MTN-020/ASPIRE: Beginning to End and Just the Beginning

Jared Baeten MD PhD & Thesla Palanee-Phillips PhD

for the MTN-020/ASPIRE Study Team

MTN Annual Meeting, March 2016

MTN-020/ASPIRE Study Team

- **MTN-020/ASPIRE leadership:** Jared M. Baeten (protocol chair), Thesla Palanee-Phillips (protocol co-chair), Elizabeth R. Brown (protocol statistician), Katie Schwartz (FHI 360 senior clinical research manager), Lydia E. Soto-Torres (DAIDS medical officer)
- **Study sites:**
  - **Malawi: Blantyre site (Malawi College of Medicine-John Hopkins University Research Project):** Bonus Makanani, Taha E. Taha
  - **Malawi: Lilongwe site (University of North Carolina Project):** Francis Martinson
  - **South Africa: Cape Town site (University of Cape Town):** Linda-Gail Bekker
  - **South Africa: Durban eThekwini site (Centre for AIDS Programme of Research in South Africa):** Gonasagrie Nair
  - **South Africa: Durban – Botha's Hill, Chatsworth, Isipingo, Tongaat, Umkomaas, Verulam sites (South African Medical Research Council):** Vaneshree Govender, Samantha Siva, Nitesha Jeenarain, Zakir Gaffoor, Arendevi Pather, Logashvari Naidoo, 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, Clemensia Nakabiito
  - **Zimbabwe: Chitungwiza-Seke South, Chitungwiza-Zengeza, Harare-Spilhaus sites (University of Zimbabwe-University of California San Francisco Collaborative Research Program):** Nyaradzo M. Mgodi, Felix Mhlanga, Zvavahera M. Chirenje
- **Microbicides Trials Network Leadership and Operations Center (University of Pittsburgh, Magee-Womens Research Institute, University of Washington, FHI 360, Population Council, RTI International):** Sharon Hillier, Ian McGowan, Katherine Bunge, Beth Galaska, Cindy Jacobson, Judith Jones, Ashley Mayo, Barbara S. Mensch. Elizabeth T. Montgomery, Patrick Ndase, 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 W. Hendrix, Edward Livant, Mark A. Marzinke, John W. Mellors, Urvi M. Parikh
- **Microbicides Trials Network Statistical and Data Management Center (Fred Hutchinson Cancer Research Center):** Elizabeth R. Brown, Jennifer Berthiaume, Marla Husnik, Karen Patterson, Barbra A. Richardson, Daniel W. Szydlo
- **US National Institutes of Health:** Nahida Chakhtoura, Donna Germuga, Cynthia I. Grossman, Lydia E. Soto-Torres
- **International Partnership for Microbicides:** Zeda Rosenberg, Annalene Nel
- **MTN-020/ASPIRE participants and their communities; MTN-020 Community Working Group; MTN-020 Study Monitoring Committee; DAIDS MNDSMB**

- The Microbicide Trials Network is funded by the National Institute of Allergy and Infectious Diseases (UM1AI068633, UM1AI068615, UM1AI106707), with co-funding from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development and the National Institute of Mental Health, all components of the U.S. National Institutes of Health. We are grateful to Dr. Roberta Black at NIAID for her oversight.

A Prelude

A quote from the ASPIRE qualitative component:

If we find something that helps us it will not just help me alone but it will also help future generations. This is something which is good.

Qualitative component, integrated into the trial protocol = 4 countries, 6 sites, 214 participants, 280 interviews (random & selected IDIs, serial IDIs, FGDs)

ASPIRE: Beginning to End

Safety and Effectiveness

Where We Started

- Antiretroviral medications used as prophylaxis can prevent HIV-1 acquisition. But key clinical trials of tenofovir-based prophylaxis among African women (VOICE, FEM-PrEP, FACTS 001) found **no reduction in HIV-1** because of low adherence to daily- or coitally-prescribed pills and vaginal gels.

- For women at risk of HIV-1, longer-acting methods, such as a vaginal ring, could simplify use and provide HIV-1 protection.

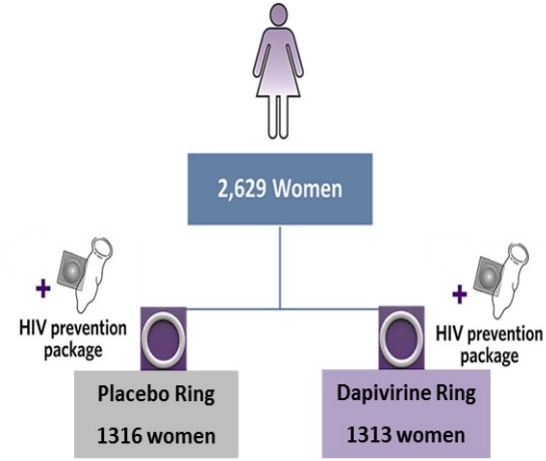
MTN-020/ASPIRE

- MTN-020/ASPIRE was a multi-center, randomized, double-blind, placebo-controlled phase III trial of a vaginal matrix ring containing the non-nucleoside reverse transcriptase inhibitor dapivirine.

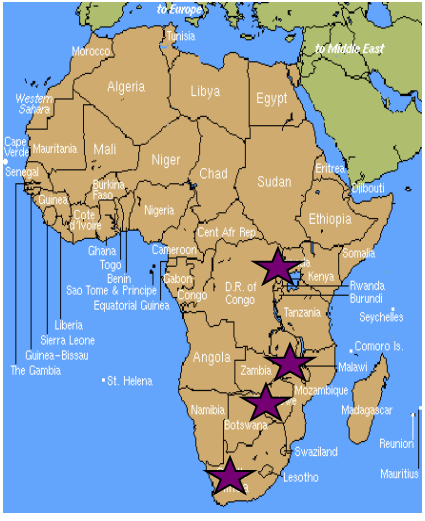
- The primary objectives were to determine the ***effectiveness*** and ***safety*** of dapivirine vaginal ring in preventing HIV-1 infection among healthy sexually active HIV-1 uninfected women.

Trial Design

- At enrollment, women were randomized 1:1 to dapivirine:placebo.
- Women were counseled to wear the ring continuously, and a new ring was provided at scheduled monthly visits.
- Follow-up was for a minimum of 1 year.
- All received a comprehensive package of HIV-1 prevention services.



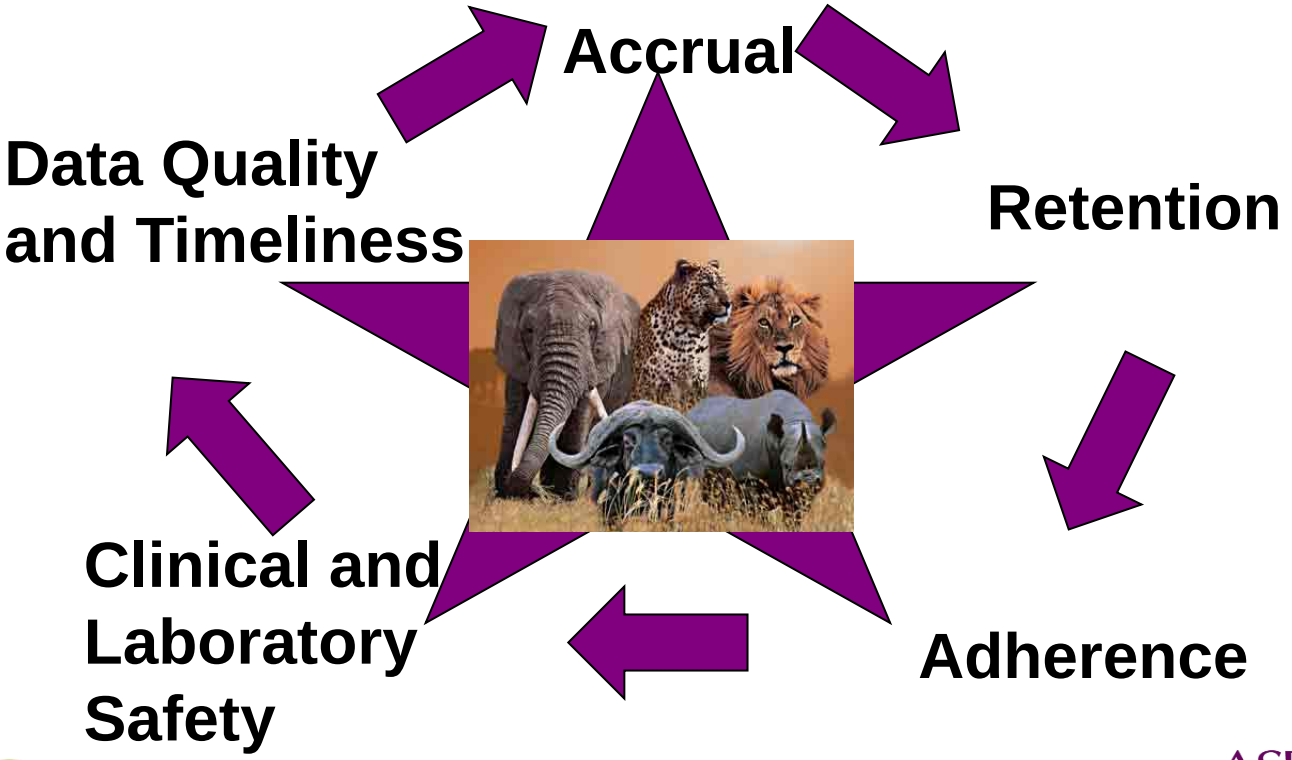
Participants



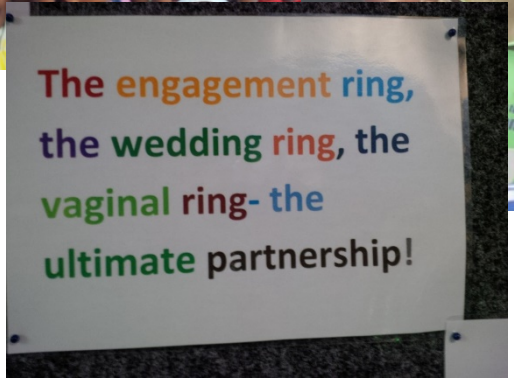
- Between August 2012 and June 2015, a total of 2629 women were enrolled and followed across 15 sites in 4 countries: Malawi (10%), South Africa (54%), Uganda (10%), & Zimbabwe (26%)

- Participant characteristics defined a population at risk for HIV-1:
  - Median age was 26 years
  - Less than half (41%) were married
  - Nearly all (>99%) reported a primary sex partner & 17% reported more than one partner
  - Nearly half did not use a condom with the last sex

Doing the Study: The Big 5



Doing the Study: Participant and Community Engagement



Quote: Acceptability

I like that the ring stays inside you and nobody can see it…. you don't have to disclose ring use to others if you want. My family doesn't know that I am using the ring. It's not something that can be seen like a necklace, it's not like a bangle that everyone can see that you are wearing. And the partner can't feel it as well.

Retention and Follow-up

- 2614 (99.4%) women completed at least one follow-up visit
- Overall, participants attended **91% of expected follow-up visits** & **97% after accounting for early withdrawals from the study**.
- A total of 4280 person-years of follow-up were accrued
  - Median follow-up = 1.6 years, maximum = 2.6 years

Primary Results

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Use of a Vaginal Ring Containing Dapivirine for HIV-1 Prevention in Women

J.M. Baeten, T. Palanee-Phillips, E.R. Brown, K. Schwartz, L.E. Soto-Torres, V. Govender, N.M. Mgodi, F. Matovu Kiweewa, G. Nair, F. Mhlanga, S. Siva, L.-G. Bekker, N. Jeenarain, Z. Gaffoor, F. Martinson, B. Makanani, A. Pather, L. Naidoo, M. Husnik, B.A. Richardson, U.M. Parikh, J.W. Mellors, M.A. Marzinke, C.W. Hendrix, A. van der Straten, G. Ramjee, Z.M. Chirenje, C. Nakabiito, T.E. Taha, J. Jones, A. Mayo, R. Scheckter, J. Berthiaume, E. Livant, C. Jacobson, P. Ndase, R. White, K. Patterson, D. Germuga, B. Galaska, K. Bunge, D. Singh, D.W. Szydlo, E.T. Montgomery, B.S. Mensch, K. Torjesen, C.I. Grossman, N. Chakhtoura, A. Nel, Z. Rosenberg, I. McGowan, and S. Hillier, for the MTN-020–ASPIRE Study Team*

MTN microbicide trials network

ASPIRE A Study to Prevent Infection with a Ring for Extended Use

Primary Results: Safety

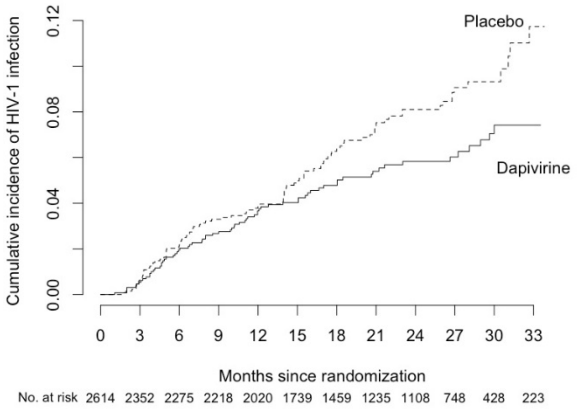
- The dapivirine ring was safe:
  - No statistically significant differences in the frequency of safety endpoints between arms (see table →)
  - No effect on pregnancy incidence
  - No increased risk of NNRTI resistance among those who acquired HIV-1

	Dapivirine	Placebo
SAE	48 (4%)	52 (4%)
Death	3 (<1%)	4 (<1%)
Grade 4 event	23 (2%)	22 (2%)
Grade 3 event	162 (12%)	151 (12%)
Grade 2 event, related	9 (1%)	7 (1%)

Primary Results: HIV-1 Protection

Overall, women in the dapivirine vaginal ring arm had a 27% reduction in the rate of HIV-1 acquisition, compared to placebo.

Primary HIV-1 effectiveness intention-to-treat analysis (15 sites)		
	Dapivirine	Placebo
# HIV-1 infections	71	97
HIV-1 incidence, per 100 person-years	3.3	4.5
HIV-1 protection effectiveness 95% CI, p-value	27% (1, 46) p=0.046	



MTN microbicide trials network

ASPIRE A Study to Prevent Infection with a Ring for Extended Use

Subgroups

- In subgroup analyses – by country, education, marital status, STIs at baseline, number of sexual partners, and partner knowledge of study participation – HIV-1 protection was similar to the overall findings.

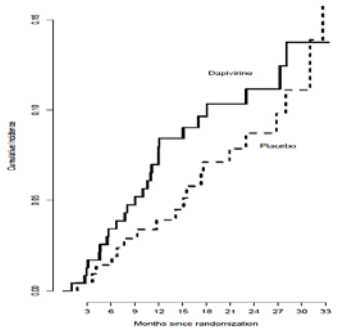
- However, HIV-1 protection differed significantly by age, with women ≥25 years demonstrating substantial HIV-1 protection while those <25 years of age no statistically significant reduction in HIV-1 incidence:

	Age <25	Age ≥25
HIV-1 protection effectiveness (95% CI)	10% (-41,43)	61% (32, 77)
Interaction p-value	p=0.02	

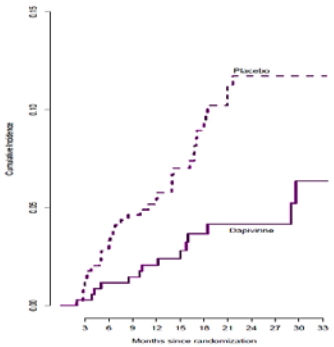
Age and HIV-1 Protection

- HIV-1 protection effectiveness was explored in additional age-stratified categories, and lack of HIV-1 protection was limited to those ≤21 years of age:

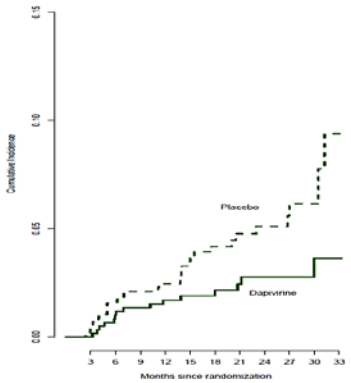
Age 18-21
-27% (-133,31)
placebo incidence 5.4%/yr



Age 22-26
56% (19,76)
placebo incidence 6.1%/yr



Age 27-45
51% (8,74)
placebo incidence 3.0%/yr



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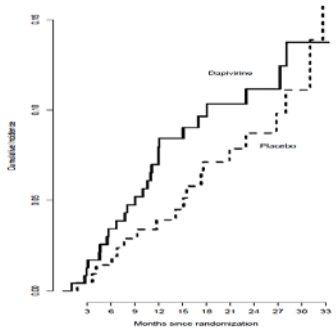

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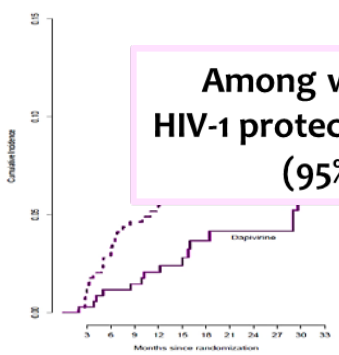

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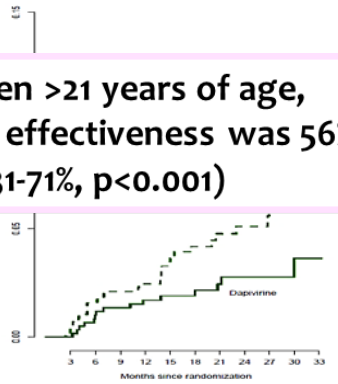


Among women >21 years of age, HIV-1 protection effectiveness was 56% (95% CI 31-71%, p<0.001)

Beginning to End: Summary

- A monthly vaginal ring containing dapivirine safely reduced incident HIV in African women.
  - Risk was reduced by ~1/3 overall and by >1/2 among those aged ≥22
- These results are the first to demonstrate HIV-1 protection by a sustained-release approach for delivery of an antiretroviral for HIV-1 prevention.

ASPIRE: Just the Beginning

So Much Learned, So Much More to Learn

Results


Terminal 5 lounges
Lounge north
BRITISH AIRWAYS
BRITISH AIRWAYS
Lounge south
ASPIRE
Aspire lounge & spa

Quote: Adherence

No, 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. Because you don't want the condom so pretend as if this is my condom because you don't want to wear a condom I am wearing mine." We never had problems about it and we never spoke about it again.

Adherence Assessment

- Two objective measures of dapivirine were used to assess adherence:
  - **Plasma.** Quarterly-collected samples: levels >95 pg/mL, indicating at least 8 hours of continuous use, defined adherence.
  - **Ring.** After the first year of the study, residual drug in returned, used rings was also measured: levels <23.5 mg (= 1.5 mg released, indicating at least some use during the month) defined adherence.

Importantly, both adherence measures could exclude those who were non-adherent but would overestimate adherence for women who used the ring only for a few hours/days prior to a clinic visit.

Adherence

- Dapivirine was detected in 82% of plasma samples at >95 pg/mL.

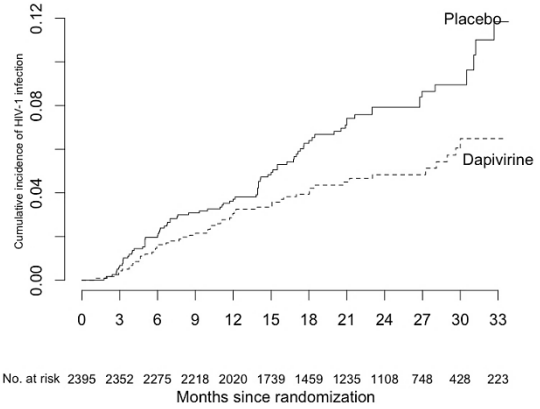
- Across all women, detection increased during the first year of use ($p<0.001$).
- Dapivirine levels in plasma and in returned rings were correlated.
- Real-time monitoring identified two study sites early in the study as having lower detection of dapivirine compared to other sites, as well as lower retention.

Unpublished data extracted

HIV-1 Protection

After excluding data from two sites with lower adherence, the dapivirine ring reduced HIV-1 acquisition by 37%.

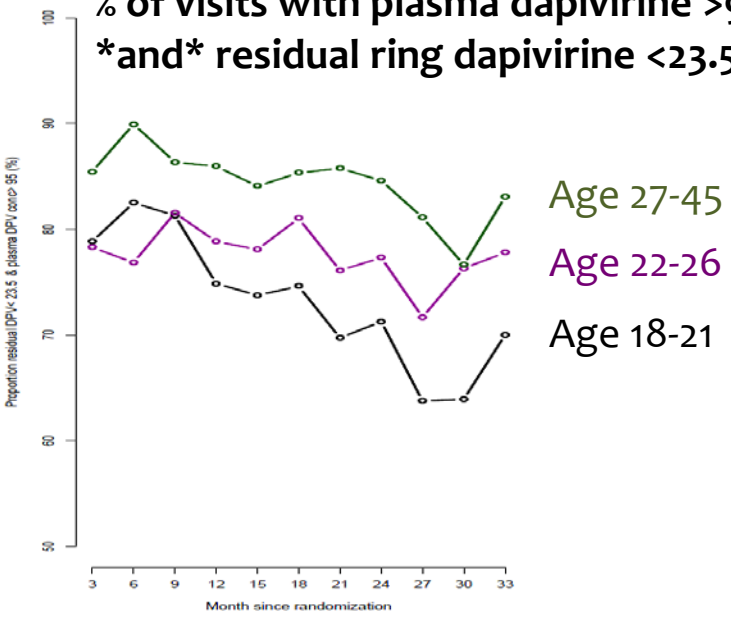
Primary HIV-1 effectiveness intention-to-treat analysis (13 sites)		
	Dapivirine	Placebo
# HIV-1 infections	54	85
HIV-1 incidence, per 100 person-years	2.8	4.4
HIV-1 protection effectiveness 95% CI, p-value	37% (12, 56) p=0.007	



Age and Adherence

- Adherence measures were statistically significantly lower among women 18-21 years compared to women >21 years

% of visits with plasma dapivirine >95 pg/mL *and* residual ring dapivirine <23.5 mg



Quote: Adherence and Age

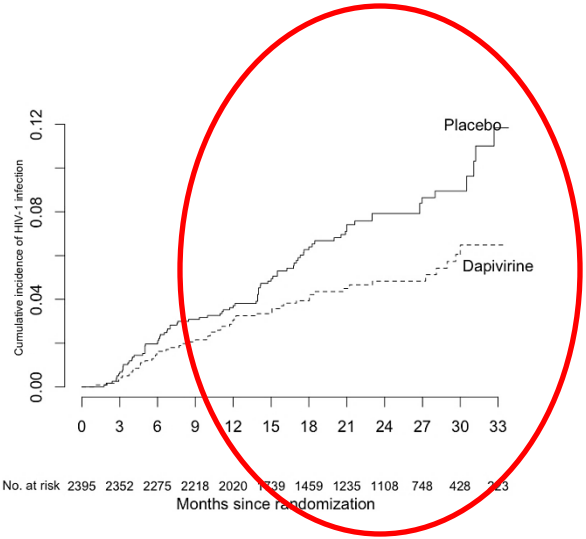
Interviewer: *We have spoken about so many things today, before we finish, I would like to ask if maybe you have anything you would like to understand, or share?*

Participant: *Yes, what I have noticed is that, most of the younger people, let me say those who are younger than me, they are not using the ring because they are saying it's just for the money; others that it's just a waste of time; they take it off when they get home and put it back again … during the week they are coming. So that is something that they need to look at.*

What is HIV-1 Protection When Adherence is High?

Preliminary results:

- Time-varying analysis of adherence vs. HIV-1 acquisition
- Ring data only
  - Cut off of <22.5 mg – more adherence than <23.5 mg
- Limited to Month 12 and beyond
  - Rings collected for everyone & higher adherence overall



HIV-1 Effectiveness with High Adherence

Unpublished data extracted

Acceptability: Women Liked the Ring

Unpublished data extracted

Ongoing Analyses (just a selection)

- Adherence
  - Impact of real-time adherence monitoring & participant engagement activities
  - Triangulation of multiple adherence measures
  - Assessment of HIV-1 protection when adherence is high
- Safety
  - Contraceptive diversification and safety of ring use with diverse methods
  - HIV-1 & STI risk related to contraceptive methods
  - Safety in early pregnancy
  - Antiretroviral resistance in seroconverters
  - Studies of biologic factors that might influence HIV-1 risk and ring protection
- Context
  - Male partners – disclosure, nondisclosure, social harm
  - Rumors and misconceptions and real-time addressing of them

Discussion – Next Steps, Next Questions

- *We are now where oral tenofovir-based PrEP was 5 years ago:*
  - Imperfect efficacy in the first results (iPrEx = 44% overall, 59% among those ≥25 years, not significant for those <25 years)
  - Experience from clinical trials only, but no real-world use where women know it works, know it is safe, and know it is not placebo.
- *What ASPIRE cannot answer:*
  - As a placebo-controlled, investigational trial, ASPIRE cannot answer whether women would have used the ring better if they had known it was effective and safe.
  - Notably, in tenofovir PrEP studies, adherence and HIV protection were much greater in open-label evaluations following placebo-controlled trials.

Open-Label Use: HOPE

- When offered an effective and safe product, will women take up the dapivirine vaginal ring, use it with high adherence and safety, and achieve HIV protection.
  - In open-label projects of tenofovir pills for PrEP, adherence and HIV-1 protection were considerably higher than in blinded, placebo-controlled trials.

- Understand acceptability and feasibility of delivery of the microbicide vaginal ring in an open-label context.
  - A unique opportunity to deliver a microbicide and build community awareness of HIV-1 prevention in women.

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

Conclusions

- In the placebo arm of this study, HIV-1 incidence was >4% per year (>6% in those aged 22-26). Effective, safe prevention options are needed for women at risk of HIV-1.

- Our results, with those of The Ring Study, for the first time provide confirmatory evidence that a microbicide can protect against HIV-1.

Quote: Adherence

It is also something to be proud of when you will tell your relatives even after 50years that, "Ah do you know that this ring being used we once-, it is us who made it to be approved for use to prevent HIV."

MTN-020/ASPIRE Team