

# Microbicides and their potential as a catalyst for multipurpose sexual and reproductive health technologies

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There is an urgent need for technologies to prevent sexual acquisition of HIV infection in young women in sub-Saharan Africa. After two decades of 11 pivotal trials of seven products, anti-retroviral-based topical microbicides are showing promise. Building on the CAPRISA 004 trial findings, several trials of new anti-viral agents, novel delivery mechanisms and combination/

multipurpose products that address challenges of adherence and meet the sexual and reproductive health needs of men and women, including preventing HIV infection, are underway.

**Keywords** HIV prevention, microbicide, tenofovir gel, women.

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## What are microbicides?

Microbicides are vaginally or rectally applied chemical products designed to prevent the sexual acquisition of HIV. Similar to the range of available fertility control options, an array of microbicides will possibly be available in the future that could be formulated as gels, creams, suppositories, films, sponges, tablets, physical barriers, implants and vaginal rings, that would enable men and women to choose products that suit them best at a particular time in their life course to meet their sexual and reproductive health needs.

## Why is the development of microbicides important?

Since 2001, substantial progress in slowing the HIV epidemic has been made globally, with a 33% decline in the number of new HIV infections from 3.4 million in 2001 to 2.3 million in 2012.<sup>1</sup> The majority of new HIV infections are taking place in five key populations; young women in southern Africa, transgender and men who have sex with men (MSM) in Africa, North America and Latin America, injecting drug users in Eastern Europe, male and female sex workers, and prisoners throughout the world. The scale-up and access to anti-retroviral therapy has drastically

reduced AIDS-related mortality between 2005 and 2012.<sup>1</sup> Anti-retroviral therapy has also been shown to have the added benefit of preventing transmission of HIV in discordant couples<sup>2</sup> and use of anti-retroviral drugs by HIV-infected pregnant women intrapartum and postpartum has virtually eliminated vertical transmission of HIV in some parts of the world.<sup>3</sup> Daily use of anti-retrovirals as pre-exposure prophylaxis (PrEP) by HIV-uninfected individuals has also been shown in clinical trials to reduce acquisition of HIV among serodiscordant couples, MSM and injection drug users.<sup>4–6</sup> Together with existing prevention options, these advances provide new hope for control of the HIV epidemic.

Despite these successes, the development of microbicides remains an important goal, especially for populations most severely affected by the HIV epidemic. For example, in sub-Saharan Africa, while women account for 60% of all HIV infections, young women aged 15–24 years represent 76% of the total cases. In addition to the high burden of HIV infection, young women typically acquire HIV infection 5–7 years earlier than their male counterparts<sup>7,8</sup> and HIV infections among women can be as much as eight-fold higher than in men of the same age.<sup>9</sup> This age–sex difference in HIV acquisition patterns between men and women is a consequence of young women partnering with older

men and is an important driver of the epidemic in this region.<sup>10</sup> Reducing the high infection rates among young women is key to controlling the epidemic in this region. Unfortunately, young women have limited ability to implement the current and new HIV prevention options that are dependent on use by their sexual partner. Microbicides therefore fill an important gap in HIV prevention options for young women and will be central to achieving the goal of an AIDS-free generation.

Furthermore, microbicides could also be used rectally and have the potential to expand the HIV prevention options available to men who have sex with men (MSM) and meet the needs of women who participate in anal sex. In countries like the USA, bisexual and other MSM are more severely affected by HIV than any other group. In 2010, 63% of all new HIV infections occurring in the USA were among MSM, yet they account for only 4% of the total male population in the USA.<sup>11</sup> New HIV infections are increasing most rapidly among young black MSM between the ages of 13 and 24 years. Between 2008 and 2010 there was a 22% increase in new HIV infections in this population group.<sup>11</sup>

## History of microbicide effectiveness trials

### Clinical trials of surfactants

Over the past 20 years of microbicide development, 11 advanced clinical trials of seven candidate products (some tested as multiple doses and formulations) have been completed. The first microbicide candidate tested for its HIV prevention potential was an existing licensed vaginal contraceptive known as nonoxynol-9 (Advantage 24; Columbia Research Laboratories, Rockville Center, NY, USA). This product was categorised as a surfactant and inactivated pathogens, including HIV, in the lumen of the vagina by disrupting cell surfaces. Sponge, film and gel formulations of nonoxynol-9 were assessed<sup>12–14</sup> but none of these were shown to reduce the acquisition of HIV. In fact, the gel formulation of nonoxynol-9 was actually shown to be harmful and almost doubled the risk of HIV infection among women who used more than 3.5 applicators per day.<sup>12</sup> Another surfactant, SAVVY<sup>®</sup> (C31G, Cellegy Pharmaceuticals Inc., Huntingdon Valley, PA, USA), was assessed in two separate trials in Africa and although it was shown to be safe, it did not prevent HIV acquisition.<sup>15,16</sup> Given the disappointing clinical trial results with surfactants, these products are no longer considered viable candidates for HIV prevention.

### Clinical trials of blockers

Products that interfere with the attachment of HIV to the host cells (blockers) were the next category of microbicide

candidates assessed. These included cellulose sulphate (Ushercell<sup>™</sup>; Polydex Pharmaceuticals, Nassau, Bahamas), Carraguard<sup>®</sup> (product number PDR98-15; FMC, Philadelphia, PA, USA), and PRO 2000<sup>®</sup>. The cellulose sulphate trial was halted prematurely because an interim analysis suggested that the product may have increased the risk of acquiring HIV.<sup>17</sup> Final analysis, however, showed that cellulose sulphate had no effect on HIV acquisition.<sup>17</sup> Carraguard<sup>®</sup> was shown to be safe but had no impact on HIV—HIV incidence was 3.3 per 100 woman-years in the Carraguard group and 3.8 per 100 woman-years in the placebo group.<sup>18</sup> In 2009, the HPTN 035 study showed a moderate, although nonsignificant, 33% lower HIV incidence in women using 0.5% PRO 2000<sup>®</sup> compared with placebo.<sup>19</sup> However, a much larger trial, the MDP 301 trial, subsequently showed that 0.5% PRO 2000<sup>®</sup> had no protective effect against HIV infection.<sup>20</sup>

### Clinical trials of buffers

Products designed to maintain a healthy vaginal milieu (buffers) were the next category of microbicides to be assessed. These products were designed to supplement or enhance the natural immune defences of the vagina by helping to maintain a low pH. By maintaining a low pH it is thought that pathogens that are sensitive to acidic environments can be inactivated. The best known product in this category was BufferGel<sup>®</sup> (ReProtect LLC, Baltimore, MD, USA), which was tested alongside 0.5% PRO 2000<sup>®</sup> in the HPTN 035 trial, but also had no impact on HIV acquisition.<sup>19</sup>

### Clinical trials of anti-retroviral agents

The current category of microbicides that are being assessed in last-stage clinical trials includes anti-retroviral agents that inhibit specific steps in the HIV life cycle. These compounds generally have potent anti-HIV-specific activity and a long half-life but need to be used correctly and consistently to work. Topical formulations of anti-retrovirals have the added advantage of acting locally in the genital tract, resulting in high concentrations of drug at the site of infection (i.e. the genital tract), and reducing potential systemic adverse effects. Tenofovir gel, developed by Gilead Sciences, was the first anti-retroviral drug that was shown to significantly reduce the risk of both HIV and herpes simplex virus type 2 (HSV-2) acquisition in women. In 2010, the Centre for the AIDS Programme of Research in South Africa (CAPRISA) 004 tenofovir gel trial showed that HIV acquisition was reduced by 39% and HSV-2 acquisition by 51% when tenofovir gel was used before and after sex.<sup>21</sup> Despite these very encouraging results, even with high levels of adherence, tenofovir gel was shown to provide only 54% protection<sup>21</sup> and in women with detectable drug levels of >1000 ng/ml tenofovir gel's effectiveness

reached 74%.<sup>22</sup> These findings suggest that other factors may be contributing to the suboptimal efficacy of tenofovir gel. Understanding what biological factors could be contributing to the reduced potency of tenofovir gel is important. Notwithstanding continued efforts to unravel this bio-behavioural nexus, modelling these findings demonstrates that tenofovir gel could potentially avert 1.3 million new HIV infections and over 800 000 deaths in South Africa over the next 20 years.<sup>23</sup>

The optimism that a safe and effective microbicide would soon be available was dampened by the outcome of the VOICE (Vaginal and Oral Interventions to Control the Epidemic) trial. This trial, which evaluated daily dosing of tenofovir gel, demonstrated an effectiveness level of 14.7% (95% confidence interval -21 to 40).<sup>24</sup> The lack of protection was primarily due to the low levels of adherence; estimated, based on detectable drug levels, to be 23%.<sup>24</sup> The outcome of the FACTS 001 trial,<sup>25</sup> which is currently in the field across multiple sites in South Africa, that was designed to confirm the CAPRISA 004 trial findings could provide the data needed for regulatory approval of tenofovir gel. An open label implementation effectiveness study (CAPRISA 008) is underway in the communities where the CAPRISA 004 trial took place and addresses critical implementation questions about how best tenofovir gel could be incorporated into current health systems and could pave the way to more rapid public sector access of a licensed product.

### Microbicide candidates in development or planned that have potential to meet multiple sexual and reproductive health needs

Although there are over 70 microbicide candidates in the preclinical development pipeline,<sup>26</sup> the majority of these products will never reach clinical trial testing in humans. The number of products currently in human trials is actually very limited and includes: probiotics like lactobacilli and six anti-retroviral agents—tenofovir, dapivirine, maraviroc, MIV-150, GSK 744 and rilpivirine.

While initial microbicides were evaluated for their anti-HIV activity as well as for fertility control and prevention of bacterial sexually transmitted infections, over time the priority focus was on HIV prevention. With increasing anti-HIV-specific products in testing and some proof of concept there has been renewed interest in the development of co-formulated and co-administered products that are capable of simultaneously meeting multiple sexual reproductive health needs of women such as HIV risk reduction, fertility control and treatment of other sexually transmitted infections. Microbicides that are based on a combination of products are seen as offering a potential for synergy,

reduced drug resistance and multiple targeting. Although barrier devices like condoms are considered multipurpose prevention technologies, only potential microbicide or PrEP candidates are discussed in this paper.

Lactobacilli, which occur naturally in the vagina and help to maintain a low pH by secreting lactic acid, are promising microbicide candidates. Phase 2 studies have demonstrated that *Lactobacillus crispatus* (LACTIN-V) is safe and well tolerated among women with bacterial vaginosis<sup>27</sup> and in a separate study, the product has been associated with a significant reduction in recurrent uterine tract infections.<sup>28</sup> Another promising probiotic candidate is a live recombinant *Lactobacillus*, *L. jensenii*, which has been shown in a macaque model to reduce simian immunodeficiency virus (SIV) transmission by 63% and may proceed to human testing soon.<sup>29</sup>

Tenofovir gel, which was shown to prevent both HIV and HSV-2,<sup>21</sup> is the microbicide in the most advanced stage of development. In addition to the FACTS 001<sup>25</sup> confirmatory trial and the CAPRISA 008 tenofovir gel implementation effectiveness trial, a number of trials of tenofovir gel are ongoing. A rectal safety study of tenofovir 1% gel in young MSM in the USA and Puerto Rico (Project gel)<sup>30</sup> and a range of pharmacodynamics and pharmacokinetic studies of various dosing strategies using tenofovir,<sup>31</sup> a study of reformulated tenofovir gel for rectal use,<sup>32</sup> and a safety study of tenofovir 1% gel use in pregnant and lactating women<sup>33</sup> are also ongoing. An intravaginal ring containing the tenofovir disoproxil fumarate prodrug has been developed by CONRAD. Preclinical studies have been completed and demonstrate that the tenofovir-containing intravaginal ring provided complete protection in pigtail macaques after repeat simian human immunodeficiency virus challenge over 16 weeks,<sup>34</sup> even in the presence of high doses of the hormonal contraceptive depot medroxyprogesterone<sup>35</sup> and the tenofovir ring may soon enter clinical trials.

Besides tenofovir, other anti-retroviral agents being assessed as candidate microbicides include dapivirine (TMC120), miraviroc, MIV-150 and rilpivirine (TMC278). Dapivirine is being developed by the International Partnership for Microbicides (IPM) and is currently being evaluated for efficacy in parallel by IPM and the Microbicide Trials Network as a monthly vaginal ring.<sup>36,37</sup> These long-acting, slow-release, monthly vaginal rings may potentially improve adherence because they are less dependent on user compliance compared with oral or gel formulations. A safety and pharmacokinetics study of a vaginal ring that includes a combination of dapivirine and maraviroc is currently underway in the USA.<sup>38</sup> The combination of multiple anti-retroviral agents in a single application mirrors the progressive advances in AIDS treatment regimens that combine anti-retroviral agents from different classes and could potentially increase their efficacy.

The Population Council is developing MIV-150 in combination with zinc acetate, a broad-spectrum anti-viral agent, in a base of carrageenan for the prevention of HIV and HSV-2 infection. In macaques, a single dose of this gel has been shown to provide protection against vaginal SIV infection for up to 24 hours,<sup>39</sup> and a phase 1 trial of this gel has been completed. The Population Council are also developing intravaginal rings with combinations of MIV-150, zinc acetate and the contraceptive levonorgestrel and human trials of these products are scheduled to start soon.

Long-acting injectable agents are also being developed as potential PrEP/microbicide agents. Janssen Research & Development, LLC (Raritan, NJ, USA) is currently assessing the safety, acceptability, pharmacokinetics and *ex vivo* pharmacodynamics of a long-acting formulation of rilpivirine (TMC278), administered intramuscularly monthly, in men and women.<sup>40</sup> GSK1265744 (GSK '744), a long-acting integrase inhibitor, is also being developed through a joint venture between GlaxoSmithKline, (Brentford, Middlesex, UK) and ViiV Healthcare (Brentford, Middlesex, UK). GSK '744 has been evaluated in phase I trials as a once monthly injection and has been shown to be well tolerated.<sup>41</sup> It may be possible to co-administer these long-acting injectable agents with injectable contraceptives.

Several anti-retroviral agents, including tenofovir, MIV-150, dapivirine, vicriviroc and MK-2048, are being considered for co-formulation with contraceptives to simultaneously prevent unintended pregnancies and HIV. One challenge in offering dual HIV–fertility control options is the uncertainty relating to the role of hormonal contraceptives on HIV acquisition.<sup>42</sup> Some studies have shown that women using injectable hormonal contraception, particularly Depo-Provera<sup>®</sup> (Pfizer, New York, USA), may be at an increased risk for HIV acquisition,<sup>43,44</sup> yet other studies have found no association.<sup>45,46</sup> With the available evidence, it is not possible to conclude that hormonal contraceptive use does or does not increase the risk of HIV acquisition. However, given the uncertainty of the association between hormonal contraceptive use and HIV risk, the use of other nonhormonal contraceptive options like intrauterine devices may increase in future clinical trials. Other nonhormonal contraceptive options are also being considered for combination with anti-retroviral agents, for example the BioRing.<sup>47</sup>

Clinical trials are also ongoing or planned to evaluate the potential of combining a barrier device, for example the SILCS diaphragm, Duet<sup>™</sup> or Device for Vaginal Delivery (DVD2), with tenofovir and other anti-retroviral agents.<sup>48</sup> Mapp Biopharmaceutical, Inc. (San Diego, CA, USA) plan to develop a vaginal ring or film that will incorporate monoclonal antibodies to prevent HIV and HSV-2 while Osel (Mountain View, CA, USA) are developing a novel microbicide suppository known as MucoCept that

contains *Lactobacillus* and cyanovirin-N for the prevention of HIV, bacterial vaginosis, candidosis and uterine tract infections.<sup>47</sup>

Although the development of microbicide candidates with multiple mechanisms of action and dual purpose products are already in early clinical trials, no products have advanced to clinical effectiveness trials. The development of products that target multiple sexual and reproductive health needs face some additional challenges besides the development of a single product. Specifically, the pharmacokinetic actions of different chemical compounds may require different conditions for formulation and release. Furthermore, drug interaction between two or more active pharmaceutical ingredients combined in one product could impact on product safety and efficacy. Ensuring the simultaneous release/bio-availability of two or three different active pharmaceutical ingredients for different indications will also be challenging. Multipurpose technologies also face an uncertain regulatory pathway.

## Challenges in microbicide development

The development of a safe and efficacious microbicide has proved challenging. The field has faced numerous setbacks and rapid advancement has been hampered by limited investments in the development of candidate products for clinical testing, formulation and delivery method challenges, methodological, ethical and design challenges, lack of a validated animal model, lack of a correlate of protection, a limited understanding of mechanism of HIV acquisition in the female genital tract, insufficient advocacy efforts, and uncertainty about user acceptability and demand. Some of these challenges are elaborated below.

### Financial commitment for microbicide research and development

Securing sufficient funding and enthusiasm for microbicide development has always been a challenge and extensive and sustained investment in research and development is required if a successful product is to be realised. Although funding of microbicide research has increased significantly over the years, rising from US\$168 million in 2005 to US\$245 million in 2012, investment still lags far behind research and development funding for HIV vaccines.<sup>49</sup> In 2012, the total global investment for HIV vaccine-related research and development was US\$847 million, 3.5 times more than microbicides.<sup>49</sup> Funding for microbicide research and development may face additional hurdles in the future if limited financial resources are redirected to implementation of PrEP, other HIV prevention strategies, HIV treatment or other diseases.



### The challenge of adherence

One of the greatest challenges in microbicide development has been suboptimal adherence to the prescribed dosing regimen. Recently completed microbicide trials demonstrate how varying levels of adherence impact on effectiveness.<sup>21,24</sup> Adherence is clearly a huge challenge in the conduct of clinical trials and a successful microbicide will require more than just an efficacious anti-HIV product. A much better understanding of motivators of adherence and more objective measures of adherence during a trial are needed as is a better understanding of what women's needs are of a product in relation to dosing strategy and formulation.

Many of the early microbicide trials relied exclusively on self-reported data for both product use and sexual behaviour, which has several limitations.<sup>50,51</sup> Dye staining of applicators was subsequently introduced in some of the trials and although this method was shown to be a reliable and objective way to assess whether an applicator had been inserted into the vagina,<sup>52</sup> differences in composition of plastics, dyes and product formulations limit the accuracy and utility of this method.<sup>53</sup> Other novel technologies to monitor applicator use include the UV light assessment of vaginal applicators<sup>54</sup> and wireless technologies like Wisebag.<sup>55</sup> Anti-retroviral-based microbicides have made it possible to measure actual drug concentrations to determine whether the product has been used or not. The limitation of this method, however, is that drug concentrations can usually only be measured at the end of the study to avoid unblinding and it is not possible to measure adherence in the placebo group. Furthermore, the measurement of drug levels as an indicator of compliance will become limited in the future when anti-retrovirals as PrEP become more widespread because it will not be possible to know if the detectable drug levels are from the use of PrEP or from the product under investigation.

The inclusion of an easily detectable marker in the product as well as the placebo to obtain objective measures of adherence in clinical trials is likely to be required. A breath test to detect alcohol and ketone metabolites from vaginal products and condoms that were tagged with esters seems promising.<sup>56,57</sup> One limitation of this approach, however, is that the product being tested will not be the same as the one intended to be marketed, which may result in regulatory hurdles.

### Understanding the vaginal microbiome and mucosal immunology

Whereas strategies for enhancing adherence through novel delivery mechanisms of anti-retroviral agents together with better ways to support and measure adherence are critical, these efforts need to be complemented with a better understanding of HIV acquisition vaginally. The establishment

of, for example, the role of genital<sup>58</sup> and systemic<sup>59</sup> inflammation and co-infection with other sexually transmitted infections<sup>60</sup> in HIV acquisition could require a different product development pathway than that used to develop anti-retroviral therapy for AIDS treatment. A cellular and immunological analysis of how other biological factors blunt the potency of anti-retroviral agents will be critically important for new product development and drug delivery systems. Empirical studies of breakthrough infections following prophylactic use of anti-retroviral-based microbicides that monitor disease progression, viral evolution and resistance patterns are also urgently needed for evidence-based decisions on prophylactic use of anti-retrovirals.

### Resistance

A unique challenge related to the use of anti-retroviral-based microbicides is the concern about the potential for drug resistance development. Although resistance cannot develop in people who do not have HIV, it could potentially develop in individuals who become infected with HIV and continue taking the prophylactic regimen. Compared with the use of anti-retrovirals in treatment, resistance acquired from prophylactic use of anti-retrovirals is anticipated to be much lower.<sup>61</sup> Nevertheless, it is important that effectiveness trials of microbicides include assessments of the development of resistance. This empirical evidence will be invaluable to address this issue definitively.

So far, the PrEP products evaluated have all been tenofovir-based. Tenofovir is also a key first-line therapeutic drug. This has raised some concern about the use of tenofovir in therapy and prevention. Therapeutic failure is associated with the development of resistance and thereby the spread of resistant viruses, which in turn may compromise the efficacy of the same drugs (or occasionally, the same class of drugs) used for prophylaxis. It is not known whether prophylactic use of anti-retrovirals in individuals who subsequently acquire HIV will compromise their future anti-retroviral treatment options. Follow-on studies of individuals who acquire HIV infection after PrEP exposure are needed to determine whether treatment regimens that contain the PrEP agent compromise therapeutic success. Given the limited number of drugs currently available for treatment, the option for setting aside a class (or classes) of anti-retrovirals for use in prevention only is not feasible.

### Future study designs for microbicide trials

Conducting placebo-controlled microbicide trials may become challenging in the future once Truvada<sup>®</sup> (Gilead Sciences Inc., Foster City, CA, USA; a combination of two oral anti-retroviral drugs, tenofovir and emtricitabine), which was recently approved for HIV prevention by the US Food and Drug Administration (FDA), becomes widely

available as PrEP.<sup>62</sup> Furthermore, if the ongoing FACTS 001 trial confirms the results of the CAPRISA 004 trial then future microbicide trials may need to include the tenofovir gel in the comparator arm. The ethics of continuing with placebo-controlled trials as well as the provision of PrEP as ancillary care in HIV prevention trials is already being questioned.<sup>63</sup> Trial design options that incorporate an active agent(s) in the comparator group include either a superiority trial or noninferiority trial. In a superiority trial, the hypothesis tested is that the new intervention under investigation is better, by a clinically relevant amount, than the comparator.<sup>64</sup> The new intervention needs to be even more potent than an active comparator to show superiority, i.e. higher efficacy. Superiority designs are, however, much larger, more costly and more logistically challenging than placebo-controlled trials. With trials to test multipurpose prevention technologies, the goal would be to show that the new technology is not worse than the best available single technologies. Trials of this nature would be designed as a noninferiority trial with an active comparator. Noninferiority trials are used when the new intervention is assumed to have some benefits (e.g. improved safety, low cost) over the comparator intervention, but has similar efficacy.<sup>65</sup>

Noninferiority trials bring additional challenges in data interpretation. First, any intervention can easily be shown to be noninferior to a non-effective comparator intervention; whether or not either intervention is superior to placebo or no intervention.<sup>66</sup> The second challenge is that any effect that dilutes the true efficacy of an intervention in a trial, such as nonadherence, loss to follow-up or protocol violations, makes it easier for the two interventions to be declared equivalent. Further, suboptimal adherence to a highly efficacious product may be as good as high adherence to a low efficacy product.

Alternate adaptive designs, which bridge the gap between Phase 2b/3 microbicide effectiveness trials, are also being considered for future microbicide trials.<sup>67</sup> This approach could increase the efficiency of the trial thereby reducing its duration. The need for a correlate of protection for HIV prevention trials analogous to CD4<sup>+</sup> T-cell count and viral load monitoring in HIV treatment is urgently needed, particularly as newer and novel drugs enter clinical testing and placebo-controlled trials become more limited.

## Microbicides for specific target populations

### Inclusion of adolescents in clinical trials

Given the limited HIV prevention options for adolescent women, they would be an ideal target population for the introduction of an effective microbicide for individual and population level benefit. However, none of the microbicide

studies to date have included this important age group, making the evaluation of microbicides in this group a high priority. Notably no topical or oral PrEP trials have demonstrated safety concerns and large numbers of HIV-infected adolescents are on anti-retroviral treatment. The first trial of daily tenofovir gel use among 16- and 17-year-old girls (FACTS 002) is planned and will provide important safety data for the use of microbicides in this group, paving the way for adolescent girls to have access to a licensed microbicide.

### Microbicides for rectal use

Rectal microbicide development has lagged behind the development of microbicides for vaginal use but is no less important. The mucosal surfaces in the rectum are vulnerable to physical damage during sex and potentially increase the risk of HIV infection. Several surveys indicate that heterosexual anal intercourse is far more common than generally acknowledged<sup>68-71</sup> and women who engage in anal intercourse may be less likely to use condoms and more likely to engage in risky behaviours.<sup>70</sup>

Although vaginal microbicide products may also be beneficial if used rectally, the distinct differences between the vagina and rectum may mean that separate products will be needed specifically for vaginal or rectal use. With some candidate microbicide products, formulations specifically for vaginal or rectal use are already available, such as a low osmolality tenofovir gel that has been specifically formulated for rectal use. Clinical trials evaluating the safety and effectiveness of rectal microbicides are under way in MSM populations<sup>30,32</sup> and a number of pharmacodynamic/pharmacokinetic studies are planned using three rectally applied tenofovir gel formulations.

### Microbicide use during pregnancy

Whereas most multipurpose technologies address fertility control needs with sexual and reproductive health needs, many young women also desire pregnancy. The safety of using microbicides during pregnancy is, therefore, important to establish. A safety study using tenofovir 1% gel in pregnant and lactating women<sup>33</sup> was initiated in 2011 and results are anticipated soon.

## Conclusion

Anti-retroviral-based microbicides provide real potential to influence the course of the HIV epidemic, as they fill an important gap for women-initiated, anti-HIV-specific prevention methods and could potentially offer an alternative HIV prevention option for men who have sex with men. So far, only coitally linked use of tenofovir gel has demonstrated moderate effectiveness in preventing HIV infection and the findings of a confirmatory trial, FACTS 001,

are eagerly awaited as an important next step towards licensing of tenofovir gel. Studies of new anti-viral agents, novel delivery mechanisms, combination/multipurpose products and the role of biological factors in blunting efficacy of anti-retroviral agents that address challenges of adherence and enhance the effectiveness of tenofovir gel are already underway. These advances in microbicide development have catalysed renewed interest in multipurpose technologies to meet the sexual and reproductive health needs of men and women and efforts to prevent HIV infection.

### Disclosure of interests

All authors were investigators of the CAPRISA 004 tenofovir gel trial. Professor Salim Abdool Karim and Professor Quarraisha Abdool Karim are co-inventors of two pending patents (61/354.050 and 61/357.892) of tenofovir gel against HSV-1 and HSV-2 with scientists from Gilead Sciences Inc.

### Contribution to authorship

All authors contributed equally to the manuscript.

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