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Acceptability and preferences for vaginal dosage forms intended for prevention of HIV or HIV and pregnancy ☆

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ABSTRACT

This paper reviews key issues found to affect acceptability and preferences for vaginal products to prevent HIV infection or HIV and pregnancy. We focus on the interplay between the biological and physico-chemical aspects of formulation and the social and behavioral issues that may affect use. The need for an HIV prevention product that women can use is driven by women's increased biological and social vulnerability to HIV infection, and thus social and behavioral research on microbicide acceptability has been conducted alongside, as well as separate from, the earliest product development efforts. Some acceptability and preference issues are specific to a product's dosage form, use-requirements, and/or use indications, while others pertain to any vaginal product used for prevention of HIV or pregnancy. Although most of the work cited here was published since 2010, it draws on a much longer trajectory of research.

1. Introduction

The vagina is an appropriate site for local and systemic delivery of a number of drugs, and vaginal products have been formulated for treatment of sexually transmitted infections and post-menopausal symptoms, to prevent pregnancy, or to induce labor. Products are also used in the vagina to improve sexual performance, such as increasing sexual pleasure for one or both parties, or easing pain during intercourse (*e.g.* lubes), and for cleaning before or after sex [1–3]. Vaginal healthcare products for treatment and prevention of health conditions encompass a wide range of formulation types and use durations including vaginal gels or creams for daily or twice daily administration, fast dissolving tablets or soft-gel capsules, extended-release drug device combinations such as a contraceptive vaginal ring worn for 21 days (Nuvaring®) and a 90-day estradiol acetate ring for estrogen replacement in post-menopausal women (Femring®, Estring®), and physical barriers for contraception such as the diaphragm and the SILCS® cervical barrier.

Two new classes of vaginal products currently under development, called vaginal microbicides and multipurpose prevention technologies (MPTs), could have a significant impact on global health by reducing sexual transmission of HIV, other sexually transmitted infections (STIs) and/or unintended pregnancy [4,5]. However, the potential global health impact of these products will only be realized if they are sufficiently acceptable and accessible to at-risk populations so that they are used correctly and consistently. It is important to bear in mind that unlike treatment therapies, use of an HIV prevention product is not driven by a medical diagnosis or symptoms needing relief, but rather an assessment of the potential risks and costs of infection, which has been particularly problematic for HIV.

Development of acceptable vaginal products for prevention of HIV, STIs or pregnancy will require consideration of a range of social and behavioral issues, since product use requires enactment of preventive health behaviors within social (*e.g.*, sexual) relationships, influenced by social and cultural norms in order for the product's biological effects to have a chance to be effective [6–9]. This paper reviews key issues pertaining to the acceptability of vaginal microbicides and MPTs, with a focus on the interplay between the biological and physico-chemical aspects of formulation, and the social and behavioral issues that may affect use. Although most of the work cited here was published since 2010, it draws on a much longer trajectory of research.

2. Terms and concepts pertaining to microbicide "acceptability"

A number of vaginal products that have demonstrated good *in vitro* profiles for prevention of HIV have failed to demonstrate efficacy *in vivo*, and a major cause of this is attributed to poor use adherence in clinical trials [10–12]. Thus, the clinical safety and potential efficacy of a number of products that have been tested in clinical trials remains unknown. Social and behavioral research provides important insights into why women may or may not use these products, and how the product could possibly be improved to meet their needs and preferences. Key concepts and terminology used in this body of research are described below, including references to publications that focus on the concept.

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2.1. Acceptability

Acceptability is a term used to describe willingness to use or willingness to try a product, and usually includes caveats about expected efficacy and perception of risk (of HIV infection or pregnancy) [6,13–15]. For example, a product may be deemed acceptable if a woman states she is willing to use it as directed to protect herself from HIV, once it is proven effective. Acceptability may imply "likeability" of a product or product attributes, but an acceptable product may only be the "least disliked" option [16] among the choices. Aspects of a product's acceptability include experiences and perceptions of the physical attributes of the product and its use requirements within the context of sexual relationships, all of which may be influenced by larger social and cultural norms, and the infrastructure within which the product is delivered.

2.2. Adherence

This concept is similar to the term "compliance," used in medical treatment, but is considered less paternalistic. Participants in microbicide and MPT clinical trials are expected to adhere to protocol requirements (*e.g.*, study visit schedules, HIV tests, condom use, *etc.*) as well as product use regimens. Although it is often assumed that acceptability is positively associated with adherence, this relationship has not been clearly demonstrated [14]. Microbicide trial participants may adhere to protocol or product-use requirements without finding either to be acceptable, and they may not use an acceptable product for a variety of reasons. Efforts are expended to motivate adherence to study protocol and product use, and measure adherence to product use through a variety of measures including self-report, bio-markers and mechanical means (*e.g.*, product counts, dye-stain assays) [9,17–19].

2.3. Use experience

Since no vaginal microbicide is currently on the market, women's experiences with these products and their views on product acceptability, preferences, and adherence are necessarily hypothetical. These concepts have been investigated in clinical trials where women use candidate products and placebos, studies that ask women to use proxy products (*e.g.*, over the counter lubricants in various formulations) during sex or with no sex, as well as studies that provide verbal descriptions, photos or actual examples of products [20]. Actual use experience with a vaginal product may be more likely to provide women with a better sense of what they might like and not like about a product's physical attributes. However, the clinical trial environment, with its repeated statements about unknown efficacy, regular study visits and medical testing, and recommendations for condom use may affect women's use experience and overall product acceptability, both positively and negatively.

2.4. User-preferences

User-preference describes the characteristics most desired out of a range of options [21–24]. For example, users could be asked about their preferences for a vaginal product that is more or less viscous, has a faster or slower rate of dispersion in the vagina, uses a plastic or paper applicator, or is a colored or clear polymer ring, *etc.* Users may also have preferences for use requirements, use indications and where to access products. A product may be acceptable and yet have some attributes that are less preferred than others.

2.5. User-perspectives

The perspectives of those who are intended to be users of vaginal microbicides and MPTs are of key interest for research on acceptability, adherence and preferences. These perspectives should be elicited from women and men within the targeted risk groups, by persons who are knowledgeable about the social, cultural and behavioral factors that influence preferences and acceptability, and skilled in collection of such data. User-perspectives also include health professionals who will prescribe microbicides and MPTs, and advise women and men about their use. Health professionals are gatekeepers to product access, and their acceptability and perspectives can greatly influence uptake and sustained use of new methods to prevent HIV and pregnancy [25–27].

2.6. Conceptual framework

The conceptual frameworks most often proposed for the study of microbicide acceptability are variations of "ecological" models, which recognize the importance of considering multiple spheres influencing acceptability, usually beginning with individual behavior which is influenced by the views and perspectives of the partner, the clinical trial environment or health care setting as well as the larger environment of family and friends, situated in a community and even larger cultural, social, political and economic context [6,14,28]. Hayes' [29] conceptualization of an ecological model for HIV prevention begins at the microbiological and cellular level, acknowledging the host defenses and biological reactions in the human body. Such an extension of a conceptual model would be appropriate for considering how the formulation of a product causes physiological interactions that can affect women's bodies and what will be required for the correct use of a product.

3. The pipeline, and attributes key to acceptability

Development of the microbicide and MPT pipelines has involved an array of academic, governmental and nongovernmental agencies and organizations and pharmaceutical companies. A number of working groups and committees have been convened with the goal of achieving efficiencies and establishing priorities in the product development process [30,31]. In 2010 there were 75 candidate products in the microbicide pipeline, including formulations for vaginal gels, rings, films, tablets and soft-gel capsules [32].

The microbicide product pipeline is often organized according to the mechanism of action of the active pharmaceutical ingredient(s) (API). When considering acceptability and user preferences, it is helpful to indicate attributes of potential importance for user acceptability, which include dosage form, use requirements, and use indications. Table 1 provides an overview of products that have advanced furthest in the development process, as well as some that are at early stages of development and those that are no longer candidates, and includes information on key acceptability issues. We next discuss acceptability and preference issues reported for these acceptability issues.

3.1. Semi-solid and film dosage forms

Gel formulations in single-use pre-filled applicators are the most widely studied, with dose volumes ranging from 1 to 4.5 mL (see Table 1). Aspects of gel formulation that users reported as problematic include leakage/discharge before, during and after sex, and the appearance of the product when discharged from the vagina [61,62]. Leaking and clumping have been reported as messy and inconvenient for cleaning, worrisome for those who feel that product which has been discharged is not providing protection, and make it difficult for women to use without telling the partner. On the other hand, some women welcome product discharge, considering that this demonstrates that the microbicide has cleansed the vagina [63,64].

Semi-solid formulations potentially change the way the vagina feels to one or both partners during sex, and concerns about increased vaginal wetness continue to receive attention in the literature [62,65,66]. There is no clear finding about the ideal viscosity or volume of a semi-solid vaginal microbicide or MPT [21]. Although some cultural groups value the sensation of a tight or dry vagina during sex [1], and research has reported that gel detracted from sexual pleasure for some study

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