MTN
microbicide trials network

HOPE
HIV Open-label Prevention Extension
Out of ASPIRE, there is HOPE

HOPE Prevails

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for the MTN-025/HOPE Study Team

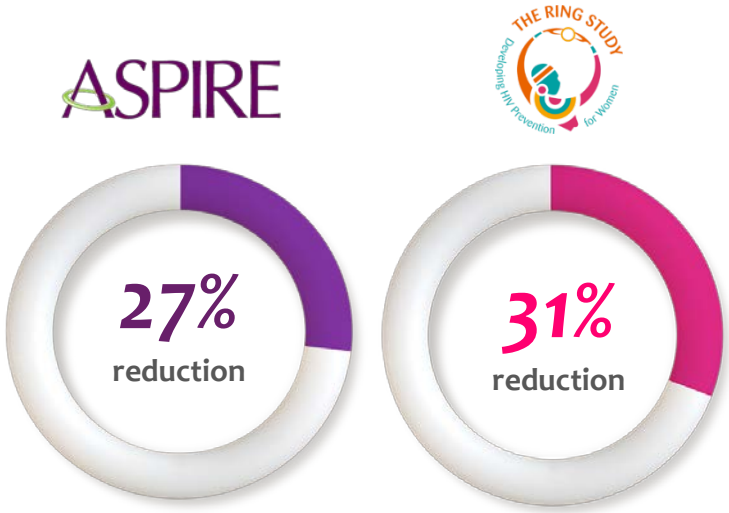
MTN Regional Meeting

Cape Town, September 2019

HOPE prevails

Phase III Trials

Two phase III clinical trials – MTN-020/ASPIRE and IPM 027/The Ring Study – showed that the monthly dapivirine vaginal ring was well tolerated and reduced HIV-1 incidence by approximately 30% compared to placebo.



Baeten et al., Nel et al., NEJM 2016

Open-label extension studies

For new HIV-1 prevention strategies, the pathway from clinical trial proof of efficacy to implementation often passes through open-label extensions

- providing early ***access*** to the effective product for those who had participated in the clinical trial
- exploring use of the product in the context of ***known clinical efficacy***
- bridging to ***potential licensure & delivery at scale***

Graphic: AVAC

MTN-025/HOPE

- A **multi-center open-label extension study** (a phase IIIb trial) of the dapivirine vaginal ring (25 mg, replaced monthly).
- The **population** was HIV-1 uninfected women who had previously participated in MTN-020/ASPIRE.
- The **primary objectives** of MTN-025/HOPE were to assess **adherence** and **safety** in an open-label setting.
- **Secondary objectives** included assessing **HIV-1 incidence** and **HIV-1 antiretroviral resistance**.

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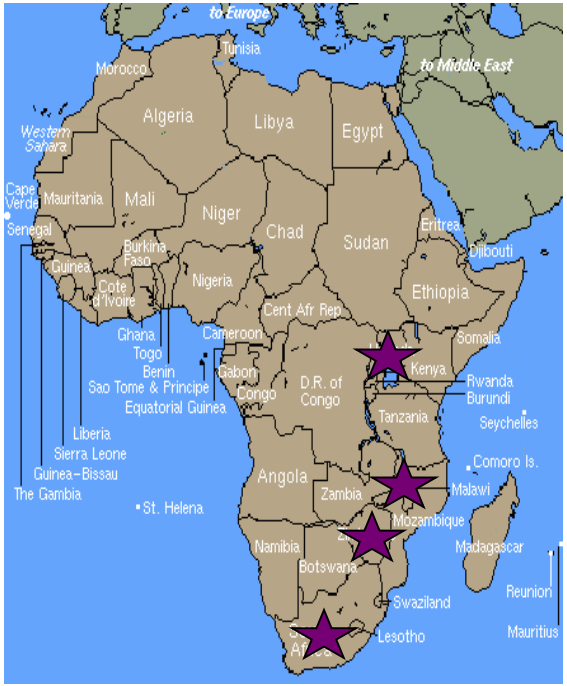
Design

- **Follow-up was for 12 months.** Monthly for the first three months, then quarterly thereafter
  - Transitioning to a more "real world" frequency for follow-up and distribution of rings
- **Using the ring was a choice.** At every visit, women could choose to accept or decline the dapivirine vaginal ring and still continue in the study.
- **Study procedures were comprehensive.** HIV testing, risk-reduction counseling, pregnancy testing, contraceptive counseling/provision, safety monitoring, product counseling/provision

Timeline

- MTN-020/ASPIRE reported its primary results in February 2016
- MTN-025/HOPE began in August 2016
- Enrollment into MTN-025/HOPE concluded in September 2017
- MTN-025/HOPE follow-up concluded in October 2018

Enrollment



- 2629 women participated in MTN-020/ASPIRE
  - 171 acquired HIV-1 during follow-up
- For MTN-025/HOPE, 1643 women were screened and 1456 women were enrolled, 59% of those HIV-1 uninfected at the completion of MTN-020/ASPIRE.
  - Most common reasons for not enrolling were having acquired HIV-1 (30%) & wanting to become pregnant (29%)
- Participants were from 14 sites in 4 countries:
  - Malawi (n=157, 11%)
  - South Africa (n=707, 49%)
  - Uganda (n=172, 12%)
  - Zimbabwe (n=420, 29%)

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Participant characteristics

Participant characteristics defined a population at risk for HIV-1:

Characteristics at study entry	MTN-025 HOPE
Age, median	31 (range 20-49)
Age, <25 years	12%
Married	47%
Sexually transmitted infection (GC/CT/TV/TP)	16%
Used a condom with last sex act	43%

Participant characteristics

Participant characteristics defined a population at risk for HIV-1

Although population characteristics had expectedly evolved since enrollment into MTN-020/ASPIRE

Characteristics at study entry	MTN-025 HOPE	MTN-020 ASPIRE
Age, median	31 (range 20-49)	26 (range 18-45)
Age, <25 years	12%	39%
Married	47%	41%
Sexually transmitted infection (GC/CT/TV/TP)	16%	21%
Used a condom with last sex act	43%	57%

Retention and Follow-up

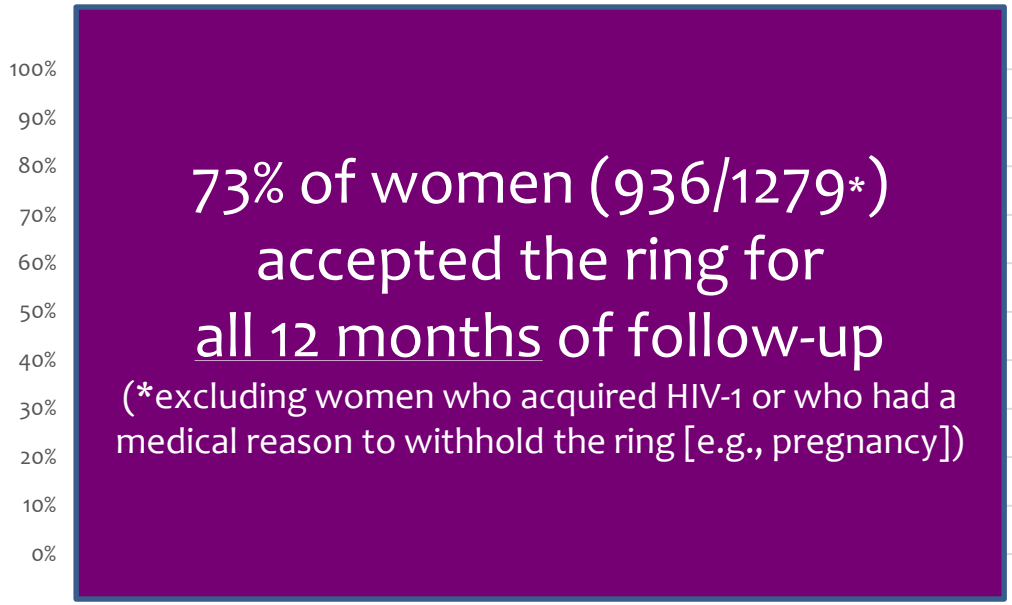
- Retention was very high - 98% of expected visits were completed (vs. 91% in MTN-020/ASPIRE).

- A total of 8436 follow-up visits were completed.

MTN-025 Visit Month	Retention, n (%)
Month 1	1428 (98%)
Month 2	1422 (98%)
Month 3	1427 (99%)
Month 6	1404 (98%)
Month 9	1379 (97%)
Month 12	1376 (97%)

Ring Uptake

- At enrollment, 1342 women (92%) accepted the dapivirine vaginal ring.
- Persistence was high: the majority continued to accept the ring.
- When declined, the most common reason was having chosen another HIV-1 prevention method.



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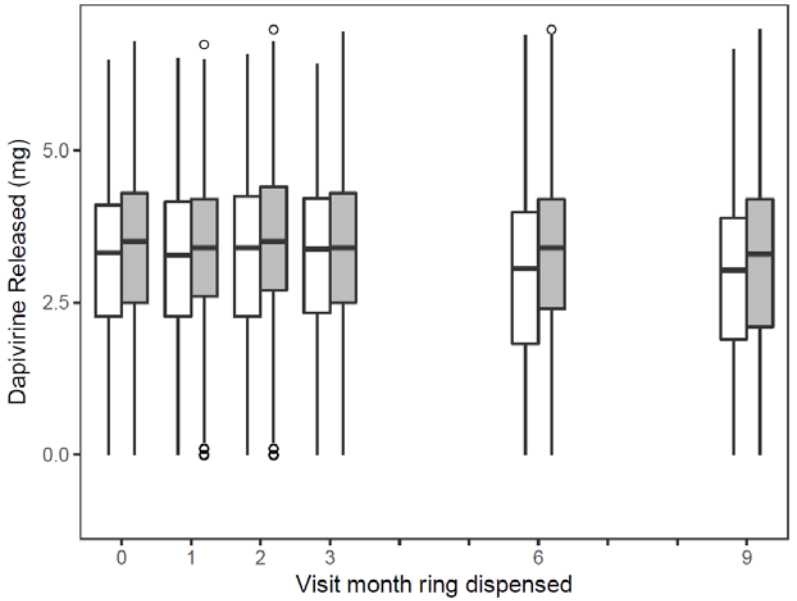
Ring Adherence (1)

- Returned, used rings were tested for residual levels of dapivirine.
  - Rings are manufactured with approximately 25 mg of dapivirine and release approximately 4 mg with a month of continuous use.
  - The amount of dapivirine released was calculated.
  - Rings that had released >0.9 mg were defined as indicating *at least some* adherence during the month (but not necessarily consistent use).

Ring Adherence (2)

- Overall, 90% of returned rings had released >0.9 mg
- The average dapivirine released was greater for MTN-025 compared to MTN-020

Dapivirine released from rings, limited to those women who participated in both MTN-020 & MTN-025



p<0.001 (GEE)

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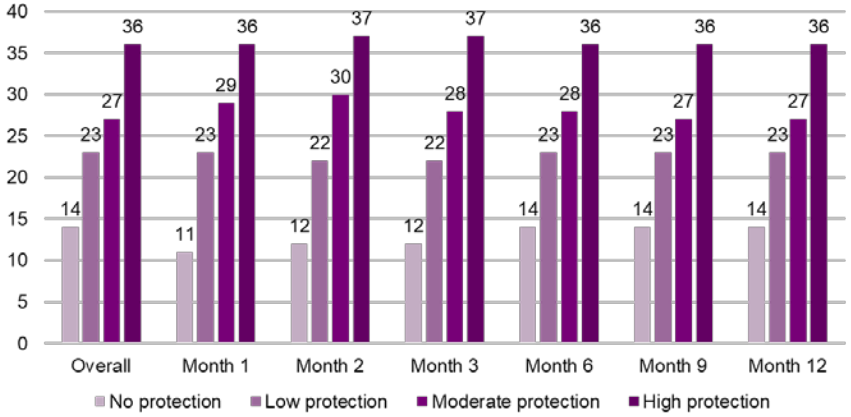
Ring Adherence (3)

- Estimated use of the dapivirine vaginal ring remained relatively constant throughout follow-up

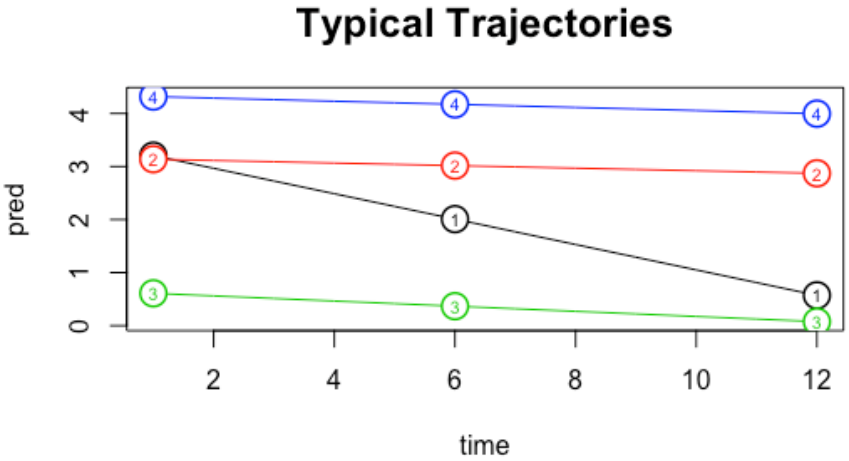


Relative level of HIV-1 protection	Average dapivirine released per month	Estimated level of HIV-1 protection (MTN-020/ASPIRE, Brown, AIDS 2016)
No	≤1.4 mg	11-20%
Low	1.4 - 3 mg	29-47%
Moderate	3 - 3.9 mg	58-75%
High	≥3.9 mg	47-92%

Ring Adherence (4)

- Preliminary analyses show women "cluster" into groups:
  - persistent users,
  - persistent mostly users,
  - declining use over time,
  - and persistent non-users

Clust	1	2	3	4
Prop %	14.56 %	36.26 %	19.64 %	29.53 %



Safety

- The frequency, severity, and type of adverse events observed was similar to that observed in MTN-020/ASPIRE – i.e., no new safety signal was seen
- No SAE or Grade 3+ adverse event was assessed by the treating clinician to be related to the use of the dapivirine vaginal ring.
- A total of 70 pregnancies occurred and had outcomes measured; no congenital anomalies were observed.

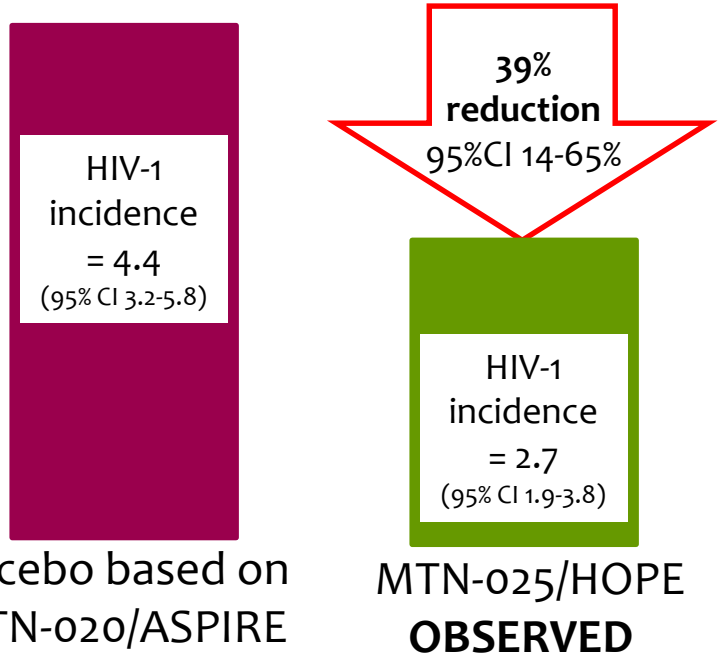
	# (%) of participants
SAE	20 (1%)
Grade 3+ event	54 (4%)
Grade 2 event, related	2 (<1%)

HIV-1 incidence

- A total of 35 HIV-1 infections occurred, at an **incidence of 2.7 per 100 person-years (95% CI 1.9-3.8)**
- This incidence is lower than the placebo arm incidence in MTN-020/ASPIRE which was **4.5 per 100 person-years (95% CI 3.7-5.5)**
- To compare HIV-1 incidence to that in MTN-020, while also accounting for differences between the populations, weighted bootstrap sampling of the placebo arm of MTN-020 was done, matched on trial site, age, and presence of a curable sexually transmitted infection at trial entry.

HIV-1 incidence comparison

- The median HIV-1 incidence was 4.4 per 100 person-years in the 10,000 samplings from MTN-020/ASPIRE.
  - An incidence of ≤2.7 would occur in <33/10,000 samplings



HIV-1 antiretroviral resistance

- Among the 35 infections, 7 had NNRTI mutations (4 K103N, 1 A98G, 1 E138A/V179D, 1 V106M/V179D), none of which suggest a dapivirine-specific resistance pattern

Summary

- Final results from this open-label extension trial of the dapivirine vaginal ring indicate high uptake and adherence, a well-tolerated safety profile consistent with that seen in the phase III studies and lower HIV-1 incidence than expected.

Discussion

- In MTN-025, women were offered the choice of the dapivirine vaginal ring – the vast majority initially accepted the ring and most continued throughout 12 months.
  - This high level of persistence compares favorably to recent open-label studies of FTC/TDF PrEP among women
- Comparing HIV-1 incidence in this study is limited:
  - lack of a contemporaneous placebo group
  - MTN-025 participants had not acquired HIV-1 during MTN-020
  - not all women accepted or used the dapivirine vaginal ring

Conclusions

- These results, along with those of a second open-label study called DREAM (presented at SA AIDS 2019), suggest **interest in**, **adherence to**, and **HIV-1 risk reduction effectiveness of** the dapivirine vaginal ring when used in an open-label setting, making the dapivirine vaginal ring a potential HIV-1 prevention option for women.

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Options counseling

CHOICE

ADHERENCE

OPEN REPORTING

- **CHOICE** and feel empowered in their decisions
- Why **ADHERENCE** is important—for herself and for the study
- That **OPEN REPORTING** is valued and without negative consequences

More is not always more

For some people, a systemic medication, perhaps particularly one they cannot easily stop/restart themselves, might not be right.

Favorable safety profile

Low levels in breastmilk and plasma

Rapidly drug gone from blood within days of ring removal

The gaps are wide

The science

Women's reality

Slide adapted from Thes Palanee-Phillips

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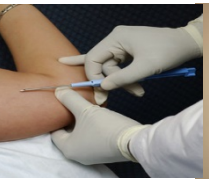
Options → Choices


Implant

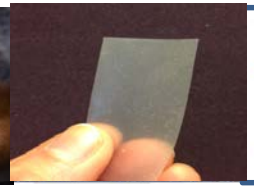

Injection


Pill


Vaginal ring


Gels


Insert

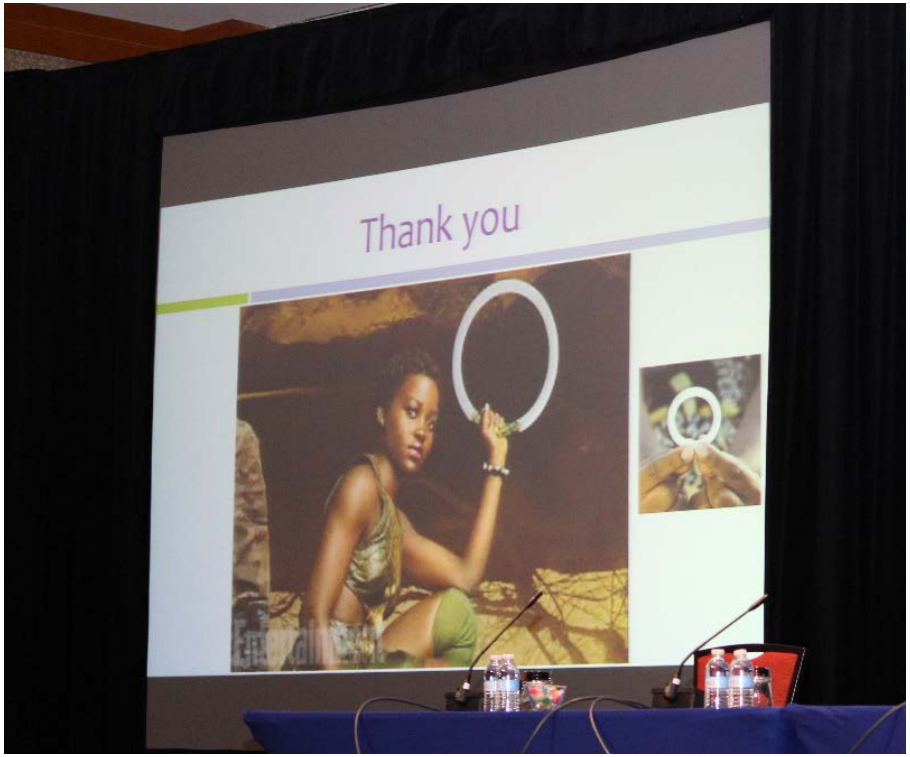

Vaginal film

Lube


Douche

Options → choices → coverage → impact

Prevention in women's hands



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Thank you

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MTN-025/HOPE Study Team

- **Leadership:** Jared Baeten (protocol chair), Thesla Palanee-Phillips (protocol co-chair), Nyaradzo Mgodi (protocol co-chair), Elizabeth Brown (protocol statistician), Ashley Mayo (FHI 360), Lydia Soto-Torres (DAIDS medical officer)
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  - **Malawi: Blantyre site (Malawi College of Medicine-John Hopkins University Research Project):** Bonus Makanani, Taha Taha
  - **Malawi: Lilongwe site (University of North Carolina Project):** Lameck Chinula
  - **South Africa: Cape Town site (University of Cape Town):** Lulu Nair, Linda-Gail Bekker
  - **South Africa: Durban eThekwini site (Centre for AIDS Programme of Research in South Africa):** Leila Mansoor
  - **South Africa: Durban – Botha's Hill, Chatsworth, Isipingo, Tongaat, Verulam sites (South African Medical Research Council):** Gita Ramjee, Anamika Premrajh, Dishiki Kalonji, Logashvari Naidoo, Nishanta Singh, Nitesha Jeenarain, Samantha Siva, Vaneshree Govender, Vimla Naicker, Zakir Gaffoor, Simone Hendricks, Shaamilah Suleman
  - **South Africa: Johannesburg site (Wits Reproductive Health and HIV Institute):** Thesla Palanee-Phillips
  - **Uganda: Kampala site (Makerere University-Johns Hopkins University Research Collaboration):** Brenda Gati, Clemensia Nakabiito
  - **Zimbabwe: Chitungwiza-Seke South, Chitungwiza-Zengeza, Harare-Spilhaus sites (University of Zimbabwe College of Health Sciences Clinical Trials Unit):** Nyaradzo Mgodi, Felix Mhlanga, Portia Hunidzarira, Zvavahera Chirenje
- **Microbicides Trials Network Leadership and Operations Center (University of Pittsburgh, Magee-Womens Research Institute, University of Washington, FHI 360, New York State Psychiatry Institute, Population Council, RTI International):** Sharon Hillier, Ivan Balan, Katherine Bunge, Morgan Garcia, Cindy Jacobson, Judith Jones, Ashley Mayo, Elizabeth Montgomery, Kenneth Ngure, Rachel Scheckter, Devika Singh, Kristine Torjesen, Ariane van der Straten, Rhonda White
- **Microbicides Trials Network Laboratory Center (Magee-Womens Research Institute, University of Pittsburgh, Johns Hopkins University):** Craig Hendrix, Edward Livant, Mark Marzinke, John Mellors, Urvi Parikh
- **Microbicides Trials Network Statistical and Data Management Center (Fred Hutchinson Cancer Research Center):** Elizabeth Brown, Jennifer Berthiaume, Marla Husnik, Karen Patterson, Melissa Peda, Daniel Szydlo
- **US National Institutes of Health:** Nahida Chakhtoura, Donna Germuga, Diane Rausch, Lydia Soto-Torres
- **International Partnership for Microbicides:** Zeda Rosenberg, Annalene Nel
- **ASPIRE & HOPE participants and their communities and Community Working Group**
- The International Partnership for Microbicides developed the dapivirine vaginal ring and provided the rings for this study. IPM receives generous support from the Danish Ministry of Foreign Affairs, Flanders Department of Foreign Affairs, Irish Aid, the German Federal Ministry of Education and Research (BMBF) through the KfW Development Bank, the Ministry of Foreign Affairs of the Netherlands, UK aid from the British people, the American people through the United States Agency for International Development (USAID) in partnership with the US President's Emergency Plan for AIDS Relief (PEPFAR), and the Bill & Melinda Gates Foundation.
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