



DAPIVIRINE RING

THE CASE FOR ACTION

RESEARCH BY



About the Dapivirine Ring

The monthly dapivirine ring is the first discrete, long-acting, HIV-prevention product designed specifically for women. Developed by the International Partnership for Microbicides through an exclusive worldwide license for dapivirine from Janssen Sciences Ireland UC, the dapivirine ring is a flexible, silicone vaginal ring that provides sustained release of the antiretroviral (ARV) drug dapivirine over one month to reduce the risk of HIV-1 acquisition. The ring is safe and reduces HIV risk.¹ Clinical trials (ASPIRE and The Ring Study) showed the ring reduced HIV infection by approximately 30 percent overall.² Post-hoc exploratory analyses suggest that HIV risk was reduced by up to 75 percent among a subset of participants who appeared to use the ring most consistently.³

The ring is now being provided in two open-label extension (OLE) studies, HOPE and DREAM, in four countries (South Africa, Malawi, Zimbabwe, and Uganda) to previous Phase III trial participants. DREAM is expanding to also offer the ring to 600 young women (ages 18–25) who have not previously used the product. Anticipated enrollment across both OLEs is approximately 3,700.⁴ Regulatory submissions are under way to license the product for use in countries where women face the highest rates of HIV infection in the world. First approvals in Africa could come as soon as early 2019.⁵

About this Report

This report was written by FSG (a member of the OPTIONS Consortium) for national governments, donors, implementers, and advocates who are planning for the launch of the monthly dapivirine ring. OPTIONS is a five-year initiative, funded by the U.S. Agency for International Development (USAID) in partnership with PEPFAR. It aims to develop a streamlined, adaptable product delivery platform for current and future ARV-based HIV prevention options, with a particular focus on women. The consortium is led by FHI 360, AVAC, and Wits RHI and includes LVCT Health in Kenya, Pangaea Zimbabwe AIDS Trust in Zimbabwe, Avenir Health, the London School of Hygiene and Tropical Medicine, McCann Global Health, and FSG. Many OPTIONS partners, the International Partnership for Microbicides, and other stakeholders contributed to this work.

1 Baeten, J. et al. "Use of a vaginal ring containing dapivirine for HIV-1 prevention in women," *New England Journal of Medicine*, 2016.

2 Ibid.

3 Brown, E., et al. *Residual dapivirine ring levels indicate higher adherence to vaginal ring is associated with HIV-1 protection*. 21st International AIDS Conference, July 2016.

4 AVAC, *PxWire: A Quarterly Update on HIV Prevention Research*, January–March 2017.

5 International Partnership for Microbicides, *IPM's Application for Dapivirine Vaginal Ring for Reducing HIV Risk in Women* (now under review by European Medicines Agency), July 2017.

Dapivirine Ring At a Glance



ABOUT THE RING

- » The first discreet, long-acting HIV prevention product designed for women
- » Flexible, silicone vaginal ring that slowly releases antiretroviral drug dapivirine over the course of a month; the cost of the ring is currently expected to be \$6-\$8 per ring or \$72-\$96 per year
- » Phase III clinical trial complete and currently under regulatory review

THE NEED

- » Women account for 52 percent of adult HIV infections in sub-Saharan Africa and need HIV prevention options that they can independently control.
- » Evidence from the contraceptive field illustrates that greater product choice leads to greater overall uptake and improved health outcomes for women.
- » The monthly dapivirine ring will provide critical insights into real-world experience with rings and accelerate future efforts in a series of next-generation ring products, including a 90-day, three-month dapivirine-only ring and rings that combine HIV prevention and contraception.

WHAT WE KNOW

- » **Acceptability:** The ring is a highly acceptable option—more than 90% of trial participants noted they were willing to use the ring if found effective.
- » **Effectiveness:** The ring reduces HIV risk when used—across studies, the ring reduced HIV risk by approximately 30%. For the most consistent users, efficacy may be as high as 75%.
- » **Safety:** The ring is safe with no serious side effects and few requirements for ongoing laboratory testing.
- » **Ease:** The ring is easy to insert, can be picked up quarterly, and is easy to store with no cold chain requirements.

WHAT WE DON'T YET KNOW

- » **Uptake:** How will acceptability of the ring in clinical trials translate to uptake in real-world settings? Who will use the ring? What investments will be needed to support uptake?
- » **Adherence:** What adherence support interventions will be most effective, particularly among young women? What are the associated costs of these efforts?
- » **Delivery Models:** What channels can efficiently and safely make the ring accessible to users? To what extent can the ring be delivered through nonclinical channels? What are the cost implications of different delivery models?

WHAT'S NEEDED NOW

- » The ring was submitted to the European Medicines Agency in June 2017 and will be submitted to the Medicines Control Council (MCC) in South Africa, Food and Drug Administration (FDA) in the United States, and the World Health Organization (WHO) for pre-qualification. Approvals in Africa could come as soon as early 2019.
- » National governments, donors, implementers, and advocates need to prepare for a set of strategic implementation projects to ensure quick, efficient introduction once approvals are received.
- » There is opportunity to improve on previous product introduction efforts. Even a subset of the resources spent on oral PrEP could deliver initial implementation projects to test the ring in real-world settings at scale in high-priority countries.



The Ring Is the Next Step in the Movement to Eradicate HIV

The monthly dapivirine ring has the potential to be a powerful tool in the fight against HIV. As the first long-acting HIV prevention product designed specifically for women, it will enable more women to protect themselves against HIV transmission without requiring action from a partner. It is also the first in a line of new ring products under development that will greatly increase the options available for women seeking HIV prevention, contraception, and products that offer dual protection.

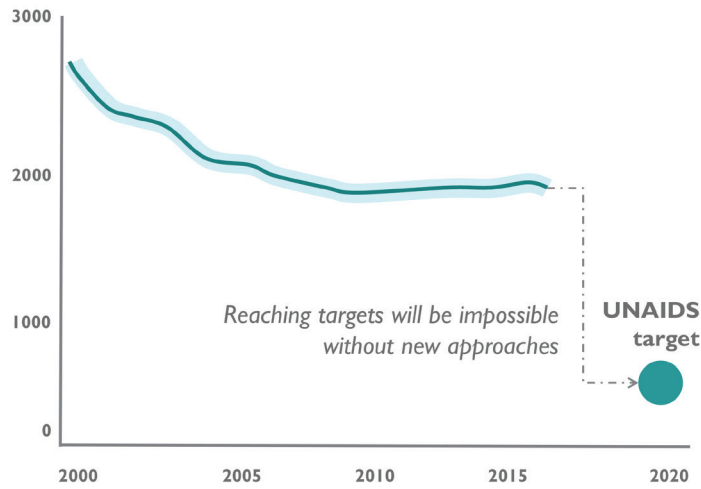
The need for the ring is urgent. Progress in reducing new HIV infections is slowing, and the annual number of new HIV infections has remained around 1.8 million for the past decade. The need is particularly acute for women, who account for 51 percent of new adult HIV infections. This includes adolescent girls and young women (AGYW) aged 15–24, who account for 22 percent of all new adult HIV infections globally—over 7,000 new infections each week (Figure 1).⁶

The dapivirine ring could prevent up to 510,000 new HIV infections in 13 sub-Saharan African countries by 2030.

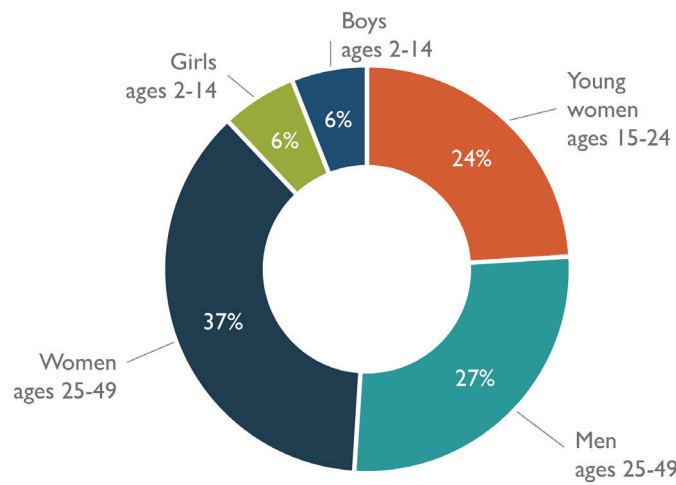
⁶ UN Joint Programme on HIV/AIDS (UNAIDS), *Prevention Gap Report*, January 2016 and UNAIDS Data 2017.

FIGURE I. THE NEED FOR HIV PREVENTION FOR WOMEN AND GIRLS

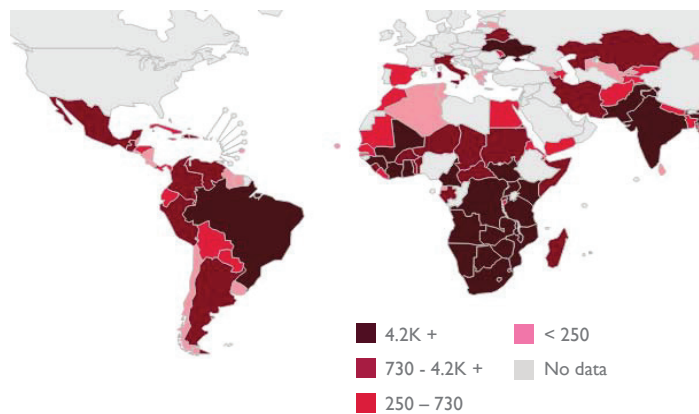
IA. NEW HIV ADULT (AGE 15+) INFECTIONS BY THOUSANDS, 2000-2016



IB. NEW HIV INFECTIONS BY AGE AND SEX BY PERCENT, 2015



IC. NEW HIV INFECTIONS AMONG WOMEN AGE 15+ BY THOUSANDS, 2015



Source: UNAIDS Prevention Gap Report 2016 and UNAIDS Data 2017.

After a decade of research and product development, the ring is undergoing regulatory agency review. The ring is a tremendous step forward in three ways:

1 WOMEN AND GIRLS NEED HIV PREVENTION OPTIONS THAT THEY CAN FULLY CONTROL

Women and girls have few HIV prevention options that they can fully control. Male and female condoms and male circumcision all require male consent, putting them out of reach for many women and girls who cannot negotiate their use.

In many sub-Saharan African countries, AGYW do not have agency over their healthcare decisions or sexual experiences.⁷ An astonishingly high 37 percent of women in the region report experiencing sexual violence—these women are, on average, 1.5 times more likely to acquire HIV and other sexually-transmitted infections (STIs) than women who have not experienced violence.⁸ This reality that few women have the ability to negotiate condom use or sexual activity with male partners underscores the need to ensure that women have the ability to protect themselves. The magnitude of this problem means that women need to have HIV prevention methods they can control in order to make any progress toward the elimination of HIV.

Experiences with contraception and HIV and STI prevention (see Box 1) demonstrate that choice is critical to uptake: The more available options, the more likely that women will use one of them. As the only new HIV prevention option that could be available in the next 5–8 years, the dapivirine ring presents a significant and immediate opportunity to strengthen efforts to fight HIV, especially for women who are most at risk.

“Using condoms is not so easy. If you try and negotiate, it’s like you’re saying you’re not being faithful. [Ring and oral PrEP] would give me ownership. I don’t have to tell my partner I’m using them.”
— REACH stakeholder consultations

7 USAID, *Demographic and Health Surveys*, 2012.

8 World Health Organization (WHO), *Global and regional estimates of violence against women: Prevalence and health effects of intimate partner violence and non-partner sexual violence*, 2013.

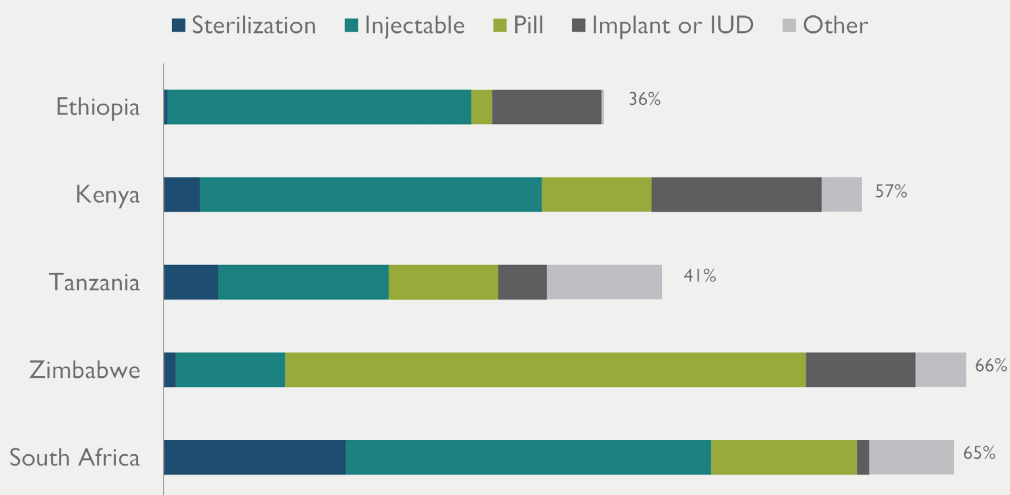
BOX I. THE POWER OF CHOICE

The history of contraception demonstrates that expanding choices for women has a significant impact on uptake of contraception overall.

Research shows that adding one new method and making it available to at least half of a country's female population correlates with a 4–8 percent increase in total use of modern contraception methods in that country.⁹ Countries where women have access to a diverse mix of contraceptive options see higher levels of overall contraceptive use.¹⁰ Indeed, current contraceptive use in sub-Saharan Africa is distributed across multiple methods including sterilization, pills, injectables, implants, and IUDs, and the balance of the mix varies significantly between countries (Figure 2).¹¹

This experience, combined with continuing high rates of HIV infection among women, suggests that making new and multiple HIV prevention options available to women will spur increased use of HIV prevention overall. Indeed, this pattern is already evident. A study among female sex workers in Thailand showed that rates of STI transmission declined by one-third when female condoms were made available in addition to male condoms. Similarly, a study in the United States found that women who were provided female condoms had fewer acts of unprotected intercourse.¹²

FIGURE 2. CONTRACEPTIVE PREVALENCE BY METHOD AMONG WOMEN AGE 15–49, SELECT COUNTRIES, 2015



Source: United Nations Department of Economic and Social Affairs, *Trends in Contraceptive Use Worldwide*, 2015.

9 Ross, J., & Stover, J. "Use of modern contraception increases when more methods become available: analysis of evidence from 1982-2009," *Global Health, Science and Practice*, 2013.

10 Delany-Moretwe, S., Mullick, S., Eakle, R., & Rees, H. "Planning for HIV preexposure prophylaxis introduction: Lessons learned from contraception," *Current Opinion in HIV and AIDS*, 2016.

11 United Nations Department of Economic and Social Affairs, *Trends in Contraceptive Use Worldwide*, 2015.

12 Gollub, E., & Warren, M. (n.d.). *The Female Condom: A guide for planning and programming*, UNAIDS, 2000.

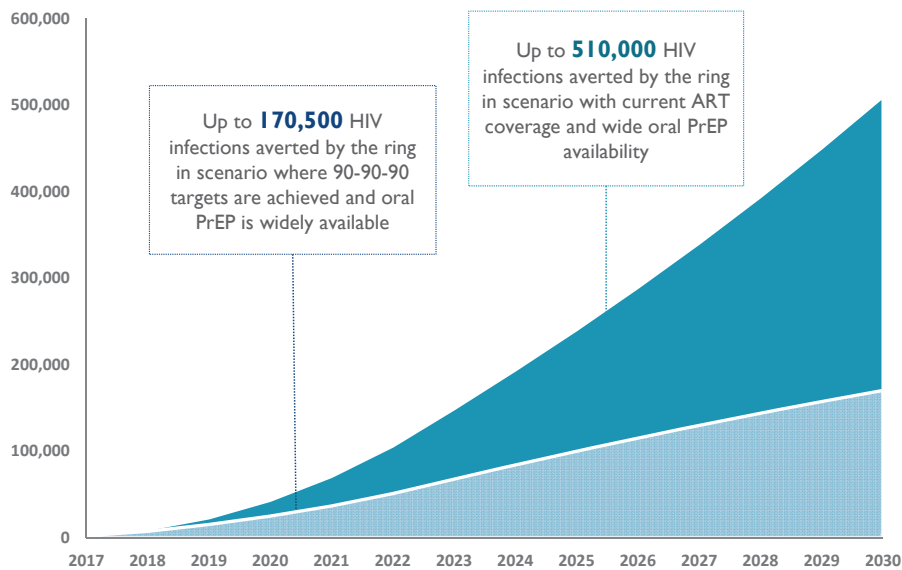
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THE DAPIVIRINE RING HAS SIGNIFICANT POTENTIAL TO COMBAT HIV TRANSMISSION

UNAIDS goals include a 90-percent reduction in new adult infections and a steep reduction in new infections among adolescent girls and young women by 2030. But no one product or strategy can meet that goal alone. Instead, a diverse range of options is needed to achieve HIV elimination goals, especially for women.

The potential impact of the ring can be illustrated by projections from a modeling analysis of 13 African countries¹³ with high HIV incidence. The projections show that even in a future where those 13 countries have achieved the 90-90-90 targets (e.g., 90 percent of people are tested for HIV, 90 percent of those who are HIV-positive are on treatment, and 90 percent of those on treatment are virally suppressed) and there is relatively strong uptake of daily oral PrEP among women at high-risk of HIV infection, the addition of the ring to the combination prevention package could prevent additional new infections. Projections demonstrate an additional 170,500 HIV infections averted in these 13 countries by 2030.

FIGURE 3. HIV INFECTIONS AVERTED BY RING IN DIFFERENT SCENARIOS, 2017-2030



Source: Avenir Health modeling analysis, 2017.

13 Countries included in analysis: Botswana, Kenya, Lesotho, Malawi, Mozambique, Namibia, Rwanda, South Africa, Swaziland, Tanzania, Uganda, Zambia, and Zimbabwe. Other assumptions: PrEP and ring accessed by women aged 15–49; adherence rates 69 percent for all products and all ages; oral PrEP uptake is 25 percent of modern contraception for high- and medium-risk women; ring uptake is 50 percent of modern contraception for high- and medium-risk women and 25 percent of modern contraception for low-risk women; and product efficacy with perfect adherence assumed to be 90 percent for oral PrEP and 75 percent for the ring.

If 90-90-90 targets are not met and antiretroviral therapy (ART) coverage rates remain at current levels, the ring could have an even bigger impact, preventing up to 510,000 new HIV infections, including nearly 200,000 in South Africa alone, by 2030 (Figure 3).¹⁴

3

RING PRODUCTS OFFER TREMENDOUS OPPORTUNITY AND THE DAPIVIRINE RING IS A SOLID START

In addition to reducing HIV incidence among women directly, the monthly dapivirine ring can accelerate introduction of other new HIV prevention products—in particular, the promising line of vaginal rings in the pipeline today. These products include the three-month dapivirine ring and multi-purpose rings that combine HIV prevention, STI prevention, and contraception. Rings offer a unique option as they are easy to access, easy to use, long-acting, and discrete. The accessibility rings offer may enable greater and more consistent use as well as reduced cost and health system burden—factors for continued study in the ongoing open-label studies for the dapivirine ring.

As with any new HIV prevention product, however, there are also difficult questions to answer. For example, rings will require significant support for end-user uptake and adherence, particularly in the initial phases of rollout. Building awareness and understanding of a new product option will take time and a detailed understanding of end user preferences. And there is a need to understand how these new products will be delivered through the health system and what investments will be needed to do so. Taking time now to explore how to provide effective support for the monthly dapivirine ring will accelerate and streamline introduction efforts for future prevention products.

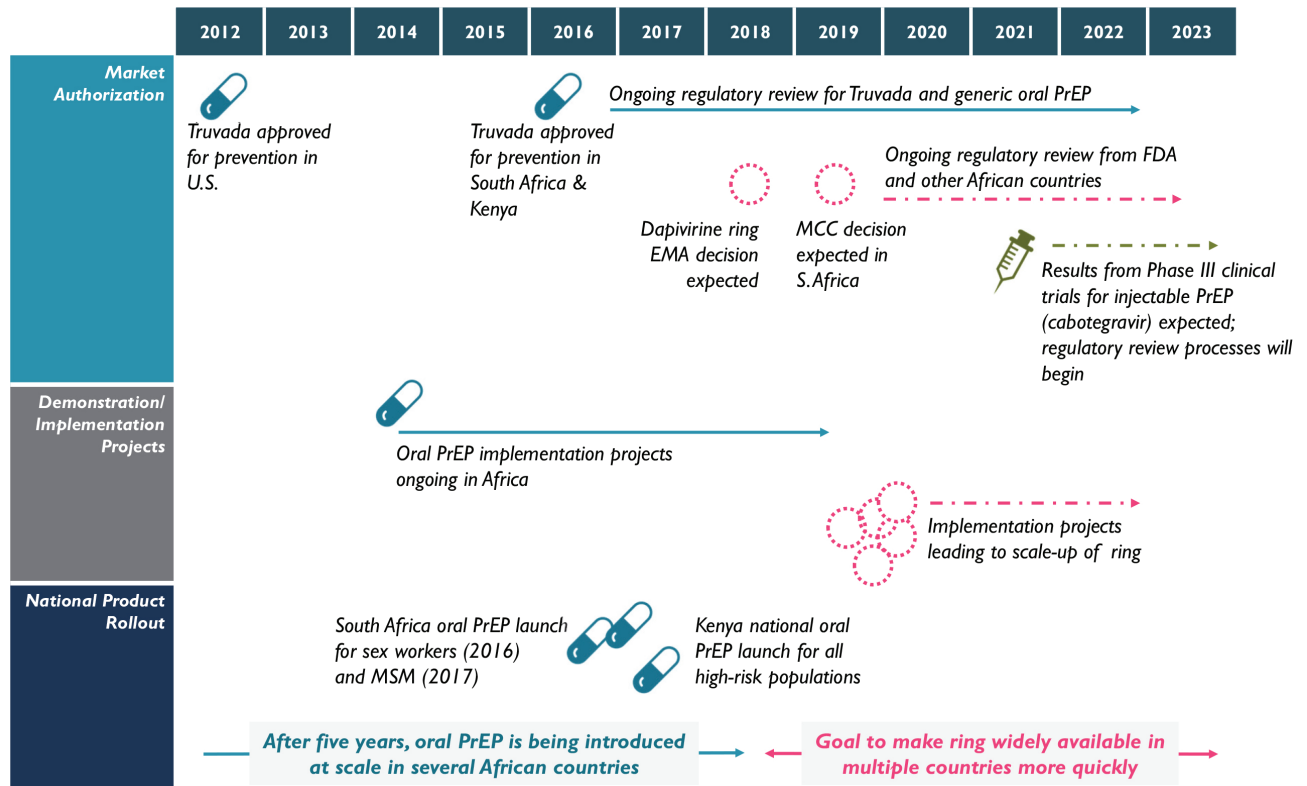
The monthly dapivirine ring is the next step in the movement to eradicate HIV, but the next round of strategic investments is critical. What is needed now is coordinated planning and investment in strategic implementation projects that will demonstrate the potential opportunities and challenges to deliver the ring at scale.

“The ring offers a distinct advantage—it is women positive. A woman’s relationship with the ring is personal. It is something intimately owned by a woman. There is a deeper sense of empowerment with this product and women are more connected to this ring than anything I’ve seen in another study.”

— Dr. Sharon Hillier, Principal Investigator, Microbicide Trials Network

¹⁴ Avenir Health modeling analysis (unpublished), June 2017.

FIGURE 4. BIOMEDICAL HIV PREVENTION TIMELINE



Lessons can be taken from the implementation of oral PrEP (Figure 4), which was introduced through a series of unrelated, sub-scale projects. Progress for the ring must be faster and more efficient. Accelerating the introduction process for the ring will ensure that more women can access and use the product as quickly as possible.

What We Know: The Ring Will Strengthen the HIV Prevention Toolkit

If granted approval, the dapivirine ring would be added to the current HIV prevention toolkit, which includes male and female condoms, male circumcision, and, most recently, daily oral PrEP.

Access to oral PrEP is growing in sub-Saharan Africa. The issuance of WHO guidance recommending oral PrEP for people at “substantial risk”¹⁵ of HIV infection in September 2015 has catalyzed efforts to make oral PrEP accessible at scale. For example, South Africa has introduced oral PrEP for female sex workers and men who have sex with men, and Kenya has established targets to reach over 100,000 oral PrEP users in 2018 and 300,000 users by 2020, including women and girls.

While oral PrEP is an important step in the right direction for women, it will not be the right HIV prevention option for all women. Early implementation experiences suggest that women have concerns, including side effects, ongoing testing requirements, the inconvenience of taking a daily pill, and the stigma associated with taking pills that are also used for treatment.¹⁶

“Sometimes we forget how urgent this situation is. There are all sorts of programs supporting young girls and women, but ultimately we need more HIV prevention tools and more choice. It’s just like with contraception: the more the better. Simple.”

— Georgina Caswell, Program Lead, International HIV/AIDS Alliance

¹⁵ WHO defines “substantial risk” as HIV incidence >3 per 100 person-years in the absence of daily oral PrEP.

¹⁶ Bhavaraju, N., & Uribe, D. *Early Lessons from South Africa’s Rollout of Oral PrEP to Sex Workers*, PrEPWatch, 2017.

“When I started using the ring, it was inserted at the clinic. The day I went home, I thought my marriage would be doomed. I was surprised that we had sex and nothing happened. It did not feel any different.”

“I would be more comfortable with the ring because you don’t have to stress about having to swallow that [pill]—I mean even the size of PrEP for me, it’s not so cool. And sometimes you go to your boyfriend’s place without planning it. Now I won’t have to stress to always have pills in my bag.”

“I like it because nothing changes regarding how we live as women.”

“I told him to take the ring as the condom. I said: ‘Because you do not want the condom, this is now our condom, just ignore it, it’s inside my body and it’s mine.’ We never had problems about it and we never spoke about it again.”

— Participants in REACH stakeholder consultations and ASPIRE trial

As an additional HIV prevention option, the ring offers four major benefits:

Acceptability: The ring meets the needs and preferences of many users.

Effectiveness: The ring reduces HIV risk when used consistently.

Safety: The ring is safe with no serious side effects found in clinical trials to-date.

Ease: The ring is relatively easy to use, transport, and store.

Acceptability: The ring meets the needs and preferences of many users

Evidence from clinical trials suggests that the ring meets the needs and preferences of many women seeking a new method of HIV prevention. At the end of the clinical trials, 96 percent of participants across four different countries reported that the ring was comfortable to wear, and 97 percent reported that they would be willing to use the ring if it was proven to be effective.¹⁷ Participants cited several benefits of the ring:

- **Comfort and discretion.** Most women in the clinical trials reported that they were never aware of the ring during their daily activities, and nearly all participants in one sub-study (264 out of 267 participants) reported that male partners could not feel the ring, that it did not interfere with sexual activity, and that this was not a barrier to continued use.¹⁸

17 Nel, A., et al. “Safety, acceptability and adherence of dapivirine vaginal ring in a microbicide clinical trial conducted in multiple countries in Sub-Saharan Africa,” *PLOS ONE*, 2016.

18 Ibid.

- **Convenience.** Because the ring is long-acting and stays in place, it does not require daily action. This convenience could result in higher levels of consistent use.
- **Agency.** Women saw the ring was “their” product and noted that the ring gave them greater control and ability to protect themselves from HIV transmission.¹⁹
- **Overcoming stigma.** The ring may alleviate a concern some women have about oral PrEP: stigma. Oral PrEP pills are indistinguishable from those used in treatment, making it less attractive for some users and creating the potential for misunderstanding among partners.

96% of study participants reported the ring was comfortable to wear.

97% of study participants reported they would use the ring when proven effective.

Effectiveness: The ring reduces HIV risk when used consistently

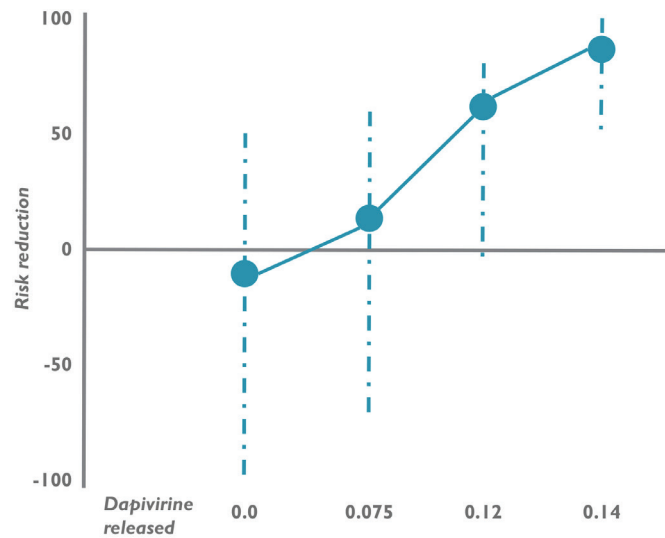
The ring reduced risk of HIV infection by approximately 30 percent across the two clinical trials. Among women who used the ring at least some of the time, HIV infection risk was cut by 45 percent.²⁰ Post-hoc exploratory analyses of data from the ASPIRE trial suggest that the ring may be even more effective when used consistently—up to 75 percent reduction in the risk of HIV infection at the highest levels of adherence (Figure 5).²¹ In all of these instances, greater HIV risk reduction was associated with more consistent ring use.

19 Microbicides Trial Network (MTN), *Meeting the HIV Prevention Needs of Adolescent Girls and Young Women: Stakeholders consultation on the MTN-034/IPM 045 (REACH) open-label safety and adherence study of the dapivirine vaginal ring and oral PrEP*, 2016.

20 Rosenberg Z, Nel A, van Niekerk N, Van Baelen B, Van Roey J, Palanee-Phillips T, Brown E, Soto-Torres L, Hillier S, Baeten J, IPM 027/The Ring Study and MTN-020/ASPIRE Study Teams. *Pooled efficacy analysis of two Phase III Trials of dapivirine vaginal ring for the reduction of HIV-1 infection risk in HIV-uninfected women in sub-Saharan Africa*. Poster presented at the 9th IAS Conference on HIV Science (IAS 2017); Paris, France: 23-26 July 2017.

21 Brown, E., et al. *Residual dapivirine ring levels indicate higher adherence to vaginal ring is associated with HIV-1 protection*, 21st International AIDS Conference, July 2016.

FIGURE 5. EXPLORATORY ANALYSIS OF RELATIONSHIP BETWEEN ADHERENCE AND RISK REDUCTION FOR DAPIVIRINE RING USERS



Source: Elizabeth Brown, *Residual dapivirine ring levels indicate higher adherence to vaginal ring is associated with HIV-1 protection*, Presentation for AIDS 2016.

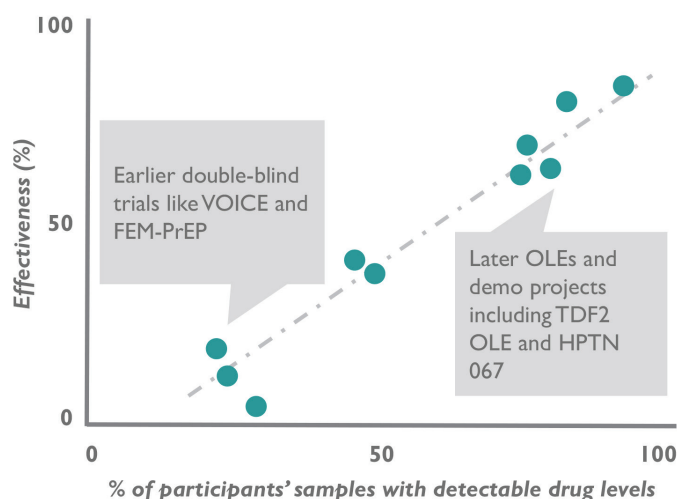
Experience with other biomedical HIV prevention products suggests that adherence is often at its lowest in blinded clinical trials, when participants do not yet know whether products are safe or effective and when some participants receive a placebo. Clinical trials for oral PrEP (Figure 6) provide a good example of this phenomenon. In double-blind efficacy trials like VOICE and Fem PrEP, adherence was estimated at 28 percent and 37 percent with no significant reduction in HIV incidence.²² In later open label studies and demonstration projects (e.g., TDF2 OLE and HPTN 067), when women knew they were using an effective product, adherence levels rose dramatically to 80–90 percent.²³ A similar adherence pattern may emerge for ongoing OLEs for the dapivirine ring. As one participant in the ASPIRE trial noted, “Now that I know the ring works, of course I want to use it so I can be protected.”

Exploratory analyses suggest the ring may reduce HIV risk by up to **75%** at the highest levels of adherence.

22 Amico, K., & Stirratt, M. “Adherence to preexposure prophylaxis: current, emerging, and anticipated bases of evidence,” *Clinical Infectious Diseases*, 2014.

23 AVAC, *Effectiveness and Adherence in Trials of Oral and Topical Tenofovir-Based Prevention*, 2016.

FIGURE 6. RELATIONSHIP BETWEEN ADHERENCE AND EFFECTIVENESS ACROSS ORAL AND TOPICAL PREP TRIALS



Source: AVAC.

Safety: The ring is safe with no serious side effects found in clinical trials to date

The dapivirine ring minimizes systemic drug absorption by delivering the drug directly to the site of potential vaginal infection. As a result, ring users in trials to date experienced few side effects and no serious side effects related to product use.²⁴ In addition, preliminary evidence from the ring trials demonstrates no increased risk of resistance to HIV treatment among ring users who are infected with HIV while using the ring.

Given this safety profile, ring users will likely require far fewer follow-up laboratory tests than people using oral PrEP or future injectable products. Use of oral PrEP will require initial hepatitis B and creatinine tests followed by quarterly creatinine level tests (and hepatitis B monitoring if positive). Ring use will likely only require a quarterly HIV test to confirm negative status, as required for all biomedical HIV prevention products (Figure 7).

Ease: The ring is relatively easy to use, transport, and store




In addition to being safe, the ring is relatively easy to self-administer. Women in the clinical trials have had few problems with use.²⁵ Further, the ring does not require cold chain for delivery or storage and can be safely stored for 48 months at regular temperatures.²⁶

24 Nel, A., et al. "Safety, acceptability and adherence of dapivirine vaginal ring in a microbicide clinical trial conducted in multiple countries in Sub-Saharan Africa," *PLOS ONE*, 2016.

25 Ibid.

26 International Partnership for Microbicides.

FIGURE 7. PATIENT PATHWAY COMPARISON—ORAL PREP AND DAPIVIRINE RING

| | Month 1 | Month 2 | Month 3 | Month 4 | Month 5 | Month 6 | Month 7 | Month 8 | Month 9 | Month 10 | Month 11 | Month 12 |
|---|---|---------|---------|---------|---------|---------|---------|---------|---------|----------|----------|----------|
| Oral PrEP  | HIV test | | | | | | | | | | | |
| | ✓ | | | ✓ | | | ✓ | | | ✓ | | |
| | ✓ | | | ✓ | | | ✓ | | | ✓ | | |
| Dapivirine Ring  | HIV test | | | | | | | | | | | |
| | ✓ | | | ✓ | | | ✓ | | | ✓ | | |
| | Hepatitis B test | | | | | | | | | | | |
| |  ✓ If HepB +, liver function monitoring required as indicated by physician | | | | | | | | | | | |

These factors could enable delivery of the ring through a broad range of channels. The ring could also result in a lower burden on health systems and a lower cost of delivery than other product forms like daily oral PrEP or injections. While the product cost is similar (the dapivirine ring will be available for \$6–\$8 per ring or \$72–\$96 per year),²⁷ savings would result primarily from reduced requirements for ongoing testing, which in turn reduce the need for high-cost laboratory services. Some estimates put the costs for quarterly creatinine testing at ~\$35–\$50 per person per year, which will be avoided with ring products.^{28,29} Costs would be further reduced with the three-month dapivirine ring, when available. Other savings could result from requirements for healthcare worker time, but how this expense would balance with other costs (e.g., demand generation) needs to be explored in implementation.

The ring could result in a lower burden on health systems and a lower cost of delivery than other product forms.

27 Ibid.

28 Bill & Melinda Gates Foundation, *PrEP Program Cost Model in RSA*, 2011.

29 CHAI, *PrEP Costing in Zimbabwe*, 2017.

What We Don't Yet Know: How the Ring Will Work in Real-World Settings

Despite the ring's benefits, there are several questions that can only be answered through implementation.

While national ministries of health, in consultation with user groups, advocates, program implementers, and others, should define areas for further exploration, several questions should be reflected in future implementation pilots to guide introduction and scale-up of the ring. Many of these questions are also highly relevant for other biomedical HIV prevention products, including oral PrEP.

Uptake: How will acceptability of the ring in clinical trials translate to uptake in real-world settings? Who will use the ring? What investments will be needed to support uptake?

Adherence: What adherence support interventions will be most effective, particularly among young women? What are the associated costs of these efforts?

Delivery Models: What channels can efficiently and safely make the ring accessible to users? To what extent can the ring be effectively delivered through nonclinical channels? What implications will different delivery models have on cost and cost-effectiveness?

Uptake: How will acceptability of the ring in clinical trials translate to uptake in real-world settings? Who will use the ring? What investments will be needed to support uptake?

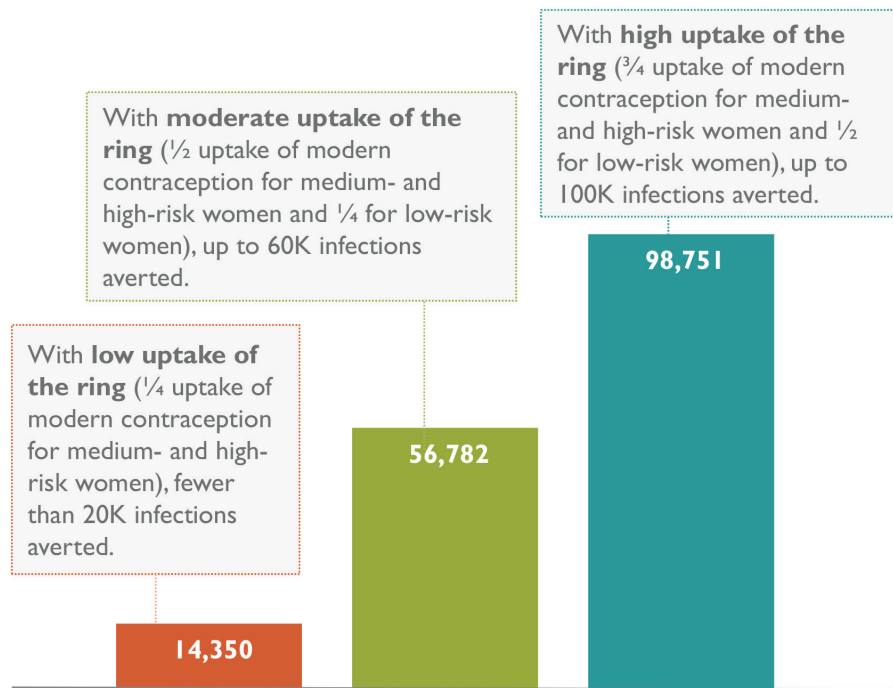
Vaginal rings are a new product form for many women in sub-Saharan Africa. While acceptability studies and trials in sub-Saharan Africa suggest that a vaginal ring is a highly acceptable form of delivery among women, there is limited real-world experience with rings in African countries.^{30,31}

30 Lemal, E., et al. "Contraceptive vaginal ring experiences among women and men in Kisumu, Kenya: a qualitative study," *Frontiers in Women's Health*, 2017.

31 Merkatz, R., et al. "Acceptability of the Nestorone/ethinyl estradiol contraceptive vaginal ring: Development of a model; implications for introduction," *Contraception*, 2014.

Experience with earlier products suggests that most products are attractive to some subset of end users and that establishing a steady user base for new products takes time. The female condom, for example, faced initial skepticism around likely user uptake, but the market for female condoms has grown over time. There have been well-recognized success stories in Zimbabwe and Malawi where investments in demand-generation have resulted in women signing petitions to ensure availability of female condoms.³² The tampon took several decades to be accepted by healthcare practitioners, including in high-income markets, but is now widely and regularly used.³³ For the ring, modeling analysis suggests that even if uptake remains relatively low, the ring could still avert 20,000 HIV infections over the next decade in South Africa alone. With effective investments to generate demand uptake, and use, the ring could result in up to 100,000 HIV infections averted in South Africa (Figure 8).³⁴

FIGURE 8. RELATIONSHIP BETWEEN UPTAKE AND IMPACT



Source: Avenir Health modeling analysis, 2017.

Notes: Baseline scenario includes 90-90-90 targets met, moderate oral PrEP uptake for high- and medium-risk women, adherence to oral PrEP and the ring at 69%, product efficacy of 75% for the ring and 90% for oral PrEP.

32 Ro, C., "The Enduring Unpopularity of the Female Condom," *The Atlantic*, June 6, 2016.

33 Fetters, A., "The Tampon: A History," *The Atlantic*, June 1, 2015.

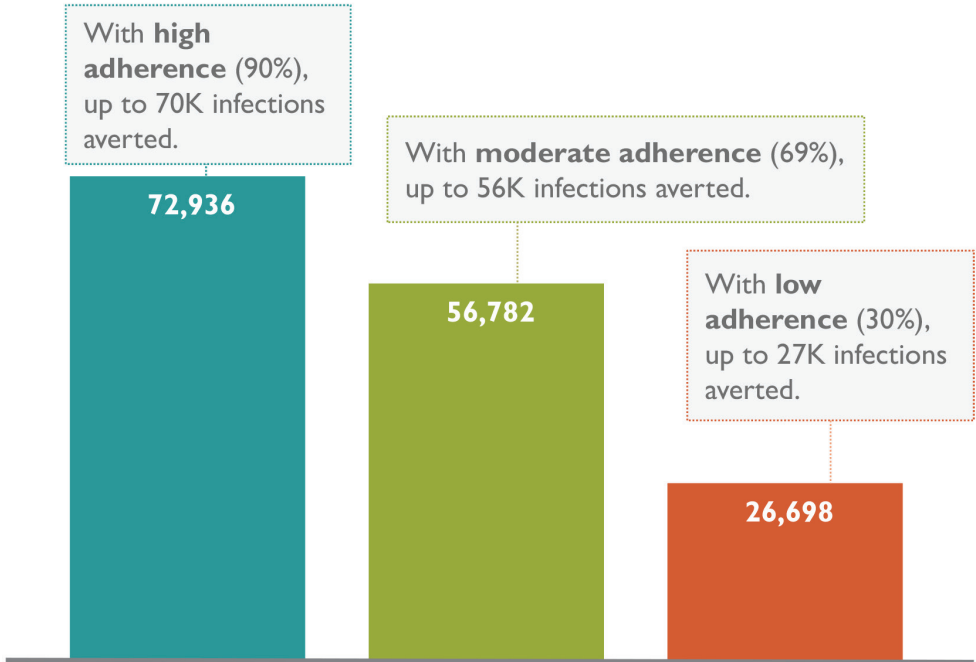
34 Avenir Health modeling analysis (unpublished), June 2017.

We do not yet know how many and which women will want to use the ring, nor how support for uptake can be accomplished at scale. The REACH study, to begin in late 2017, will assess the acceptability of the ring and oral PrEP among adolescent girls and young women ages 16–21 in four African countries. REACH will provide initial insights, but larger-scale demonstration projects will be needed to inform demand forecasts and refine demand-generation strategies.

Adherence: What adherence support interventions will be most effective, particularly among young women? What are the associated costs of these efforts?

Adherence is absolutely critical to achieving public health impact from the ring. Modeling analyses show that increasing adherence from 30 percent to 90 percent would result in an additional 50,000 HIV infections averted in South Africa alone from 2017 to 2030 (Figure 9).³⁵

FIGURE 9. RELATIONSHIP BETWEEN ADHERENCE AND IMPACT



Source: Avenir Health modeling analysis, 2017.

Notes: Baseline scenario includes 90-90-90 targets met, moderate oral PrEP uptake for high- and medium-risk women, low ring uptake for low-risk women and moderate ring uptake for medium- and high-risk women, adherence to oral PrEP at 69%, product efficacy of 70% for the ring and 90% for oral PrEP.

35 Ibid.

Effective adherence support models for women and girls are needed across prevention products, including the ring. Adherence support interventions for oral PrEP have yielded moderate results. In CAPRISA, mean adherence rose from 54 percent to 66 percent following the study's adherence interventions.³⁶ In the Partners PrEP study, mean adherence was 76 percent before and 84 percent after adherence interventions were implemented.³⁷ Given lower levels of dapivirine ring adherence among young women in The Ring Study and ASPIRE, it will be critical to test appropriate interventions for that age group in implementation projects across all prevention products. These projects should also capture cost data to assess the feasibility and scalability of effective adherence support interventions in real-world settings.

Delivery Models: What channels can efficiently and safely make the ring accessible to users? To what extent can the ring be effectively delivered through nonclinical channels? What implications will different delivery models have on cost and cost-effectiveness?

The safety and relative ease-of-use of the ring may create a number of benefits for delivery. One, the ring likely can be distributed more widely than other prevention forms (e.g., pills, injections) because it does not require specialized laboratory testing. For example, Kenya has nearly 6,000 HIV testing centers throughout the country but only 500 facilities that can conduct creatinine tests. This difference could enable greater uptake and make it easier for women to use the ring.^{38,39} In the long term, rings have the potential to be delivered outside of clinical settings (e.g., through pharmacies). If nonclinical delivery were feasible, it would reduce the burden on health clinics and end users, potentially resulting in higher levels of use.

These dynamics need to be further explored in large-scale demonstration projects. Actual implementation will shed light on whether the ring can indeed be effectively delivered in a wider range of channels, such as family planning and mobile clinics, youth centers, and other less medicalized settings. These efforts could also explore the implications of offering the ring in rural settings and remote communities that may have difficulty accessing oral PrEP and maintaining the required testing schedule. Finally, implementation will deepen our understanding of what it costs to deliver the ring and how that cost compares to other forms of HIV prevention.

Each of these dimensions has significant implications for the public health impact and cost-effectiveness we can expect from the ring. But these questions cannot be understood fully through further research studies or clinical trials; they require implementation.

36 Mansoor, L. "Adherence in the CAPRISA 004 Tenforvir Gen Microbicide Trial," *AIDS and Behavior*, May 2014.

37 Psaros, C., et al. "An intervention to support HIV pre-exposure prophylaxis (PrEP) adherence in HIV serodiscordant couples in Uganda," *Journal of Acquired Immune Deficiency*, August 2014.

38 Kenya National AIDS & STI Control Programme, *Kenya HIV Prevention Revolution Roadmap: Countdown to 2030*, June 2014.

39 Health facility data, PSI/Zimbabwe (unpublished).

A Call to Action

After significant investment and decades spent on product development for the ring and other HIV prevention technologies, an effective, female-initiated, long-acting HIV prevention method could finally be available for women and girls in sub-Saharan Africa and the rest of the world. This product can have significant impact, including contributions toward the elimination of HIV; improved access to contraception; and empowerment, health, and education for women and adolescent girls (Figure 10).

“The imperative now is to accelerate product development and delivery to have real impact on the epidemic. Translating the efficacy trial results of the dapivirine ring into public health impact will not be easy, but it is essential. With more than 17,000 women newly infected with HIV each week, we must go even faster, be more strategic, and more creative than ever before.” — Mitchell Warren, Executive Director, AVAC

FIGURE 10. WHY INVEST IN THE RING?

| | |
|--|---|
| To achieve the SDG aim of ending AIDS by 2030 | The addition of a new prevention option to the existing portfolio will strengthen efforts to reduce HIV transmission, especially for women and girls who have few other options. In addition, investments in the dapivirine ring will continue to build the market for biomedical HIV prevention and accelerate introduction of future HIV prevention and multi-purpose technologies. |
| To expand access to reproductive health products | The introduction of a vaginal ring product into sub-Saharan African markets will improve countries' abilities to deliver similar contraceptive and multi-purpose technologies by familiarizing users and healthcare workers with a new modality and by establishing a supply chain for ring products. |
| To empower and improve outcomes for women, young women, and adolescent girls | Improvements in the ability of women, young women, and adolescent girls to protect themselves against HIV transmission with the ring will have ripple effects beyond health, including impact on empowerment, educational attainment, and economic security. ⁴⁰ |

40 UNAIDS, *Empower young women and adolescent girls: fast-tracking the end of the AIDS epidemic in Africa*, 2015.

To ensure the ring is made available to women at high risk as soon as possible, investment and planning is needed now in strategic early implementation projects. Without robust evidence on how to effectively and cost-efficiently deliver this new HIV prevention option, national governments, donors, and implementers will be constrained in their ability to provide women and girls with effective solutions for HIV prevention for the next five years and likely beyond.

For example, in 2017—five years after Truvada was first approved for prevention in the United States and two years after it was approved by the Medicines Control Council (MCC) in South Africa—it remains inaccessible to most women and girls outside of specific projects like PEPFAR’s DREAMS initiative. Kenya is the only African country to date that has committed to making oral PrEP available for women and girls beyond sex workers. In the five years since Truvada was first approved for prevention in the U.S. in 2012, an estimated 5 million women and girls worldwide have contracted HIV worldwide—all while there was a known and highly effective prevention option.⁴¹

One of the biggest challenges with oral PrEP was lack of coordination. While significant funding of over \$50 million was committed for demonstration projects, that investment was scattered across a number of efforts. Across 32 countries, 58 projects are either complete, ongoing, or planned for oral PrEP, some with as few as 48 participants. For those projects that are completed or underway, the average participant size was only 1,330—far below what could serve as a meaningful implementation pilot for a national government making decisions about national scale-up. These projects also differed widely by cost, ranging from an incredibly costly \$11,000 per participant in smaller studies to a much more manageable \$600 per participant in larger studies.⁴² This discrepancy suggests that larger implementation pilots can both deliver better insights to guide implementation at scale and be more cost efficient.

Globally, nearly 5 million women and girls age 15+ have contracted HIV since Truvada was first approved for prevention in the U.S. in 2012.

41 UNAIDS, *Prevention Gap Report*, January 2016.

42 AVAC and FSG data analysis, 2017.

What Can Be Done Today?



With the ring, we can and must do better to ensure that women and girls will have access to the product in more countries more quickly. Reaching this goal will require four key actions in the next year as the ring is clearing initial regulatory approvals:

- 1 DEVELOPMENT OF A COMMON AGENDA**
for implementation projects that is directly linked to national government policy decisions on introduction and scale-up of the dapivirine ring.
- 2 LEADERSHIP FROM THREE TO FIVE COUNTRIES**
seeking to invest in HIV prevention for women and girls by including the ring as a component of combination HIV prevention.
- 3 COORDINATED INVESTMENT FROM GLOBAL DONORS**
for large-scale, strategic implementation pilots that are aligned with the common agenda and needs of country decision-makers in countries that are likely to be early adopters of the ring.
- 4 CONTINUED ADVOCACY**
from civil society, women, community leaders, researchers, and medical associations to build momentum for the ring and ensure the needs of women are central to implementation efforts.

Action across these areas from all the stakeholders in the system, from local activists to global donors, from national ministries to product developers, will be essential to realizing the promise of the ring for women and girls. And this is the time for action. We must learn from experiences with contraception and oral PrEP to do better, move faster, and reach more women at risk.



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Our teams work across all sectors by partnering with leading foundations, businesses, non-profits, and governments in every region of the globe. We seek to reimagine social change by identifying ways to maximize the impact of existing resources, amplifying the work of others to help advance knowledge and practice, and inspiring change agents around the world to achieve greater impact.

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