# In search of the optimal delivery method for anti-HIV microbicides: are intravaginal rings the way forward?

### Nina Derby
*Center for Biomedical Research, Population Council, 1230 York Avenue, New York, NY 10065, USA*

### Thomas Zydowsky
*Center for Biomedical Research, Population Council, 1230 York Avenue, New York, NY 10065, USA*

### Melissa Robbiani
*Author for correspondence: Center for Biomedical Research, Population Council, 1230 York Avenue, New York, NY 10065, USA*
*Tel.: +1 212 327 7794*
*Fax: +1 212 327 7764*
*mrobbiani@popcouncil.org*

> **"The ability of intravaginal rings to deliver drugs like contraceptives, which require tightly controlled release, gives intravaginal rings an advantage over gels."**

### Intravaginal rings are an advantageous microbicide delivery platform

Microbicides are urgently needed to help stem the HIV epidemic [1]. With time and resources at a premium, donors, researchers and regulators agree that only the most promising candidates should be pursued (although they do not always agree on how to prioritize them) [2]. Following the realization that microbicides comprising non-specific inhibitors were not effective [3], the field has focused principally on topical gels and oral pre-exposure prophylaxis containing antiretroviral drugs, especially reverse transcriptase inhibitors (RTIs). Significant protection was achieved in clinical trials of a pericoital 1% tenofovir (TFV) gel (CAPRISA 004) [1] and a pill of Truvada once daily (iPrex) [4], positioning microbicides solidly in the fight against HIV. Nevertheless, the best correlate of microbicide efficacy is drug concentration at the exposure site [5,6]. Low adherence to gel regimens results in sub-therapeutic drug levels in the mucosa [1,5], and oral dosing achieves substantially lower vaginal levels than vaginally applied agents [7]. These factors probably contributed to the failure of the VOICE (topical 1% TFV gel) and FEM-PrEP (oral Truvada) trials [7], and indicate that other HIV prevention strategies are still needed.

Intravaginal rings (IVRs) provide an alternative delivery method for topical microbicides. Widely used for contraception and hormone replacement therapy [8], IVRs offer sustained release of active pharmaceutical ingredients (APIs), having the potential for long-acting protection [2,8]. Used discretely, independent of coitus and requiring minimal effort after insertion, IVRs have been accepted by users [9] and may improve adherence over gels [9,10]. Moreover, recent macaque data show that IVRs releasing the non-nucleoside RTI (NNRTI) MIV-150 offer significant protection against HIV reverse transcriptase in a simian immunodeficiency virus background (SHIV-RT) [11], demonstrating the promise of IVRs for reducing HIV transmission.

### Optimizing IVRs for efficacy

IVRs are produced from silicone elastomer or thermoplastic polymers like ethylene vinyl acetate (EVA) and polyurethane (PU). The choice of polymer depends on API solubility, API stability during IVR manufacturing and API release rates needed to achieve sustained delivery of therapeutic doses of drug(s) to the cervicovaginal tissue. In macaque studies performed to date, drug levels in tissues correlate best with microbicide efficacy [11–13]. NNRTIs are compatible with silicone and EVA. A silicone dapivirine (25 mg) IVR is currently in a Phase III clinical trial [101]. This IVR is safe in healthy women [14] and pharmacokinetic evaluation has

10.1586/ERI.12.155 © 2013 Expert Reviews Ltd **5**

demonstrated that dapivirine levels in excess of the $IC_{50}$ are detected in cervicovaginal fluid and tissues within hours and for up to 7 days after IVR insertion [14]. Silicone IVRs releasing either of the entry inhibitors, Maraviroc (4.5 mg/day) or CMPD167 (0.1 mg/day), delivered sustained drug levels to macaque vaginal fluids and tissues, which were influenced by Depo Provera treatment [15]. A matrix PU IVR released TFV at rates greater than 2 mg/day for 90 days *in vitro* (better than that from silicone or EVA) [16]. Improving on that IVR, a PU reservoir IVR loaded with TFV was recently reported to release more than 10 mg/day for 90 days *in vitro* and significant amounts in sheep (resulting in $10^4$ ng/g TFV in vaginal tissue) [17]. However, no efficacy studies in animals have been performed on the above IVRs.

We have shown that silicone and EVA IVRs release MIV-150 *in vivo* and that 14–28 days use of an EVA IVR loaded with 100 mg of the NNRTI MIV-150 offers significant (83%) protection against a single high dose of SHIV-RT in macaques [11]. *In vitro* studies show that 5.3% of the MIV-150 in the IVRs is released over 28 days, suggesting the potential for a 90-day IVR [11, Zydowsky, Unpublished Data].

> **"Intravaginal rings offer sustained release of active pharmaceutical ingredients, having the potential for long-acting protection."**

Achieving sustained release of two or more APIs with differing physicochemical properties from a single polymer is challenging. A PU IVR was recently described that releases both TFV and dapivirine [18]. These matrix IVRs were created by joining segments of water swellable and non-water swellable PU containing TFV and dapivirine, respectively. In another design, pods of TFV and acyclovir were coated with a sustained release polymer and embedded in empty silicone rings with delivery channels to provide independently controlled release of TFV and acyclovir *in vitro* [19]. These IVRs maintained drug levels for over 28 days in rabbit and sheep vaginal fluids and tissues [20]. Simpler designs, such as the matrix design of the MIV-150/zinc acetate (ZA) IVR are being developed by the Population Council, by nature should remain more cost effective. Together, these examples demonstrate that IVRs can effectively deliver APIs with varying physical properties.

Microbicides containing multiple APIs may have their advantages despite these development challenges: increased efficacy, broader spectrum of activity and less resistance issues. A MIV-150/ZA gel released more MIV-150 *in vitro* than a MIV-150-only gel and resulted in a higher tissue drug concentration *in vivo* that correlated with improved efficacy (compared with either API alone) [12]. ZA-containing gels also protected mice against high-dose HSV-2 infection [21] [Fernández-Romero, Zydowsky, Robbiani, Unpublished Data]. Thus, inclusion of ZA increases the anti-HIV activity as well as potentially broadening the activity to combat HSV-2. Recent work has confirmed that MIV-150/ZA IVRs containing as little as 3 mg of MIV-150 still provide significant protection against SHIV-RT in macaques [Aravantinou, Derby, Zydowsky, Robbiani, Unpublished Data]. The dapivirine/TFV IVR combines an NNRTI with a

nucleoside RTI [18], and the combination of TFV and acyclovir [19,20] potentially also targets both HIV and HSV-2.

The ability of IVRs to deliver drugs like contraceptives, which require tightly controlled release, gives IVRs an advantage over gels. IVRs to prevent HIV, HSV-2, and unintended pregnancy [22] are being developed by CONRAD (VA, USA, TFV/levonorgestrel [LNG]), IPM (MD, USA; dapivirine/LNG) and the Population Council (NY, USA; MIV-150/ZA/LNG).

## The way forward: user options to increase effectiveness

Although IVRs are a promising microbicide platform, obstacles remain: IVRs are designed for vaginal, not rectal, protection. Vaginally applied gel affords detectable drug levels in the rectum [23], but they may not be effective, and IVRs have not yet been tested in this capacity. Differences in API release from the device may influence tissue absorption, distribution of the product in the vagina and the kinetics of protection. In our studies, the kinetics of protection by MIV-150 differed between gels and IVRs. MIV-150 IVRs had to remain in place after challenge to protect while a gel containing MIV-150 protected when the last of 14 daily doses was given 8–24 h before challenge [12]. Furthermore, the benefits of coitally independent products like IVRs might not outweigh the benefits of a coitally dependent ones. By introducing the drug only as needed, the latter may put less mutation pressure on the virus and reduce the risk of drug resistance (if the product were used by an HIV-infected individual). Little drug resistance has been reported with gels in macaques and women [1,12,13,24–26] and we found none in the few animals that became infected while fitted with MIV-150 IVRs [11]. However, more studies are needed to determine the threshold of drug concentration and duration of exposure that can be tolerated without causing resistance (especially if used in already infected individuals).

> **"Microbicides containing multiple active pharmaceutical ingredients may have … increased efficacy, broader spectrum of activity and less resistance issues."**

The variety of birth control delivery systems on the market speaks to women's desire for choices. Preference between gels, IVRs and vaginal tablets has been reported across different cultural groups [7]. The development of biofilms on IVRs [27] and the potential for menstrual blood and vaginal fluid to stain them might influence their success and impact the set of women who choose to use them. Moreover, the availability of medical grade polymers at low cost has proven difficult [2], undermining the potential for roll out in resource poor settings.

Other drug delivery devices are in development and may compete with IVRs if they are acceptable, cheap and efficacious. Highly acceptable quick dissolve films are already on the market for use as contraceptives and antifungals [28]. Tablets also have a high acceptability rating in certain populations where they are widely used [28]. Dapivirine and TFV tablets are both in development [28].

Recent work on biodegradable drug-eluting nanofibers also looks promising [29].

While there are numerous challenges to the success of any microbicide, IVRs have great potential to be adapted for microbicide delivery, helping to prevent infection with HIV (and potentially other sexually transmitted pathogens) and, through combination with contraceptives, to block unwanted pregnancy.

## References

1 Abdool Karim Q, Abdool Karim SS, Frohlich JA *et al.*; CAPRISA 004 Trial Group. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. *Science* 329(5996), 1168–1174 (2010).

2 Kiser PF, Johnson TJ, Clark JT. State of the art in intravaginal ring technology for topical prophylaxis of HIV infection. *AIDS Rev.* 14(1), 62–77 (2012).

3 Romano JW, Robbiani M, Doncel GF, Moench T. Non-specific microbicide product development: then and now. *Curr. HIV Res.* 10(1), 9–18 (2012).

4 Grant RM, Lama JR, Anderson PL *et al.*; iPrEx Study Team. Pre-exposure chemoprophylaxis for HIV prevention in men who have sex with men. *N. Engl. J. Med.* 363(27), 2587–2599 (2010).

5 Karim SS, Kashuba AD, Werner L, Karim QA. Drug concentrations after topical and oral antiretroviral pre-exposure prophylaxis: implications for HIV prevention in women. *Lancet* 378(9787), 279–281 (2011).

6 Anderson PL, Glidden DV, Liu A *et al.*; For the iPrEx Study Team. Emtricitabine–tenofovir concentrations and pre-exposure prophylaxis efficacy in men who have sex with men. *Sci. Transl. Med.* 4(151), 151ra125 (2012).

7 van der Straten A, Van Damme L, Haberer JE, Bangsberg DR. Unraveling the divergent results of pre-exposure prophylaxis trials for HIV prevention. *AIDS* 26(7), F13–F19 (2012).

8 Malcolm RK, Edwards KL, Kiser P, Romano J, Smith TJ. Advances in microbicide vaginal rings. *Antiviral Res.* 88(Suppl. 1), S30–S39 (2010).

9 van der Straten A, Montgomery ET, Cheng H *et al.* High acceptability of a vaginal ring intended as a microbicide delivery method for HIV prevention in African women. *AIDS Behav.* 16(7), 1775–1786 (2012).

10 Montgomery ET, van der Straten A, Cheng H *et al.* Vaginal ring adherence in sub-saharan Africa: expulsion, removal, and perfect use. *AIDS Behav.* 16(7), 1787–1798 (2012).

11 Singer R, Mawson P, Derby N *et al.* An intravaginal ring that releases the NNRTI MIV-150 reduces SHIV transmission in macaques. *Sci. Transl. Med.* 4(150), 150ra123 (2012).

12 Kenney J, Aravantinou M, Singer R *et al.* An antiretroviral/zinc combination gel provides 24 hours of complete protection against vaginal SHIV infection in macaques. *PLoS ONE* 6(1), e15835 (2011).

13 Dobard C, Sharma S, Martin A *et al.* Durable protection from vaginal simian-human immunodeficiency virus infection in macaques by tenofovir gel and its relationship to drug levels in tissue. *J. Virol.* 86(2), 718–725 (2012).

14 Romano J, Variano B, Coplan P *et al.* Safety and availability of dapivirine (TMC120) delivered from an intravaginal ring. *AIDS Res. Hum. Retroviruses* 25(5), 483–488 (2009).

15 Malcolm RK, Veazey RS, Geer L *et al.* Sustained release of the CCR5 inhibitors CMPD167 and maraviroc from vaginal rings in rhesus macaques. *Antimicrob. Agents Chemother.* 56(5), 2251–2258 (2012).

16 Clark JT, Johnson TJ, Clark MR *et al.* Quantitative evaluation of a hydrophilic matrix intravaginal ring for the sustained delivery of tenofovir. *J. Control. Release* 163(2), 240–248 (2012).

17 Johnson TJ, Clark MR, Albright TH *et al.* A ninety day tenofovir reservoir intravaginal ring for mucosal HIV prophylaxis. *Antimicrob. Agents Chemother.* 56(12), 6272–6283 (2012).

18 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.* 39(4), 203–212 (2010).

19 Baum MM, Butkyavichene I, Gilman J *et al.* An intravaginal ring for the simultaneous delivery of multiple drugs. *J. Pharm. Sci.* 101(8), 2833–2843 (2012).

20 Moss JA, Malone AM, Smith TJ *et al.* Simultaneous delivery of tenofovir and acyclovir via an intravaginal ring. *Antimicrob. Agents Chemother.* 56(2), 875–882 (2012).

21 Fernández-Romero JA, Abraham CJ, Rodriguez A *et al.* Zinc acetate/carrageenan gels exhibit potent activity *in vivo* against high-dose herpes simplex virus 2 vaginal and rectal challenge. *Antimicrob. Agents Chemother.* 56(1), 358–368 (2012).

22 Han YA, Singh M, Saxena BB. Development of vaginal rings for sustained release of nonhormonal contraceptives and anti-HIV agents. *Contraception* 76(2), 132–138 (2007).

23 Nuttall J, Kashuba A, Wang R *et al.* Pharmacokinetics of tenofovir following intravaginal and intrarectal administration of tenofovir gel to rhesus macaques.

*Antimicrob. Agents Chemother.* 56(1), 103–109 (2012).

24  Aravantinou M, Singer R, Derby N *et al.* The nonnucleoside reverse transcription inhibitor MIV-160 delivered from an intravaginal ring, but not from a carrageenan gel, protects against simian/human immunodeficiency virus-RT infection. *AIDS Res. Hum. Retroviruses* 28(11), 1467–1475 (2012).

25  Kenney J, Singer R, Derby N *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.

26  Parikh UM, Dobard C, Sharma S *et al.* Complete protection from repeated vaginal simian-human immunodeficiency virus exposures in macaques by a topical gel containing tenofovir alone or with emtricitabine. *J. Virol.* 83(20), 10358–10365 (2009).

27  Gunawardana M, Moss JA, Smith TJ *et al.* Microbial biofilms on the surface of intravaginal rings worn in non-human primates. *J. Med. Microbiol.* 60(Pt 6), 828–837 (2011).

28  Garg S, Goldman D, Krumme M, Rohan LC, Smoot S, Friend DR. Advances in development, scale-up and manufacturing of microbicide gels, films, and tablets. *Antiviral Res.* 88(Suppl. 1), S19–S29 (2010).

29  Ball CS, Krogstad EK, Chaowanachan TC, Woodrow KA. Nanofibers for HIV-1 inhibition and contraception. *PLoS ONE* doi:10.1371/journal.pone.0049792 (2012) (Epub ahead of print).

**Website**

101  Phase III Trial of Dapivirine Ring Begins in Africa: ASPIRE testing new HIV prevention approach for women. Pittsburgh: Microbicide Trials Network, 24 July 2012. www.mtnstopshiv.org/node/4546