use requires co-optimization of drug delivery and retention and USPEs.

We sought to determine the role of applied volume in USPEs during vaginal/penile sex, using quick-dissolving film, and 2 and 3.5 mL volumes of hydroxyethyl cellulose (HEC) gel. Several clinical studies evaluated polymeric thin films as potential dosage forms for vaginal delivery of anti-HIV drugs.[35–38] Vaginal films offer potential advantages of discreet use, minimal-to-no leakage, and no requirement for applicator insertion, leading to lower product cost. Films were shown to deliver drug at least as well as comparator gel products; their stealth nature and minimal impact within the vagina was confirmed. A polymeric film can be considered a dehydrated gel, and as such, was included here as a representative formulation. We posited that film would add minimal physical volume to the vaginal environment, but, like gels, may cause changes in the rheology of endogenous vaginal fluids as it dissolved, changing how the dissolved film ''behaves'' (i.e., flow mechanics) and how it feels to the user. Thus, the chosen product panel allowed an examination of a relevant formulation volume range for anti-HIV microbicides: (1) no/minimal volume, (2) relatively low volume, and (3) relatively high volume. Using HEC gel for both the low- and high-volume formulations allowed us to hold constant all other gel formulation properties unrelated to volume.

Methods

All study activities were approved by the local IRB. We conducted a mixed-methods study to assess female and male USPEs of two volumes of vaginal gel and a quick-dissolving vaginal film during vaginal/penile sex (clinicaltrials.gov: NCT01334827).

Participants

Mutually monogamous heterosexual couples (females 18–45 years old; males 18+ years) in good health enrolled. Volunteers were excluded if: STI or HIV positive upon screening; pregnant, planning to become pregnant during the study period, breastfeeding, or having completed menopause (females only); reported a pregnancy outcome or gynecological/genital surgery in the 30 days before screening; and/or allergies to latex or study formulation ingredients. Both members reported being mutually monogamous, having vaginal/penile sex together (previous 6 months), and agreed to all study guidelines/procedures.

Recruitment/screening

Couples were recruited through word-of-mouth, materials distributed broadly in the community, and advertisements (e.g., public transportation, online). Either member of a couple could make initial contact with the study team: once preliminary eligibility was ascertained for the person who made first contact, the team requested that they have their partner contact the team if interested.

Individuals were independently prescreened for preliminary eligibility through phone: that is, age, sexual and reproductive history, sexual behavior, and allergies. If preliminarily eligible, each was privately enrolled for clinical screening [medical exam; pregnancy (females), STI/HIV testing]. Given limited clinical experience[39] with the vaginal film, a safety lead-in was conducted: once both members of the couple were cleared clinically, a ''film tolerance'' visit evaluated dissolution of film *in vivo* and assured no adverse reactions/sensitivities. Clinicians conducted baseline visual pelvic exams. The participant inserted the film, waited 15 minutes (dissolution), and was examined again for signs of sensitivity. She then simulated intercourse with a condom-covered phallus and was examined again to ensure no reactivity, sensitivity, or safety concerns as a function of

intercourse. Given clinical clearance (i.e., through Visit 1B), both members of the couple were again assessed for interest: only if both individually and privately agreed did scheduling for the formulation evaluation enrollment proceed. Thus, each volunteer's interest was privately assessed at each recruitment/screening encounter: if, at any point, either member of a couple indicated they were not interested in participating, the couple was deemed ineligible; they were each subsequently told they were ineligible as a couple [reason(s) for ineligibility withheld to protect each person's privacy].

Study formulations

The low- and high-volume gels were the same gel manufactured as the ''universal placebo[40]'' in several microbicide trials (CONRAD, Arlington, VA). ''HEC gel,'' is an isotonic, slightly acidic (pH = 4.4) gel composed of ingredients generally recognized as safe for topical pharmaceutical preparations[40]: 96.3% purified water, USP; 2.7% HEC, NF (Natrosol 250; HX Pharm); 0.85% sodium chloride, USP; 0.1% sorbic acid, NF; and sodium hydroxide, NF, qs pH 4.4. HEC gel was manufactured following good manufacturing practices (GMP) and FDA guidelines. Prefilled HTI Comfort Tip® applicators were used for insertion.

The vaginal film was a placebo quick-dissolving polymeric thin film. GMP quality film was manufactured by MonoSol (Merrillville, IN). Film composition: 25% w/w glycerin; 25% w/w polyvinyl alcohol; 20% w/w hydroxypropyl methylcellulose; 20% w/w polyethylene glycol; 5% w/w propylene glycol; and 5% w/w croscarmellose sodium. Films were cut into 1″ × 2″ individual dosing units and packaged. The dissolving specification was defined as <15 min postinsertion.

Perceptibility scales

The USPE scales capture a range of sensory experiences related to using topical products during vaginal sex. The USPE scales were validated previously, using four vaginal

Table 1. Sexual Activity User Sensory Perception and Experience (Users' Sensory Perceptions and Experience: Perceptibility) Scales, Summaries of Constructs Each Scale Captures, Number of Items in Each Scale, and Average Coefficient Alphas Across All Three Formulations Evaluated

Perceptibility scale	*Constructs captured*	*No. of items*	*Average coefficient alpha*[a]
SEX: initial penetration[b]	Smoothness and lubricity at initial penetration	3	0.79
SEX: initial lubrication[b]	Coating and lubricating sensations during the first few strokes of coitus	5	0.88
SEX: spreading behavior[b]	Perceptions of ease of stroke and product spread as coital strokes continued	3	0.74
SEX: product awareness[b]	Feeling the product intravaginally during coitus (feeling the product moving around in the vagina, feeling the product between the vaginal wall and the phallus)	7	0.84
SEX: perceived wetness[b]	Feeling as though the product was covering the entire vagina by the end of coitus; sensations of wetness, as they would after having sex or having an orgasm	F: 3; M: 2	0.43
SEX: stimulating[b]	Whether or not they felt the product enhanced sexual pleasure or stimulated them	6	0.88
SEX: messiness[b]	Perceptions of the product feeling watery or leaking/dripping/messiness as coitus continued	6	0.71
SEX: leakage[b]	Sensations of the product leaking out during and after coitus; sensation of the product close to the introitus by the time coitus was ending; sensation of product in the pubic hair after coitus; feeling the need to clean up after coitus	5	0.64
SEX: pre-coital leakage[c]	Sensations of the product leaking out beyond the labia before initial penile penetration	3	0.82
SEX: naturalness[c]	Perceptions of ''naturalness'' of lubrication before (females) and during sex; whether product leakage looked like natural vaginal fluids (females)	F: 4; M: 2	0.69
SEX: lubricity[c]	Sensations of wetness before (females) and slipperiness of product and lubricity during sex	F: 3; M: 2	0.72
SEX: effortful[c]	Sensations of lubrication within labia; effort needed for (and/or difficulty of) penile penetration and continued strokes during intercourse; dryness increasing difficulty toward end of strokes	4	0.74
SEX: pleasure[c]	Whether or not product improved sex and stimulation for partner; sensations of pleasure	3	0.78
SEX: noticeable[c]	Perceptions of partner sensations of product during sex and noticing messiness on condom/penis; perceptions of product thickness/viscosity	3	0.67

[a]Internal consistency reliability (i.e., Cronbach's coefficient alpha): average across products and sexes.
[b]Original Perceptibility Scales, Morrow (2013)©.
[c]Novel Perceptibility Scales, Guthrie (2019)©.
F, female; M, male.

gels representing ranges in viscosity, yield stress, and other rheological performance properties.[20] The USPE scales consist of factual statements of primarily observable sensations, with little room for interpretation or judgment on the part of the respondent.[20,21] Higher scores on USPE measures are not indicative of endorsement or preference, but rather degree of agreement with the occurrence of the sensation/experience as queried. Table 1 describes the constructs captured in each sexual activity USPE scale and its internal consistency reliability (i.e., Cronbach's coefficient alpha) within the current sample, including six additional scales identified in this study. Further details regarding development of the original scales can be found elsewhere.[20,21]

Procedures

Formulations were randomly ordered by visit: 2 mL HEC gel, 3.5 mL HEC gel, and 1″×2″ quick-dissolving vaginal film. Couples together attended three product evaluation visits (visits ≥5–7 days apart). Individuals were separated to start a visit, each working with a different staff member. Female participants were tested for pregnancy before visit start. The first part of visits consisted of either: (1) manipulating one of two study gels in their hands (i.e., *in mano*, completed by females and males independently), or (2) discussing film dimensionality and predissolution property preferences[25] (females only). For gel visits, participants then completed questionnaires regarding their experiences *in mano*. Females were instructed in product insertion and then applied study product in a private room: gels were inserted with an applicator (HTI Comfort Tip), whereas the film was inserted digitally. For gel visits, women immediately ambulated for 2 min. For film visits, women waited for film to dissolve and then ambulated for 2 min. The couple was then taken to a private room and given 45 min to have condom-protected vaginal/penile sex (study provided nonlubricated condom). After they finished having sex, they, separately, completed application/ambulation perceptibility surveys (females only) and sexual activity perceptibility surveys.

Quantitative analyses

All quantitative analyses were conducted using IBM SPSS Statistics 20.0. Descriptive statistics were calculated for demographics and behavioral variables. Exploratory dimensional analyses employed principal component analysis to re-examine internal structure of the eight original UPSE scales,[20] and to identify new USPE scales within the expanded evaluable parameter space of volume (3.5, 2, ~0 mL) and formulation (addition of film). We compared the original and new USPE scale scores between each pair of formulations using paired *t*-tests. Separate paired *t*-tests were conducted within female and male subsamples. Effect sizes were quantified using Cohen's *d* statistic.[41] Data are available through appropriate Data Sharing Agreement.

Results

Participants

Twenty-four mutually monogamous heterosexual couples enrolled in the product evaluation study. Figure 1 presents flow through the study. Forty-two couples were preliminarily eligible: 12 declined to enroll in clinical screening and 6 were no longer interested or eligible after clinical screening and film tolerance evaluation. All 24 couples completed all 3 product evaluation visits (100% retention).

Female participants' mean age was 29.0 years [standard deviation (SD) = 7.7], with an average of 1.5 male vaginal sex partners (SD = 1.1; previous 12 months). Male participants' mean age was 30.8 years (SD = 9.9), with an average of 1.5 female vaginal sex partners (SD = 1.2; previous 12 months). Seventy-one percent ($n = 17$) of women used hormonal contraceptive methods, 17% ($n = 4$) used a nonhormonal intrauterine device (IUD), and 13% ($n = 3$) reported history of tubal ligation. Forty-two percent ($n = 10$) reported regular condom use with their enrolled partner. Table 2 presents additional demographics and sexual and reproductive health history information. There were no significant differences ($p > .05$) in age, race, Latinx/Hispanic ethnicity, number of sexual partners, or STI history among participants who completed the study and those who screened but did not enroll.

Perceptibility scales

There are thirteen Sexual Activity USPE scales of relevance in both female and male sexual partners. See Table 3 for pairwise formulation comparisons across all perceptibility scales in female participants and Table 4 for pairwise formulation comparisons across sexual activity perceptibility scales in male participants. Figure 2 provides a visual representation of each scale score by formulation.

Perceptibility: low- and high-volume gel comparisons

USPEs before sex. There were no differences in pairwise comparisons between low- and high-volume gels with respect to application/insertion experience, nor were there differences in ambulation sensations of product stickiness, awareness in the vagina, or spreading behavior. There were significant differences in women's ambulatory sensations of product movement (Product Movement), leakage (Leakage), and hygiene (Hygiene), with effect sizes in the medium-to-large range.

Sexual activity (SEX) USPEs. There were no significant differences in pairwise comparisons between the low- and high-volume gels, for either females or males, in sensations associated with the Initial Lubrication, Product Awareness, Perceived Wetness, Stimulating, Naturalness, Lubricity, and Noticeable USPE Scales. Both females and males had significantly higher averaged scale item scores for high-volume gel (compared with low-volume gel) on the Spreading Behavior, Messiness, and Leakage Scales, all in the medium-to-large effect size range. Men reported significantly higher scores for low-volume gel (compared with high-volume gel) on the Effortful Scale. Scores indicate that the degree of effort to penetrate and complete strokes was perceived differently between low- and high-volume gels among the men, and in this case, indicate that high-volume gel allowed for greater ease of strokes. Women reported significantly higher scores for high-volume gel (compared with low-volume gel) on the Initial Penetration, Pleasure, and Precoital Leakage Scales.

Perceptibility: film and gel comparisons. For both males and females, and with only one exception (i.e., Effortful scale), USPE scores were lowest for vaginal film compared

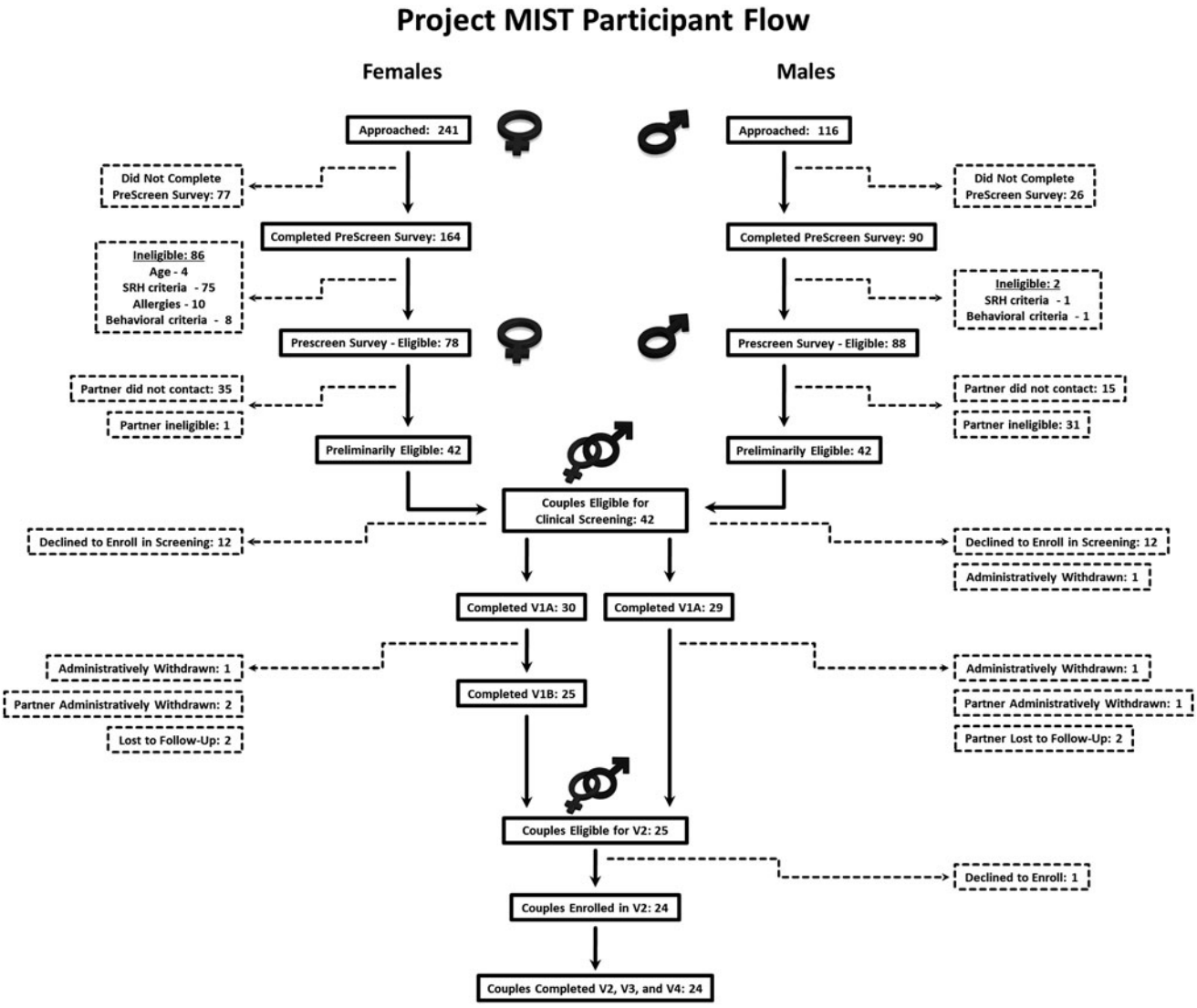

FIG. 1. Project MIST participant flow. Prescreening eligibility assessed age, sexual and reproductive health history (currently pregnant or planning to become pregnant; currently breastfeeding; SRH surgery or delivery in last 3 months; effective contraceptive use; menopause; STI diagnosis in previous 12 months; HIV positive or of unknown status; current yeast infection), sexual behavior requirements (i.e., monogamy, vaginal sex with partner in last 6 months), and lack of allergies to latex or formulation ingredients. If both members of a couple were prescreen eligible, their membership as a couple would be confirmed and they would be evaluated as a couple during clinical screening. Thus, all volunteers were assessed as individuals through preliminary eligibility, when membership in a couple was confirmed and clinical screening visits scheduled. Visit 1A: clinical screening visit for general health and STI/HIV testing. Visit 1B: film tolerance visit (females only) for sensitivity to formulation ingredients. Visits 2–4: product evaluation visits, order of products randomized for each couple. (See Methods section for further details: Ineligibles may not add up due to some individual volunteers having more than one reason for ineligibility.) HIV, human immunodeficiency virus; SHR, sexual/reproductive health; STI, sexually transmitted infection.

with low-volume and high-volume gels. Differences between low-volume gel and film, and between high-volume gel and film, were nearly always statistically significant, with only three exceptions: low volume gel and film did not differ on the Messiness or Noticeable Scales for women, and high-volume gel and film did not differ on the Naturalness Scale for men.

Formulation preference. Almost half the participants reported a preference for high-volume gel overall (46% of females; 42% of males). More women preferred low-volume gel to film (38% vs. 17%), while more men preferred film to low-volume gel (38% vs. 21%).

Discussion

USPE scale development

Both women and men were able to rate their perceptions of various sensations elicited by three different volumes of topical formulations during vaginal/penile sex and to distinguish meaningfully between those sensations. USPE scale scores varied by formulation for both women and their male

Table 2. Means, Standard Deviations and Range, or Sample Size and Percentage, for Selected Demographic Information and Sexual and Reproductive History Variables

	Female	*Male*
Age: mean (SD); range	29.0 (7.7); 18–45	30.8 (9.9); 20–57
Latino/Latina ethnicity	3 (13%)	2 (8%)
Racial identification (all that apply)		
Black	3 (13%)	4 (17%)
White	15 (63%)	17 (71%)
Asian	0 (0%)	0 (0%)
American Indian/Alaska Native	0 (0%)	0 (0%)
Native Hawaiian/Other Pacific Islander	0 (0%)	0 (0%)
Multiracial	4 (17%)	1 (4%)
Other	1 (4%)	2 (8%)
None selected	1 (4%)	0 (0%)
No. of sexual partners, past 12 months: mean (SD); range	1.5 (1.1); 1–6	1.5 (1.2); 1–6
No. of vaginal sex partners, past 12 months: mean (SD); range	1.5 (1.1); 1–6	1.5 (1.2); 1–6
Ever diagnosed with an STD	4 (17%)	2 (8%)
Ever pregnant	13 (54%)	N/A
Ever given birth (vaginally or C-section)	11 (46%)	N/A
No. of vaginal deliveries (across 11 who gave birth)		
0	2 (18%)	N/A
1	1 (9%)	N/A
2–4	7 (64%)	N/A
5+	1 (9%)	N/A
Length of sexual relationship with study partner		
3–6 Months	1 (4%)	1 (4%)
6–12 Months	6 (25%)	4 (17%)
1–5 Years	13 (54%)	15 (62%)
>5 Years	4 (17%)	4 (17%)
Typical weekly vaginal sex frequency		
1–2 Times per week	6 (25%)	6 (25%)
3–4 Times per week	11 (46%)	13 (54%)
5–6 Times per week	4 (17%)	2 (8%)
>7 Times per week	3 (13%)	3 (13%)
History of product use/exposure		
Vaginal medication	12 (50%)	0 (0%)
Vaginal lubricants	21 (88%)	17 (71%)
Anal lubricants	7 (29%)	5 (21%)
Spermicides	5 (21%)	2 (8%)
Desiccants	1 (4%)	1 (4%)
Vaginal douche (females only)	8 (33%)	N/A
Penile medications (males only)	N/A	1 (4%)

SD, standard deviation; STD, sexually transmitted disease.

sexual partners. Interestingly, in most scales, female and male scores mirrored each other; that is, women's and men's sensory experiences of each formulation were largely in concordance with each other, providing credibility to the generalizability of the USPE scales across sexes, as well as formulation parameter space. As in previous work, scale scores were in concordance with sensory experiences and formulation ''behaviors'' expected as a function of each formulation's rheological and biophysical properties.

Eight sexual activity USPE scales, developed previously,[20] were confirmed. In the current study, we increased the parameter space within which we evaluated USPEs by varying product volume [i.e., 3.5 mL gel and 2 mL gel (all other rheological and biophysical properties identical before insertion) and film contributing minimal volume post-dissolution]. In addition, we added additional context by including both female and male evaluations. In this context, psychometric analyses identified six new sexual activity (SEX) scales: Naturalness, Lubricity, Effortful, Pleasure, Precoital Leakage (females only), and Noticeable.

Examining USPE scores

Users reported different sensory experiences with each formulation, including postinsertion/precoital sensations (females only) and sensory experiences during/following sex. Pairwise comparisons between low- and high-volume gels reflected those sensations theoretically linked to differences in volume, as well as diluted volume over time. Furthermore, additional and particularly large effect sizes were noted in pairwise comparisons between 2 mL gel and film and between 3.5 mL gel and film, the contexts of greatest discrepancy in volumes evaluated.

Overall, the 3.5 mL gel was generally considered the most lubricating and the messiest. The 2 mL gel was perceived as less messy and less lubricating than 3.5 mL gel, but this was

Table 3. Averaged Scale Item Scores for Female Users: Cohen's *d* (Effect Size), and Significance Level for Each Pair-Wise Comparison Across Three Topical Vaginal Formulation Conditions

Pairwise formulation comparison	*Low to high volume*			*Low volume—film*			*Film—high volume*		
	ASIS[a]			*ASIS*[a]			*ASIS*[a]		
Perceptibility Scale	*Low*	*High*	d[b]	*Low*	*Film*	d[b]	*Film*	*High*	d[b]
Application perceptibility scales									
APP: leakage[c]	1.53	1.49	0.07	1.53	1.36	0.29	1.36	1.49	0.24
APP: ease[c]	4.67	4.61	0.12	4.67	3.34	1.73***	3.34	4.61	1.42***
APP: discreet-portable[c]	3.79	3.42	0.51	3.79	4.08	0.46	4.08	3.42	1.00**
APP: product awareness[c]	2.33	2.83	0.53	2.33	1.92	0.46	1.92	2.83	0.94**
APP: lack of product awareness[c]	2.78	2.92	0.14	2.78	3.24	0.49	3.24	2.92	0.31
Ambulation perceptibility scales									
AMB: product movement[c]	1.72	2.28	0.91**	1.72	1.22	1.12**	1.22	2.28	1.54***
AMB: leakage[c]	1.62	2.06	0.68*	1.62	1.19	0.90*	1.19	2.06	1.44***
AMB: hygiene[c]	1.85	2.26	0.60*	1.85	1.33	0.74*	1.33	2.26	1.39***
AMB: stickiness[c]	1.07	1.14	0.30	1.07	1.51	0.84*	1.51	1.14	0.59
AMB: product awareness[c]	3.47	3.27	0.20	3.47	2.96	0.59	2.96	3.27	0.30
AMB: spreading behavior[c]	3.39	3.48	0.14	3.39	2.32	1.33***	2.32	3.48	1.41***
Sexual activity perceptibility scales									
SEX: initial penetration[c]	3.64	4.35	0.88**	3.64	1.74	1.86***	1.74	4.35	2.53***
SEX: initial lubrication[c]	3.54	3.89	0.38	3.54	2.55	1.09***	2.55	3.89	1.09***
SEX: spreading behavior[c]	3.54	4.10	0.76*	3.54	2.68	1.09***	2.68	4.1	1.66***
SEX: product awareness[c]	2.55	2.89	0.46	2.55	1.73	1.16***	1.73	2.89	1.46***
SEX: perceived wetness[c]	2.88	3.43	0.59	2.88	1.74	1.10***	1.74	3.43	1.90***
SEX: stimulating[c]	2.35	2.72	0.48	2.35	1.36	1.41***	1.36	2.72	1.91***
SEX: messiness[c]	1.65	2.11	0.85**	1.65	1.39	0.51	1.39	2.11	1.31***
SEX: leakage[c]	2.05	2.44	0.61*	2.05	1.48	0.81*	1.48	2.44	1.41***
SEX: naturalness[d]	3.38	3.44	0.09	3.38	2.40	1.11***	2.40	3.44	1.00**
SEX: lubricity[d]	3.10	3.50	0.48	3.10	1.38	2.39***	1.38	3.50	2.66***
SEX: effortful[d]	1.41	1.17	0.48	1.41	3.08	2.17***	3.08	1.17	2.21***
SEX: pleasure[d]	2.35	2.93	0.71*	2.35	1.43	1.28***	1.43	2.93	1.53***
SEX: precoital leakage[d]	2.08	2.89	0.77*	2.08	1.25	0.75*	1.25	2.89	1.69***
SEX: noticeable[d]	2.14	2.65	0.59	2.14	1.75	0.55	1.75	2.65	0.75*

[a]ASIS: 5-point Likert response format for all items: 1 = do not agree at all; 2 = agree a little; 3 = agree somewhat; 4 = agree a lot; 5 = agree completely.

[b]Effect sizes using Cohen's *d* statistic: values of 0.2, 0.5 and 0.8 conventionally considered small, medium, and large effect sizes, respectively. Low-volume: 2.0 mL HEC; high-volume: 3.5 mL HEC; film: quick dissolving film.

[c]Original Perceptibility Scales, Morrow (2013)©.

[d]Novel Perceptibility Scales, Guthrie (2019)©.

*Significant at alpha ≤.05.

**Significant at alpha ≤.01.

***Significant at alpha ≤.001.

AMB, ambulation for 2 min before sex; APP, application/insertion; ASIS, averaged scale item scores; HEC, hydroxyethyl cellulose; SEX, penetrative intercourse [in this study, vaginal/penile intercourse with partner wearing a nonlubricated nonlatex condom (see Methods section)].

not universal across participants. The film was generally perceived as not adding volume and most participants reported that it did not provide lubrication. Vaginal films, and even low-volume gels, may add minimal volume to the vaginal environment but may also change the rheological properties of endogenous fluids. In qualitative interviews, some noted greater leakage with low-volume gel compared with high-volume gel: this may be an example of just such a phenomenon, with diluted low-volume gel rheology changing such that it leaked more quickly or noticeably. In our sample, the film was primarily associated with a perceived loss of moisture and vaginal dryness, reducing sexual pleasure for several participants, both female and male. Previous research found that vaginal films are unlikely to be associated with leakage and messiness[42]; our results support these findings. USPE scores here indicate that, while participants did not endorse a high level of agreement with items assessing messiness and leakage for any of the study products, there were significant and noticeable differences across the three formulations in the expected directions given the range of volumes represented. It is not surprising that the largest effect sizes were seen between film and 2 mL gel and between film and 3.5 mL gel. It is also not surprising that the high-volume gel had the highest ratings on scales associated with factors such as leakage, messiness, and spread, whereas film had the lowest ratings on these scales and others, including initial penetration (a measure of lubricity) and product awareness.

It is important to note that higher scores on USPE measures are not indicative of endorsement or preference. The USPE scales consist of factual statements of primarily observable sensations, with little room for interpretation or judgment on the part of the respondent.[20,21] As an example, in our

Table 4. Averaged Scale Item Scores for Male Users: Cohen's *d* (Effect Size), and Significance Level for Each Pair-Wise Comparison Across Three Topical Vaginal Formulation Conditions

Pairwise formulation comparison	*Low to high volume*			*Low volume—film*			*Film—high volume*		
	ASIS[a]			*ASIS*[a]			*ASIS*[a]		
Sexual activity perceptibility scale	*Low*	*High*	d[b]	*Low*	*Film*	d[b]	*Film*	*High*	d[b]
SEX: initial penetration[c]	3.86	3.83	0.05	3.86	2.06	2.67***	2.06	3.83	2.14***
SEX: initial lubrication[c]	3.58	3.78	0.43	3.58	2.60	1.51***	2.60	3.78	1.76***
SEX: spreading behavior[c]	3.56	3.86	0.62*	3.56	2.47	1.53***	2.47	3.86	1.76***
SEX: product awareness[c]	2.72	3.10	0.58	2.72	2.04	0.90**	2.04	3.10	0.99***
SEX: perceived wetness[c]	3.00	3.38	0.54	3.00	1.94	1.99***	1.94	3.38	1.57***
SEX: stimulating[c]	2.58	2.66	0.17	2.58	1.99	0.74*	1.99	2.66	1.07***
SEX: messiness[c]	1.84	2.18	0.64*	1.84	1.32	0.99***	1.32	2.18	1.57***
SEX: leakage[c]	1.73	2.10	0.76*	1.73	1.38	0.94**	1.38	2.10	1.38***
SEX: naturalness[d]	3.17	3.17	0.00	3.17	2.60	0.72*	2.60	3.17	0.50
SEX: lubricity[d]	3.15	3.42	0.41	3.15	1.63	1.80***	1.63	3.42	2.05***
SEX: effortful[d]	1.53	1.19	0.78*	1.53	2.81	1.24***	2.81	1.19	1.71***
SEX: pleasure[d]	2.88	2.92	0.08	2.88	2.08	0.90**	2.08	2.92	0.96**
SEX: noticeable[d]	2.54	2.89	0.50	2.54	1.78	1.12**	1.78	2.89	1.27***

[a]ASIS: 5-point Likert response format for all items: 1 = do not agree at all; 2 = agree a little; 3 = agree somewhat; 4 = agree a lot; 5 = agree completely. APP USPE scales, Ambulation USPE scales (and the SEX: Precoital Leakage USPE scale) do not apply to male sexual partners and are reported for female participants only (Table 3).

[b]Effect sizes using Cohen's *d* statistic: values of 0.2, 0.5, and 0.8 conventionally considered small, medium, and large effect sizes, respectively. Low-volume: 2.0 mL HEC; high-volume: 3.5 mL HEC; film: quick dissolving film.

[c]Original Perceptibility Scales, Morrow (2013)©.

[d]Novel Perceptibility Scales, Guthrie (2019)©.

*Significant at alpha ≤.05.

**Significant at alpha ≤.01.

***Significant at alpha ≤.001.

USPE, users' sensory perceptions and experience.

qualitative interviews, some participants stated that they liked the film because it was the least noticeable (i.e., low Noticeable score) and would be the least disruptive of ''typical'' sex (i.e., high Naturalness score) and, potentially, the easiest to use covertly. For others, more noticeable but less natural sensations provided users with a sense of comfort in its presence and effect. What can be felt can mean different things to different users, and it is this meaning and the patterns of meaning throughout the product experience that appear to ultimately have impact on willingness to use.

The bigger picture: multiple scale score patterns as experience

Similarly, any one USPE scale score does not indicate an ideal—or problematic—formulation. Rather, USPE analyses can consider patterns of sensory experiences elicited by product properties that are acceptable to most users, and, for example, provide the best functionality for covert use, maintain sensory neutrality and allow a couple's sexual experience to remain as it normally is for them, and/or promote other patterns of optimal user experience.

Examining relationships between USPE scores and patterns can be particularly helpful.[21] For example, the Initial Penetration, Pleasure, and Precoital Leakage Scales in combination provide insight into relationships between formulation characteristics as manifest in the body: if precoital leakage is associated with greater lubricity and smoothness on initial penetration, is pleasure attenuated? How any specific user would value this ''cluster'' of experience is unclear: some may weigh comfort at initial penetration more important than overall pleasure, whereas others may accept some discomfort at initial penetration for the promise of greater pleasure overall.

In another example, Stimulating and Pleasure scores suggest that both women and men reported that high-volume gel elicited sensations resulting in greater stimulation and greater pleasure for themselves and their partner than low-volume gel. However, the degree of difference in scores for men in contrast to women was elicited by the film point to additional information. Women's averaged scores indicate little if any agreement of stimulating and pleasure sensations, while men's averaged scores were higher, providing potential evidence consistent with a greater number of men versus women who chose film as their preferred formulation overall.

Similarly, comparisons between formulations and willingness-to-use scores can elucidate user priorities and weightings of various sensory experiences in their product use decision making. Pairwise comparisons between the film and gels suggest that film elicited minimal sensation during sex. The exception is that use of the film seems to have required greater effort to penetrate and complete strokes than either low- or high-volume gel. How do such patterns of experience impact decisions to use?

Willingness to use

Almost half the sample ($n = 10$ men; $n = 11$ women) selected 3.5 mL gel as their preferred study formulation. Interestingly, more women selected 2 mL gel when compared with film (low-volume = 9; film = 4), whereas the opposite was true for males (low-volume = 5; film = 9). Again, qualitative interviews shed some light on this result: a few participants noted that

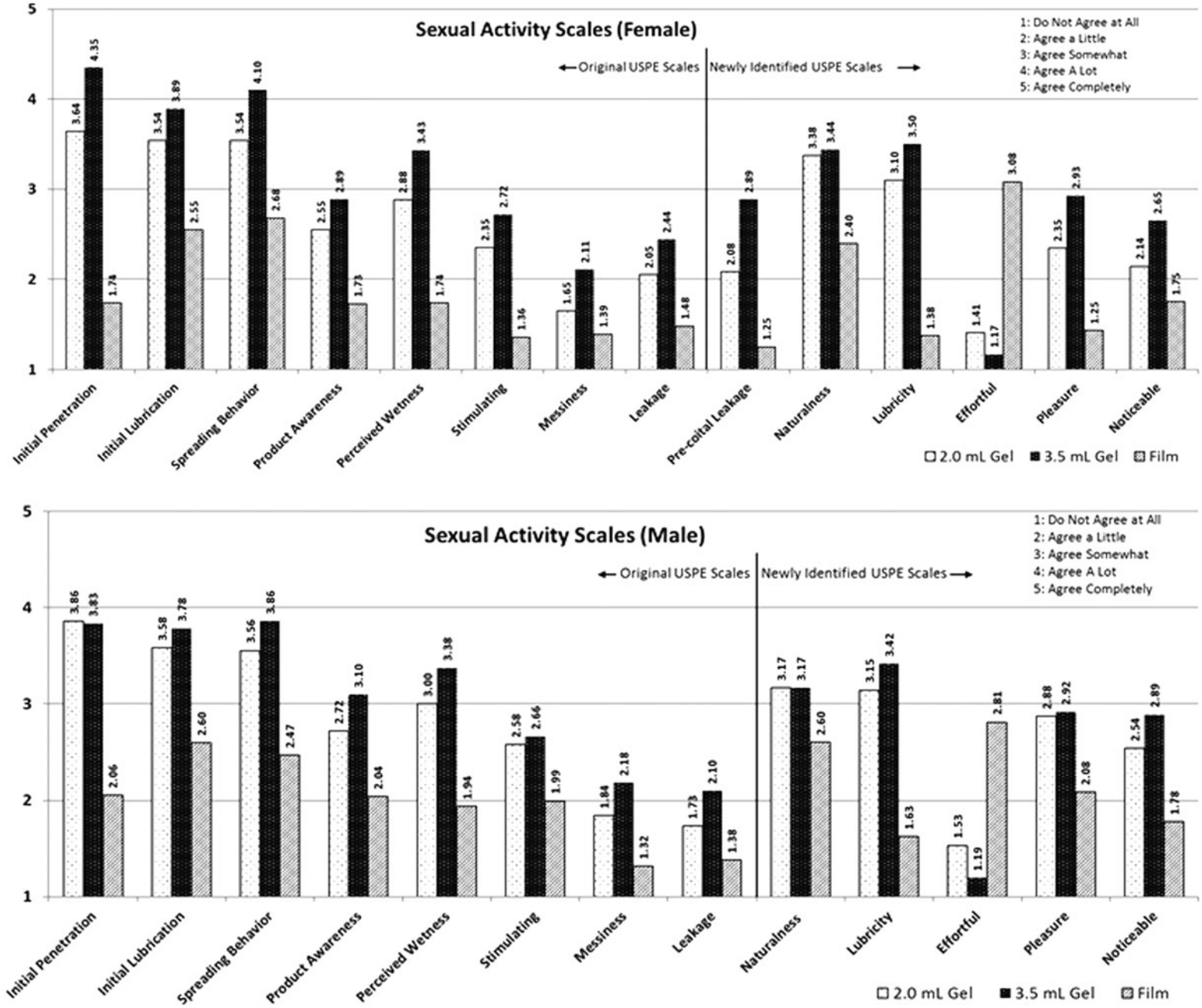

FIG. 2. Scale scores by formulation for female and male sexual partner participants.

some men prefer a slightly less wet sexual experience that provides more sensation of grip/friction around their penis during strokes. Some men may prefer a formulation that does not add excess wetness to the vaginal environment, and the dryness, or changes in rheological functionality, associated with the film, may have enhanced the sexual experience for some men. This has merit, for example, in instances where greater arousal, and therefore greater volumes of endogenous vaginal/cervical fluids with varying rheological properties, might already be contributing to greater (or even ''too much'') lubricity/wetness of the vaginal environment: the film's dilution functions may attenuate this in favor of less wetness. Alternatively, women may have preferred gels to film because of the presence of gel near the introitus during initial penetration. While scale scores for initial penetration and pre-coital leakage were significantly different between all three formulations in pairwise comparisons, women rated both gel volumes markedly higher than film on those two scales. It is possible that the presex/penetration aspect of the sexual experience is particularly salient for some women, and that a product that enhances this experience (however defined by the user) will be ideal. Of course, these are hypotheses that would require testing in future research.

The Perceived Awareness and Noticeable Scales offer an additional example of how interpretation of scale scores cannot be offered merely as a function of absolute value in scale scores (i.e., high vs. low scores). In terms of noticeability, the high-volume gel more prominently entered into participants' physical awareness, being rated more highly as wet and lubricating, and may have offered additional wetness compared with participants' typical experiences. Awareness of the film, conversely, was often perceived as dryness in the vaginal environment, outside of typical sexual experiences for many of these couples. However, some participants identified the film as a candidate for covert use, whereas, very few people thought that the 3.5 mL gel, or the 2 mL gel, could be used without male partners' awareness. It seems that participants view atypical wetness as more of an indicator of product use than atypical dryness, which may be less likely to be noticed and/or may be easier to explain as due to natural processes (e.g., needing more foreplay). This also indicates that a product that has a neutral impact on sex, that is, does not disrupt or enhance the sexual experience, might be preferred by some women, whether the goal is covert use or just to maintain their typical sexual experience.

Finally, perceived and preferred wetness and lubrication are a function of age and social and relationship factors. We also expect that they will be, at least in part, culturally determined. An advantage of USPE measures is the items' focus on observable phenomena: therefore, the same set of items may function in many different settings both domestically and abroad. For example, among young women in noncommitted relationships, a certain profile of formulation properties may be preferred, whereas a different profile may be preferred among married women. We posit that it will be scale scores and their patterns that differentiate formulation preferences among various cohorts and that scale items will largely remain constant (with the exception of linguistic translation). Future studies should determine if we can use a limited bank of items to evaluate products within and between cohorts in various age ranges, relationship contexts,[34,43] or locales.

In addition, it should be noted that the perceptibility of gels and films once inserted into the vagina is only one element of the user experience (for both females and male sexual partners), to be considered in formulation design. Others include instructions for use and their ease or difficulty, inclusive of insertion instructions, and dosing. Does insertion require—or even encourage—use of an applicator? How complicated or not is that process, whether through applicator or digitally inserted? How important is practiced accuracy, especially, we might presume, for films inserted digitally? Does a single dose confer protection, or are multiple or regular doses required; for example, is dosing required daily regardless of the potential for sexual activity or is dosing pericoital? If users use the product often (by whatever definition i.e., useful in their lives) does product accumulate and does that accumulation elicit certain USPEs and become problematic or not? In sum, the ''product'' is the combination of formulation, application, and dosing, as much as active pharmaceutical ingredient: all, in concert, will likely impact the user experience and subsequent adherence.

This study contributes a wealth of new information to the literature in support of greater involvement of users in drug development. Perceptibility measurement and discernment of user experiences plays a critical role in acceptability and adherence of myriad prevention and treatment products. We believe USPEs will also play an important role in rectally administered products, as well as across various types of sexual interactions and relationships. Future perceptibility work should include evaluation of additional formulations, compartments, and activities, as well as focus upon both single-target and multipurpose prevention and treatment of sexual and reproductive health morbidities. Additionally, USPEs are likely to be of import in the use of sexual and reproductive health devices (e.g., intravaginal rings, implants), which also can be studied using the perceptibility approach. These measures will enable product developers to better evaluate preferred formulation/device experiences and, ultimately, design better products that have the best chance of being used correctly and consistently to prevent negative health outcomes. Finally, USPEs might also be of value in other disease contexts using topical formulations (e.g., ophthalmologic, dermatologic) and devices. A clear and intentional evaluation should be given to the patient experience, and, where applicable, the experiences of partners and/or caregivers.

Several elements of the study should be considered when discussing interpretations and implications. First, couples had vaginal intercourse in a private locked room at our research facility. While this enhanced standardization of product use experience for scale development purposes, having sexual intercourse in an unfamiliar setting may have altered participants' sexual experiences, especially at the first product visit. To counterbalance the effect of a new environment on USPE evaluations, formulations were randomly ordered for each couple. Anecdotally, our retention of couples was perfect (100%) and several participants commented, even following the first visit that the ''study sex'' experience was not as awkward as they had anticipated. The study team created a motel-room-like space, with soft lighting, music of their choosing, and comfortable queen-sized bed. Second, couples were required to use male

nonlubricated nonlatex condoms for sex with all three formulations, potentially affecting the sexual experience, especially for couples who were not regular condom users. Third, the volume range studied here was chosen as a function of theoretical volume microbicide developers were targeting based on a number of efficacy factors; other formulation volumes will likely provide additional USPE-relevant outcomes and require further study. We acknowledge that the assessment of USPEs would be one factor in the multifactorial decision-making process around product use. We expect that numerous factors in addition to USPEs will drive product adherence, including perceived effectiveness, perceived risk, relationship characteristics, and social norms. USPEs help us understand product-specific factors perceived by users and how those factors might support or hinder use in various populations.

Conclusions

In summary, three primary gaps in previous work were addressed in the current study. The USPE (i.e., perceptibility) scales previously validated in female users of gel formulations[20] were further tested: (1) in male partners with respect to their own sensory experiences, (2) in the additional parameter space of a quick-dissolving vaginal film, and (3) in consideration of formulation volume as a critical determinant of the user sensory experience. USPEs differed in meaningful ways indicating that both female and male users can perceive differences in vaginal products of different volumes and biophysical properties. Product volume has implications, not only for drug delivery, but will also need to fall within a range of preferred formulation properties for any population or subpopulation of potential users. In addition, six novel scales were identified, providing further evidence of sensory experiences impacting product use.

Acknowledgments

The authors would like to wholeheartedly thank the research participants who completed this study. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Author Disclosure Statement

The authors have no conflicts of interest to report; this includes no competing interests, nor any personal financial, employment, or other competing interests.

Funding Information

Research reported in this article was supported by the Division of AIDS, the National Institute of Allergy and Infectious Diseases of the National Institutes of Health (NIH/NIAID) under award R33 AI076967 [R.W. Buckheit, principal investigator (PI); K.M.G. (neé Morrow), Project PI], the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NIH/NICHD) under award K24 HD062645 (K.M.G., PI), by NIH/NIAID under grant U19 AI082639 (PI L.C.R.), and by product donations from CONRAD, Magee-Womens Research Institute, and HTI Plastics.

References

1. CDC Fact Sheet: Reported STD's in the United States, 2018. Available at https://www.cdc.gov/nchhstp/newsroom/docs/factsheets/STD-Trends-508.pdf (2018), accessed October 18, 2020.
2. Centers for Disease Control and Prevention: Diagnoses of HIV infection in the United States and dependent areas, 2018 (preliminary). Available at https://www.cdc.gov/hiv/statistics/overview/ataglance.html (2018), accessed October 18, 2020.
3. Kaiser Family Foundation: Women and HIV in the United States. Available at https://www.kff.org/hivaids/fact-sheet/women-and-hivaids-in-the-united-states (2020), accessed October 18, 2020.
4. Finer LB, Zolna MR: Declines in unintended pregnancy in the United States, 2008–2011. N Engl J Med 2016;374:843–852.
5. Guttmacher Institute: *Fact Sheet: Unintended Pregnancy in the US.* Available at https://www.guttmacher.org/fact-sheet/unintended-pregnancy-united-states# 2019.
6. Reece M, Herbenick D, Schick V, Sanders SA, Dodge B, Fortenberry JD: Condom use rates in a national probability sample of males and females ages 14 to 94 in the United States. J Sex Med 2010;7(Suppl 5):266–276.
7. Nesoff ED, Dunkle K, Lang D: The impact of condom use negotiation self-efficacy and partnership patterns on consistent condom use among college-educated women. Health Educ Behav 2016;43:61–67.
8. CAMI Health: Initiative for multipurpose prevention technologies. MPT Product Development Database. Available at http://mpts101.org/mpt-database (2019), accessed April 16, 2020.
9. AVAC: Global Advocacy for HIV Prevention: The future of ARV-based prevention and more. Available at https://www.avac.org/sites/default/files/infographics/AVAC4301D_ARVpipeline_R11.pdf (2019), accessed October 18, 2020.
10. Ferguson LM, Rohan LC: The importance of the vaginal delivery route for antiretrovirals in HIV prevention. Ther Deliv 2011;2:1535–1550.
11. Barnhart KT, Pretorius ES, Timbers K, Shera D, Shabbout M, Malamud D: In vivo distribution of a vaginal gel: MRI evaluation of the effects of gel volume, time and simulated intercourse. Contraception 2004;70:498–505.
12. Krishna SV, Ashok V, Chatterjee A: A review on vaginal drug delivery systems. Int J Biol Pharm Allied Sci 2012;1:152–167.
13. Rohan LC, Sassi AB: Vaginal drug delivery systems for HIV prevention. AAPS J 2009;11:78–87.
14. Katz DF, Yuan A, Gao Y: Vaginal drug distribution modeling. Adv Drug Deliv Rev 2015;92:2–13.
15. Anton PA, Cranston RD, Kashuba A, *et al.*: RMP-02/MTN-006: A phase 1 rectal safety, acceptability, pharmacokinetic, and pharmacodynamic study of tenofovir 1% gel compared with oral tenofovir disoproxil fumarate. AIDS Res Hum Retroviruses 2012;28:1412–1421.
16. Carballo-Dieguez A, Balan IC, Brown W, 3rd, *et al.*: High levels of adherence to a rectal microbicide gel and to oral pre-exposure prophylaxis (PrEP) achieved in MTN-017 among men who have sex with men (MSM) and transgender women. PLoS One 2017;12:e0181607.
17. Hendrix CW, Chen BA, Guddera V, *et al.*: MTN-001: Randomized pharmacokinetic cross-over study comparing tenofovir vaginal gel and oral tablets in vaginal tissue and other compartments. PLoS One 2013;8:e55013.

18. McGowan I: Rectal microbicides: Can we make them and will people use them? AIDS Behav 2011;15(Suppl 1):S66–S71.
19. Baeten JM, Hendrix CW, Hillier SL: Topical microbicides in HIV prevention: State of the promise. Annu Rev Med 2020;71:361–377.
20. Morrow KM, Fava JL, Rosen RK, *et al.*: Designing preclinical perceptibility measures to evaluate topical vaginal gel formulations: Relating user sensory perceptions and experiences to formulation properties. AIDS Res Hum Retroviruses 2014;30:78–91.
21. Guthrie KM, Dunsiger S, Vargas SE, *et al.*: Perceptibility and the ''choice experience'': User sensory perceptions and experiences inform vaginal prevention product design. AIDS Res Hum Retroviruses 2016;32:1022–1030.
22. Carballo-Dieguez A, Giguere R, Dolezal C, *et al.*: ''Tell Juliana'': Acceptability of the candidate microbicide VivaGel(R) and two placebo gels among ethnically diverse, sexually active young women participating in a phase 1 microbicide study. AIDS Behav 2012;16:1761–1774.
23. Rosen RK, van den Berg JJ, Vargas SE, *et al.*: Meaning-making matters in product design: Users' sensory perceptions and experience evaluations of long-acting vaginal gels and intravaginal rings. Contraception 2015;92:596–601.
24. Morrow KM, Underhill K, van den Berg JJ, Vargas S, Rosen RK, Katz DF: User-identified gel characteristics: A qualitative exploration of perceived product efficacy of topical vaginal microbicides. Arch Sex Behav 2014;43: 1459–1467.
25. Guthrie KM, Rohan L, Rosen RK, *et al.*: Vaginal film for prevention of HIV: Using visual and tactile evaluations among potential users to inform product design. Pharm Dev Technol 2018;23:311–314.
26. van der Straten A, Montgomery ET, Musara P, *et al.*: Disclosure of pharmacokinetic drug results to understand nonadherence. AIDS 2015;29:2161–2171.
27. Notario-Perez F, Ruiz-Caro R, Veiga-Ochoa MD: Historical development of vaginal microbicides to prevent sexual transmission of HIV in women: From past failures to future hopes. Drug Des Devel Ther 2017;11:1767–1787.
28. Montgomery ET, Mensch B, Musara P, *et al.*: Misreporting of product adherence in the MTN-003/VOICE trial for HIV prevention in Africa: Participants' explanations for dishonesty. AIDS Behav 2017;21:481–491.
29. McCormack S, Ramjee G, Kamali A, *et al.*: PRO2000 vaginal gel for prevention of HIV-1 infection (Microbicides Development Programme 301): A phase 3, randomised, double-blind, parallel-group trial. Lancet 2010;376: 1329–1337.
30. Microbicide Trials Network: Women who took part in VOICE study speak up about why they didn't use the HIV prevention products being tested. Available at https://www.mtnstopshiv.org/news/women-who-took-part-voice-study-speak-about-why-they-didnt-use-hiv-prevention-products-being (2014), accessed October 18, 2020.
31. Bentley ME, Morrow KM, Fullem A, *et al.*: Acceptability of a novel vaginal microbicide during a safety trial among low-risk women. Fam Plann Perspect 2000;32:184–188.
32. Coggins C, Elias CJ, Atisook R, *et al.*: Women's preferences regarding the formulation of over-the counter vaginal spermicides. AIDS 1998;12:1389–1391.
33. Koo HP, Woodsong C, Dalberth BT, Viswanathan M, Simons-Rudolph A: Context of acceptability of topical microbicides: Sexual relationships. J Soc Issues 2005;61: 67–93.
34. Hoffman S, Morrow KM, Mantell JE, Rosen RK, Carballo-Diéguez A, Gai F: Covert use, vaginal lubrication, and sexual pleasure: A qualitative study of urban US Women in a vaginal microbicide clinical trial. Arch Sex Behav 2010; 39:748–760.
35. Robinson JA, Marzinke MA, Bakshi RP, *et al.*: Comparison of dapivirine vaginal gel and film formulation pharmacokinetics and pharmacodynamics (FAME 02B). AIDS Res Hum Retroviruses 2017;33:339–346.
36. Robinson JA, Marzinke MA, Fuchs EJ, *et al.*: Comparison of the pharmacokinetics and pharmacodynamics of single-dose tenofovir vaginal film and gel formulation (FAME 05). J Acquir Immune Defic Syndr 2018;77:175–182.
37. Bunge KE, Dezzutti CS, Hendrix CW, *et al.*: FAME-04: A phase 1 trial to assess the safety, acceptability, pharmacokinetics and pharmacodynamics of film and gel formulations of tenofovir. J Int AIDS Soc 2018;21:e25156.
38. Bunge KE, Dezzutti CS, Rohan LC, *et al.*: A phase 1 trial to assess the safety, acceptability, pharmacokinetics, and pharmacodynamics of a novel dapivirine vaginal film. J Acquir Immune Defic Syndr 2016;71:498–505.
39. Nel AM, Mitchnick LB, Risha P, Muungo LT, Norick PM: Acceptability of vaginal film, soft-gel capsule, and tablet as potential microbicide delivery methods among African women. J Womens Health (Larchmt) 2011;20:1207–1214.
40. Tien D, Schnaare RL, Kang F, *et al.*: In vitro and in vivo characterization of a potential universal placebo designed for use in vaginal microbicide clinical trials. AIDS Res Hum Retroviruses 2005;21:845–853.
41. Cohen J: *Statistical Power Analysis for the Behavioral Sciences.* 2nd ed. Lawrence Erlbaum, Hillsdale, NJ, 1988.
42. Machado RM, Palmeira-de-Oliveira A, Martinez-De-Oliveira J, Palmeira-de-Oliveira R: Vaginal films for drug delivery. J Pharm Sci 2013;102:2069–2081.
43. Auslander BA, Rupp RE, Short MB, Rosenthal SL: Male partners of young women: Assessing their attitudes toward topical microbicides. J Adolesc Health 2008;42:626–628.

Address correspondence to:
Kate M Guthrie, PhD
Center for Behavioral & Preventive Medicine
The Miriam Hospital
Coro West, Suite 309
164 Summit Avenue
Providence, Rhode Island 02906
USA

E-mail: kate_guthrie@brown.edu