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Acceptability of OCT and Abstinence Requirements among Women Participating in Microbicide Safety Trials

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Abstract

Background—Developing effective and safe microbicides requires study procedures (e.g. technology used, abstinence requirements, and product use) that are acceptable to participants.

Methods—Thirty women completed 4 study visits including pelvic examination, colposcopy, optical coherence tomography (OCT), and semi-structured, qualitative interviews. Additional requirements included abstinence (for approximately 16 days) and twice daily vaginal product use (for 5.5 days). Interviews were audio-recorded, transcribed, and analyzed using framework analysis. Themes addressing OCT experiences, acceptability of abstinence, and vaginal product use were examined.

Results—OCT was viewed favorably as an imaging technology. Some women reported feeling the fiber-optic probe “poking” them and over one-third spontaneously reported feeling pressure or pinching upon rotation of the speculum in connection with the OCT evaluation. Compliance with vaginal gel use was high, but for many women assigned to use a product containing nonoxynol-9 (versus placebo), the post-product use exam was more uncomfortable, relative to the initial exam or one week following product discontinuation. Nearly all women experienced product leakage; acceptability of leakage varied. Two women were not abstinent and several more found abstinence challenging. Some women involved their partner in decision making regarding trial enrollment. Strategies to remain abstinent included participating when the partner was away, avoiding early intimacy, and engaging in alternative sexual activities.

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Conclusions—Qualitative interviews in early-phase studies provide insights and capture information that would be missed by behavioral inference alone. Understanding participant's experiences is important in order to provide anticipatory guidance and plan future microbicide studies that facilitate adherence with trial requirements.

Keywords

microbicides; optical coherence tomography (OCT); qualitative interviews; framework analysis; abstinence

INTRODUCTION

Vaginal topical microbicides are products that hold potential to offer an important option for women with regard to STI/HIV prevention. A recent Phase III study shows promise that a vaginal microbicide may prevent acquisition of HIV and HSV.[1,2] Since microbicides will be used by healthy women, they must have an exceptional safety profile, and previous Phase III trials have raised concern because products believed to be safe may have been associated with an increased risk of HIV acquisition.[3–5] One novel method that is being developed to evaluate safety is optical coherence tomography (OCT). OCT is a non-invasive, high-resolution imaging method that reveals tissue microstructure. The method has shown promise for the preclinical evaluation of topical microbicides in animals[6,7] and has been used in humans to evaluate cervical dysplasia.[8–13]

As part of a Phase I study to evaluate the utility of OCT (relative to colposcopy) for clinical safety assessments of microbicides, we conducted a qualitative assessment of women's perceptions and experiences regarding OCT, the abstinence requirement, and vaginal product use. Such information will aid in the development of future trials and in the ability to provide guidance to participants to enhance adherence.

MATERIALS AND METHODS

Women were recruited through flyers and web-based announcements at the medical center and by word-of-mouth. The study was approved by the University of Texas Medical Branch Institutional Review Board (IRB) and written informed consent was provided by each participant. Participants were reimbursed $100 for a Screening Visit (approximately 60 minutes' duration) and $125 each for Visits 1–3 (60–90 minutes each).

Enrollment criteria included: healthy female, 18–45 years of age, pre-menopausal, willing to discontinue use of vaginal products during the study (e.g., douches, tampons) and deodorant pads, and being considered low risk for sexually transmitted disease (STD) infection. In addition, women were required to abstain from intercourse for 48 hours prior to the first study visit until completion of the study (approximately 16 days).

After a Screening Visit which consisted of a pelvic examination, Papanicolaou (Pap) test and STD evaluation, participants completed three study visits, each including a pelvic examination, collection of pooled vaginal secretions, colposcopy, OCT, and an audio-recorded, semi-structured interview. Between Visits 1 and 2, women were asked to use a vaginal gel product twice daily for 5.5 days (11 doses) and to record their use of the product and panty liners on a diary card. Women were randomized 2:1 to receive either an over-the-counter nonoxynol-9 (N-9) product or placebo gel in pre-filled applicators. Visit 2 was scheduled after 5.5 days of twice daily usage (on the afternoon following the last morning dose); Visit 3 occurred one week later.

Semi-structured interviews assessed women's experiences with regard to OCT, abstinence, and product use. The interview guide included the following questions about OCT: "How would you describe your physical experience with the OCT exam? "; "How did you feel about this new technique being used today?"; "How was the length and timing of the exams for you?" and "Can you describe in your own words how the imaging works?" Key questions about abstinence included: "Were you able to abstain from intercourse for the whole study? How did you manage this requirement?"; "How was it for you to abstain during the study?" and "Were there any situations during the study period that could have led to intercourse?" Questions regarding product use included: "What was your experience with using the vaginal gel product?"; "Did you have any particular concerns about using the product?"; "Was anything surprising to you about using the product?" ; and "How did you remind yourself to use the product?" Consistent with a semi-structured interview format, interviewers followed up as appropriate for clarity or to pursue important points.

Interviews were audio-recorded, transcribed, and analyzed using framework analysis, a participant-generated, systematic, and comprehensive approach toward analyzing qualitative data.[14,15] Familiarization with the data included independently reading and annotating the transcripts to identify a thematic framework. Electronic files were subsequently generated to reflect each theme using content from the transcripts; subfiles were created as appropriate. Coding and interpretation of the qualitative data was an iterative process. This process was initiated while the interviews were ongoing to enable further exploration of themes which required further understanding. At the time of the interviews, participants and interviewer were blind to product group. Transcripts were subsequently unblinded and themes were re-examined with regard to treatment group (N-9 versus placebo gel).

RESULTS

Participants

Women (N=30) had a mean age of 29.5 ±5.7 years (range: 22–45 years) and were non-Hispanic white (n=13), Hispanic (n=11), black (n=4), and Asian (n=2). Nineteen women worked at the medical center and five were medical students, the remaining participants were neither associated with the medical center nor in the medical profession. Of the 28 sexually experienced women, 22 were involved in sexual relationships at study initiation. All women reported prior experience with having a pelvic examination.

Acceptability of OCT

Women reported a variety of experiences surrounding OCT. In general, women were intrigued by the technology, using descriptors such as "exciting" and "interesting." One woman expressed her understanding of the technology with regard to tissue layers: *"I think it's cool, you know especially if there's something underneath that you can't see that could help in diagnosing something later on down the road."*

Regarding the length of the exam, women drew comparisons relative to Pap testing indicating it was "just a little bit longer than" or "like an extended" Pap. Several women referred to positional fatigue related to the additional time in stirrups. Specifically, women indicated their legs were "wobbling" or they were "tired" or "tensing up a little bit". One woman reported feeling "dryness" toward the end of the exam possibly resulting from the combination of positioning and time.

To obtain OCT images of the vagina under direct visualization, the gynecologist rotated the speculum 90 degrees for the last portion of the exam in order to visualize the anterior and posterior vagina. The fiber-optic probe must be in contact with the epithelium; however, it is not necessary to do this under direct visualization. Several women indicated they could feel

the probe touching them and described it as "a tiny bit of pressure," "a little pushing," "scratchy" and *"a mild pain poke…with the little tiny wand,"* while other women said they could feel the probe only because the gynecologist informed them that she was using it. Over one-third of women spontaneously reported that they could feel when the speculum was being turned. Women's perceptions of the speculum insertion and rotation varied across study visits and by treatment group. Nearly all women who commented on the speculum rotation at Visit 1 (prior to product use) indicated that it caused mild discomfort (e.g., pinching, pressure). However, at Visit 2 (immediately post-product use), differences emerged in perceptions of the exam by treatment group. Specifically, 11 of the 20 women in the N-9 group indicated discomfort at the Visit 2 exam, as compared to 1 out of 10 women in the placebo group (P = 0.02). The woman in the placebo group characterized her discomfort in the following way: *"I think I was quite sensitive this time. I'm not sure why really, but it was a little bit more painful than last time. Especially when the speculum was moved around, but it wasn't too bad…Like a sharp kind of… like something poking."* In contrast, expressions of discomfort in the N-9 group ranged from feeling "tender" and "sensitive" to "irritated" and "raw". Examples include: *"It was a little more painful. I was a little more sensitive, probably because of the gel… there's definitely a lot of tenderness." ; "there's a lot of irritation right now and so the speculum is very painful" ; "It really just felt like there were some cuts or something. You know, it just feels irritated."* and *"moving the speculum was just… it was awful."* Unlike the woman in the placebo group who wasn't sure why Visit 2 was more uncomfortable, many women in the N-9 group attributed their discomfort to irritation resulting from use of the vaginal product.

The remaining 9 women in the N-9 group characterized their Visit 2 OCT experience as "the same" as Visit 1 (n = 6), "different" from Visit 1 "but not uncomfortable" (n = 1), while two women reported that Visit 2 was more comfortable than Visit 1. In the placebo group, four women characterized their Visit 2 exam as more comfortable or better than the Visit 1 exam while the remaining women (n=5) believed the exams to be about the same. The perception of increased comfort was attributed to increased familiarity with the procedures, i.e., "knowing what to expect" and feeling more relaxed for the exam. Most, but not all women in both groups described the Visit 3 exam as more similar to Visit 1 than Visit 2.

Acceptability of Abstinence

All but two women reported being adherent to the abstinence requirement, although at least six additional women found abstinence challenging. One woman who was non-adherent began to have penile-vaginal intercourse but interrupted it and converted to oral sex. The second woman engaged in multiple episodes of intercourse in one night. This woman stated that the relationship had changed in intensity since she enrolled. She called the research assistant immediately to disclose the non-adherence because she did not want to interfere with the research. She reported not understanding that the reason for abstinence included reducing risk of STD infection, and had only focused on the data quality.

Women who enrolled in the study presumably found abstinence at least manageable; however, two participants indicated that friends of theirs did not want to be in the study because of the abstinence requirement. For some, the range of strategies employed to manage abstinence began prior to study enrollment. For instance, some women planned participation around their partner's absence. Other women informed the partner about the abstinence requirement prior to enrolling and sought their partner's permission to be in the study: Still, others with partners made their decisions independently, despite the abstinence requirement which presumably would involve the partner's cooperation.

During the study, women reported using several other strategies to manage the abstinence requirement. Some avoided early intimacy, such as this woman: *"…we didn't make out or*

anything…we didn't want to start anything because we didn't want to put ourselves in that situation." Others engaged in activities such as oral sex or manual stimulation, which were identified as acceptable options during the informed consent process. One woman planned to lie to her partner, if necessary, to manage the abstinence requirement: "*But I was thinking…I would tell him that we couldn't do it because he would get a rash or something, but he was OK with it so I didn't tell him that."* Finally, one woman disclosed that a fear of "being caught" by the investigators helped her maintain abstinence even when challenged by her husband: "*My husband said: 'It'll be okay,' because it was right at the very beginning* [of the study], *and I'm like,' no, it's not. I told you beforehand.' He said: 'How are they going to know?' And I was like, 'I don't know, but they'll probably know. They have to take images.'"*

Several women commented that personality characteristics were helpful in managing the abstinence requirement. Specifically, being "stubborn" or "strong-willed" was mentioned, as well as having conviction: *"Well, you know, once I decide to do something, that's what I'm going to do. So that was easy."* Similarly, other participants expressed that having a commitment to the study or the investigators helped, such as this woman: *"I'm thinking I've got to do these things because I said, 'Yes, I'm participating in this study,' so I don't feel like it's right for me to go back and say that, oh well, I'll do it this time. I'll go ahead and have sex, and they won't know. That's not fair to the study, so I wouldn't have done something like that."*

Acceptability of Vaginal Gel Use

Interview data regarding use of the vaginal gel enhanced the information collected on the diary cards and provided accounts of symptoms suggesting toxicity. For instance, while nearly all women reported experiencing product leakage on the diary card, women varied in their acceptance of leakage, with descriptions ranging from slightly bothersome: *"A little bit leaky and stuff, but if you wear a panty liner it wasn't like so bad you had to worry about it leaking through your pad or anything, so it was just minor"* to unacceptable: *"If it hadn't leaked so much it wouldn't have been that big a deal…But I was counting the days down till I could stop… If there was a way to cut down on leakage, um it would have been fine. That was just the worst part."*

Experiences with product use were qualitatively distinct and varied between treatment groups. For instance, with regard to the leakage, a number of women commented that the product was not well-absorbed by the panty liners but instead would "sit on top"; subsequent unblinding revealed this comment was unique to women in the N-9 group. Also, in response to a more general line of questioning regarding how it was to use the product (i.e., vaginal symptoms were not specifically queried), 8 out of 20 women in the N-9 group reported experiencing vaginal symptoms including itching, irritation, sensitivity, or burning associated with product use. In contrast, few women in the placebo group commented on side effects of the gel; when asked about her experience using the gel, one woman indicated she felt "wet" from the product while another woman said: *"no irritation from the product or anything."* Some women linked irritation to the continuous contact of the product with their skin or to the increased wiping necessitated by the leakage, as this woman (N-9 group) describes: *"When I went to wipe after going to the restroom, I felt the tenderness… kind of a diaper rash feeling. It was a raw, irritated feeling."* Another woman stated that she thought about quitting the study because of the irritation, and still another who experienced irritation indicated that she was worried until she re-read her consent form: "*Yeah, the consent form… it was saying that these kind of gels can sometimes be irritating. So…I guess it's alright."* Finally, despite adherence to product use in the context of the study (all women reported using all doses except one woman who was advised by study staff to discontinue product use

after reporting multiple episodes of intercourse), many women when asked (8/10 N-9 and 1/5 placebo) indicated they would not use the product outside of a research context.

DISCUSSION

Overall, women found OCT generally acceptable within the clinical trial context and provided a fairly consistent vocabulary for describing the physical experience including feeling “pressure” and “poking” from the OCT probe, discomfort upon speculum rotation, and fatigue from being positioned in stirrups for the exam. The differences in descriptions between women in the N-9 versus placebo gel group suggest that the experience of the exam is impacted by the level of irritation caused by the product. Still, a number of women indicated that their exam experience improved over time as they knew what to expect and were able to relax. Thus, the information obtained in this study can directly inform consent processes in future trials using OCT and vaginal products by providing specific language to depict physical experiences. Moreover, the data can be used to provide anticipatory guidance to healthy volunteers in research protocols that include similar requirements and procedures.

Abstinence was required in this study because of uncertainty surrounding the effects of N-9 on cervicovaginal epithelium at the dosing and frequency outlined for the study.[16] Enrolling women who were willing to be abstinent was feasible, however, abstinence is clearly a challenge for some and not attainable for all. This finding is consistent with the experience of males enrolled in a microbicide study in which 3/36 participants reported they did not remain abstinent as required, and two other participants reported they did not refrain from masturbation as requested.[17] Thus, abstinence as a study requirement deserves careful re-consideration. Designing studies that test vaginal microbicides as they are intended to be used (with intercourse) may enhance external validity and, by placing fewer behavioral constraints, may be less burdensome for research participants. Finally, although early microbicide studies have often included an abstinence requirement to eliminate possible cervicovaginal changes related to intercourse rather than study gel, it is possible that abstinence is not necessary given that in a Phase I study of BufferGel, the rate of abnormal colposcopic findings was higher among abstinent women than among monogamous, sexually active women enrolled in the study.[18] Should abstinence be required, a variety of strategies may aid in compliance, including involving the partner in the initial decision making, scheduling participation for a time when the partner was away, avoiding early intimacy, and engaging in sexual activities that did not involve vaginal penetration. While the investigative team employed anticipatory guidance and discussed acceptable alternatives to intercourse as part of the informed consent process, the women themselves expressed a strong commitment to the science and to the “agreement” they made with the investigators as a research subject.

Behavioral inference and routine clinical trial data collection alone might have missed key aspects of the women’s experiences. For instance, the lack of attrition and the fact that women were compliant with gel use did not fully capture women’s experiences with the vaginal gel and OCT exams. In addition, noting leakage on the diary cards did not capture the impact on quality of life nor the associated irritation that some experienced as evidenced by their qualitative reports. Additionally, it was not anticipated that N-9 use would result in particular discomfort during the post-treatment exam (Visit 2), yet by including interviews at the conclusion of each exam and maintaining a double-blind, within-subject changes in perceptions could be observed over time and ultimately, by treatment group. No participant complained of discomfort during the exams, and questions about exam comfort are not generally included as part of microbicide safety protocols. As information regarding differences across visits was offered during the interviews, future studies with new products

and technologies should continue to elicit this information qualitatively and systematically to better understand these experiences. In addition, although women expected leakage, women's shared experiences regarding product leakage indicated a range of acceptability. It is not known if the abstinence requirement contributed to the leakage women experienced by not allowing the natural spread of the product throughout the vagina, as would occur with the intended use of vaginal microbicides. Importantly, as in other trials,[19] including a qualitative component yielded unique information on product acceptability that can be directly applied to planning future trials.

Several limitations should be noted. First, unlike most Phase 1 trials involving an experimental product, the "active" product used in this study was an over-the-counter spermicide with known properties, about which women were informed; women's reported experiences may have been influenced by this information. However, double-blinding was used to minimize interviewer and participant bias in soliciting and reporting experiences. Second, participants were a small sample of highly motivated women, many of whom themselves worked in research; adherence with study requirements and lack of attrition may reflect self-selection bias and limit the generalizability of the findings.

Although interview questions were designed to examine acceptability of OCT and abstinence and experience with product use in a trial setting, a wealth of data emerged specifically about toxicity of the products that can be used to enrich and understand the OCT and colposcopy findings. The iterative process of examining qualitative data with an interdisciplinary team holds great potential for increasing participant understanding and acceptability[20] and advancing the field of microbicide development and testing.

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