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ACCEPTABILITY OF PC-1005 GEL ADMINISTERED RECTALLY TO HIV-1 SERONEGATIVE ADULTS AT THREE DIFFERENT VOLUME LEVELS (MTN-037)

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Multipurpose prevention technologies (MPT) have been increasingly researched for their dual-purpose preventative properties against HIV and other STIs. The acceptability of PC-1005, a topical MPT candidate, was explored among men and women participating in the MTN-037 Phase I trial at two U.S. sites (Pittsburgh, PA, and Birmingham, AL). We triangulated quantitative and qualitative assessments of the acceptability of three volumes (4 mL, 16 mL, 32 mL) of PC-1005 administered rectally (N = 12; 6 males, 6 females). Participants rated overall gel acceptability on a scale of 1–10, with a median of 7.17 (SD = 2.04) and had positive feelings about all three dose volumes, citing them to be very comfortable or comfortable (dose 1 = 91.7%; dose 2 = 91.7%; dose 3 = 83.3%). High acceptability of and comfort with all three dose volumes shows promise for PC-1005 as an MPT to prevent HIV and STIs, warranting future clinical development.

Keywords: rectal, sexually transmitted infections, MPT, HIV prevention, microbicide

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INTRODUCTION

Individuals who have a sexually transmitted infection (STI) are more likely to acquire HIV (Katz et al., 2016). While biomedical HIV prevention methods (e.g., daily oral pre-exposure prophylaxis [PrEP]) are efficacious in reducing new HIV infections among key populations (e.g., men who have sex with men [MSM] and transgender individuals; Fonner et al., 2016), STI incidence has been in an upward trajectory since 2015 (Centers for Disease Control and Prevention, 2019). To address both HIV and STI infections concurrently, researchers and advocates have called for the development and testing of multipurpose prevention technologies (MPTs) that could prevent HIV and STIs concurrently (Fernandez-Romero, Deal, et al., 2015; Malcolm et al., 2014; Woodsong et al., 2015). Previous animal studies with mice and macaques have demonstrated the feasibility and viability of a MPT as a topical microbicide candidate (Fernandez-Romero, Deal, et al., 2015; Fernandez-Romero, Teleshova, et al., 2015; Kenney et al., 2011). In studies with humans, participants have expressed interest in using such MPTs (Hynes et al., 2018; Woodsong et al., 2014); at present, however, little is known about the safety, efficacy, and acceptability of these products (Woodsong et al., 2015). The limited available clinical data on MPTs to combat HIV and other STIs suggests that some level of protection can be achieved vaginally; however, more research is warranted to understand if these dual protection candidates can provide protection against HIV/STIs acquired rectally (Fernández Romero et al., 2019).

PC-1005 is a MPT microbicide candidate posited to be protective against HIV, HPV, and HSV-2, and has been formulated to be suitable for both vaginal and rectal use (Friedland et al., 2016; Villegas et al., 2016). PC-1005 is a translucent gel containing 50 μM MIV-150, a potent non-nucleoside reverse transcriptase inhibitor (NNRTI) not used for HIV treatment; 13.7 μM zinc acetate (ZA) dihydrate, a selective antiviral agent; and carrageenan (CG), a gelling agent derived from seaweed. PC-1005 uses both luminal and tissue concentration mechanisms of action, making it a unique combination product. Therefore, the Microbicide Trials Network (MTN) supported a Phase I, open label, sequential dose/volume escalation study of PC-1005 (MTN-037) for use as a rectal microbicide gel in a sample of healthy, HIV seronegative adults at two clinics in the U.S. (Pittsburgh, PA and Birmingham, AL).

As part of MTN-037, we report on participants' acceptability of PC-1005 after receiving three doses (4 mL, 16 mL, and 32 mL) administered by clinic staff. While the analysis of PC-1005's safety, pharmacokinetic and pharmacodynamic characteristics for rectal use are underway (Ho et al., 2021), it is equally important to assess participants' early acceptability of rectal microbicide (RM) candidates throughout the clinical trial process (Bauermeister et al., 2020; Carballo-Dieguez et al., 2008; Frasca et al., 2017; Mensch et al., 2012; Nel et al., 2016; van der Straten et al., 2013;

The authors declare that there are no conflicts of interest. CWH has served on the Population Council scientific advisory board and is a founder of PRIÖNDE Biopharma, LLC, a microbicide development company. BAF is an employee of the Population Council, the developer of PC-1005.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from all individual participants included in the study.

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van der Straten et al., 2016). Mensch et al.'s (2012) conceptual model, for example, notes how product characteristics (e.g., formulation, perceived side effects), delivery mechanism (e.g., need for an applicator, ease of use), and dosing regimen (e.g., quantity and volume) can contribute to participants' willingness to use the product in the future. Therefore, we employ this framework to describe the acceptability of PC-1005 among participants in MTN-037, and inform ongoing and future MPT development.

METHODS

SAMPLE

MTN 037 was conducted between June 2018 and April 2019 at two clinics in the United States (Pittsburgh, Pennsylvania and Birmingham, Alabama) among healthy, HIV seronegative adults aged 18 or older and who had a history of receptive anal intercourse (RAI). Twelve participants (six per site) were to be enrolled and administered PC-1005 gel (0.002% MIV-150/0.3% zinc acetate in a 3.0% carrageenan gel formulation) in three escalating rectal doses (4 mL, 16 mL, and 32 mL) using an applicator. Participants were deemed evaluable if they received all three doses. Participants were recruited through clinic registries of former participants interested in future studies, community outreach events, and word of mouth.

Eligible participants had to agree to return for all study visits and express willingness to comply with study participation requirements, which included not taking part in other research studies involving drugs, medical devices, genital or rectal products, or vaccines for the duration of study participation (including the time between screening and enrollment), and adhering to abstinence requirements for the duration of study participation. Additionally, participants of childbearing potential had to have a negative pregnancy test at Screening and Enrollment and report using an effective method of contraception for the duration of the study. The study was reviewed and approved by the institutional review boards (IRBs) of all participating institutions. All enrolled participants provided written informed consent to voluntarily participate in the trial prior to undergoing any screening procedures. Participant reimbursement was based on local guidelines and approved by the local IRB prior to study implementation.

STUDY PROCEDURES

After the eligibility screening visit (Visit 1), participants returned to the clinic within a 45-day screening window for the enrollment visit (Visit 2) where they completed administrative, behavioral, and laboratory procedures (see Figure 1). Once enrolled, the study product was administered by study staff via a BD™ Luer-Lok™ Tip syringe with a rectal tip in escalating volume sequence with a 2–6 week washout period between each dose (Visits 3, 5, and 7). Participants completed behavioral, clinical, and laboratory assessments at each dosing visit and then returned within 24 hours of each dose to complete safety and pharmacokinetic/pharmacodynamic (PK/PD) sample collection (Visits 4, 6, and 8). Participants were also randomly assigned (1:1:1) to provide samples of blood, rectal tissue, rectal fluid, vaginal fluid (if applicable), and effluent from rectal lavage samples 48 hours following one of the threee volumes of PC-1005 (4 mL, 16 mL, or 32 mL). Participants attended a final follow-up safety

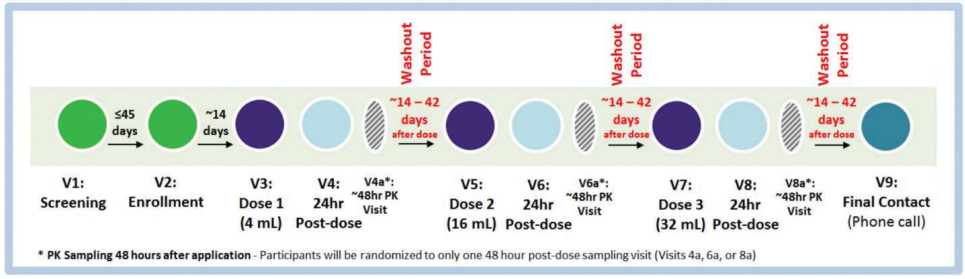

FIGURE 1. MTN-037 study visit schedule.

contact and termination visit (Visit 9) and completed administrative and regulatory procedures. Test results and treatments for urinary tract infections, reproductive tract infections, sexually transmitted infections (UTIs/RTIs/STIs) or other findings were addressed as clinically indicated at all visits.

BEHAVIORAL PROCEDURES

Participants completed a baseline web-based self-interview (WSI) during their enrollment visit (Visit 2) and brief WSIs after their dosing visits (Visits 3, 5, and 7). Additionally, participants completed an online in-depth interview (IDI) with staff during Visit 8.

Survey Instruments

Sociodemographic Characteristics. At baseline, participants self-reported their age, sex assigned at birth and current gender, race/ethnicity, sexual identity, relationship status, employment, educational attainment, and the number of male sexual partners with whom they had had RAI in the previous 30 days.

Product Use. At each dosing visit, participants rated their overall comfort with the study product using a 4-point scale (Very Comfortable, Comfortable, Uncomfortable, Very Uncomfortable). For purposes of the analysis, this question was collapsed into two categories given limited variability across response options: Very Comfortable/Comfortable and Uncomfortable/Very Uncomfortable. Participants also noted whether they had experienced any side effects (e.g., leakage, soiling, diarrhea, abdominal pain) due to the study product. During the first two dosing visits (Visits 3 and 5), participants were asked to note their likelihood of using the study product if it was half or double the amount they used during that visit, respectively. Both scales used the same 5-point Likert scale of Extremely unlikely, Unlikely, Neither, Likely, and Extremely likely.

Product Acceptability. As part of the Visit 7 survey, participants answered a series of questions related to their overall acceptability of the study product. Consistent with Mensch et al.'s (2012) conceptual framework, we asked participants: (1) how much they liked the gel, (2) how much they liked its consistency, (3) how much they liked the gel immediately after it was inserted into their rectum, and (4) how much they

liked the gel 30 minutes post-insertion. Participants answered each of these questions on a 10-point scale (1 = Disliked very much; 10 = Liked very much).

Future Product Use. Participants self-reported their future willingness to use the study product if it was deemed to be effective against HIV/STIs through a series of scenarios (e.g., using it every time they had anal sex; using it when engaging in RAI with a one-night stand or lover, respectively; using the gel when condoms aren't used). Participants could answer each scenario on a 5-point scale (1 = Extremely unlikely; 5 = Extremely likely).

Qualitative Exit In-Depth Interview

After their final in-person visit (Visit 8), participants completed an online IDI with trained qualitative interviewers. Only the audio portion of the IDI was recorded. Interviewers were trained in the study-specific procedures, and completed mock interviews prior to the start of the data collection. In preparation for the IDIs, the interviewers examined participants' WSI data across Visits 3, 5, and 7 to identify domains that might require clarification during the IDI. A total of 12 interviews were completed using a semi-structured interview guide that explored participants' general study experiences, gel perceptions and acceptability, social influence, anal sex experiences, lubrication preferences, and potential product marketing. Acceptability probes explored general impressions of the gel, perceived changes during each dosing experience, physical and emotional discomfort attributed to the gel, likes and dislikes about the gel, and comparisons to personal lubricant use. The audio recording was transcribed verbatim, de-identified, and checked for accuracy. Interviews lasted for an average of 34 minutes (range = 22 to 51 minutes).

DATA ANALYTIC STRATEGY

For purposes of this report, we include data from the participants' baseline questionnaire (e.g., sociodemographic characteristics) and their three dosing visit questionnaires (e.g., product acceptability indicators and side effects), alongside qualitative data emergent from the in-depth interviews. Using a mixed methods approach, we employed a convergent parallel design (Schoonenboom & Johnson, 2017) whereby we analyzed the quantitative and qualitative data separately and then brought both sources of data together to examine where there was convergence or divergence in the findings. We used IBM SPSS, version 27, to compute descriptive statistics (e.g., percentages, means and standard deviations) from WSI data. We compared participants' gel acceptability between the three doses of administration using Wilcoxon signed ranked tests for continuous endpoints and McNemar's test for binary endpoints. We did not impute a score for item-specific missing data; where appropriate, we note the subsample included in the analysis.

The thematic analysis of the in-depth interviews was facilitated by Dedoose, version 7. Throughout our analyses (Braun & Clarke, 2006), we used a thematic codebook informed by Mensch's conceptual model that included code names, explicit definitions, and inclusion and exclusion criteria to ensure coding accuracy. To validate and finalize the codebook, three researchers independently coded three transcripts and discussed coding discrepancies to reach consensus. The codebook was then updated as needed for clarification. All 12 transcripts were coded independently by a pair of researchers, who then met to discuss the codes. Discrepancies

between coders were resolved with input from a third coder to reach consensus. To differentiate between participants' quotes while protecting their confidentiality, we assigned a pseudonym to each participant.

RESULTS

Thirteen participants were enrolled, of whom 12 completed the study and were evaluable. The mean age of the 12 participants was 34.0 years of age (*SD* = 8.12). The sample was evenly split by sex. Participants self-identified as White (*n* = 6; 50.0%), African American (*n* = 5; 41.7%), or bi-racial (African American and White; *n* = 1; 8.3%). One participant identified as Hispanic or Latinx (*n* = 1; 8.3%). Most of the sample had begun (*n* = 5; 41.7%) or completed (*n* = 6; 50.0%) a college education. Participants identified as heterosexual (*n* = 6; 50.0%), gay (*n* = 3; 25.0%), or bisexual (*n* = 3; 25.0%). Six participants (50%) reported having a primary sex partner at the beginning of the study.

OVERALL GEL ACCEPTABILITY

Overall, participants liked the study gel after the three doses (*M* = 7.17; *SD* = 2.04), which was echoed in the IDIs. During his exit interview, one participant explained why he had rated the gel as a 10:

I: Ok. And how did you feel about the gel overall?

P: I feel pretty good about it. I, I would give it a 10. Like no matter what, what dosing sizes are, or anything like that. I feel, I'd give it a 10.

I: And what makes you kind, what makes you give it a 10? What makes it so good for you?

P: Learning how it works and all, and seeing how easy it was to apply, especially with it being able to start working in like 30 minutes or less, before whatever events would come up, I would say that would be pretty good as part of the prepping to do such activity. So, what I'm used to bottoming, it would be easy for prepping to participating in having sex. It's easy to throw it in the mix of preparing to do so. (Henry)

When asked what they did not like about the gel, several participants proactively expressed that there was nothing they did not like about the gel.

P: I really don't think I felt any different with it. Other than noticing it when it goes inside, I haven't really felt any different. I didn't have any negative effects of it, I wouldn't be able to say anything negative about it. (Mario)

In general, participants liked the consistency of the gel (*M* = 7.58; *SD* = 1.98) and reported that it was comfortable immediately after insertion (*M* = 6.92; *SD* = 2.02) as well as after the gel was inside their rectum for 30 minutes (*M* = 7.00; *SD* = 2.13). During the IDIs, we explored whether participants' perceived comfort and awareness of the gel inside their bodies could be related to how thick they perceived the gel to be. Although participants differed in their characterization of the gel (e.g., thick consistency, not too thick or too thin, liquidy), they reported similarly positive experiences with the gel.

TABLE 1. Participants' Product Experiences Across the Sequential Volume Escalation Trial

Dose Comparisons	Dose 1 (4 mL)	Dose 2 (16 mL)	Dose 3 (32 mL)	*p*
How did it feel to have the gel inside you?				
Very comfortable/Comfortable	*n* = 11 (91.7%)	*n* = 11 (91.7%)	*n* = 10 (83.3%)	
Uncomfortable/Very uncomfortable	*n* = 1 (8.3%)	*n* = 1 (8.3%)	*n* = 2 (16.7%)	
Side-effects attributed to study gel after use				
Experience any Leakage?	*n* = 0 (0%)	*n* = 2 (16.7%)	*n* = 2 (16.7%)	
Experience any Soiling?	*n* = 1 (8.3%)	*n* = 2 (16.7%)	*n* = 0 (0%)	
Experience any Diarrhea?	*n* = 0 (0%)	*n* = 2 (16.7%)	*n* = 0 (0%)	
Experience any Abdominal pain?	*n* = 1 (8.3%)	*n* = 1 (8.3%)	*n* = 2 (16.7%)	
How likely would you be to use the gel if it were double the amount?[a]	3.67 (1.07)	3.25 (1.36)		.17
How likely would you be to use the gel if it were half the amount?[a]	4.25 (.45)	4.08 (.52)		.35

[a]Participants answered the volume question using a 5-point scale from 1 (Extremely unlikely) to 5 (Extremely likely).

P: I like that the consistency was nice and thick, and it stayed in place and it didn't go all over the place. Like it stayed right where, you know, they put it. The doctors even mentioned like when they were doing the biopsies after they gave me an enema to clean me out. . . . I've done some studies in the past for this hospital and they used some other kind of gel for something, and the consistency was wrong. For this study the consistency is—is really good. (Martha)

Dosing Regimen

Most participants found all three doses to be very comfortable or comfortable (dose 1: 11 of 12, 91.7%; dose 2 = 11 of 12, 91.7%; dose 3 = 10 of 12, 83.3%). As noted in Table 1, few participants reported any side effects from the study gel. One or two subjects reported leakage, soiling, diarrhea, or abdominal pain after one or more product doses, at varying times, and without a clear volume related frequency (see Table 1). In recalling his experience after receiving his second dose of the gel, for example, a participant shared how the gel made him have a sense of urgency similar to using an enema:

I: When you say it feels like a douche, do you feel the urge to expel relatively soon after?

P: Yeah. Yeah, that is one thing that I will say is different. This one did make me want to expel much faster than all the others. That is something that I've noticed.

I: And about how soon after do you have that urge?

P: Oh, it was pretty immediate. Like it was within five minutes that I felt the urge. Now [at the third dosing visit] I held it in a bit longer—usually I can hold it in and not really feel like anything's in there but this one for some reason it was like it wanted to come out, come out pretty quickly. (Marcus)

TABLE 2. Participants' Gel Acceptability as Self-Reported at Their Visit 7

	M (*SD*)
Overall, how much did you like the gel?	7.17 (2.04)
How much did you like the consistency of the gel (how thick or thin it was)?	7.58 (1.98)
How much did you like how the gel felt inside your rectum immediately after inserting it?	6.92 (2.02)
How much did you like how the gel felt inside your rectum 30 minutes after inserting it?	7.00 (2.13)

Note. Participants responded to each of the questions using a 10-point scale from 1 (Disliked very much) to 10 (Liked very much).

Most participants, however, did not report any perceived side effects in either the surveys or interviews. For example, a participant appreciated that the gel did not result in gastrointestinal discomfort once inserted:

> P: It wasn't too thick it, wasn't too watery. It was pretty consistent—it absorbed in your system pretty fast, so you didn't really feel like you had to go use the bathroom, so I really like that part. (Jack)

When comparing the three doses, there was 91.7% congruence between participants regarding comfort between doses 1 and 2, and 83.3% congruence in comfort between doses 2 and 3 and doses 1 and 3 (Table 2). McNemar tests comparing comfort between doses were not statistically significant. The absence of meaningful differences based on dosage were echoed in the in-depth interviews. Although participants reported feeling comfortable with all three volumes, some acknowledged in the interviews their preference for a gel volume ≤16 mL per dose given greater awareness of the 32 mL dose inside their body than the other two dosing volumes. Overall, participants perceived minimal differences between the first two dosing amounts. Four participants mentioned having more awareness of the third dose (32 mL), yet did not experience discomfort because of this awareness.

> I: In terms of the general experiences with the gel, can you share in detail what your experience was like with the rectal gel used in the study?
>
> P: I thought it was fine. I didn't have any issues with the application. I didn't have any issues or feel any physical effects after it was inserted. I didn't have any leakage. I didn't have, I didn't feel anything to be quite honest.
>
> I think this last one that I had yesterday because the volume was so large because it was my largest volume. That's the only one I felt a little different with. Because it was such a large volume. But other than that, I didn't have anything associated with it. Good or bad.
>
> I: Okay. How did you feel during the application process of the last dose that you had?
>
> P: I just thought it was a lot. It was a huge amount versus the other two . . . it just felt like that was like was kinda the threshold of the amount before you start feeling like, "Okay, I don't necessarily want more than that." I felt like this was kinda like the volume threshold. It wasn't like a bad noticing. It was just like your brain just knows it's there, but it wasn't uncomfortable or anything.
>
> I: Now when you say that you noticed it more, what was it that made it more noticeable?

TABLE 3. Participants' Intentions to Use the Study Product in the Future as Self-Reported at the Baseline and Exit CASIs.

Intentions and Future Use	Baseline Score	Exit Score	*p*
How likely would you use it every time you have anal intercourse?	4.08 (.79)	4.33 (.65)	.34
Use it every time you have RAI with a lover?	3.58 (1.44)	4.08 (1.08)	.20
Use it every time you have RAI with a one-night stand?	4.58 (.67)	4.83 (.39)	.37
How likely would you be to use a microbicidal gel for RAI if you were using alcohol or drugs?	4.00 (.85)	4.33 (.65)	.07
How likely would you be to use a microbicidal gel in the occasions when you don't use condoms?	4.58 (.52)	4.58 (.52)	1.00
How likely would you be to use a microbicidal gel if you have to wait 30 minutes after application before having RAI?	3.42 (1.38)	3.67 (1.37)	.41

Note. Participants answered each question using a 5-point scale from1 (Extremely unlikely) to 5 (Extremely likely).
CASI: computer-assisted self-interview.

P: I think it was just the dosage size, but, once again, that just comes with the territory. You know it's one of those things where you just know it's there, so you're just aware of it. (Martha)

Product Characteristics and Future Use

As noted in Table 3, participants expressed high interest in using the study gel in the future if it provides protection against HIV and STIs. Compared to baseline, after using the gel, a higher percentage of participants said they would be more likely to use the gel if they were going to be under the influence of alcohol or drugs when engaging in RAI ($p = .07$). We observed no other statistical differences over time in participants' intentions to use the product in the future across various scenarios.

Participants also discussed how the MPT could be differentiated from daily oral PrEP to encourage its uptake:

P: Throw out the main factors that it does: try to help HIV, that it could offer lubrication during anal sex, and that it also could provide a little bit protection for STIs also if they wanted. (John).

This participant further expanded that the MPT could have multiple advantages over daily oral PrEP:

P: If the gel did more than prevent HIV maybe then more people would be bargained to use it, I guess. Because [daily oral] PrEP is just so easy—it's just one pill a day but maybe if the gel offered a little bit more than HIV prevention. They would use it more.

I: And what do you think the gel should offer? In your opinion.

P: Um . . . . maybe like one of the main STIs. I guess throw a little, um, antibiotics in there maybe. If that's possible . . . . prevent like chlamydia or gonorrhea; maybe like one of the mains ones. (John)

Participants also shared other reasons for liking the gel, including its ability to serve as a sexual lubricant during anal sex, and its potential to help prevent HIV and

STIs in lieu of condoms. For example, one participant noted how he would frame the advantages of the gel if he had to describe the gel to his friends:

I: Ok. How would you describe the study product to them?

P: . . . I would talk about its medical aspects: preventing HIV/AIDS and then also the lube as well. If it's given in a lube type of way then it could eliminate all the other lubes that you would have to buy. . . . I think it's cool. I personally would use it. I'm not a condom person so I feel this would help eliminate that. And also, I feel it could help—I feel like it could be used as a, as a lube. (Mario)

In thinking of its future use, participants highlighted that the potential study product could serve as a rectal lubricant during anal sex, which could enhance its appeal, as it would be behaviorally congruent with their current practices. Two participants, for example, argued that using the gel as a lube was "more natural and less disruptive" or that "It can be put, inserted or used and forget about it, cause like you don't really know that it's there." Participants also noted that the study product could be used discreetly (i.e., not having to explain to partners that the gel had microbicidal properties if they didn't want to have that conversation). As one participant noted,

P: Let's say it was noticed by somebody else. If that ever came up, you could just say its lube or something and, which with it being clear—it looked like lube and somewhat acted like it as well . . . so, it's easy to not want somebody else to know that you're using it for whatever reasons, you know, it's easy and discreet. (Henry)

On the other hand, other participants noted that the study gel could lose its appeal and interrupt a sexual encounter if it could not serve a dual purpose as a sexual lubricant. As one participant discussed,

P: Even though it's medicine and it's supposed to prevent HIV, like that's the goal of it, but I personally don't really see people inserting gel to do that. Maybe a pill would be better. But then again, like if you're doing that, you're supposed to be using lube, so it doesn't hurt. So, I don't know if maybe people think, "Oh, I can use this as a lubricant?" I don't know. I just don't see people saying, "Ok, hold on, let me take this gel." 'Cause, just say if it's like a one-night stand for some people. I mean I don't do one-night stands, but some people do, and I mean how would that look? "Hold on one second while I go insert this, please." (Lucille)

The same participant also shared that the length of time that the gel would need to be inserted before sexual intercourse could be confusing or inconvenient, highlighting the importance of ensuring that the gel could be used in a behaviorally congruent fashion with sexual partners.

P: I think it would be—me personally I think it would be really hard to sell it if you have to insert it 30 minutes to an hour before you actually have sex because like I said you're already in the moment and you already have it on your mind and you don't want to like ruin the moment and say, "Hey, hold on a second, I'm gonna go to the restroom real quick and you know freshen

> up and whatnot." Some people are just not gonna want to walk away from what they're already involved in. (Lucille)

Discussion

Through our multimethod analysis derived from Mensch et al.'s (2012) microbicide acceptability framework our findings suggest that participants perceived the study product to be acceptable, as noted by their overall comfort with all three doses of the gel, their reporting of minimal side effects, and satisfaction with the gel's thickness. While the appeal for the study product was relatively high, participants weighed multiple considerations including the gel's potential to be behaviorally congruent with other sexual practices, particularly if it could double up and serve as a lubricant during sex. Nevertheless, concerns about the application process (e.g., having to wait 30 minutes prior to sex; interrupting sex) were raised as potential barriers for use in the future.

Although participants reported feeling comfortable with all three volumes and reported liking the consistency of the gel in their self-reported surveys, some acknowledged in the interviews their preference for a gel volume ≤16 mL per dose given greater awareness of the 32 mL dose inside their body than the other two dosing volumes. Our findings align with prior research about the preferred volume for RM candidates (Carballo-Diéguez et al., 2007; Weld et al., 2017). In particular, Carballo-Diéguez and colleagues (2007) examined the acceptability of three doses (20, 35, and 50 mL) of a placebo gel self-administered rectally using an applicator and found that 35 mL was the most acceptable volume among participants. Further research is needed to assess whether 32 mL of PC-1005 when self-administered using an applicator during sex would be acceptable. In light of these findings, future efforts should examine the likelihood of ensuring that there is optimal luminal and tissue concentrations of a drug (e.g., PC-1005) within the aforementioned volume range, as it may influence users' acceptability to use a RM candidate in the future.

In thinking of the gel's potential as a future biomedical prevention product, participants highlighted the promise of a MPT candidate like PC-1005 during their interviews. In discussing its potential for future use, for example, participants noted that having a gel that protected against both HIV and STIs would be appealing and would have added value when compared to existing HIV prevention products (e.g., daily oral PrEP). This finding indicates the willingness and desirability of having an all-inclusive protective product that protects against HIV and other STIs. Furthermore, consistent with prior research on candidate RM gels (Bauermeister et al., 2021; Carballo-Dieguez, Giguere, Dolezal, Bauermeister, Leu, Valladares, Frasca et al., 2014; Cranston et al., 2017), participants also voiced the potential for the gel to double as a lubricant (Carballo-Dieguez, Giguere, Dolezal, Bauermeister, Leu, Valladares, Frasca, et al. 2014; Chakrapani et al., 2017; Frasca et al., 2017) that could be easily incorporated into their lives. Future research is warranted to understand PC-1005 and other MPT candidates as both a HIV/STI prevention product technology as well as a sexual lubricant.

Participants also supported the potential for the gel when thinking about using it in the future across diverse contexts (e.g., sex with different partner types; Giguere et al., 2016, 2018). Interestingly, compared to their baseline opinions, participants were more likely to endorse using PC-1005 in the future while under the influence of alcohol or drugs after the three doses. While participants did not explicitly discuss

using the gel under the influence of alcohol or drugs, prior research has indicated that individuals may be interested in the potential of a RM candidate that can be used alongside substances (Pines et al., 2013, 2014) given challenges to negotiate or correctly wear condoms while under the influence. Given the risk factors associated with the acquisition of HIV and STIs, this finding highlights the importance of examining situational use with future participants to identify factors that could potentially influence gel uptake.

Our study has several limitations. First, as a Phase I safety trial, we recruited a small sample of low-risk individuals to participate in the study. Individuals who are at high-risk of HIV or STI infections may have different needs and perceptions of the study gel. Future research examining their experiences with the product may be warranted. Second, our participants were asked to remain abstinent for 72 hours before and after their visits where fluid/tissue collection occurred. This limits the study's ability to identify how the gel would fare in real world scenarios prior to and during anal sex. Therefore, several dimensions of acceptability articulated in the Mensch model are not possible to assess in this study. Moreover, the gel was administered by study team members in a clinical setting and was not used during sex. Since study staff administered the doses of the gel, it remains unclear whether acceptability to PC-1005 will change when used outside of the clinical setting during sex and whether its use in a real-world setting may impact how much product is correctly inserted during self-administration and whether it offers sufficient lubrication when used. Fourth, self-reported responses tend to be favorable due to social desirability; however, we tried to minimize bias by having participants complete their IDIs virtually with non-clinic staff and ensuring that they had a private room where they could complete their WSIs privately. Finally, future research examining whether the administration of PC-1005 will require an applicator is crucial, as prior research has suggested that some users may have challenges with an applicator-assisted mode of delivery (Bauermeister et al., 2016; Carballo-Dieguez, Giguere, Dolezal, Bauermeister, Leu, Valladares, Rohan, et al., 2014; Cohen et al., 2007; Gengiah et al., 2014; Pines et al., 2013; Vail et al., 2004) and may desire a RM delivered as a lubricant (Bauermeister et al., 2021, 2022; Carballo-Dieguez et al., 2008; McGowan, 2011, 2014). Therefore, additional research assessing PC-1005 acceptability with and without an applicator is essential in its future development.

Our findings align with prior RM gel research regarding its potential as a lubricant and supports participants' acceptability of a rectal MPT microbicide gel candidate across all three volumes. Given the promise of MPT microbicide as a strategy to help decrease HIV and STIs if found to be effective, future trials should continue to evaluate the PC-1005 RM gel and other MPT candidates as potentially efficacious, safe, and acceptable prevention tools.

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