

Microbicide acceptability research: recent findings and evolution across phases of product development

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Purpose of review

Research on the acceptability of microbicides has the potential to inform the microbicide development process by shedding light on desirable product characteristics, issues around product use and potential barriers. The purpose of this review is both to synthesize recent findings that are related to microbicide acceptability, highlight areas of deficiencies, and to point to the new directions in which research is needed.

Recent findings

Recent studies have assessed acceptability using candidate microbicides in clinical trials, surrogate products, and descriptions of hypothetical products. While most studies have focused on physical characteristics of products, some small studies have investigated participants' short-term experiences with products during sexual intercourse. Overall, as currently measured and in their present formulations, vaginal microbicides have been found to be acceptable to adolescent girls, women, heterosexual men, whereas rectal microbicides were acceptable to men who have sex with men. Few studies have examined acceptability among high-risk HIV-uninfected women. The relationship between acceptability and adherence in trials, and ultimately in real-world settings, remains unknown.

Summary

Data are needed on acceptability of microbicides from larger populations, high-risk HIV-uninfected women, as well as long-term acceptability and contextual factors surrounding acceptability. The association between acceptability and long-term adherence in clinical trials or ultimately in the open market has yet to be demonstrated.

Keywords

acceptability, HIV, microbicide

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Introduction

It is estimated that half of the total people living with HIV/AIDS, or 15 400 000, are women. In sub-Saharan Africa, the region worst affected by the epidemic, 61% of HIV-infected individuals are women [1]. Currently, condoms are the only effective method to prevent the sexual transmission of HIV; use of both female and male condoms requires male cooperation. To halt the continuing incidence of HIV/AIDS, women-controlled prevention methods are urgently needed. Topical microbicides could provide an option for HIV prevention for women who are unable or unwilling to use condoms.

This article reviews and synthesizes microbicide-acceptability research published from November 2006 to March 2008. Although this review focuses on vaginal microbicides, the few available studies on rectal microbicides are also discussed.

Assessing acceptability: what is acceptability, how is it measured, and where?

Although microbicides offer a promising method of HIV prevention, their effectiveness at the population level will ultimately depend not only on their efficacy but also on their use. Acceptability of new reproductive health technologies has been defined as the 'voluntary sustained use of a method in the context of alternatives' [2]. A conceptual model examining the sustained acceptability of microbicides posits that acceptability hinges on multiple levels: the individual woman, the couple, and ultimately the provider (or clinical trial) context [3].

Currently, there is no consensus regarding the definition and measurement of acceptability in microbicide research [4]. Only one of the publications reviewed provided a specific definition of acceptability, as 'the ability and willingness to correctly and consistently use a product' [5].

Yet, little information is available on consistent use in the reviewed publications, resulting in a focus on ability and willingness to use products in the recent literature. Moreover, few acceptability measures are comparable across studies, making the resulting contrasting findings across formulations and populations problematic.

Four methods have been used to assess microbicide acceptability. The first approach consists of measuring the acceptability of candidate microbicides in clinical trials [6^{*},7,8,9^{*},10–16,17^{*}]. This type of acceptability measurement is often a secondary objective of phase I studies aimed at assessing product safety and, as such, have small sample sizes. The second is the assessment of acceptability of the use of surrogate products such as lubricants, vaginal moisturizers, spermicides or placebo gels [5^{*},18–21]. The third approach involves assessment of the prevalence of the use of microbicide-compatible products, such as douches and lubricants [22–25]. This method differs from the former in that, while the former involves an intervention study, the latter is purely observational, relying on participants' reports of product use. The fourth approach is the evaluation of acceptability using reports of intention to use hypothetical products [25–29].

Most studies published during the review period have focused on: (1) preferences for the physical characteristics of products (formulation, odor, color, packaging, stickiness, consistency, lubrication) [6^{*},9^{*},10,14,18,20,26,28,29]; (2) experience during product insertion (ease of use of product and applicator, comfort, leakage, volume, preference for timing of insertion, possibility for covert use) [5^{*},6^{*},7,9^{*},10,13–16,17^{*},18,20,21,26,28]; and (3) side effects (burning, itching, stinging, pain, irritation, genital symptoms) [9^{*},12,14,18,26,28]. Ten studies have investigated acceptability during sexual intercourse, focusing on the effect of the product on sexual pleasure [6^{*},7,9^{*},10,13,14,16,17^{*},18,21]. Specific results are discussed below.

While some studies have used dual methods of quantitative and qualitative data in the form of focus groups or in-depth interviews to assess acceptability, most studies have relied on quantitative data only. Four studies incorporated qualitative data collection methods to assess the acceptability of candidate microbicides in clinical trials [6^{*},9^{*},10,14]. Rosen and colleagues [6^{*}], have shown that supplementing quantitative data with qualitative research can provide insightful information on acceptability that quantitative data alone cannot capture. This includes specific information regarding situations in which participants might not use the product. Similarly, Morrow and Ruiz [30] have argued that qualitative data can explain quantitative findings by providing detailed information on the circumstances surrounding a particular event. Regardless of the method of data collection,

however, all studies published to date have relied on small samples and covered short timeframes.

The majority of recent studies were conducted in the United States. Only six publications report acceptability research in Africa (three in South Africa, one in Zambia, one in Tanzania and one in Cameroon), only one in the Caribbean (Dominican Republic), only five are available on Asia from China, India and Thailand.

Acceptability among women

Not surprisingly, most microbicide-acceptability studies have been conducted among women. Presumably, a microbicide that makes sex at least as pleasurable as intercourse with no product is likely to have a positive impact on acceptability. Studies have shown that candidate microbicides either increased or had no effect on women's sexual pleasure. Most women in a US tenofovir gel trial [6^{*}], a PRO2000 (Indevus Pharmaceuticals, Lexington, Massachusetts, USA) trial in India [14] a Carraguard (Population Council, New York, New York, USA) trial in Thailand [17^{*}], a Carraguard trial in South Africa [9^{*}], and a BufferGel Duet (ReProtect Inc., Baltimore, Maryland, USA) trial in the USA and Santo Domingo [7] reported that the product either increased or had no impact on sexual pleasure. On the other hand, in another Carraguard study conducted in Thailand, 70–78% of women reported that the gel had no impact on sexual pleasure and women enrolled in the Invisible Condom study in Quebec city also reported that the gel had no effect on libido [13,16]. It is encouraging that overall, there is no evidence of a negative effect on sexual pleasure. In the absence of sexual intercourse, over half those studied have reported that they like the product [8,11,12].

Reports of physical properties of microbicides during sex, however, have been less positive. Messiness, stickiness, leakage before, during, and after sex, and soiled clothes have been reported [6^{*},7,9^{*},13,14,16,17^{*}]. Women have also found the volume of the product to be excessive or the product to be too wet [9^{*},16]. In terms of covert use, 70% of women in India said they would prefer a product that would not be noticeable during sex, while surprisingly only 26% of women in South Africa said they would use the gel without their partner's knowledge [9^{*},14].

Studies using microbicide surrogates corroborate findings from microbicide clinical trials. A preference for lower product volume has also been reported in a study of vaginal moisturizers in Zambia. Women reported that the most important factors in determining preference were the efficiency of the product, its ability to increase sexual pleasure, and its comfort and ease of use. Perceived partner's acceptability of products also affected women's preference [18].

The acceptability of hypothetical microbicides among women has also been explored. Interestingly, two of these studies are among the few that investigated the role of contextual and interpersonal factors on acceptability. Willingness to use a hypothetical microbicide was associated with having non main partners in a US-based sample and having either only paying partners or both paying and main partners rather than a steady partner only among women in sex establishments in rural China [26,27]. In addition, women who believed that they had less control over their sex behaviors than their partners were more willing to use microbicides [26].

Additional factors associated with acceptability among women include single-use applicator design, effectiveness of product in preventing disease, and contraceptive properties [31]. The importance of product characteristics was found to vary among women; they were less important among women of lower socioeconomic status and women with a history of douching [27]. Similarly, in rural Southern China, women who use douches with applicators and antibiotic suppositories could be more predisposed to accepting microbicides [26].

Acceptability among adolescent girls

Three of the papers reviewed here examined microbicide-acceptability among sexually experienced adolescent girls aged 14–21 years in the United States. The first paper posits that mothers might be able to play a role in influencing their daughters' willingness to use microbicides [32]. In the second study, after being shown two vaginal moisturizers, adolescents reported that they had a more favorable view of microbicides than condoms and perceived them to be 'pleasurable' and 'comfortable' [28]. The major limitation of this study is that it relied on hypothetical products that the girls had not tried. The third paper reported that the use of vaginal moisturizers was associated with the product being comfortable, not leaking and not being messy [21]. It is worth noting that sexually active adolescent girls who participate in such trials with parental consent might not be representative of the larger adolescent population.

Acceptability among heterosexual men

Although vaginal microbicides are designed to be used by women, the fact that men are exposed to them during sexual intercourse makes male acceptability an important area of research. Acceptability research conducted among heterosexual men falls into two categories: some studies investigated the acceptability of vaginal microbicides when used by women during intercourse while others investigated the acceptability of microbicides or microbicide surrogates when applied directly to the man's penis.

Five studies investigated the acceptability of microbicide candidates among male partners of women enrolled in clinical trials and, overall, studies reported that vaginal microbicides were acceptable to male sexual partners. However, messiness, stickiness, excessive wetness, excessive volume and leakage before, during and after sex have been reported [7,9,10,16]. The impact of products on sexual pleasure varied [7,10,13,16].

A study assessing the acceptability of products applied on the men's genitalia found that men like the stickiness and slowness of drying of the gel the least. In addition, side effects were often reported. The most reported complaint was burning followed by tingling, and itching. The authors argue that in reality, the gel would not be applied directly to the penis, leading to less direct contact with the product and, therefore, the possibility for fewer side effects [15]. On the other hand, in Kenya, three over-the-counter topical microbicides designed to be used directly on the genitalia were highly acceptable to men, with 91–97% of men reporting that they would use the product again [19].

It has been suggested that a main advantage of vaginal microbicides is that they could be used covertly, without the male partners' knowledge. Some men, however, found it doubtful that these products could be used without the partner's knowledge mainly due to excess vaginal wetness [9,10].

Acceptability among men who have sex with men

Acceptability of microbicides has been assessed among men who have sex with men (MSM) in the United States. It has been suggested that the high prevalence of lubricant use during anal intercourse and rectal douching before and after sex may facilitate the introduction of microbicides delivered as lubricant gels or harmless rectal douches in MSM populations [23,25]. Overall, men have responded positively to hypothetical microbicides and believed that microbicides would be easier to use if formulated as lubricants [22]. A study evaluating the volume of microbicide that would be acceptable to insert rectally before receptive anal intercourse reported that up to 35 ml of gel were deemed acceptable by most participants. Interestingly, volumes that were deemed acceptable without intercourse were not always acceptable during intercourse [5]. This finding emphasizes the importance of assessing acceptability during sexual intercourse.

Although the recent research conducted among MSM provides useful information about the potential acceptability of microbicides in this population of high interest, it is worth noting that only one study [5] evaluated the

acceptability of an actual product, a placebo gel. The findings derived from these studies, although limited, set the stage for the first rectal candidate microbicides being currently tested. Although acceptability of rectal microbicides have only been assessed among MSM, when available, rectal microbicides could benefit both men and women who practice anal intercourse. Therefore, research is also needed on women's responses to rectal microbicides.

Evolution of microbicide acceptability across phases of product development

Recent research on microbicide acceptability has increased knowledge of aspects of use that may influence development of future microbicides. It is clear from the literature, however, that what may motivate individuals to use microbicides is a complex process that is likely to vary across social and cultural contexts. While Severy and Newcomer [3] introduced the importance of context in acceptability research, it has received little attention in the literature. Future acceptability research would benefit from investigating the contextual and interpersonal factors related to acceptability.

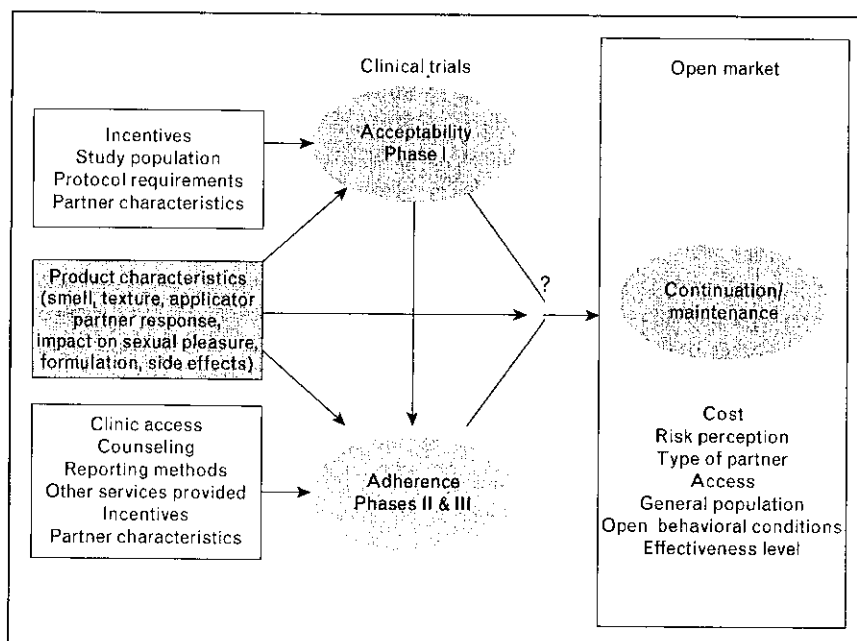
Findings derived from microbicide acceptability research are inherently limited because acceptability has only been assessed in the absence of a proven product, and using small samples of individuals within clinical trials, all of which may have an influence on acceptability. In clinical trials, study protocols often restrict the type of sexual intercourse participants can engage in. For hetero-

sexual couples, protocols require that intercourse be limited to vaginal intercourse; couples have to abstain from oral or anal intercourse, and MSM are asked to practice anal intercourse only. In addition, for ethical reasons, study protocols mandate condom use. Therefore, in addition to the fact that rigid protocol mandates are likely to be violated, it is doubtful that acceptability findings obtained from these clinical trials will reflect 'real world' acceptability [5*,6*]. Acceptability may differ when individuals are able to report on product use within their full range of sexual habits.

With few studies conducted in sub-Saharan Africa and Asia and only one in the Caribbean, the geographic coverage of acceptability research is clearly not representative of the geographic need in terms of HIV prevention; especially in light of the fact that 96% of new HIV infections occur in low- or middle-income countries [1]. Product preference and the social context surrounding acceptability are likely to be population-specific. The extent to which acceptability research conducted in the US can inform the development of products that would be of most use in the developing world remains unclear.

Figure 1 presents a conceptual model illustrating how as the next phase of research emerges, the context in which the candidate microbicides are evaluated will also change. The model lists factors that influence acceptability, adherence and continued use across the microbicide product development process, and eventually in the open market. Acceptability, as measured by single or short-term use of a product in a phase I or phase II trial,

Figure 1 Conceptual model of microbicide acceptability and adherence across phases of product development



should be measured as adherence in phase IIb or phase III trials that require extended product use and as continuation/maintenance in the open market. Therefore, factors predicting adherence in phase IIb or phase III trials might differ from those that influence acceptability in phase I or phase II trials. Similarly, factors that influence continued use of an effective product in the open market might differ from those that predicted acceptability and adherence in trials. We present this model as a way of encouraging investigators to consider the next steps in understanding acceptability and to standardize measures to define acceptability as the context in which the research is conducted changes.

Conclusion

Until acceptability and sustained use of microbicides have been assessed within large, high-risk, and geographically diverse populations the potential effect of microbicides on the HIV epidemic will remain unknown.

In the next year it is expected that findings on acceptability from larger and longer duration clinical trials of microbicides will be available, moving this field into an exciting new phase. Ultimately, behavioral research on microbicides will need to tackle issues beyond acceptability, such as how perceived effectiveness may affect risk compensation behaviors (i.e. decreased condom use). This issue is particularly salient, as it is very unlikely that any microbicide will provide as much protection as do condoms against HIV.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 602).

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