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microbicide trials network

HOPE
HIV Open-label Prevention Extension
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High uptake and reduced HIV-1 incidence in an open-label trial of the dapivirine ring

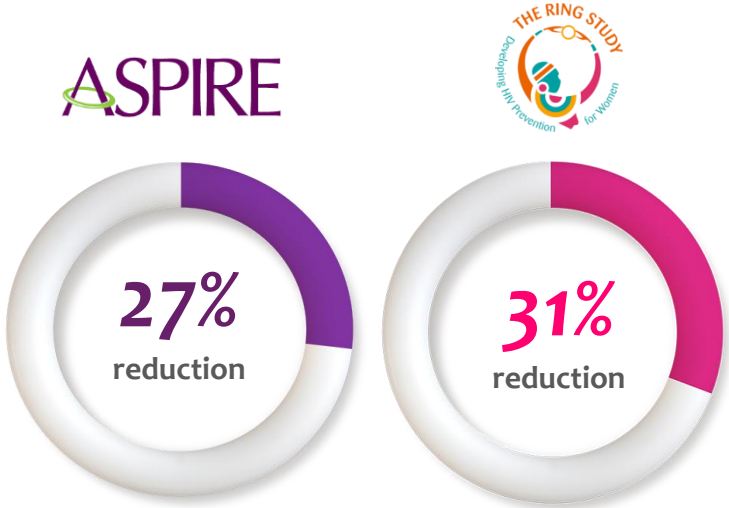
The MTN-025/HOPE Study Team

CROI 2018, Boston, USA

AVAC Webinar, March 2018

Background

Two phase III clinical trials showed that a monthly vaginal ring containing dapivirine was well tolerated and reduced HIV-1 incidence by approximately 30% compared to placebo.

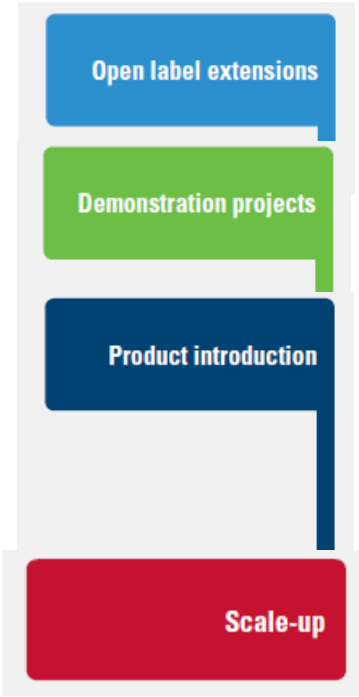


Baeten et al., Nel et al., NEJM 2016

Open-label extension studies

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

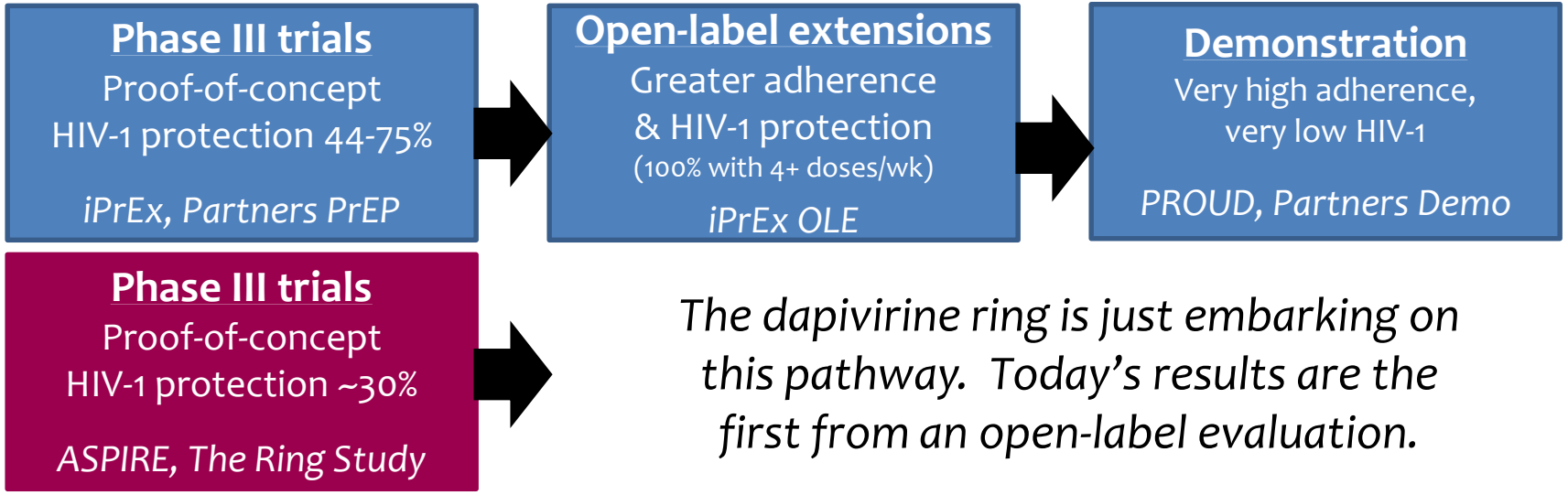
- providing ***first access*** to a new, effective product
- understanding use and effectiveness in the context of ***known efficacy***
- bridging to potential ***licensure and delivery at scale***



Graphic: AVAC

Open-label HIV-1 prevention

For PrEP, open-label extensions provided key information beyond what was learned in phase III trials, moving the field towards demonstration and scale-up:



Grant et al., NEJM 2010; Baeten et al., NEJM 2012; Grant et al., Lancet ID 2014; McCormack et al. Lancet 2016; Baeten et al., PLoS Med 2016

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MTN-025/HOPE

- MTN-025/HOPE is a multi-center, open-label, phase IIIb trial of the dapivirine vaginal ring (25 mg, replaced monthly).
- The population is HIV-1 uninfected women who had previously participated in MTN-020/ASPIRE. Women may choose to accept or not accept the dapivirine vaginal ring at each follow-up visit.
- The primary objectives of MTN-025/HOPE are to assess adherence and safety in an open-label setting.

Timeline

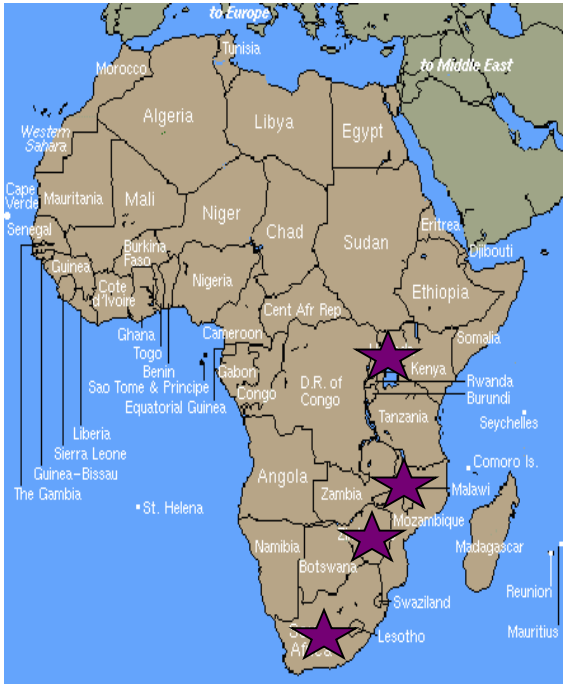
- MTN-020/ASPIRE reported its primary results in February 2016
- MTN-025/HOPE began in August 2016
- Enrollment into MTN-025/HOPE concluded in September 2017
- MTN-025/HOPE will be ongoing until ~October 2018

Ongoing Monitoring

- Throughout MTN-025/HOPE, the study team, in conjunction with an independent Study Monitoring Committee (SMC), follows:
  - **Enrollment** (characteristics, % of eligible choosing to enroll)
  - Dapivirine ring **uptake** (at enrollment and during follow-up)
  - **Adherence** (by testing residual dapivirine in returned rings)
  - Incident **HIV-1 infection**

Data for this presentation are through October 2017, the last SMC review

Enrollment



- Between August 2016 and October 2017, a total of 1407 women were enrolled, 57% of those HIV-1 uninfected at the completion of MTN-020/ASPIRE.

- Participants are from 14 sites in 4 countries:
  - Malawi (n=155, 11%)
  - South Africa (n=691, 49%)
  - Uganda (n=171, 12%)
  - Zimbabwe (n=390, 28%)

Participant characteristics

Participant characteristics defined a population at risk for HIV-1

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

Characteristics at study entry	MTN-025 HOPE	MTN-020 ASPIRE
Age, median	31 (IQR 27-37)	26 (IQR 22-31)
Age, <25 years	13%	39%
Married	53%	41%
Sexually transmitted infection (GC/CT/TV/TP)	16%	21%
Used a condom with last sex act	44%	57%

Retention and Follow-up

- Follow-up in MTN-025/HOPE is monthly for 3 months, then quarterly until 12 months.
- Through October 2017, a total of 4112 follow-up visits have been completed (reflecting 98% retention of visits expected).

Ring Uptake

- At enrollment into MTN-025/HOPE, 1299 women (92%) accepted the open-label dapivirine ring.
- During follow-up, most participants continue to choose to accept the ring:
    - 90% at Month 1
    - 89% at Month 2
    - 87% at Month 3
    - 86% at Month 6
    - 81% at Month 9

Ring Adherence

- Returned, used rings are 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.
  - Rings with levels <23.5 mg are defined as indicating *at least some* adherence during the month.
  - Thus, <23.5 mg does not necessarily indicate consistent use.
- To date, 89% of returned rings have levels <23.5 mg
  - Compared to 77% of rings in MTN-020/ASPIRE

HIV-1 incidence

- A total of 12 HIV-1 infections in 616 person-years of follow-up have been observed
  - **HIV-1 incidence = 1.9 per 100 person-years (95% CI 1.0-3.4)**

- This incidence is considerably lower than the placebo arm incidence in MTN-020/ASPIRE
  - **HIV-1 incidence = 4.5 per 100 person-years (95% CI 3.7-5.5)**

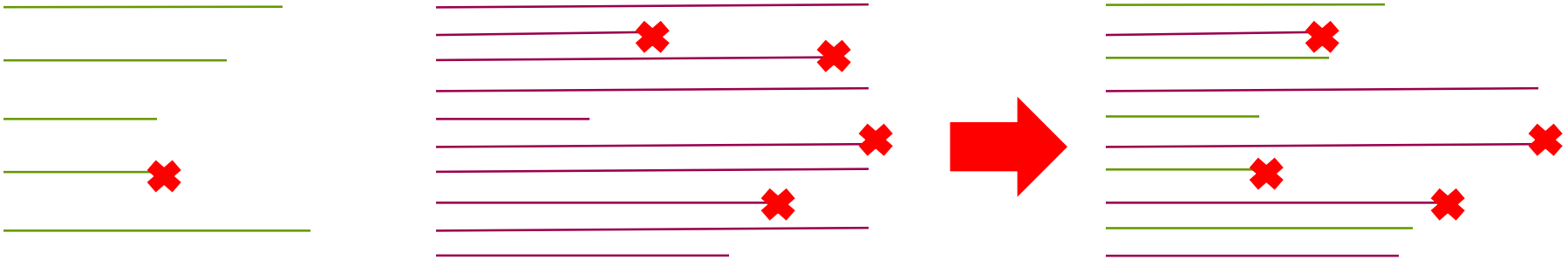
- However, the populations for MTN-025/HOPE and MTN-020/ASPIRE differ somewhat…

HIV-1 incidence comparison

- HOPE has no contemporaneous placebo group – because denying the dapivirine vaginal ring to former MTN-020/ASPIRE participants would not be ethical.
- A previous open-label study of oral TDF/FTC PrEP used historical comparison data to sample a population similar to the open-label population, creating a counterfactual comparison. (Baeten et al. Partners Demonstration Project. PLoS Med 2016)
- We took a similar approach, using data from the placebo arm of MTN-020/ASPIRE.

HIV-1 incidence comparison

- HIV-1 incidence is compared by randomly sampling individual data from MTN-020/ASPIRE.
  - Sampling a similar distribution of risk (defined by age, site, and STI)



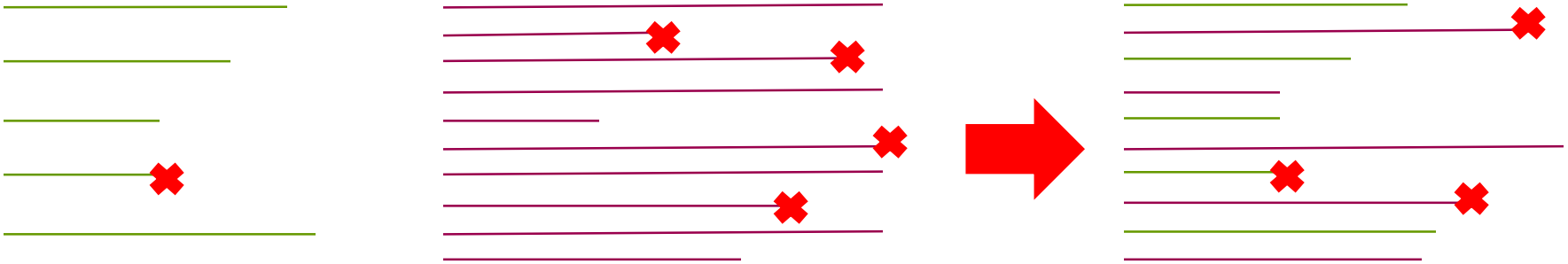
MTN-025/HOPE open-label

MTN-020/ASPIRE placebo arm

Comparison

HIV-1 incidence comparison

- This sampling was then repeated 10,000 times (bootstrapping), and a range of HIV-1 incidences in the sampled MTN-020/ASPIRE population was generated.



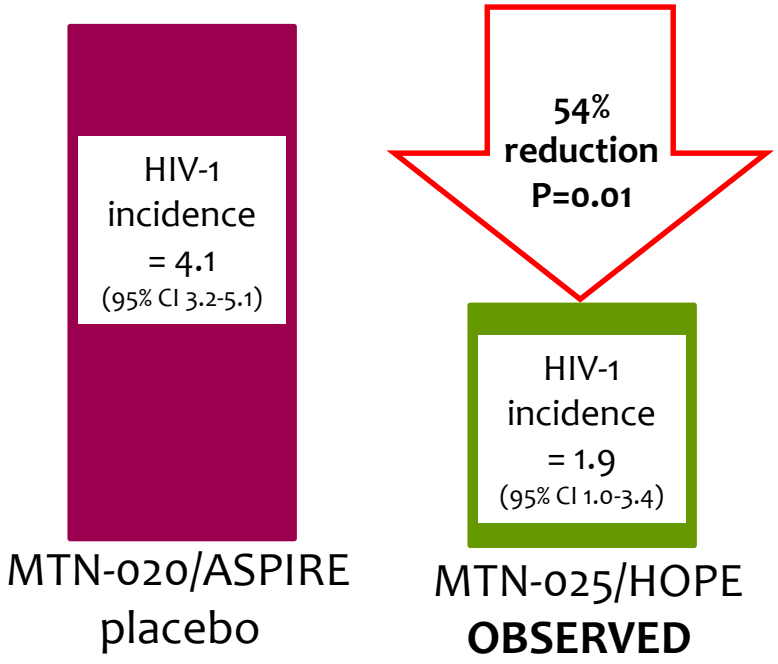
MTN-025/HOPE open-label

MTN-020/ASPIRE placebo arm

Comparison

HIV-1 incidence comparison

- The median HIV-1 incidence was 4.1 per 100 person-years in the 10,000 samplings from MTN-020/ASPIRE.
  - Thus, the expected HIV-1 incidence was **twice as high** as observed in MTN-025/HOPE.
- Across 10,000 samplings, there was none with an HIV-1 incidence of ≤1.9 per 100 person-years

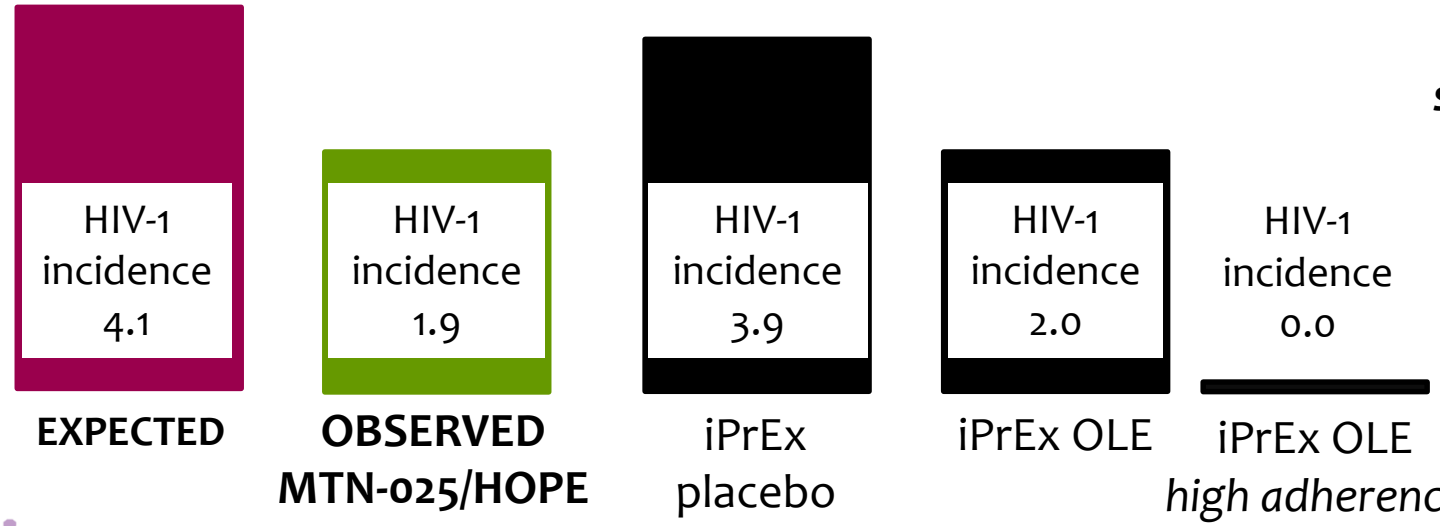


Summary

- Interim results from this open-label extension trial of the dapivirine vaginal ring indicate high uptake and adherence, and HIV-1 incidence has been half of the expected rate.
- These are the first data to assess use of the dapivirine vaginal ring and HIV-1 protection in an open-label context.

Comparison to other open-label data

- The HIV-1 incidence observed to date in MTN-025/HOPE compares favorably to that seen in prior open-label extension studies, for example iPrEx OLE:



HIV incidence in iPrEx OLE among the subset with high PrEP adherence was zero. Similar adherent subset analyses are not yet available for MTN-025/HOPE.

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What if women had PrEP instead?

- The HIV-1 incidence that would have been seen in MTN-025/HOPE if women had used TDF/FTC PrEP instead of the dapivirine ring is difficult to estimate, but potentially could range widely:

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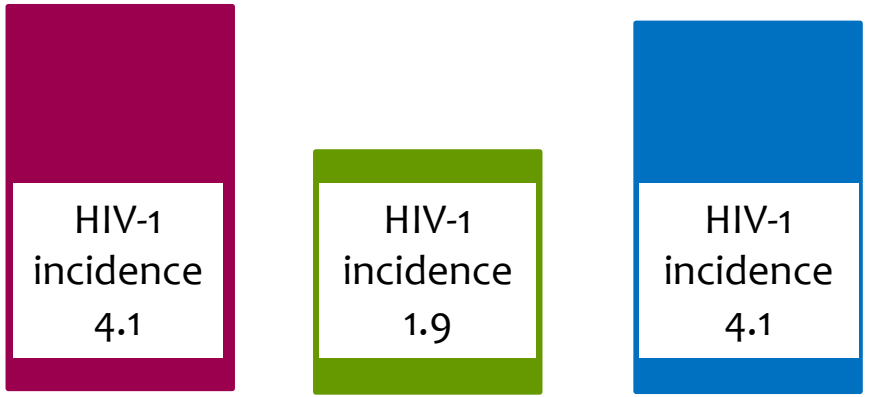

If PrEP effectiveness in women is similar to that seen in the VOICE trial (no protection, low adherence), there would be no reduction in HIV-1 incidence.

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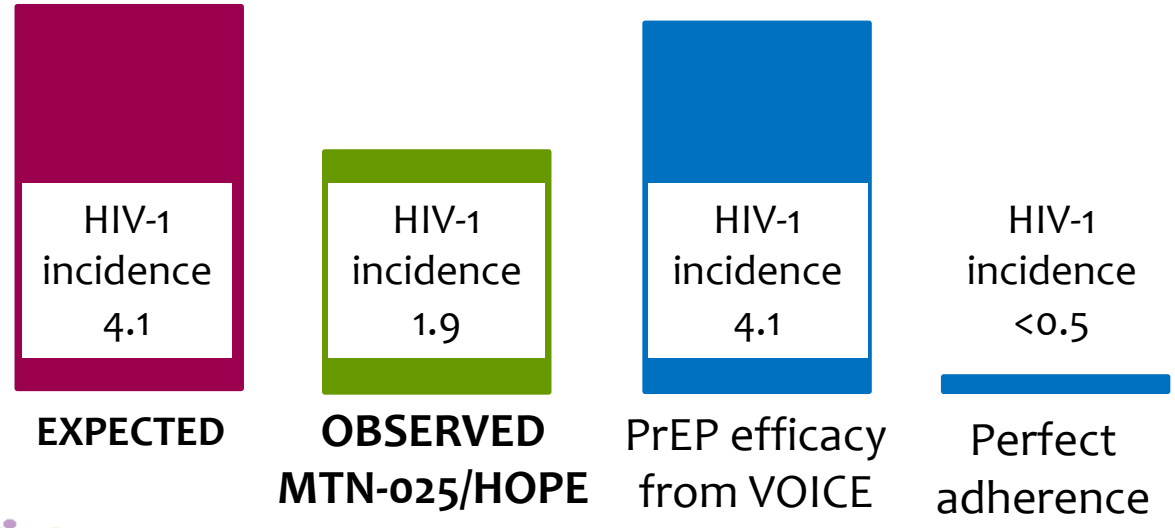

WHO guidance suggests PrEP provides >90% with perfect adherence, so if PrEP adherence was perfect, HIV-1 incidence would be very low.

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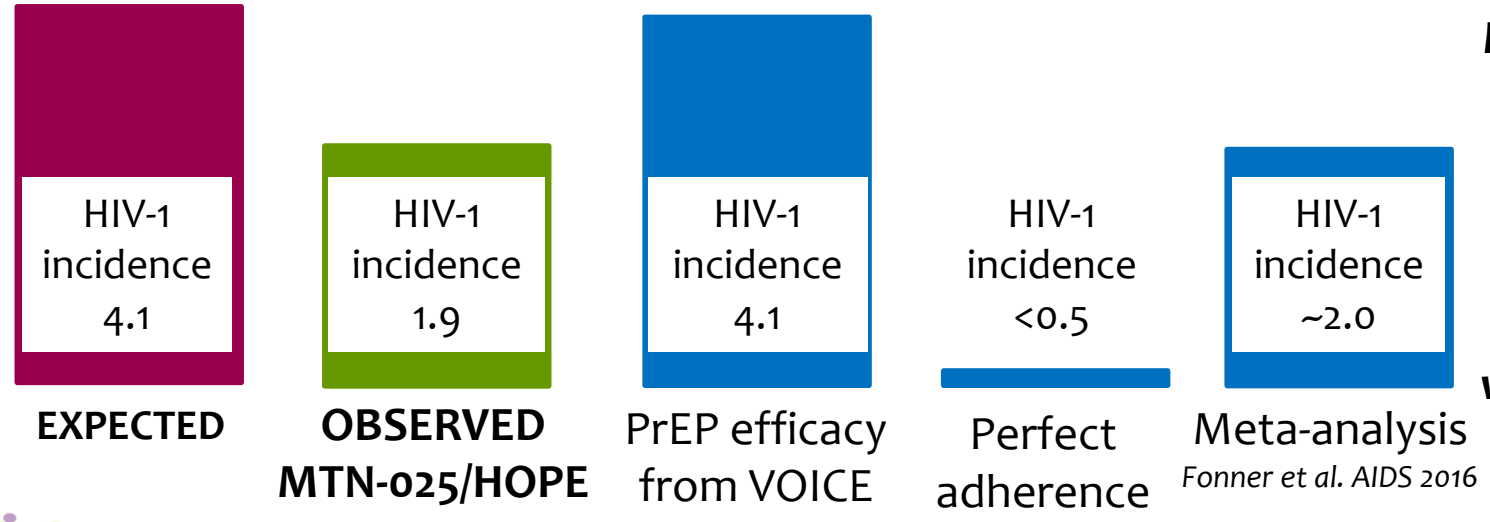

Meta-analysis of PrEP data suggests something in between, with an overall effectiveness of ~50%, similar to what we are seeing in MTN-025/HOPE.

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Limitations

- There are important limitations to this analysis:
  - There is no contemporaneous control population
    - *Withholding access to the dapivirine ring would have been unethical.*
  - All women had previously participated in MTN-020/ASPIRE and thus may have lesser HIV-1 infection risk than estimated.
    - *Substantial declines in HIV-1 incidence over time have not been seen in populations similar to this previously.*
  - MTN-025/HOPE is still ongoing.
    - *Updated findings will be available in 2019.*

Conclusions

- These interim results, along with those of DREAM, suggest important HIV-1 prevention effectiveness of the dapivirine vaginal ring when used by African women in an open-label setting.

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), Katie Schwartz & Ashley Mayo (FHI 360), Lydia Soto-Torres (DAIDS medical officer)
- **Study sites:**
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  - **Malawi: Lilongwe site (University of North Carolina Project):** Francis Martinson, 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, Umkomaas, Verulam sites (South African Medical Research Council):** Anamika Premrajh, Arendevi Pather, Logashvari Naidoo, Nishanta Singh, Nitesha Jeenarain, Samantha Siva, Vaneshree Govender, Vimla Naicker, Zakir Gaffoor, Simone Hendricks, Shaamilah Suleman, Gita Ramjee
  - **South Africa: Johannesburg site (Wits Reproductive Health and HIV Institute):** Thesla Palanee-Phillips
  - **Uganda: Kampala site (Makerere University-Johns Hopkins University Research Collaboration):** Flavia Matovu Kiweewa, 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, Ian McGowan, Ivan Balan, Katherine Bunge, Beth Galaska, Morgan Garcia, Cindy Jacobson, Judith Jones, Ashley Mayo, Barbara Mensch, Elizabeth Montgomery, Patrick Ndase, 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, Barbra Richardson, Daniel Szydlo
- **US National Institutes of Health:** Nahida Chakhtoura, Donna Germuga, Cynthia Grossman, Diane Rausch, Lydia Soto-Torres
- **International Partnership for Microbicides:** Zeda Rosenberg, Annalene Nel
- **ASPIRE & HOPE participants and their communities and Community Working Group**
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