EXPERT OPINION

Drug delivery in multiple indication (multipurpose) prevention technologies: systems to prevent HIV-1 transmission and unintended pregnancies or HSV-2 transmission

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Introduction: The development of multiple indication (multipurpose) prevention technologies (MIPTs) is driven by overlapping relationships in the area of female reproductive health.

Areas covered: In this review, the basis for MIPTs is detailed. The current state of the field for the use of drug delivery in novel MIPTs is covered. Of particular interest is the application of intravaginal rings (IVRs) for the delivery of two drugs simultaneously, to prevent one STI and pregnancy, or two STIs. IVRs are currently available commercially for contraception and have been developed for release of microbicides to prevent sexual transmission of HIV-1. Novel IVRs capable of releasing relatively large amounts of drugs such as tenofovir are discussed, along with those that contain independent delivery elements, such as pods, that can be used to release drugs at independent rates. The vaginal administration of macromolecules (antibodies and vaccines) is also reviewed in the context of MIPTs.

Expert opinion: The field of MIPTs remains one of potential. There is yet to be a proven microbicide effective at preventing sexual transmission of HIV-1. Development of MIPTs in the near term will proceed under the assumption that one or more antiretroviral (ARV) drugs will eventually be proven successful. IVRs have already demonstrated success in the area of contraception. Prevention of sexual transmission of HIV-1 and herpes simplex virus-2 (HSV-2) (or suppression of recurrence) remains an attractive MIPT target. In the long term, development of MIPTs will require validation of surrogate end points, particularly for prevention of HIV-1 transmission.

Keywords: contraception, HIV-1 prevention, HSV-2 prevention, multiple indication (multipurpose) prevention technologies

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1. Introduction

There is a large unmet need, especially in the developing world, for prevention of transmission of sexually transmitted infections (STIs), including HIV-1 and herpes simplex virus-2 (HSV-2). In addition, unintended (or mistimed) pregnancies are far too common in both the developing and developed worlds [1,2]. There is now an acknowledgement that the interrelationship between STIs and unintended pregnancies represents a special need for women's reproductive health [3]. To address this need, new technologies

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Article highlights.

- Multiple indication (multipurpose) prevention technologies offer the ability to protect against transmission of two different sexually transmitted infections (STIs).
- Multiple indication (multipurpose) prevention technologies offer the ability to protect against transmission of a STI and unplanned pregnancy.
- Intravaginal rings (IVRs) are a key drug delivery system capable of co-administration of two different drugs.
- IVRs are low-cost and will maximize user adherence.
- Vaginal delivery of antibodies and vaccines in addition to antiretroviral (ARV) drugs is possible through IVR technology.
- Advancement of MIPTs into the clinic and eventual approval may require development of surrogate end points for establishing the effectiveness of prevention of HIV-1 sexual transmission.

This box summarizes key points contained in the article.

including novel drug delivery systems that provide unique combinations of drugs and/or devices for multiple indications must be developed.

The statistics on STI incidence rates around the world as well as the number of unintended pregnancies have been presented elsewhere [1,2]. There are several approaches under development to prevent sexual transmission of HIV-1 to women. Of these, drug products that prevent transmission of HIV-1 (and other STIs), also known as microbicides, appear promising, particularly in light of the positive results from the CAPRISA 004 Phase IIb clinical trial conducted in South Africa. This trial showed that tenofovir (TFV) 1% gel administered vaginally before and after coitus reduced HIV transmission by 39%. However, the TFV 1% gel arm and the Viread® (oral) arm of another efficacy trial entitled Vaginal and Oral Interventions to Control the Epidemic (VOICE) were recently discontinued due to futility. As discussed below, these trials used different dosing regimens which, along with adherence issues, may have rendered the gel ineffective in VOICE. A TFV-releasing intravaginal ring (IVR) is currently under active development for potential improved adherence and lower costs compared with daily or pericoital gels containing TFV [4]. Another potential microbicide product is an IVR capable of releasing the non-nucleoside reverse transcriptase inhibitor (NNRTI) dapivirine (DPV) for 28 days [5]. Other formulations for delivery of microbicidal compounds include films and fast-dissolve tablets.

Contraceptive methods have been available for many years. These methods include male and female condoms, diaphragms, intrauterine devices, IVRs (NuvaRing®) and oral and sustained release (parenteral) estrogens/progestins. The effective use of these methods varies around the world, as do the specific methods used [6]. A case in point is male condom use. Like most devices and drug products, condoms must be used correctly and consistently to provide protection against conception as well as transmission of HIV-1 [7]. However, real-world experience demonstrates significant challenges in the correct and consistent use of male condoms [6,8].

There is some overlap between dosage forms used for vaginal delivery of antiretroviral (ARV) drugs and delivery of contraceptives (e.g., the IVR). There is also the possibility of combining existing barrier methods such as diaphragms with delivery of microbicidal compounds directed at the prevention of HIV-1 and other STIs such as HSV-2 and possibly human papillomavirus (HPV).

Combining technologies to address treatment or prevention of more than one disease or potential infection has been addressed to a limited extent over the past few years [7,9-12]. These unique combinations have been called dual-protection technologies (DPTs) as well as multipurpose prevention technologies [3]. This article will use the term MIPT (as it is a more descriptive phrase than multipurpose prevention technologies) when discussing drug delivery technologies that could prove useful in successful development of products with two different indications. While conceptually possible, products with three different indications are not discussed herein.

2. Vaginal drug delivery

A comprehensive review of vaginal drug delivery was published in 2000 [13]. Since then, other review articles on vaginal drug delivery have been published [14-19]. Specific reviews on various dosage forms used to deliver microbicides and contraceptives vaginally are also available [20-23].

The type of dosage forms available for vaginal administration range from those that require a single or multiple applications per day (gels, films, fast-dissolve tablets and capsules) to extended release systems that require user action only once per month or once every 2 – 3 months (i.e., IVRs). Presently, the choice of dosage form for MIPTs is based on assumptions rather than supportive clinical data. Since most, if not all, MIPTs are expected to include a component designed to prevent transmission of HIV-1 adherence is an issue as the product is prophylactic rather than a treatment. In most Phase III microbicide clinical trials, lower than desired adherence is an acknowledged problem [24-28]. Dosage forms must be acceptable to be used and, therefore, products should be designed accordingly. To date, most products developed for use as microbicides have been gels. Gels offer the benefit of ease of formulation and relative simplicity compared with other, more complex dosage forms such as IVRs. However, gels are short-acting, require an applicator (often composed of plastic) and may be unacceptable to women if there is excess gel leakage. To address issues of acceptability and improved efficacy, IVRs are a practical alternative [29]. IVRs are typically used over a period of 3 weeks to 3 months (NuvaRing and Progering®, respectively). IVRs also have the advantage of being able to release two active ingredients, as presented in more detail below.

3. HIV-1 prevention and contraception

Delivery of hormones intravaginally has been proven clinically efficacious [30,31]. The availability of contraceptive products has reduced maternal mortality and child mortality while reducing the number of induced abortions around the world [32]. IVRs offer the advantage over oral contraceptives of improved adherence by eliminating the possibility of missed doses associated with oral, once-daily administration. Contraceptive IVRs also provide, in addition to effective cycle control, relief of symptoms such as menorrhagia and dysmenorrhea, and polycystic ovarian disorder. IVRs also have a relatively long history of use as hormone (estrogen) replacement delivery systems [33].

Early work on IVRs relied on the use of silicone elastomers. This was a logical starting point since most commercial IVRs rely on silicone (see **Table 1**). However, the range of drug molecules that can be delivered at rates believed to be therapeutically effective from silicone is limited [29]. The next material to be considered based on commercial use was ethylene vinyl acetate copolymer (EVAc). More recently, polyurethanes (PUs) have been investigated as controlled release polymers in IVRs [17,29].

NuvaRing represents a unique IVR design compared with earlier silicone elastomer IVRs. It has a relatively small cross-sectional diameter of 4.0 mm. It contains 2.7 mg ethinyl estradiol (EE) and 11.7 mg etonogestrel (ENG) loaded into a core of EVAc (28% vinyl acetate content) which is surrounded by a drug-free EVAc sheath (9% vinyl acetate content). This ring structure is created through coaxial extrusion [34]. The product releases 15 µg/day EE and 120 µg/day ENG [35]. The clinical pharmacokinetics of EE and ENG over the intended period of release (21 days) and extended release (days 22 – 35) have been studied [36]. Overall, NuvaRing is efficacious, well tolerated and well accepted by women [37-39]. Progering is another contraceptive IVR that is available in Chile, Bolivia, Peru and Ecuador for use in lactating women. The ring, composed of silicone elastomer, is designed to release progesterone at a rate of 10 mg/day [40]. This rate is relatively high compared with most drugs released from IVRs. Clinical trials showed Progering to be safe and effective in breastfeeding women [40,41].

From a development perspective, a two-drug combination (e.g., a microbicide and a progestin) represents a less challenging product development pathway compared with development of a three drug combination (e.g., a microbicide, a progestin and an estrogen). The added benefit of low-dose estrogen delivery (reduced bleeding irregularities, improved cycle control) may be insufficient to justify the added time and expense of developing a dosage form capable of controlling the prolonged release of three different drugs.

A review covering the use of IVRs to deliver microbicides intravaginally was published by Woolfson *et al.* [23] about the same time that DPV-releasing IVRs were being developed [42,43]. A review of microbicide IVRs addressing development, scale-up and manufacturing challenges was recently published [29].

DPV is a potent NNRTI [44] under development as a microbicide in both gel [45,46] and IVR dosage forms. The IVR dosage form for DPV is composed of silicone elastomer. The device is designed to release DPV intravaginally over a 28-day period. Matrix and reservoir devices were evaluated in a Phase I clinical safety/pharmacokinetic study [5]. Pharmacokinetic data from this study are shown in **Figure 1**. The reservoir design provided more constant vaginal fluid levels over time, but these levels were markedly lower compared with the matrix device. Presumably due to the higher vaginal fluid levels compared with the reservoir device, the matrix form of the DPV IVR is scheduled to be tested in a Phase III efficacy study in Africa.

A logical combination for an MIPT IVR for prevention of HIV-1 transmission and contraception would be the controlled release of DPV and a suitable progestin from a silicone matrix. Both compounds have been successfully formulated in such matrices [47,48] and these systems are capable of releasing compounds at effective rates (progestin) or believed-to-be-effective rates (DPV). Duration of action of IVRs in the developing world setting is important when cost of goods is considered. A 3-month IVR would have a cost advantage over a ring discarded after 28 days of use. Thus, new combination IVRs should be developed to act longer than 28 days. Given the potency of DPV (< 1.0 ng/ml *in vitro* [49,50]) and the ability to release a progestin such as levonorgestrel (LNG) for greater than 28 days, it should be possible to develop a long-acting multipurpose IVR using these drugs.

An alternative thermoplastic polymer to EVAc is based on PUs. There is a range of chemical and physical properties available using PUs which allows for the creation of unique IVRs capable of controlling the release of drugs with a wide range of physicochemical properties. The primary creation of various PU compositions involves synthesis of copolymers with varying ratios of hard block (hydrophobic) and soft block (hydrophilic) segments [29]. These properties are obtained by reacting hydrophilic polymeric diols such as polytetramethylene oxide (PTMO) or polyethylene oxide (PEO) with aliphatic diisocyanates [51]. Of the two hydrophilic monomers, PTMO provides hydrophilic properties to the final PU. Drugs recently incorporated into PU-based IVRs include UC781, DPV and TFV [52-54].

The use of PU-based IVRs has been explored with TFV and DPV. TFV targets reverse transcriptase but acts at a different location on the enzyme than NNRTIs. As presented in Section 1, two clinical trials have provided inconclusive results concerning the effectiveness of TFV 1% vaginal gel. However, the gel was administered differently in each study. In the successful trial (CAPRISA 004), the gel was administered once within 12 h prior to sex and again within 12 h after sex (coitally dependent). The women in the VOICE trial used a dosing regimen of once-daily gel administration (coitally independent). In the CAPRISA 004 study, women self-reporting higher adherence had a higher percentage (54%) of prevention of HIV-1 acquisition. If low user adherence proves to have contributed to the results of the VOICE trial,

Table 1. Commercially available IVRs for hormone replacement (Estring®, Femring®) and contraception (NuvaRing®, Progering®, Fertiring®).

Product	Active(s)	Polymer	Device/Active
Estring®	17β-Estradiol	Silicone	Reservoir/non-ionizable, logP = 3.6
Femring®	17β-Estradiol-3-acetate	Silicone	Reservoir/non-ionizable, logP = 4.0
NuvaRing®	ENG + EE	EVAc	Reservoir/non-ionizable, logP = 3.4, 4.3
Progering®	Progesterone	Silicone	Matrix/non-ionizable, logP = 3.5
Fertiring®	Progesterone	Silicone	Matrix/non-ionizable, logP = 3.5

EE: Ethinyl estradiol; ENG: Etonogestrel; IVR: Intravaginal ring.

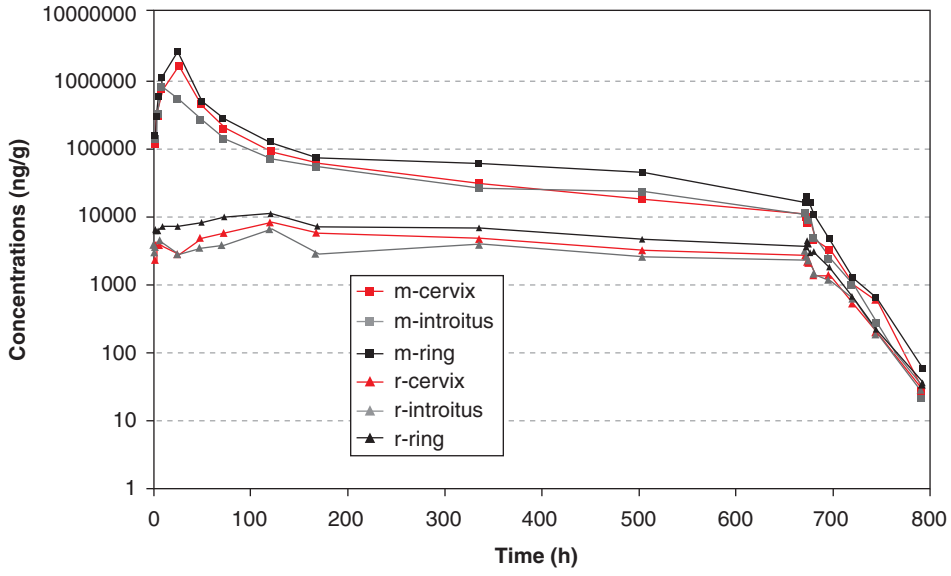

Figure 1. Vaginal fluid levels of DPV based on samples collected from the vagina near the IVR using Sno-Strips.
Reproduced with permission from Wolters Kluwer Health [5].
m: Matrix IVR; r: Reservoir IVR.

IVRs capable of delivering relatively high amounts of TFV might offer a reasonable alternative. Such an IVR would need to release relatively large amounts (ideally > 10 mg/day) to provide the TFV tissue concentrations believed to be required to prevent HIV-1 transmission [55].

PUs are thermoplastics that require heating, as the name implies, to effectively mix drug and other additives, followed by extrusion or injection molding. PUs generally require temperatures around 150°C or higher to create sufficient flow properties. Therefore, the drug must be stable at these temperatures at least for short periods of time (min), assuming the drug is incorporated into a matrix device. An alternative design is to use PUs as rate-controlling membranes, as recently reported for TFV. This IVR reservoir design, coupled with the appropriate PU and core containing a high concentration of TFV, can deliver up to 30 – 35 mg/day of TFV for 1 month or about 10 – 15 mg/day for 90 days [56].

Since TFV is water soluble and requires a high daily dose be delivered, co-formulating with traditional contraceptive agents such as LNG, which is relatively hydrophobic, may require a segmented IVR design similar to the one seen in **Figure 2**. A prototype for such an IVR has been published [54]. The IVR described in this paper is a matrix design, but the concept is also applicable to reservoir devices. If high delivery rates (i.e., nearly 40 mg/day) of TFV are required, this MIPT IVR product may be limited to 28-day use.

4. HIV-1 and HSV-2 prevention

HSV-2 is the most common cause of genital ulcers and is 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 to more than 80% in people infected with HIV-1 [57,58]. HSV-2 infections are associated with an increased risk of HIV-1 acquisition, presumably owing to frequent infectious HSV-2 ulcerations

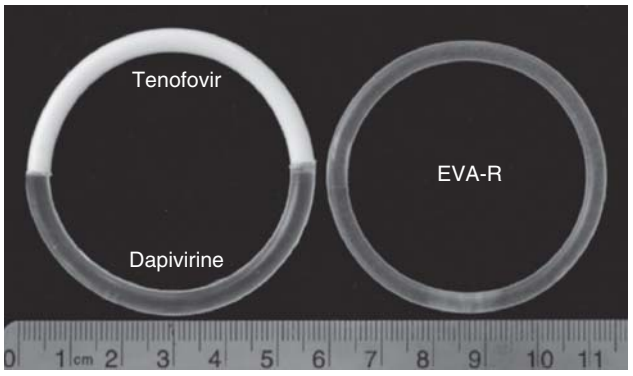

Figure 2. Left, segmented IVR consisting of TFV in Tecophilic HP-60D-20 (top section) and DPV in Tecoflex EG-85A (bottom section). Right: NuvaRing®.
Reproduced with permission from Elsevier [54].

and the associated influx of activated $CD4^+$ T cells that provide HIV easier access to large numbers of potential target cells [59]. 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 to integrated HIV-1 in co-infected cells and promote the transcription of HIV-1 [60-62]. In persons infected with both HIV-1 and HSV-2, symptomatic and asymptomatic reactivation of HSV-2 is associated with increased HIV-1 levels in the blood and genital tract [63,64].

Based on the foregoing, it is reasonable to hypothesize that suppression of reactivation (i.e., recurrence) of HSV-2 could reduce the risk of HIV-1 transmission. Oral acyclovir (ACV) is used to treat patients with HSV-2 symptomatic ulcer disease and asymptomatic reactivation of genital HSV-2 [65]. Despite this relationship, suppression of HSV-2 with oral ACV is unable to suppress HIV-1 acquisition and transmission [57,58]. The biological explanation for these findings is unknown. One possible explanation could be 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 [57]. In addition, oral doses of ACV may not lead to sufficient local tissue concentrations to reduce recurrent genital epithelial replication and shedding.

In the CAPRISA 004 study, it was found that TFV 1% gel reduced transmission of HSV-2 by 51% [66]. TFV is not particularly potent toward inactivation of HSV-2 compared with compounds such as ACV. Combining TFV and ACV in a single MIPT product could lead to an effective product for the prevention of HIV-1 and HSV-2. In this case, it is reasonable to consider both a pericoital gel and a long-acting IVR system. A gel can easily accommodate relatively large doses of both TFV and ACV (e.g., a single dose of TFV 1% gel delivers about 40 mg of TFV). In the case of an IVR, the need to release relatively large amounts of two drugs might represent a challenge.

Two approaches to the delivery of TFV and ACV using IVRs have been investigated. The first is based on a technology being developed by Auritec and Oak Crest Research Institute (Pasadena, CA, USA). This system relies on polymer-coated pods embedded in a standard silastic IVR (see **Figure 3**). A small opening communicates between a limited area of the pod and vaginal fluid. Release rates from this system are highly controlled compared with most other IVR designs. A combination IVR releasing both TFV and ACV demonstrated reasonably constant release rates in rabbits and sheep [67]. A limitation of this design is the total amount of drug that can be loaded and hence released over an extended period of time. For potent compounds, this loading limit will not present a significant hindrance but for drugs that lack adequate potency (e.g., TFV) the IVR may be incapable of delivering sufficient drug over a minimum of 28 days to be efficacious.

Another approach to co-delivery of TFV and ACV from an IVR is based on a matrix PU system. This system, developed by Controlled Therapeutics (East Kilbourne, Scotland) contains 10% TFV and 10% ACV dispersed in a hydrophilic PU matrix. The system can release milligram quantities of both drugs over a 28-day period. Release is expected from a matrix device (proportional to the square root of time [17]). Release of TFV and ACV from matrix PU IVRs under *in vitro* conditions and in sheep over 28 days is shown in **Figure 4** [68]. The data in **Figure 4** were collected by retrieving the rings from groups of sheep at specific times followed by analysis of residual drug content. The amount released *in vivo* is compared with the *in vitro* release rates of both drugs.

Attempts have been made to combine barrier methods of contraception such as the SILCS diaphragm and the PATH Woman's Condom with microbicides [1,29,69,70].

5. MIPTs and biopharmaceuticals

Vaginal delivery of biopharmaceuticals in the field of prevention technologies encompasses peptides/proteins, antibodies and vaccines. An example of a peptide that can potentially prevent vaginal HIV-1 transmission is the chemokine RANTES and its various analogs [16]. Antibodies have the potential of reducing HIV-1 (and other viral) transmission through specific neutralization, agglutination and mucus trapping when administered into the vaginal lumen. Vaccines can be designed to bind to the HIV-1 envelop and, when combined with microbicides, may provide added protection against HIV-1 transmission [71].

The potential of vaginal protein delivery was first reported in 1992 [72]. This work was directed at releasing antibodies from EVAc devices directly in an attempt to provide vaginal immunoprotection using IgG against STIs. The devices were tested *in vivo* in mice to examine the release of bovine serum albumin (BSA) or anti-human chorionic gonadotropin (anti-hCG) antibodies. The ring devices were sutured into the vaginas of mice and were capable of releasing BSA and anti-hCG to the vaginal mucus for 30 days [72].

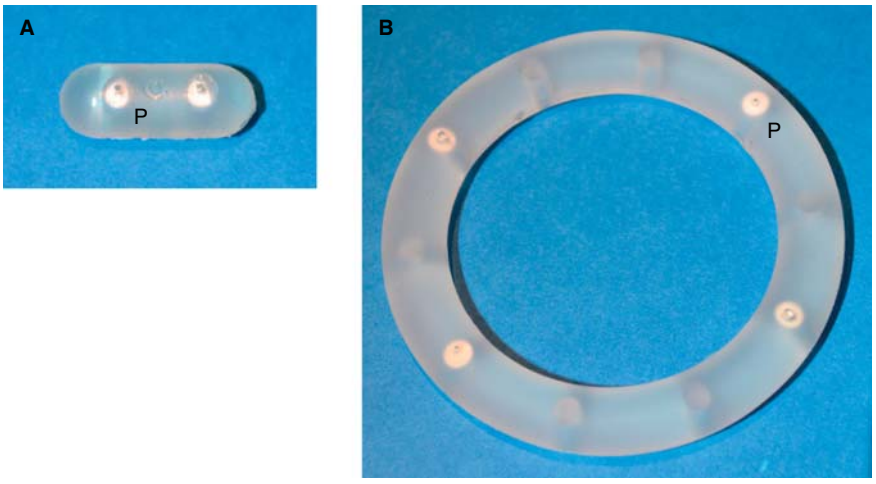

Figure 3. Photographs of rabbit (A) and sheep (B) intravaginal devices.
Reproduced with permission from the American Society for Microbiology [67].
P: Pod.

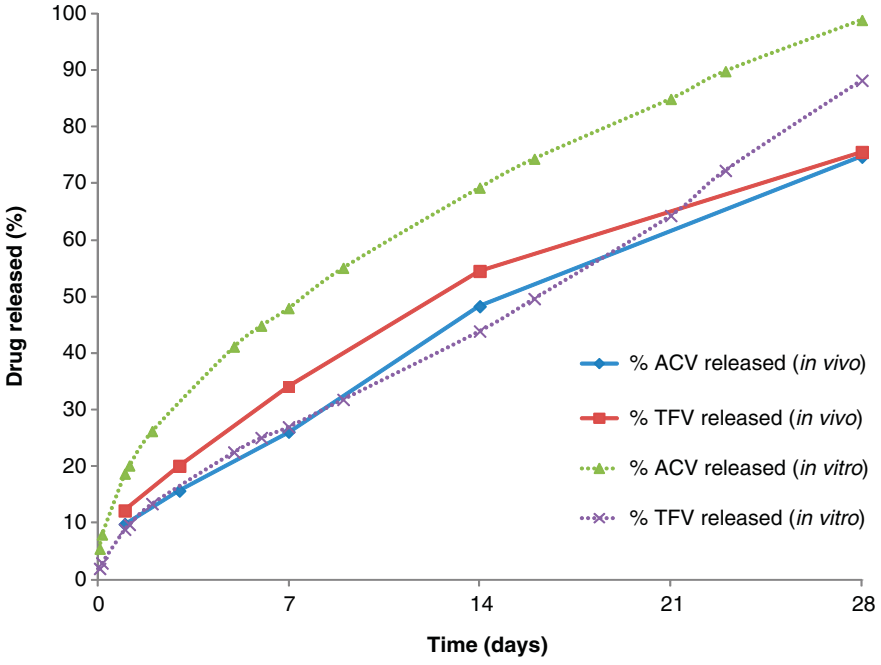

Figure 4. *In vitro* and *in vivo* (sheep) release of TFV and ACV from PU matrix IVRs containing 10% of each TFV and ACV. Sheep data collected by retrieving IVRs at specific time points, then measuring residual drug content.

Sustained release vaginal devices were used to provide topical passive immunoprotection in female mice [73]. An antibody (IgG2a monoclonal antibody (MAb) III-174) capable of neutralizing HSV-2 [74] was loaded into EVAc disks. Mice challenged with 10 or 500 times the infectious dose needed to infect one-half of untreated mice (10 ID_{50} and 500 ID_{50}, respectively) were protected by disks releasing III-174 compared with devices releasing non-specific IgG. Despite this work, no further reports on vaginal delivery of proteins have appeared until recently.

One approach to delivery of proteins from IVRs is based on placing protein-containing inserts into the ring. While similar in concept to the pod design described above, the composition of the insert is designed to prolong release of the protein [75]. The inserts (and pods) can be prepared from standard tableting excipients or lyophilized gels. These inserts

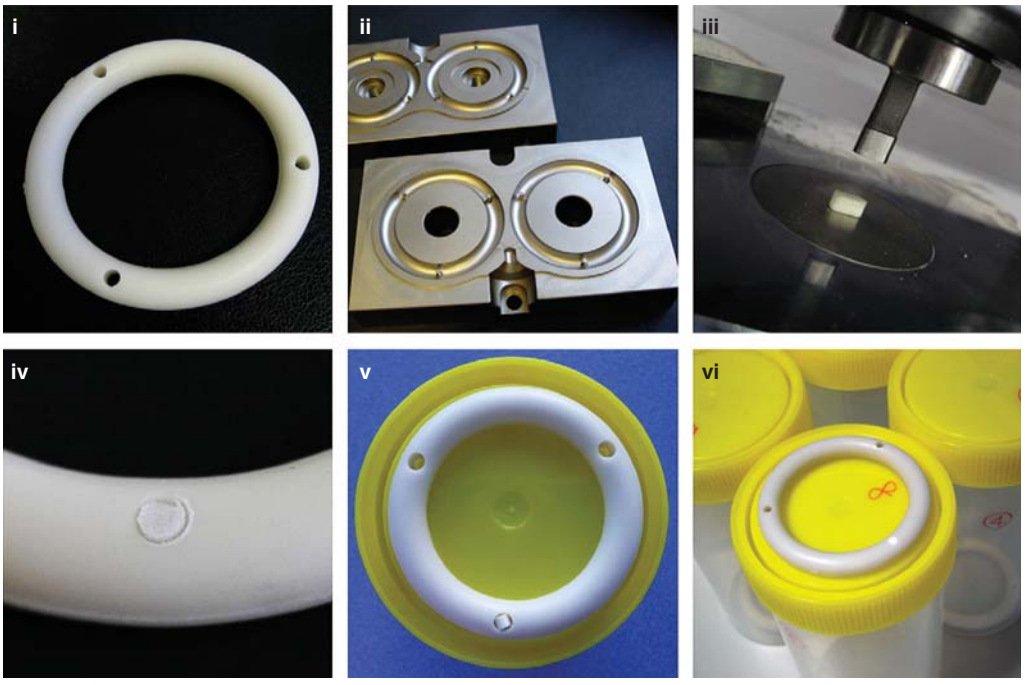

Figure 5. (i) Silicone insert vaginal ring, (ii) injection moulds for insert vaginal ring manufacture, (iii) directly compressed insert manufacture, (iv) silicone insert, (v) directly compressed tablet insert and (vi) lyophilized insert.
Reproduced with permission from Elsevier [75].

are placed in small holes in rings prepared from silicone elastomers (**Figure 5**). Using this technology, over 1 mg of the MAb 2F5 was released from a device prepared with lyophilized gels composed of varying molecular weights of hydroxypropyl methylcellulose. The advantage of the insert (and pod) approach as compared with traditional IVR configurations is the ability to simultaneously release two drugs with considerably different physicochemical properties. Thus, ARV or contraceptive drugs could be combined with an antibody or vaccine to create novel and potentially effective MIPT delivery systems.

6. Novel drug delivery systems

In the short term, MIPT delivery systems will need to rely on existing technology. However, there are new approaches under investigation for vaginal delivery of drugs that could at some point in the future provide advantages over gels and IVRs. Nanoparticles are under investigation for every conceivable application, including vaginal drug delivery. A recent example is a pH-responsive system designed to release TFV [76,77]. Nanoparticles must be co-formulated into a delivery vehicle such as a gel to create a viable vaginal drug delivery system. Tablet or film-based dosage forms are also suitable candidates for administration of nanoparticles. The nanoparticles can be co-formulated with a second drug to provide novel MIPTs.

Another new approach to vaginal delivery relies on dispersion of cationic liposomes in a thermosensitive gel [78]. The use of surfactant molecules in a delivery system designed to prevent transmission of HIV-1 could be problematic, however, due to the known enhanced transmission findings with nonoxynol-9, a non-ionic surfactant [79-81].

Bio- or mucoadhesive dosage forms have been investigated for many years. Papers on this subject continue to be published despite limited successful development of products based on mucoadhesion. In the area of vaginal drug delivery, a recent example includes a bioadhesive film designed to treat bacterial vaginosis with clindamycin phosphate [82]. Vaginal tablets with antifungal drugs have been prepared with thiolated polymers for enhanced mucoadhesive properties [83]. In both instances, the overall goal was to increase the presence of drug in the vagina to extend duration of action. Both film and tablet dosage forms lend themselves to co-administration of two different drugs with different indications. Neither approach, however, will provide extended duration of action due to the mechanisms of drug release which rely on dissolution or disintegration of the excipients.

7. Expert opinion

The field of MIPTs remains one of potential. While TFV gel has been successful in significantly reducing transmission of HIV-1 in women, its effectiveness was less than desired (39% reduction in sexual transmission compared with placebo gel) [4]. In a separate study (VOICE), the same gel used in a different dosing regimen proved ineffective, with the gel arm of

this trial stopped early due to futility. Thus, the lack of availability of an effective microbicide limits successful development of MIPTs where one of the objectives is prevention of HIV-1 transmission. Follow-up clinical trials with TFV gel and the DPV IVR will yield efficacy data no sooner than 2 – 3 years from now. Thus, it will be some time before a microbicide effective against HIV-1 transmission is identified (assuming at least one of the two compounds in or about to begin efficacy testing is successful). Thus, the correct dose or delivery rate for MIPTs to prevent transmission of HIV-1 will remain a matter of some uncertainty.

A significant benefit of testing new MIPTs designed to prevent transmission of HIV-1 will be the development of validated surrogate end points that will obviate the need for large Phase III clinical trials. After an HIV-1 microbicide is found to be effective, it will be unethical to perform placebo-controlled trials. Thus, superiority or non-inferiority trials that compare the proven product against the innovative product will be required. The cost of such trials will probably be prohibitive.

Contraceptive systems have proven effective, so the challenge is one of combining a microbicide with an existing contraceptive vaginal dosage form. Thus, IVRs are the logical choice for delivery of an anti-HIV-1 microbicide and a contraceptive agent. Microbicides are already well advanced in IVR drug delivery systems, so technically the challenges should be manageable. The challenge with IVRs will be the ability to release an effective dose over a long period of time (ideally 3 months or longer). Another issue is selection of the contraceptive agent or agents (progestin vs progestin/estrogen combination). It is unclear if the added benefits of the combination of a progestin with an estrogen outweigh the added technical challenges in creating a controlled release drug delivery system capable of releasing three drugs at the correct rates over an extended period of time.

There has been some recent controversy around the relationship between hormonal contraception and HIV-1 transmission [84]. A secondary analysis of data from a recent clinical trial suggested that hormonal contraception might increase the risk of HIV-1 transmission [85]. It is unlikely that a clear relationship between the use of contraceptives and their possible role in HIV-1 transmission will be delineated any time in the near future.

The prevention of HSV-2 transmission was demonstrated in the CAPRISA 004 trial, although this outcome was unexpected [66]. Other than this isolated observation, it is unclear if topically applied agents such as ACV (either alone or in combination) will actually prevent transmission of HSV-2 or possibly work to reduce the transmission of HIV-1 in those already infected with HSV-2.

As the field of MIPTs matures, other challenges to be addressed include the clinical evaluation of MIPT products, the technical and cost implications associated with manufacturing, the assessment of potential drug–drug interactions and the regulatory approach required to gain approval for multiple indication products.

Declaration of interest

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