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Review

Combining prevention of HIV-1, other sexually transmitted infections and unintended pregnancies: Development of dual-protection technologies

David R. Friend [a,*], Gustavo F. Doncel [b]

[a] CONRAD, Department of Obstetrics and Gynecology, Eastern Virginia Medical School, 1911 North Fort Myer Drive, Suite 900, Arlington, VA 22209, United States
[b] CONRAD, Department of Obstetrics and Gynecology, Eastern Virginia Medical School, 601 Colley Avenue, Norfolk, VA 23507, United States

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ABSTRACT

A significant number of women, especially in developing countries, need protection against more than one sexually transmitted infection (STIs), for instance HIV-1 and HSV-2, and family planning methods to prevent unwanted pregnancies. Dual protection technologies (DPTs; also known as multipurpose technologies) are designed to address two different indications with one product. Examples of DPTs are vaginal products capable of preventing transmission of HIV-1 in women while simultaneously providing contraceptive properties and a vaginal product capable of reducing HIV-1 transmission while preventing transmission of a second STI. DPTs can be categorized into three main approaches: 1) physical barriers, 2) chemical barriers, and 3) a combination of physical and chemical barriers. Examples of physical barriers are male and female condoms, diaphragms and cervical caps. Chemical barriers include use of a single drug with two mechanisms of action (viz., dual-activity compounds with microbicidal and contraceptive properties or activity against HIV-1 and a second STI pathogen such as HSV-2) or a combination of two drugs each targeted against separate mechanisms for achieving contraception and inhibition of HIV-1. Combinations of chemical and physical barriers are based on physical barriers such as a diaphragm along with a microbicide. Examples of each approach and current prototypes (such as vaginal gels and intravaginal rings) under development are described in this paper. Challenges facing development and regulatory approval of DPTs are also reviewed. This article forms part of a special supplement on a presentation covering DPTs, based on the symposium "Trends in Microbicide Formulations", held on 25 and 26 January 2010, Arlington, VA.

Contents

Abbreviations: STIs, sexually transmitted infections; HSV, herpes simplex virus; HPV, human papillomavirus; DPT, dual protection system; FC, female condom; LNG, levonorgestrel; CD, cyclodextrin; RTI, reverse transcriptase inhibitor; NtRTI, nucleotide reverse transcriptase inhibitor; TFV, tenofovir; NNRTI, non-nucleoside reverse transcriptase inhibitor; IVR, intravaginal ring; EVAc, ethylene vinylacetate copolymer; PU, polyurethane; PK, pharmacokinetic; PD, pharmacodynamic; TDF, tenofovir disoproxil fumarate; IPA, isopropyl alcohol; ACV, acyclovir; NHP, nonhuman primates.

* Corresponding author. Tel.: +1 703 276 3906; fax: +1 703 524 4770.
E-mail address: dfriend@conrad.org (D.R. Friend).

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1. Introduction

The risk of acquiringSTIsremains high throughout the world and efforts to reduce transmission of STIs, in particular HIV-1, are a high priority in the global public health agenda. UNAIDS/WHO recentlyreported 33.4 million people living with HIV-1 and 2.7 million new infectionsin 2008 (UNAIDS/WHO, 2009). There were 2.0 million deaths due to HIV/AIDS during that year. The number of those infected with HIV-1 in sub-Saharan Africa was 22.4 million, and the majority of them were women. The continuing rise in the population of people living with HIV-1 reflects the combined effects of continued high rates of new HIV-1 infections and the beneficial impact of antiretroviral therapy. Although important progress has been achieved in preventing new HIV-1 infections and in lowering the annual number of AIDS-related deaths, the number of people living with HIV-1 continues to increase. AIDS-related illnesses remain one of the leading causes of death globally and are projected to continue asa significant global cause of premature mortality in the coming decades (World Health Organization, 2008).

Regarding other STIs, the WHO estimates that 340 million new cases of syphilis, gonorrhea, chlamydia and trichomoniasis occurred throughout the world in 1999 in men and women aged 15-49 years (WHO, 2001). The largest number of new infections occurred in the region of South & Southeast Asia, followed by sub-Saharan Africa, Latin America and the Caribbean. Viral STIs are also a major health problem. The number of women infected with HPV, a main cause of cervical cancer, is about 20% of the population under 24 years of age (Glasier et al., 2006). HSV-2 is the commonest cause of genital ulcers and a highly prevalent infection in sexually-active people worldwide. Seroprevalence rates of HSV-2 range from 22% of sexually-active adults in the USA, to up to 60% in HIV-negative women in sub-Saharan Africa and men who have sex with men (MSM) in Latin America, and to more than 80% in people infected with HIV-1 (Celum et al., 2008).

Equally disappointing is the number of unwanted pregnancies in both the developed and developing world. This problem will only get worse as the world population continues to grow and is estimated to reach 9.1 billion by 2050 (Aitken et al., 2008). Annually there are over 75 million unwanted pregnancies (Glasier and Shields, 2006). Of these, 45 million pregnancies are terminated through abortions. Significant numbers of deaths are associated with unsafe abortions performed primarily in the developing world (Åhman and Shah, 2002; Ciment, 1999; Glasier et al., 2006). Contextual similarities make women at risk of unplanned pregnancies also at risk for STIs, including HIV-1. Family planning could therefore save hundreds of thousands of lives, not only by reducing maternal mortality but also by averting mother-to-child transmission of HIV-1 (Hladik and Hope, 2009).

The HIV-1 pandemic and the unabated prevalence of STIs and unintended pregnancies are intricately intertwined with poverty, malnutrition, poor education and gender inequality. A significant number of women, especially in developing countries, need protection against sexually transmitted diseases, in particular HIV/AIDS, and family planning methods to prevent unwanted pregnancies. There is an urgent need for the development of multipurpose (e.g., contraceptive and microbicidal) prevention technologies. This paper reviews their developmental strategies and prototypes.

This paper forms part of a group of seven reviews covering presentations from the Trends in Microbicide Formulations Workshop that was held on 25-26 January, 2010 in Arlington, Virginia, USA. The other articles discuss the prevention of mucosal transmission (Hladik and Doncel, 2010), preclinical evaluation of microbicides (Doncel and Clark, 2010), gels, tablets, and films (Garg et al., 2010), intravaginal rings (Malcolm et al., 2010), clinical evaluation of microbicides (Morrow and Hendrix, 2010), and novel approaches to microbicide delivery and safety assessment (Whaley et al., 2010).

2. Dual protection technologies

Given the cited transmission commonalitiesamong STIs and between HIV-1infection and fertilization/pregnancy (Doncel, 2006), there is a logic thread unifying the development of dual-protection technologies, which are aimed at preventing two STIs or an STI and unintended pregnancy (Berer, 2006; Brady, 2003; Bull and Shlay, 2005; Cates and Steiner, 2002; Chandran and Kabir, 2010; Baptista and Ramalho-Santos, 2009). In a more general sense, DPTsare also called "multipurpose technologies" (Young Holt et al., 2010).

The main strategies for combining multipurpose STI prevention and HIV-1 prevention and contraception are the development or improvement of physical barriers, chemical barriers, and physical/chemical barrier combinations. The first DPT approach is to use a physical barrier method normally associated with contraception, for instance male condoms, yet also capable of preventing HIV-1 transmission. The second approach is to develop improved chemical barriers such as coformulation of two or more microbicides with different targets. Related to this approach is the design of dual function drugs, i.e., drugs that potentially act against two distinct targets, displaying, for instance, both antiviral and contraceptive properties. The third approach to DPTs is the combination of a physical barrier with a chemical barrier. An example of this case is a drug-releasing barrier such as a female condom or diaphragm. Examples of these various approaches and current prototypes are discussed in greater detail in the following sections.

3. Improved physical barriers

Male condoms, typically used to reduce the incidence of pregnancy, also reduce the risk of HIV transmission (Cates, 2001; Pazoi et al., 2010). However, in terms of effectiveness, the male condom ranks behind other contraceptive methods (sterilization, hormonal methods, intrauterine devices) with better records of prevention. Additionally, like most devices and drugs, male condoms must be used correctly and consistently to provide adequate protection (Cates and Steiner, 2002). While "perfect use" has an annual failure rate of about 2%, failure rates under"typical use" rise up to 15% on average (Trussell, 2007). Regarding HIV-1 prevention, several cross-sectional studies have shown that male condoms confer about 60-96% protection for male-to-female transmission (Davis and Weller, 1999). Real-world experience demonstrates significant challenges to consistently ensuring protected sex among women, especially in the developing world (Gollub, 2006).

An alternative to the male condom is FC. Examples of the FC are shown in Fig. 1. Like the male condom, the FC is a physical barrier preventing semen from reaching the vagina or cervixthus providing a barrier to pregnancy and HIV-1transmission (Vijayakumar et al., 2006). Typical- and perfect-use contraceptive failure rates are slightly higher than those of the male condom (Trussell, 2007). For non-HIV STIs, a randomized controlled trial showed similar degree of protection to the male condom (French et al., 2003). Regarding HIV-1 prevention, mathematical models predict about 63-82% effectiveness (Mukandavire and Garira, 2007).

Diaphragms have similar contraceptive failure rates to male condoms (6 and 16% for perfect and typical use). Cross-sectional studies on *Neisseria gonorrhoeae* and *Chlamydia trachomatis* infections have demonstrated 60-70% protection conferred by the use of the device (Minnis and Padian, 2005). In the more recent MIRA trial (n = 5,045), the investigators evaluated the effectiveness of the Ortho All-Flex® Diaphragm, lubricant gel (Replens®) and condoms compared to condoms alone on the incidence of HIV-1, chlamydial and gonococcal infections in an open-label randomized controlled trial among women at risk of HIV-1/STI infections (Padian et al.,

Fig. 1. Three examples of FCs. The condom shown in A is the Female Condom 2. The PATH Woman's condom is shown in B. The Reddy female condom is found in C.

2007; Ramjee et al., 2008). The HIV incidence was 4.1% in the intervention group (n = 2472) and 3.9% in the control group (n = 2476), corresponding to a relative hazard of 1.05 (95% CI 0.84-1.32, intention-to-treat analysis). The proportion of women using condoms was significantly lower in the intervention than in the control group (54%vs. 85% of visits, $p < 0.0001$). There was also no statistically significant differences in the incidence of *N. gonorrhoeae* and *C trachomatis* infections in both arms. The investigators concluded that they observed no added protective benefit against HIV-1, GC and CT infections when the diaphragm and lubricant gel were provided in addition to condoms and a comprehensive STI prevention package. Lower condom use in women provided with diaphragms, however, did not result in increased rates of infection.

4. Chemical barriers

Chemical barriers are currently the front line approach being evaluated to prevent transmission of HIV-1. These chemical barriers are called microbicides. In the case of DPTs, the chemical barrier should work against two different STIs or a specific STI and pregnancy. For instance, a drug acting as a vaginal contraceptive and another as a microbicide (i.e., a drug administered intravaginally that inhibits HIV-1 transmission) can be combined into a single dosage form. An early example of a proposed DPT was published in 1993 when cholic acid was formulated into a vaginal sponge (Psychoyos et al., 1993).

4.1. Contraceptive microbicides

First generationmicrobicides were based primarily on surfactants (e.g., nonoxynol-9 and C31G) and polyanionic compounds administered as intravaginal gels (Hillier et al., 2005; Mauck and Doncel, 2000; Doncel and Mauck, 2004; Friend, 2010). Nonoxynol-9 and C31G inactivated sperm and HIV-1 by disrupting their lipid membranes (Thompson et al., 1996). The polyanions were found to inhibit HIV-1 cell entry (Nakashima et al., 1989; McClure and Dalgleish, 1992; Neurath et al., 2002). Several of these polyanions (polyvinylsulfate, polystyrene sulfonate, cellulose sulfate) also demonstrated contraceptive properties through inhibition of sperm-oocyte interaction (Anderson et al., 2000; Anderson et al., 2002). Cellulose sulfate proved to be contraceptive in vitro, in animals and in a non-comparative clinical trial where a 6% cellulose sulfate gel was used by 200 couples as their only means of contraception (Mauck et al., 2008). Density of the negative charge and the position and alignment influenced inhibitory activity of these polyanions for both sperm and HIV-1 binding (Moulard et al., 2000; Oehninger et al., 1991). Unfortunately, both surfactants and polyanions failed to provide protection against HIV-1 transmission in pivotal Phase III clinical trials (Van Damme et al., 2008; Skoler-Karpoff et al., 2008; Abdool Karim, 2010). As a result, development of these compounds asDPTs has been suspended. Nonetheless, the exploitation of anatomical, physiological and molecular commonalities between HIV-1 infection and fertilization (see Fig. 2) remains a viable approach to dual-activity drug design (Doncel, 2006). Other dual-activity compounds have also shown increased anti-HIV and contraceptive activities (Uckun and D'Cruz, 1999).

Another approach to the development of microbicide/contraceptive combinations is the use potent hormonal contraceptives and antiretrovirals. The current generation of microbicides is based on antiretroviral drugs used in the treatment of HIV-1 infection (Klasse et al., 2008). The leading class of compounds under investigation isreverse transcriptase inhibitors (RTIs). Within this class are TFV, a NtRTI, and NNRTIs dapivirine, UC781 and MIV-150). These and other drugs are being investigated as both single entity and combination microbicide drug products in clinical trials. Microbicides are typically formulated as gels, administered once or twice daily, or controlled release IVRs. IVRs are torus-shaped devices prepared from silicone elastomers and more recently thermoplastic materials. While first described in 1970, commercial products indicated for hormone replacement and contraception were introduced in Europe and the US during the mid-1990 s. The first recognition of IVRs as potential delivery systems for microbicides was published in 2001 (Malcolm and Woolfson, 2001). While there are advantages and disadvantages of gels and IVRas dosage forms, they both offer a means to administer two drugs capable of providing dual protection.

IVRs offer the potential to extend release of one or more drugs to vaginal and ectocervical tissues for several months or potentially a year. The success of Nuvaring® as a contraceptive IVR provides the basis for DPT technologies that simultaneously release a contraceptive steroid (e.g., levonorgestrel) and a microbicide (e.g., TFV or UC781). To this end, DPT IVRs capable of delivering UC781 and LNG and dapivirine and LNG intravaginally are under active. The CONRAD IVR under investigation is composed of thermoplastic

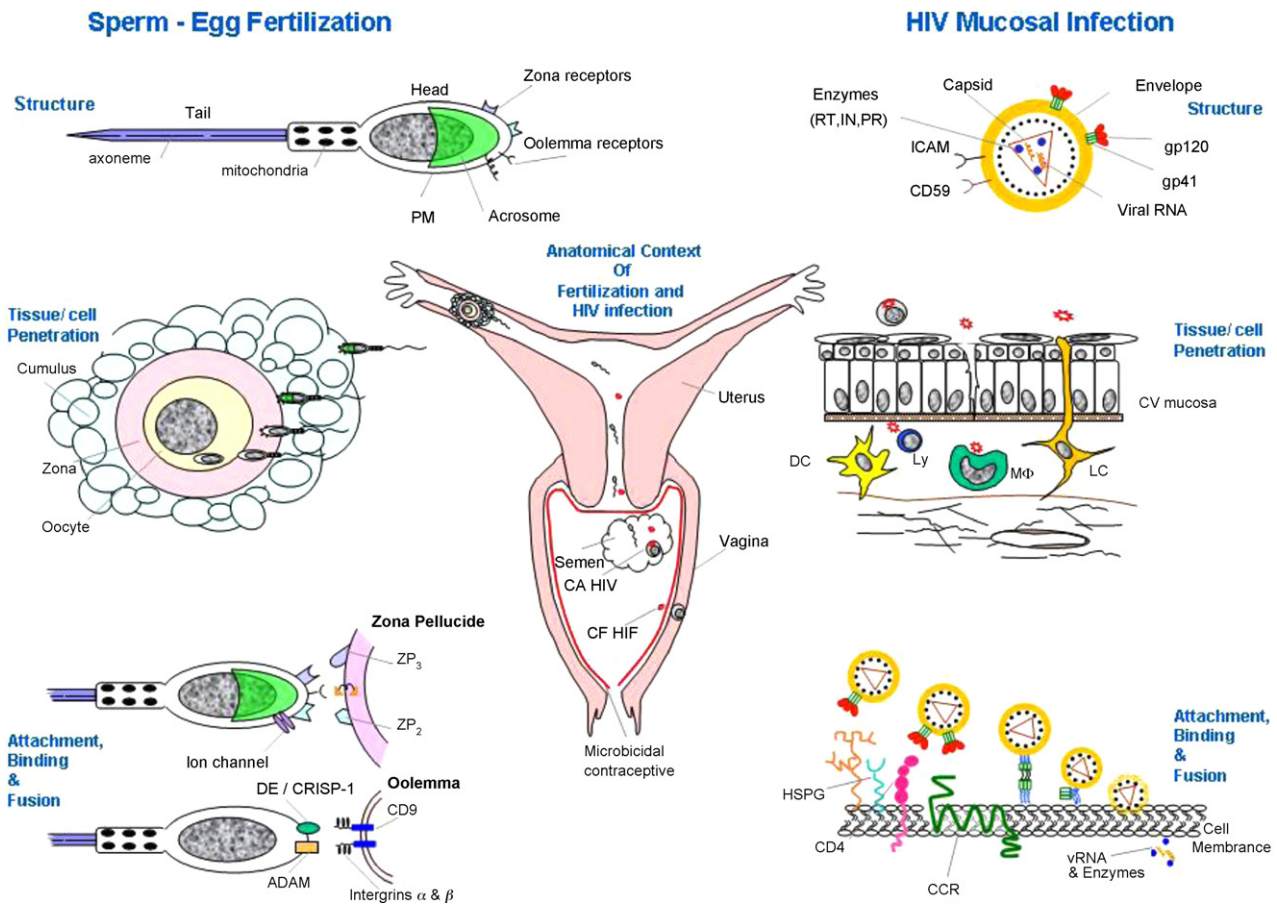

Fig. 2. Commonalities between mammalian fertilization and human immunodeficiency virus (HIV) infection. In addition to occurring within the same anatomical context, both processes involve similar steps of target cell recognition, binding, fusion and signal transduction (additional details in text). This figure presents an overview of mammalian fertilization and HIV mucosal infection. It does not depict all the molecules or mechanisms involved. AC, adenyl cyclase; ADAM, A desintegrin and metalloproteinase; AMP, adensoine monophosphate; AR, acrosome reaction; CA, cell-associated; cAMP, cyclic adenosine monophosphate; Cap, capacitation; CCR, chemokine receptor; CF, cell free; CHO, cholesterol; CV, cervicovaginal; DAG, diacylglycerol; DC, dendritic cell; DE/CRISP-1, epididymal protein DE/cysteine-rich secretory protein-1; ERK, extracellular signal-regulated protein kinase; G Prot, G protein; gp120, glycoprotein 120; gp41, glycoprotein 41; HA, hyperactivation; HSPG, heparin sulphate proteoglycan; ICAM, intracellular adhesion molecules; IN, integrase; InsP3/IP3, inositol 1,4,5, triphosphate; LC, Langerhans cell; Ly, lymphocyte; MΦ, macrophage; MAPK, mitogen-activated protein kinase; PDE, phosphodiesterase; PI3K, phosphatidyl inositol-3-kinase; P56-Ick = PKA, protein kinase A; PKC, protein kinase C; PLC, phospholipase C; PM, plasma membrane; PR, protease; PTK, protein tyrosine kinase; RT; vRNA, viral RNA; ZP2, zona pellucida glycoprotein 2; ZP3, zona pellucida glycoprotein 3; ZP-R, zona pellucida receptor. From Doncel (2006) with permission.

polymers such as EVAc, similar to that used in Nuvaring, or PUs. Release of both drugs under two different dissolution conditions is shown in Fig. 3. The ability to extrapolate these dissolution rates to in vivo release rates is challenging due to the limited water solubility of both UC781 and LNG. Another combination under development is the LNG/TFV IVR. LNG has an excellent track record of safety and efficacy, and it is, arguably, the best progestin to be incorporated in a controlled-release device. The feasibility of this concept has been clearly demonstrated by numerous clinical studies (World Health Organization, 1979; Health Organization World et al., 1990). After careful product development and selection, a silastic ring releasing 20 μg/day of LNG was tested by WHO for safety and effectiveness in 1005 women (8,177 woman-months). Pregnancy rate was 3.6% after 1 year of use (Health Organization World et al., 1990). A quarter of the ring users experienced some type of menstrual bleeding irregularity, but only 15% discontinued due to that reason. Menstrual blood loss, hemoglobin and serum ferritin levels were not significantly different from baseline after one year of ring use (Ji et al., 1993). Previous safety, PK and PD studies demonstrated no effect on plasma lipid profiles and glucose tolerance (Elder et al., 1984). A redesigned, softer ring, later tested for cervicovaginal irritation, showed no clinically significant changes in the vaginal and cervical mucosa (Weisberg et al., 2000).

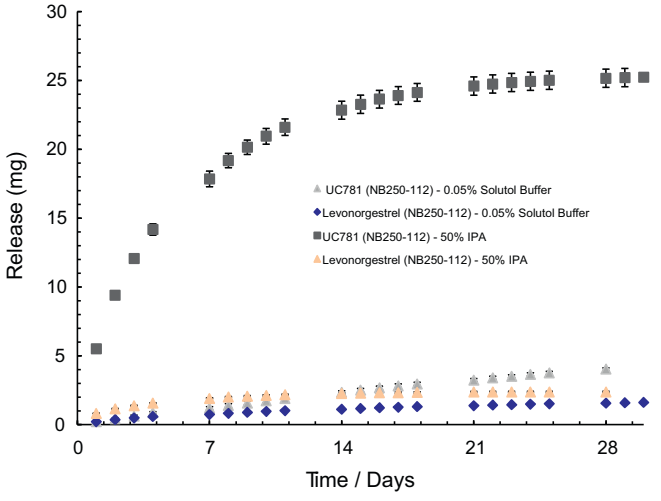

Fig. 3. The in vitro release of EVAc rings loaded with 25 mg UC781 and 2.5 mg levonorgestrel was performed under sink (100 mL of 1:1 v/v IPA:water) and non-sink (100 mL of pH 4.2 acetate buffer containing 0.05% Solutol) conditions. Samples were incubated at 37 °C and shaken at 60 rpm for 30 days. Release media was collected for assay and fully replaced daily. Mean ± SD, N = 3.

TFV, a NtRTI orally administered as a bioavailable prodrug (TDF; Viread®), is an important component of today's anti-HIV-1 therapeutic drug armamentarium. With over 1.5 million patient-years of use, it has been demonstrated to be safe and effective when administered orally, with low risk of developing resistance. Safety and pharmacokinetic studies of TFV 1.0% gel have demonstrated its suitability as a microbicide. NHP studies have shown high efficacy after vaginal or rectal administration (Parikh et al., 2009; Garcia-Lerma et al., 2008).

A major advantage of IVRs over other dosage forms is the ability to provide controlled release of the drug(s) over extended periods of time using a single device. As contraceptive delivery systems, other advantages are a more uniform hormone concentration both locally and systemically, no hepatic first-pass, more pronounced local effect, no fitting required, high user acceptability, and ease of insertion and removal (Woolfson et al., 2006; Oddsson et al., 2005). Users of NuvaRing® currently represent almost 10% of the U.S. market for hormonal contraceptives.

A novel DPTIVR should be highly contraceptive and potentially protect women against HIV-1 acquisition. Importantly, it could be used by breastfeeding women assuming both drugs are safe during lactation. It will also confer additional health benefits such as reduced incidence of menorrhagia, anemia and dysmenorrhea. By the multipurpose nature of its activities and the resulting compounded reproductive health benefits this technology should have a high uptake among women seeking family planning and protection against HIV-1.

4.2. Combination microbicides

Although less advanced than the combination of contraceptive and microbicide drugs, the combination of two antivirals aimed at reducing HIV-1 and HSV-2 genital infections is also under development by CONRAD. Both incident and prevalent HSV-2 infections are associated with anincreased risk of HIV-1 acquisition, presumably owing to frequentinfectious HSV-2 ulcerations and the associated influx of activatedCD4+ T cells that provide HIV easier access to large numbers ofpotential target cells (Zhu et al., 2009). The relationship between HSV-2 infection and HIV-1 transmission suggests that treatment of HSV-2 may impact HIV-1 transmission and infection. HSV-encoded proteins bind integrated HIV-1in coinfected cells and have been found to promote the transcription of HIV-1 (Kucera et al., 1990; Diaz et al., 1996; Heng et al., 1994). In persons infectedwith both HIV-1 and HSV-2, symptomatic andasymptomatic reactivation of HSV-2 has been associatedwith increased HIV-1 levels in the bloodand genital tract (Schacker et al., 1998; Schacker et al., 2002; Mbopi-Keou et al., 2000). Suppression of reactivation (i.e., recurrence) of HSV-2 could reduce the risk of HIV-1 transmission. ACV is used orally to treat patients with HSV-2 symptomatic ulcer disease and asymptomatic reactivation of genital HSV-2 (Gupta et al., 2004). Despite this relationship, suppression of HSV-2 with oral ACV is unable to suppress HIV-1 acquisition and transmission. In one study, ACV 400 mg bid was ineffective in reducing HIV-1 acquisition in HSV-2 seropositive women and men who have sex with men (Celum et al., 2008). In a more recent study, the ability of oral ACV (400 mg bid) to reduce the risk of HIV-1 transmission was tested in a large study in Africa involving 3,408 couples. Daily ACV therapy did not reduce the risk of HIV-1 transmission despite a reduction in plasma HIV-1 RNA (0.25 $\log_{10}$) and a 73% reduction in occurrence of genital ulcers (Celum et al., 2010). The biologic explanation for these findings is unknown. Persistence of HIV-1 receptor-positive cells after HSV-2 reactivation, even with daily antiviral therapy, has been postulated as a potential mechanism for increased HIV-1 acquisition. Other possible explanations are related to the study populations which did not include HSV-2 seronegative participants or subjects with frequent recurrences in whom ACV could be more effective (Celum et al., 2008).

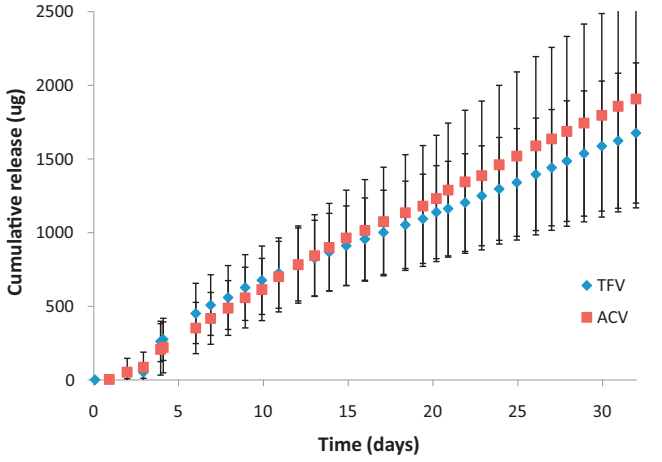

Fig. 4. The in vitro release of TFV (15 mg, 1 mm diameter delivery window) and ACV (15 mg, 1.5 mm diameter delivery window) Versaring ring segments (one pod of composed of TFV and ACV. Ring segments were incubated in 10 mL of pH 4.2 acetate buffer under static, ambient temperature conditions. Release media was collected daily for assay by UV-Vis and was fully replaced approximately every three days to assure sink conditions. Mean ± SD, N = 4.

An alternative approach is administration of ACV locally rather than systemically. To date, little is known about the local PKs of ACV in the reproductive tract following oral or topical administration. Topical drug administration normally leads to higher local tissue concentrations thanthose obtained through systemic (e.g., oral) administration. With the goal of reducing HSV-2 and HIV-1 acquisition in women at risk, and possibly HSV-2 symptomatic recurrences in HSV-infected women, groups are pursuing local administration of two microbicides, one with anti-HIV-1, activity (TFV), and the other with anti-HSV-2 activity (ACVor derivatives). Controlled release of both drugs is being explored from IVRs as dual protection delivery systems. In vitro release of TFV and ACV from a pod-based IVR is shown in Fig. 4. Both nucleoside derivatives would act independently and synergistically to protect women for HSV-2 and HIV-1 infections.

5. Chemical and physical barrier combinations

Barrier methods have been the corner-stone of contraception. These barriers include male condoms, diaphragms, cervical caps, intrauterine devices, and more recently female condoms. Combining them with a microbicide creates a DPT. The need for use the FC with a microbicide has recently been highlighted (Bisika, 2009). The Woman's Condom developed by PATH can accommodate a microbicide in the polyvinyl alcohol capsule encasing a portion of the condom (see Fig. 1). Once the capsule dissolves, a microbicide would be released providing additional protection against HIV-1 should the barrier be compromised (Ferguson et al., 2010).

Diaphragms are another effective barrier contraceptive method. Since a large portion of the vaginal epithelium remains exposed when a diaphragm is used, incorporation of a microbicide could provide added protection against HIV-1 transmission. BufferGel has been tested with a diaphragm clinically (Barnhart et al., 2007) but this particular combination is not viable due to the lack of microbicidal activity of BufferGel (Morris and Lacey, 2010). Another possibility for combining a microbicide with a barrier is the Duet™. The "sombrero" shape can deliver and distribute a gel containing a microbicide both to the cervix and to the vagina providing potentially three layers of protection for the cervix: vaginal-side gel, barrier film, and cervical-side gel (see Fig. 5). While tested in

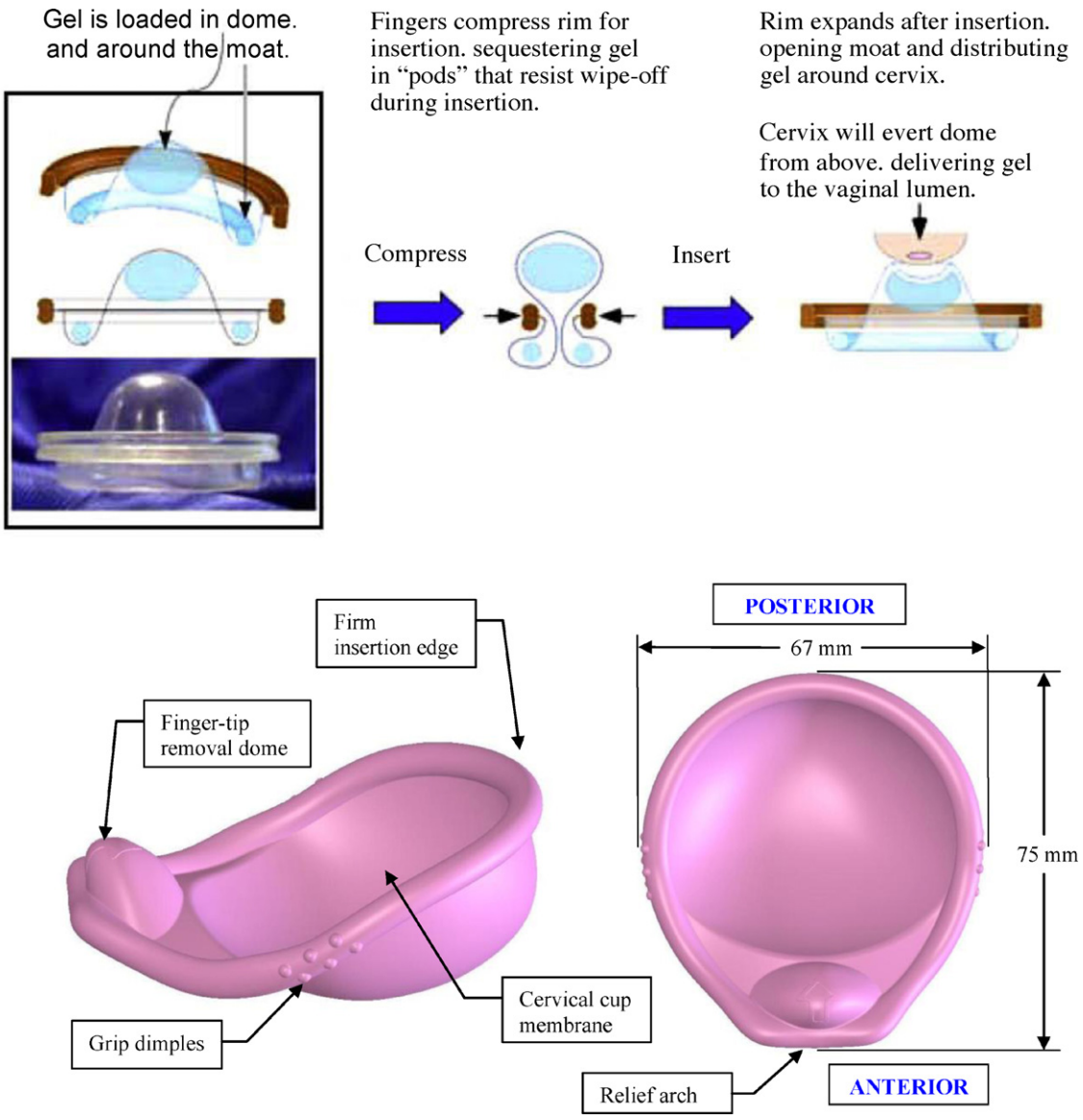

Fig. 5. Duet (top) delivers gel on both the cervical and vaginal-lumen sides (Ballagh et al., 2008). The SILCS diaphragm (bottom) is composed of silicone and nylon spring (Schwartz et al., 2008).

a Phase I study with BufferGel, the Duet can be used with other microbicide-containing gels (Ballagh et al., 2008).

A recently developed diaphragm (SILCS) offers another option for DPTs. The SILCS diaphragm (see Fig. 5) is composed of silicone elastomer with an internal nylon spring to provide sufficient force against the vaginal walls to hold it in place. Incorporation of a microbicide into the silicone body of the SILCS diaphragm could impair its physical properties (Major et al., 2010). Therefore, a more suitable location of the microbicide is in the nylon spring. However, the processing temperatures of the nylon is too high for most microbicides, therefore other materials with acceptable mechanical and drug compatibility are under investigation to replace the nylon spring.

6. Challenges facing DPTs

There are a number of challenges, scientific, technical and regulatory, to be addressed before DPTs can become viable strategy. On the scientific side, there remain questions concerning site of application, tissue concentration and mechanisms of action of a microbicide in order for it to be effective in preventing HIV-1 genital transmission. Significant resources are being directed to finding a safe and effective microbicide but lack of consensus regarding the answers to those questions impede a clear developmental path. DPTs are affected by the same gaps in the knowledge.

Technically, the DPT prototypes under development are for the most part combinations of a device (e.g., an IVR) and one or more drugs. With a few exceptions, there is usually a poor in vitro/in vivo correlation in terms of drug release from IVRs. Better in vitro dissolution test systems, such as flow-through systems, may lead to improved correlations, thereby accelerating development and entry into the clinic. On the in vivo side, validated animal models of microbicide activity have yet to be clearly defined. Several NHP models for testing antivirals, including a model capable of assessing impact of HSV-2 infection on transmission of HIV-1 (Crostarosa et al., 2009) have been developed but their ability to predict efficacy in humans must await clinical correlation. Other potential issues are drug stability in the vaginal environment and formation of a biofilm, particularly for vaginal devices designed for use over 3 or more months.

Regulatoryissues are also to be considered. Silicone elastomers and EVAc are currently used in commercially available IVRs. However, these polymers are not suitable for all drugs including hydrophilic drugs. The development of new polymers requires biocompatibility studies as defined in ISO 10993. Specific toxicology studies on IVRs composed of new materials may also be required. These extra studies add time and cost to development. Suppliers of new materials are often reluctant to allow intravaginal use due to litigation issues such as those encountered with silicone breast implants. Taken together, the regulatory and supply issues have hindered innovation and limited development of new IVR products. Fortunately, some suppliers are willing to provide new materials such as PUs for clinical development and commercialization.

7. Conclusions

DPTs offer considerable potential to address pressing needs in the areas of HIV-1 and other STI transmission, and unplanned pregnancies and its associated consequences to mother and child. There are millions of women who need protection against STIs/HIV and family planning methods. This urgent need warrants the development of multi-purpose prevention technologies with dual microbicidal and contraceptive and microbicidal properties. Leading prototype dosage forms under development include gels and IVRs. The latter provide the potential for prolonged release, better adherence, and lower cost, particularly suitable for the developing world. Leading anti-HIV microbicides are RTIs such as tenofovir, dapivirine, and MIV-150. Some regulatory concerns remain including the nature of pivotal clinical trial data required to register such products in the countries most affected by these problems.

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