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Factors Supporting and Hindering Adherence to Rectal Microbicide Gel Use with Receptive Anal Intercourse in a Phase 2 Trial

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Abstract

Adherence to product use in biomedical HIV prevention trials is essential to success. In MTN-017, a Phase 2 rectal microbicide gel trial, participants discussed applicator-inserted gel use in the context of receptive anal intercourse (RAI) with adherence counselors. We analyzed counseling session data to identify barriers to and facilitators of gel use for 26 participants in the United States who used gel with RAI as their first of three study regimens. The most common barriers were finding the gel application process cumbersome, physical discomfort after applying gel, difficulty with BAT-24 dosage regimen, and negative effects of gel on sex. The most common facilitators were incorporating gel use into routines, using gel in anticipation of sex, carrying gel when going out, reminders received via Short Message Service, and ease of gel use. These findings can inform

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Compliance with Ethical Standards

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product development and future adherence counseling interventions for rectal gel trials to improve adherence outcomes.

Introduction

Clinical trials of self-administered medications cannot succeed if study participants do not adhere sufficiently to product regimens. This is especially important for biomedical HIV prevention research, since many existing and emerging strategies depend on otherwise healthy end-users' ability and willingness to take or apply products. In previous clinical studies of oral pre-exposure prophylaxis (PrEP) and vaginal microbicide gels for HIV prevention, ensuring participant compliance with medication protocols was challenging. For example, in the FEM-PrEP trial, which aimed to examine daily emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) for HIV prevention among women [1] and in the VOICE trial, which aimed to compare efficacy of daily oral TDF, FTC/TDF, and 1% tenofovir (TFV) vaginal gel for HIV prevention among women [2], research teams could not evaluate product efficacy due to low adherence to product use [2,3]. As these biomedical HIV prevention strategies continue to expand and move through the development pipeline, research to understand barriers and facilitators to product use adherence within the context of trials is critical, since this work could improve clinical data quality.

Barriers to product use adherence among participants in biomedical HIV prevention trials of oral PrEP and vaginal microbicide gels include concerns about clinical and social implications of product use. For example, gel users reported physical discomfort or pain upon inserting the gel applicator and gel leakiness [4–6], and tablet users reported physical distress after taking the tablet, in particular gastrointestinal distress such as abdominal pain, diarrhea, flatulence, nausea, or vomiting [7]. Some gel users had concerns that the product would be less effective following leaking [8], while those taking oral PrEP also had concerns that the study product was not sufficiently efficacious to prevent HIV or worried about potential randomization into the placebo arm [9–11]. Additionally, oral PrEP users were worried that they would be mistakenly identified as being HIV-infected if seen taking the tablet and were concerned about conflicts with partners [11–13], while gel users did not want partners to find out about the gel [5,14] or were hindered from using the gel after partners told them they disliked it [6,15]. Being away from home [5,11,15,16], lacking privacy to apply the gel [5,6], having a change in routine [5,15–17], or simply forgetting [4,5,15] also made study product use difficult.

Alternatively, facilitators to adherent use of biomedical HIV prevention strategies included incorporating the product into a daily routine (e.g., using the product as a part of one's bedtime routine) [5,18,19], using external reminders like a digital alarm [5,18,19], and proactively anticipating schedule fluctuations [18,19]. Women in vaginal gel studies who disclosed trial participation to partners [6,14] and had partner support for gel use [5,6] found using the gel easier than those who did not disclose gel use [14]. For those who chose to use the gel covertly, timing gel use well in advance of or after sex were helpful strategies [5]. Oral PrEP studies showed that participants who perceived themselves to be at risk for HIV but wanted to reduce that risk [20], or felt a personal commitment to the study [13,19,21]

were more likely to adhere to product use regimens. Lastly, participants who received adherence counseling were also more likely to use medications as directed in the study protocol [10,17,19]. The identification of such barriers/facilitators can improve the effectiveness of adherence counseling sessions by 1) helping counselors to anticipate the issues that clinical trial participants may have, and 2) arming them with tools and solutions that other participants have found helpful. This way, potential adherence challenges can be addressed in advance, which could extend the amount of time and degree to which participants are adherent to the medication regimen.

Rectal microbicide gels, which are intended to be used in conjunction with receptive anal intercourse (RAI), represent one emerging HIV prevention strategy for which barriers and facilitators have not been adequately studied. Candidate rectal microbicide gels studied thus far contain anti-HIV medications and are inserted into the rectum via a pre-filled vaginal applicator. Although a rectal applicator was developed, a sample of MSM did not rate it more acceptable than the vaginal applicator, which has already been tested for stability with tenofovir gel and is used in rectal gel trials. [22] Rectal microbicide gel development has progressed to Phase 2 of the clinical trials process and, if successful, it would be a topical HIV prevention approach that reduces systemic drug exposure compared to an oral tablet and that could be used specifically in the context of RAI. Therefore, barriers and facilitators to rectal gel use may both overlap with and diverge from those seen with oral PrEP and vaginal microbicides. To characterize barriers to and facilitators of adherent use of rectal microbicide gels in conjunction with RAI, we examined these factors in MTN-017, the first Phase 2 rectal microbicide study of the Microbicide Trials Network.

MTN-017 was a Phase 2, three-period, randomized sequence, open label, crossover study conducted in four countries and eight sites with HIV-uninfected non-transgender men who have sex with men (MSM) and transgender women. The study was designed to compare the safety and acceptability of three HIV prevention regimens: (1) daily oral FTC/TDF, (2) daily rectal use of reduced-glycerin 1% TFV (RG-TFV) gel, and (3) RG-TFV gel applied before and after RAI (i.e., RAI rectal regimen). A prior publication by our team [23] showed that high adherence to product use was observed in all three regimens of MTN-017, and that adherence to the RAI rectal regimen was as high as adherence to the daily oral regimen. Given that daily adherence to oral PrEP had already been shown effective for preventing HIV transmission at the time this study started [24], high adherence to the daily oral regimen during our trial was unsurprising. However, the potential efficacy of a rectal gel as a microbicide to prevent HIV transmission has not been demonstrated yet. From this perspective, high adherence to the RAI rectal regimen in our trial was remarkable, and prompted us to conduct further in-depth analysis of the barriers and facilitators to product use in this regimen. Yet, barriers and facilitators to gel use have been shown to vary based on cultural and structural factors, and vaginal gel trials comparing participants in international contexts with those in the United States (US) showed that US participants had lower acceptability of gel use [5,25]. Similarly, in MTN-017, acceptability of the RAI rectal regimen was significantly lower for US participants compared to those from Thailand, Peru or South Africa [26]. Therefore, we restricted our analysis to the United States, where the majority of study participants were enrolled. In sum, this paper examines barriers and

facilitators to rectal gel use in the context of RAI among MSM and transgender women in the US.

Methods

Study sites, participants and procedures

Clinical study sites in the contiguous US included Pittsburgh, San Francisco, and Boston. All clinical study sites were home to large HIV prevention research institutes that acted as partners in this study. Institutional Review Boards at all sites reviewed and approved the research.

Participants were HIV-uninfected MSM and transgender women who were at least 18 years old. All participants had good general health and reported at least one episode of RAI in the past three months. The sample for the current analysis included only those participants randomized to the RAI rectal regimen as their first study regimen to capture the specific experiences of initial use and learning. Participants were instructed to use a pre-filled plastic applicator measuring approximately 1.5 cm wide by 11.5 cm long and consisting of a barrel with a plunger and a cap to insert one 4 mL dose of the gel into the rectum within 12 hours before they anticipated having RAI and a second dose as soon as possible within 12 hours after RAI. If they inserted one dose before anticipating RAI and RAI did not occur, they were instructed to insert a second dose at any time up to 24 hours after the first dose. Furthermore, to fulfill the safety objective of this Phase 2 study, a minimum of two doses per week was required. Hence, participants were also instructed to use at least two doses of gel in a 24-hour period per week in the event of no RAI by inserting one dose on the evening of the sixth day and a second dose within 12 hours. In sum, participants were expected to use at least 8 doses in a 4-week period, and for our analysis we considered high adherence to be 8 doses or more. In the course of adherence counseling sessions, we collected data on tools and strategies that helped participants adhere to the gel regimen and on problems that made compliant use difficult. We did not examine adherence counseling session data from participants who were assigned to the RAI rectal regimen in their second or third period; doing so would have biased our results by allowing participants to compare their experiences using the gel with RAI to their previous experiences using other HIV prevention regimens in the study, especially the daily gel regimen, during which they may have already experienced and overcome gel-related barriers.

Enrollment took place from September 2013 to November 2014, and participants were recruited from primary health clinics and community based organizations. The study consisted of three 8-week periods where participants used one of the three HIV prevention regimens mentioned above during each period. Potential participants completed a preliminary screening visit and eligible individuals were asked to return to the clinic to enroll in the study. During the enrollment visit, participants were randomly assigned to one of the six study regimen sequences in equal numbers (two of which included the RAI rectal regimen as the first regimen) and were set up with SMS reminders at a time of their choosing to help them remember to use the product and to collect adherence data [27,28]. In addition, trained study staff gave participants verbal instructions on how to apply the gel using the applicator. While in the clinic at their enrollment visit, participants simulated

insertion using an empty applicator, since the first dose of gel was to occur around the time of sex. They could choose to do so in a private space, with study staff standing by in case of questions, or with direct staff observation. Any participant who had difficulty with applicator insertion was given further guidance and additional hands-on practice before going home. In addition, all participants were given illustrated instructions for using the gel to take home (See Figure 1).

After four weeks of using their designated HIV prevention regimen, participants returned to the clinic for their first mid-period visit. During the mid-period visit, trained adherence counselors worked with participants to determine accurately how often they used the product, explore their experiences using it, gauge their willingness to improve adherence, and identify ways to do so. After another four weeks, participants came back to the clinic to complete their end-period visit for their current regimen. After a one-week washout period, the process was repeated for each remaining regimen. A more detailed description of the study procedures and adherence measures can be found elsewhere. [23,29]

Measures

Adherence counseling sessions from the mid-period visit were reviewed to identify barriers to and facilitators of product use for participants in the RAI rectal regimen. The mid-period visit was selected instead of the end-period visit for two reasons: (1) participants at this stage would not have discussed product use with a counselor yet and would therefore be more likely to discuss unique challenges and facilitators in detail, and (2) participants would be motivated to think about challenges and facilitators to product use, since they would have another month left to use the gel with RAI. Counselors followed an adherence counseling guide in which they asked participants about what helped them to adhere to the product, their thoughts on their current adherence, and what made using the product difficult. All counseling sessions were audio-recorded. A sub-sample of recordings was randomly selected for review during the course of the study for quality control. This ensured fidelity to the counseling guide during sessions and the use of participant-centered counseling techniques (e.g., use of open-ended questions, affirmation of participant decisions).

Analysis

A trained research assistant reviewed the audio-recorded sessions of the mid-period visit to identify the timestamps in each session where discussions about barriers and facilitators to gel use with RAI were located within the recording. Using this information, three coders, trained in qualitative research methods, individually listened to these excerpts of all recordings. An inductive approach [30] was used for the analysis, meaning that coders independently developed a list of recurring themes, entering the themes and related quotes in a spreadsheet. Themes represented commonalities across participants and items through which the meanings of participants' responses could be interpreted [31]. Coders worked independently to ensure that themes represented data in the most reasonable and least biased way possible. After each coder had listened to all sessions, the three coders convened to compare themes, which were examined alongside the examples of data (e.g., direct quotes from participants) they were intended to represent. Common themes were added to a merged spreadsheet, with separate sheets for barriers and facilitators, each listing the name of the

theme, a description of the theme, and supporting quotes with corresponding participant ID's, including study site and number of times product was used by the participant. Discrepant themes, those identified by two or fewer coders, were discussed by all three at length until reaching consensus. At that point, they were either discarded or added to the merged spreadsheet. Then, the coders took a second pass through the audio files to ensure all possible themes had been identified. Coders met again to discuss any new themes that emerged, confirm consensus, and ensure that the quotes represented the intended themes. Due to the nature of this descriptive, qualitative analysis, we did not conduct statistical comparisons. However, almost every theme was represented by quotes from participants at more than one site and varying adherence levels.

Results

Of the 187 participants in the larger study, 26 participants (24 men, 1 transgender woman, 1 declined to state gender) from three study sites in the continental US (San Francisco N=13; Pittsburgh N=10; Boston N=3) were randomly assigned to the RAI rectal regimen first. Table I summarizes the demographic characteristics of the participants in the sample. All 26 individuals participated in the first adherence counseling session.

Over three-quarters (N=20) of participants used the prescribed 8 doses of gel or more in the first 4-week period. Nevertheless, both participants with high adherence (8 doses) and those with low adherence (< 8 doses) encountered barriers to and facilitators of gel use with RAI, and several themes emerged. Table II summarizes these themes by product adherence level for descriptive purposes.

Barriers

Finding the Gel Application Process Challenging—Almost half of the participants (N=11, 8 high adherers) found the gel application process challenging. Specifically, participants described the process as time-consuming and difficult, since inserting the gel correctly required individuals to complete several steps, including: open the applicator packaging, assemble the applicator by inserting the plunger, remove the cap, tear open a lubricant packet, dip the tip of the applicator into the lubricant, place their bodies in a position that allowed them to insert the gel, check that the applicator was inserted far enough into the rectum, and depress the plunger to insert the gel while holding the applicator in place. One participant revealed that he found it difficult to stay motivated to use the product because of the application process.

“I just think it’s kind of cumbersome and it’s kind of a hassle. It [the gel] has to get in there somehow. You gotta get lubed up and bend over and it’s not the easiest thing to remember to do it. To want to do it.” (26-year-old man; San Francisco site; low adherence)

However, despite these difficulties, respondents found that using the gel became easier over time. Specifically, participants improved their application skill level through repeated use of the product. This, in turn, improved their attitudes about the application process. One participant explained that he was able to feel comfortable with the application process after using the gel a few times.

“... the last handful of times I used it - it just feels like not a big deal anymore. It took me a couple times to get, ‘ok this is the most comfortable way for me to stand. This is how much lube I’m gonna put on the applicator. This is the speed at which I’m gonna insert it.’ Now I know the routine. It’s like, the practice of it.” (29-year-old man; San Francisco site; high adherence)

Physical Discomfort After Applying Gel—Participants (N=10, 8 high adherers) described how bothersome symptoms perceived as related to gel use, such as nausea (N=2), urge to evacuate the bowels (N=3), bloating, gas or a feeling of fullness (N=4), and anal leakage (N=8), deterred them from using the gel. Accidentally discharging gas and visibly leaking the product onto clothing were considered especially undesirable, since they caused embarrassment for participants. One person described wearing extra clothes to prevent leaked product from staining the seat of his pants:

“Today I’m wearing an extra layer [of clothes]. I really feel for a woman who gets her monthly visit. [Addressing female counselor] You guys have pads for that thing. A man doesn’t. And I don’t know if a man would be interested in putting something on his bum to secure from that leakage.” (30-year-old man; Pittsburgh site; high adherence)

Three participants noted that physical discomforts following gel application, such as gas, a feeling of fullness, or the urge to evacuate bowels, went away over time with consistent gel applications. For example:

“There was some discomfort the first two times I used it, afterwards I had a feeling of fullness. But after the first two applicators I used, those feelings dissipated.” (24-year old man; Pittsburgh site; high adherence)

Additionally, participants worried that evacuating the gel from their bowels would reduce the effectiveness of the product. Specifically, some users reported an uncontrollable urge to use the bathroom shortly after applying the product, and observed that the gel was discharged with their bowel movement. For these individuals, this was cause for concern; they felt that the product was eliminated before it could be absorbed, reducing its effectiveness. One user explained that his concerns about product efficacy and bowel evacuation would prevent him from becoming a regular user of the gel.

“If this were a product that were being sold to me as a consumer, I would have concerns. As a user I feel and see that some of the gel is coming out when I have to evacuate, even if it’s just gas. How effective can this be if the product isn’t staying in or doesn’t have enough time to absorb into the tissue?” (38-year-old man; San Francisco site; high adherence)

Difficulty with the Product Dosage Regimen—Participants (N=10, 8 high adherers) expressed uncertainty about some aspects of the product dosage regimen. Specifically, gel users reported feeling that the product use protocol was confusing or cumbersome. Participants who felt confused about the gel dosage regimen primarily felt unsure about when to use the product. Users were instructed to use the gel up to 12 hours before RAI and up to 12 hours afterwards, or at least twice within 24 hours each week if they did not have

receptive sex. Some participants were unsure whether they needed to take the second dose of gel if they did not end up having receptive sex within the 12-hour window. One participant expressed confusion about the second gel application during a time he erroneously anticipated sex.

“I pre-dose myself thinking that I’m going to have sex and then I don’t have sex and I dosed myself afterward within 12 hours of the first one. And then what if I have sex the next day? Do you take one afterwards if it’s been after 24 hours?” (33-year-old man; San Francisco site; high adherence)

Other participants were confused about the dosage protocol if they had sex twice in a 24-hour period. That is, users were unsure when to give themselves the second dose of gel, since they were unclear about whether it should be applied before or after the second episode of sex. One respondent explained how he missed a dose, since he had RAI twice in a short period of time.

“I’m not gonna say it’s easy. The only thing I get confused about is the after part, really. Like, before is easy and I don’t wanna sound like a big old slut or anything. But there’s times where, you know, you use it after sex but then you have sex again shortly after that. And you can’t take more than 2 in a 24-hour period. So what do you do? So I think that might have been why I missed that one because that was an after after event.” (44-year-old man; San Francisco site; high adherence)

Other participants were confused about douching while using the gel. Namely, some participants were unclear about whether or not douching after applying the product would wash the gel from their system. One participant recounted an instance where she wanted to douche a second time, but felt unsure; she feared that douching would evacuate the medication from her body, but she did not want to use two doses of gel before sex.

“...But you know, as much as you try, sometimes there would be a mishap. I talked to my boyfriend and he was like, ‘Well go douche again.’ And I was like, ‘Well I don’t know if I’m going to need to go use the product again or not. The doctor said you can’t double your dose.’” (38-year-old transgender woman; San Francisco site; high adherence)

Some participants found the medication regimen cumbersome due to time constraints surrounding gel use and timing of sex. Additionally, participants had difficulty calculating when they should use the gel, based on their anticipated and actual intercourse times. One participant described feeling annoyed about having to remember when he should use the gel.

“It is a pain to sort of stop and think about it and make sure that I’ve used the gel. The whole 12-hour timeframe is something you have to stop and think about, ‘Ok well it is 7 o’clock so if I wait until the next morning then if I don’t remember until 9:30 I’m not supposed to use it.’ It’s a little cumbersome and it’s difficult.” (57-year-old man; San Francisco site; high adherence)

Negative Effects of Gel on Sex—Eight participants (seven high adherers) disclosed that using the gel with RAI had a negative effect on their sex life. First, some reported that applying the gel interrupted sexual encounters. Individuals who disclosed gel use to their

sexual partners revealed that explaining the product to partners in the middle of sex could be awkward. One participant explained that stopping a sexual encounter to apply the gel was uncomfortable.

“When you don’t think you’re gonna be having sex and then all of a sudden you’re in a situation where you are gonna have sex it’s kinda like, ‘Gee, can I go in the bathroom and insert this thing?’ That’s a – little it can be a little awkward.” (64-year-old man; San Francisco site; high adherence)

Even those who had discussed gel use with partners beforehand did not like having to interrupt sex to apply the gel. One participant discussed his partner’s impatience with having to wait while he applied the gel.

“The only difficulty was, I am in a monogamous relationship and my boyfriend knows that I’m using this product...but there were some issues with - we would start and I was like, hold on, and I’d come back and he’d be like, really?...That was the only real issue was the break in the intimacy.” (26-year-old man; Pittsburgh site; high adherence)

Second, participants reported that the gel made sex less enjoyable. They worried about anal leakage during intercourse, or that their partners might taste the gel during anilingus. Some respondents found that the product noticeably loosened the contents of their bowels or made fully evacuating after douching difficult. A few users reported that they had actually leaked on partners during anal intercourse, which they found to be stressful and embarrassing. One participant explained how she had difficulty douching and using the gel together, which caused problems during anal intercourse.

“...I used it 15 minutes before the sexual experience and that might not be a good idea because it hadn’t absorbed fully. And another thing that I may need to add is that douching sometimes could go wrong. So - douching is an art, and sometimes you don’t get it right. It’s not always gone correctly. Sometimes some of it stays in, and sometimes it really quick comes out on the partner. Or whoever you’re having sex with. So that also may have happened. So all things went wrong on all spectrums at the same time. There was some water that came out, the gel came out, and I was stressed out. We were both kinda stressed out. So maybe everything went wrong.” (38-year-old transgender woman; San Francisco site; high adherence)

Disliking Applicator Design—Seven participants (five high adherers) disliked the applicator used to apply the gel, and were concerned about its design and conspicuousness. Participants who had issues with the applicator’s design reported discomfort when applying the gel, mostly due to its thickness, bluntness, and size. One individual explained that he felt apprehensive when he had to apply the gel, since the applicator lacked a tapered tip.

“The only thing I had to call out was the thickness of the applicator. And it’s not really the thickness, it’s the bluntness of the applicator. It’s really blunt. If it was tapered or something it would be a little bit easier and I wouldn’t have to dread—actually, I’m not going to say dread—but it’s one of those things where I’m like, ‘Oh

god I gotta do it again.’ That’s how I feel about the product.” (33-year-old-man; San Francisco site; high adherence)

Several participants expressed concern that the applicator would attract attention, particularly when disposing of it. One participant described hiding the applicators in the garbage can so his roommates would not find them.

“I didn’t tell my roommates I was in the study, so I was conscious of putting the applicator deep in the trash can.” (26-year-old man; San Francisco site; low adherence).

Other participants were reluctant to travel with the applicators, since Transportation Security Administration or customs officials might see them. One participant reported not bringing the product on a recent trip to Italy, since he feared the applicators would attract the attention of airport officials.

“...I don’t want to deal with customs in Rome asking about the applicators.” (57-year-old man; San Francisco site; high adherence).

Forgetting—Seven participants (five high adherers) forgot to use the gel. This most often occurred with the second dose of the product, since participants reported engaging in other activities post-sex (e.g., cuddling, sleeping), or felt too relaxed to use the gel right away. Consequently, some users applied the second dose of the product outside the 12-hour timeframe, or forgot completely. One respondent explained that since he typically had sex at night, he found it easy to miss the second dose of gel; the 12-hour timeframe created a lack of urgency to use the product, so he would put it off until the next morning, leading him to forget.

“Sex was always at night. It was usually the next morning when I got up, I would use it. It is post-intercourse and I think it just is like, ‘Oh, I don’t need to do that right now.’ There is no sense of urgency except for the 12-hour timeframe. That would make it easy to miss.” (57-year-old man; San Francisco site; high adherence)

Having to Anticipate Sex—Five participants (three high adherers) revealed that it was difficult to anticipate sex, which made using the product with RAI challenging. This was especially true for users who met new partners during the course of the study. Participants described instances where they did not anticipate sex, but unexpectedly had RAI more than 12 hours after their last product application. If users did not have the gel readily accessible, they were unable to use it with receptive sex. One participant explained that he would often leave the house in the morning without planning to have sex, but might meet somebody unexpectedly that led to intercourse.

“If the 12-hour window were longer it would make things easier. Twelve hours is actually kind of a short time. I’m often out all day doing stuff and I might end up going out or meeting somebody that I hadn’t planned on meeting 12 hours ago when I left my house. So that’s a challenge.” (30-year-old man; San Francisco site; low adherence)

Facilitators

Incorporating Gel Use into Routines—Eleven participants (eight high adherers) described how they incorporated gel use into their pre-existing routines. These included routines that were associated with sex and those that were not. Respondents who incorporated gel use into a non-sexual routine during weeks in which they did not plan to have RAI explained that they used the product in conjunction with other regular activities; for instance, their bedtime and morning routines. One participant explained, “*I think incorporating it into the morning routine on Fridays and then that night before going to bed was easy*” (28-year-old man; San Francisco site; high adherence).

Participants who incorporated gel use into their sexual routines described using the product as part of their process to get ready for sex, or incorporating it into foreplay. One participant explained that he used the gel in combination with rectal douching to prepare for dates.

“In all four cases I knew I was going to have sex because I had a date. So I knew that in the process of getting ready for the date, I was douching. And therefore it was easy after I douched. It was easy to automatically go on and use the applicator.” (57-year-old man; San Francisco site; high adherence)

Another participant had his partner apply the product for him during foreplay.

“The second time I did it, I did it with the partner. He actually did it before and after. He did it for me...It was kind of erotic, in a sense.” (39-year-old man; San Francisco site; low adherence)

Among participants who used the gel with partners, five reported that it was important to feel at ease discussing the product with them. That is, users felt that gel use depended on how comfortable they were disclosing their involvement in the study to sexual partners. Partners who were using oral PrEP or who worked in the healthcare field were perceived as especially understanding. One participant described how he felt able to reveal his gel use to a partner who was on PrEP, but had reservations about telling others.

“I hadn’t planned ahead and we go back to my place, start fooling around. He was already on PrEP so I didn’t feel weird saying, ‘Hey I’m on this study, I’m gonna have to go put this gel in.’ If he weren’t on PrEP I don’t know how I’d feel about that.” (30-year-old man; San Francisco site; low adherence)

Using Gel in Anticipation of Sex—Though some participants felt that having to anticipate sex was a barrier to product use, 10 (eight high adherers) identified this as an advantage. Specifically, users inserted the gel well in advance of the sexual encounter so that they did not have to worry about applying it immediately before intercourse. These participants explained that it was not difficult to guess when they might have sex. For instance, some reported that they would apply the product earlier in the day if they planned to go to a social event where they might meet a new partner. One respondent explained that he would insert the product ahead of time if he even slightly suspected he might have RAI.

“It was really helpful to know that it was fine to use it even if I wasn’t entirely sure that I would have, I guess to like to say, applicable sex. That it would be necessary

to just be like, ‘well it’s likely [that I’ll have sex], so we’ll go ahead and just use it ahead of time.’ So now I don’t have to get to the moment of negotiating with somebody and just be like, ‘And just a moment. I just have to go do the gel.’ So that’s useful. It’s like... the biggest tool [that you can have sex] after 12 hours.” (26-year-old man; Boston site; high adherence)

Taking Gel When Going Out—Eight participants (five high adherers) revealed that they took the product with them when they left the house and kept gel applicators in bags they commonly took with them (e.g., work bag, overnight bag). That way, they had access to the gel, even in instances when sex was unexpected. One participant explained that he kept applicators in multiple bags, so that he never had to think about packing them.

“I have them [the product] in my computer bag, the overnight bag. Cause that’s one less thing you have to remember ‘Oh, gotta go to the medicine cabinet. I’m gonna be gone for 3 days, better take 6 of these...’” (64-year-old man; San Francisco site; high adherence)

SMS Reminders—Eight participants (six high adherers) found that the daily SMS messages they received as part of the study helped them to remember to use the product. Although they were using the gel with RAI and therefore did not necessarily apply the product when they received the messages, users reported that having a daily reminder about the study was helpful. Additionally, some participants used SMS messages to track product use, by checking their sent messages to remind themselves when they had last reported using the product to make sure they used it at least twice per week. One respondent explained, “*I get the text and that serves as a reminder.*” (32-year-old man; Pittsburgh site; high adherence). Another gel user revealed that the SMS reminded him to use the gel after a sexual encounter.

“There was one time where I had sex later on, but I had to wake up early for work. And it was in between that time frame and it [the SMS] helped me remember - it actually kept me in check with the study.” (47-year-old man; San Francisco site; high adherence)

Ease of Gel Use—Although some participants disliked the design of the product and applicator, eight (all high adherers) reported that this helped to promote adherence. Users felt that the applicator was small and portable, and that inserting the gel was not difficult. One participant explained, “*The applicator is fairly easy just to throw in your pocket*” (64-year-old man; San Francisco site; high adherence). Another revealed, “*It didn’t hurt and it wasn’t a discomfort. It was very easy to open and apply. Ripping it open, the good lube, everything worked well*” (30-year-old man; Pittsburgh site; high adherence). Another, participant described how inserting gel in advance of sex was easier than using condoms.

“I think it’s even simpler than the stress of condom use. You’re cutting off that stimulus in the moment where you pull out the condoms and stop. But this [gel use] happens prior, so the climax is not interrupted. So that’s even better - I think that’s a plus.” (38-year-old transgender woman; San Francisco site; high adherence)

Having Gel Accessible at Home—For six participants (five high adherers) who reported having sex at home, keeping the gel in an easily accessible place helped them to use it. For instance, some participants reported leaving the gel next to their bed or in their bathroom. Others took this one step further and left the product out where they could see it, so they never had to search for it while a partner was over. Additionally, for some participants, putting the gel in a visible place helped them to remember the second dose. One respondent described how keeping the product in sight close to his bed helped him to administer both applications of the product.

“I mean, I had it - keeping it close, right next to my bed and, I mean, if I did use it I would usually take out the other packet so that I would probably see it and remember it the next morning.” (26-year-old man; Boston site; high adherence)

Commitment to Study—Finally, seven participants (six high adherers) reported that feeling a commitment to the study helped them to use the gel. While some participants had mixed feelings about the product, many of them felt a responsibility to honor their word. That is, respondents disclosed that because of their involvement in the study, they felt it was important to make a concerted effort to use the gel as instructed, regardless of how they felt about the product. One participant explained that he remained adherent to the medication regimen, despite misgivings about the gel, because he felt a commitment to the study and wanted to help advance research about biomedical HIV prevention strategies.

“The product doesn’t make me happy, but I committed to it and I’m committed to the work and the people so - it’s successful. I think that’s a good word instead of happy, ‘cause every time I went to use one of the products it wasn’t like I was jumping up and down for joy...I committed to it and when I commit to something I commit.” (46-year-old man; Boston site; high adherence)

Discussion

This study identified barriers and facilitators to pericoital rectal microbicide gel use among participants who were assigned to the RAI rectal regimen as their first product regimen in a Phase 2 three-period, randomized sequence, open label, crossover study that compared the safety and acceptability of this regimen to daily gel and daily tablet use. All participants, regardless of adherence level, reported barriers to and/or facilitators of gel use with RAI. Most themes were mentioned by both those with high and those with low adherence. A greater proportion of low adherers disliked the applicator design, forgot to use the gel, or had trouble anticipating sex. A greater proportion of high adherers found the gel easy to use, felt committed to the study, and made sure to keep the gel in accessible locations at home.

Interestingly, barriers reported by some gel users were actually identified as facilitators by others. For instance, some participants found the gel application process challenging; others felt that the ease of gel use enabled them to use the product more often. Likewise, some respondents noted that the applicator was portable and easy to use; others reported that it deterred gel use, since they felt it was bulky, uncomfortable, or too conspicuous. In addition, some found anticipating sex to be difficult and they had trouble using the gel within 12 hours

of RAI; others stated that being able to use the gel within a broad time frame gave them the flexibility to use the gel hours prior to sex to avoid interruptions in the moment.

Our findings indicate that many of the barriers to rectal gel use with RAI are similar to those reported by participants in other biomedical HIV prevention trials [4–6,15], while some may be unique and regimen-specific. In general, barriers to gel use in the context of RAI centered on three issues: (1) problems with gel application, whether due to disliking the application process or the applicator itself, (2) discomforts perceived as related to gel use, whether physical side effects or negative effects of the gel on sex, and (3) issues with using the gel before or after RAI, whether due to forgetfulness, confusion about the product regimen, or difficulty anticipating when the product would be needed. Notably, many of the individuals who had difficulty applying the gel reported that it became easier with practice, so this may not represent a long-term barrier for some gel users. Issues around the application process and the applicator itself may be specific to a rectal gel.

A second important barrier, reported in prior research [7], was the physical discomfort experienced after inserting the gel. Those who experienced problems such as gas/bloating, urge to defecate, or anal leakage, particularly if they occurred in public or during sex, were clearly bothered by these symptoms. Some questioned the efficacy of the product if it was expelled quickly after insertion, which was a barrier reported in other studies as well [8–10]. A careful analysis of adverse events during the study demonstrated that they did not occur with sufficient frequency or severity to indicate safety concerns with the gel [29]. Nevertheless, such discomforts may have caused apprehension about using the product. Given that the gel is designed for use in conjunction with sex, product developers should pay special attention to ensuring that it enhances a pleasurable sex experience in order to maximize adherence and effectiveness, or, at a minimum, that it have a neutral impact on the sexual experience. Also, for some individuals, using the product in combination with rectal douching may have exacerbated problems with anal leakage. Clear instructions around common rectal practices, such as douching or rectal lubricant use, will be essential if the product becomes available on the market. Finally, for those concerned about gel efficacy following rapid discharge of gel after insertion, information on necessary absorption times for adequate protection will be important.

A third barrier included issues using the gel before or after RAI. The dosing protocol for this study was complex given the safety aims of the study. Our results indicate that many scenarios arose in which participants anticipated sex but did not have it, had sex multiple times in a short period, or forgot to use the gel after sex. In addition, events that cause a change in routine, including being away from home, have been observed as barriers to adherence in prior research [5,15–17]. A simplified gel regimen requiring a single dose before sex would likely aid adherence in future studies or once a rectal gel is available on the market. Also, as product development advances, more precise instructions on the number of doses that can be used in a set time period can be given to potential users to reassure them that they will not “overdose” by using the gel too frequently, which could confer more flexibility.

Fortunately, many facilitators to gel use with RAI included techniques to aid with reminding participants to use the gel, such as incorporating gel use into routines, using gel in advance of sex, taking gel when going out, keeping the gel accessible/visible at home, or using the SMS reminders. Some of these facilitators were also identified in other studies, such as incorporating product use into routines and using digital reminders [5,18,19]. In our study, for participants who found it difficult to anticipate whether or when sex would occur, making sure to have the gel accessible, taking it with them when they left the house, and storing it in easy-to-reach or visible places at home helped them to use the gel with RAI. In addition, some participants reported that incorporating the gel into sexual or non-sexual routines helped them to use the product. Those who incorporated the gel into sexual routines did so in one of two ways: they used the gel while preparing to have intercourse (e.g., after rectal douching), or they made using the gel a part of foreplay. Using the gel during foreplay may be especially useful for participants who reported that the gel had a negative effect on sex. Specifically, if participants and their partners could use the gel together, participants would not need to excuse themselves to apply it alone, which was perceived as awkward and disruptive. Additionally, users would not need to worry about their partners being surprised by the gel during sex, since they would already know it is there.

Nevertheless, incorporating the gel into foreplay does not address all barriers associated with the gel disrupting sex; participants would still need to feel comfortable talking about the product with their partners and they may still experience physical side effects. One advantage of rectal microbicide gel is that it can be inserted covertly, prior to sex. Though too few participants reported using the gel without partners knowing for it to be a theme in this study (N=1), other studies of biomedical HIV prevention strategies (i.e., oral PrEP, vaginal gel) have shown that this does occur [5,12,14]. Therefore, if users want to use the gel without disclosing it to their partners, applying it well in advance of sex could be a solution, and several participants did report applying the gel before going out to a bar or on a date.

This study provides valuable information for future rectal gel trials and product development. Given that participants found that gel application became easier over time, future trials may benefit from allowing participants to take the product home and complete multiple insertions to become comfortable before asking them to use the product in conjunction with intercourse. There are multiple benefits of this approach: first, if participants feel they can easily insert the product, they will use it more often. Second, allowing users to become familiarized with gel application will allow the research team to separate barriers associated with applying the product from barriers associated with the product itself. Third, research staff can address with participants any problems with the gel that are encountered in a run-in trial, such as leakage, by giving them tips for how to minimize such problems prior to sending them home with the product for a lengthy period. While this solution may not work for all phases of trials and would not address other barriers to gel use that may arise during the sexual encounter, it could be useful for longer, late phase trials. In addition to a run-in trial, to address concerns about the applicator, future clinical trials should continue to evaluate new microbicide gel delivery methods, including whether a microbicide gel formulation can be developed that allows for manual application without the applicator, similar to existing lubricants [32].

Furthermore, future studies should ensure participants are knowledgeable about potential gel-associated discomforts by offering routine counseling to participants, and emphasizing that they may go away with consistent product use. Counselors could also advise participants who douche to use the product only after all douching liquid has been fully evacuated from the rectum, and encourage these gel users to apply the product well before initiating sexual activity, rather than immediately before intercourse, if they are able to anticipate when RAI will occur. While using the gel after douching means that a multi-product, multi-step process would be necessary, some participants mentioned that incorporating the gel into their pre-sex douching routine helped them to remember to use it. Researchers are currently investigating the possibility for a microbicide douche that could reduce the number of products and steps necessary [33].

In this study, a daily SMS helped participants remember to use the gel. This was especially true at the beginning of the study, when product use was still new for respondents. Given that forgetting to use the gel was a barrier for over a quarter of the participants in our sample, incorporating an automated reminder system into future studies is advisable. This may be particularly important for the current product regimen. Several participants reported confusion around the product regimen. All gel users were given written and verbal instructions about how and when to use the gel. However, it is unknown how many participants saved this information or kept it accessible so they could refer back to it when they had questions. Instead, it may be beneficial for counselors to distribute study materials, such as guides about how to use the product correctly, answers to frequently asked questions, and tips to remain adherent to the medication regimen, differently. MTN-017 participants reported that applying the gel after sex was an especially difficult task, and that the SMS messages helped them to remember to do so. Given that the popularity of smartphones in the US has doubled in the past five years, with over three-quarters of the population owning one as of late 2016 [34], future studies in the US may consider incorporating an app that could send customized reminders to gel users, since the reminders were important for many participants. Unlike SMS, app-based reminders could incorporate a “snooze” feature so that the participant can receive a second reminder in a short while if he/she cannot use it right away. The app could be downloaded during the enrollment visit, and it could also store product use instructions. This strategy has two major advantages: (1) since this information would be stored on a smartphone, participants would always have access to it, regardless of their location, and (2) gel users could easily find information whenever they needed it, since it would be stored within the central repository of an app, rather than on paper or in an email inbox. For participants without smartphones, the information could be sent via SMS or multimedia messaging service (MMS) and stored on one’s cell phone for ease of access. Furthermore, if product development leads to a successful rectal microbicide on the market, such an app could also be used in clinical practice to assist patients with remembering to use the gel. Nevertheless, if a rectal microbicide becomes available on the market, simplifying the product regimen to be more user-friendly may be a more practical and sustainable way to promote gel adherence. Future studies should examine the efficacy of a single-dose application of microbicide gel administered prior to RAI for preventing new HIV infections, since more participants reported forgetting to use the gel after RAI than beforehand.

The barriers and facilitators identified here can be shared with future participants as part of the adherence counseling sessions. During the enrollment visit, counselors can brief participants on findings from this study, encourage them to identify their own perceived barriers, and help them to formulate strategies to overcome these challenges. This technique is currently used in other studies, such as MTN-025 (HOPE), but has not yet been adapted for future studies that examine microbicide gel use with RAI.

This study had some limitations. The data were extracted from counseling sessions that were not designed to gather information in a systematic fashion. All counseling sessions inquired about what helped and what hindered product use, but these broad questions were not followed up with specific probing as such exploration was not the main purpose of the counseling session. Therefore, as is typical in qualitative research, the duration and depth of discussion varied by session. Also, the majority of the quotes presented in our paper come from participants at the San Francisco site. This site enrolled more participants and, given that MSM in San Francisco are generally very aware of HIV prevention options, their observations on gel use were particularly nuanced. A cross-site comparison of themes showed that almost all of them were mentioned by participants from two or more sites. However, the data presented may not be representative of MSM in the US. Nevertheless, the findings from this study are important and provide a foundation for other studies examining gel use with RAI to build upon.

Despite these limitations, this study clearly identifies barriers and facilitators to microbicide gel use with RAI. Findings from this paper may be incorporated into adherence counseling sessions for future efficacy and safety trials of similar products and can inform product development, leading to improved adherence during trials and a successful HIV prevention product that can be used in the context of RAI.

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Figure 1.
MTN-017 Before and After Sex Gel Use Instructions

Table I

Sample Characteristics (N=26)

	M (SD)	Range
<i>Age</i>	35 (10.5)	20–64
	N	%
<i>Employment</i>		
Full-time	11	42.3%
Part-time	9	34.6%
Unemployed	6	23.1%
<i>Completed High School</i>		
Yes	25	96.2%
No	1	3.8%
<i>Gender *</i>		
Man	24	96.0%
Transwoman	1	4.0%
<i>Sexual Orientation *</i>		
Gay	21	84.0%
Bisexual	3	12.0%
Straight	1	4.0%
<i>Adherence</i>		
High (8 doses of gel)	20	76.9%
Low (<8 doses of gel)	6	23.1%

* One participant declined to answer questions on gender and sexual orientation

Table II
Barriers and Facilitators to Gel Use During First Four Weeks of RAI Rectal Regimen

Theme	Theme Definition	Total (N= 26)	High Adherers * (N=20)	Low Adherers * (N=6)
<i>Barriers</i>				
Finding the Gel Application Process Challenging	Participants describe difficulties during the application process	11	8	3
Physical Discomfort After Applying Gel	Participants describe being bothered by physical symptoms that occurred after applying the gel	10	8	2
Difficulty with the Product Dosing Regimen	Participants describe that instructions of when to use the gel were confusing or cumbersome	10	8	2
Negative Effects of Gel on Sex	Participants describe being bothered by having to interrupt sex to apply the gel or by the gel making sex less enjoyable	8	7	1
Disliking Applicator Design	Participants dislike the applicator's design and/or do not want others to see the applicators	7	5	2
Forgetting	Participants describe forgetting to use the gel either before or after sex	7	5	2
Having to Anticipate Sex	Participants find it challenging to anticipate sex and to use the gel when they are not expecting to have sex	5	3	2
<i>Facilitators</i>				
Incorporating Gel Use into Routines	Participants incorporate using the gel into their weekly or sexual routine	11	8	3
Using Gel in Anticipation of Sex	Participants describe using the gel when they expect to have sex	10	8	2
Taking Gel When Going Out	Participants take the gel with them when going out in case they need to use it	8	5	3
SMS Reminders	Participants use the SMS as their reminder to use the gel	8	6	2
Ease of Gel Use	The product design or applicator promote adherence by making it easy to use	8	8	0
Commitment to Study	Participants describe how being committed to the study helped them to use the gel	7	6	1
Having Gel Accessible at Home	Participants put applicators in an easily accessible place to facilitate use	6	5	1

* High Adherer = 8 doses of gel per 4-week period; Low Adherer <8 doses of gel per 4-week period