

Microbicides for the prevention of HIV infection in women: an overview of recent trials

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Purpose of review

As the HIV/AIDS pandemic continues, the development of new prevention technologies is urgently needed.

Microbicides, products applied to genital mucosal surfaces, are being developed to reduce the transmission of HIV during sexual intercourse. Microbicides have been designed to inhibit HIV from the time the virus enters the genital tract to any of the multiple steps in local virus replication.

Recent findings

Preclinical research and development of microbicides has led to the advancement of many candidates into human clinical trials. This research has shown that cervicovaginal irritation is an important safety concern and needs to be evaluated carefully and early. New approaches to measuring local irritation are currently under investigation.

Summary

Five broad-spectrum microbicides are now being tested in large-scale effectiveness trials to measure their effects on the reduction of HIV incidence. Next-generation candidates, based on highly active antiretroviral drugs, are currently undergoing safety studies. This paper reviews the findings from trials of these products and discusses several challenges that are encountered in the clinical development of microbicides. Although complex and resource intensive, the successful completion of ongoing studies and the initiation of efficacy trials of next-generation candidates are critical to the successful development of a microbicide.

Keywords

efficacy trials, human clinical trials, microbicide, safety trials

Introduction

The inability to stop the spread of HIV/AIDS over the past 25 years has resulted in an unprecedented level of research into new prevention technologies. Areas of focus include HIV vaccines, drugs used as pre-exposure prophylactic agents, better condoms including female condoms, and microbicides. Microbicides, drugs applied topically to genital mucosal surfaces to prevent the transmission of sexually transmitted infections, in particular HIV/AIDS, are being explored for their potential safety and efficacy. First-generation microbicides are gel-based, broadly reactive products that are designed either to disrupt the viral membrane, buffer vaginal acidity in the presence of semen, or non-specifically block the attachment of HIV to its target cells. These products are designed to be used with each act of intercourse, and are generally delivered in disposable vaginal applicators.

Newer microbicide candidates are based on the highly active antiretroviral drugs that specifically target molecules on HIV or its target cells. These newer generation products can be designed as once-a-day gels and do not have to be used at the time of intercourse. In addition, longer-acting sustained release delivery approaches are being investigated, including intravaginal rings, which have been successfully licensed and used to deliver hormonal and contraceptive drugs.

Recent reviews by D'Cruz and Uckun [1], Lederman *et al.* [2] and Madan *et al.* [3] provided background on the preclinical development of the current microbicides in the pipeline. This paper focuses on the clinical development of vaginal microbicides for the prevention of HIV transmission from an infected man to an uninfected woman.

Clinical safety trials

Following preclinical laboratory and animal safety and efficacy studies, the clinical development of microbicides in humans begins with dose and frequency-ranging studies to evaluate systemic toxicity (as measured by hematology and liver and renal function tests) for candidates that are absorbed, as well as local toxicity to cervicovaginal epithelium, including frank trauma such as breaches in the integrity of the epithelium and inflammation because these might facilitate HIV transmission [4]. Local toxicity is determined by naked-eye and

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colposcopic examination of cervicovaginal mucosa [5]; effects on vaginal pH; and effects on normal vaginal microflora, specifically hydrogen peroxide-producing lactobacilli species.

In general, the first human studies of vaginal microbicide candidates have been conducted in HIV-negative women of reproductive age in north America and Europe, with the exception of candidates developed in India. Subsequent safety studies then usually take place in developing countries in women who are representative of both future efficacy trial populations and intended primary users. The eventual target populations for efficacy trials need to be recruited from areas with high baseline HIV incidence, which is predominantly found in sub-Saharan Africa and India [6].

Microbicide safety studies have been designed as either open-label or randomized controlled trials, with the number of women per dose/frequency group ranging from 12 to 35. The duration of exposure in initial safety and pharmacokinetic studies ranged from 7 to 14 days [7–12,13[•],14–17,18^{••},19[•]]. Although the doses chosen for these studies are generally determined empirically from preclinical assessments and formulation constraints, the measurement of drug in cervicovaginal lavages from participants in human safety studies has been used to determine the concentration of drug available at different timepoints post-application [20^{••}]. In addition, as adequate vaginal distribution of some gels may be relevant to efficacy, magnetic resonance imaging has been used to determine the deployment and duration of gel intravaginally [21[•],22].

Whereas some of the earlier studies were restricted to women who agreed to be sexually abstinent, later studies enrolled successive cohorts of sexually abstinent and sexually active women as well as successive cohorts of HIV-negative and HIV-positive women [18^{••},23,24[•],25[•]]. Although HIV microbicides are being developed to block the transmission of infection from an infected man to an uninfected woman, safety in HIV-infected women is measured because many women who are unaware of their infection may also use a marketed microbicide. In addition to vaginal safety, male tolerance studies are also carried out to evaluate toxicity to penile epithelium. In such trials, the microbicide is applied to the penis once a day for 7 days. Participants are observed for any signs or symptoms of genital irritation, as measured by self-report and examination by naked eye and hand-held magnifying lens of the penis [26–28,29[•]].

Safety studies of several classes of microbicides have been conducted. The first class consists of membrane-disruptive agents, such as the surfactants nonoxynol-9

and C31G. In the case of nonoxynol-9, multiple safety studies [30–33,34^{••}] of different concentrations and formulations demonstrated that high doses (100 mg per dose or higher) of nonoxynol-9 used many times a day resulted in epithelial disruption of the vaginal and cervical mucosa. Lower doses were not associated with genital lesions with or without epithelial disruption [35–37]. The results from several studies [14,15,38] with C31G in different concentrations and formulations showed that 0.5 and 1.0% C31G in a co-polymer vehicle did not cause discomfort to participants and were not associated with genital mucosal disruption, whereas 1.7% C31G was similar to high-dose nonoxynol-9 with respect to the signs and symptoms of irritation and product-related events.

A second microbicide class, the polyanions, include carageenans (PC-213, 503, and 515), dextrin 2-sulfate, cellulose sulfate, polynaphthalene sulfonate (PRO 2000), and polystyrene sulfonate. As a class, these compounds have demonstrated good safety profiles in multiple safety studies [9,11,12,16,17,23,24[•],25[•],26,39–41,42[•],43,44] as measured by irritation and ulceration. Two polyanions, Buffergel and Acidform, have also been evaluated in human trials [7,8,10,19[•],27,29[•]] as microbicides. In addition to their in-vitro activity as non-specific inhibitors of HIV attachment, these products have been designed with pH-lowering capacity to maintain an acidic pH in the presence of semen. Whereas Buffergel showed low rates of genital irritation, participants in a study of Acidform [45] had a statistically significant increase in the signs and symptoms of genital irritation, including superficial epithelial disruption, when compared with the control group.

A third class of candidates currently undergoing safety studies [2,18^{••},46] is composed of products based on highly active antiretroviral drugs including tenofovir, dapivirine (TMC120), thiocarboxanilide (UC781), and MIV-150. Extensive oral safety data are already available for tenofovir, a nucleotide reverse transcriptase inhibitor licensed for the treatment of HIV infection [47]. Results from the first safety study of 1% tenofovir gel showed that the gel was well tolerated in both sexually abstinent and sexually active HIV-negative and HIV-positive women. Low levels of tenofovir were detected systemically in 56% of the women for at least one timepoint, with the median plasma concentration less than 7% of that observed after a single oral 300 mg dose in previous treatment studies. Dapivirine – a non-nucleoside reverse transcriptase inhibitor, which has been evaluated in studies of both a gel formulation as well as an intravaginal ring – has also shown good safety profiles and hardly quantifiable but detectable levels of systemic absorption (J. Van Roey, J. Romano, personal communication).

One potential safety concern with the use of antiretroviral-based microbicides is the selection of drug-resistant HIV variants. This may potentially occur in an HIV-infected woman who is unaware of her infection and uses the microbicide, or through a new infection occurring during exposure to the product. Clinical trials – both small focused studies in HIV-positive individuals and large efficacy trials – are needed for a definitive evaluation of the risks associated with exposure to antiretroviral-based products. The very low plasma levels seen to date after vaginal exposure may indicate that there is insufficient drug available systemically to select for resistant virus. In the safety study of tenofovir gel [18**], no new reverse transcriptase resistance mutations were detected in the 22 HIV-infected women exposed to the gel for 14 days.

Although it is not known whether low levels of systemic absorption will lead to the selection of drug resistance, this potential must be appreciated within the context of the overall risks and benefits of product use, as is the case for all pharmaceuticals. It is also important to bear in mind that antiretroviral-based microbicides are unlikely to be available before 2010, by which time new classes of antiretroviral agents may be available. In addition, as antiretroviral drugs become more widely available in developing countries, HIV testing may be more common and may become an integral part of screening for microbicide use. Clearly, the benefit of antiretroviral-based microbicides can only be evaluated in randomized, controlled phase III efficacy trials.

Another approach that has been tested in safety trials is Praneem, a polyherbal formulation extracted from seeds from the neem tree [13*]. Praneem tablets were found to be safe for once daily intravaginal use over 2 weeks in sexually active HIV-uninfected women. Most recently, a safety trial [48] of lime juice as a potential microbicide was conducted, which demonstrated significant genital irritation.

Although irritation can present clinically as in the case of nonoxynol-9 and lime juice, subclinical irritation may also be present. For example, a microbicide could potentiate proinflammatory cytokine production that could result in a local influx of T cells in the absence of visible systemic or colposcopic findings. In order to have a better measure of this effect, researchers are focusing on identifying chemical markers of inflammation that may predict adverse outcomes [3,34**,49,50]. This approach has recently been applied to a study [51] of PRO 2000 vaginal gel use in which white blood cells, cytokines, chemokines, defensins, and other protective factors present in cervicovaginal lavage fluid were measured. The results showed the absence of a detectable inflammatory response alongside normal colposcopic findings. These

types of studies may be important to conduct in advance of efficacy trials to ensure that products are not associated with subclinical inflammation and thus pose an increased risk of HIV infection. It is important to note, however, that regulatory bodies do not require this type of information because its interpretation is difficult and its clinical corollaries are not well established.

Clinical efficacy trials

The gold standard for determining the clinical efficacy of HIV microbicides, as with other therapeutics and vaccines, is the randomized, placebo-controlled trial with incident HIV infection as the primary outcome. As the sample size calculations for HIV endpoint trials are dependent on the HIV incidence rate in the study population, efficacy trials generally involve thousands of women in order to meet the statistical rigor required for regulatory licensure. The ethical conduct of microbicide studies requires that all women in the study have access to available HIV prevention strategies including education and the provision of condoms and treatment for sexually transmitted infections [52].

Several efficacy trials [53–56] of nonoxynol-9-containing products were conducted in the 1990s. In those studies, nonoxynol-9 failed to protect against infection with HIV, gonorrhea or chlamydia, and in some studies showed a trend towards an increased risk of infection in those women who used the product many times a day. Those studies led to a shift in focus to microbicide candidates with higher therapeutic indices and lower potential to cause irritation.

The COL-1492 study [54] – one of the nonoxynol-9 efficacy studies – also brought into question the possibility that the placebo – a vaginal lubricant with different physical properties and lower pH than the experimental product – might have had a protective effect against HIV acquisition as a result of a reduction in genital irritation caused by friction during sex as well as a pH effect. To address this concern, a universal hydroxyethylcellulose placebo gel was developed and was shown *in vitro* and *in vivo* to be safe and sufficiently inactive for use in microbicide efficacy trials [57*].

There are presently six microbicides in large efficacy field trials in Africa: carrageenan (Carraguard), C31G (Savvy), cellulose sulfate (Ushercell), PRO 2000 at 0.5%, PRO 2000 at 2.0%, and Buffergel [2]. All six products are designed to be used coitally (applied before each sex act), and all but one of the trials – the study of Carraguard – is comparing the product with the hydroxyethylcellulose universal placebo. One trial – HPTN 035 [58] – is designed as a four-arm study with PRO-2000 at 0.5%, Buffergel, hydroxyethylcellulose placebo and a no-treatment control arm. The stated purpose of the no-treatment control arm

was to determine the effect, if any, of the hydroxyethyl-cellulose placebo on HIV infection. HPTN 035 is also the only study that is powered as a phase IIb intermediate-sized efficacy trial, as well as the only study to enroll women in the United States. One study involving cellulose sulfate is also being conducted in two sites in India.

Some of the trials are encountering several challenges, including lower than expected HIV incidence rates and high pregnancy rates, the latter leading to the interruption of product use. In addition, several studies are finding low rates of product use in the absence of condoms, as measured by self-report or a biological adherence marker [59]. Low product use can result in a significant reduction in the power of the study to determine a protective effect [60••]. With some of the next generation of long-acting antiretroviral-containing microbicides, the potential for once daily or monthly dosing allows for new trial designs that address the issue of low product compliance. One such design is a directly observed therapy trial, which for a once a day usage would require daily observation of product use in either home, mobile clinic, or trial center settings.

Regardless of the study designs employed, each new microbicide efficacy trial will require many thousands of participants enrolled at multiple sites. These sites will have to be located in high HIV-incidence countries at research sites capable of conducting licensure trials. As experience with highly active antiretroviral therapy has taught us, it will also probably require a series of such trials as new single agents, combination products, and delivery vehicles are developed. The demand for trial populations will also increase with the testing of candidate HIV vaccines and other HIV prevention strategies, such as cervical barriers, sexually transmitted disease treatment and oral prophylaxis.

A strategy for selecting the highest priority candidates for phase III trials thus needs to be implemented. Such a strategy would involve head-to-head comparisons within a mechanism of action class in in-vitro assays and in animal models, if available, for safety and efficacy. As the need for microbicides is most acute in women in very resource-poor settings, additional considerations for product selection include the cost of production, an ability to manufacture at large scale, and intellectual property agreements that will meet the access needs of millions of women worldwide.

Conclusion

The drug development path of a microbicide closely mirrors that of other drugs through discovery, preclinical work and safety testing. Prevention efficacy trials are, however, by their very nature, fundamentally different from treatment trials because only a fraction of partici-

pants will be expected to contribute to study endpoints. In HIV microbicide trials, pregnancy and product compliance are additional complicating factors that, along with low seroincidence, result in large, difficult, and expensive studies.

Much progress has been made in recent years, resulting in six presently ongoing large-scale efficacy trials and a number of promising new microbicide candidates in safety studies. Although the future of the microbicide product pipeline appears very promising, the challenges to microbicide development are great. Extensive trial preparations to ensure adequate clinical site capacity and an assessment of seroincidence, as well as creative trial designs, will be required to overcome these obstacles. The long-term commitment of funders, researchers, local and international institutions, industry, communities, and governments is needed to achieve our common goal: a safe and effective microbicide for women worldwide.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 523–524).

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