



Setting the Stage: Overview and status of the dapivirine ring

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**Meeting the HIV Prevention Needs of Adolescent Girls and Young Women:
Stakeholders consultation on the MTN-034/IPM 045 open-label
safety and adherence study of the dapivirine vaginal ring and oral PrEP**

29 September 2016, Johannesburg

Why a vaginal ring for HIV prevention?

Longer Acting:

Used monthly or longer - sustained release of drug

May help with consistent use
Higher adherence → increased effectiveness

Ease of Use:

Flexible ring – women insert and remove the ring themselves

Little or no impact on sexual activity

Safety:

Studies have shown the ring is safe to use and has very few side effects

Privacy:

Vaginal rings can be inserted and removed in private

Rarely felt by women or male partners



Vaginal rings are used in the US and Europe to deliver contraception

The Dapivirine Ring



- Flexible silicone vaginal ring developed by the International Partnership for Microbicides (IPM)
 - A nonprofit group
- Intended to be used for a month at a time
 - Women can insert and remove the ring themselves
 - Discreet
- Slowly releases ARV drug dapivirine
- Two Phase III trials – ASPIRE and The Ring Study – conducted in parallel to enable rapid regulatory submission if ring found safe and effective

The Ring Study and ASPIRE



Conducted by the International Partnership for Microbicides (IPM)

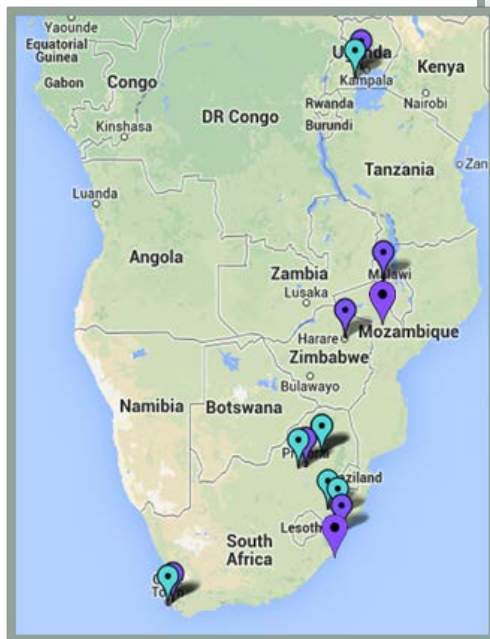
- Supported by governments, multilateral organizations and foundations
- Conducted at 7 sites in South Africa and Uganda



Conducted by the Microbicide Trials Network (MTN)

- Funded by the US National Institutes of Health (NIH)
- Conducted at 15 sites in Malawi, Uganda, South Africa and Zimbabwe

4,588 women in four countries



📍 The Ring Study: 7 Research Centres (n = 1959)

- **South Africa**
 - Kwa-Zulu Natal (3 sites)
 - North-West
 - Western Cape
 - Limpopo
- **Uganda**
 - Masaka

The Ring Study

Enrolment	Total Number Enrolled
South Africa: Kwa-Zulu Natal	1064
South Africa: North West	482
South Africa: Western Cape	97
South Africa: Limpopo	119
Uganda: Masaka	197

📍 ASPIRE: 15 NIH Clinical Research Sites (n = 2629)

- **South Africa**
 - Western Cape
 - Kwa-Zulu Natal (7 sites)
 - Gauteng
- **Uganda:**
 - Kampala
- **Zimbabwe:**
 - Harare (3 sites)
- **Malawi:**
 - Blantyre
 - Lilongwe

ASPIRE

Enrolment	Total Number Enrolled
Malawi: Blantyre	130
Malawi: Lilongwe	142
South Africa: Western Cape	166
South Africa: Kwa-Zulu Natal	1047
South Africa: Gauteng	213
Uganda: Kampala	253
Zimbabwe: Chitungwiza	448
Zimbabwe: Harare – Spilhaus	230



Study Questions **ASPIRE**

Will the
ring
PREVENT
HIV?

Is the
ring
SAFE?

Is the
ring
ACCEPTABLE?

Will
women **USE**
the ring?
(adherence)

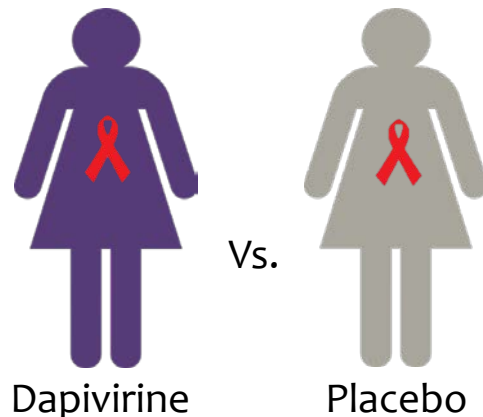
Was the ring safe?



- Dapivirine vaginal ring was shown to be very safe in both studies
- No difference between the dapivirine and placebo groups in:
 - number of adverse events (side effects / health problems) experienced
 - number of pregnancies
 - number of sexually transmitted infections
- No significant HIV drug resistance

How do we know if the ring is effective?

- We compared the number of HIV infections that occurred in the dapivirine ring group with those in the placebo ring group
- If effective, we would expect that **fewer** women in the dapivirine ring group would acquire HIV



HIV Prevention in ASPIRE and The Ring Study

ASPIRE



HIV Prevention in ASPIRE and The Ring Study

Combined, the *dapivirine ring prevented*
about $1/3$ of *HIV infections* – about *1 in 3 women*
who may have otherwise acquired HIV *did not*



= Women who might have
otherwise acquired HIV *but did*
not



= Women who *acquired*
HIV

HIV protection differed by age

In ASPIRE :

- Among **women who were 25 and older** when they enrolled, **61% fewer acquired HIV** in the dapivirine ring group compared to the placebo ring group.
- Further analysis of data found the age cutoff for HIV protection was **age 21**
 - **Age 18-21 – no protection** (and lowest adherence)
 - **Age 22-45 – 56% fewer HIV infections** among women in the dapivirine ring group vs. placebo group

HIV protection differed by age

HIV risk was *reduced by more than half (56 percent)*
among women *age 22 and older* in ASPIRE



= Women age 22 and older who
might have otherwise acquired
HIV *but did not*



= Women age 22 and older
who *acquired HIV*

Higher Adherence, Greater HIV Protection

- Recent analysis of ASPIRE data found: E Brown, IAS 2016
 - At least 56% HIV protection with evidence of adherence (based on drug levels in blood and drug left in used rings)
 - As high as 75% or greater (92 %) with most consistent use**



= Women who used the ring
most consistently



= Women who did not use the
ring or use the ring
consistently

**Women under age 25 who used most
consistently, level of protection
estimated to be 84%**

After ASPIRE and The Ring Study: HOPE and DREAM



- A core principle of ethical conduct of biomedical HIV prevention research is provision of access to proven products
- Former participants should have the opportunity to access the dapivirine vaginal ring; As the ring is not yet licensed, access must be provided through a research protocol called an open-label extension study (OLE), with no placebo ring
 - HOPE for former ASPIRE participants
 - DREAM for former Ring Study participants

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


DREAM
Dapivirine Ring Extended Access and Monitoring

What we can learn in HOPE and DREAM

HOPE and DREAM:

- Will adherence – and efficacy – be higher in the context of knowing they are using the active ring and that it is safe and can protect against HIV?
- Will providing feedback on individual adherence results help with adherence?

In ASPIRE, woman may enroll even if they do not wish to use it

- What are the reasons for not wanting the ring?
- What are the reasons women choose to accept the ring, but are not able to or do not want to use it?

Why might the ring work well as an HIV prevention strategy for some women but not for others?

Status of HOPE and DREAM

- HOPE opened for accrual July 2016
 - 5 sites now screening/enrolling
 - All sites expected to open by November, pending in-country approvals
- DREAM study started July 2016
 - All South African sites are enrolling; Uganda site pending in-country approvals



The dapivirine ring was empowering

“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. ... And the partner can’t feel it as well.”

“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.’ We never had problems about it and we never spoke about it again.”

Dapivirine Ring Studies Roundup

- **HOPE and DREAM** – Help understand whether women's adherence is greater with knowledge of efficacy (enrolling)
- **MTN-032**: understanding factors influencing adherence in ASPIRE and HOPE (enrolling Stage 1 – former ASPIRE ppts)

And....

- **MTN-034/REACH**: understand safety and adherence of ring (and oral PrEP) in young women, and preferences for either

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Setting the Stage: Overview and status of oral PrEP in women

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PrEP: Pre-Exposure Prophylaxis



- Studies have proven that daily use of an ARV tablet (PrEP) is very effective in preventing HIV.
- However, PrEP studies among African women did not have similar results due to low adherence to the products (tablets or gels).



What do we know about PrEP?

The basics about PrEP

- Daily oral PrEP is safe.
- PrEP works if you take it. Adherence is essential.
- PrEP is highly protective in both men and women.
- People with high rates of HIV risk behaviors can also be highly adherent to PrEP.
- Resistance to PrEP drug(s) can arise if the person starts PrEP with undiagnosed HIV and/or if he or she acquires HIV and keeps on taking PrEP afterwards.
- Daily dosing is recommended.

Does PrEP work in young women?

- Yes, if taken. Partners PrEP Study efficacy about 70%
 - No difference in efficacy between women younger and older than 25 years/recent STIs/ partner with high VL
 - Drug detected in 82% of pk samples
- No efficacy with low uptake in VOICE & FEM-PrEP
 - <30% with drug detected
 - Low risk perception and possible challenge with a daily pill regimen in FEM-PrEP (Van Damme NEJM 2012)
 - Fear of taking PrEP in VOICE: concern with side effects and social stigma

What we learned about PrEP in young African women

- Young women & single women had lower PrEP adherence in placebo-controlled studies

Findings about PrEP adherence from qualitative research

- Low adherence to study product in VOICE & FEM-PrEP trials:
 - Accuracy of risk perception
 - Uncertainty when randomized to placebo or product of unknown efficacy
 - Influence of other women in the trial
 - Concerns: stigma, side effects, partner's reaction, & losing benefits if disclose non-adherence

van der Straten et al PLoS One 2014; Cornelli et al AIDS 2015

Young women can adhere to PrEP

High adherence to *open label* PrEP among young women in Cape Town in HPTN 067/ADAPT

- 179 women randomized to one of 3 arms in Cape Town (daily; twice weekly + post sex; event-driven)
 - **79% adherence, based on drug levels, at 30 weeks among women in daily arm**
 - Young women equally as adherent as older women
- Daily dosing may foster better habit formation and provide the most forgiveness for missed doses
- Adherence decreases at 6 months; need adherence support & reevaluate motivations for continuation

Consider the comparison....

	PrEP	Oral contraceptive pills
Initial approval	Treatment (of HIV)	Treatment (menstrual disorders)
What it offers	Individual control over prevention	
Concerns	Sexual behavior, adherence	
Perfection	Perfect use is the ideal, but real-world use has real individual and population-level benefits	



And the pill isn't for everyone

Myers and Sepkowitz A pill for HIV prevention: déjà vu all over again? CID 2013



IS PrEP WANTED?

Next steps for implementation of PrEP for young African women

- Use oral PrEP as an ‘exemplar’ for understanding adoption of biomedical HIV prevention among young African women
- PrEP as part of combination HIV prevention including partner testing, condoms, behavioral interventions, and FP
- Social marketing to promote PrEP as a healthy choice
- Learn from early adopters: who chooses to use oral PrEP, how well do they adhere, and how long do they use PrEP?
- Evaluate effect of drug level feedback & incentives
- Pilot delivery models for integrated reproductive health and HIV prevention services

Moving forward with efficacy & effectiveness data

- PrEP as part of combination HIV prevention for young African women in PEPFAR DREAMS initiative
- WHO guidelines Sept 2015
 - Oral PrEP with TDF should be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination prevention approaches



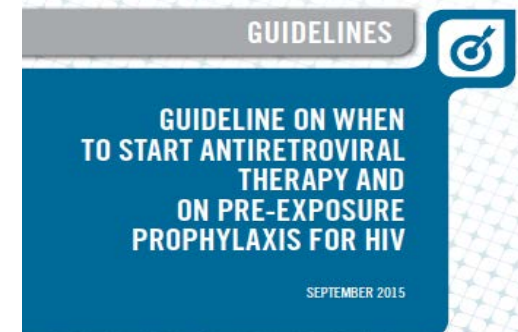
**WORKING TOGETHER FOR AN
AIDS-FREE FUTURE FOR GIRLS**



PEPFAR

BILL & MELINDA
GATES foundation

Nike Foundation



We need to learn from delivering what works now

- Learn about reaching & motivating populations
- Addressing user & provider barriers in delivering primary HIV prevention strategies
- While evaluating new prevention strategies, in parallel
 - Because PrEP is not for everyone

PrEP Summary

- Highly effective when used consistently
- Good safety
 - there are rare risks of effects on kidney that are reversible and can be monitored
- Must not be HIV infected to avoid resistance
 - Regular HIV testing to determine not infected
 - Resistance has not been an issue