

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 by 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 incidence• Specifically 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.



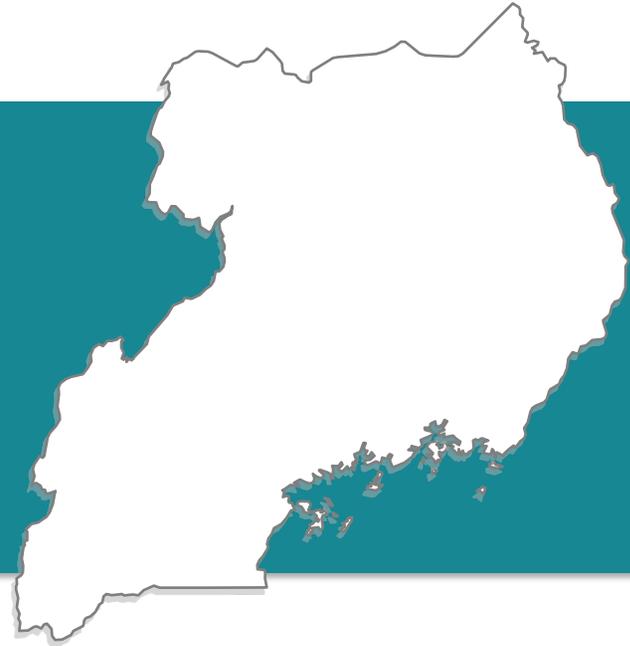
COUNTRY STAKEHOLDERS

- 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.

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UGANDA





Uganda: Potential for the ring

EARLY ADOPTER due to favorable policy environment, receptivity of the MoH, and pre-existing institutional infrastructure from oral PrEP introduction

Opportunities

- **Positive stakeholder impressions:** Overall, stakeholders were receptive and interested in the ring. They appreciated the opportunity for a **woman-controlled** product, and thought it would be applicable to range of woman: from young women and girls to people in serodiscordant relationships to commercial sex workers.
- **Existing processes and structure:** Stakeholders believe they will be able to **build on the existing national guidelines for oral PrEP** where the ring is already listed as a “promising” new technology. The country can also leverage the **same Technical Working Group** as oral PrEP.
- **Widespread familiarity:** There is strong **existing in-country knowledge** of the dapivirine ring and **general excitement** about it.

Challenges

- **Slow pace of past introductions:** Oral PrEP implementation in Uganda was **slow** to move forward, and it was **not an easy process**.
- **Likelihood to follow a similar process:** While stakeholders believe the ring will **avoid many of the obstacles** that oral PrEP faced, there is still reason to believe it will take time. Stakeholders do not see significant barriers to demonstration.
- **Limited financial resources:** The MoH relies on **international partners** to fund oral PrEP. The government would also rely on international funding for ring demonstration and rollout which raises questions about **sustainability**. This is not unique to Uganda; financial limitations are a challenge for many other countries in the region.



Uganda: Assessment overview

High-level assessment for the ring	
 HIV epidemic characteristics	SIGNIFICANT NEED: There is a high prevalence rate of 6.5% and it is estimated that there are 52,000 new infections per year. Women are most impacted and HIV prevalence is ~4 times higher among young women than young men.
 HIV prevention program	STRONG OPPORTUNITY: Uganda has oral PrEP and other biomedical interventions included in the NSP, and has dedicated about 23% of its NSP budget to prevention. Still, like other countries in the region, Uganda faces funding constraints for adding additional products.
 Oral PrEP experience	MODERATE OPPORTUNITY: Uganda was somewhat slow to incorporate oral PrEP into national guidelines and plans. However, the resulting processes and structures (e.g., PrEP TWG) now can be leveraged for the ring.
 Ring trial experience to-date	STRONG OPPORTUNITY: Government, academic, and civil society stakeholders were relatively familiar with the ring, and Uganda has been a site for several landmark ring trials.
 Stakeholder reactions to the ring	STRONG OPPORTUNITY: Stakeholders were interested in the ring and saw the benefits of adding an additional product controlled by women to the HIV prevention toolkit.
 Product introduction process	STRONG OPPORTUNITY: Uganda has a clear introduction process that can be sped up through strong partnership with government. Early indications from government stakeholders suggest the process could be sped up.

Additional details on following slides



Uganda: HIV context

Uganda has an estimated

1.4 million

people living with HIV, which accounts for

6.5% of the adult population

and

52,000 new infections

occur annually¹

HIV prevalence among Uganda's fishing communities is estimated to be **three times higher** than the general population. A 2013 study of 46 fishing communities found **HIV prevalence to be at 22%**.¹

Women, particularly **young girls and adolescent women**, are disproportionately affected by HIV. Other impacted populations include **sex workers, MSM, PWID**, and people from transient **fishing communities**.

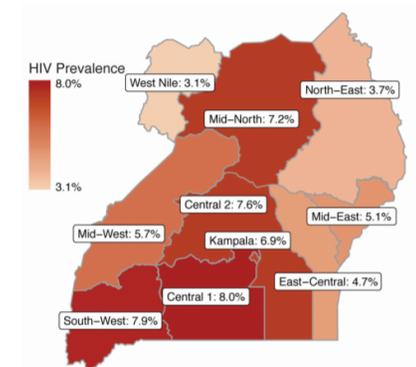
Women are disproportionately affected¹

Prevalence among adult women is **7.6% compared to 4.7%** among Ugandan men. Sex workers are also greatly impacted (37% prevalence)

The gender disparity is greatest among young women¹

HIV prevalence is **almost four times higher among young women** (ages 15-24) than young men of the same age

HIV among adults is highest in the central, mid-north, and southwest regions²





Uganda: HIV prevention context

Context

- **Political landscape:** While Ugandan government stakeholders generally expressed positive perceptions of the dapivirine ring, some past HIV prevention efforts have been hindered by legal, cultural, or political barriers. For instance, the recently passed HIV Prevention and Control Act criminalizes HIV transmission and behavior that could result in transmission.²
- **Recent progress with prevention and treatment:** Uganda has experienced declines in new infections between 2010 and 2016, and there has been considerable progress toward the first two 90's, but viral suppression remains a challenge.²

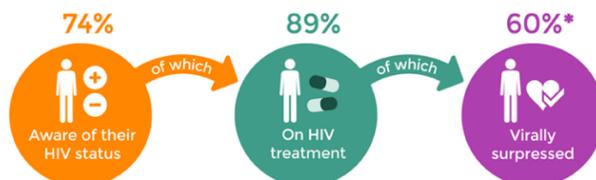
National Policies and Strategies for Prevention

- **Goal:** Uganda's prevention strategy goal is to **reduce the number of youth and adult infections by 70%** and the number of new paediatric HIV infections by 95% by 2020.¹
- **Strategy:** The country's prevention strategy has three objectives: (A) Increase **adoption of safer sexual behaviors** and **reduction in risky behaviors**; (B) Scale-up **biomedical HIV prevention interventions** (such as oral PrEP) delivered as part of health care services; (C) **Mitigate underlying socio-cultural, gender, and other factors** that drive the HIV epidemic.¹
- **Budget:** Prevention will account for **23% of the \$3.6B** projected to be spent on prevention from 2015-2020.¹

Remaining Challenges with Prevention

- **Lack of sexual education:** In 2014, **only 38.5%** of young women and men (ages 15-24) could correctly identify ways of preventing sexual transmission of HIV and rejected major misconceptions about HIV transmission.²
- **Inconsistent condom use:** In 2017, **only 60% of men and 45.5% of women** reported using a condom the last time they had high-risk sex.²
- **FSW face financial pressure and violence:** Sex workers and their clients accounted for **~18% of new HIV infections** in 2015/16. Yet, sex workers are often unable to use condoms: between **33% and 55% of sex workers report inconsistent condom use**. Over 80% of sex workers experience client-perpetrated violence, which may lead to coerced sex without a condom.²
- **Legal and cultural barriers:** Stigma and discrimination against MSM and criminalization of sex work remain barriers to health care access.²

UGANDA Progress towards 90/90/90 targets among adults aged 15-59



AVERT.org Source: UNAIDS data 2017. *Ugandan Ministry of Health (2017)



Uganda: Status of oral PrEP rollout

Oral PrEP Rollout

- Oral PrEP is currently in **early implementation** stages. There are an estimated **4,000 – 5,000** current oral PrEP users in Uganda.¹
- Uganda has been the site of **clinical trials, demonstration projects, and large-scale implementation initiatives** for oral PrEP.¹ Generic versions of TDF/FTC are **approved for prevention**. Gilead's Truvada (TDF/FTC) registration is planned and in progress.¹
- In July 2008, couples in Uganda and Kenya were enrolled in the **Partners PrEP study** on serodiscordant couples. Results from this critical study were released in 2011, and data about oral PrEP was included in a section on **recent evidence** in an updated version of Uganda's 2011-2015 National Strategic Plan (NSP). Oral PrEP was later included as a **strategic action** in the 2015-2020 NSP.^{4,5}
- In 2012, the WHO released guidelines on oral PrEP for SDC and high risk MSM. However, the Ugandan MoH did not release **technical guidelines** on oral PrEP for people at high risk of HIV until 2016.² Some stakeholders mentioned frustration that Uganda was **slower to incorporate oral PrEP into national guidelines** and plans and slower to implement oral PrEP than other countries (e.g., Kenya).³
- Interviewees cited a range of reasons for the **slower pace**, including **limited financing, disbelief** that HIV could be prevented, **lack of updates** to the MOH along the way, **perceived competition with ARVs** for treatment, and **moral challenges** and **myths** (i.e., oral PrEP is for MSM, oral PrEP encourages promiscuity).³
- The MoH and civil society representatives expressed that the process for the dapivirine ring has been better than the oral PrEP process because they have been **authentically engaged** throughout the trials to date.

Sources: (1) PrEP Watch <https://www.prepwatch.org/uganda/>; (2) *Technical Guidance on Pre-Exposure Prophylaxis (PrEP) for Persons at High Risk of HIV in Uganda (2016)* Ministry of Health; (3) FSG interviews; (4) *National HIV and AIDS Strategic Plan 2015/2016-2019/2020* (2015) UAC; (5) *National Strategic Plan for HIV and AIDS (revised) 2011/2012-2014/2015* (2012) UAC



Uganda: Ring trials activity

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

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• Site: MRC/UVRI Uganda Research Unit on AIDS, Masaka
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)• Site: Makerere University Johns Hopkins University Research Collaboration (MU-JHU)• Site Investigators: Flavia Matovu, Clemensia Nakabiito
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• Site: MRC/UVRI Uganda Research Unit on AIDS, Masaka
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)• Site: MU-JHU• Site Investigators: Flavia Matovu, Clemensia Nakabiito
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 months)	<ul style="list-style-type: none">• Led by: MTN• Funding: US NIH, US NIMH, US NIAID, US NICHD• Sponsors: IPM, Gilead Sciences, Inc.

Sources: (1) <https://mtnstopshiv.org/news/studies/mtn020/factsheet> (2) <https://mtnstopshiv.org/news/womens-use-vaginal-ring-higher-open-label-study-level-hiv-protection> (3) <https://mtnstopshiv.org/news/reach-study-mtn-034> (4) <https://www.avac.org/ipm-027-ring-study-0> (5) <https://www.niaid.nih.gov/news-events/vaginal-ring-provides-partial-protection-hiv-large-multinational-trial>



Uganda: Impressions of the ring

Opportunities

“We are really interested in a **women-controlled** HIV prevention method. We have been desiring that given our **patriarchal society**.”
– Civil society representative

“I am happy with the ring because there is **information already**. **Women are asking about the ring**. The local people are asking ‘now you say the ring will work, now when will we get it?’”
– Civil society representative

“The stage we’ve reached in the epidemic is that we need to **control new cases**, the last mile is never easy. The ring is a good addition, and when the science proves it is **efficacious enough** it will be good.”
– Policymaker

“Having a demonstration is **very welcome**. We will **ride on existing structures** so it should not be a problem to set up one.”
– Policymaker

Challenges

“Our government is a **late adopter** of new options. They are preoccupied with what’s currently happening. **We don’t jump on everything new** most of the time. We should anticipate that same approach with the ring. I can bet it will take **quite a bit of advocacy** to have the ring accepted.”
– Civil society representative

“In spite of our current guidelines, oral PrEP is still not distributed by government, but rather it’s distributed by partners. While the government has signed of the guidelines, they are **concerned with resources** and less willing to spend its own resources on PrEP.”
– Civil society representative



Uganda: Key questions about the ring

- 1 How can **acceptability** be increased among **different age groups** (e.g., young women) and how does **behavior change** vary across age groups?
- 2 What does behavioral data demonstrate about the impact of the ring on “**sexual disinhibition**” (i.e., can data allay concerns about “promiscuity”)?
- 3 How does the ring’s **cost-effectiveness compare** to other prevention methods (e.g., condoms, oral PrEP, VMMC)? How much will the government **save** by investing in the ring?
- 4 How much does **efficacy** increase with more consistent use? What factors promote better **adherence**?
- 5 With extended use, does the ring continue to demonstrate minimal **side effects** and minimal **drug resistance**?
- 6 Does ring usage impact **prevalence rates** or **risk** of contracting **other STIs** as a result of behavior changes?

In addition to questions that will need to be answered in demonstration, stakeholders raised the following **technical questions** that will need to be **answered now** and have **clear messaging** during introduction:

- Is silicone biodegradable? What is the **disposal process** for the ring and what are the environmental repercussions of ring disposal?
- How often should a woman using the ring be **tested for HIV**? Is self-testing sufficient or should a woman report to a health facility for HIV testing?
- Why is the ring **one size fits all**? How does the ring fit everyone regardless of size? Can the ring fall out?



Uganda: Interviews

Policymakers

1. Dr. Herbert Kadama, PrEP TWG Coordinator, Ministry of Health
2. Dr. Peter Mudiope, Coordinator of HIV Prevention, Ministry of Health
3. Dr. Nelson Musoba, Director General, Uganda AIDS Commission
4. Dr. Dan Byamukama, Head of HIV Prevention, Uganda AIDS Commission
5. Dr. Caroline Nakkazi, HIV Prevention Officers, Uganda AIDS Commission

Civil Society

6. Margaret Happy, Advocacy Manager, International Community of Women Living with HIV East Africa (ICWEA)
7. Brenda Facy Azizuyo, Sparked Women Project Coordinator, ICWEA
8. Charles Brown, Executive Director, Preventive Care International
9. Sylvia Nakasi, Policy and Advocacy Officer, Uganda Network of AIDS Service Organizations (UNASO)
10. Milly Katana, Community Working Group Co-Chair, MTN
11. Macklean Kyomya, Executive Director, Alliance of Women Advocating for Change (AWAC)

International Donors / Partners

12. Armstrong Mukundane, National Technical Assistance Coordinator, FHI 360
13. Sheila Kyobutungi, Program Specialist, USAID/PEPFAR
14. Elizabeth Meassick, USAID/PEPFAR
15. Joseph Lubwama, HIV Prevention, CDC

Researchers / Academia

16. Dr. Timothy Muwonge, Coordinator, PI at the Infectious Diseases Institute (IDI)
17. Dr. Flavia Matovu, Epidemiologist/Investigator with the Makerere University-Johns Hopkins University (MU-JHU) Research Collaboration
18. Dr. Andrew Mujugira, Head, IDI
19. Dr. Sylvia Kusemererwa, Project Leader, Medical Research Council/Uganda Virus Research Institute
20. Vincent Basajja, Community Liaison, Medical Research Council/Uganda Virus Research Institute
21. Dr. Fred Magala, Makerere University Walter Reed Project