



OPTIONS

*Dapivirine Ring
Early Introduction Considerations
Seven Country Analysis*

August 2018



SUMMARY FINDINGS

DETAILED COUNTRY FINDINGS



Executive summary

THE OPPORTUNITY FOR THE RING

- Across countries, there was significant enthusiasm for the ring as a female-controlled technology that could be appropriate for adolescent girls and young women as part of a combination HIV prevention approach.
- The ring also raised questions from country stakeholders including questions on how to improve adherence among 16-24 year olds and how policies should be crafted to build the ring into a comprehensive prevention package.
- Importantly, policymakers and USAID/PEPFAR missions in most countries advised that a demonstration in each country addressing local conditions and concerns is the best way to expedite inclusion of the ring in national policies and plans. However all stakeholders emphasized the importance of linking demonstration projects to implementation – standalone demonstration projects were discouraged. This guidance is based on the experience with the introduction of oral PrEP in many countries.
- While all of the countries included in this analysis were interested in the ring, some are better positioned to be “early adopters.”
- At present, Zimbabwe and Uganda show immediate promise for a demonstration project with the ring due to national stakeholder interest and the anticipated pace of the process. South Africa and Kenya are also promising locations, though in Kenya there are still questions about how to move forward given the constraints of US funding and in South Africa stakeholders are cautious about adding new products and note that demonstrations before regulatory approval would require greater scrutiny.
- To expedite access to the ring, two steps should be pursued simultaneously over the coming year:
 1. A coordinated global effort to prepare demonstration projects in several “early adopter” countries, in close collaboration with key stakeholders and policymakers at the country level
 2. A consistent effort to communicate about the ring at the country level, especially as additional evidence is generated and the regulatory process advances

OVERVIEW OF PROCESS

- The OPTIONS (Optimizing Prevention Technology Introduction on Schedule) Consortium is a five-year, USAID funded effort to expedite and sustain access to new ARV-based HIV prevention products in sub-Saharan Africa with a focus on women and girls.
- In May 2018, seven countries (Rwanda, Uganda, Kenya, Zimbabwe, Malawi, Tanzania, and South Africa) were prioritized for analysis due to the state of the HIV epidemic in each country and experience with ring trials.
- OPTIONS conducted secondary research and interviews with key stakeholders in these countries to understand questions about the ring that could inform demonstration and processes for introducing new biomedical HIV prevention products.
- Interviews comprised a mix of policymakers, civil society representatives, donors, implementing partners, and trial contributors.



Key findings from country consultations

1

Most country stakeholders are intrigued by the ring

Country stakeholders cited female control and limited risk of creating resistance as valuable attributes of the ring. Stakeholders in Zimbabwe expressed a readiness to start a demonstration project on the ring as soon as possible. Stakeholders also had many questions about the ring (*noted on next slide*).

2

Interest in a demonstration to inform implementation

Most country stakeholders indicated a need for a local demonstration on the ring to inform policy-making and implementation planning, noting that evidence generated elsewhere would not provide the contextual detail required. Standalone projects not linked to implementation were strongly discouraged.

3

Need to leverage learnings from oral PrEP and potential to integrate the ring into roll-out in several countries

The recent experience with oral PrEP provides lessons on messaging, processes, and stakeholder engagement for the ring. Existing structures for PrEP, such as Technical Working Groups (TWGs), can also be used for the ring. The ring needs to be assessed as part of a combination prevention approach.

4

Criticality of AGYW populations across countries, and need to better understand adherence

Country stakeholders saw potential for the ring with AGYW populations that have been difficult to serve with other options, though they also requested additional evidence on how to support adherence amongst this population.

5

Thoughtful, sustained engagement process needed to introduce the ring

In many countries there is limited existing knowledge of the ring that will need to be overcome to start planning. The approval process for some countries is straightforward but each product introduction process has idiosyncrasies that need to be managed. Regular stakeholder engagement will be necessary to maintain progress.



Questions raised by policymakers

Across the seven countries, several key questions were regularly raised policymakers

ASKED BY NEARLY ALL POLICYMAKERS

Key policymakers from five out of six countries analyzed asked the following questions:

- What would be the **impact** of the ring? How many infections would be averted?
- How does the ring **fit into a comprehensive package** of prevention?***
- What is the **effectiveness of the ring in the real-world?**
- What will be the **cost of investing** in the ring?
- What are **adherence to and uptake of** the ring in the real-world?
- Which **populations** are recommended for the ring?
- What are the implications for the **health system and healthcare workers?** What additional demands will the ring place on the health system?

ASKED BY HALF OF POLICYMAKERS

Key policymakers from three out of six countries analyzed asked the following questions:

- Will the ring be **affordable** for end users?
- Has the ring been proved to be **safe?***
- To what extent does the **effectiveness of the ring differ** among various populations? Is the ring **effective among AGYW?****
- What does behavioral data demonstrate about the impact of the ring on **condom use and other reproductive health practices?**

* Questions that have been adequately demonstrated through past clinical trials







** Questions that are partially studied in the upcoming REACH study

Note: Policymakers in Kenya were not surveyed due to US government restrictions



Country readiness assessment framework

A preliminary assessment for each country is included based on six dimensions. More dimensions may be added (e.g., availability of implementing partners) as discussions progress

High-level assessment for the ring	
 HIV epidemic characteristics	<ul style="list-style-type: none">Assesses the level of need in the country based on HIV prevalence and incidenceSpecifically notes the HIV burden faced by women and girls
 HIV prevention program	<ul style="list-style-type: none">Assesses the national HIV prevention program for comprehensiveness, inclusion of biomedical prevention, and dedicated prevention funds
 Oral PrEP experience	<ul style="list-style-type: none">Assesses speed and ease of previous oral PrEP research, demonstration, and implementation, including inclusion in national guidelines and strategic plans
 Ring trial experience to-date	<ul style="list-style-type: none">Highlights in-country dapivirine ring trials that could be leveraged for awareness-building and ring introduction
 Stakeholder reactions to the ring	<ul style="list-style-type: none">Assesses knowledge, interest, and enthusiasm about the ring from a range of stakeholders including government, civil society, and academia
 Product introduction process	<ul style="list-style-type: none">Assesses clarity and speed of typical product introduction process



Cross-country assessment for ring potential

	ZIMBABWE	UGANDA	SOUTH AFRICA	KENYA	MALAWI	TANZANIA	RWANDA
HIV epidemic characteristics	SIGNIFICANT NEED	SIGNIFICANT NEED	SIGNIFICANT NEED	SIGNIFICANT NEED	SIGNIFICANT NEED	SIGNIFICANT NEED	MODERATE NEED
<i>Prevalence rate</i>	13.5%	6.5%	18.8%	4.8%	9.2%	4.7%	3.1%
<i>New infections annually</i>	40,000	52,000	270,000	53,000	36,000	55,000	7,500
<i>Incidence rate</i>	3.03	1.50	5.46	1.21	2.29	1.19	0.70
HIV prevention program	STRONG OPPORTUNITY	STRONG OPPORTUNITY	STRONG OPPORTUNITY	STRONG OPPORTUNITY	MODERATE OPPORTUNITY	MODERATE OPPORTUNITY	MODERATE OPPORTUNITY
Oral PrEP experience	STRONG OPPORTUNITY	MODERATE OPPORTUNITY	STRONG OPPORTUNITY	STRONG OPPORTUNITY	POTENTIAL LIMITATION	MODERATE OPPORTUNITY	MODERATE OPPORTUNITY
Ring trial experience to-date	STRONG OPPORTUNITY	STRONG OPPORTUNITY	STRONG OPPORTUNITY	MODERATE OPPORTUNITY	MODERATE OPPORTUNITY	POTENTIAL LIMITATION	POTENTIAL LIMITATION
Stakeholder reactions to the ring	STRONG OPPORTUNITY	STRONG OPPORTUNITY	MODERATE OPPORTUNITY	STRONG OPPORTUNITY	MODERATE OPPORTUNITY	MODERATE OPPORTUNITY	MODERATE OPPORTUNITY
Product introduction process	STRONG OPPORTUNITY	STRONG OPPORTUNITY	MODERATE OPPORTUNITY	MODERATE OPPORTUNITY <i>Due to USG ban</i>	MODERATE OPPORTUNITY	POTENTIAL LIMITATION	STRONG OPPORTUNITY



Implications of findings for ring planning



GLOBAL STAKEHOLDERS

- Country stakeholder interest and questions about the ring should **be shared with global stakeholders to inform planning and prioritization.**
- Feedback from country stakeholders underscores **the need for demonstration projects** as part of the global rollout and **the importance of coordinated demonstration planning** amongst global actors.
- Supporting awareness-building about the ring and its potential within **USAID, WHO, Global Fund and their relevant missions** is a fundamental step in the introduction process as planning, financing and approval of rollout in most countries hinges on their involvement.



COUNTRY STAKEHOLDERS

- Introducing the ring through demonstration projects will require resources and may mean that the **first phase of rollout should take place in a subset of “early adopter” countries.**
- Identifying **strong implementing partners in each priority country** to steward the stakeholder engagement and planning process will be a critical first step.
- The limited existing knowledge of the ring, coupled with country stakeholders’ eagerness to engage on demonstration planning, suggests a need for thoughtful, **consistent communications and engagement of priority stakeholders** in country between now, the EMA opinion and thereafter.
- A **customized engagement approach for different types of stakeholder groups** in each country could support introduction. For example, civil society members across countries were supportive of the new option, though they have varying levels of influence on policy-making. They can be engaged to generate demand for the ring through formal or informal channels.

SUMMARY FINDINGS

DETAILED COUNTRY FINDINGS

SOUTH AFRICA





South Africa: Potential for the ring

STANDARD ADOPTER due to the significant burden of HIV on South Africa and the reputation as an early implementer of new prevention approaches. However, recent regulatory requirements may delay the start of demonstration projects, depending on interest of key officials in the National Department of Health and regulatory bodies.

Opportunities

- **High need:** Of all seven countries in this analysis, South Africa has the greatest HIV burden, including both the highest prevalence and incidence.
- **Strong knowledge of the ring:** Stakeholders were familiar with the ring and were largely supportive of adding another option to the prevention portfolio.
- **Recognized early adopter:** South Africa is regarded as a quick adopter of new prevention technologies, and was the first country to implement oral PrEP after WHO guidelines.
- **Strong partners:** Reputable research institutions, a coordinated and powerful civil society, and wide breadth of implementation partners will be strong partners to support demonstration and implementation.
- **Potential to develop an early demonstration proposal:** A key regulatory stakeholder suggested an opportunity to draft a demonstration proposal with the key questions before the EMA opinion, which may be able to expedite a demonstration after regulatory decisions.

Challenges

- **Potential regulatory challenges:** Regulatory approval in South Africa recently underwent changes, as the former regulatory body, Medicines Control Council, has now been replaced by South African Health Products Regulatory Authority (SAHPRA). Stakeholders expressed that this could be a roadblock, as the process with SAHPRA remains unclear to many.
- **Capacity of NDoH:** The National Department of Health (NDoH) has a relatively small team that manages the HIV prevention and treatment portfolio. Their current capacity is limited due to the recent roll-out of oral PrEP, self-testing and new treatment options. For example, policymakers were unavailable to be interviewed for this analysis.
- **Funding:** While South Africa spends a larger portion of national funds on their HIV response relative to other countries, it is likely that demonstration and the first few years of a new product need to be funded by donors.



South Africa: Assessment overview

High-level assessment for the ring

A monitor displaying a bar chart and a pie chart.	HIV epidemic characteristics	SIGNIFICANT NEED: South Africa has the highest HIV burden in the world, with 7.1 million people living with HIV and an additional 270,000 new infections annually.
A building with a cross on top, representing a clinic or hospital.	HIV prevention program	STRONG OPPORTUNITY: South Africa has developed the largest treatment program in the world and recently renewed their commitment to prevention. Additionally, the NDOH has shown an openness to biomedical products.
A blue pill bottle with a white cross on the label.	Oral PrEP experience	STRONG OPPORTUNITY: South Africa has the largest number of oral PrEP users in the region, and was the first country in the region to implement oral PrEP. However, challenges with funding and adherence have slowed scale-up.
A blue circle with a white ring inside, representing a ring trial.	Ring trial experience to-date	STRONG OPPORTUNITY: South Africa has been involved in both phase III trials and OLEs. Sites from South Africa are also included in REACH.
Two overlapping speech bubbles, representing communication or stakeholder input.	Stakeholder reactions to the ring	MODERATE OPPORTUNITY: Stakeholders were largely familiar with the ring and eager about additional prevention options. Some stakeholders expressed concerns about efficacy and the challenge of introducing multiple new products simultaneously.
A clipboard with a checklist and a pencil, representing a process or document.	Product introduction process	MODERATE OPPORTUNITY: Changes among the national regulatory process have created some uncertainty about the process. However, with compelling evidence and political buy-in the process can be easier.

Additional details on following slides



South Africa: HIV context

South Africa has an estimated

7.1 million

people living with HIV, which accounts for

18.9% of the adult population

and

270,000 new infections

occur annually.¹

South Africa = 1 in 5 people living with HIV globally²



AGYW face higher risk of infection²

AGYW account for **100,000 new cases annually** out of 270,000 new infections countrywide. Their **HIV burden is 4x** that of male peers

Young women have the highest incidence rate²

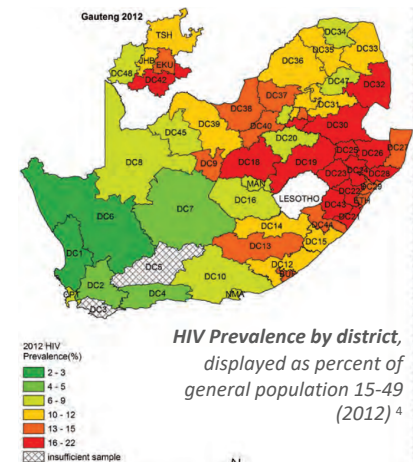
Approximately **2,000 new HIV infections occur weekly** among women ages 15-24

FSWs face high burden of HIV, but it varies geographically³

Prevalence among FSWs ranges from **39.7% in Cape Town** to **53.5% in Durban** to as high as **71.8% in Johannesburg**

Urban and semi-urban areas show higher prevalence⁴

Prevalence rates among provinces **vary greatly**. KwaZulu-Natal has the highest prevalence in the country, at 16.9% among all adults, relative to Western Cape, with a prevalence of 6.4%.



HIV Prevalence by district, displayed as percent of general population 15-49 (2012)⁴

Sources: (1) UNAIDS Data 2017, (2) South Africa's National Strategic Plan for HIV, TB and STIs 2017-2022, (3) Let Our Actions Count: Reflections on NSP 2012-2016 and moving forward to NSP 2017-2022, (4) https://www.heads.ac.za/site/assets/files/1267/sabssm_iv_leo_final.pdf ; (5) http://sanac.org.za/wp-content/uploads/2016/06/GARPR_report-high-res-for-print-june-15-2016.pdf



South Africa: HIV prevention context

Context

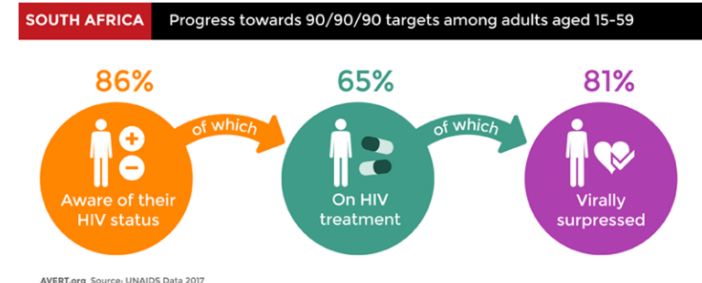
- **Political landscape:** South Africa is recognized as a quick adopter of new approaches to combat HIV. However, recent challenges with funding, a new regulatory body, and less capacity due to oral PrEP and HIV self-testing implementation may lessen political buy-in for the ring. If the ring is evidenced to be effective among AGYW, political buy in among NDoH would likely follow.
- **Recent progress with prevention and treatment:** South Africa has made significant process in the last decade. New infections have declined from 360,000 in 2012 to 270,000 in 2016. South Africa has the largest HIV treatment program in the world, with over 3.7 million people initiated on ART as of December 2016.¹

National Policies and Strategies for Prevention ¹

- The **National Strategic Plan for HIV, TB and STIs (NSP) 2017-2022** is South Africa's fourth plan. The NSP is published by SANAC in partnership with NDoH and other stakeholders.
- The most recent NSP has **eight goals**, including accelerating prevention efforts, reducing mortality, focusing on **key and vulnerable populations**, and addressing the social and structural drivers of HIV, TB, and STIs, among others.
- The prevention goal aims to reduce new infections from 270,000 in 2016 to **100,000 in 2022**, by **eliminating MTCT** and **reducing new infections among AGYW** from 2000 infections each week to fewer than 800.
- The **combination prevention** approach includes comprehensive education in community settings, eMTCT, and oral PrEP, and others. The NSP highlights the role **biomedical products** can play, with an objective to “implement targeted biomedical prevention services tailored to setting and population.”

Remaining Challenges with Prevention

- **Health system:** Stakeholders shared that there is great variability of health services across provinces, districts, and clinics. Training among frontline healthcare workers has been a challenge for oral PrEP. One stakeholder shared that the NDoH of Health has been facing pressure to improve basic health system functioning.
- **Education:** A 2015 UNFA survey found that only 59% of young people in South Africa have comprehensive knowledge of how to prevent HIV.¹¹
- **Capacity of NDoH:** The core team leading HIV Prevention is focused on the rollout of oral PrEP and self-testing.





South Africa: Status of oral PrEP rollout

Oral PrEP Rollout

- Oral PrEP is currently in **early implementation** stages. There are an estimated **8,500 – 9,500** current oral PrEP users in South Africa.¹
- South Africa was the site of **clinical trials, open-label extensions, implementation projects, large-scale implementation initiatives, and product introduction / support projects** for oral PrEP.¹
- Both Gilead's Truvada (TDF/FTC) and generic versions of TDF/FTC are **approved for prevention**.¹
- Eligibility criteria state that oral PrEP is available for HIV-negative individuals who are at **significant risk for acquiring HIV infection**. The oral PrEP guidelines note that oral PrEP is suitable for the following populations:
 - Any MSM or transgender person who wants PrEP,
 - Heterosexual women and men who want PrEP, targeting especially sex workers and those who have multiple sexual partners, among others, and
 - People who inject drugs.
- South Africa became the **first country to implement oral PrEP** when policymakers quickly formed the oral PrEP TWG **one month after WHO guidance**. South Africa introduced oral PrEP eight months later through a phased implementation approach, beginning with FSW and MSM, which has recently extended to AGYW.
- While policymakers indicated an early commitment to oral PrEP, South Africa has encountered challenges that have slowed down implementation. Key challenges have included **low adherence**, sustaining **sufficient funding**, and **low health system capacity**.



South Africa: Ring trial activity

Dapivirine Ring Trials

- South Africa was a **Phase III test site for The Ring Study and ASPIRE**, and is currently enrolled in the **open-label extensions HOPE and DREAM**. South Africa will also be a site for the **REACH** trial for AGYW.

Study	Phase	Results	Partners
The Ring Study (TRS) (ages 18-45) IPM-027	III	The ring reduced risk of HIV-1 infection by ~31% overall compared to a placebo	<ul style="list-style-type: none"> • Led by: International Partnership for Microbicides, Inc. (IPM) • Funding: Bill and Melinda Gates Foundation, PEPFAR, USAID, and several European governments and organizations
ASPIRE (ages 18-45) MTN-020	III	The ring reduced risk of HIV-1 infection by ~27% overall compared to a placebo. HIV risk was cut by 56% in women older than 21, who appeared to use the ring most consistently	<ul style="list-style-type: none"> • Led by: Microbicide Trials Network (MTN) • Funding: US NIH, US NIMH, US National Institute of Allergy and Infectious Disease (IND Sponsor: IPM)
DREAM (ages 18-45) IPM-032	IIIb OLE	(Preliminary) Risk reduced by ~54%	<ul style="list-style-type: none"> • Led by: IPM • Funding: Bill and Melinda Gates Foundation, PEPFAR, USAID, and several European governments and organizations
HOPE (ages 18-45) MTN-025	IIIb OLE	(Preliminary) Risk reduced by ~54%	<ul style="list-style-type: none"> • Led by: MTN • Funding: US NIH, US NIMH, US National Institute of Allergy and Infectious Disease (IND Sponsor: IPM)
REACH (ages 16-21) MTN-034	OLE	(Pending) Will collect safety and adherence data over the course of study product use for young women. Will also examine the acceptability of the study products. (6mo ring, 6mo oral PrEP, then choose for 6 mo)	<ul style="list-style-type: none"> • Led by: MTN • Funding: US NIH, US NIMH, US NIAID, US NICHD • Sponsors: IPM, Gilead Sciences, Inc.

Site information: South Africa had nine sites for ASIPRE and HOPE, including one site in both Cape Town and Johannesburg, and seven sites in Durban. For TRS and DREAM, there are six sites in South Africa



South Africa: Impressions of the ring

Opportunities

“Participants find the ring acceptable because it is **easy to use, female initiated**, and women are able to protect themselves. They also like that the ring **only requires monthly action.**”

– Trial researcher

“We should not be thinking about the ring as an independent technology, but rather **contributing toward our prevention portfolio**. When we do this, I think a 50% efficacy rate would generate interest among regulators.” – Key policymaker

“From the experiences with the PrEP working group, one of the advantages is that the **PrEP infrastructure will have been built** around TDF.

We will be able to leverage that.”

– Implementation partner

“In South Africa there are a lot of **high quality implementers and research institutions**.

Their ability to move things is significant.”

– International donor

Challenges

“My biggest concern is how we position it in terms of efficacy. The **efficacy with among AGYW** is a bit of a concern. I spoke to a clinician and asked him if I were on the ring and knew I was exposed to HIV, would he recommend I take PEP, and he said yes. The same is not true about PrEP.”

– Implementation partner

“There has been very little conversation about the ring in South Africa. This is not due to lack of interest, but just **because so many other things are happening** in prevention and treatment.” – International donor

“I see the ring entering the market at a **time of pressure and a lack of resources**. When we talk about where to put funding, if we put funding into the ring, it's coming out of PrEP. What's the comparative benefit of the ring relative to PrEP, condom promotion, or community interventions?”

– International donor

“There **haven't been many conversations** about the ring outside of prevention research.

There have been no discussions about programmatic implications.”

– Implementation partner



South Africa: Key questions about the ring

1

What is the **efficacy** of the ring? To what extent does efficacy change among different populations? Is the ring effective among AGYW and serodiscordant couples?

2

To what extent do **end-users adhere** well to the ring in real world settings? Do **AGYW adhere** well? What are the implications of low adherence?

3

What is the **impact** of the ring? How many infections will the **ring prevent relative to other prevention approaches** (oral PrEP, condom promotion, behavior change and communication)? What does **ring modeling look like** in combination with other prevention options? What is the impact among AGYW?

4

What are the **costs** of investing in the ring? How do the costs compare with other prevention options?

5

What is the **delivery method** that will be used for the ring (e.g. ARV clinics for SDC, family planning clinics for AGYW, etc.)? What are the impacts on the **health system**? What kind of **training** will be necessary for healthcare providers? How feasible is the training of healthcare providers?



South Africa: Interviews

Polymakers

1. Helen Rees, SAHPRA and Wits RHI

Researchers and Implementation Partners

2. Dr. Saiqa Mullick, Wits RHI
3. Elmari Briedenhann, Wits RHI
4. Diantha Pillay, Wits RHI
5. Krina Reddy, Wits RHI
6. Florence Mathebula, Wits RHI (Qualitative Researcher for ASPIRE)
7. Andile Twala, Wits RHI (Community liaison officer for ASPIRE)
8. Zonke Madubi, Match Research Unit
9. Sarah Jenkins, Clinton Health Access Initiative
10. Katie Callahan, Clinton Health Access Initiative

International Donors

11. Tim Mah, USAID