

# Developing *Options* to Improve *Choices* in HIV Prevention

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# Options vs Choices

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- **Options** are the things and **choices** are our decision.
  - A condom is a prevention option
  - Using condoms is a choice (but often not a choice that women gets to make)
- **Options** are fixed and **choices** aren't.
- *Option is a noun for a thing and choice is a noun for your decision.*
- Wearing a mask to reduce the spread of SARS-CoV-2 is an **option**. Deciding to wear a mask is a **choice**.

# The right to vote provided the first opportunity for women to choose their leaders in the US

- My grandmother born in 1899
- Named Sigurbjorg Edvaldsdottir at birth and immigrated from Iceland at two years of age
- Chose the name Bertha in first grade (after a favorite teacher)
- Graduated from high school in 1917
- **Granted the right to vote in 2020**
- Attended Linfield College, graduating in 2025, first in her class



# How do we misinterpret Options vs Choices?

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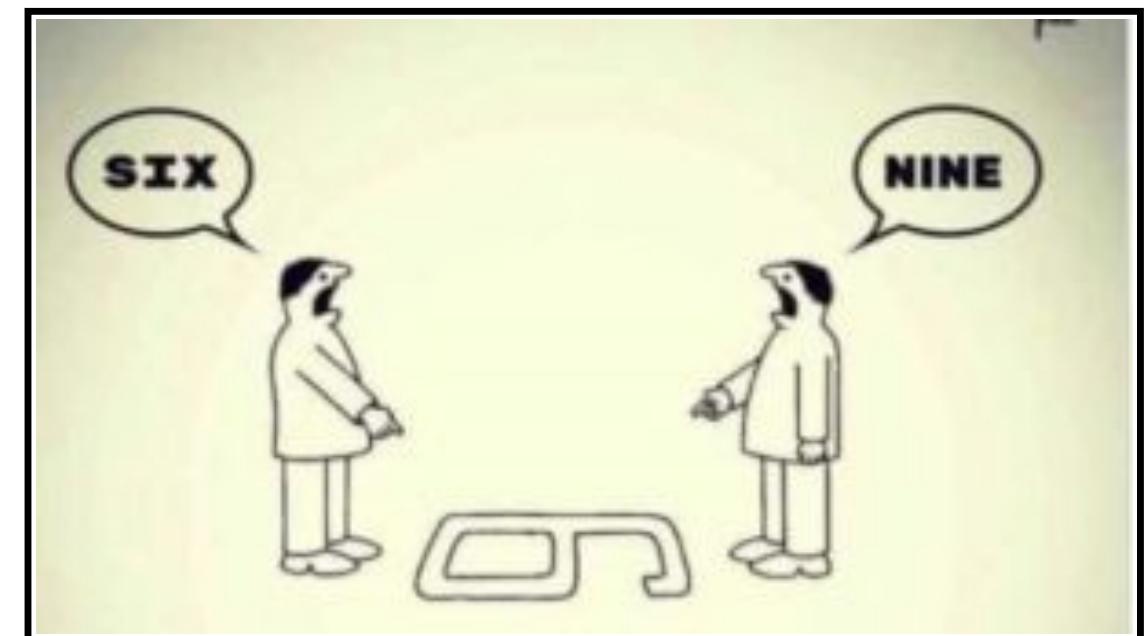
- Contraception:
  - Although there are many contraceptive available globally, many family planning settings are understaffed and under resourced
  - Although contraceptive implants and intrauterine devices are extremely effective, their implementation requires skilled providers
- What is available across SubSaharan Africa?
  1. Injectables
  2. Oral contraceptives
- With limited *options*, many women *choose* injectables

# How do we misinterpret Options vs Choices?

Two possible interpretations of the same data (predominant selection of injectable contraceptives by women in SSA):

1. Women really love injectable contraceptives
2. Women only had 2 options (OCs or DMPA), so they chose injectables

*Same information,  
different interpretations*

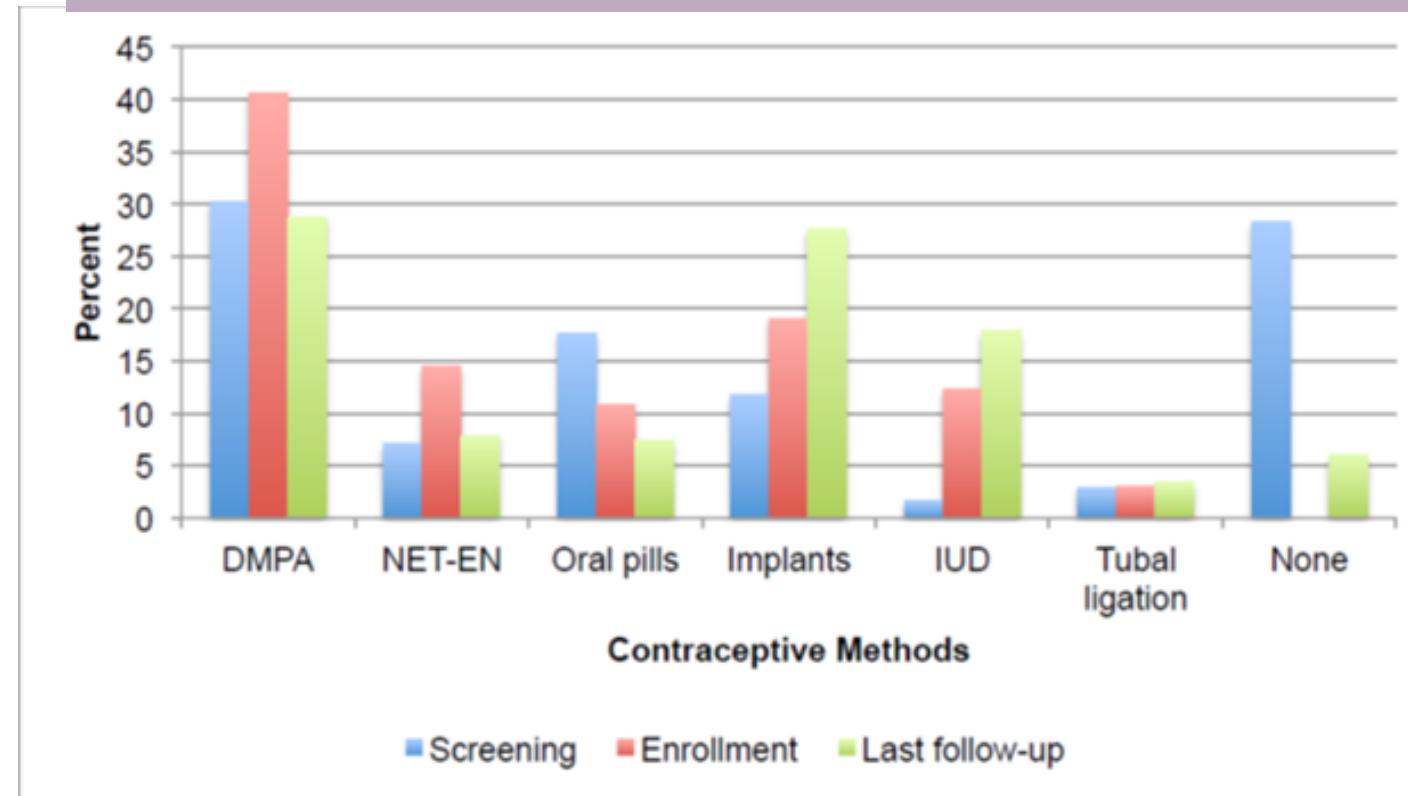


# What Happens if More Options are Provided in Contraceptives?

In multiple studies, most women used injectable contraceptives, OCs or no contraception

	DMPA	COC	IMPLANTS	IUD
HPTN 035	22%	72%	4%	<1%
VOICE	71%	22%	5%	<1%
CAPRISA 004	83%	15%	0%	0%
FEM PrEP	55%	43%	<2%	<2%
PARTNERS PrEP	27%	7%	5%	9%

In the ASPIRE study of the dapivirine ring in 2600 women, at least 4 contraceptive options were offered to every study participant, and women's choices diversified and 95% used contraception!





# Why Do Options Matter in HIV Prevention?

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- “Deciders” look at new technologies or new drugs to determine what men and women at risk of HIV need
  - It is tempting to decide that one approach or strategy will be the best because it is simpler and cheaper to offer fewer options
- Little attention has been paid to what men and women who “fall through the HIV prevention gaps” want, and whether providing more *options* will result in different (better) prevention *choices*

# Options for Prevention of HIV Sexual Transmission

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- Abstinence (often not under receptive partner control)
- Condoms (controlled by insertive male partner)
- Circumcision (only for men)
- Knowing partner status and if HIV positive, virally suppressed
- Oral PrEP: Truvada for men and women; Descovy only for men and trans women
- Injectable Cabotegravir: proven but not yet approved for use in men and trans; data not available yet cis women

# Women, especially young women, account for a large proportion of new infections

**UNAIDS  
DATA  
2020**

Eastern and southern Africa

Remaining population  
72%

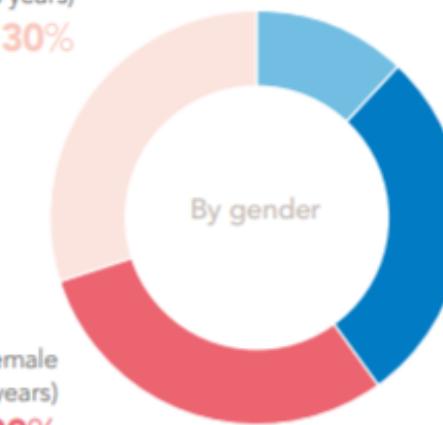


Male (15–24 years)  
12%

Female (15–24 years)  
30%

Male (25–49 years)  
28%

Female (25–49 years)  
30%



“Gender-based violence and inequalities continue to drive the epidemic. In sub-Saharan Africa, young women and adolescent girls accounted for one in four new infections in 2019, despite making up about 10% of the total population.”

# Why Topical Prevention (Microbicides)?

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- Receptive sexual partners have a higher vulnerability to HIV from vaginal and anal sex
- Receptive partners often do not control condom use.
- Microbicides deliver high levels of drugs to the site of infection (cervicovaginal mucosa or rectum) with lower systemic exposure to drugs than oral PrEP, which in turn reduces risk of systemic toxicity
- Topical products can be less “medicalized”- they are not treatments and could be provided in community settings

# More Options → Better Choices



Implant



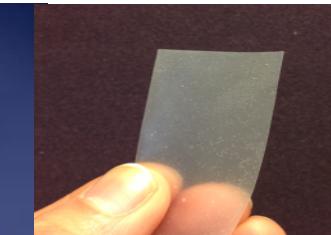
Injection



Pill



Vaginal ring



Vaginal  
film



Insert



Douche



Lube



Topical HIV Prevention Options

Options → choices → coverage → impact

# Tenofovir Gel

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- Water based gel containing 1% tenofovir
- Shown to be very effective at blocking infections in the monkey model
- Several phase 1 studies showing safety

- Clinical trial evaluated tenofovir gel applied before and after sex in a phase 2 study in Durban, S Africa showed an efficacy of 39% overall ( $p=0.04$ )
- 54% reduction in HIV among women with higher adherence (Science 2010)



# The NEW ENGLAND JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

FEBRUARY 5, 2015

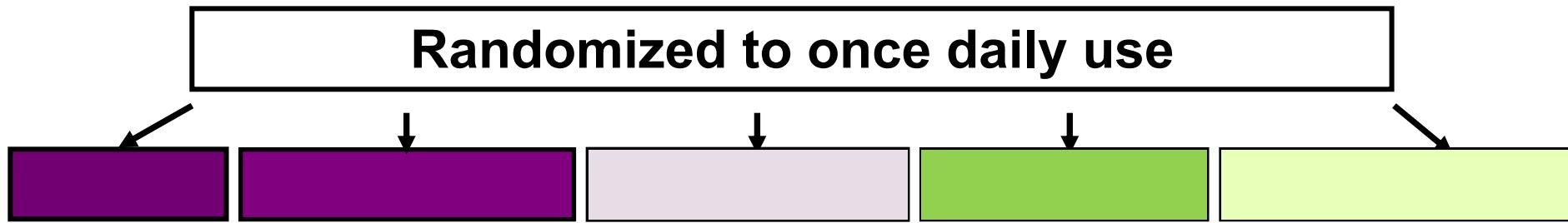
VOL. 372 NO. 6

## Tenofovir-Based Preexposure Prophylaxis for HIV Infection among African Women

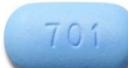
Jeanne M. Marrazzo, M.D., Gita Ramjee, Ph.D., Barbra A. Richardson, Ph.D., Kailazarid Gomez, M.P.A., Nyaradzo Mgodi, M.Med., Gonasagrie Nair, M.B., Ch.B., M.P.H., Thesla Palanee, Ph.D., Clemensia Nakabiito, M.Med., Ariane van der Straten, Ph.D., Lisa Noguchi, M.S.N., Craig W. Hendrix, M.D., James Y. Dai, Ph.D., Shayhana Ganesh, M.Med., Banningi Mkhize, M.B., Ch.B., Marthinette Taljaard, B.S., Urvi M. Parikh, Ph.D., Jeanna Piper, M.D., Benoît Mâsse, Ph.D., Cynthia Grossman, Ph.D., James Rooney, M.D., Jill L. Schwartz, M.D., Heather Watts, M.D., Mark A. Marzinke, Ph.D., Sharon L. Hillier, Ph.D., Ian M. McGowan, M.D., and Z. Mike Chirenje, M.D., for the VOICE Study Team\*

# VOICE Study (Sept 2009- Aug 2012)

5,029 women enrolled At 15 sites in South Africa, Uganda, Zimbabwe  
Aged 18-45; HIV-negative, sexually active, contracepting, non-pregnant



## Final results: products safe but not effective

Active products	Effectiveness	Hazard Ratio	95% confidence interval
Oral TDF 	-49%	1.49	0.97-2.29
Oral FTC/TDF 	-4%	1.04	0.73-1.49
Vaginal TFV 	14.5%	0.85	0.61-1.21

# VOICE Product Adherence

Marrazzo, NEJM 2015

	Truvada Tablet	Tenofovir Tablet	Tenofovir Gel
Returned Pill or Applicator Counts	92%	87%	86%
Self Report	<u>91%</u>	90%	90%
Drug Detected: Blood	29%	28%	23%
Hair (subset) (Koss, 2017, AHRV)	55%	ND	ND

- Baseline characteristics (plasma TFV detection):
  - age older than 25 years ( aOR 1.62; 95% CI, 1.12-2.34 )
  - being married (aOR 2.24; 95% CI 1.12- 4.49)
  - independent income (aOR 1.42; 95% CI 0.98-2.07)
  - multiparity (aOR 1.84; 95% CI 1.26 to 2.69)
- These characteristics were also associated with **lower risk of HIV-1 acquisition** in both placebo arms, suggesting that more adherent participants had lower HIV risk than those less likely to adhere

# Was Tenofovir Gel Effective in Those Who Used It?

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- Tested the blood samples from women in the tenofivir gel group and grouped women as “users” or “non-users” based on the presence of tenofovir in the plasma sample obtained at the 1<sup>st</sup> quarterly visit
- Women in the TFV gel arm with detectable TFV had a significantly lower likelihood of HIV acquisition relative to those with no TFV detected:
  - **HIV incidence 1.9% vs 6.1% (adjusted HR 0.34; 95% CI [0.13,0.87], p-value 0.025)**
  - Limitations of secondary analysis

# HIV PREVENTION CLINICAL TRIAL SITE



# What Women Told Us

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- They highly value the reproductive health services which we provide
  - Contraception
  - STI and HIV screening
  - Cervical cancer screening
- The youngest women are the least able to balance investigational product risks vs benefits, and are the most susceptible to peer advice regarding safety of products
- Having a placebo leads to greater uncertainty about whether to adhere to study products
- There is stigma associated with use of ARVs
  - It can be difficult to explain to a partner or family member why it is being used





# PrEP is rolling out in women.....

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- We are learning that lots of women start PrEP but persistence is hard for many women

## HPTN 082: Evaluation of daily oral PrEP as a primary prevention strategy for young African women



### Study Population

Uninfected women  
Ages 16-25 yrs

Johannesburg & Cape Town,  
South Africa  
Harare, Zimbabwe

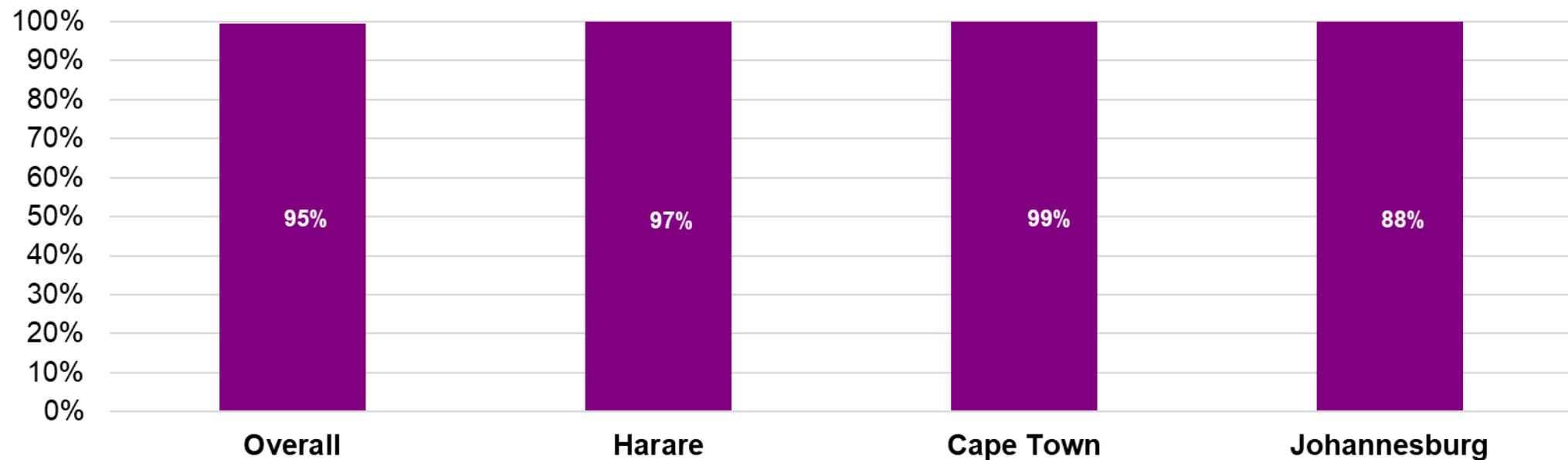
### Target Enrollment

- 400 women who accept PrEP at enrollment
- ≤ 200 women who decline PrEP at enrollment

Eligibility criteria: Sexually active in past month; VOICE risk score  $\geq 5$ ; interest in PrEP; access to mobile phone; hepatitis B seronegative

# HPTN 082: PrEP Uptake was High

PrEP uptake overall and by site



# Adherence Measures

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- Primary adherence outcome: TFV-DP  $\geq 700$  fmol/punch at 6 months
- Predictors of high adherence at 6 months (TFV-DP  $\geq 700$  fmol/punch)
  - Logistic regression, adjusted for site
- Persistence: Detectable TFV-DP or plasma TFV at 3, 6 & 12 months

# Tenofovir levels at 3, 6, & 12 months

	3 months	6 months	12 months
<b>Tenofovir diphosphate (TFV-DP), DBS</b>	<b>N=371</b>	<b>N=363</b>	<b>N=347</b>
Detectable	83.6%	56.5%	31.4%
$\geq 700$ fmol/punch* (among those with detectable TFV-DP)	24.8%	20.9%	8.6%

**Lots of enthusiasm for starting PrEP in young women.  
Very low levels of persistence at 6 and 12 months**

# Vaginal Rings for Sustained Delivery of ARV Drugs

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## The idea:

It will be easier to use – put it in and forget about it for a month

- The dapivirine ring was evaluated in two Phase III trials – ASPIRE and The Ring Study – that together involved 4,279 women in Africa
- Ring was developed by the International Partnership for Microbicides (IPM) through royalty-free license from Janssen



## Status:

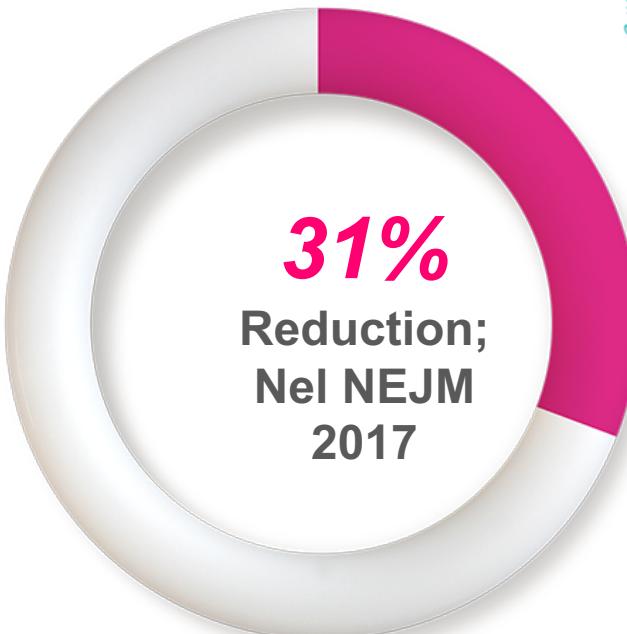
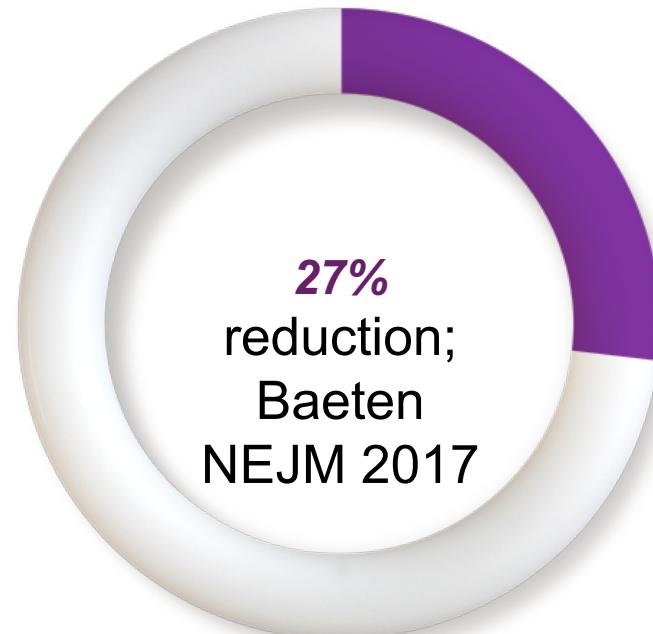
- Open label follow on studies completed
- Regulatory packages just reviewed by EMA and will be submitted to FDA later this year

*Drug is in the ring itself and released continuously over a month*



# HIV Incidence in ASPIRE and The Ring Study

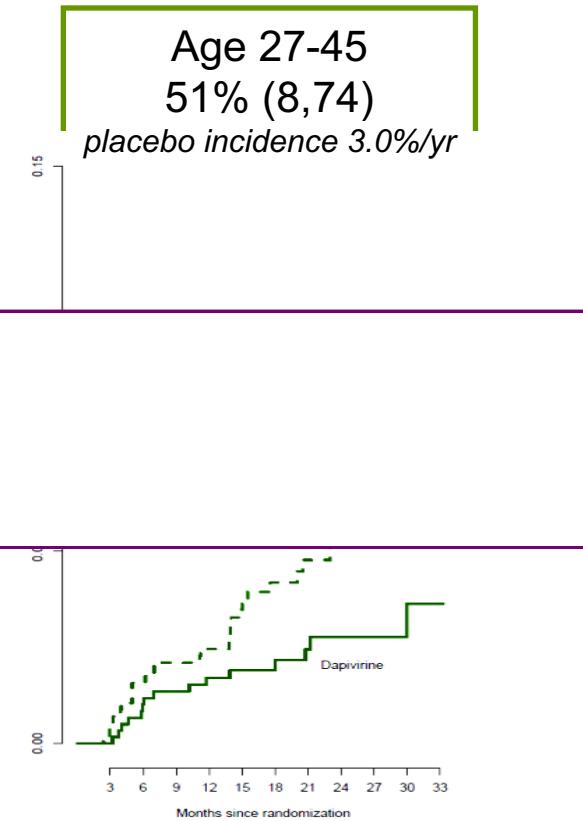
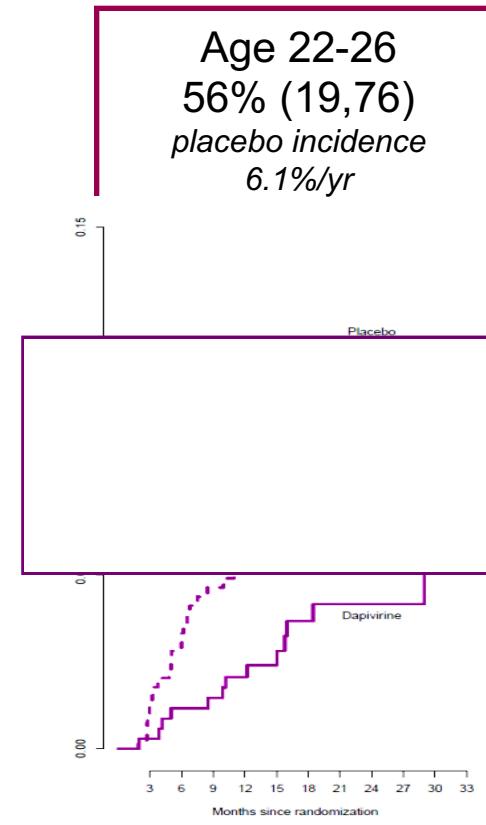
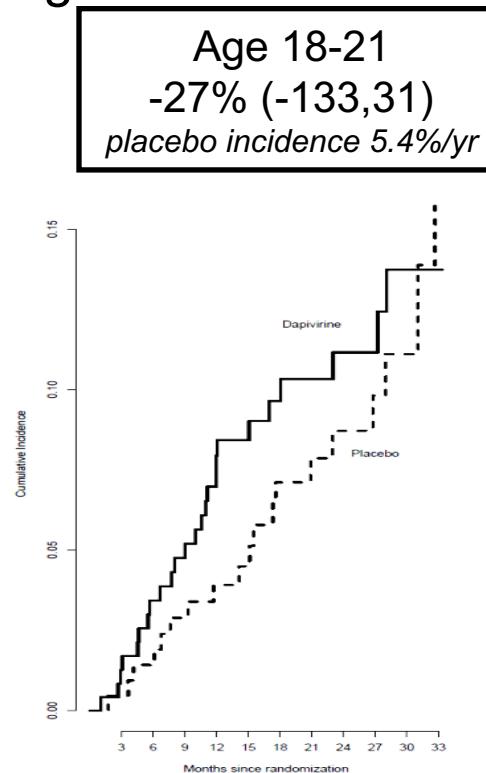
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Moderate efficacy and extremely safe

# ASPIRE 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  $\leq 21$  years of age:



# MTN-025/HOPE Open Label Extension Study

- Multi-center, open-label, phase IIIb trials of the dapivirine vaginal ring (25 mg, replaced monthly).
- Population was HIV-1 uninfected women who had previously participated in the randomized trials.
- Women could choose to accept or not accept the dapivirine vaginal ring at each follow-up visit.
- The primary objectives were to assess adherence and safety in an open-label setting.



## HIV-1 incidence 4.4

# HIV-1 incidence 2.7

# Expected MTN-025/HOP

# OBSERVED MTN-025/HOPE

# HOPE 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.

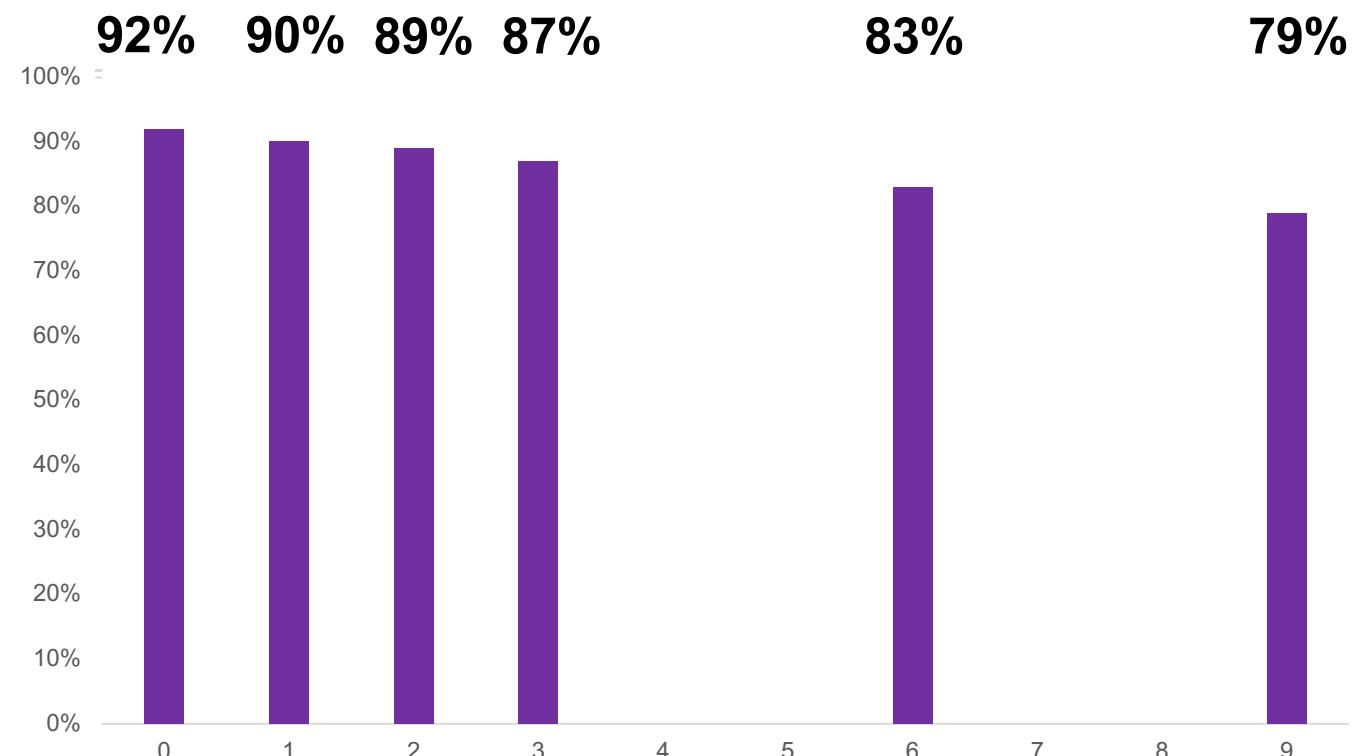
MTN-025 Visit Month	Retention, n (%)
Month 1	1428 (98%)
Month 2	1422 (98%)
Month 3	1427 (99%)
Month 6	1404 (98%)
Month 9	1379 (97%)
Month 12	1376 (97%)



# Ring Uptake and Persistence

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- At enrollment, 1342 women (92%) chose to use the dapivirine vaginal ring.
- Persistence was high: the majority continued to accept the ring.
- 



# Ring Persistence was High in HOPE

- In MTN-025, women were offered the option of using the dapivirine vaginal ring – the vast majority initially chose the ring and most continued throughout 12 months.
  - 73% of women (936/1279\*) accepted the ring for all 12 months of follow-up
- This high level of persistence compares favorably to recent open-label studies of FTC/TDF PrEP among women

# Regulatory Pathway for the Dapivirine Ring

- EMA Submission under Article 50 for WHO prequalification
  - Does not allow for marketing in the EU
  - Provides assurance to LMIC regulators that the product meets risk/benefit standards
  - Expedites in country approvals
  - First country approvals could occur in mid 2021
- US Food and Drug Administration
  - Pathway followed for other prevention products (Truvada, Descovy) to date
  - Would allow for use in the US
  - Would support use of product for use with PEPFAR funding

# Regulatory Status of the Dapivirine Ring



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

Vaginal ring to reduce the risk of HIV infection for women in non-EU countries with high disease burden

News 24/07/2020

EMA's human medicines committee (CHMP) has adopted a positive opinion for Dapivirine Vaginal Ring (dapivirine) used to reduce the risk of infection with the human immunodeficiency virus type 1 (HIV-1), in combination with safer sex practices when oral pre-exposure prophylaxis (PrEP) is

# Next Steps for the Dapivirine Ring

## Regulatory Process

IPM has received a positive through European Union; African and US regulatory submissions underway

## Additional Research

Safety studies of ring and PrEP among **adolescent girls, pregnant and breastfeeding women in Africa**

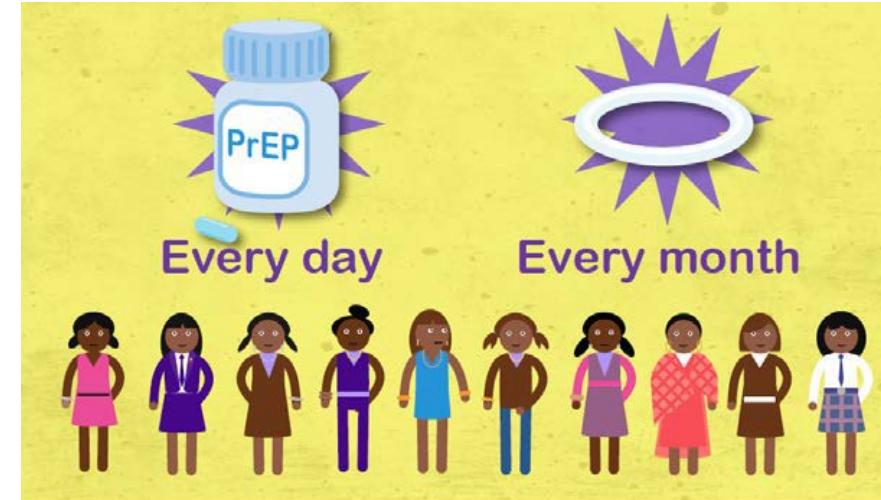
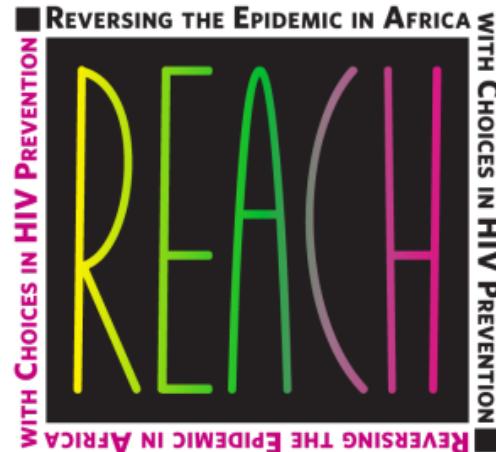
## Potential Introduction in priority countries



INTERNATIONAL  
PARTNERSHIP FOR  
MICROBICIDES

# Why REACH?

We need to see that PrEP and the ring can work for and be made available to adolescent girls and young women  
...How?



REACH aims to:

- Learn how to help young women use these methods better so they have the benefit of protection
- Collect more information about the safety of PrEP and the ring – including in girls under age 18 – so drug regulatory authorities can consider expanding approval



Be attractive!  
Have FUN!  
Do what I want!



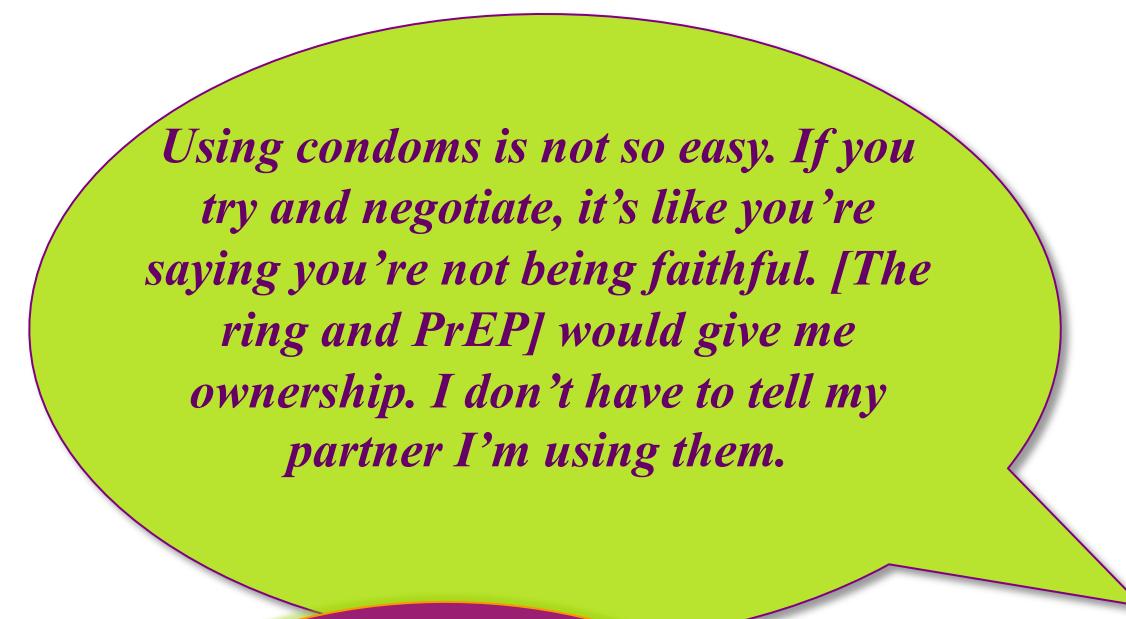
**DON'T** have sex.  
**USE** Condoms!  
**GET** Contraceptives.  
**TAKE** PreP!



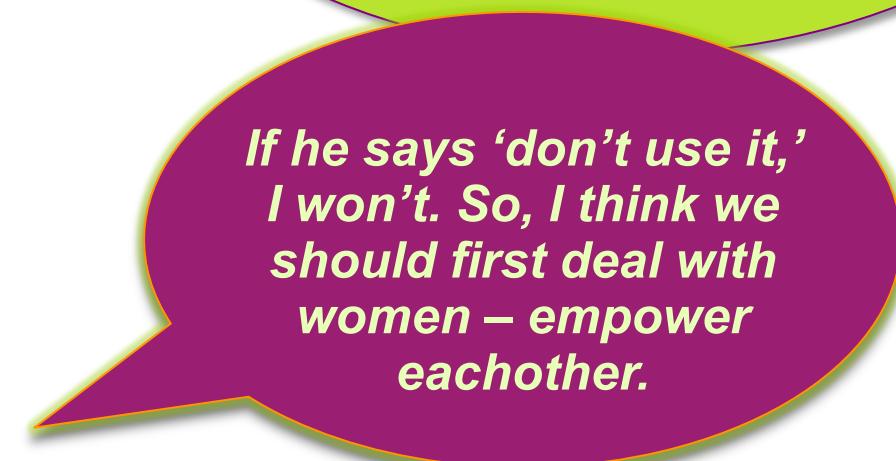
# What we have heard young women say

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- Neither the ring nor PrEP (or other methods) will be right for everyone
- Having choice is empowering; gives us control of our health and lives
- The products in REACH are themselves empowering
- It's time we placed our own health above our partner 's desires

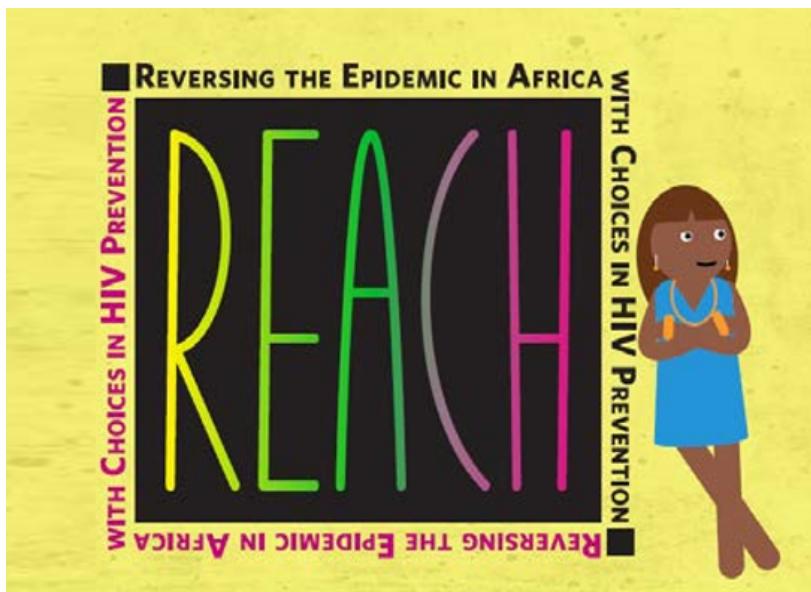
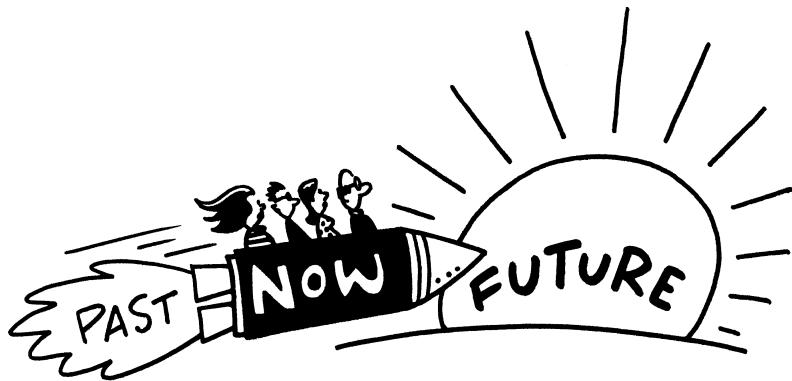


*Using condoms is not so easy. If you try and negotiate, it's like you're saying you're not being faithful. [The ring and PrEP] would give me ownership. I don't have to tell my partner I'm using them.*



*If he says 'don't use it,' I won't. So, I think we should first deal with women – empower each other.*

# REACH Study Timeline and Update



- Study launched February 2019; enrollment discontinued after COVID-related shutdowns in March 2020
- 247 enrolled with more than 33% 16-17 years of age
- Surprises:
  - Parents eager for their daughters to prevent pregnancy and prevent HIV
  - Local IRBs and country authorities have been supportive
- Follow-up to be completed by late 2021
  - Results in early 2022

# Try each option, then choose





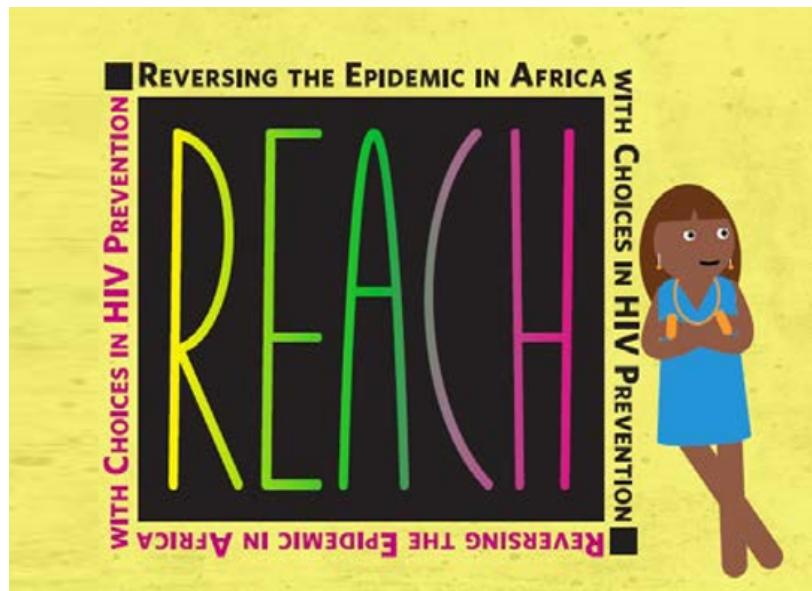
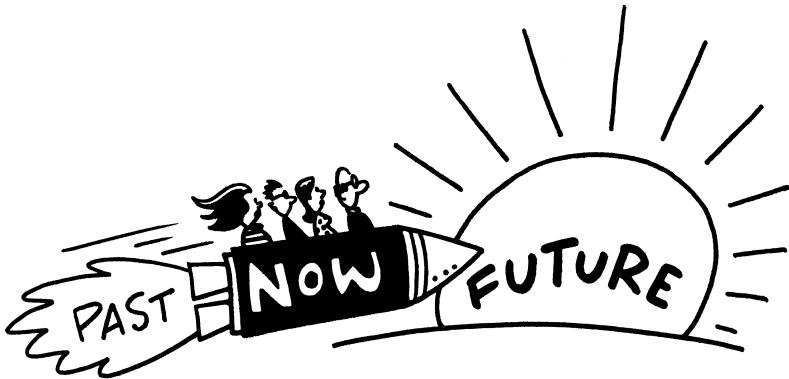
# Questions being asked in REACH

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- Will young women be more inclined to use these products...
  - In a study with no placebo?
  - Knowing that previous studies found them safe?
  - Knowing they can only work with consistent use?
- Is one easier to use than the other?
- Do they like one more than the other?  
Or do they not like either oral PrEP or the ring?
- How might life circumstances influence choice?
- What can we do to help them to use these products?
- What about girls younger than 18? Do they have different challenges?

# Study Timeline and Update

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# HIV Risk for Pregnant and Breastfeeding Women

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- Women in high HIV incidence setting are either pregnant or breastfeeding during 25% of their reproductive years
- Pregnancy is a time of heightened HIV risk
- Postpartum may also be a time of heightened risk
- Increases in risk are likely due to behavioral and biological factors
- Most products are not prospectively studied until years after licensure

# Evaluating dapivirine ring and oral PrEP in pregnant and breastfeeding women



200 breastfeeding woman-infant pairs for 3 months of exclusive breastfeeding; open for enrolling in Johannesburg

**deliver**  
A Study of PrEP and the  
Dapivirine Ring in Pregnant Women

750 pregnant women using a staged approach to enrollment; enrolling in South Africa and Uganda

# Women's Sexual & Reproductive Health Risks are Interlinked

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- Unintended Pregnancy
- Sexually Transmitted Infections (STIs)
- HIV



# Options for MPTs

## Co-formulated:

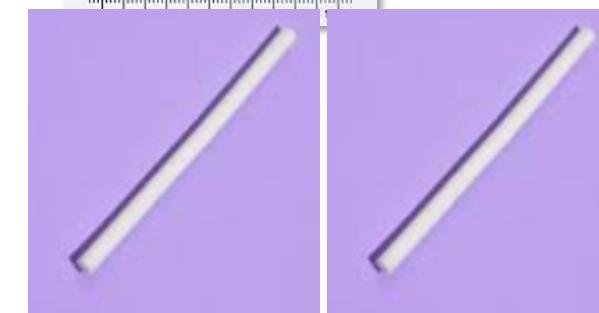
Multiple API formulated into a single dose



Vaginal ring containing ARV plus LNG

## Co-administered:

Two independent products used together



Two implantable rods, one containing ARV, the second containing contraceptive

## Co-packaged:

Two different doses packaged together in a single product for simultaneous co-use



Two tablets, one containing ARV, the second containing contraceptive



# Rectal Microbicides

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- Used “on demand” at the time of sex
- Provides delivery of drug to tissue where cells are easy targets for HIV
- Drug absorption into the body low, therefore less potential for toxicity
- Broad range of formulations under evaluation:
  - Gels containing ARVs used as sexual lubes (MTN-033)
  - Enemas or rectal douches containing ARVs (Hendrix DREAM program)
  - Rectal inserts and suppositories containing ARVs (MTN-039)



# Lessons Learned from Study of Topical vs Oral PrEP

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- Compared daily oral PrEP to coital or daily use of tenofovir gel rectally in Thailand, Peru and 3 sites in the US (SF, Pittsburgh, Birmingham)
- Least Preferred:
  - 28% oral PrEP
  - 28% Before/After Sex rectal microbicide gel
- Geographical differences observed in terms of product acceptability
  - Non-US participants more favorable to gels than pills when compared to US participants.



# Behaviorally Congruent Prevention Methods

Rectal douching within the context of anal intercourse is a common practice acknowledged in academic literature, social media, and gay websites.

[AIDS and Behavior](#)  
pp 1-9 | [Cite as](#)

Rectal Douching Among Men Who Have Sex with Men in Paris: Implications for HIV/STI Risk Behaviors and Rectal Microbicide Development

[Authors](#) [Authors and affiliations](#)

H. Rhodes Hambrick, Su Hyun Park, William C. Goedel, Jace G. Morganstein, Noah T. Kreski, Ofole Mgbako, Dustin T. Duncan [✉](#)



CLEANING OUT - For Anal Sex

**ADVOCATE**

17 Tips for Happier, Healthier Bottoming  
By Alexander Cheves

**BMJ Open**

[Home](#) / [Archive](#) / [Volume 7, Issue 5](#)

[Article Text](#)

Article menu

HIV/AIDS  
Research

Prevalence and types of rectal douches used for anal intercourse among men who have sex with men in Brazil  
[✉](#)

[Luiz Carlos Ribeiro Lamblet<sup>1</sup>](#), [Roberto José Carvalho da Silva<sup>2</sup>](#)

# DREAM Program

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- Development of “rectal douche” to deliver anti-HIV drugs
- Clinical program
  - DREAM-01
    - Comparison of different formulations of tenofovir
    - UCLA, University of Pittsburgh, and Johns Hopkins

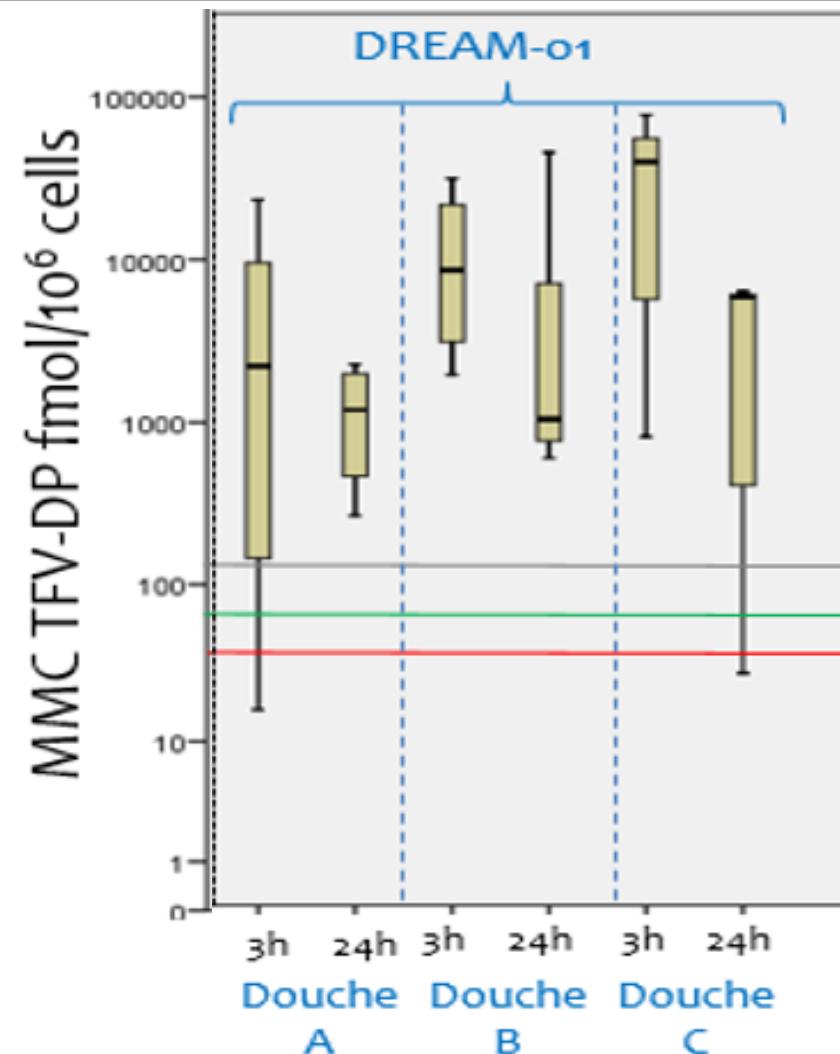


Tenofovir enemas

PI: Craig Hendrix Johns Hopkins Medical School

# DREAM-01: Can a Rectal Douche Deliver Tenofovir to Colorectal Tissue as Well as Oral Tenofovir?

Very High TFV-DP in colon tissues within 3 hours and persisting at 24 hours after a single rectal douche

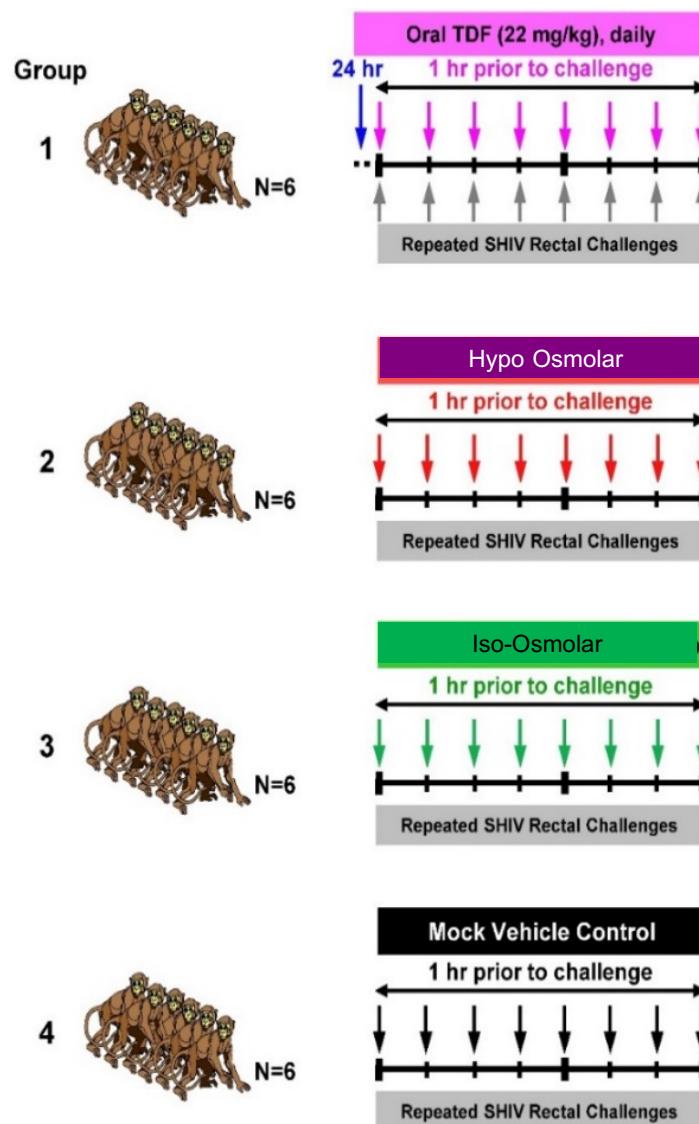


Daily Oral  
7/wk  
4/wk  
2/wk

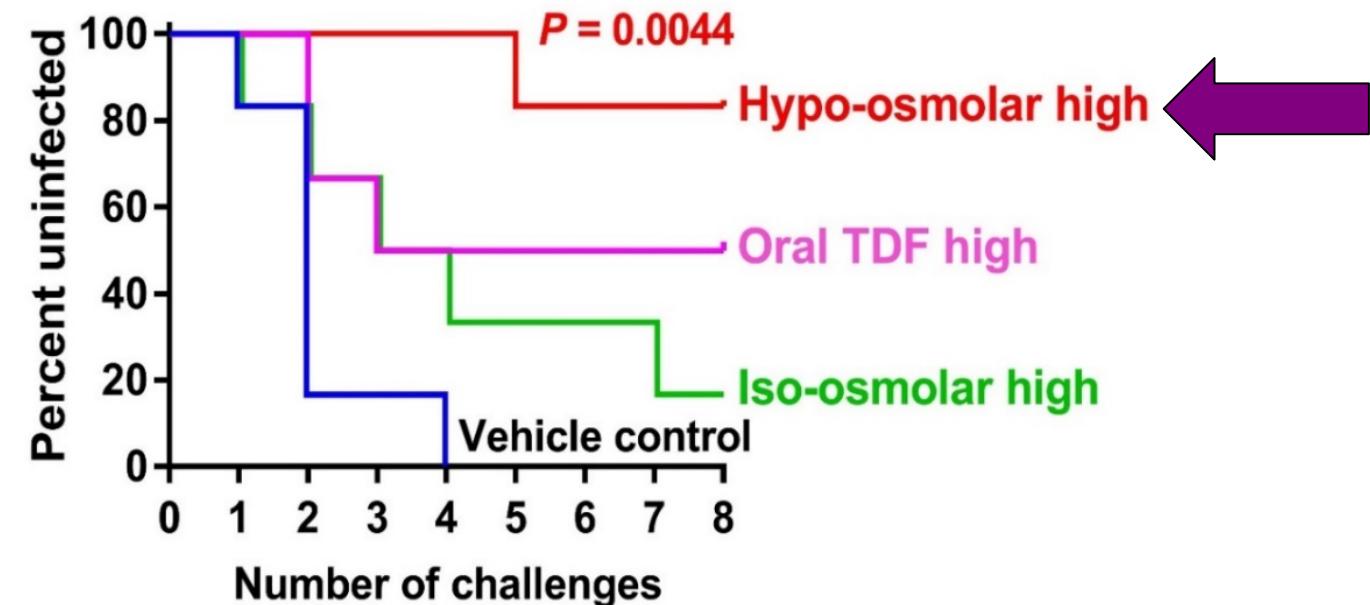


TFV-DP levels  
achieved in colon  
tissue with oral  
tenofovir

# Nonhuman primate study of Oral TDF v. TFV Douche



- Weekly intrarectal  $10^3$  TCID<sub>50</sub> R5 SHIV
- Weekly plasma viral RNA by qPCR



# What Other Products Might be Desirable for People Having RAI?

- Need to acceptability data for “rectal douche” rectal inserts and suppositories as on demand dosage forms
- Crossover study of MSM living in the US (San Francisco, Birmingham, and Pittsburgh), Peru, Thailand, South Africa and Malawi-just completed!
- Will these product delivery platforms fill a niche for people who do not want to be on oral PrEP?



# Rectal Products Under Evaluation

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## Lube Containing Dapivirine:

- MTN-033 Adonis Phase 1 study
  - Does using gel containing dapivirine gel as a lube provide enough drug to tissues?
  - HIV uninfected MSM & TGW (N = 16)
  - Completed

## Phase 1 study of a fast dissolving tablet (rectal insert)

- CONRAD collaboration
- Men and women (N = 30)
- Single dose study under development
- Elvitegravir (integrase inhibitor) plus TAF
- Study enrolling



# Gaps and Unanswered Questions:

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- Can vaginally administered ARVs at low doses provide an attractive prevention option for women who do not want to use oral PrEP? Who will be most likely to choose these products and why?
- Will use of microbicides be less stigmatizing than use of oral PrEP for HIV prevention? Will that translate to better uptake? Persistence?
- Can contraceptive microbicides succeed as contraceptives?
- Is it possible to provide protection with rectal application of ARVs and who will be most interested in these product delivery platforms?
- Will these products be desirable to the young MSMs and transgender men and women?



# Paternalism is the Enemy of Choice

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- Paternalism: the policy or practice on the part of people in positions of authority of restricting the freedom and responsibilities of those subordinate to them in the subordinates' supposed best interest.
- In health care, studies of shared decisionmaking link increased inclusion of the person involvement to improved treatment adherence, disease coping, and quality of life, whereas lack of patient involvement correlates with lower adherence to treatment, patient satisfaction, and health outcomes (Kon AA. The shared decision-making continuum. *JAMA*. 2010;304(8):903-904)

# More Options → Better Choices

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Implant



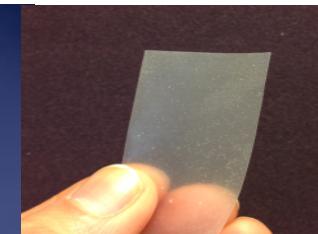
Injection



Pill



Vaginal ring



Vaginal  
film



Insert



Douche



Lube

More Options → Better choices →  
Greater coverage → More impact on HIV



# Thanks so much for all that you do.....

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