Antiviral Research 100 (2013) S3–S8

Contents lists available at ScienceDirect

Antiviral Research

journal homepage: www.elsevier.com/locate/antiviral

Review

Development of dapivirine vaginal ring for HIV prevention

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ARTICLE INFO

Article history:
Received 3 June 2013
Revised 3 September 2013
Accepted 29 September 2013
Available online 1 November 2013

Keywords:
Microbicides
HIV prevention
Dapivirine
Vaginal ring

ABSTRACT

In the continuing effort to develop effective HIV prevention methods for women, a vaginal ring containing the non-nucleoside reverse transcriptase inhibitor dapivirine is currently being tested in two safety and efficacy trials. This paper reviews dapivirine ring's pipeline development process, including efforts to determine safe and effective dosing levels as well as identify delivery platforms with the greatest likelihood of success for correct and consistent use. Dapivirine gel and other formulations were developed and tested in preclinical and clinical studies. Multiple vaginal ring prototypes were also tested, resulting in the current ring design as well as additional designs under consideration for future testing. Efficacy results from clinical trials are expected in 2015. Through ongoing consultations with national regulatory authorities, licensure requirements for dapivirine vaginal ring approval have been defined. This article is based on a presentation at the "Product Development Workshop 2013: HIV and Multipurpose Prevention Technologies," held in Arlington, Virginia on February 21–22, 2013. It forms part of a special supplement to *Antiviral Research*.

Contents

1. Introduction

As the HIV/AIDS epidemic persists into yet another decade, so do efforts to develop products to prevent its spread. Novel prevention methods combining advances in drug development and drug delivery have the potential to make a significant contribution to slowing the incidence of HIV infection. This article outlines the drug development process that has led to identification and development of a vaginal microbicide product, dapivirine ring-004, currently being tested for efficacy, safety and acceptability in two pivotal trials in sub-Saharan Africa. In this paper, we first provide a brief background on the International Partnership for Microbicides (IPM) and its approach to product development. We then summarize the process of selecting the active drug product and delivery platform to advance to efficacy evaluation.

2. Background

As the HIV epidemic became firmly established worldwide, women's disproportionate rates of infection spurred recognition of the need to develop prevention methods that could be used by women (UNAIDS, 2011). The International Partnership for Microbicides (IPM) was founded in 2002 as a public–private-partnership with the mission of accelerating the development and availability of topical vaginal products, commonly referred to

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http://dx.doi.org/10.1016/j.antiviral.2013.09.025

as "microbicides," for use by women in developing countries to prevent HIV infection. Since that time, IPM's primary focus on products for HIV prevention has expanded to include multipurpose prevention technologies (MPTs) that, in addition to protecting against HIV, could also prevent unintended pregnancy and other STIs. Although IPM's pre-clinical and some early clinical work has been conducted primarily in the US and Europe, most of the later stage clinical trials and acceptability studies were conducted in sub-Saharan Africa, where the need for these products is greatest (UNAIDS, 2012).

The microbicide research field initially focused on products with non-specific mechanisms of action (Nuttall, Romano et al., 2007; Romano et al., 2013; Friend and Kiser, 2013). However, as potent and highly specific antiretrovirals (ARVs) began to show potential for prophylactic effect (Harrison et al., 2003), IPM acquired royalty-free licenses to eight ARV compounds from pharmaceutical companies for development as microbicides. If these products are proven successful, IPM has the rights for distribution in developing-country settings. Importantly, these compounds have a variety of mechanisms of action and affect HIV at different stages in the infection lifecycle. This allows for the development of combination microbicides that have the potential for greater efficacy by broadening the range of activity as well as the HIV-1 subtype against which a microbicide product is active.

Dapivirine, a non-nucleoside reverse transcriptase inhibitor (NNRTI), has advanced the farthest in the IPM pipeline and will be the focus of this paper. Dapivirine was developed by Janssen R and D Ireland (one of the Janssen pharmaceutical companies of Johnson and Johnson) as an oral therapeutic. In eleven clinical studies with oral administration, the compound was shown to have high potency against HIV-1. However, etravirine was ultimately selected by Janssen R and D Ireland as its lead NNRTI candidate for treatment, and the dapivirine program focused on a microbicide/prevention indication. A royalty-free license was granted to IPM in 2004 for development as a topical microbicide for intended distribution in developing countries.

As a number of candidate microbicide products advanced through late stage clinical trials, it was becoming increasingly clear that one of the greatest challenges to assessing safety and efficacy was measuring and motivating user adherence (Hankins and Dybul, 2013; Van Damme et al., 2012; van der Straten et al., 2013; Woodsong et al., 2013). Consequently, the microbicide research community began to focus on dosage forms that could facilitate good adherence. The first generation of topical microbicides were gels to be used pre-coitally; subsequent efforts centered on gels containing ARVs intended for peri-coital or daily use, with more flexibility in the time at which they had to be administered (Rosenberg et al., 2006). Since vaginal rings that provide continuous release of ARVs are disassociated from the sex act, IPM considered that this dosing platform had potential to facilitate use-adherence.

At IPM, market research studies were conducted to determine user-perspectives and preferences for dosage forms in order to help design products that have a high probability of correct and consistent use. Vaginally administered gel, film, tablet, soft gel capsules, and rings were considered (Nel et al., 2011). Although all showed promise, the vaginal ring was selected as the lead candidate, because it was considered easier to use, not-coitally associated, and requires a relatively low frequency of administration, all of which could support a higher level of adherence and user-acceptability (van der Straten et al., 2012). In 2012, a ring containing dapivirine was advanced into Phase 3 clinical trials.

3. Product development process

Drug substance. Dapivirine is a substituted di-amino-pyrimidine (DAPY) derivative that binds directly to HIV-1 reverse transcriptase, thereby blocking enzymatic activity and preventing viral replication. Dapivirine is a promising candidate for development as a topical microbicide because of its potent activity against HIV-1 (Fletcher et al., 2009) and favorable safety profile, as well as its physical and chemical properties. Dapivirine binds allosterically to HIV-1 RT and prevents viral replication. *In vitro*, dapivirine exhibits potent activity against wild-type HIV-1, African isolates of HIV-1 (including subtype C virus), and NNRTI-resistant viruses. EC50 values range from 0.3 ng/mL (0.9 nM) against laboratory isolates to approaching 33 ng/mL (100 nM) for HIV-1 isolates encoding one or more known NNRTI resistance mutations. Dapivirine potently inhibits HIV-1_{BaL} infection of human ectocervical explant tissue in a dose-dependent manner, as evaluated by the reduction in both p24 release and provirus content in cultured explants, with >99% inhibition of provirus formation at concentrations down to 0.3 ng/mL (1 nM). In a hu-SCID mouse model in which animals received a single vaginal application of dapivirine gel prior to a vaginal challenge with human peripheral blood lymphocytes (hu-PBL) previously infected *in vitro* with CCR5-tropic and dual tropic (CCR5/CXCR4) HIV-1 strains, dapivirine prevented a systemic infection at concentrations of 0.7 μg/mL (2.25 μM) and higher (Di Fabio et al., 2003). Dapivirine is not active against HIV-2 RT. The physicochemical properties of dapivirine are outlined in Table 1.

Dapivirine is synthesized via a two-step process, with an established 4-year re-test period. The relatively simple synthesis, commercially available starting materials and reagents, and long re-test period lends itself to potential significant cost savings on scale-up in support of commercial use, making it well-suited for products intended for use in developing countries.

Gels. To address a topical prevention approach for dapivirine, Janssen Pharmaceuticals, Belgium, developed a gel formulation. This formulation encountered stability problems, as did a later formulation developed by IPM. Based on experience gained with these early prototypes, along with information on user preferences obtained from a market research study evaluating three gels of differing viscosities, a number of additional gel formulations were developed from which lead candidates were later selected. In total, five gel formulations were tested in five clinical trials that enrolled approximately 260 women (Nel et al., 2010a,b, 2009a) The maximum dapivirine concentration tested was 0.05%. In all trials, dapivirine vaginal gels were safe, well-tolerated and acceptable, with no reported serious adverse events related to the gels. All formulations demonstrated effective distribution of dapivirine throughout the vaginal tract, with concentrations well above the *in vitro* IC_{99} in cervical tissue. Systemic exposure to dapivirine was low, with plasma concentrations less than 1 ng/mL.

Vaginal rings. Simultaneous to the development of dapivirine vaginal gels, by 2006, IPM began evaluation of the feasibility of dapivirine release from a ring formulation. There was an increasing body of evidence about serious adherence challenges with coitally-associated gel use and it was thought that the simpler use-requirements of vaginal rings could potentially address these challenges (McGowen 2010; Rosenberg and Devlin, 2012; Grant et al., 2008). In addition, when compared to gels used daily or peri-coitally in pre-filled applicators, the cost, storage and disposal requirements of vaginal rings are expected to be low, and these are important attributes for products to be used in resource-poor settings.

IPM's focus on vaginal rings intensified after a Phase I clinical trial of an early prototype dapivirine vaginal ring demonstrated safety with continuous delivery of adequate levels of dapivirine throughout the cervicovaginal vault for at least one month after ring insertion (Romano et al., 2009). Adequate levels of drug were defined as levels that were multiple orders of magnitude above the IC_{99}. A placebo vaginal ring safety and acceptability study, along with experience gained from other marketed vaginal ring products,

Table 1
Physicochemical properties of dapivirine.

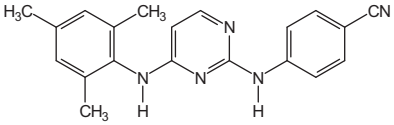
Chemical name:	4-[[4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile
CAS registry number:	244767-67-7
Molecular structure:	
Formula	$C_{20}H_{19}N_5$
Weight	329.40 amu
Physical description	White to off-white or slightly yellow powder, free from visible impurities, practically insoluble in water
pKa	The ionization constant of 5.8 indicates the compound is a weak base stemming from the pyrimidinyl amino moiety
Polymorphism	Using the current synthetic process, the drug substance crystallizes as polymorphic Form I, the most stable form at room temperature (up to ~98 °C). Form I, transforms to Form II, as indicated by the small endotherm at 98 °C. The endotherm observed at ~220 °C corresponds to the melt of Form II. Form II is not stable at RT, and converts instantly to Form I below 98 °C. Form I and Form II are therefore related enantiotropically with a transition temperature of ca. 98 °C. Polymorph form I has been confirmed for all batches listed in Section 3.2.S.4.4, Batch Analysis, for release and up to 3 years real time stability
Solubility characteristics	Dapivirine is virtually insoluble in water. The aqueous solubility can be increased through ionizing the compound by lowering the pH, although at pH 1, the compound is only very slightly soluble. The compound is slightly soluble in propylene glycol, and more soluble in polyethylene glycol 400
Melting point	220 °C (transition from Form I to Form II occurs at 98 °C, 220 °C is the melt of Form II)
Partition coefficient	5.27 at pH 9

Fig. 1. IPM matrix ring.

indicated a high level of acceptance from women using vaginal rings with physical characteristics similar to the dapivirine vaginal ring (van der Straten et al., 2012).

Vaginal rings were already commercially available in developed countries for delivery of hormonal products, either for contraception or treatment of post-menopausal symptoms, and were considered potentially well-suited for delivery of ARVs (Saxena et al., 2009; Woolfson et al., 2006). Four prototypes containing dapivirine were developed, with physical properties similar to those of Warner Chilcott's Femring®/Menoring®, which releases estradiol acetate for the treatment of vasomotor symptoms and vulvar and vaginal atrophy due to menopause (Warner Chilcott, 2010). The polymer silicone elastomer used for the dapivirine vaginal rings has been widely used in commercial polymeric medical devices (e.g. catheters, tubing, valves, implants) and drug delivery devices (e.g. Norplant®, Estring®, Femring®).

IPM developed four different dapivirine vaginal ring formulations in an effort to find a ring that delivers dapivirine with properties most advantageous for clinical use (Nel et al., 2009b; Romano et al., 2009). The design of the IPM prototype rings focused on the configuration and composition that could achieve the desired drug release rate and level. The two configurations evaluated were a central "reservoir" containing the active drug surrounded by a sheath, and a "matrix" design with the drug permeating the ring. All of the rings have a cross-sectional diameter of 7.7 mm and an outer diameter of 56 mm (Fig. 1). The color has varied slightly, from an opaque clear to a soft white. The first three rings were tested in Phase I trials but were not developed further. Ring-004 was studied in several Phase I/II trials and has moved forward into the Phase III licensure program (Nel et al., 2012; Nuttall et al., 2012; Holt et al., 2012; Fetherston et al., 2012). Table 2 and the discussion which follows provide a brief overview of the development of the four vaginal ring designs.

4. Dapivirine Ring-001

The earliest formulation of the dapivirine vaginal ring (Ring-001) was developed in collaboration with the Population Council (US) and QPharma (Sweden). The ring body consisted of two reservoir cores containing dapivirine surrounded by a controlled-release outer sheath, all made of cured silicone elastomer. The ring contained a total of 200 mg of dapivirine distributed between the two reservoirs. Ring-001 was tested in a Phase I, open-label, cross-over trial in 12 healthy, sexually abstinent, HIV-negative women at a single research center in Belgium. Women used the placebo ring for seven days followed by the dapivirine ring for seven days. Ring-001 was considered generally safe and well tolerated (Romano et al., 2009).

5. Dapivirine Ring-002

Ring-002 was also a reservoir ring system developed in collaboration with Warner Chilcott UK Ltd. The excipients are similar to those used in Femring and Menoring (*i.e.* estradiol acetate vaginal ring, marketed by Warner Chilcott for the treatment of

Table 2
Vaginal ring prototypes.

Ring 001	• Developed in collaboration with the Population Council and QPharma. • Cured silicone consisting of two reservoir cores in a controlled release outer sheath. • 200 mg of dapivirine distributed between two reservoir cores.
Ring 002	• Developed in collaboration with Warner Chilcott • Reservoir ring system • Single reservoir containing 25 mg dapivirine • Excipients similar to Femring® and Menoring®
Ring 003	• Developed in collaboration with Warner Chilcott o Matrix ring system (dapivirine dispersed throughout silicone matrix versus API-containing cores inserted into ring reservoirs) o 25 mg dapivirine o Excipients similar to Femring and Menoring o Silicone curing: tin-catalyzed condensation reaction
Ring 004	• Developed by Queen's University Belfast and IPM • Matrix ring system • 25 mg dapivirine • Excipients similar to Estring® • Silicone curing: platinum-catalyzed hydrosilylation reaction
Placebo ring	• Developed by Queen's University Belfast and IPM • Matrix ring system • No API, contains titanium dioxide as colorant • Excipients similar to estring • Silicone curing: platinumcatalyzed hydrosilylation reaction

postmenopausal symptoms). Ring-002 consisted of a single dapivirine-containing core (25 mg) encapsulated in a non-medicated sheath, designed for continuous release of the Active Pharmaceutical Ingredient (API) over a 28-day period. The core consisted of dapivirine and barium sulphate dispersed in silicone elastomer. The non-medicated sheath was made of the same cured silicone elastomer. Ring-002 was tested in a phase I, placebo-controlled trial conducted in Belgium. The trial included 13 healthy women and assessed the feasibility of 7-day use. Trial results showed Ring-002 to be safe and well-tolerated (Romano et al., 2009).

6. Dapivirine Ring-003

Ring-003 was a matrix ring system developed in collaboration with Warner Chilcott with excipients similar to those used in Femring and Menoring. Ring-003 contained 25 mg of API dispersed throughout a cured silicone matrix, rather than API-containing cores inserted into reservoirs of the ring. It was designed to provide continuous release over a 28-day period. Ring-003 was compared with Ring-002 in a phase I, randomized, placebo-controlled trial conducted in Belgium (IPM 018) (Nel et al., 2009b). This trial showed that the delivery of dapivirine was significantly higher from the matrix ring (Ring-003) than from the reservoir ring, and was characterized by a high initial release of the drug shortly after insertion of the ring (known as a 'burst effect'), followed by a gradual decrease in drug release over the remainder of the 4-week period of use (first-order kinetics). In contrast, the reservoir configuration (Ring-002) showed a longer time to reach maximum local and systemic drug concentrations, but thereafter the levels of dapivirine remained similar for the duration of the four weeks of use (zero-order kinetics). However, local and systemic drug concentrations were consistently lower for Ring-002 than Ring-003.

7. Dapivirine Ring-004 (current vaginal ring formulation)

Although Ring-003 proved safe and better suited for dapivirine delivery than the previous rings tested, further ring development was needed to improve a stability issue that was occurred as a result of the curing process. The production of solid state silicone (cured or cross-linked silicone) can be achieved in a number of ways, including hydrosilation cure and condensation cure. The catalyst selected depends on the targeted cross-linking reaction. Ring-003 was based on a tin-catalyzed condensation reaction for cross-linking, resulting in the formation of propanol by-product. This cross-linking reaction, or curing phase, continues beyond manufacture of the ring product. As the cross-linking reaction continues, the generation of volatile by-product (in this case, propanol) also continues. This generation of propanol by-product contributed to an increased rate of migration of dapivirine from within the matrix of the ring to the surface, resulting in crystalline deposits of dapivirine on the surface of the rings. This was noted on inspection of rings on stability at both long term (25 °C/60% relative humidity (RH) and 30 °C/65% RH) and accelerated (40 °C/75% RH) storage conditions.

This stability issue was addressed by using a different catalyst for the cross-linking reaction. Platinum (in the form of a platinum–siloxane complex), rather than tin, is used as the catalyst for the silicone crosslinking reaction. This process is readily applied in scale-up production and does not involve a propanol by-product produced during curing. The hydrosilation reaction results in a cross-linked system with no new soluble or leachable components (Bondurant et al., 1999), and has been used for Estring (Pfizer, NY). Estring is an FDA-approved vaginal ring product indicated for treatment of menopausal symptoms that also utilizes a platinum-catalyst for the silicone curing reaction. Similar specifications for Ring-003 (target for dimension, weight, physical characteristics such as compression and tensile strength, dissolution profiles, assay, and impurities), were applied to Ring-004. Although Estring is a reservoir ring configuration, the catalyst and filler used to form the shell of Estring is the same as the catalyst and filler components used to form the silicone matrix in Ring-004.

The pharmacokinetics (PK) of dapivirine delivered by Ring-004 was assessed in two clinical trials conducted in Belgium with healthy participants for variable ring use periods up to three months (Rosenberg and Devlin, 2012). Results indicated that dapivirine is detectable in plasma and vaginal fluids by 1.5 h post ring insertion. Although inter-individual variation was substantial, the mean maximum concentrations were reached by Day 7 (plasma) and Day 1 (vaginal fluids). Systemic exposure to dapivirine was low; plasma levels did not exceed 1 ng/mL. In vaginal fluids, mean maximum concentrations of 58.8 μg/g (introitus), 66.6 μg/g (cervix), and 79.9 μg/g (near the ring) were observed. At 24 h following ring removal, vaginal fluid concentrations remained at least 500 times higher than the *in vitro* IC99 in cervical tissue (3.3 ng/mL). These levels decreased with a mean half-life of 12–14 h at the three locations. Only a fraction of the dapivirine dose was released over 28 days (≈4 mg). Results of these trials demonstrate that dapivirine Ring-004 has a favorable PK profile for use as a monthly microbicide (Nuttall and van Niekerk, 2012).

Since vaginal rings are not currently available in sub-Saharan Africa, where the need is the greatest, it was also critical to investigate African women's willingness and ability to use this technology correctly and consistently. Demographic and parity characteristics for African women in need of HIV prevention methods differ from women in the US and Europe using vaginal rings for hormone replacement therapy or contraceptives (Novak et al., 2003). Thus, a safety and acceptability trial of a placebo tin-catalyzed vaginal ring of the same dimensions and similar physical characteristics as the dapivirine ring was conducted in four research centers in two countries: Durban, Johannesburg and Cape Town in South Africa, and Moshi, Tanzania. One-hundred seventy women were randomized in a cross-over design to use the ring for 12 weeks, followed by a period of 12-weeks of non-use, or

the reverse-order regimen. (Nel et al., 2012). The trial showed that the ring was highly acceptable and easy to use, and caused no safety issues (Montgomery et al., 2012; van der Straten et al., 2012).

Vaginal Ring-004 has a 36-month shelf life, applicable to WHO climate zones III and IV. The ring provides continuous release *in vivo* over a minimum period of 35 days. Evaluation of the vaginal ring *in vitro* shows continued release of drug with a slow decrease over time. Ring-004 was produced at IPM's US facility for use in two safety trials of the dapivirine ring–with women using a ring for three 28-day cycles. These trials showed no safety signals, the dapivirine rings were reported to be acceptable and easy to use (Montgomery et al., 2012; van der Straten et al., 2012), and thus Ring-004 was slated to move to Phase III clinical evaluation.

8. Current status of dapivirine vaginal ring development

Two pivotal efficacy trials of Ring-004 are currently being conducted in sub-Saharan Africa. IPM 027 (''The Ring Study,'' http://www.ipmglobal.org/the-ring-study) is currently being conducted at multiple locations in South Africa. It is investigating long-term safety, efficacy and acceptability, with 1650 participants who will be enrolled for 2 years of ring use. The second study is MTN 020 (''ASPIRE'') and is being conducted by the Microbicide Trials Network (MTN: http://www.mtnstopshiv.org/news/studies/mtn020/factsheet), funded by the US National Institutes of Health. This trial is investigating safety, acceptability and efficacy, with 3476 participants who will be followed for 1–2 years at 16 MTN-affiliated sites in Malawi, Uganda, South Africa and Zimbabwe. Both trials initiated in 2012 and are planned to finish in 2015. They are randomized placebo-control trials; IPM 027 has a 2:1 active-placebo randomization, and MTN 020 has 1:1. Used rings from Phase III trials are being collected for post-use adherence testing which is accomplished by extracting the remaining drug out of the used ring. Additionally, plasma and vaginal fluid samples are being collected and analyzed.

Licensure plans. As the product developer, license holder and regulatory sponsor, IPM leads the overall dapivirine ring licensure program and will maintain responsibility for worldwide product approvals. Gaining approvals in multiple markets requires significant resources and dedicated attention to registration requirements from each national regulatory authority (NRA) throughout the product development process (Nuttall et al., 2007). IPM has engaged in a series of consultations with the European Medicines Authority (EMA), the US Food and Drug Administration (FDA), and regulatory NRAs in six African countries, to ensure that the portfolio being developed for dapivirine ring will be sufficiently robust for licensure and meet all local regulatory requirements.

In addition to the two pivotal trials described above, the NRAs require three types of trials which are currently being conducted or are planned. These include drug-drug interaction, condom compatibility and safety studies in special populations. A drug-drug interaction study is ongoing and will be completed in 2013. The trial is an open-label, randomized, three-period crossover design conducted in healthy HIV-negative women in Belgium to assess the drug-drug interaction potential between dapivirine as administered in Ring-004 and miconazole, administered as a 1200 mg vaginal capsule. A male condom functionality trial is being conducted in the US, to be followed by a female condom functionality trial. These trials are both randomized controlled open-label trials with a cross-over design in which condoms are used with and without the presence of an IPM-004 placebo ring to assess the total clinical failure rate, as well as safety, tolerability and user-acceptability of male and female condoms used during vaginal intercourse in the presence and absence of the vaginal ring. The trials are scheduled for completion in 2014. Finally, a safety study of adolescents and one with older women (aged 45–60) will be conducted in the US, to address the need for safety data from these populations, as well as provide safety data from the US, as required by the FDA. These trials will be conducted by the MTN and are scheduled to be completed by 2015.

Additional products in development. Vaginal film, soft gel capsule and tablet formulations of dapivirine are also being considered as potential drug delivery formulations. Market research studies reported that women and men in multiple African countries found these formulations to be acceptable, particularly the soft gel capsule and film. Research conducted by other organizations provides mixed support for user-acceptability of films, with some noting high acceptability of this delivery mode (Ayman Akil et al., 2011; Steiner et al., 1995) and others reporting user preferences for other modes compared to film (Abbott et al., 2013; Hardy et al., 1998; Raymond et al., 2005). Film is a relatively simple delivery platform to produce, can provide accurate dosing and quick release, with minimal packaging and good potential for discrete use (Neurath et al., 2003). The film has the added benefit not needing an integrated applicator, and reduced waste of product that remains in the applicator/device after use and then must be safely discarded.

Initial work on vaginal films was conducted through collaboration between IPM and Magee Women's Research Institute. A 1″ by 2″ film strip containing 1.25 mg of dapivirine and applied using a finger, was developed and is currently being evaluated in a Phase I pharmacokinetic and safety trial (FAME 02) at Magee Women's Research Institute through an NIH grant.

An additional component of the dapivirine program focuses on the combination of dapivirine with maraviroc, which is a CCR5 antagonist (Fetherston et al., 2012). Such combination products are less likely to favor the selection of drug-resistant viruses if used by HIV-infected individuals, and should be active against a broader range of HIV-1 subtypes. Dapivirine is also being developed in combination with the contraceptive hormone levonorgestrel, for multipurpose prevention of HIV and pregnancy. IPM is currently exploring options for extended release of 60 days or more for the combination single-purpose ring as well as a multipurpose prevention ring with a matrix ring design.

9. Conclusion

Vaginal rings containing ARVs continue to garner interest as potential HIV prevention tools. (Derby et al., 2013). Evidence to-date from clinical trials points to the critical importance of adherence, and although a gel, film, soft gel capsule or tablet formulation of a highly potent ARV may be capable of providing a safe and effective dose of an ARV to prevent HIV infection; it will not be effective if it is not used correctly and consistently. Adherence to product remains challenging for microbicide as well as oral pre-exposure prophylaxis (PrEP) trials. Two recent trials conducted among women in Africa (the FemPreP trial testing oral Truvada® and the VOICE trial testing oral Truvada®, oral tenofovir, and 1% tenofovir vaginal gel) were stopped for futility, both citing adherence as a major issue (Van Damme et al., 2012; Microbicide Trials Network, 2013). To address adherence issues associated with tenofovir gel and oral tablets, a tenofovir disoproxil fumarate vaginal ring is being developed. Smith et al. (2013) tested the ring in multiple vaginal simian-HIV challenges and showed protection.

Vaginal rings could have an advantage over other delivery forms in that they can provide a continuous release of adequate drug in a user-friendly format that does not require daily or coitally-associated action. Furthermore, when compared to peri-coital or daily gel formulations, vaginal rings have lower requirements for supply, transport, storage and disposal logistics, all of which are critical considerations in developing countries. As the

contraceptive field has long taught us, a range of tools are needed to meet women's needs and preferences.

A vaginal ring composed of silicone and dapivirine in a matrix configuration delivers dapivirine continuously for at least 28 days and has potential for preventing HIV infection in women. The process of developing this drug delivery platform was built on experiences from the pharmaceutical industry, government-sponsored research, academic and not-for-profit organizations, drawing on a broad base of knowledge in reproductive health as well as HIV. IPM's development process is established on three critical aspects: highly active drug, effective delivery platform, and user-friendly product profile. Dapivirine has clearly demonstrated strong *in vitro* performance, vaginal ring technology is capable of providing continuous delivery of dapivirine at levels that can inhibit HIV infection, and a product that requires less action of the user should improve correct and consistent use Two pivotal trials powered to demonstrate efficacy, safety and acceptability of this product are on schedule to be completed in 2015, and all supportive materials for the registration dossier are being prepared. This overall approach will help efficiently bring important products to markets where they are needed most.

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