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Review Article

# HIV Microbicides and Multipurpose Prevention Technology in Preventing the Spread of HIV/AIDS

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**Abstract**

Human Immunodeficiency Virus (HIV) is a retrovirus that can result in rare opportunistic infections occurring in humans. The onset of these infections is known as Acquired Immune Deficiency Syndrome (AIDS).Sexual transmission is responsible for the majority of infections, resulting in transmission of HIV due to infected semen or vaginal and cervical secretions containing infected lymphocytes.HIV microbicides are formulations that can be applied to the vagina or rectum with the intention of reducing the acquisition of HIV. An effective microbicide product has the potential to significantly reduce the global HIV infection rate.The recent Centre for the AIDS Program of Research in South Africa (CAPRISA) 004 trial demonstrated that a 1% vaginal gel formulation of tenofovirwas safe and effective while reducing HIV transmission by 39% and has encouraged the development and clinical evaluation of other microbicide products such as a vaginal rings, tablets and films. However, researchers are now starting to focus their attention on the development of the next generation of microbicides, which are products containing multiple antiretroviral drugs or a combination of an antiretroviral and another type of microbicide such as a protease or entry inhibitor as well as the development of Multipurpose Prevention Technologies (MPTs) products, which are preferably single device products, administered via a single route, that are expressly designed to simultaneously address multiple sexual and reproductive health needs, such as unintended pregnancy, HIV infection and other STIs.

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## ABBREVIATIONS

**HIV:** Human Immunodeficiency Virus; **AIDS:** Acquired Immune Deficiency Syndrome; **CAPRISA:** Centre for the AIDS Program of Research in South Africa; **MPT:** Multipurpose Prevention Technology; **STI:** Sexually Transmitted Infection; **CAMI:** Coalition Advancing Multipurpose Innovations; **FDA:** Food and Drug Administration; **PATH:** The Program for Appropriate Technology in Health; **EVA:** Ethylene–Vinyl-Acetate Copolymer; **LNG:** Levonorgestrel; **IPM:** International Partnership for Microbicides; **HEC:** Hydroxyethycellulose; **NNRTI:** NonnucleosideReverse Transcriptase Inhibitor; **HPMC:** Hydroxypropyl Methyl Cellulose; **NaCMC:** Sodium Carboxymethylcellulose; **POM:** Polyoxymethylene copolymer; **WHO:** World Health Organisation

## INTRODUCTION

Human Immunodeficiency Virus (HIV) is a retrovirus that can result in rare opportunistic infections occurring in humans. The onset of these infections is known as Acquired Immune Deficiency Syndrome (AIDS). The major modes of HIV transmission are sexual contact, exposure to infected blood, infected needles and mother-to-child. Sexual transmission is responsible for the majority of infections [1], resulting in transmission of HIV due to infected semen or vaginal and cervical secretions containing infected lymphocytes [2]. HIV destroys the human immune system by attacking the CD4+ T helper cells, a sub group of lymphocytes, which are a type of white blood cell that is part of the adaptive immune system [3,4]. This leaves the body susceptible to opportunistic infections, which leads to the onset of AIDS.

## HIV MICROBICIDES

HIV microbicides are formulations of chemical or biological agents that can be applied to the vagina or rectum with the intention of reducing the acquisition of HIV. An effective microbicide product has the potential to reduce the global HIV infection rate [5-7]. The ideal vaginal HIV microbicide must have activity against cell free and cell associated HIV, it must not cause damage to the tissue or flora of the vagina, it must be retained in the vagina, act locally and retain its activity in the presence

of semen and across a broad pH range [8]. There are a range of mechanisms by which vaginal microbicides may prevent HIV infection (Figure 1) from providing a physical barrier that prevents HIV entering the vaginal mucosa [9] or protecting against other sexually transmitted infections (STIs) such as HSV-2, which enhance HIV transmission, to destroying the virus as soon as it enters the vagina [10,11] and the maintenance of the vaginal flora, which provides a protective vaginal pH [12,13], or the prevention of either HIV binding to CD4 receptors [14,15] or its replication process [16,17].

For the last twenty years researchers have been developing and evaluating a range of vaginally administered HIV microbicide formulations for their potential at preventing the sexual transmission of HIV. In the early years the focus was more on non-specific microbicide candidates, which either destroyed the virus upon entry to the vagina or maintained the protective pH of the vagina. However, due to a lack of efficacy with these strategies the focus has shifted to more specific candidates such as antiretrovirals, protease inhibitors and entry inhibitors. The positive result of the Centre for the AIDS Program of Research in South Africa (CAPRISA) 004 trial, which assessed the effectiveness and safety of a 1% vaginal gel formulation of tenofovir and demonstrated a 39% reduction in HIV transmission [18] has encouraged the microbicide field and there are a number of lead candidate vaginal microbicide products currently under clinical evaluation, including a tenofovir vaginal ring, tenofovir vaginal gel, tenofovir vaginal tablet and a dapivirine vaginal ring. Furthermore, this study demonstrated that tenofovir had activity against HSV-2 and thus a dual mechanism of protection.However, it is important to develop new products with different resistance patterns to those currently being investigated, especially as these products contain single actives that are currently used to treat HIV and development of a resistant strain of HIV to one of these actives could have a detrimental effect on the treatment of HIV. Therefore, researchers are now starting to focus their attention on the development of the next generation of microbicides, which are products containing multiple antiretroviral drugs or a combination of an antiretroviral and another type of microbicide such as a protease or entry inhibitor. These combination products offer significant advantages over their single antiretroviral counterparts, which include greater protection by targeting different stages in the viral replication cycle, reduced drug levels needed for efficacy due to synergistic effects and a broader range of activity against resistant strains of HIV [19].

## MULTIPURPOSE PREVENTION TECHNOLOGIES (MPTS)

Multipurpose Prevention Technologies (MPTs) are

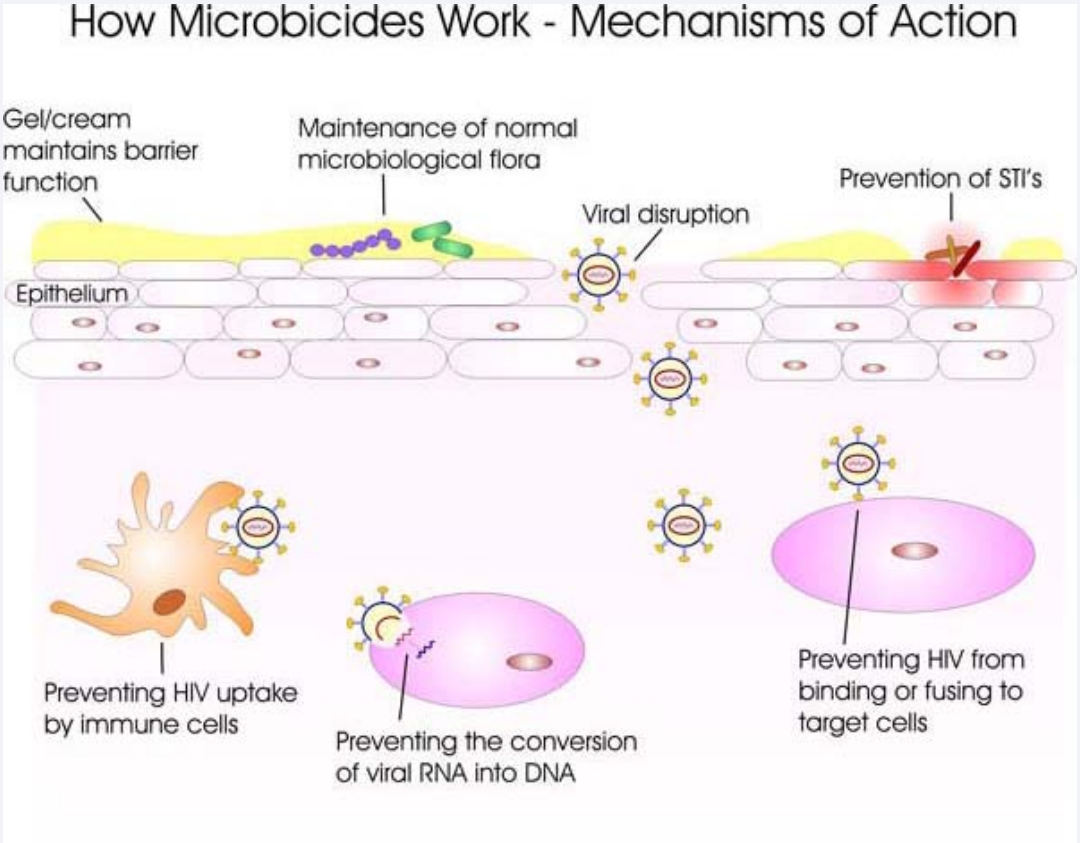


**Figure 1** Potential mechanisms of HIV prevention by a microbicide or MPT formulation: (1) provision of a physical barrier that prevents HIV from entering the vaginal mucosa [9], (2) maintenance of the vaginal flora, which provides a protective vaginal pH [12,13], (3) prevention of sexually transmitted infections (STI's) which may increase the possibility of HIV infection, (4) by destroying the virus as soon as it enters the vagina [10,11], (5) prevention of HIV binding to CD4 receptors [14,15], (6) preventing the HIV replication process [16,17] ultimately leading to the prevention of HIV uptake by the immune cells.

products, preferably single device products, administered via a single route, that are expressly designed to simultaneously address multiple sexual and reproductive health needs, such as unintended pregnancy, HIV infection and other STIs [20]. STIs such as HSV-2 and bacterial vaginosis etc. can cause inflammation and thus increase the transmission of HIV.MPTs can fall into a number of categories: 1) a drug delivery device or formulation that releases multiple active agents of which each is effective against a different indication, 2) a drug delivery device or formulation that release a single active agent that is effective against a range of different indications or 3) a barrier device such as a condom or diaphragm in combination with one or more active agents which are effective against multiple indications. According to the Coalition Advancing Multipurpose Innovations (CAMI), every minute a woman is infected with HIV, there are 86 million unplanned pregnancies around the world annually and 1 million people contract an STI every day [20]. MPTs offer a solution to these reproductive health issues using a single device, which will result in a number of benefits for the users, including convenience, adherence, improved effectiveness, reduction in cost and environmental impact [21].

## Current MPT products

There are currently a number of MPT products on the market, such as the male and female condom and the cervical diaphragm (Figure 2). The male condom is one of the key MPT barrier methods, which when used correctly is highly effective in protecting against pregnancy and HIV infection [22,23], while its availability as an over-the-counter product and its low cost of manufacture make it extremely accessible even in low resource settings. However, inconsistent and improper use, as a result of poor acceptability, has resulted in failure rates, after one year of use, of approximately 15% [24]. Furthermore, many women cannot negotiate condom use with their partners and thus many sexual health experts are encouraging the development of other female controlled MPT options [25]. Sexual health education has increased the acceptance and use of condoms, particularly in men [25], while reducing their price or even the distribution of free condoms has reduced the incidence of STIs in certain populations [26,27].

The female condom is a female controlled barrier method, which has been shown to have a comparable or slightly higher contraceptive efficacy when compared to the male condom [28,29] and was just as effective in reducing the recurrence of bacterial STIs [30]. Although there is no actual data on HIV prevention, mathematical modelling has suggested an effectiveness of 63 to 82% [33,34]. The first female condom was manufactured from polyurethane and approved by the Food and Drug Administration (FDA) in 1993. However, it was quite expensive and user complained that the polyurethane made a crinkling noise during intercourse. The second female condom was manufactured from synthetic latex and was slightly cheaper than the first [34]. However, the cost of the female condom is still higher than that of the male. Various strategies, such as the washing, disinfecting

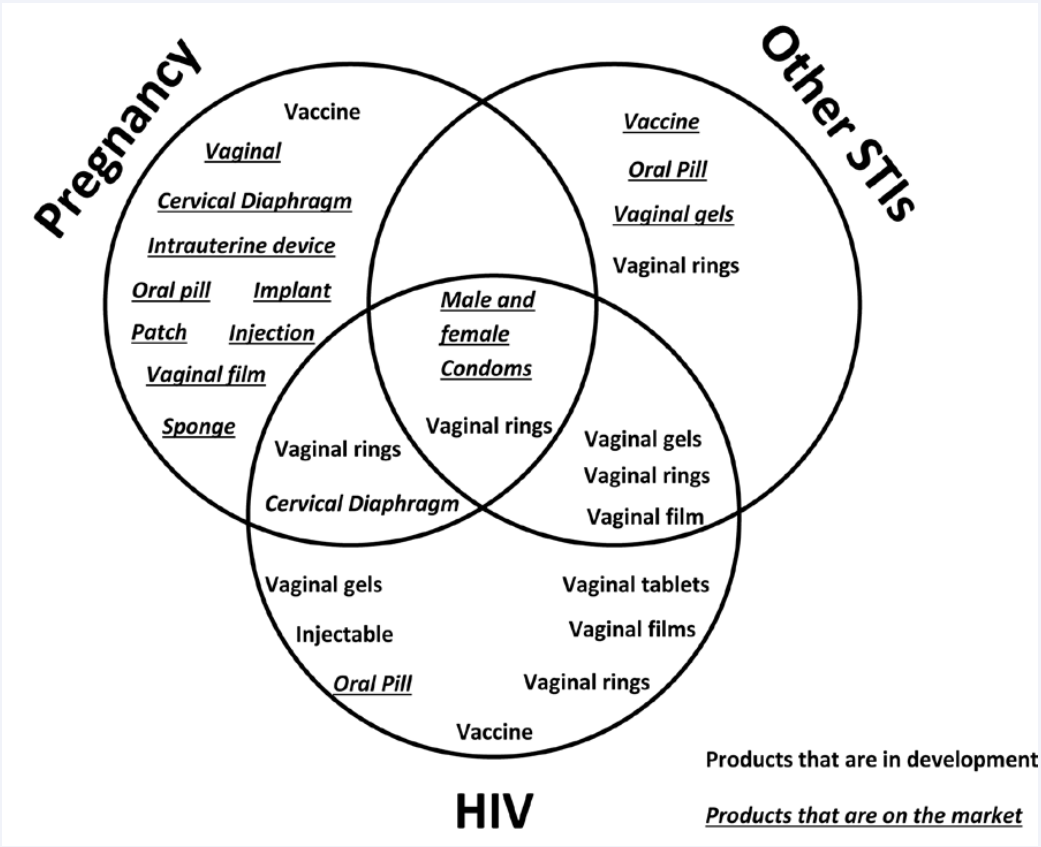


**Figure 2** Single and Multipurpose Prevention Technologies for the prevention of HIV, other STIs and unwanted pregnancies.

and reusing of the female condom, have been developed to try and reduce its relative cost by reusing it a number of times and thus increase its acceptability. An in vitro study, where the condom was subject to washing, disinfecting, drying and re-lubrication demonstrated that the integrity of the condoms remained high [35], while a study investigating the experiences of commercial sex workers in Swaziland with the female condom, demonstrated that some of the women disinfected and reused the condom [36]. However, this is not a practice current endorsed by the World Health Organisation. Although designed for single use, studies have shown that the second female condom has comparable cost effectiveness when compared to the male condom as a method of preventing HIV transmission [32].

Cervical diaphragms are designed to sit on the cervix and are traditionally used for contraception and have a similar rate of effectiveness to the male condom [37]. The cervix has a density of CD4 cells and CCR5 chemokine receptors, compared to other parts of the vagina [38], while macaque studies have shown the cervix to be the initial site of infection [39]. This would suggest that the cervix is a primary site of infection for HIV and other STIs [40]. Therefore, diaphragms may offer protection from HIV and other STIs and thus act as an MPT. Studies have shown that the incidences of gonorrhoea and chlamydia infections are lower in those women who use diaphragms over other barrier methods of contraception [41]. However, a large scale trial comparing the efficacy of using a diaphragm and a condom to condoms alone in preventing HIV-1, gonorrhoea and chlamydia in at-risk women demonstrated that there was no statistically significant difference between the two groups [42,43]. A major disadvantage of using the cervical diaphragm as an MPT strategy, particularly in low resource settings, is the fact that they require fitting by a healthcare professional and are thus only available on prescription in most countries. The Program for Appropriate Technology in Health (PATH), in collaboration with CONRAD, have developed a new 'one size fits most' SILCS diaphragm, which is manufactured from silicone and contains a polymer spring, rather than the metal spring used in most standard diaphragms. The SILCS diaphragm is designed to be easier to insert and remove, offer increased comfort, eliminate latex-related odours and allergic reactions, while being more durable than standard latex diaphragms. The SILCS diaphragm performed well in phase I postcoital barrier effectiveness testing. However, it was recommended that for it to be most effective adjunctive use of a chemical barrier or spermicidal gel was needed [44]. Furthermore, a study demonstrated that couples in low resource settings preferred the SILCS diaphragm over the Ortho All-Flex diaphragm [45]. CONRAD studied the clinical efficacy of the SILCS diaphragm with BufferGel® in 450 women over six sites in the US and concluded that SILCS and the standard diaphragm offer similar protection. Furthermore PATH, in collaboration with Queens University Belfast, is looking at developing a SILCS diaphragm which releases the HIV microbicide dapivirine [9].

## The future of MPT products

Adherence and compliance issues are well understood in contraceptive and microbicide fields, with a recent phase IIb study of a gel containing 1%w/w of the NRTI tenofovir lowering the risk of HIV infection in sexually active women by 54% provided they reported greater than 80% adherence, which fell to 38% protection if they had between 50% and 80% adherence and to 28% with less than 50% adherence [18]. This study clearly demonstrates the influence of adherence and compliance on the efficacy of a microbicide product and suggests that any future MPT products need to consider patient adherence to the required dosing regimen, particularly for those products which are coitally dependent.

Figure 2 demonstrates that most of the current marketed formulations are in the contraceptive field, with a range of different types of formulations and routes of administration available. Therefore, it is more than likely that any future MPT products will be based on the types of formulations and routes of administration within the contraceptive field and figure 2 demonstrates that current focus is on the development of vaginal rings, vaginal gels, vaginal films and cervical diaphragms.

**Vaginal rings:** Vaginal rings are torus-shaped drug delivery devices that have the capability to provide the controlled delivery of drugs to the vagina for up to a period of 1–12 months [46-49]. Vaginal rings have already seen clinical and commercial success in contraception (Nuvaring®) [48,50,51] and oestrogen replacement therapy (Estring® and Femring®) [46,52]. Femring® and Estring® are both manufactured from silicone elastomer, whereas Nuvaring® is manufactured from ethylene–vinyl-acetate copolymer (EVA). The clinical and commercial success of these rings in the contraceptive and hormone replacement therapy has resulted in a growing interest in their potential use for preventing HIV transmission through vaginal delivery of microbicides and vaccines [53-57] and as a potential MPT strategy. Furthermore, the vaginal ring overcomes many of the disadvantages associated with other vaginal dosage forms, such as gels, tablets and pessaries, which are often messy, interfere with intercourse and are poorly retained within the vagina. However, its major advantage is in providing long-term, continuous release of drug(s) at constant pre-determined rates, thereby increasing cost-effectiveness, patient compliance and therapeutic efficacy. The vaginal ring is user controlled and thus does not require minor surgery or a physician for it to be placed in the vagina.

Here we will discuss the three most advanced vaginal ring MPT products currently in the developmental pipeline. The most advanced of the MPT vaginal ring products is the tenofovir reservoir vaginal ring, which is manufactured from hydrophilic polyurethane loaded with more than 1 gram of tenofovir. It has a daily release rate of at least 10mg per day, with a duration of 90 days [58] and was shown to completely protect macaques from multiple vaginal challenges with simian-HIV [59]. This vaginal ring falls into category 2 of MPT products 'a drug delivery device or formulation that release a single active agent that is effective against a range of different indications', as it only releases a single active agent, tenofovir, which is effective against both HIV and HSV infections [18]. The vaginal which is next in the MPT product development pipeline is based on the aforementioned tenofovir vaginal ring and allows for the controlled delivery of both tenofovir and the contraceptive levonorgestrel (LNG) [60]. The main development challenges in the design of this combination ring was the three orders of magnitude difference in the release rate of the drugs and the fact that LNG is hydrophobic

and thus is more suited to delivery from hydrophobic polymers, while tenofovir is hydrophilic and suited to delivery from hydrophilic polymers. To overcome these challenges the drugs where formulated separately into two drug-loaded segments. Tenofovir, into segment manufactured from a hydrophilic polyurethane and comprising more than 80% of the ring, in order to maintain the 10mg per day delivery rate of tenofovir, while LNG was formulated into a much shorter segment manufactured from a hydrophobic polyurethane and designed to deliver 20μg per day of LNG [60]. This type of ring would fall into catergory 1 of MPT products 'a drug delivery device or formulation that releases multiple active agents of which each is effective against a different indication'. The final MPT vaginal ring product is the International Partnership for Microbicides (IPM) dapivirine (microbicide) and LNG (contraceptive) releasing vaginalring, which is currently being developed in partnership with Queens University Belfast and is designed to release both active agents for up to 60 days. This ring builds on a vaginal ring that contains 25mg of dapivirine dispersed within a silicone elastomer matrix [53,54,56], which is currently being evaluated in two Phase III studies (MTN-020 193 and IPM027) in Africa. Unlike the tenofovir/LNG ring previously mentioned, the dapivirine and LNG are co-formulated into the silicone ring body. This is because both dapivirine and LNG are hydrophobic and are suited to delivery from hydrophobic polymers such as silicone elastomer. Furthermore, because dapivirine and LNG can be co-formulated into the ring body it makes for a much simpler manufacturing process with less processing steps compared to the tenofovir/LNG ring.

**Vaginal gels:** Gels are semisolid systems in which a liquid phase is constrained within a three dimensional, cross-linked matrix. The drug may be dissolved or suspended within the liquid phase and vaginal gels may swell when applied, thus spreading over the vaginal wall. These characteristics allow the gels to localise drug delivery and sustain release for longer periods of time. However vaginal gels can be messy to apply, uncomfortable and inconvenient if they leak from the vagina and studies have shown that vaginal gels as a microbicide strategy suffer from patient compliance and adherence issues [18]. However, vaginal gels are relatively cheap and easy to manufacture offering a cheap and convenient vehicle for the delivery of contraceptives, anti HIV and HSV drugs to the vagina. The lead vaginal gel MPT product is the 1.0% tenofovir-loaded hydroxyethycellulose (HEC) vaginal gel, which was assessed in the CAPRISA 004 trial for effectiveness and safety reducing the incidence of HIV and HSV-2 by 39% and 51% respectively [18]. This gel would fall into category 2 of MPT products as it is releasing a single agent, which is effective against multiple indications. The next gel in the MPT product pipeline is VivaGel®, which was developed by StarPharma and is currently undergoing Phase II clinical evaluation. VivaGel® is a water based Carbopol® vaginal gel, buffered to a pH physiologically compatible with the normal human vagina and loaded with 3% w/w of the active ingredient SPL7013, which is a dendrimer specifically designed to have HIV and HSV antiviral activity [61]. A phase I clinical trial of VivaGel containing between 0.5 and 3% SPL7013 and involving 36 women found that all concentrations where as safe and as well tolerated as a placebo gel [62]. As with the 1% tenofovir gel, this gel also falls into category 2 of MPT products as it is releasing a single agent effective against multiple indications. The final vaginal gel in the MPT product pipeline is the MIV 150/Zinc Acetate Carraguard® gel being developed by the Population Council. This gel is based on the Carraguard® gel, which is a 3% carrageenan based gel that was shown to be safe and acceptable in phase I clinical trials [63-65]. However, it did not demonstrate efficacy in preventing HIV acquisition in a phase III clinical trial [66]. The MIV 150/Zinc Acetate Carraguard® gel contains the nonnucleoside reverse transcriptase inhibitor (NNRTI) MIV 150 and Zinc Acetate formulated in a 3% carrageenan gel. MIV 150 is highly active against HIV, while Zinc Acetate is added to boost antiviral activity [67]. However, there is evidence to suggest that zinc salts have antiviral activity against HIV and HSV-2 [68-70]. A single dose of a MIV-150/Zinc Acetate Carraguard® Gel provided 24 h protection after challenge with simian Human HIV in a macaque model [71]. Based on the safety and efficacy of the MZC gel in animal studies, the Population Council is currently testing the gel in a Phase I clinical trial in women.This type of gel would be classed as a category 1 MPT product as it releases multiple active agents of which each is effective against a different indication.

**Vaginal films:** Vaginal films are thin strips of a water-soluble polymer, loaded with an active ingredient, which gel then dissolve when placed on the vaginal mucosal subsequently releasing the active ingredient. Vaginal films have the advantages of being cheap to manufacture, convenient, can be administered without an applicator, portable, easy to store, discreet and no leakage. They begin as solid dosage forms, which are subsequently hydrated to form a gel when placed in the vagina. However, there is limited (less than 1mL) fluid in the vagina at any one time and this may reduce the rate of or even stop hydration of the film, which in turn reduces release of the active agent. Vaginal films containing 10 and 40mg of tenofovir are currently being assessed in a phase I safety study (FAME 04) in comparison with the 1% tenofovir gel. Vaginal films containing 20 and 40mg of tenofovir where shown to be safe in a macaque model [72]. The tenofovir vaginal films are manufactured by dissolving the required amount of tenofovir, hydroxypropyl methyl cellulose (HPMC), HEC, Sodium Carboxymethylcellulose (NaCMC), and glycerine in water, which is subsequently spread to the required thickness and dried. The large film is then cut into smaller films of the required dimensions. The tenofovir film falls into category 2 for MPT products as it releases a single active agent that is effective against a range of different indications.

**Cervical diaphragms:** As mentioned previously cervical diaphragms are designed to sit on the cervix and are traditionally used for contraception with a similar rate of effectiveness to the male condom [37]. Two strategies employing cervical diaphragms are currently being considered within the MPT field 1) the diaphragm is used in combination with a microbicide gel and 2) the diaphragm is used to deliver the microbicide. Combining a microbicide gel with a diaphragm would significantly improve women's health by providing protection from STIs and unwanted pregnancy. The SILCS diaphragm in combination with the microbicidal and contraceptive BufferGel® was tested in an acceptability study involving 36 couples [73]. The study investigated 3 delivery options; single-sided delivery from the SILCS diaphragm, double-sided gel delivery from the

SILCS diaphragm and gel from an applicator after the diaphragm was inserted. The study concluded that all three scenarios received favourable ratings for ease of application, acceptability and perceived effectiveness. However, overall the participants found the gel applicator to be more acceptable than either single- or double-sided gel delivery from a SILCS diaphragm [73]. This type of approach falls into category 3 of MPT products, 'a barrier device in combination with one or more active agents which are effective against multiple indications'. The second option using diaphragms is to formulate the active agent into the diaphragm, which subsequently acts as a barrier and drug delivery device. An example of this is the dapivirine releasing SILCS diaphragm being developed by PATH in collaboration with Queens University Belfast [9]. In this diaphragm dapivirine was directly incorporated into the Polyoxymethylene copolymer (POM) spring core of the diaphragm, which was subsequently over-moulded with silicone elastomer to form the finished diaphragm. The diaphragm had a mean in vitro daily release rate of 174µg per day [9]. This study provided proof of concept of the use of a diaphragm to deliver the HIV microbicide dapivirine, thus preventing both HIV transmission and unwanted pregnancy. This type of diaphragm would also fall into category 3 of MPT products as it is a barrier device in combination with an active agent.

## CONCLUSION

MPT products offer simultaneous protection against infection from HIV and other STIs as well as unintended pregnancies, with established products including barrier devices, such as the male and female condom and cervical diaphragms. However, even though MPT or microbicide products are a preventative strategy and not a cure for HIV and other STI infections or unwanted pregnancy, it is imperative that a safe and effective HIV microbicide product is developed, with second generation microbicide and MPT products following shortly behind. The reason for this is that next to an effective vaccine, microbicide and MPT products can provide a range of preventative methods to address some of the most serious issues in women's sexual and reproductive health.

## REFERENCES

1. http://www.cdc.gov/hiv/risk/behavior/index.html
2. Mann J, Tarantola D, Netter T. AIDS in the world. A global report. Part I: Chapters 2 and 3. Cambridge, MA: Harvard University Press, 1992.
3. Rosenberg ES, Billingsley JM, Caliendo AM, Boswell SL, Sax PE, Kalams SA. Vigorous HIV-1-specific CD4+ T cell responses associated with control of viremia. Science. 1997; 278: 1447-1450.
4. McNeil AC, Shupert WL, Iyasere CA, Hallahan CW, Mican JA, Davey RT Jr. High-level HIV-1 viremia suppresses viral antigen-specific CD4(+) T cell proliferation. Proc Natl Acad Sci U S A. 2001; 98: 13878-13883.
5. Watts C, Vickerman P. The impact of microbicides on HIV and STD transmission: model projections. AIDS. 2001; 15: S43-S44.
6. Stone A. Microbicides: a new approach to preventing HIV and other sexually transmitted infections. Nat Rev Drug Discov. 2002; 1: 977-985.
7. Shattock RJ, Moore JP. Inhibiting sexual transmission of HIV-1 infection. Nat Rev Microbiol. 2003; 1: 25-34.
8. Krebs FC, Miller SR, Catalone BJ, Welsh PA, Malamud D, Howett MK, et al. Sodium dodecyl sulfate and C31G as microbicidal alternative to nonoxynol 9: comparative sensitivity of primary human vaginal keratinocytes. Antimicrobial Agents and Chemotherapy. 2000; 44 :1954-1960
9. Major I, Boyd P, Kilbourne-Brook M, Saxon G, Cohen J, Malcolm RK. A modified SILCS contraceptive diaphragm for long-term controlled release of the HIV microbicide dapivirine. Contraception. 2013; 88: 58-66.
10. Bestman-Smith J, Piret J, Désormeaux A, Tremblay MJ, Omar RF, Bergeron MG. et al. Sodium lauryl sulfate abrogates human immunodeficiency virus infectivity by affecting viral attachment. Antimicrob Agents Chemother. 2001; 45: 2229-2237.
11. Bax R, Douville K, McCormick D, Rosenberg M, Higgins J, Bowden M. Microbicides--evaluating multiple formulations of C31G. Contraception. 2002; 66: 365-368.
12. Hillier SL. The vaginal microbial ecosystem and resistance to HIV. AIDS Res Hum Retroviruses. 1998; 14 Suppl 1: S17-21.
13. Olmsted SS, Khanna KV, Ng EM, Whitten ST, Johnson ON 3rd, Markham RB. Low pH immobilizes and kills human leukocytes and prevents transmission of cell-associated HIV in a mouse model. BMC Infect Dis. 2005; 5: 79.
14. Reimann KA, Khunkhun R, Lin W, Gordon W, Fung M. A humanized, nondepleting anti-CD4 antibody that blocks virus entry inhibits virus replication in rhesus monkeys chronically infected with simian immunodeficiency virus. AIDS Res Hum Retroviruses. 2002; 18: 747-755.
15. Vermeire K, Schols D. Cyclotriazadisulfonamides: promising new CD4-targeted anti-HIV drugs. J Antimicrob Chemother. 2005; 56: 270-272.
16. Van Herrewege Y, Michiels J, Van Roey J, Fransen K, Kestens L, Balzarini J, Lewi P, Vanham G, Janssen P. In vitro evaluation of nonnucleoside reverse transcriptase inhibitors UC-781 and TMC120-R147681 as human immunodeficiency virus microbicides. Antimicrob Agents Chemother. 2004; 48: 337-339.
17. Wainberg M. The prospect for RT inhibitors as topical microbicides. London: Microbicides. 2004
18. Abdool Karim Q, Abdool Karim SS, Frohlich JA, Grobler AC, Baxter C, Mansoor LE. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. Science. 2010; 329: 1168-1174.
19. Shattock RJ, Rosenberg Z. Microbicides: topical prevention against HIV. Cold Spring Harb Perspect Med. 2012; 2: a007385.
20. www.cami-health.org
21. Thurman AR, Clark MR, Doncel GF. Multipurpose prevention technologies: biomedical tools to prevent HIV-, HSV-2, and unintended pregnancies. Infect Dis Obstet Gynecol. 2011; 2011: 1-10.
22. Gallo MF, Grimes DA, Lopez LM, Schulz KF. Non-latex versus latex male condoms for contraception. Cochrane Database Syst Rev. 2006.
23. Davis KR, Weller SC. The effectiveness of condoms in reducing heterosexual transmission of HIV. Fam Plann Perspect. 1999; 31: 272-279.
24. Mansour D, Inki P, Gemzell-Danielsson K. Efficacy of contraceptive methods: a review of the literature. Eur. J. Contracept. Reprod. Health Care. 2010; 15: 4–16.
25. Gollub EL. Choice is empowering: Getting strategic about preventing HIV infection in women. Int Fam Plan Perspect. 2006; 32: 209-212.
26. United States Navy. Sexual Health and Responsibility Program. 2010,

27. A. Treerutkuarkul. Free condoms at gay nightspots. The Bangkok Post, 2011.

28. Trussell J, Sturgen K, Strickler J, Dominik R. Comparative contraceptive efficacy of the female condom and other barrier methods. Fam Plann Perspect. 1994; 26: 66-72.

29. Farr G, Gabelnick H, Sturgen K, Dorflinger L. Contraceptive efficacy and acceptability of the female condom. Am J Public Health. 1994; 84: 1960-1964.

30. French PP, Latka M, Gollub EL, Rogers C, Hoover DR, Stein ZA. Use-effectiveness of the female versus male condom in preventing sexually transmitted disease in women. Sex Transm Dis. 2003; 30: 433-439.

31. Mukandavire Z, Garira W. Sex-structured HIV/AIDS model to analyse the effects of condom use with application to Zimbabwe. J Math Biol. 2007; 54: 669-699.

32. Dowdy DW, Sweat MD, Holtgrave DR. Country-wide distribution of the nitrile female condom (FC2) in Brazil and South Africa: a cost-effectiveness analysis. AIDS. 2006; 20: 2091-2098.

33. Warren M, Philpott A. Expanding safer sex options: introducing the female condom into national programmes. Reprod Health Matters. 2003; 11: 130-139.

34. Hatcher RA, Trussell J, Nelson AL, Cates W, Stewart FH, Kowal D, Eds, Contraceptive Technology, Ardent Media, New York, NY, USA, 2007.

35. World Health Organization, The Safety and Feasibility of Female Condom Reuse: Report of aWHO Consultation, World Health Organization, Geneva, Switzerland, 2002.

36. Mathenjwa T, Maharaj P. 'Female condoms give women greater control': a qualitative assessment of the experiences of commercial sex workers in Swaziland. Eur J Contracept Reprod Health Care. 2012; 17: 383-392.

37. Cook L, Nanda K, Grimes D. Diaphragm versus diaphragm with spermicides for contraception. Cochrane Database Syst. Rev. 2001; 2.

38. Patterson BK, Landay A, Andersson J, Brown C, Behbahani H, Jiyamapa D. Repertoire of chemokine receptor expression in the female genital tract: implications for human immunodeficiency virus transmission. Am J Pathol. 1998; 153: 481-490.

39. Li Q, Estes JD, Schlievert PM, Duan L, Brosnahan AJ, Southern PJ. Glycerol monolaurate prevents mucosal SIV transmission. Nature. 2009; 458: 1034-1038.

40. Moench TR, Chipato T, Padian NS. Preventing disease by protecting the cervix: the unexplored promise of internal vaginal barrier devices. AIDS. 2001; 15: 1595-1602.

41. Minnis AM, Padian NS. Effectiveness of female controlled barrier methods in preventing sexually transmitted infections and HIV: current evidence and future research directions," Sex. Transm. Infect. 2005; 8: 193–200.

42. Padian NS, van der Straten A, Ramjee G, Chipato T, de Bruyn G, Blanchard K. Diaphragm and lubricant gel for prevention of HIV acquisition in southern African women: a randomised controlled trial. Lancet. 2007; 370: 251-261.

43. Ramjee G, van der Straten A, Chipato T, de Bruyn G, Blanchard K, Shiboski S. The diaphragm and lubricant gel for prevention of cervical sexually transmitted infections: results of a randomized controlled trial. PLoS One. 2008; 3: e3488.

44. Schwartz JL, Ballagh SA, Creinin MD, Rountree RW, Kilbourne-Brook M, Mauck CK. SILCS diaphragm: postcoital testing of a new single-size contraceptive device. Contraception. 2008; 78: 237-244.

45. Coffey PS, Kilbourne-Brook M, Brache V, Cochón L. Comparative acceptability of the SILCS and Ortho ALL-FLEX diaphragms among couples in the Dominican Republic. Contraception. 2008; 78: 418-423.

46. Woolfson AD, Elliott GR, Gilligan CA, Passmore CM. Design of an intravaginal ring for the controlled delivery of 17 beta-estradiol as its 3-acetate ester. J Control Release. 1999; 61: 319-328.

47. Malcolm RK. Vaginal rings for controlled release drug delivery, in: Rathbone MJ, Hadgraft J, Roberts MS, Lane ME (Eds.). Modified Release Drug Delivery Technology, second ed, Informa Healthcare, New York, 2008; 499–510.

48. Brucker C, Karck U, Merkle E. Cycle control, tolerability, efficacy and acceptability of the vaginal contraceptive ring, NuvaRing: results of clinical experience in Germany. Eur J Contracept Reprod Health Care. 2008; 13: 31-38.

49. Woolfson AD, Malcolm RK, Gallagher RJ. Design of a silicone reservoir intravaginal ring for the delivery of oxybutynin. J Control Release. 2003; 91: 465-476.

50. Ahrendt HJ, Nisand I, Bastianelli C, Gomez MA, Gemzell-Danielsson K, Urdl W, et al. Efficacy, acceptability and tolerability of the combined contraceptive ring, NuvaRing, compared with an oral contraceptive containing 30 mg of ethinylestradiol and 3 mg of drospirenone. Contraception 2006; 74: 451–457.

51. Chaplin S, Peers T. NuvaRing: new combined hormonal contraceptive device. Prescriber 1999; 20: 17–20.

52. Henriksson L, Stjernquist M, Boquist L, Cedergren I, Selinus I. A one-year multicenter study of efficacy and safety of a continuous, low-dose, estradiol-releasing vaginal ring (Estring) in postmenopausal women with symptoms and signs of urogenital aging. Am J Obstet Gynecol. 1996; 174: 85-92.

53. Woolfson AD, Malcolm RK, Morrow RJ, Toner CF, McCullagh SD. Intravaginal ring delivery of the reverse transcriptase inhibitor TMC 120 as an HIV microbicide. Int J Pharm. 2006; 325: 82-89.

54. Malcolm RK, Woolfson AD, Toner CF, Morrow RJ, McCullagh SD. Long-term, controlled release of the HIV microbicide TMC120 from silicone elastomer vaginal rings. J Antimicrob Chemother. 2005; 56: 954-956.

55. Johnson TJ, Gupta KM, Fabian J, Albright TH, Kiser PF. Segmented polyurethane intravaginal rings for the sustained combined delivery of antiretroviral agents dapivirine and tenofovir. Eur J Pharm Sci. 2010; 39: 203-212.

56. Nel A, Smythe S, Young K, Malcolm K, McCoy C, Rosenberg Z. Safety and pharmacokinetics of dapivirine delivery from matrix and reservoir intravaginal rings to HIV-negative women. J Acquir Immune Defic Syndr. 2009; 51: 416-423.

57. McConville C, Major I, Friend DR, Clark MR, Malcolm RM. Development of a UC781 releasing poly ethylene vinyl acetate vaginal ring. Drug Deliv. Transl. Res. 2012; 2: 489–497.

58. Johnson TJ, Clark MR, Albright TH, Nebeker JS, Tuitupou AL, Clark JT. A 90-day tenofovir reservoir intravaginal ring for mucosal HIV prophylaxis. Antimicrob Agents Chemother. 2012; 56: 6272-6283.

59. Smith JM, Rastogi R, Teller RS, Srinivasan P, Mesquita PM, Nagaraja U, et al. Intravaginal ring eluting tenofovirdisoproxilfumarate completely protects macaques from multiple vaginal simian-HIV challenges. ProcNatlAcadSci 2013; 110: 16145-16150.

60. Clark JT, Clark MR2, Shelke NB, Johnson TJ, Smith EM, Andreasen AK1. Engineering a segmented dual-reservoir polyurethane intravaginal ring for simultaneous prevention of HIV transmission and unwanted pregnancy. PLoS One. 2014; 9: e88509.

61. Rupp R, Rosenthal SL, Stanberry LR. VivaGel (SPL7013 Gel): a candidate dendrimer--microbicide for the prevention of HIV and HSV infection. Int J Nanomedicine. 2007; 2: 561-566.

62. McCarthy TD, Karellas P, Henderson SA, Giannis M, O'Keefe DF, Heery G. Dendrimers as drugs: discovery and preclinical and clinical development of dendrimer-based microbicides for HIV and STI prevention. Mol Pharm. 2005; 2: 312-318.

63. Whitehead SJ, McLean C, Chaikummao S, Braunstein S, Utaivoravit W, van de Wijgert JH. Acceptability of Carraguard vaginal microbicide gel among HIV-infected women in Chiang Rai, Thailand. PLoS One. 2011; 6: e14831.

64. Kilmarx PH, van de Wijgert JH, Chaikummao S, Jones HE, Limpakarnjanarat K, Friedland BA. Safety and acceptability of the candidate microbic

65. van de Wijgert JH, Braunstein SL, Morar NS, Jones HE, Madurai L, Strickfaden TT, et al. Carraguard Vaginal Gel Safety in HIV-Positive Women and Men in South Africa. J Acquir Immune DeficSyndr. 2007; 46: 538-546.

66. Skoler-Karpoff S, Ramjee G, Ahmed K, Altini L, Plegianos MG, Friedland B, et al. Efficacy of Carraguard® for prevention of HIV infection among women in South Africa: a randomized, placebo-controlled trial. Lancet 2008; 372: 1932–1933.

67. Fernandez-Romero JA, Thorn M, Turville SG, Titchen K, Sudol K, Li J et al. Carrageenan/MIV-150 (PC-815), a combination microbicide. Sexually Transmit. 2007; 34: 9–14.

68. Kumel G, Schrader S, Zentgraf H, Daus H, Brendel M. The mechanism of the antiherpetic activity of zinc sulphate. J. Gen. Virol. 1990; 71: 2989–2997.

69. Haraguchi Y, Sakurai H, Hussain S, Anner BM, Hoshino H. Inhibition of HIV-1 infection by zinc group metal compounds. Antivir. 1999; 43: 123–133.

70. Arens M, Travis S, Zinc salts inactivate clinical isolates of herpes simplex virus in vitro. J. Clin. Microbiol. 2000; 38: 1758–1762.

71. Kenney J, Singer R, Derby N, Aravantinou M, Abraham CJ, Menon R et al. A Single Dose of a MIV-150/Zinc Acetate Gel Provides 24 h of Protection Against Vaginal Simian Human Immunodeficiency Virus Reverse Transcriptase Infection, with More Limited Protection Rectally 8–24 h After Gel Use AIDS Res. Hum. Retroviruses 2012; 28: 1476-1484.

72. Patton DL, Cosgrove Sweeney Y, Rohan LC, Hillier SL. P3.365 Tenofovir Vaginal Film: Safety Assessment in the Macaque Model. Sex. Transm. Infect. 2013; 89: 263.

73. Frezieres RG, Walsh T, Kilbourne-Brook M, Coffey PS. Couples' acceptability of the SILCS diaphragm for microbicide delivery. Contraception. 2012; 85: 99-107.

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