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Topical delivery of long-acting antiretrovirals to prevent HIV acquisition

Thesla Palanee-Phillips, M Med Sci, PhD, MSc,

Wits Reproductive Health and HIV Institute, University of the Witwatersrand, Johannesburg, South Africa

Jared M. Baeten, MD, PhD

Departments of Global Health, Medicine, and Epidemiology, University of Washington, Seattle, USA

Abstract

Purpose of review—While tremendous successes in HIV treatment and prevention have occurred in the past decade, existing HIV prevention options are inadequate, unacceptable or inaccessible to many. Topical antiretroviral-based pre-exposure prophylaxis (PrEP) options may offer effective, long-acting prevention to those who do not desire systemic exposure to anti-HIV drugs or who want greater control over their own prevention.

Recent findings—Among long-acting topical PrEP agents, the dapivirine vaginal ring has advanced the furthest in product development; recent studies have shown high adherence and persistence and evidence of HIV protection in open-label studies as well as a well-tolerated safety profile, across the life cycle in women. A range of other long-acting topical PrEP products for vaginal or rectal drug delivery are under development. Rigorous end-user research has explored how to develop products that are behaviorally congruent for the population at risk and has shown that no single product option will be desired by all, but rather different options will achieve the greatest prevention coverage.

Summary—Topically-delivered, long-acting antiretroviral PrEP options are being designed to align with user preferences and lifestyles, providing the potential to more effectively expand the HIV prevention method mix and use and achieve an important impact on HIV globally.

Keywords

HIV prevention; microbicide; dapivirine vaginal ring; pre-exposure prophylaxis

Introduction

An estimated 1.7 million persons acquired HIV in 2018, a number that has reduced by only 16% in the past decade [1]. Despite global roll-out of effective antiretroviral treatment for

Corresponding author: Jared Baeten, MD, PhD, International Clinical Research Center, Department of Global Health, University of Washington, Box 359927, 325 Ninth Avenue, Seattle, WA 98104, 206 520-3808, jbaeten@uw.edu.

Conflicts of Interest

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persons living with HIV, new infections continue to outpace treatment initiations, and recent studies show that high rates of transmission persist in many geographies despite high treatment coverage [2]. Women continue to be disproportionately affected by HIV, especially in sub-Saharan Africa, with recent evidence suggesting that HIV incidence in young African women remains among the highest globally [3]. Men who have sex with men and transgender women and men globally have higher incidence of HIV and often limited non-discriminatory access to prevention and treatment services [4]. New, safe and effective HIV prevention options for populations at greatest HIV risk are essential. Given that stigma often impedes access to and use of effective prevention options, new strategies must be ones that people can use safely without prejudice.

This review focuses on long-acting antiretroviral-based prevention strategies that are delivered locally to prevent HIV acquisition. The use of antiretroviral medications as pre-exposure prophylaxis (PrEP) by HIV uninfected persons to prevent HIV acquisition was established at the beginning of this decade [5–7], and numerous studies of novel PrEP agents are ongoing [8]. Current use of PrEP (~400,00 cumulative global initiations) falls far short of global goals (3 million on PrEP by 2020) [1]; moreover, not everyone at risk of HIV can effectively or consistently use currently-available PrEP. For users who desire an HIV prevention option that they can self-administer – easily, quickly, and discreetly – the development of user-friendly, topical dosage forms remains a global imperative. Filling prevention gaps could be addressed by offering more prevention choices, similar to how expanded method mix has led to greater uptake in the contraceptive field [9].

Rationale for long-acting PrEP delivered topically

The idea of a topically-delivered prevention agent, or microbicide, applied to the vagina or anus and rectum to prevent the sexual acquisition of HIV was first proposed nearly three decades ago [10], and more recently the concepts of PrEP and microbicides have converged as antiretroviral-based topical agents have shown promise for HIV prevention [11,12]. The development pathway for topically-delivered PrEP products has been driven by desire to develop tools that are fully under the control the user – to initiate, continue, and discontinue, driven by their own perceptions of risk and circumstances. Topical agents, because they deliver active PrEP medication directly to the site of HIV exposure, generally use small amounts of drug and are conceptually framed as having limited systemic side effects and needing little clinical monitoring; thus, they potentially provide a low burden, cost-efficient choice for HIV prevention [13]. PrEP delivered topically could provide a direct, first-line defense against HIV infection. The VOICE and recently-published FACTS-001 trials [14,15] and other studies of daily use of oral pills and topical microbicides gels, brought to the fore that adherence is the Achilles' heel for PrEP, driving the development of longer-acting HIV prevention formulations. Dosage forms such as tablets/inserts, capsules, suppositories, pessaries, gels, films, rings, and douches, both long-acting and on-demand, are being pursued as additional modes of drug delivery via the vagina and/or rectum and make up a large fraction of PrEP products in development (Figure 1).

Dapivirine Vaginal Ring

Antiretroviral-containing intravaginal rings, which are kept in place for a month or more at a time, allowing continuous release of drug, offer a long-acting topical delivery system for women. A silicone matrix vaginal ring containing 25 mg of dapivirine was assessed in two phase III clinical trials: MTN-020/ASPIRE and IPM 027/The Ring Study [11,12], demonstrating in 2016 that a monthly-worn antiretroviral-containing ring could be very well-tolerated and reduce HIV incidence by approximately 30% compared to placebo, with greater efficacy in groups with evidence of better use.

Open-label extension studies.

MTN-025/HOPE, the open-label extension trial following MTN-020/ASPIRE offered women (n=1456) 12 months of access to the dapivirine vaginal ring at 14 sites in Malawi, South Africa, Uganda, and Zimbabwe [16]; visits were monthly for 3 months, then quarterly, mimicking what happens in real-world PrEP delivery. At baseline, 92% accepted the dapivirine vaginal ring and ring acceptance remained high: 90%, 89%, 87%, 83%, and 79% at Months 1, 2, 3, 6, and 9, respectively. Notably, 86% of returned rings had residual dapivirine levels consistent with some use during the prior month (>0.9 mg released) and residual levels of dapivirine suggested greater use in MTN-025/HOPE than in MTN-020/ASPIRE. HIV incidence (2.7 per 100 woman-years, n=35 infections) was 39% lower than anticipated (4.4 per 100 person-years), based on counterfactual estimates drawn from the placebo arm of MTN-020/ASPIRE. Similarly, IPM 032/DREAM (n=941) was the open-label extension study that provided the dapivirine ring to women who participated in the phase III IPM 027/The Ring Study [17]. IPM 032/DREAM, like MTN-025/HOPE, found the ring to be well-tolerated, with a safety profile similar to that seen in phase III. The fraction of returned rings that indicated at least some use was higher in IPM 032/DREAM (95%) compared to IPM 027/The Ring Study (83%). Counterfactual analyses suggested a 63% reduction in HIV risk: incidence of 1.6 per 100 woman-years, compared to an expected 4.3. Thus, both dapivirine vaginal ring open-label extension trials have shown high uptake, high adherence, and lower than anticipated HIV incidence in a high-risk population.

Dapivirine vaginal ring across the life cycle (Figure 2).

Any new biomedical HIV prevention strategy for women will by necessity need to be safe to use across their life cycle – from adolescence through adulthood and by women who are on contraception or alternatively are pregnant or lactating. Recent data have addressed each of these populations for the dapivirine vaginal ring. Safety studies in adolescent girls aged 15–17 years and in postmenopausal women have shown that the ring is well-tolerated and acceptable in those groups [18,19]. From the MTN-020/ASPIRE trial, a secondary analysis assessed the potential for drug-drug interactions with concomitant use of the ring and hormonal contraception, by examining contraceptive efficacies with and without dapivirine vaginal ring use [20]. Pregnancy incidence did not differ by study arm for any of the hormonal contraceptive methods, providing robust evidence that the dapivirine vaginal ring does not undermine contraceptive effectiveness. Among those who became pregnant (n=169, resulting in 181 pregnancy outcomes) there was no significant difference in pregnancy incidence for those assigned the active ring versus placebo [21] and pregnancy outcomes

(live birth, preterm birth, pregnancy loss, congenital anomalies) and infant growth were also similar by study randomized group. A recent trial assessed dapivirine excretion into breastmilk [22] and found low concentrations of dapivirine in milk with low estimated daily levels of infant dapivirine exposure. Together, these studies provide support for additional safety evaluations of the dapivirine ring throughout pregnancy and lactation, which are now planned (<https://mtnstopshiv.org/research/studies/mtn-042> & <https://mtnstopshiv.org/research/studies/mtn-043>).

Behavioral and social science related to the dapivirine vaginal ring.

For any new technology, understanding how the target user interfaces with it is a high priority, so that developers may optimize attributes to bolster product uptake and use. Mixed-methods work from the MTN-020/ASPIRE study assessed worries about ring use over time and their association with adherence [23]. Worry about wearing the ring decreased from 29% at baseline to 4% at month 3 ($p<0.001$); qualitative data showed initial ring anxieties subsided with becoming comfortable with wearing the ring. Other data showed that self-reported adherence was associated with objective measures of adherence, in contrast to phase III oral pill PrEP trials [24]. Other important qualitative work explored menstrual experiences in the context of dapivirine ring use [25]. Some women were uncomfortable touching their own menstrual blood when removing vaginal rings and felt embarrassed about study staff seeing blood on returned rings. A significant reason for imperfect ring adherence cited by participants was related to vaginal bleeding [26], and understanding menstruation effects on comfort with use of topical drug delivering interventions should be explored further. Finally, mixed-methods work has explored the potential for social harms related to dapivirine ring use, finding social harms were uncommon ($<5\%$ of women with >1 year of use), but those reporting social harms by male partners had lower adherence to the dapivirine ring [27]. Deeper understanding of social harm risk related to both topical or systemic PrEP use should be prioritized.

Next steps.

The dapivirine ring is currently under regulatory review by the European Medicines Agency (EMA) through the Article 58 procedure, which allows the EMA, in cooperation with the World Health Organization (WHO), to provide a scientific opinion on the ring's use in low- and middle-income countries. Mathematical modelling work has explored the impact and cost-effectiveness of the ring in different implementation scenarios [13], finding that addition of the ring to other prevention roll-out, including oral PrEP, resulted in 11% to 132% more impact than oral PrEP alone.

Other vaginal rings, including multipurpose prevention technologies

Dapivirine is not the only antiretroviral agent being evaluated in vaginal ring formulations. Recent results of a phase I trial of an intravaginal ring releasing the tenofovir prodrug, tenofovir disoproxil fumarate, are important for the field. This ring, which had solid preclinical testing, including evaluation providing 100% protection in a nonhuman primate model, was discontinued in early-phase clinical testing because of cervicovaginal ulceration, an unexpected finding which occurred in two-thirds of women compared with none using

placebo rings [28]. In contrast, another vaginal ring containing tenofovir (alone or in combination with the contraceptive hormone levonorgestrel) has been tested without evidence to date of a similar side effect [29]. Multipurpose prevention technologies – i.e., a single product with one or more active agents that result in prevention of HIV as well as unintended pregnancy or one or more sexually transmitted infections – are of particular appeal to the topical PrEP field and several early studies are in progress [29]. A combined dapivirine/levonorgestrel ring has also been evaluated to date in two phase I studies for up to 90 days [30]. A pod intravaginal ring – i.e., a ring scaffold with spaces to insert drug cores, against HIV, other sexually transmitted infections, and/or a contraceptive – has been tested with tenofovir and other antiretroviral agents and supporting behavioral science has been positive [31,32]. Vicriviroc, a CCR5-receptor antagonist, and MK-2048, an integrase inhibitor, were tested alone or in combination, in two placebo-controlled phase I studies with use continuously for 28 days [33,34]. Both drugs achieved high vaginal levels; however, tissue concentrations did not correlate with antiviral activity in an ex vivo challenge assay. Concurrent behavioral science work supported the rings as acceptable prevention options [35]. Extended-release vaginal inserts (essentially a dissolving tablet applied topically) could offer a user-friendly form that would provide protection both on-demand and have some sustained pharmacokinetics topically for a longer, “intermediate” duration (e.g., days to a few weeks).

Rectal products: on-demand but potentially with longer-acting effects

While vaginal PrEP products have moved towards long-acting formulations, for rectal products, options that function on-demand, although potentially with some extended, longer-acting benefit, are being investigated. Recently completed highlights of work related to rectal microbicides have included work related to gels, douches, and suppositories. A phase I cross-over trial comparing the cross-compartment pharmacokinetics of a gel containing tenofovir found that after 14 days of application, only a small degree of cross-compartment distribution of drug occurred [36], emphasizing how, for women, topical products generally should be thought of as protecting only the relevant compartment of use. Considerable work is ongoing to develop medicated douches, potentially leveraging an existing behavior to which some men who have sex with men adhere ahead of receptive anal sex [37,38]. A phase I study of a tenofovir douche demonstrated good acceptability and colorectal tissue cell concentrations of tenofovir diphosphate from one hour through 72 hours after a single dose that exceeded concentrations achieved with the on-demand oral PrEP [39,40]. Suppositories may similarly offer an on-demand, fast-acting PrEP agent with some ability for protection beyond a single sex act. An ongoing study (<https://mtnstopshiv.org/research/studies/mtn-035>) is assessing three placebo rectal microbicide formulations – suppository, douche, and fast-dissolving insert – to measure key safety, acceptability, tolerability, and adherence data when each is used on-demand (i.e., just before sex) in 4-week period cross-overs.

Developing better topical prevention products: novel end-user research

End-user research can and should inform product development in order to improve the design of products and increase their future uptake. Exciting new end-user work is leading

the way with behavioral science to inform new prevention tools, for long-acting products delivered topically and systemically. The TRIO study assessed three placebo delivery forms: daily oral tablets, a monthly vaginal ring, and two monthly intramuscular injections, in order to understand key attributes of a future multipurpose prevention technology product [41]. HIV-negative, sexually active, non-pregnant women aged 18 to 30 (n=277, from Kenya and South Africa) were randomized to use each placebo delivery form for one month and then were able to choose one to use for two additional months. Overall, 85% preferred a TRIO product over condoms, and all three products were chosen by a significant number of women (injections 64%, tablets 21%, vaginal ring 15%). Tablet and ring adherence, based on direct observations and self-reports, improved over time. The Quatro study assessed preferences across four vaginal placebo products (film, insert, gel and ring) among women in Zimbabwe and South Africa using a randomized crossover design [42]. Products were ranked by participants at baseline and after use. While at baseline the gel was selected as the most preferred product (41%) and the ring as least preferred (61%), rankings changed after use with no clear overall preference for one product (film 29%; ring 28%, insert 26%, and gel 16%). In South Africa, however, after the use phase, the insert was chosen as the preferred product (35%).

Conclusions

HIV PrEP holds substantial promise to, in combination with other prevention strategies, address the global HIV epidemic with benefits both to the individual and to population-level health [43]. Moreover, PrEP can also serve as a gateway to broader sexual and reproductive health services [44]. Long-acting topical HIV PrEP might improve adherence by lowering the burden of daily regimens, simplifying dosing schedules and providing constant concentrations of drug [45]. Although systemically-delivered long-acting methods, such as some under development now, will undoubtedly be acceptable to many users [41,46], reversibility in the event of a side effect or simple desire to discontinue presents a challenge, particularly for injectable formulations that cannot be removed but also for implants requiring trained personnel proficient in minor surgery. Similarly, long-acting injectables may have a long plasma “tail” of sub-therapeutic drug levels that will persist in those discontinuing [47,48]. Long-acting topical agents, in contrast, could be more easily removed, offer less potential for systemic side effects, and simply offer another option that might be the preferred choice for some persons. A robust pipeline of novel vaginal and rectal topical products is under development and potentially offers important choice to have a meaningful impact on reducing HIV incidence in populations globally.

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Key points

- The development pathway for topically-delivered PrEP products has been driven by desire for prevention tools that people can initiate, continue, and discontinue, driven by their own perceptions of risk, circumstances and decision-making.
- Among long-acting topical PrEP agents, the dapivirine vaginal ring has advanced the furthest in product development; recent studies have shown high adherence and persistence and evidence of HIV protection in open-label studies as well as a well-tolerated safety profile, importantly also including across the life cycle in women.
- A range of other long-acting topical PrEP products for vaginal or rectal drug delivery are under development; rigorous end-user research supports that no single product option will be desired by all but rather different options will achieve the greatest prevention coverage.

Figure 1. PrEP development pipeline

A substantial of new PrEP products under development are topically-delivered, both long-acting and on-demand, including gel, film, enema, insert, and other modalities.

Source: <https://www.avac.org/infographic/future-arv-based-prevention>

Adolescence	Contracepting Adults	Conception and Pregnancy	Lactation	Post-menopausal
<p>MTN-023/IPM 030 (N=96, aged 15-17, US) Randomized, double-blind, placebo-controlled trial <i>Status:</i> Completed <i>Findings:</i> well-tolerated, acceptable [19]</p> <p>MTN-034/REACH (N=300, aged 16-21, South Africa, Uganda, Zimbabwe) Randomized, open-label, cross-over design with dapivirine vaginal ring and FTC/TDF oral tablets <i>Status:</i> Enrolling</p>	<p>MTN-020/ASPIRE (N=2310, aged 18-45) Secondary analysis of placebo-controlled trial <i>Status:</i> Completed <i>Findings:</i> No effect of dapivirine on hormonal contraception pregnancy prevention effectiveness</p>	<p>MTN-020/ASPIRE (N=169 pregnant, 179 incident pregnancies, 181 outcomes) Secondary analysis of placebo-controlled trial <i>Status:</i> Completed <i>Findings:</i> Dapivirine ring use in peri-conception period not associated with adverse effects on pregnancy or infant outcomes [21]</p> <p>MTN-042/DELIVER (N=750, aged 18-45, Malawi, South Africa, Uganda, Zimbabwe) Randomized open-label safety and pharmacokinetic study of dapivirine vaginal ring and FTC/TDF oral tablet when used during pregnancy <i>Status:</i> Anticipated start Q4 2019</p>	<p>MTN-029/IPM 039 (N=16, aged 18+, US) Open label, pharmacokinetics of dapivirine transfer breast milk <i>Status:</i> Completed <i>Findings:</i> Dapivirine vaginal ring use was associated with lower concentrations of detectable dapivirine in milk and plasma than in cervicovaginal fluid samples and a favorable safety profile [22]</p> <p>MTN-043/B-Protected (N=200, aged 18-45, Malawi, South Africa, Uganda, Zimbabwe) Randomized, open-label mother-infant safety and drug detection study of dapivirine vaginal ring and FTC/TDF oral tablets when used during breastfeeding <i>Status:</i> Anticipated start Q1 2020</p>	<p>MTN-024/IPM031 (N= 96, aged 45-65, US) Randomized, double-blind, placebo-controlled trial <i>Status:</i> Completed <i>Findings:</i> well-tolerated, acceptable [18]</p>

Figure 2. Studies evaluating the dapivirine vaginal ring across the life-cycle in women Ongoing studies:

MTN-034/REACH = <https://mtnstopshiv.org/research/studies/mtn-034>

MTN-042/DELIVER = <https://mtnstopshiv.org/research/studies/mtn-042>

MTN-043/B-Protected = <https://mtnstopshiv.org/research/studies/mtn-043>