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 tenofovir was safe and effective while reducing HIV transmission by 39% and has encouraged the development and clinical evaluation of other microbicide products such as 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.

ABBREVIATIONS


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 body fluids and must be safe.
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
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 CCRS 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].

Further, 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 initially 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 category 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 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.

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 microbicidal. Combining a microbicidal 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.

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