Perspective

Should microbicides be controlled by women or by physicians?

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1. Introduction

In 2007, nearly 7000 new cases of HIV infection occurred each day. There is a constant increase in the proportion of women newly infected with HIV in the global population; this increase is particularly high in some areas of the world such as sub-Saharan Africa. Microbicides are products that are being developed to empower women against HIV. First- and second-generation microbicides are broad-spectrum products that include surface active agents, vaginal defense enhancers, and blocking agents. Third-generation microbicides are HIV-specific and include replication and entry inhibitors formulated as gels or as vaginal rings. However, there is a concern that antiretroviral-based microbicides could lead to drug resistance if they are used by HIV-positive women who are unaware of their HIV status. To reach the highest number of women possible, microbicides should be available over-the-counter, which might not be the case with antiretroviral-based formulations. In contrast, non-antiretroviral-based microbicides will have the advantage of being initiated and controlled by women themselves and they will not jeopardize the use of lifesaving drugs.

2. Microbicides

First- and second-generation microbicides tend to be broad-spectrum products that disrupt the viral envelope, maintain vaginal pH, and/or bind to the virus to inhibit entry. More recently, pharmaceutical companies have granted royalty-free licenses to develop, manufacture, and distribute some antiretrovirals (ARVs) as microbicides in resource-poor countries. Third-generation microbicides may have implications regarding the emergence of drug-resistant HIV. Indeed, ARVs administered vaginally could be absorbed systemically and may select for resistance if used by HIV-positive women who are unaware of their HIV status. Therefore, women using ARV-based microbicides should be monitored for HIV, leading to increased costs and reduced accessibility to these products, especially if in the future the Food and Drug Administration (FDA) or other health authorities require that they be prescribed. We believe that non-ARV-based microbicides will have the advantage of being initiated and controlled by women themselves and they will not jeopardize the use of lifesaving drugs.

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cellulose sulfate, Carraguard®, and PRO 2000/5 gel). In addition to their effect on HIV, they may be effective against other sexually transmitted pathogens. Some of these products may also demonstrate a contraceptive efficacy, while others may not. Most phase I and phase II clinical trials completed to date have found these products to be safe and well-tolerated. However, phase III trials with nonoxynol-9 and cellulose sulfate have shown that they could be harmful to the vaginal mucosa and increased the risk of HIV acquisition in women.

Phase III trials with Carraguard® and BufferGel have not demonstrated efficacy in preventing HIV transmission. Moreover, two phase III trials with C31G did not produce meaningful results due to lower-than-expected HIV incidence in the study populations. More interestingly, a phase II/III trial with PRO 2000/5 gel (a naphthalene sulfonate polymer) involving 3099 participants showed that it might have some effectiveness for the prevention of HIV infection. Women in the PRO 2000/5 gel arm had a 30% lower rate of HIV infection compared with those in the no gel at all, universal placebo gel, and BufferGel arms, but this effect was not statistically significant. Unfortunately, the phase III clinical trial with PRO 2000/5 gel which involved a larger number of women (9395) found no evidence that this product reduced the risk of HIV infection.

Other promising first- and second-generation microbicides that are in an earlier stage of preclinical and clinical investigation include the Invisible Condom® (a physical/chemical barrier; phase II/III planned), praneme polymer hydrogel vaginal tablet (unknown mechanism of action; phase II completed), VivaGel (a dendrimer-based entry inhibitor; phase II/I ongoing), ACID-FORM (a buffering agent; phase I ongoing), and SAMMA (a mandelic acid condensation polymer; in preclinical studies). Bioengineered lactobacilli are also being developed to express proteins (such as CD4, a derivative of gp41, or cyanovirin® that bind to HIV and block either viral–host cell fusion or viral entry into host cells.

Third-generation microbicides include HIV replication and entry inhibitors. In contrast to earlier generations, they are not effective against other sexually transmitted pathogens and are not contraceptive. The most advanced compounds include ARV medications such as a nucleoside reverse transcriptase inhibitor (NRTI) (tenofovir; Gilead) and two non-nucleoside reverse transcriptase inhibitors (NNRTI) (dapivirine (Tibotec/Virco) and UC781). These products formulated as vaginal gels are presently in the early phases of clinical investigation. The NRRTI MIV-150 suspended in Carraguard® gel base (PC-815; Population Council) is in advanced pre-clinical testing. Third-generation microbicides could also inhibit HIV infection by interfering with the binding of the virus to cellular receptors. Two inhibitors of the chemokine receptor CCR5 (CMPD167 (Merck) and PSC-RANTES) have been shown to protect rhesus macaques after intravaginal challenge with a simian human immunodeficiency virus. Recently, maraviroc, the CCR5 inhibitor developed by Pfizer, entered the development pipeline as a candidate microbicide. It is suggested that fusion and integrase inhibitors could also be candidates.

In addition to gel formulations, coitaly-independent microbicides are being developed in the form of vaginal rings made of silicone elastomer, which allow a controlled sustained release of ARV drugs over a long period of time, eliminating the need to apply a formulation before each sexual intercourse. However, there is a concern that ARV-based microbicides could lead to drug resistance if they are used by HIV-positive women unaware of their HIV status. Therefore, the protocols of clinical trials testing ARV-based microbicides have been redesigned to evaluate the risk of HIV-positive women developing resistance (e.g., the VOICE study – Vaginal and Oral Interventions to Control the Epidemic).

3. Why should we care about the risk of developing resistance with ARV-based microbicides?

The risk of developing resistance is more elevated with formulations or vaginal rings containing a single ARV agent compared with combinations of drugs with different targets in the viral lifecycle. All classes of ARV-based microbicides could be formulated alone or in combination. However, FDA regulations require that microbicides containing more than one active ingredient should show the clinical superiority of combined active agents over each individual component before they can be approved. This will add enormously to the cost and duration of product development.

Considerable work has been accomplished in making ARV therapy accessible to individuals living in low- and middle-income countries, though much remains to be done in order to attain universal coverage. In resource-poor countries, it is important to preserve first-line treatment regimens because second-line therapies are rare and expensive. First-line regimens, usually zidovudine (Retrovir), lamivudine (Epivir), and nevirapine (Viramune), costs nearly $240 per year, whereas second–line regimens, which often include tenofovir (Viread), emtricitabine (Emtriva), and lopinavir (Kaletra), cost as much as $750 per year. Tenofovir is a highly desired ARV in these countries because it is safe, requires relatively limited toxicity monitoring, and is administered once daily. The systemic tenofovir absorption from a 1% vaginal gel suggests that the development of resistance is plausible. However, tenofovir is currently being evaluated in clinical trials as a gel-based microbicide and a vaginal ring-based microbicidal, as well as an ‘anti-HIV pill’ in pre-exposure prophylaxis (PrEP). It cannot be excluded that, if marketed, an inconsistent use of these prevention options for long periods of time by populations at high risk of acquiring HIV could lead to resistance to tenofovir (such as the high level tenofovir mutation K65R), which could thereby compromise future use of this highly desired life-saving drug.

Currently, in regions that are the most hard hit by the HIV/AIDS epidemic, there is insufficient laboratory capacity as well as personnel and financial resources to perform regular HIV viral load monitoring and detection of resistance mutations. The World Health Organization (WHO) is launching a public health strategy through the Global HIV Drug Resistance Surveillance Network (HIVResNet) and national governments, but the global implementation still needs the support of policymakers and money. In these countries, viral load measurement costs $20 to $50 per test, which is four-times more than the CD4 cell count test. Therefore, patients put on ARV therapy are monitored on the basis of clinical and immunological parameters only, as recommended by the WHO. Clinical and immunological parameters are less reliable than viral load monitoring and detection of resistance mutations to evaluate therapy failure, leading to unnecessary switches to second-line regimens in the absence of treatment failure or to longer administration of a failing treatment regimen. This could create the conditions for an accelerated development of HIV resistance to ARV drugs. This situation will be even more complicated if individuals, at high risk of infection, use microbicides containing ARVs inconsistently and for long periods of time without knowing their HIV status. Therefore, there should be laboratory capacity, personnel, and financial resources in place to perform HIV diagnostics and detection of resistance mutations before introducing ARV-based formulations in resource-poor countries.

4. Non-ARV- versus ARV-based microbicides

To reach the highest possible number of women, microbicides should be available over-the-counter, which might not be the case with ARV-based formulations. In contrast, women will not need to
be tested for HIV or obtain a prescription from a physician in order to gain access to non-ARV-based microbicides. Therefore, these products could be made readily available over-the-counter to a large number of women in countries most in need of microbicides. It has been estimated that a microbicide with even a low effectiveness, but with a wide distribution could have a substantial impact against the global HIV epidemic. In addition, infections by other sexually transmitted pathogens, especially those causing ulcerations to the vaginal mucosa, are important risk factors for HIV acquisition. Therefore, although HIV is the primary target for most microbicides, broad-spectrum products that have the ability to cover additional sexually transmitted pathogens may demonstrate enhanced protection against HIV.

The development of safe and effective microbicides has been delayed by limitations in understanding the mechanism of HIV transmission, the lack of validated animal models, the lack of established surrogate markers of safety, and the need to enroll and follow large cohorts of high-risk participants for several years in order to demonstrate efficacy. Clinical trial failures with the first candidate microbicides has underscored the urgency of identifying and validating biomarkers predictive of safety and efficacy. Several biomarkers have been proposed for the preclinical evaluation of candidate microbicides, such as epithelial barrier disruption, efficacy in preventing HIV infection in human cervical explant tissue cultures, and effect of seminal plasma on product efficacy, as well as mucosal inflammation and susceptibility to genital herpes in mice. In addition, biomarkers such as evaluation of induction of inflammatory response or loss of host defense, altered vaginal microflora, and ex vivo assessment of microbicide efficacy could give information in early clinical trials about the safety and likely effectiveness of candidate microbicides. This would allow a better characterization of candidate microbicides and the detection of less promising products before they move to large phase IIb/III clinical trials. Finally, biomarkers of sexual behavior, such as vaginal exposure to semen and adherence to product use could help with interpretation of study results.

With these new tools in hand, we suggest that the development of over-the-counter non-ARV-based microbicides should be reinvigorated. There are now new biomarkers of safety and efficacy to characterize the other promising first- and second-generation products that are in the pipeline for a more rationale selection of those that could enter into large and expensive phase IIb/III clinical trials. Non-ARV-based microbicides may have an important role in the arsenal of HIV preventive options that are urgently needed by women, especially those living in low- and middle-income countries, to control their sexual destiny without jeopardizing the use of life-saving drugs.

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References


