Historical development of vaginal microbicides to prevent sexual transmission of HIV in women: from past failures to future hopes

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Abstract: Infection with human immunodeficiency virus (HIV) remains a global public health concern and is particularly serious in low- and middle-income countries. Widespread sexual violence and poverty, among other factors, increase the risk of infection in women, while currently available prevention methods are outside the control of most. This has driven the study of vaginal microbicides to prevent sexual transmission of HIV from men to women in recent decades. The first microbicides evaluated were formulated as gels for daily use and contained different substances such as surfactants, acidifiers and monoclonal antibodies, which failed to demonstrate efficacy in clinical trials. A gel containing the reverse transcriptase inhibitor tenofovir showed protective efficacy in women. However, the lack of adherence by patients led to the search for dosage forms capable of releasing the active principle for longer periods, and hence to the emergence of the vaginal ring loaded with dapivirine, which requires a monthly application and is able to reduce the sexual transmission of HIV. The future of vaginal microbicides will feature the use of alternative dosage forms, nanosystems for drug release and probiotics, which have emerged as potential microbicides but are still in the early stages of development. Protecting women with vaginal microbicide formulations would, therefore, be a valuable tool for avoiding sexual transmission of HIV.

Keywords: vaginal formulations, microbicides, prevention, sexual transmission, acquired immunodeficiency syndrome (AIDS), human immunodeficiency virus (HIV)

Introduction

Acquired immunodeficiency syndrome (AIDS) is a global health concern. It is a chronic infectious disease caused by the human immunodeficiency virus (HIV), an enveloped virus in the Retroviridae family with a lipid membrane and is capable of interacting with CD4+ T cells, thanks to gp120. The virus infects the cells of the immune system, destroying or impairing their function and causing a progressive deterioration of the immune system until the sufferer falls into an immunodeficient state. Primary HIV infection is symptomatic in over half the reported cases, but may be overlooked as the symptoms resemble those of a common viral infection. There are two serotypes of the virus (HIV-1 and HIV-2), whose key difference in functional terms is that in HIV-2 infection, the amount of circulating viruses is lower than in HIV-1 infection, making its evolution slower and incubation period longer. Nevertheless, both serotypes ultimately cause AIDS.1 AIDS is the most advanced stage of HIV infection, in which the immune system ceases to respond effectively and diseases develop due to the loss of the body’s defense capability.2

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Table 1 Classification of antiretroviral drugs

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entry inhibitors or FIs</td>
<td>Enfuvirtide, maraviroc</td>
</tr>
<tr>
<td>NRTIs</td>
<td>Tenofovir, adeovir, didanosine, stavudine, emtricitabine, abacavir, lamivudine</td>
</tr>
<tr>
<td>NNRTIs</td>
<td>Efavirenz, rilpirine, nevirapine, dapivirine or etravirine</td>
</tr>
<tr>
<td>PIIs</td>
<td>Ritonavir, darunavir</td>
</tr>
<tr>
<td>IIs</td>
<td>Dolutegravir, raltegravir</td>
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**Abbreviations:** FIs, fusion inhibitors; IIs, integrase inhibitors; NRTIs, nucleoside reverse transcriptase inhibitors; NNRTIs, non-nucleoside reverse transcriptase inhibitors; PIIs, protease inhibitors.

The goal of ending the AIDS epidemic is becoming more attainable through the elimination of HIV transmission and AIDS-related deaths, which is now possible thanks to the numerous antiretroviral drugs with different mechanisms of action currently available for the treatment of HIV (Table 1). These drugs are able to inactivate the virus at different stages of the viral cycle (Figure 1).

However, stigma and discrimination, violence against women and girls and unjust laws continue to hamper efforts to achieve global targets. If these challenges can be overcome, and if efforts to prevent HIV continue to gain in efficacy — and with the rapid rise in the number of people receiving treatment — the world will attain its goal of ending the AIDS epidemic in the not-too-distant future.

The seventh objective set by the United Nations for bringing an end to AIDS specifically raises the question of the current status of women – particularly in low- and middle-income countries – in terms of protection against HIV, since the likelihood of transmission of sexually transmitted infections (STIs) from men to women has been observed to be alarmingly high.

This is because current methods of preventing STIs, such as abstinence, condoms and monogamy, are often ineffective and outside the control of women; many men oppose the use of condoms and women do not have the authority to insist that their partners use them. Thus, today, over 50% of new HIV infections are in women.

Sexual behavior is more likely to be the cause of STI transmission in certain countries, and there are indications that unsafe sex has increased in several nations. The latest data point to a significant rise in polygamy in a number of countries (Burkina Faso, Congo, Ivory Coast, Ethiopia, Gabon, Guyana, Rwanda, South Africa, Uganda, Tanzania and Zimbabwe) as well as a decline in condom use (Ivory Coast, Niger, Senegal and Uganda).

The main setbacks to efforts to prevent HIV transmission are the lack of access to sexual education services and sexual violence against young women and girls. Each year, about 380,000 women aged between 10 and 24 years suffer from HIV infection, meaning that 50 young women become infected with HIV every hour. Furthermore, 80% of women aged 10–24 with HIV live in sub-Saharan Africa.

It is, therefore, necessary to have female-controlled methods such as microbicides that may be used to prevent vaginal acquisition of HIV.

Microbicides are currently seen as a promising tool to protect women from acquiring this type of infection. The use of microbicides is be controlled by women, who can apply them before intercourse without the man’s cooperation. A vaginal microbicide can be defined as any agent included in a topical formulation designed to prevent the spread of sexually transmitted pathogens either through cell death, inactivation of cell mechanisms, inhibition of viral replication, the formation of a physical barrier between cells and pathogens, or by enhancing the natural protection mechanisms of the cervix and vagina.

Unfortunately, many vaginal microbicide formulations may fail to produce a protective effect due to their lack of efficacy and their unsuitable formulation. Some of the most frequently used vaginal dosage formulations include creams, gels, tablets, films and intravaginal rings, each of which has particular advantages and drawbacks.

In view of the above, there is little doubt that the development of a safe, effective and affordable vaginal microbicide that is easy to manufacture, stable under different environmental conditions and comfortable for women to administer themselves would represent a major breakthrough in preventing HIV transmission.

**Historical development of vaginal microbicides**

In recent decades, very different strategies have arisen to prevent the sexual transmission of HIV. According to their mechanism of action, we can distinguish microbicides

![Figure 1: Targeting site of antiretroviral drugs at different stages of the viral cycle.](Image)
without antiretroviral drugs, such as surfactants, polyanions, acidifiers and gp120 neutralizing monoclonal antibodies, and microbicides-containing drugs used for HIV treatment, for example, entry inhibitors or inhibitors of viral enzymes. These microbicides can inhibit virus transmission at different sites: while the virus is in the vaginal environment, it can be inactivated by microbicides containing surfactants, polyanions or monoclonal antibodies, or due to acidic pH achieved with the use of acidifiers; or, once HIV has passed through the vaginal epithelium, it can be prevented from internalizing in CD4⁺ T cells by entry inhibitors, or else, viral replication can be prevented with reverse transcriptase inhibitors (Figure 2). However, after years of research with different potential microbicide substances, the current trend is toward the development of microbicides with antiretroviral drugs such as maraviroc (MVC) (ViiV Healthcare, Brentford, United Kingdom), tenofovir (TFV) (Gilead Sciences, Cambridge, United Kingdom) or dapivirine (DPV) (IPM, Silver Spring, MD, USA), which have offered the most promising results in clinical trials.

First attempts to prevent sexual transmission of HIV: vaginal gels

Gels are possibly the most widely studied pharmaceutical formulations for developing vaginal microbicides. They were the pharmaceutical dosage form of choice for the first vaginal microbicides, possibly because they have the advantage of being easily and conveniently applicable by women, which makes the use of such formulations greatly improve adherence to treatment. In addition, their manufacturing cost is not very high, especially compared to more sophisticated forms, and they are easy to mass produce. Gels are optimal formulations for ensuring the microbicide begins to exert its action quickly; however, they are generally unable to retain the drug and provide sustained release over time. They also require certain conditions of conservation, as they are not particularly stable against adverse environmental conditions.

Surfactants, the first failure

Surfactants such as nonoxynol-9 or Savvy gel were the first substances evaluated as microbicides. They act as a virucide by lowering the surface tension of the pathogen, resulting in the death of the microorganism before it comes into contact with the vaginal mucosa. However, the lack of effective protection for women highlighted by the studies led to the rapid rejection of the use of surfactants in microbicide formulations.

Screening of alternative substances: acidifiers, polyanions, monoclonal antibodies and entry inhibitors

After the failure of surfactants, new strategies to develop vaginal microbicides turned toward mechanisms that work by preventing the pathogen from entering the cells. The most

Figure 2 Diagram of the action sites of different microbicides against HIV.
basic formulations simply prevent contact between the surface of the vaginal mucosa and pathogens.

Carraguard® is a gel under research whose active ingredient is carrageenan, a sulfated linear polysaccharide extracted from seaweed. The microbicidal was formulated as a gel to be applied to the vaginal mucosa in the hour prior to sexual intercourse.25 Studies have shown that its use is safe for women, and the associated side effects are mild and infrequent.26,27 This gel also proved its ability to reduce the risk of sexual transmission of human papillomavirus.28 However, Phase II trials failed to show efficacy in preventing HIV transmission.29–31
The use of the gel is currently being assessed as a carrier of an antiretroviral drug.32

Another mechanism designed to prevent the entry of pathogens into the cells was the use of acidifiers such as BufferGel®. This acidifier acts as a buffer and is capable of maintaining normal vaginal acidity in the presence of ejaculated semen. This microbicidal is based on studies suggesting that an acidic environment could inhibit HIV.31 However, although studies on BufferGel have shown it to be safe, it has not demonstrated effectiveness in preventing HIV transmission.32,33

The lack of efficacy of these strategies prompted the search for a very diverse range of substances capable of interacting directly with the virus,34 from polyanions or monoclonal antibodies able to recognize the HIV and bind to it are antiretroviral drugs that act as fusion inhibitors, such as MVC.

One example of the gels tested as a means of blocking the pathogen is PRO 2000, whose active ingredient is the synthetic polymer naphthalene sulfonate. This is a negatively charged polyanion capable of interacting with the positive charges of viral gp120 to block virus entry into cells.35 It has proven antiviral activity against HIV-1 in vitro and in animal models, and a favorable risk profile.36,37 Nevertheless, although trials in women have demonstrated high adherence and safety, it has not demonstrated effectiveness in preventing sexual transmission of HIV.33,37

VivaGel® is another polyanion currently under study, whose active ingredient is SPL7013, a dendrimer expressly created using nanotechnology to show antiviral activity against HIV.38 and is formulated in a mucoadhesive carbopol gel.39 It has shown antiviral activity against HIV in the presence of seminal plasma,40 as well as in animal models.38,41
Along with good tolerance in animals and humans.38,42–44 However, subsequent clinical trials revealed adverse effects associated with this formulation, leading to its rejection on the grounds of being unsafe for continued use in women.45,46

A further study confirmed the inefficacy of polyanions in clinical trials despite their in vitro efficacy. This ineffectiveness was due to the formation of a semen-derived enhancer of virus infection, which promoted HIV infection in the presence of semen.47,48 Although Sonza et al reported that this enhancement effect is not applicable to all polyanions,49 it highlighted the importance of performing the effectiveness tests in the presence of semen.

Some microbicidal formulations also include gp120-neutralizing monoclonal antibodies, which recognize and bind to the viral gp120, thus preventing the virus from binding to CD4+ T lymphocytes. Examples include vitamin B12 and the monoclonal antibodies 2G12 and PRO-140.50–53

Other agents with the ability to bind to gp120 are lectins.54 The lectins most widely studied for its ability to bind HIV is probably CV-N, a protein from cyanobacteria capable of potently inactivating HIV-1, HIV-2 and simian immunodeficiency virus by binding irreversibly to gp120. Research into this active ingredient has proved its effectiveness in blocking infection by HIV-1 in ectocervical human explants.55 It was formulated in 1% and 2% CV-N gels, and in all cases showed protection against the virus in monkeys without any adverse or cytotoxic effect.56 CV-N could, therefore, be a good candidate for human trials as a topical microbicidal against HIV. In order to reduce the high cost of its production, efforts have been made to develop transgenic plants capable of producing CV-N, achieving positive results in rice endosperm, Nicotiana tabacum and soybean seeds.57–59 Griffithsin, a protein from red seaweeds, is another drug with the same mechanism of action. Studies to date are encouraging, as they have demonstrated its activity in picomolar concentrations and absence of irritability and inflammation.60,61 It has also been successfully expressed and purified from transgenic plants, which would make it more economical.62–64 Although it has yet to be tested in animals, it already has proven features that represent a significant step forward in the development of vaginal microbicides based on gp120-neutralizing monoclonal antibodies, as it would solve the main problem found during experimentation with other active ingredients in this family, namely, the need for high concentrations and the high production costs.60,62

Finally, it is worth mentioning microbicides that contain entry inhibitors such as MVC, an approved antiretroviral drug for treatment of HIV-1 CCR5-tropic in adults.65 It is specifically an antagonist of the CCR5 receptor, a protein located in T lymphocytes, which binds to HIV at the time of cell entry. MVC binds to these receptors and prevents HIV
from infecting cells and multiplying. However, this drug is not active in all patients, as in some subjects, the virus uses another receptor called CXCR4 to enter the cells.66

There are several studies aimed at testing the efficacy of MVC as a microbicide, which have proven its efficacy even in the presence of semen68,69 and its tendency to concentrate in the cervicovaginal fluid and vaginal tissue.69 One of these trials assessed the efficacy of a topical vaginal gel of hydroxyethyl cellulose containing 2.2% MVC in humanized mouse strains (RAG-hu). The gel was applied to female mice before exposing them vaginally 1 hour later to HIV-1, in order to compare its protective efficacy versus the placebo gel; no mouse was infected with the virus, while those treated with the placebo were.69

Another trial with this active ingredient studied the effectiveness of a hydroxyethyl cellulose gel with different concentrations of MVC in macaques, where it was found that complete protection was achieved against the virus with the gel with 3.3% MVC. However, this protection could only be achieved with a high concentration in the vaginal fluid, which was only attained between 30 minutes and 2 hours after the administration of the gel. Protection, therefore, largely depends on the time elapsed between application and contact with the virus.70,71

Following these assays, several studies have sought to lengthen the residence time of the gel. One proposed formulation tested in macaques was a silicone gel with MVC72 compared to a hydroxyethyl cellulose gel with the same load of MVC, which achieved greater and more sustained MVC concentrations in the vaginal fluid.73

**Inclusion of viral enzyme inhibitors: first positive results**

Although, as we have seen, the initial trend in the search for an effective microbicide was to use substances to prevent the entry of the virus in order to block the first step of infection,74 after unsuccessfully evaluating numerous compounds in clinical trials, the focus switched to the study of potential microbicides with antiretroviral drugs that prevent virus replication.75

Nucleoside reverse transcriptase inhibitors (NRTIs) were the first antiretroviral drugs to show activity against HIV. Several drugs in this family are used today to treat HIV patients and are being studied as potential microbicides. Possibly, the most widely studied drug in this group is TFV, which acts in the case of HIV infection by blocking the activity of reverse transcriptase and preventing the virus from infecting cells and replicating.76,77

Although the antiretroviral activity of TFV has been confirmed and it has been approved for oral use, research is required into its potential microbicidal effect against HIV, in addition to efficacy and safety studies, before vaginal pharmaceutical forms with this active ingredient can be developed. TFV microbicide formulations have proven antiviral efficacy in vitro78 and in animal models,79,80 and have been evaluated in Phase III clinical trials. Studies with a TFV-based vaginal gel have shown it has no significant cytotoxicity in women.81,82 Finally, several safety studies with this microbicide indicate that TFV has no toxicity for vaginal mucosa at concentrations commonly used as a microbicide.11,18,84 It has also proven to be acceptable and well tolerated by women.81,85,86

The CAPRISA 004 study evaluated the effectiveness of a 1% TFV gel in preventing HIV transmission in South African women.87 The gel was found to reduce HIV infection by 39% and even 54% when women had high adherence to treatment.87,88

Following the successful CAPRISA 004 study, numerous further projects sought to reproduce the TFV gel. The MTN-001 study compared the use of a TFV gel with the oral administration of this drug, and found that higher concentrations of the drug could be achieved in the vaginal tissue with vaginal administration.89 The same study also demonstrated lower adherence to microbicides in sub-Saharan Africa compared to the USA.90 More recent studies have confirmed the effectiveness of the gel,91 but in the VOICE trial, using a 1% TFV gel in African women was not observed to reduce the likelihood of HIV infection, although adherence to treatment was low.10

Although the recent negative results of some tests are puzzling,91 evidence supports the efficacy of this antiretroviral in preventing the transmission of HIV-1,88,92,93 offering a cost-effective method that can be controlled by women.94,95 The success of the TFV gel was a milestone in the development of an effective vaginal microbicide to prevent sexual transmission of HIV.93,96

However, the clinical trials with this gel also served to highlight the importance of analyzing the different parameters that could influence its efficacy.96 According to the results of the clinical trials, adherence is the key factor in achieving protection.97–100 Other factors influencing its effectiveness include adhesion of the formulation to the mucosa, which could alter the drug concentration and the integrity of the vaginal mucosa,97 and the time elapsed between gel application and sexual intercourse.101 Another factor that has been shown to be important in the efficacy of the...
formulation is systemic innate immune activation prior to infection; one possible mechanism to increase the efficacy of the TFV gel is the addition of a suppressor of innate immune system activation.102

Another family of antiretroviral drugs consists of non-nucleoside reverse transcriptase inhibitors (NNRTIs). These are noncompetitive inhibitors that bind to an allosteric site on the reverse transcriptase and induce conformational changes in the enzyme.103 Various NNRTIs have been studied as microbicides, including DPV and rilpivirine,104–106 and multiple NNRTIs have been specifically designed with the ability to bind more closely to HIV-1 retrotranscriptase, such as MIV-150, a derivate of urea–phenethylthiazolylthiourea,65,103 and UC78, a thiocarboxanilide.103

Several studies have been carried out in macaques using different pharmaceutical forms containing MIV-150, an example of which is the combination of MIV-150 with Carraguard.107 As previously described, Carraguard is a carrageenan gel that showed no efficacy in clinical trials, but has been assessed as a vehicle for antiretroviral drugs in the development of vaginal microbicides.25 In vitro assays demonstrated greater antiretroviral activity of the MIV-150/carrageenan combination compared to Carraguard, and this efficacy was not modified by the presence of seminal fluid.107 However, in vivo assays with this combination ruled out its potential as a microbicide due to the predominance of the barrier effect of Carraguard, which prevented the combination with MIV-150 from being more effective.108 Nevertheless, the MIV-150 in the placebo gel limited vaginal infection, confirming the potential of topical NNRTIs in preventing sexual transmission of HIV.108 Another gel combining MIV-150 and zinc acetate showed protection in animal models against simian–human immunodeficiency virus (SHIV) for 24 hours after vaginal administration, improving the protection achieved when the gel contained only one of the agents.109,110 The MIV-150/zinc acetate/Carraguard combination (MZC) was also evaluated, and was found to provide significant protection in macaques with its pre- and postcoital application.110–114 An in vitro study comparing the efficacy of MZC gel versus 1% TFV gel showed increased activity against SHIV-retrotranscriptase with MZC gel.115 After the promising data shown by this formulation, the first clinical trials were eagerly awaited. The results of the first clinical trial with MZC gel have recently been published, showing that the gel is safe and well tolerated by women.116

DPV is a much studied drug in this group, and has undergone clinical trials as one of the most promising drugs for the development of microbicides to prevent HIV-1 transmission. The studies have demonstrated its in vitro activity to prevent infection even in the presence of semen,117 and further trials in animal models showed that DPV does not irritate the vagina.118 Gels containing this antiretroviral were formulated and evaluated in animal models, and a high concentration of DPV was found in the vaginal tissue after administration.119 The first clinical trials with DPV gel were subsequently performed, demonstrating that its administration is safe and well tolerated by both women120–122 and men.123 Another finding was that much higher concentrations were achieved with the vaginal release of DPV from the gel than were required to achieve HIV inhibition in vitro.121

However, the effectiveness of drugs from this family must be evaluated in women, and especially in continuous prophylactic use, as their main drawback is the rapid development of HIV resistance to these drugs.124

Trend change in microbicide formulation: development of vaginal rings

Although the results obtained in recent years with gels containing reverse transcriptase inhibitors increase the hope of developing a microbicide that will significantly reduce HIV transmission, the creation of an effective vaginal microbicide also implies knowledge of the circumstances of the target population, and transmission prevention strategies must be adapted accordingly.125 This is why much of the current effort focuses on understanding the aspects that govern the effectiveness of microbicides, among which a key factor is considered to be adherence in trials. Strategies must, therefore, be designed to improve adherence and the factors that influence it. These range from supporting the users, assessing their perception of risk and analyzing their social background and relationship problems, including whether or not their partners allow them to use microbicides. As a result, attention has shifted toward the development of formulations that require less commitment from the user to show efficacy, such as sustained drug release formulations.126,127 Since adherence to treatment has been seen as a crucial factor, sustained-release formulations of antiretrovirals, such as vaginal rings, may lead to increased adherence, requiring less frequent application to achieve the necessary efficacy to avoid transmission.127–129

Vaginal rings could, therefore, represent a real alternative, as although they require a higher financial investment and are more complicated to manage, they have the advantage of allowing the sustained release of the drug over time periods of almost a month.130,131 The increase in cost could be significantly offset by the decrease in the number of
applications and the subsequent improvement in adherence to treatment. The mass production of this dosage form is becoming increasingly advanced.

Since TFV has been the only vaginal microbicideto date to demonstrate protective efficacy in clinical trials, a wide range of formulations emerged that sought to improve the initial design in order to achieve effective microbicides that provide greater benefit than 1% TFV gel.132

Silicone133 and polyurethane134 rings containing TFV were formulated, and were able to release the drug for 25–30 days in the in vitro assays. In vivo assays with silicone rings on macaques demonstrated the safety of the formulation, as no adverse effects were observed, and they provided sustained release of TFV for >28 days.135 The polyurethane-based rings were studied in sheep, where a good safety profile was also observed, with the drug release up to 90 days in this case.132

As an alternative formulation, vaginal rings were also developed with tenofovir disoproxil fumarate (TDF), a prodrug of TFV (Figure 3). The in vitro models showed that TDF can inhibit HIV at concentrations hundreds of times lower than TFV, and maintain its antiviral activity in the presence of semen.136 The efficacy of intravaginal rings loaded with TDF was tested in female macaques versus placebo, where the rings showed complete protection against repeated exposure to the virus in the form of weekly exposure for 16 weeks.137 In a similar study, macaques were exposed to the virus vaginally once a week for 12 weeks. All the monkeys treated with the placebo were infected, but only one of the six that received the TDF-loaded ring was infected.137 These results indicate that the TDF ring provides lasting protection even against repeated exposure to the virus. Continuous-use trials of the formulation also showed that following continuous 6-month administration of these rings in macaques, the TFV levels in vaginal tissues and secretions remained constant and no adverse effects were observed.16

Given the excellent results in the animal tests, clinical trials were begun with TDF rings. It has recently emerged from the results of the Phase I trials that their use is safe and well tolerated by women, and that TFV concentrations in the vaginal mucosa from the ring are capable of offering protection against HIV.138

Leveraging the intravaginal ring as an excellent vehicle for multiple drug administration, the combination of TFV and acyclovir was also evaluated to prevent the transmission of the herpes simplex virus,139 or with the addition of levonorgestrel to devise a ring that protected against HIV transmission and also had a contraceptive effect.139

TFV was not the only drug assessed for use in microbical vaginal rings. Another study on the same subject was designed to obtain sustained-release dosage forms of entry inhibitors. This involved pharmacokinetic studies with silicone elastomer vaginal rings containing MVC or CMPD167, two CCR5 receptor inhibitors, which release the active substances in a controlled manner over 28 days. The study showed that in macaques, this formulation could achieve vaginal fluid concentrations of above the inhibitory concentration in 50% of cases (IC50) for both drugs, although the concentration of MVC was significantly higher than in the case of CMPD167.140

However, vaginal rings containing NNRTIs are the most widely studied for preventing the sexual transmission of HIV. The antiretroviral MIV-150 was initially the most commonly used, probably due to the results obtained with the gel.141–143 An intravaginal ring loaded with MIV-150 demonstrated significant protection against SHIV infection in macaques.141 As in the MIV-150 gel, the drug was subsequently evaluated in association with zinc acetate and carrageenan in order to improve the protection offered and reduce the dose of MIV-150, with a view to minimize its toxicity, the development of resistances and the cost of the formulation. These rings demonstrated their ex vivo effectiveness in monkey genital mucosa.144

Other NNRTIs evaluated for the development of vaginal rings are MIV-160,145 UC781146,147 and MC1220.148 The efficacy of the vaginal ring with MIV-160 was compared with a carrageenan gel containing the same drug, but efficacy was observed only with the vaginal ring when the two dosage forms were assessed in vitro, highlighting the importance of choosing the appropriate formulation for the development of vaginal microbicides.145 Poorer results were observed when evaluating UC781 in macaques, as no in vivo correlation was observed with the data obtained in vitro studies due to the poor solubility of the drug.147 In the case of rings containing the drug MC1220, only partial protection against HIV infection was observed in studies with macaques.148

Figure 3 Chemical structure of tenofovir (A) and tenofovir disoproxil fumarate (B).
Based on the results to date, undoubtedly, the most successful drug for use in vaginal rings to protect against sexual acquisition of HIV is another NNRTI, DPV. Vaginal rings were developed that were capable of releasing DPV in a sustained manner for 28–30 days. The materials used in their manufacture (polyurethane, silicone and others) and the type of ring (reservoir type or matrix type) were also assessed to obtain information about their impact on the effectiveness of the formulation (Figure 4). Various safety trials were conducted in women with vaginal rings loaded with DPV, all of which showed safety and good tolerance, in addition to controlled drug release for 28 days, and the ability to obtain far greater DPV concentrations in the genital tract than in the case of IC, against HIV-1.

These excellent results led to the DPV rings undergoing Phase III clinical trials, the furthest stage for any microbicide containing an NNRTI. The ASPIRE Phase III study evaluated the efficacy of a silicone matrix ring containing DPV in African women. Recent results from this study have shown that the DPV ring reduces HIV infection by 27%, and even up to 37%, excluding data from places where adherence was low. It was also noted that efficacy was much greater among women over 21, who also had greater adherence to ring use. Finally, it should be emphasized that there was neither an increase in adverse effects among users nor any development of resistance among the infected women. Another Phase III study with a ring containing DPV, known as The Ring Study, found it reduced the risk of HIV acquisition by 31%. The results of this study coincide with the ASPIRE trial in claiming that the efficacy is much greater in women over 21, suggesting the influence of the physiology of the vaginal tract, a lower adherence to the use of the ring or the frequency of sexual intercourse as potential factors affecting efficacy. This study also coincides with the ASPIRE trial by ruling out the incidence of adverse effects and the development of resistances.

These findings undoubtedly suggest that intravaginal ring delivery of DPV is a viable option for HIV prevention that merits further study, since as in clinical trials with the TFV gel, adherence was once again highlighted as a key factor in the efficacy of HIV prevention.

Development of alternative dosage forms

While initially gels were the pharmaceutical form of choice for vaginal microbicides, and although in recent years vaginal rings have gained acceptance due to their ability to control release over long periods of time, these are not the only dosage forms that have been investigated for this purpose. This variety is necessary because the efficacy of the same antiretroviral drug varies depending on the formulation selected, and because the development of different pharmaceutical forms ensures that women have a wide range of options to protect themselves from the transmission of the virus, and therefore, each user can select the one that best suits her characteristics.

Vaginal tablets

Tablets have the advantage of being easy and economical to manufacture on an industrial scale, easy to handle and stable under different environmental conditions. If the aim is instant protection after administration, fast-dissolving tablets can be obtained depending on the excipients used in their development. Tablets can also be manufactured to release the drug in a sustained manner, enabling controlled drug release and remaining effective for longer, in turn requiring fewer applications and favoring adherence to treatment. One example of this is the tablets made from polymers capable of gelling in the presence of vaginal fluid (Figure 5).

The first references to vaginal tablets to prevent sexual transmission of HIV were of Praneem polyherbal vaginal tablets. Their active ingredient was purified extract of *Azadirachta indica*, which had shown some in vitro activity against HIV. Certain adverse effects such as genital itching or irritation were observed in Phase I clinical trials, but it was concluded that the use of the tablets daily for 14 days was safe and accepted by women. Phase II clinical trials to evaluate their long-term safety concluded that their use for 6 months was equally safe and acceptable. However, failures experienced by other formulations contemporary to these tablets, such as nonoxynol-9 or Carraguard gels, demonstrated the need for further preclinical evaluations to verify their effectiveness, and these tablets ultimately never underwent Phase III trials.

Years later, the idea of developing vaginal tablets for HIV prevention was revisited, with the key candidates...
being the antiretroviral drugs that had proved most successful in other pharmaceutical forms. TFV vaginal tablets were found, alone or in combination with emtricitabine, another NRTI, to achieve similar concentrations of TFV in the vaginal environment to the 1% TFV gel, and proved effective in clinical trials.\(^{14,76,165}\) Vaginal tablets\(^ {166}\) and lyophilized gels\(^ {167}\) containing DPV, the other drug shown to be effective in clinical trials, have also been developed.

However, these tablets were intended for daily application, or for use in a coitus-dependent manner in the case of immediate-release tablets, so the trend toward pharmaceutical forms capable of releasing the drug for several days led to the abandonment of these tablets.

More recently, we have seen the emergence of some alternatives such as osmotic tablets with IQP-058, which have shown an ability to achieve high levels of the drug in the vaginal mucosa for 10 days (Figure 6).\(^ {168}\) Lastly, current research is exploring the possibility of manufacturing controlled-release TFV vaginal tablets formulated with mucoadhesive polymers – such as carrageenan, chitosan or cellulose derivatives – that have high binding capacity to the mucosa for significant periods of time. Several studies include these polymers in vaginal formulations to increase their dwelling time at the site of action. If these formulations were to include a suitable mucoadhesive polymer or a polymer mixture, an optimum formulation could be developed for the controlled release of the drug in the area where HIV transmission occurs.\(^ {76}\)

**Vaginal films**

Quick-dissolving films are promising and attractive dosage forms that may provide an alternative platform for the vaginal delivery of microbicide drug candidates. These are thin strips of water-soluble polymers that dissolve when they are placed in the vaginal mucosa, releasing the active ingredient.\(^ {159}\) Vaginal films have advantages such as discreet use, no product leakage during use, not requiring an applicator for insertion and offering rapid drug release with minimal packaging and reduced waste.\(^ {169}\) Some of the possible disadvantages after administration are local irritation and influence on sexual intercourse. It should also be noted that their large-scale production today would be more complicated than the options described above, not because of the cost of the materials required, but because of the underdevelopment of the production resources. Women’s preferences regarding the physicochemical characteristics of these films have been evaluated, and according to one study, they prefer smooth, thin, translucent, square films.\(^ {170}\)

The history of films as microbicides to prevent sexual acquisition of HIV began in a similar way to gels, since the first references found date from the 1990s, with vaginal films containing the spermicide nonoxynol-9. As with the gel, trials in women showed that continued use of nonoxynol-9 did not block HIV transmission and produced lesions in the vaginal tract that may increase the sexual transmission of STIs.\(^ {171,172}\)

Sometime after the failure of nonoxynol-9, films were developed containing other substances with potential activity
against HIV, such as sodium polystyrene sulfonate\textsuperscript{173} and RC-101,\textsuperscript{174} although none of them reached clinical trials.

Recent years have seen a growing interest in the development of microbical vaginal films, now produced with the incorporation of antiretroviral drugs. Films can be found incorporating NRTIs, such as a hydroxypropyl methylcellulose (HPMC) film containing abacavir, evaluated in vitro and in vivo in rabbits, and which has proven to be nonirritating to the vagina and capable of releasing the drug.\textsuperscript{175,176} 4′-Ethynyl-2-fluoro-2′-deoxyadenosine is another NRTI that has been incorporated into films made with HPMC and polyvinyl alcohol (polyvinylpirrolidone [PVP]), both alone\textsuperscript{177} and combined with 5-chloro-3-phenylsulfonylindole-2-carboxamide.\textsuperscript{178} In vitro studies on these formulations corroborate their potential to inhibit HIV transmission.

Research has also been done on NNRTIs incorporated in vaginal films, of which DPV is unsurprisingly the most studied. These DPV-loaded films have been shown to prevent HIV-1 infection in vitro and ex vivo and have acceptable characteristics.\textsuperscript{180} Recent Phase I clinical trials have demonstrated their safety and ability to release the drug and attain sufficient concentrations in the vaginal tissues to block HIV activity.\textsuperscript{179} Further studies are thus awaited to evaluate the effectiveness of the formulation.\textsuperscript{180}

There are also microbicidal films containing other NRTIs, such as a polyvinyl alcohol (PVA) film with the pyrimidine-4′-edione IQP-0528\textsuperscript{181} and an HPMC and polyethylene glycol (PEG) 400 film with the antiretroviral UAM01398.\textsuperscript{182}

### The future of microbicides

#### Growing interest in nanosystems: nanomicrobicides

The high versatility of nanoparticles, which have transformed several fields of biomedical science, has led to intense research activity in this area in recent years.\textsuperscript{183} These nanoparticles can be made using both inorganic materials and a wide variety of biodegradable and biocompatible polymers.

Thanks to their small size, they are able to internalize in cells and release the drug directly to the cytosol.\textsuperscript{184} Their large surface area improves the dissolution and absorption of slightly soluble drugs, and also allows optimization of these nanoparticles according to their functionalization; they can bind to specific targets by multivalent conjugations and attach at the drug release site.\textsuperscript{183–185} However, the complexity of the equipment required to obtain particles of this size would increase the cost of the formulation.

These nanosystems can either exhibit HIV inhibitory activity by themselves or serve as a vehicle for drug delivery.\textsuperscript{183}

Recent research has focused on the possibility of developing microbicides based on nanoparticles for HIV prevention. These nanoparticles consist of crosslinked polymer chains formed thanks to crosslinking agents, creating a structure within which to load the drug (Figure 7).

Their small size means that some of these particles can interact directly with HIV. In vitro viral adhesion has been observed with silver nanoparticles, and silver-coated PVP nanoparticles have demonstrated antiviral activity ex vivo at nontoxic concentrations.\textsuperscript{186} This adhesion could be applicable to other noble metals such as gold.\textsuperscript{187} The same researchers demonstrated the additive effect of the antiviral activity of silver nanoparticles when used in combination with monoclonal antibodies.\textsuperscript{188}

Another option is to load nanoparticles with antiretroviral drugs, of which the most common are again TFV and DPV. For example, solid lipid nanoparticles of polylysine–heparin loaded with TFV have been shown to improve the cellular internalization of the microbicide and are not cytotoxic.\textsuperscript{189} In the case of DPV, there are several references for nanoparticles based on polycaprolactone (PCL).\textsuperscript{190,191} Other researches focused on developing nanoparticles of poly(D,L-lactic-co-glycolic acid) (PLGA) loaded with DPV, a formulation that has interesting technological and biologic characteristics for use in safe and effective vaginal microbicides. These nanoparticles are capable of releasing the drug for 24 hours at both pH 4.2 and 7.4, and their cytotoxicity is no higher than that of the free drug.\textsuperscript{192} Another NNRTI evaluated for the prevention of sexual transmission of HIV is rilpivirine. PLGA nanoparticles have been developed with this drug and incorporated in a thermo-sensitive gel capable of offering significant protection against HIV-1 in mice.\textsuperscript{106} However, most efforts to prevent HIV with rilpivirine do not focus on vaginal administration,

![Figure 7 Structure of a drug-loaded polymer nanoparticle.](https://example.com/figure7.png)
but on the intramuscular administration of long-acting rilpivirine.\textsuperscript{104,105}

Once a nanogel that can retain the drug during loading and release it in a sustained way has been obtained, it is sometimes necessary to fit another set of parameters to affect the time of permanence of the nanoparticles and their concentration in the place they are required to exert their action.\textsuperscript{193} The mucoadhesion can be changed by modifying the nanoparticle surface, for example, as in the case of chitosan nanoparticles loaded with TFV, which were coated with sodium triphosphate pentabasic to improve their mucoadhesion.\textsuperscript{194} When these particles were made with a mixture of chitosan and thioglycolic acid, the mucoadhesion was even higher.\textsuperscript{195}

Other modifications to the surface of the nanoparticles aim to improve their internalization in the vaginal mucosa. For example, PCL nanoparticles loaded with DPV have been developed and coated to assess how the surface charge affects their internalization in a simulated vaginal fluid medium incorporating mucin. The results of this study suggest that negatively charged particles are more suitable for the release of DPV into the vaginal mucosa, as they were able to pass through the medium much faster than positively charged particles.\textsuperscript{196} Their ability to internalize in the cells was evaluated, and was observed to be greater than in the case of uncharged particles; there was also a correlation between the increase in intracellular drug release and antiviral activity.\textsuperscript{190,191,197}

Finally, the nanoparticle surface can also be modified to increase its concentration at the site of action. Specific ligands are added to the surface and find their target at the drug’s action site, allowing them to be retained and release the drug when they reach the target.\textsuperscript{193} PLGA nanoparticles loaded with the antiretroviral drug saquinavir have been conjugated to the anti-CD4 antibody. The nanoparticles thus bind to the CD4\textsuperscript{+} immune cells and the drug is specifically released inside them.\textsuperscript{198}

Stimuli-sensitive materials are of significant interest in obtaining nanoparticles, since their physical and chemical nature can be modified in response to external stimuli such as pH or temperature. Nanoparticles of PLGA and methacrylic acid copolymer (Eudragit\textsuperscript{S} S-100) have been loaded with TFV and are capable of releasing the drug in a pH-dependent manner in the presence of seminal fluid.\textsuperscript{199} Another example of release in response to stimuli is the nanoparticles of hyaluronic acid loaded with TFV, which release the drug in the presence of semen due to the degradation of hyaluronic acid in the presence of the enzyme hyaluronidase.\textsuperscript{200}

An alternative option is to include the nanoparticles in a stimuli-sensitive dosage form, such as temperature-sensitive gels that are liquid at room temperature, convenient to apply and gain consistency at body temperature, thus avoiding vaginal seepage after application and maintaining the nanoparticles in contact with the mucosa for longer. Formulations with PLGA nanoparticles loaded with TFV\textsuperscript{201} or with rilpivirine\textsuperscript{106} have been developed using these gels.

After manufacturing the nanoparticles, they must be properly formulated to develop vaginal microbicides that women can apply easily. The most common dosage form is as a gel, but the inclusion of nanoparticles in polymer films has recently been evaluated.\textsuperscript{202} The advantages of nanoparticles combine with the benefits of the films described above; examples of this are PVA films incorporating nanoparticles loaded with small interfering RNA.\textsuperscript{203} The incorporation of nanoparticles loaded with TFV or efavirenz into a film based on HPMC, PVA and glycerine was also evaluated,\textsuperscript{204} and was found to produce sustained release of the drug for 24 hours and was found to be safe at in vivo trials.\textsuperscript{205} Finally, it is worth mentioning another similar case in which PLGA nanoparticles were loaded with another antiretroviral, IQP-0528, and incorporated into a fast-dissolving film.\textsuperscript{206}

For all these reasons, despite the current scarcity of microbicides based on nanosystems for the prevention of HIV, coming years will see a boom in research in this field, since nanoparticles provide a delivery strategy for targeted and controlled delivery of drugs to the vagina.\textsuperscript{183,185}

**Novel dosage forms: electrospun fibers**

Although research based on more traditional pharmaceutical forms continues to be the main route for the development of vaginal microbicides, other less widely studied alternatives have been gaining importance in recent years and could offer a therapeutic alternative.

A recent new pharmaceutical form consists of drug-loaded polymer fibers known as electrospun fibers, which are produced by electrospinning, a technique that applies electrostatic forces to form polymeric fibers (Figure 8).\textsuperscript{207} Polyglycolic acid, polylactic acid, PCL and PLGA are the most common polymers used in their manufacture.\textsuperscript{208}

Unlike nanoparticles, which can internalize in the cells and release the drug, the fibers can only control the release of the drug through erosion and degradation of the polymer and diffusion of the incorporated drug. These materials offer an alternative to existing microbicides, as they can quickly – in <15 minutes – release the active ingredient in wet areas, especially if they contain a wetting agent as a carrier.\textsuperscript{207,209}
The development of an effective microbicidal in this formulation would be a useful tool for preventing HIV transmission, since its application prior to sexual relations would provide almost immediate protection. However, polymers that take longer to degrade in the vaginal medium can also be used in order to achieve sustained release of the drug, in some cases with over 7 days of sustained release. As in the case of nanomicrobicides, a significant financial investment is required to purchase the equipment needed to obtain these formulations.

Some examples of vaginal microbicicides formulated as electrospun fibers include TFV. PVA nanofibers loaded with this antiretroviral are capable of releasing 95% of the drug within 5 minutes in vitro studies at a pH of both 4.3, equivalent to the pH of vaginal fluid, and 7.4, equivalent to the pH of seminal fluid. Stimuli-sensitive, TFV-loaded nanofibers have also been developed based on thiolated hyaluronic acid, which release the drug only in the presence of semen, when the polymer degrades in the presence of the seminal hyaluronidase enzyme.

Other nanofibers have incorporated antiretrovirals with a different mechanism of action, such as MVC, an entry inhibitor. A new study formulated electrospun solid dispersions of MVC with PVP or with poly(ethylene oxide). In the MVC in vitro release assays, 95% of the dose was released in 14 minutes when it was included in PVP fibers and in 18 minutes with the poly(ethylene oxide) fibers. When these electrospun fibers were manufactured with the addition of Tween 20 as a wetting agent, drug release was accelerated and at least 95% of the drug was released within 6 minutes. As a variant of these MVC-loaded PVP fibers, more recently, PVP fibers in coaxially electrospun fibers were coated with ethyl cellulose, achieving sustained release of MVC for up to 120 hours.

Finally, to highlight the rise of this new dosage form, it is worth noting that other antivirals are also being evaluated for this form of delivery, such as the recent development of electrospun nanofibers with griffithsin, which has shown in vitro efficacy against HIV-1 infection.

This formulation could represent a major step forward in the development of vaginal microbicides, since it could improve their adherence regardless of their release rate. Rapidly dissolving electrospun fibers could offer immediate protection against the virus, and their use would be coitus dependent, so their administration would only be required prior to sexual intercourse. Fibers capable of delivering sustained release of the drug over several days would also offer a therapeutic advance in terms of adherence, since although the administration is coitus independent, daily applications would not be required.

**Genetically modified microorganisms: microbicidal probiotics**

Although the potential of microbicidal probiotics as microicides is still controversial, they are rapidly gaining acceptance. They work by promoting vaginal colonization by genetically modified microorganisms that can express molecules capable of inhibiting HIV. This strategy would require a high initial investment to genetically modify the microorganisms, but the possibility of these bacteria colonizing the vaginal medium would provide lasting protection that could offset such a substantial investment.

Currently under study are bacteria from the genera *Lactobacillus* and *Bifidobacterium*, common in the human vaginal microbiota, to determine whether these genetically modified microorganisms are stable, adhere and persist in the vaginal mucosa and produce the compound of interest in sufficient and sustained concentrations to inhibit the virus without damaging the normal balance of the vaginal microflora.

A strain of *Lactobacillus jensenii* has been developed that is capable of colonizing mice vaginas and producing high levels of CV-N for long periods of time. The same bacterial strain was studied in macaques, where it was demonstrated that its use is not only safe, but can also have a positive impact on the vaginal environment. A subsequent...
study showed that macaques colonized with this bacterium had a significant reduction in the transmission of a chimeric simian-HIV strain (SHIV-SF162P3).219 The safety and toxicity of this strain have also been evaluated, as these are the most contested aspects when using probiotics as microbicides. In vivo tests on macaques have shown that their use is not only safe, but could also have a beneficial impact on the vaginal environment, with lower levels of inflammation in the macaques retaining this strain.218 Another therapeutic alternative explored by the authors of these studies is the modification of this strain to express fragments of antibodies against HIV on its surface.220

Although there is still a need for more studies on the subject, this strategy undeniably represents an important step in the development of a lasting and inexpensive microbicide to block sexual transmission of HIV in women.

**Broadening the spectrum of microbicides: combining drugs with different mechanisms of action**

Following the successful combination of antiretroviral drugs for the treatment of HIV infection, strategies for microbicide development today involve designing dosage forms that combine drugs with different mechanisms of action which are released simultaneously in order to boost the effectiveness of the protection.

One widely studied combination is TFV, antiretroviral NRTI and DPV, an NNRTI, which have been used to develop polymeric films15,221 and intravaginal polyurethane rings.18 It was observed in ex vivo studies on the films that the coadministration of the two drugs caused a higher concentration of DPV in the tissue, whereas TFV was not affected. In the case of vaginal rings, both drugs were seen to be released together in vitro for 30 days.

Another well-studied combination is of DPV with the entry inhibitor MVC. Although films have also been developed that combine these two drugs,15 this combination has been studied mainly for use in vaginal rings, since its objective is to improve the protection offered by successful DPV rings. After evaluating the combination of DPV with different amounts of MVC, a ring with 25 mg of DPV and 100 mg of MVC was selected for clinical trials.222 Phase I trials demonstrated that the rings were safe and well tolerated,223 but the plasma concentration of DPV was much higher when the ring contained both drugs than when it included only DPV. However, detectable concentrations of MVC were found only in cervicovaginal fluid, but not in plasma.224

Another option is the combination of TFV and MVC, used to develop intravaginal rings,225 films15 and even more novel formulations such as nanolipogels–nanoparticles whose core is a hydrogel wrapped in a lipid shell.226

Although TFV, DPV and MVC are the most commonly used drugs in antiretroviral combinations, alternative combinations of other active substances have also been evaluated, such as PLGA nanoparticles loaded with raltegravir and efavirenz, which are subsequently included in a thermosensitive ethyl cellulose gel.227

These studies demonstrate that combinations of antiretrovirals capable of inhibiting HIV transmission have potential as prevention strategies against sexual transmission of the virus.

There are a large number of vaginal microbicide formulations currently under investigation. Table 2 summarizes

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Microbicide</th>
<th>Pharmaceutical form</th>
<th>Animal tests</th>
<th>Clinical trials</th>
<th>Current status</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surfactants</td>
<td>Nonoxynol-9</td>
<td>Gel</td>
<td>–</td>
<td>Not safe</td>
<td>Rejected</td>
<td>20, 24</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Film</td>
<td></td>
<td>Not effective</td>
<td></td>
<td>171, 172</td>
</tr>
<tr>
<td>Savvy gel®</td>
<td></td>
<td>Gel</td>
<td>–</td>
<td>Safe</td>
<td>Rejected</td>
<td>21, 23</td>
</tr>
<tr>
<td>Acidifier</td>
<td>BufferGel®</td>
<td>Gel</td>
<td>–</td>
<td>Safe</td>
<td>Not effective</td>
<td>32, 33</td>
</tr>
<tr>
<td>Polyanions</td>
<td>Carraguard®</td>
<td>Gel</td>
<td>–</td>
<td>Safe</td>
<td>Its use as a carrier is being assessed</td>
<td>25–28, 30</td>
</tr>
<tr>
<td></td>
<td>PRO 2000®</td>
<td></td>
<td>Safe</td>
<td>Not effective</td>
<td>Safe</td>
<td>32, 33, 35–37</td>
</tr>
<tr>
<td></td>
<td>VivaGel®</td>
<td></td>
<td>Safe</td>
<td>Not safe</td>
<td>Rejected</td>
<td>38–46</td>
</tr>
</tbody>
</table>

(Continued)
some of these and shows only those for which references to clinical trials or at least in vivo studies have been found. The different mechanisms of action and the various pharmaceutical forms give a clear picture of the benefits and drawbacks of each microbicide, and highlight the advances in these formulations. The ultimate goal is to achieve a vaginal microbicide that is lasting, safe, highly efficient and economical, in order to ensure protection of women against the acquisition of HIV.

**Conclusion**

On the basis of the above, it can be concluded that microbicides are a promising tool for the prevention of sexual transmission of HIV, although there is still a long way to go. The large number of microbicides tested in the last two decades have produced more failures than successes, but it is crucial to learn from the mistakes in ineffective formulations to develop an effective vaginal microbicide.

In the short term, microbicides based on reverse transcriptase inhibitors, such as TFV gel or DPV vaginal rings, are at a more advanced stage of development and have yielded the best results to date. It is imperative to continue the research into the potential of these drugs, so that other pharmaceutical forms can be developed to ensure women have multiple options for protecting themselves against infection with the virus.

In the long term, it is worth assessing other microbicides whose clinical application is currently far down the line, either because they are at an earlier stage of development – such as products created by nanotechnology, electrospun...
solid dispersions or genetically modified microorganisms – or owing to the need to overcome certain barriers such as high cost, lack of adherence or difficulty in maintaining sustained concentrations.

Acknowledgment
This study was funded by the project MAT2012-34552 from the Spanish Ministry of Economy and Competitiveness (MINECO) entitled, “Mucoadhesive formulations for the sustained release of vaginal microbicides for the prevention of sexually transmitted diseases”.

Authors’ contributions
RRC and MDVO were responsible for the approach to this work, and all the authors participated in the design. FNP wrote the article, and MDVO and RRC conducted a critical review with important intellectual contributions. All three authors have approved the final version for publication.

MDVO, on behalf of the other signatories, guarantees the accuracy, transparency and truthfulness of the data and information contained in the study, and also that no relevant information has been omitted, and that all discrepancies between authors have been adequately resolved and described.

Disclosure
The authors report no conflicts of interest in this work.

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