Photo: Aurelio Alaya III

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A HealthTech Report

Landscape of Alternative Delivery Methods for Sustained Delivery of Rilpivirine for HIV Preexposure Prophylaxis

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List of abbreviations

API	Active pharmaceutical ingredient
ARV	Antiretroviral drug
FTC	Emtricitabine
IM	Intramuscular
IUD	Intrauterine device
IVR	Intravaginal ring
MNP	Microneedle patch
MVC	Maraviroc
PCL	Polycaprolactone
PrEP	Preexposure prophylaxis
QUB	Queen’s University, Belfast
TDF	Tenofovir disoproxil fumarate
TFPD	Thin-film polymer device
TFV	Tenofovir
TPP	Target product profile
USFDA	United States Food and Drug Administration
USAID	United State Agency for International Development
WHO	World Health Organization

Executive summary

In response to a USAID request, PATH has conducted an analysis of potential alternative delivery methods that could be applied to rilpivirine for use for HIV preexposure prophylaxis (PrEP). Additional antiretroviral drug (ARV) presentation and delivery options have been identified as a critical area of public health need to prevent HIV infection.

PATH's analysis included discussions with stakeholders, review of the current landscape of products in development for PrEP (both short and long acting), and identification of other technologies that could potentially be used for rilpivirine delivery. A target product profile (TPP) listing attributes for PrEP technologies for systemic and local delivery of rilpivirine was developed and input received from internal and external experts. The landscape analysis identified a variety of technologies that could be utilized for delivery of rilpivirine, including vaginal gels and fast-dissolving tablets, intravaginal rings, the SILCS diaphragm, microneedles, intrauterine devices (IUDs), and implants. Following review of the technology landscape, identification of gaps in current research efforts, as well as discussion with stakeholders, we utilized the criteria in the TPP (Annex 1) to identify technologies to recommend for further development for rilpivirine delivery and feasibility assessment. A key area of emphasis was the identification of technologies suitable for the delivery of a long-acting rilpivirine formulation. Our initial analysis identified three top candidate technologies: a drug-eluting IUD, a dissolving microneedle patch (MNP) for local (vaginal) delivery, and a hydrogel MNP for systemic delivery.

After further investigation and comparison with the TPP, we recommend dissolving and hydrogel microneedles for initial exploration and feasibility determination. A critical consideration informing final selection was the potential for self-administration, which is not possible with IUD technology. The two microneedle-based technologies represent different forms of protection against HIV infection (systemic and vaginal), and could each potentially be self-administered at home by users.

Background

HIV preexposure prophylaxis

Despite significant progress over the past ten years, AIDS is still the leading cause of mortality among adults 15 to 59 years of age, and women are increasingly bearing the disproportionate burden of the AIDS epidemic. In Africa, women are 1.3 times more likely than men to be infected with HIV; young women aged 15 to 24 are 2.5 times more likely to be infected than young men. In part because of the slow progress in developing effective HIV vaccines, significant product development effort is now focused on use of ARVs for prophylactic prevention of HIV infection, particularly those that could be effectively used by women at risk of infection. ARVs for PrEP are under development; these ARVs have the potential to provide local protection against vaginal infection or systemic protection against HIV infection by all routes of transmission.

Current formulations of rilpivirine

Rilpivirine, a non-nucleoside reverse transcriptase inhibitor developed by Janssen Pharmaceuticals, Inc., is approved by numerous regulatory authorities for HIV treatment and is sold commercially under the trade name Endurant. Janssen has also developed a long-acting injectable formulation of rilpivirine, TMC278LA, which may be effective for HIV PrEP. PATH has licensed certain development rights from Janssen for TMC278LA, which is delivered by intramuscular (IM) injection for the HIV PrEP indication. PATH, with funding from the Bill & Melinda Gates Foundation and in collaboration with the Division of AIDS at the US National Institute of Allergy and Infectious Diseases, is sponsoring a multicenter Phase 2 clinical study of IM-administered TMC278LA for HIV PrEP.

The need for alternative delivery methods

There is a need for highly effective, well-tolerated, low-cost, and easy-to-administer long-acting methods for ARV-based HIV PrEP. A long-acting PrEP product would not require daily patient compliance, which has been shown to be difficult to achieve in studies of oral PrEP approaches. Injectable formulations for PrEP, such as TMC278LA and GSK-744, an HIV integrase inhibitor also in early clinical development, could be administered every two to three months and offer promise in this regard. However, current formulations of TMC278LA and GSK-744 require IM injection of relatively high volumes (up to 2 mL).

Such products may be limited by their IM mode of delivery, which requires administration by a trained health care worker and ongoing patient access to health facilities. In addition, IM injections, particularly of higher volumes of liquid, can be painful, which could also limit product acceptance. A low-cost, self-

administered, sustained-delivery PrEP product could be an attractive alternative for many individuals. Alternative delivery methods should be explored that could allow patient self-administration of sustained release rilpivirine for local or systemic PrEP.

Target product profile—local and systemic rilpivirine delivery

HealthTech developed a draft TPP for rilpivirine to help inform the assessment of potential delivery technologies (see Annex). This TPP is focused on both systemic and local delivery of rilpivirine over a long duration with preference for the potential of self-administration by women in resource-poor settings. Key attributes include safety, efficacy, presentation, formulation, dosage, packaging, etc. We used the TPP in our review of technologies that could be used for rilpivirine delivery and also for the selection of candidates for further development. Under future project funding, the draft TPP will be further adapted to serve as the guide for development of one or more technology platforms identified during the technology landscape assessment phase.

Delivery technology landscape

HealthTech conducted a landscape review of potential alternative delivery methods that could be applied to rilpivirine or TMC278LA (rilpivirine formulated in nanoparticles to effect slow release of drug from the site of administration). Technologies reviewed included those investigated or currently in development for delivery of other ARVs (intravaginal rings [IVRs], diaphragms, and implants). The landscape focused on technologies that could enable sustained delivery of rilpivirine over a long duration; but for completeness, short-acting delivery methods, such as vaginal gels, films, and fast-dissolving tablets, were included. Several technologies that are not currently under development for delivery of ARVs were identified, including systemic and local delivery via microneedles and drug-eluting IUDs.

Intravaginal rings

IVRs are one method of delivering ARV drugs for HIV PrEP. Marketed IVR products, including contraceptives and hormone replacement therapies, can be worn for 3 weeks or 90 days at a time, depending on the drug and dosage. Because they can be worn continuously for this period, they eliminate many of the problems associated with inconsistent adherence. IVRs are made from a flexible thermoplastic elastomer that can be inserted by the user herself (Figure 1). Most IVRs have diameters of 54 to 56 mm, and they fit comfortably inside the vagina for 28 days. IVRs as contraceptives work by releasing

Figure 1: Examples of intravaginal rings. The reservoir system contains a core infused with drug and a non-medicated outer membrane that controls the rate of drug release. (Photo: PATH.)

either progesterone alone or progestin in combination with estrogen. These devices act by preventing ovulation and thickening the cervical mucus, thereby inhibiting sperm entry into the uterus. There are two major IVR device designs, the matrix and the reservoir system. Generally, reservoir designs can produce consistent concentrations of drug or hormone throughout the period of use, whereas matrix designs can release more drug in a given period of time.

Reservoir system

The NuvaRing® is the only contraceptive IVR approved in the United States. Manufactured by the American pharmaceutical company Merck & Co., Inc. (Merck), the device was first approved by the USFDA in 2001. It is made from polyethylene vinyl acetate and magnesium stearate, and it releases a combination of etonogestrel (a progestin) and ethinyl estradiol (an estrogen) over 3 weeks. Manufactured by injection molding, the device has a polyethylene vinyl acetate core impregnated with the hormones and a non-medicated polyethylene vinyl acetate perimeter. This reservoir design, with a rate-controlling membrane, allows a constant dose of hormones to be released over the 3 weeks of use. Over this time, the NuvaRing® releases 0.120 mg/day etonogestrel and 0.015 mg/day ethinyl estradiol, producing serum concentrations of 1272 ± 311 pg/mL etonogestrel and 16.8 ± 4.6 pg/mL ethinyl estradiol.[1] Fertiring and Progering, both releasing progesterone, are other IVRs used as contraceptives. They can be used for 90 days, but they are not currently marketed in the United States.

Femring® (Warner Chilcott, LLC.) and Estring® (Pfizer, Inc.) are IVRs currently used as hormone replacement therapies. Both of these rings have reservoir-type systems. Femring has an outer diameter of 56 mm, a cross-sectional diameter of 7.5 mm, and an inner core diameter of 2 mm. Estring has slightly different dimensions: a 55-mm outer diameter, 9-mm cross-sectional diameter, and 2-mm core diameter. Both Femring and Estring use the hormone estradiol to alleviate the symptoms of menopause.

The reservoir system is also being studied for the release of an ARV.[2] The University of Utah is currently conducting research on a 90-day tenofovir (TFV)-releasing IVR. Manufactured by hot-melt extrusion, the ring has a 55-mm outer diameter and a 5.5-mm cross-sectional diameter. Tested in vivo using sheep are two IVR prototypes, one containing 10 mg TFV and one containing 10 mg TFV in combination with 21 µg levonorgestrel. In the TFV IVR, drug concentrations remained relatively consistent at 10 µg/g (vaginal tissue), and 0.01 µg/mL (plasma).[3] Similarly, a dapivirine (25 mg) reservoir IVR has been developed with the inner core containing 25 mg of dapivirine surrounded by an unmedicated outer sheath. The outer diameter of these ring is 56 mm and weighs approximately 9 grams. These rings were found to be safe and well tolerated in HIV-negative women undergoing a Phase 1 clinical study. The peak mean plasma concentration were reached at 120 hours post insertion with the dapivirine reservoir IVR.

Matrix system

The most clinically advanced IVR used for HIV PrEP is being studied and developed by International Partnership for Microbicides. The leading IVR contains the ARV dapivirine (25 mg), but research is also being conducted on an IVR containing both dapivirine (25 mg) and maraviroc (100 mg). Both rings are

intended to be in place for 28 days. Also manufactured by injection molding, these devices have matrix designs where the drug is evenly dispersed throughout the ring. The drug near the surface is released first and as then the thickness of the drug-free zone increases, the amount of drug released decreases. Pharmacokinetic studies have shown that after 1 hour of use, plasma concentrations rapidly increased to 107 pg/mL. A mean peak concentration of 1,060 pg/mL was seen 24 hours post IVR insertion, and on day 28, mean plasma concentrations lowered to 160 pg/mL.

Pod system

The pod IVR uses separate compartments to release different drugs, each with unique release rates. Drug cores are coated with biocompatible polymer membranes to create separate compartments, which are contained in an inert elastomer ring. Pod IVRs have already been studied extensively for the release of ARVs. One such example is the tenofovir disoproxil fumarate (TDF)-emtricitabine (FTC) IVR, currently researched by John Moss, et al. at Oak Crest Institute of Science. Being tested in animal studies are both a dual-combination IVR, releasing TDF and FTC, and a triple combination IVR releasing TDF, FTC, in addition to maraviroc (MVC). Over the 28-day period of use, the TDF-FTC IVR has median drug concentrations in vaginal tissues: TDF, 30 μg/g; FTC, 500 μg/g; and TDF-FTC-MVC has median concentrations; TFV, 10 μg/g; FTC, 150 μg/g; MVC, 20 μg/g.[4] Another pod design developed by J.A. Moss contains two pods (16 g each) TDF, nevirapine, saquinavir, and estradiol and two pods (10 g each) etonogestrel. With ten total pods, the device functions as both an ARV and a contraceptive and can be used for a total of 28 days.

Considerations for rilpivirine delivery

An IVR containing rilpivirine has great potential. To date, research assessing rilpivirine in an IVR presentation has apparently not occurred. Feasibility of this technology has been demonstrated, however, with other ARVs. Unlike IUDs, whose design limits the loading dose of the device, the loading dose of rilpivirine would not be restricted by the design of the IVR. The ring delivers drug directly to the surface of the cervix and vaginal mucosa, thought to be the sites of vaginal infection with HIV. Additionally, the device can be inserted by the user herself, eliminating the need for a skilled health care worker.

Intrauterine devices

IUDs are another potential option for HIV PrEP because they can deliver drug locally, and they can stay in place for years, minimizing the issues that result from inconsistent adherence. The IUD was developed in the 1960s as an effective and long-acting contraceptive technology. There are three types of IUDs that have been marketed since that time: inert IUDs, copper-bearing IUDs, and hormone-releasing IUDs. Although the exact mechanism by which they prevent pregnancy is unclear, all IUDs rely on a foreign-body response of the uterus to produce a spermicidal inflammation that inhibits sperm motility and affects ovum implantation. Complications, such as ectopic pregnancy, pelvic inflammatory disease, expulsion of the IUD, heavy menstrual blood loss, and uterine perforation have occurred with certain IUDs. Many of

these complications (expulsion, perforation, and pelvic inflammatory disease) are linked to improper IUD insertion. IUD insertion varies from device to device, but in every case, the process requires a health care professional, trained in the insertion procedure. IUD expulsion rates are generally much higher for inexperienced inserters. Many countries have demonstrated that well-trained non-physicians can insert IUDs as well as do physicians. The faculty of Family Planning and Reproductive Healthcare (United Kingdom) have created training requirements for health care professionals intending to insert IUDs. The professional must obtain a letter of competence in intrauterine techniques and must update their letter of competence every 5 years to ensure continuing competence.[5]

Inert devices

Early IUDs, such as the Dalkon Shield, the Lippes Loop, the Margulies coil, and the Saf-T-Coil, were inert devices (Figure 2). These inert devices were attractive to users because they could be left in place for decades.[6] As time passed, some of the devices were withdrawn from the market due to economic reasons (as copper and hormone IUDs became more popular) and others due to negative side effects. For example, the Dalkon Shield, whose multifilament tail was known to cause pelvic infection, was discontinued in 1975.

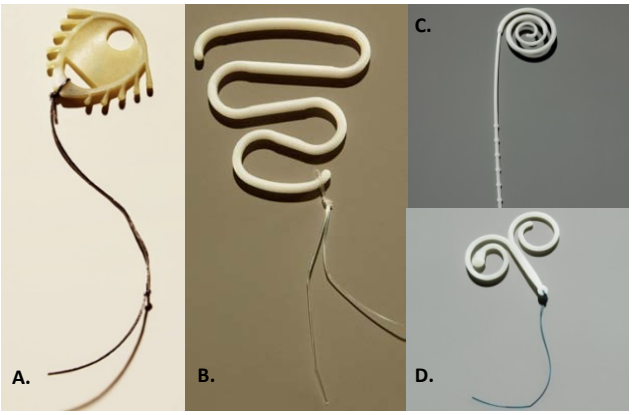

Figure 2: Inert intrauterine devices.
A.) Dalkon Shield (A. H. Robins, 1971); B.) Lippes Loop (Jack Lippes, 1962); C.) Margulies Coil (Lazer Margulies, 1960); D.) Saf-T Coil (Photos: Jamie Chung, Dittrick Medical History Center and Museum/Case Western Reserve University and Jamie Chung.

Copper-bearing devices

Copper-bearing IUDs contain a bioactive copper wire with surface areas ranging from 200 $mm^2$to 400 mm^2 (Figure 3). The copper is slowly released over time, but unlike the inert IUDs, they must be removed after a specified interval due to erosion of the copper. In addition to producing a spermicidal inflammation in the uterus, the copper contraceptive devices act by releasing copper ions that are able to change the structure of the endometrium and alter the endometrial secretions and the cervical mucus.[7]

Figure 3: Copper-bearing IUD. (Photo: ©iStock.com/ PrimeTime_Productions.)

Modern copper-bearing IUDs contain more copper, and part of the copper is in a solid sleeve form. Examples of this are the TCu380A (ParaGard®), TCu380S (Slimline), TCu-220C, the Nova-T®, and the Flexi-T® 380. In a series of recent trials, TCu380A and TCu380S were shown to have the lowest pregnancy rates.[8] These devices also have the longest duration of use (10 years), which minimizes the need for replacement and the difficulties that arise from inconsistent adherence.

In the mid-1980s, frameless IUDs were developed in the hopes of lowering expulsion rates and pain resulting from a bulky or ill-fitting frame that might warrant an early removal. One such example is the GyneFix® IUD, a polypropylene thread carrying four (GyneFix mini) or six (GyneFix standard) copper sleeves with a copper surface area of either 200 mm^2 or 330 mm^2. Whereas the T-framed devices stay in place in the uterus, the frameless IUD is anchored in the myometrium of the uterine fundus. It has been shown that despite the original intention to alleviate pain and bleeding associated with polyethylene frames, the frameless device performs similarly to traditional IUD devices and does not reduce any bleeding or pain.[9] In recent years, Israel's Ocon Medical has developed the Intrauterine Ball IUB™, a device carrying 17 small copper beads on a flexible, spherical wire. After one year of use in Europe, physicians have reported that the IUB is readily inserted and that there have been no observed perforations, expulsions, or pregnancies.[10]

Hormone-releasing devices

In the 1970s, IUDs were developed to release progesterone into the uterus and effectively serve as contraceptives.

The Mirena® IUD (LNG-IUS), a device currently marketed in the United States by Bayer Healthcare Pharmaceuticals, has a similar structure to IUD Progestasert, but contains levonorgestrel, a potent synthetic form of the hormone progesterone and is approved for 5 years of use (Figure 4). The device has a T-shaped polyethylene frame and a reservoir (3.6 mm diameter by 19 mm in length) containing 52 g levonorgestrel dispersed in polydimethylsiloxane. The LNG-IUS releases levonorgestrel into the uterine cavity where it is absorbed by the endometrium vessels and circulated systemically. Plasma concentrations reach a maximum after a couple of hours and then plateau at 150 to 200 pg/mL within weeks of insertion. The endometrium shows a much higher concentrations of the hormone; the local release of levonorgestrel results in concentrations of 470–1500 ng/g in vaginal tissue after a few weeks. Bayer Healthcare also manufactures an IUD named the Skyla® (LCS12). This device has a similar construction to the Mirena but is slightly smaller (28 mm by 30 mm versus 32 mm by 33 mm). It contains 13.5 mg levonorgestrel (reservoir: 2.8 mm diameter, 12 mm length) that is released at 14 µg/d, and it can be worn for 3 years.

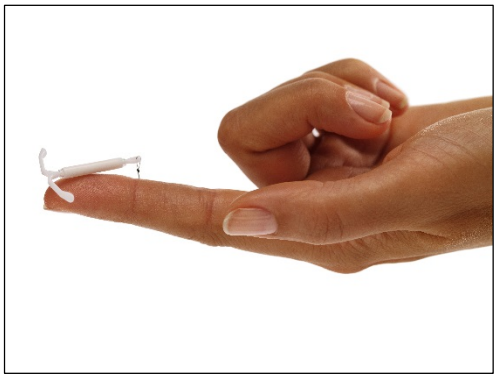

Figure 4: Hormone-releasing Mirena IUD. (Photo: Bayer.)

Considerations for rilpivirine delivery

An IUD releasing both a hormone and rilpivirine could be an attractive option for women as it would provide protection not only against HIV transmission but also against pregnancy. However, the size of existing IUDs might prove to be a limitation for a rilpivirine-releasing IUD. Modern hormone-releasing IUDs have reservoirs with the maximum dimensions of 3.6 mm (diameter) x 19 mm (height), and they can release a maximum of 52 g hormone. In the Mirena IUD, levonorgestrel doses average 20 µg/d.

Although the target concentration of rilpivirine in plasma and vaginal tissues is unknown, it is expected that the drug will require a much larger loading dose in comparison to the 52 mg reservoir of the Mirena IUD. Due to size and dose limitations of the Mirena IUD, a rilpivirine-releasing IUD with the same design is unlikely.

To determine the feasibility of a rilpivirine-releasing IUD, other IUD designs must be investigated. Alternative designs such as the Lippes Loop and the Saf-T-Coil (Figure 2) have more plastic surface area than the T-framed devices that are often seen today. These designs, or one similar, might be better suited for rilpivirine. In order to increase the dose of the device, the size of the device must be increased, but with limitations; the device must be able to compress into an insertion tube and fit comfortably in the uterus. All IUDs are made from a flexible and form-resuming material so that they can be inserted past the cervix in an insertion tube. Generally, IUDs have widths of 28 to 36 mm to fit comfortably in the uterus, but they must also be flexible so as to fit through the cervix in an insertion tube (size generally remains consistent among IUD products at ~4.5 mm for the outer diameter).

When considering an IUD that would protect the user from both HIV and pregnancy, multiple systems could be considered. The first is a drug-releasing device that would contain two active ingredients, an antiretroviral and a hormone. One challenge that may arise with such a system is drug/drug interactions that might occur if they are in the same reservoir. This might hinder the effectiveness of either drug or change their release rate. In order to design an IUD that could contain both rilpivirine and levonorgestrel, separate reservoirs may need to be included. This would, however, add to the cost and complexity of the IUD. Another system to consider is a copper-bearing IUD containing a rilpivirine drug reservoir. In this case, the copper would act as the contraceptive component rather than a hormone. This system would likely be less expensive than hormone-eluting systems.

Another challenge for introduction of an IUD for HIV PrEP is the current low uptake of this method of contraception in some regions, including those with high transmission rates of HIV. In sub-Saharan Africa, the prevalence of IUDs is less than 1%.[11] IUDs are currently underutilized in part because the provision of IUDs requires skilled health care workers with ongoing training and an adequate health care system infrastructure for aseptic IUD insertion.

Diaphragms

Technology description

Diaphragms are a nonhormonal, reusable contraceptive method, which relies on physically blocking the cervix and preventing passage of sperm into the uterus. Traditional diaphragms are made of latex, typically come in multiple sizes, and require that a trained health care worker conduct a pelvic exam to select the appropriate size and ensure a good fit. PATH developed the SILCS diaphragm (Caya®) with a contoured shape that fits most women without requiring a pelvic exam. It consists of a thermoplastic elastomer core spring covered with a layer of silicone. User studies involving women and couples around

the world have contributed to the development of a design which is acceptable, durable, and easy to use (Figure 5).

Figure 5: The SILCS diaphragm (Caya®). (Photo: PATH.)

Current status and uses

The SILCS diaphragm was licensed by PATH to Kessel Marketing & Vertriebs-GmbH of Frankfurt, Germany, and received regulatory clearance in Europe in 2013 and in Canada and the United States in 2014.[12] It is currently marketed as the Caya® contoured diaphragm.[13] With HealthTech funding, the SILCS diaphragm has been investigated for use by PATH and Queen's University, Belfast (QUB) as a controlled-release technology for delivery of dapivirine for HIV PrEP. Similar to a reservoir-type IVR, dapivirine was incorporated into the diaphragm's polymer spring with the rate of release controlled by the external silicone sheath. In vitro studies found that a prototype diaphragm released consistent levels of drug over 6 months.[14] Mechanical compression testing found the physical performance and durability of the spring containing dapivirine was similar to the currently used material.

Considerations for rilpivirine delivery

As rilpivirine has similar chemical properties to dapivirine, prior research on the use of the SILCS diaphragm as a drug delivery device could easily be applied to advance the development of a rilpivirine-releasing diaphragm as well. Assuming typical discontinuous use, a drug-eluting diaphragm could potentially be used to provide vaginal HIV PrEP and prevent pregnancy for up to 3 to 5 years.[14]

Microneedles

Microneedles are a minimally invasive technology that enables the delivery of drugs by creating small perforations through the stratum corneum, thus accessing the skin's microcirculation and achieving systemic delivery by the transdermal route. They can also be used for targeted delivery into tissue to elicit immune responses or achieve other local effects. MNPs (50 μm to 900 μm in height, up to 2,000 projections/cm^2) have been produced in various geometries and materials using recently developed microfabrication techniques. Microneedles could inform a paradigm shift in terms of drug and vaccine delivery scenarios, potentially providing public health entities added flexibility to address challenges of usability, reliability, and the logistics of current delivery options. Furthermore, self-administration is a focus of some microneedle technology efforts. Due to the broad range of potential benefits, there has been a wide breadth of research and development conducted with microneedles by multiple academic groups and industry to date.[15] Areas of research focus include pharmaceutical applications for both high- and low-income settings.

Microneedle technologies can be classified into two broad groups, hollow microneedles and MNPs. Hollow microneedles facilitate delivery of a liquid drug through a passage within the projections themselves and have similarities to other intradermal delivery methods for liquid vaccines, such as the Mantoux technique with needle and syringe. MNPs can be subdivided further into the following four main categories: 1) solid microneedles, tiny projections used to puncture the epidermis prior to the subsequent topical application of a drug; 2) coated microneedles that are solid projections coated with a dry form of the drug that then diffuses into the skin after penetration; 3) dissolvable microneedles that are projections themselves formed from a polymer/drug blend designed to dissolve into the skin after penetration; and 4) hydrogel microneedles, which elute drug from within a solid matrix but do not themselves dissolve.

Two forms of microneedles have the potential to be developed for delivery of HIV PrEP, hydrogel MNPs for systemic delivery and dissolving MNPs for local delivery (Figure 6).

Hydrogel microneedle patch for systemic delivery

Technology description

Transdermal patches are currently available for self-administration of drugs including hormonal contraception (example: Ortho Evra®), pain medication (example: Duragesic®), and nicotine replacement therapy (example: NicoDerm CQ) which require continuous, sustained systemic delivery. However, due to the barrier properties of the skin, transdermal patches are only an option for relatively lipophilic, low-dose, and low molecular weight drugs. Traditional solid coated and dissolving MNPs are better able to breach the stratum corneum to access local microcirculation but are also limited in dosage to the amount of drug which can be contained within the needles themselves. More recently, hydrogel microneedles have been developed that employ an array of cross-linked, hydrophilic polymer projections that swell and soften as

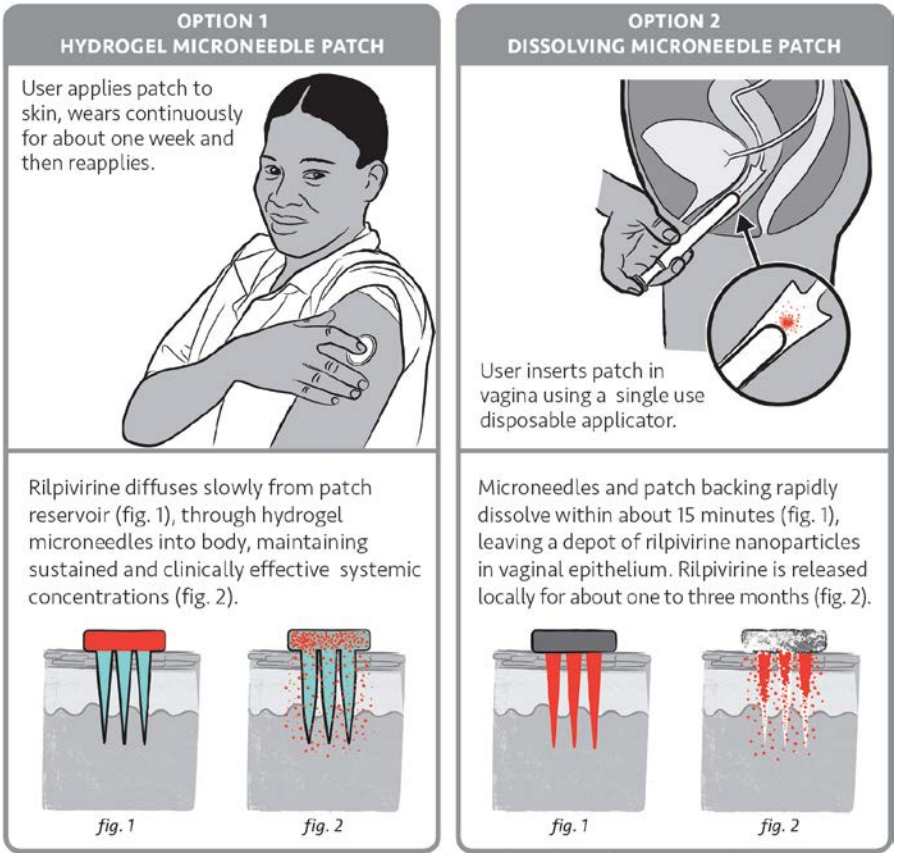

Figure 6: Two forms of microneedles that could be applied to rilpivirine delivery. (Images: PATH)

they take up interstitial fluid after insertion into the skin (see Figure 7).[16] Once hydrated, these projections form conduits that facilitate the release of drug from the backplate of the microneedles or an adjoining lyophilized reservoir. This type of MNP allows for the delivery of larger quantities of drug, resists closure of the perforations, and can be removed intact so no polymer remains in the skin, which may be important for drugs requiring repeated doses. Following use, the needles soften and lose their shape, thus preventing inappropriate reuse or injury if the patch is not disposed of properly.

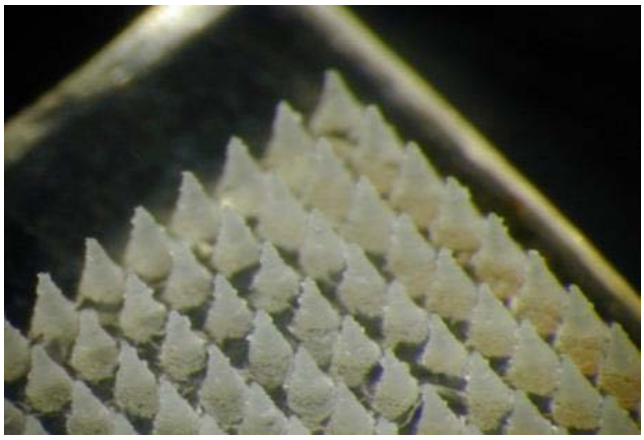

Figure 7: Hydrogel microneedle, designed by Queen's University, Belfast.
Photo: Queen's University Belfast.)

Current status and uses

The School of Pharmacy at QUB, United Kingdom, has developed hydrogel MNPs for drug delivery. Preclinical studies using ibuprofen as a model drug have led to estimates that hydrogel microneedles could serve as a rate-controlling delivery system and enable consistent, sustained release of hundreds of milligrams of drug over an extended time frame.[17] A clinical study of a placebo patch found that the patches were well-tolerated by recipients and the skin's barrier function recovered quickly following removal of the patch.[18] Self-administration has been assessed and found to be a feasible delivery option.[19]

Considerations for rilpivirine delivery

A patch delivery system for rilpivirine could offer benefits in enabling a thermostable, self-applied delivery method for systemic protection against all routes of HIV infection. Due to the required dose of rilpivirine to achieve sufficient systemic concentrations for HIV PrEP, a hydrogel MNP is the leading option for skin-based delivery. Most MNP development efforts have focused on enhancing delivery of substances traditionally regarded as relatively hydrophilic, with Log *P* values in the range of -0.2 to 1.5. QUB has employed novel solubility enhancement technology (developed for applications in oral drug delivery and nanoencapsulation techniques) to produce microneedles. This technique is intended to permit transdermal and local administration of hydrophobic drug substances, which could be applied to rilpivirine (Log *P* = 5.4). Hydrogel microneedles are at an early stage in development, and it is yet to be determined whether an adequate dose can be loaded and delivered and whether this approach would be acceptable to users. The length of time a hydrogel MNP could continuously deliver rilpivirine must also be investigated, but the technology has the potential to allow for approximately weekly application rather than the daily dose required of oral rilpivirine. If successful, this technology has the potential to be applied to other HIV medications as well as other drugs which could benefit from a self-administered, sustained-release delivery mechanism. A segmented patch could also be developed containing a contraceptive transdermal patch on one side and a rilpivirine hydrogel MNP on the other, allowing for multipurpose prevention against HIV and pregnancy.

Dissolving microneedles for local delivery

Technology description

Dissolvable microneedles are those where the projections themselves are composed of a concentrated polymer/drug/excipient blend that dissolves when in contact with interstitial fluid. These projections have been fabricated from a variety of polymers such as carboxymethyl cellulose, poly (vinyl pyrrolidone), poly-L-lactic acid, poly-glycolic acid, poly-lactic-co-glycolic acid, and poly (vinyl) alcohol and sugars such as trehalose, galactose, maltose, and dextrin, and even silk.[20] [21] The wear time required for the microneedles to dissolve is typically in the range of a few minutes. In order to achieve reliable and consistent dosing when dissolving MNPs are used, applicators may be required. An applicator is designed to impart a precise and reproducible force to the microneedle array using a spring-loaded or other mechanical mechanism, ensuring penetration by all projections in the array. The quantity of drug that can be loaded in dissolvable microneedles is dependent on the size of the microneedle and the number of projections in the array, with an upper limit of a few milligrams.

Current status and uses

Many varieties of dissolvable MNPs have been developed by academic and industry groups, including Georgia Tech, Corium, CosMED, TheraJect, and QUB.[15] Dissolving microneedle patches have been studied for delivery of vaccines including those for influenza, rotavirus, polio, and drugs such as parathyroid hormone for treatment of osteoporosis.[22,23,24,25,26] MicroHyala®, produced by CosMed in Japan, is a dissolvable MNP that is used to deliver hyaluronic acid and other active compounds intradermally for treatment of wrinkles.[27] This product was introduced in 2008 and is currently sold in Japan. Bioadhesive patches (without microneedles) for vaginal and vulval delivery of drugs have been investigated for local delivery of drugs for HIV and precancerous neoplasias.[28,29,30]

Considerations for rilpivirine delivery

Preclinical studies have found very high, sustained concentrations of rilpivirine in local tissues following subcutaneous and IM injection of TMC278LA.[31] This suggests that vaginal delivery of a reduced dose of TMC278LA could enable sustained release of drug locally over time for protection against HIV infection in the vaginal region. However, as the nanoparticle formulation of TMC278LA will not easily cross the vaginal epithelium, a delivery method would be needed which could deposit the drug within the tissue. Dissolving MNPs have primarily been developed for skin delivery but could be adapted for delivery of TMC278LA to the vaginal wall. The patch's backing could be made of a bioadhesive material which upon contact with the vaginal mucosa would rapidly form a gel and dissolve entirely within 15 minutes. The microneedle tips would then dissolve within the vaginal tissue, releasing the nanoparticles which could potentially maintain local concentrations of rilpivirine for up to several months. A disposable or reusable applicator would potentially be needed to protect the microneedles until they reach the desired location and provide the appropriate force so that the microneedles penetrate the tissue. An acceptable, intuitive, and low-cost design for an applicator might enable self-administration of the patch at home.

Vaginal delivery

ARV gels

For sustained delivery of drugs for HIV PrEP, one important consideration is continuous use of the product to maintain therapeutic drug levels in the vaginal region for an extended period of time. This in turn requires high loading levels of the drug in the delivery system at the time of administration. A majority of clinical trials have evaluated gel-based systems for vaginal drug delivery for coital-dependent HIV prevention. The ARV used in many of these trials is TFV, a nucleoside reverse transcriptase inhibitor. TFV gel was originally developed by Gilead Sciences, Inc., which then transferred rights to the International Partnership for Microbicides and CONRAD. Two notable trials for this gel are the CAPRISA-004 and the VOICE trial. CAPRISA 004, a Phase 2b trial, was the first to demonstrate effectiveness of an ARV as preexposure prophylaxis. With 889 women from South Africa enrolled in the trial, it assessed the safety and effectiveness of a 1% TFV gel. Results showed that after 30 months, women using the TFV gel were 39% less likely to get HIV than those using a placebo. Among high adherers (above 80% adherence), the effectiveness of the gel was 54%.[32]

The VOICE trial compared an ARV tablet (containing either TFV or Truvada®) to the 1% TFV gel applied daily. Tested on a total of 5,029 women in Uganda, Zimbabwe, and South Africa, the trial stopped prematurely when it was determined that the ARV was no more effective in preventing HIV than the placebo.[32] The results of the placebo and the TFV gel groups were almost identical; in the placebo group, there was a 6.1% HIV incidence rate per year, and in the TFV group, the rate was 6.0%/year.[33] Inconsistent adherence was one likely cause of these results. During the study, blood samples taken at quarterly visits from 773 participants revealed that 55% of those participants using the TFV gel had no detectable drug in their sample.[34]

It can be understood from the VOICE trial, that adherence has a strong impact on gel efficacy. This dosage has other drawbacks as well; there have been user complaints of product leakage and “messiness” due to poor retention in the vaginal lumen.[35] In addition, frequent vaginal administration of the gel has the potential to cause adverse effects such as inflammation, irritation, tissue infiltration, and changes to the vaginal flora which may potentially increase the risk of HIV transmission.[36] It should be noted that PATH (under the HealthTech program) and partners are also evaluating lower-cost, user-filled paper applicators for gel delivery (Figure 8).

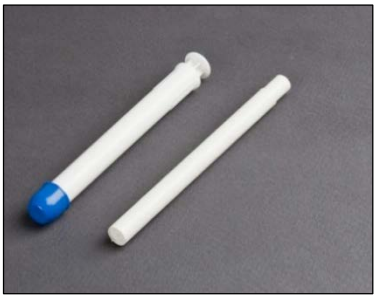

Figure 8: Applicators for microbicide gels.
(Photo: PATH.)

Fast-dissolving tablets

Tablets that dissolve rapidly when inserted into the vaginal region are another method of delivering ARV locally. When dissolved, these tablets form a viscous suspension throughout the vaginal cavity that is able to provide systemic absorption. A vaginal applicator is not needed for these tablets, thereby reducing

packing materials and manufacturing costs. CONRAD is currently conducting clinical trials on TFV, FTC, and TFV-FTC fast-dissolving vaginal tablets (applied once daily for 14 days).

Vaginal films

Fast-dissolving vaginal films are a potential alternative to gels; they are cleaner and easier to apply. Due to the size of the film and the lack of an applicator, the cost of manufacturing these vaginal films could be less. These characteristics may lead to broader acceptance of the delivery system. There are several vaginal films being researched currently. In 2008, a vaginal film containing 100 μg RC-101 (a drug that has shown activity against X4 and R5 strains of HIV-1) was developed. The vaginal film was clear, flexible, and could dissolve in less than 5 minutes in water.[37] The film was demonstrated to be efficacious and safe in vitro and ex vivo. More recently, a vaginal film loaded with EFdA, a nucleoside reverse transcriptase inhibitor, has been evaluated in ex vivo and in vitro studies. Developed and researched by Stefan Sarafianos and researchers from the University of Pittsburgh and the National Institutes of Health, the film looks like a promising candidate for temporary HIV prevention.[38] Additionally, dapivirine has been formulated into fast-dissolving vaginal films.[39] Films containing 1.25 mg of dapivirine were designed to release over 50% of the drug locally within the first 10 minutes of application. Studies demonstrated that dapivirine permeated the target tissue in vitro and inactivated HIV-1 ex vivo.[40]

Considerations for rilpivirine delivery

Although fast-dissolving tablets and films offer a promising platform for vaginal delivery of HIV drugs, the longest sustained effect achieved in these dosage forms is under 24 hours.[40,41] In addition, lower drug loading levels and the need for repeat applications/administrations in these presentation formats make these dosage forms an unattractive option for sustained delivery. Lastly, the changing physiology of the vaginal flora may potentially pose challenges during repeat administration of these dosage forms (films, tablets, gels, ovules).

Implants

Technology description

Implant technology includes small rods or capsules that contain the API and provide controlled release of the drug through a membrane over a set duration to achieve target bioavailability or alternatively is completely composed of the API within a biodegradable material matrix that both releases the API and degrades, allowing absorption by the body over time. Drug delivery applications for this technology class include contraceptives (long-acting, reversible contraceptive) and other hormonal-based pharmaceuticals, cancer treatment drugs, as well as vaccines and other biologics. In the case of contraceptive delivery, pregnancy protection can last several years depending on the specific contraceptive implant.

The predominate type of implant used for hormonal (progestin) contraceptive applications involves placement into the target tissue and area of the body (e.g., upper arm) of the patient, through a small

incision made into the skin by means of a reusable or disposable trocar or other similar insertion device. A trocar has a cannula (needle) that allows for penetration into the target tissue (e.g., subcutaneous tissue) and an obturator for pushing the implant through the cannula and into the tissue. The implant is deposited and the cannula is then removed from the injection site. Removal can occur at any time to reverse the contraceptive action and can be achieved through an incision into the site of the implant and extraction by means of forceps. One or more implants may be inserted depending on the specific API, dosage concentration, and target duration of controlled release for the implant. This approach to implant delivery requires a trained medical professional and potentially local anesthetic for both insertion and removal. Examples of this type of implant technology include Jadelle® (levonorgestrel), Implanon®/Nexplanon® (etonogestrel), and Zarin®/ Sino-implant II (levonorgestrel).

Other implant-type technologies that are smaller than traditional contraceptive implants with geometry similar to a needle utilize a powered actuator that forces the implant into the skin for delivery. The implant is contained within a cartridge or cassette that interfaces with the actuator to allow for implant delivery. Controlled release is also possible with this implant technology approach, however, with vaccine delivery as a target. A more rapid release and thus more immediate bioavailability is a key performance characteristic. The Glide Pharma Solid Dose Injection System is an example of this technology approach (Figure 9).[42]

Figure 9: Glide SDI® solid dose injection system.
(Photo: Glide Pharma.)

The use of biopolymers that are biodegradable for implant drug delivery is an emerging area of research with relevant examples in both contraceptive and ARV delivery.

Current status and uses

Contraception

Jadelle®. Jadelle is a two-rod (silicone) implant system based upon the Norplant® system (the first hormonal implant technology) and was developed by the Population Council. Each rod contains containing 75 mg of levonorgestrel with a duration of 5 years of use. Jadelle is produced by Bayer Health Care as part of the Jadelle Access Program, which is a partnership with the Bill & Melinda Gates Foundation. Bayer has agreed to provide 27 million implants over a period of 6 years. Jadelle was the first hormonal contraceptive implant to obtain World Health Organization (WHO) prequalification.[43,44]

Zarin® (Sino-implant II). Zarin is produced by Shanghai Dahua Pharmaceutical Company Ltd (Figure 10). Two rods composed of silicone contain 75 mg of levonorgestrel. The implants have a 4-year duration of use.[45] Zarin is registered in a number of countries and is currently under review by WHO for prequalification. Through Bill & Melinda Gates Foundation and USAID support, FHI 306 is working to provide programmatic, clinical and other technical assistance for successful approval and country-level use.[46,47,48]

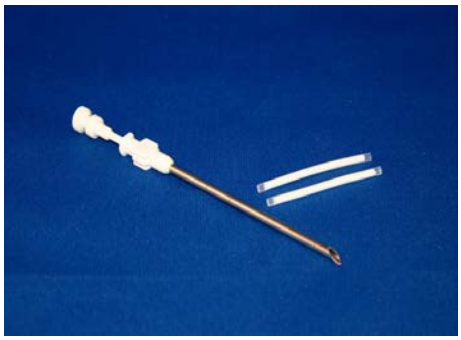

Figure 10: Contraceptive implant Zarin®, Pharm Access Africa Limited (Sino-implant II produced by Shanghai Dahua Pharmaceutical Company Limited).
(Photo: Aida Cancel, FHI 360.)

Implanon® and Nexplanon®. Implanon is produced by Merck and is a single implant rod system, 4 cm in length/2 mm diameter with 68 mg of etonogestrel and a duration of 3 years.[49] It comes preloaded in a needle of a disposable applicator. Merck is also working with the Gates Foundation to achieve availability of this technology for developing-country use.[50] Nexplanon is similar to Implanon; however, it is radiopaque (addition of 15 mg barium sulfate) to allow noninvasive confirmation of implant location (x-ray imaging) to increase ease of removal.[51]

FHI 360 biodegradable implant. FHI 360, through funding from USAID, has developed a biodegradable contraceptive implant composed of a levonorgestrel microsphere formulation that will be effective for 18 months and does not need to be removed. The requirement for clinical removal of more traditional implants is perceived to be a barrier to use. Currently, this technology is at a proof-of-concept stage. This research is in collaboration with Obris Biosciences (microspheres supplier) and Yale University (novel biodegradable biopolymer).[52]

Capronor biodegradable implant. Capronor is a biodegradable implant containing levonorgestrel in a reservoir-type configuration. The implant is composed of polycaprolactone (PCL) that will degrade over a period of up to 2 years and have an effective contraceptive duration of 1 year of use. The implant would essentially break down through hydrolysis into carbon dioxide and water. Capronor II consists of two rods of PCL, each rod contains 18 mg of levonorgestrel, and Capronor III is a single capsule of 32 mg of levonorgestrel with a copolymer of caprolactone and trimethylenecarbonate. Preclinical and early stage clinical studies were conducted with this technology, however the current development status is not known.[53,54]

ARV delivery—biodegradable implant

RTI International is one known developer of an implant technology for ARV delivery. Through a five-year award from USAID, RTI will develop the biodegradable thin-film polymer device (TFPD) for preexposure systemic ARV delivery with target effectiveness for HIV prevention up to 3 months in duration. TFPD is a membrane-based system composed of a reservoir containing the solid drug surrounded by thin flexible PCL films. The films have a thickness of 5 to 20 μm, and the currently reported target dimensions (maximum) are 2 mm x 2 mm x 50.8 mm (<500 μL volume in reservoir). The TFPD would be delivered subcutaneously with a trocar or other suitable applicator technology (such as

Implanon). Permeation of the membrane occurs which allows for contact and dissolution of the drug which allows for drug release through passive diffusion (constant release rate). Controlled release is not a function of the degradation of the PCL biopolymer but rather through the diffusion of the drug through the PCL membrane. Several different ARVs are under consideration for the TFPD, including TMC278.[55,56]

Considerations for rilpivirine delivery

The use of implants for ARV delivery appears technically feasible, and biodegradable implants in particular are a promising area of research, which is exemplified by RTI's TFPD technology platform. The elimination of the need to remove the implant (as is the case with traditional contraceptive implants) increases the flexibility by which such a system can be utilized for either contraceptive or systemic ARV delivery. However, placement of the implant does require a trained health care professional, and self-administration would appear to be technically challenging and/or not a practical consideration for successful implant delivery. Research focused on local (vaginal) ARV delivery has not been identified to date and may represent another possible area of consideration. The same challenge of administration/ application would also be a consideration. The use of biodegradable polymers such as PCL for the development of implants in different/nonstandard configurations may also be an area of potential research and exploration.

Summary and recommendations

Following review of the technology landscape and discussion with stakeholders, we utilized the criteria in the TPP (Annex 1) to identify technologies to recommend for further development for rilpivirine delivery and feasibility assessment. Preliminary criteria included technologies which would be long acting (at least 1 week, and preferably greater than a month). In addition we focused on technologies which are not currently under development for other ARVs for HIV PrEP, as well as those that filled empty spaces in the technology matrix shown in Table 1 below. The purpose of this prioritization was to avoid duplicating ongoing development efforts and to provide additional options for potential users of HIV PrEP (and address unmet needs) among the landscape of products which could potentially enter the market in the future.

Table 1. Matrix of existing or potential antiretroviral delivery technologies.

Administration	Drug distribution	Short acting (≤1 day)	Long acting (≥1 week)
Self-administered	Local (vaginal)	• Gels/creams*/** • Fast-dissolving tablets** • Drug-eluting diaphragm** • Vaginal films***	• Intravaginal ring** • Dissolving microneedle patch***
	Systemic	• Oral tablet*	• Hydrogel microneedle patch***
Administered by health care worker	Local (vaginal)	Not applicable	• IUD***
	Systemic	Not applicable	• TMC278LA injection** • Implant**

ARV delivery technology key:

* Market available

** Technology in development (preclinical or clinical research stage)

*** Potential technology candidate

Our preliminary analysis identified three top candidate technologies, a drug-eluting IUD, a dissolving microneedle patch (MNP) for local (vaginal) delivery, and a hydrogel MNP for systemic delivery. Upon further consideration of the TPP requirement for self-administration, we recommend dissolving and hydrogel microneedles for initial exploration and feasibility determination. A brief summary of all three technologies and our analysis are included below.

Intrauterine device

A drug-eluting IUD is a potential delivery method for rilpivirine which could meet the need for very long-term delivery (1 year or more) without the need for user compliance and could serve as a multipurpose prevention technology if contraceptive action is included. Some technical feasibility challenges with this approach will include developing a large enough IUD to load and release a sufficient quantity of rilpivirine and whether the drug will diffuse from the uterus to the cervical and vaginal sites of infection. Programmatic challenges with this approach include the current underutilization of IUDs in regions at high risk of HIV infection (such as sub-Saharan Africa) as well as the need for a health care worker with specific training to insert the IUD. However, the potential for very long-term delivery of ARVs as well as contraception could be of significant public health benefit if these challenges could be overcome. Preliminary feasibility work to develop device design concepts and assess key issues such as dose loading could be conducted in the future to more definitively determine the degree of technical challenges this technology could represent.

Microneedle patch

As noted, the two forms of MNPs which could potentially be used to deliver either rilpivirine or TMC278LA are the hydrogel and disposable microneedles. These represent two different forms of protection against HIV infection (systemic and vaginal) and could each potentially be self-administered at home by users.

Hydrogel microneedle patch

This technology could be self-administered to the skin for systemic delivery of rilpivirine. Hydrogel microneedles swell with contact with skin moisture and enable diffusion of small-molecule drugs from an attached patch-type drug reservoir for sustained systemic delivery over a period of up to 1 week. The reservoir of a hydrogel MNP could enable delivery of much greater quantities of drug than other more conventional MNP technologies (coated and dissolvable MNPs) which are limited to delivering the quantity of drug contained on the microneedles themselves.

Dissolvable microneedle patch

The second potential approach is a dissolvable MNP containing TMC278LA nanoparticles applied intravaginally using a disposable applicator. Upon contact with the vaginal mucosa, the bioadhesive patch's backing would rapidly form a gel and dissolve entirely within 15 minutes. The microneedle tips would dissolve within the vaginal tissue, thus releasing the nanoparticles. Local concentrations of rilpivirine could potentially be maintained for several months.

Annex: Target product profile for long-acting, self-administered rilpivirine for HIV preexposure prophylaxis

There is an urgent need for highly effective, well-tolerated, low-cost, and easy-to-administer long-acting methods for antiretroviral (ARV)-based HIV preexposure prophylaxis (PrEP) that are less dependent on daily patient compliance, such as oral tablet delivery. Injectable formulations for PrEP, such as TMC278LA, which could be administered every 2 to 3 months, offer promise in this regard, but these may also be limited by their mode of administration (intramuscular injection) which often requires administration by a trained health care worker and ongoing patient access to health facilities. A low-cost delivery presentation and method are needed that can be self-administered. In this regard, alternative methods of delivery are a potentially important and so far unexplored option which may enable sustained release of rilpivirine for systemic or local PrEP.

The following is a generic target product profile for both a systemic and local PrEP delivery presentation of rilpivirine suitable for self-administration by women in resource-poor settings.

Variable		Minimum	Optimistic
Indication	Systemic	Prevention of HIV infection.	Prevention of HIV infection.
	Local	Same	Same
Product description	Systemic	Long-acting presentation for prevention of HIV infection for all routes of HIV transmission.	Long-acting presentation for prevention of HIV infection for all routes of HIV transmission.
	Local	Long-acting presentation for prevention of HIV infection in women by vaginal transmission.	Long-acting presentation for prevention of HIV infection in women by vaginal transmission.
Product registration path	Systemic	United States Food and Drug Administration and/or European Medicines Agency with World Health Organization prequalification and local country regulatory approval	Worldwide regulatory approval.
	Local	Same	Same

Variable		Minimum	Optimistic
Target population	Systemic	Reproductive age, HIV-negative, non-pregnant women at risk for HIV infection in resource-poor settings.	Same as minimum, but also including any populations at risk or seeking protection from HIV infection including men who have sex with men.
	Local	Same—women only	Same—women only
Target countries	Systemic	Low and middle income countries with high prevalence.	Global: High-risk populations within LMICs and developed countries (expanded market of use).
	Local	Same	Same
Primary target delivery channel	Systemic	Funding via governments and private foundations; distribution through nongovernmental organizations and other entities; user availability likely to be prescribed for either self-administration at home or provided at clinic visits with appropriate clinical follow-up (e.g., HIV/pregnancy testing).	Same as minimum with no need for clinic visits.
	Local	Same	Same
Safety	Systemic	No serious adverse events; no product-related adverse events >2. Safety and side-effect profile comparable to available antiretroviral (ARV) treatment products.	No serious adverse events; no product-related adverse events >1. Safety and side-effect profile superior to available ARV treatment products.
	Local	Same	Same
Efficacy	Systemic	~70% efficacy for HIV prevention.*	>70% efficacy for HIV prevention.
	Local	Same	Same

* The minimal acceptable efficacy based on efficacy observed with oral Truvada use in the Partners PrEP study (systemic ARV delivery). Available at: http://www.ncbi.nlm.nih.gov/pubmed/22784037.

Variable		Minimum	Optimistic
Presentation	Systemic	Dosage contained within a format suitable for self-administration (with possible separate applicator/administration aid).	Dosage contained within a format suitable for self-administration (no separate applicator required).
	Local	Dosage contained within a format suitable for vaginal self-application (with possible separate applicator/administration aid).	Dosage contained within a format suitable for vaginal self-application (no separate applicator required).
Formulation	Systemic	Formulation containing rilpivirine as active ingredient with necessary excipients/additives.	Same
	Local	Same	Same
Dosage	Systemic	Dosage sufficient to maintain systemic drug concentrations at maximum range consistent with injectable (intramuscular [IM]) formulation.[†]	Dosage sufficient to maintain systemic drug concentrations at minimum range consistent with injectable (IM) formulation.
	Local	Dosage sufficient to maintain drug concentration in vaginal tissue at maximum range of clinically established local amount required for PrEP.	Dosage sufficient to maintain drug concentration in vaginal tissue at minimum range of clinically established local amount required for PrEP.
Packaging	Systemic	Product contained within suitable secondary packaging to allow for consumer supply and use within existing ARV or pharmacy distribution channels.	Same
	Local	Same	Same
Administration	Systemic	Self-administered by user at the home level once a week.	Self-administered by user at the home level every 2 to 3 months.
	Local	Same	Same

[†] Note: IM formulation dosage parameters still to be determined.

Variable		Minimum	Optimistic
Human factors	Systemic	Self-administration design interface and procedure for use in accordance with the general principles laid out in IEC 62366 and AAMI HE75.	Same
	Local	Same	Same
Skill level	Systemic	Minimal training required; user can self-administer alternative rilpivirine presentation correctly after maximum 1-hour training session at health care provider.	No training required; user can self-administer alternative rilpivirine presentation correctly using printed instructions only.
	Local	Same	Same
User time required for delivery	Systemic	Comparable to other non-oral self-administered medicines.	Less time when compared to other non-oral self-administered medicines.
	Local	Same	Same
Stability/shelf life	Systemic	36 months, 15°–30°C.	60 months, Zone IVb[‡] ambient conditions.
	Local	Same	Same
Cost/price	Systemic	<highest cost HIV PrEP products available for use in LMICs.	<lowest cost HIV PrEP products available for use in LMICs.
	Local	Same	Same
Disposal	Systemic	Safe disposal at level of home/community. No special precautions/disposal practices required.	Same
	Local	Same	Same
Resistance profile	Systemic	Similar resistance profile to other presentations of rilpivirine.	Improved resistance profile compared to other presentations of rilpivirine.
	Local	Same	Same
Discreet use	Systemic	Once applied, product is not visible to casual observers (i.e., can be hidden under clothing)	Once applied, product is not detectable by casual observers or sexual partners
	Local	Same	Same

[‡] Available at: http://www.who.int/medicines/services/expertcommittees/pharmprep/QAS05_146Stabilitywithcomments.pdf.

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