MTN 034: REACH
Reversing the epidemic in Africa with choices in HIV prevention

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On behalf of MTN 034 protocol team

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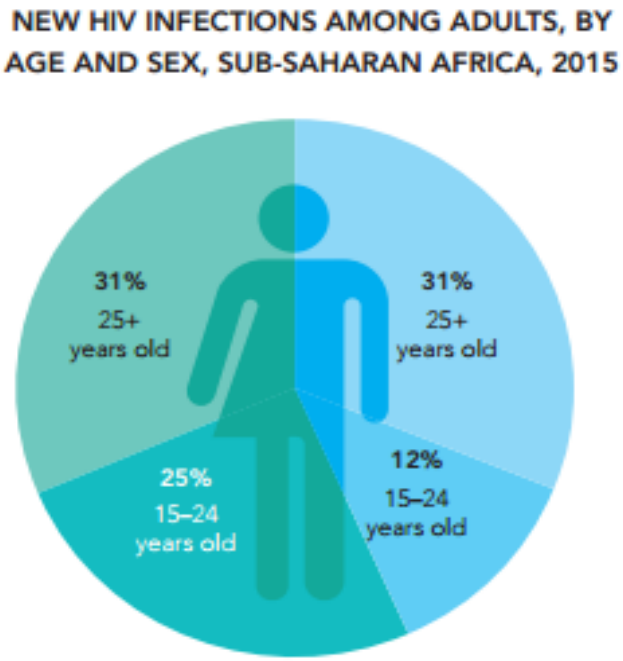
Overview

- Background and Rationale:
  - Burden of HIV among adolescents in SSA
  - Factors that increase the vulnerability of young women to HIV acquisition
  - Proven prevention choices and factors likely to influence uptake
- Next steps to explore safety, acceptability and adherence to dapivirine VR
- MTN 034

Burden of HIV among adolescent girls in SSA

- AIDS related deaths decreased by 32% overall, but increased by 50% among adolescents between 2005-2012 (*UNAIDS 2012*)
- Among girls 10-19 years AIDS is the leading cause of death (*UNAIDS 2016-AIDS by the numbers*)
- In SSA, 25% of new infections occur among young women in the 15-24 year age group (Source: *UNAIDS 2016 estimates*)
- A microbicide with 60% efficacy could prevent 2.5 million new infections over a 3 period.



Factors that make young women vulnerable to HIV infection

- Poverty & limited livelihood opportunities : Transactional sex
  - Young girls have sex with older men to access resources.
- Gender inequality & violence:
  - Women have difficulty negotiating /condom use when economically dependent on partner &/or fear violence
- Limited availability of youth-friendly services

  -Lack of awareness regarding safe sexual practices
- Possible biological vulnerability of the genital tract, potentially including:
  - HSV-2 infection/bacterial vaginosis?
  - Increased HIV co receptors in cervical cells?
  - Hormonal contraception?
  - Vaginal cleansing or drying practices?

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

Acceptability & adherence to oral PrEP among Young South African Women

- ADAPT HPTN 067 Study:
  - 179 women randomized to one of 3 arms in Cape Town (daily; twice weekly + post sex; event-driven)
  - Median age in daily dosing arm: 25 years
  - Daily dosing resulted in better coverage of sex acts, and aderence: 79% detectable tenofovir at 30 wks

    PrEP likely to be used when counseled about efficacy *(Bekker CROI 2015)*
- Factors that impacted on PrEP use:
  - Beliefs about safety
  - Desire to make a positive contribution to community
  - Trust in integrity of study and researchers*(Amico, AIDS Behaviour, 2016)*

HIV prevention- not a one size fits all approach

Pill

Vaginal ring

Injectable

Vagina/rectal tablets

Vaginal/rectal film

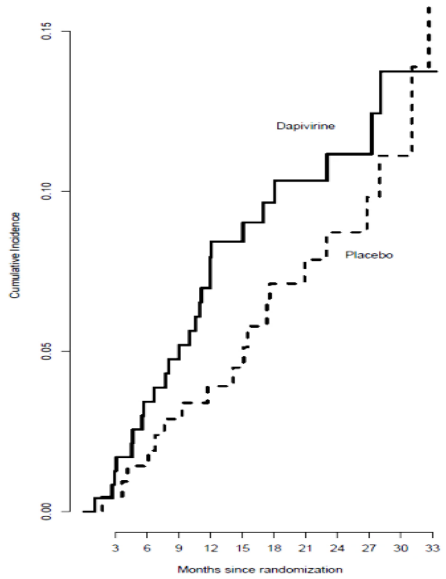
Implants

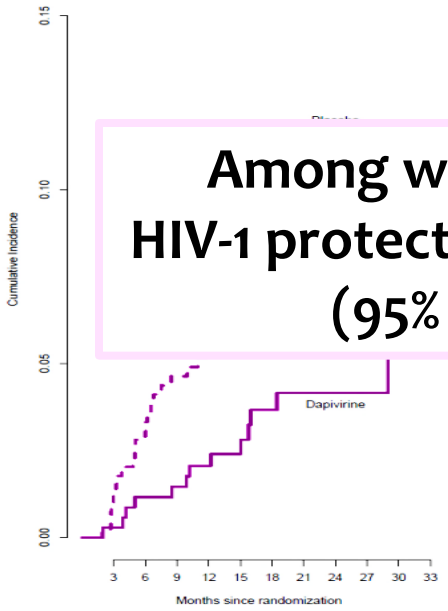
- Tenofovir-containing pills may not be feasible for everyone
- Choice required to meet diverse needs
- There is a pipeline of new PrEP prevention products that could deliver additional options.

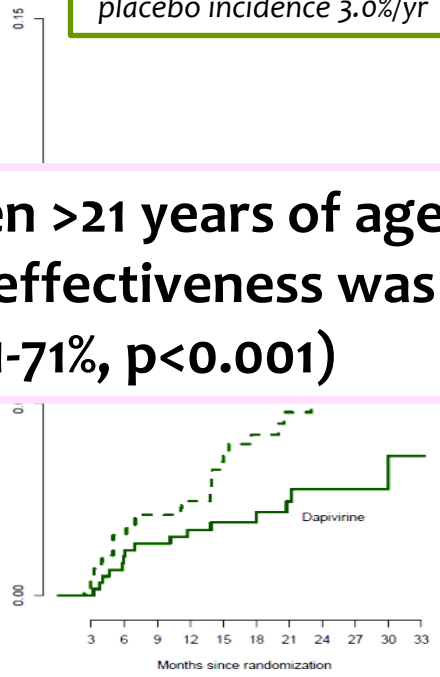
ASPIRE: Age and HIV-1 Protection

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

Age 18-21	Age 22-26	Age 27-45
-27% (-133,31)	56% (19,76)	51% (8,74)
placebo incidence 5.4%/yr	*placebo incidence 6.1%/yr*	*placebo incidence 3.0%/yr*



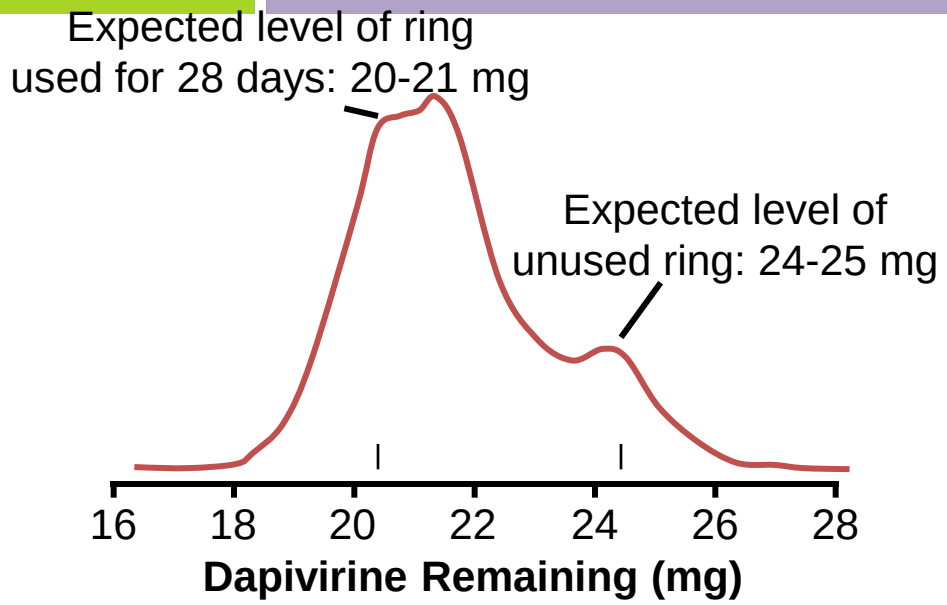




Among women >21 years of age, HIV-1 protection effectiveness was 56% (95% CI 31-71%, p<0.001)

Baeten J, NEJM 2016

MTN-020/ASPIRE Sub cohort: Adherence by Residual Dapivirine in Vaginal Ring



- A lower level of residual dapivirine in the returned ring is indicative of higher adherence

Outcome	Placebo	Nonadherent (≥ 23.5 mg*)	Low-High Adherence (< 23.5 mg*)	Med-High Adherence (< 22 mg*)
HIV infections, n	50	13	14	7
HIV incidence/100 PY	4.6	3.6	1.9	1.5
Risk reduction vs PBO, % (95% CI; *P* value)	--	31 (-28 to 63; .24)	**56** (20 to 76; .007)	**65** (22 to 84; .01)

*Residual levels of dapivirine remaining in returned rings.

Rationale for evaluating PrEP & vaginal rings in young African women

- Oral PrEP and dapivirine VR ring have efficacy & adherence predicts efficacy
- Given lower adherence & efficacy with FTC/TDF & dapivirine ring among young women in clinical trials
  - Need to assess biological factors that may influence safety & efficacy of products in adolescents & young women
  - Need to understand acceptability and adherence to oral PrEP & vaginal rings
  - Need safety data in <18 year old women for regulatory approvals

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Safety and Adherence Study of the DPV (25 mg) VR and TDF/FTC Tablet in a Young African Female Population

- VR safety data will be provided by MTN 020, MTN 023 and other studies
- MTN 034: safety and tolerability amongst African adolescent and young women

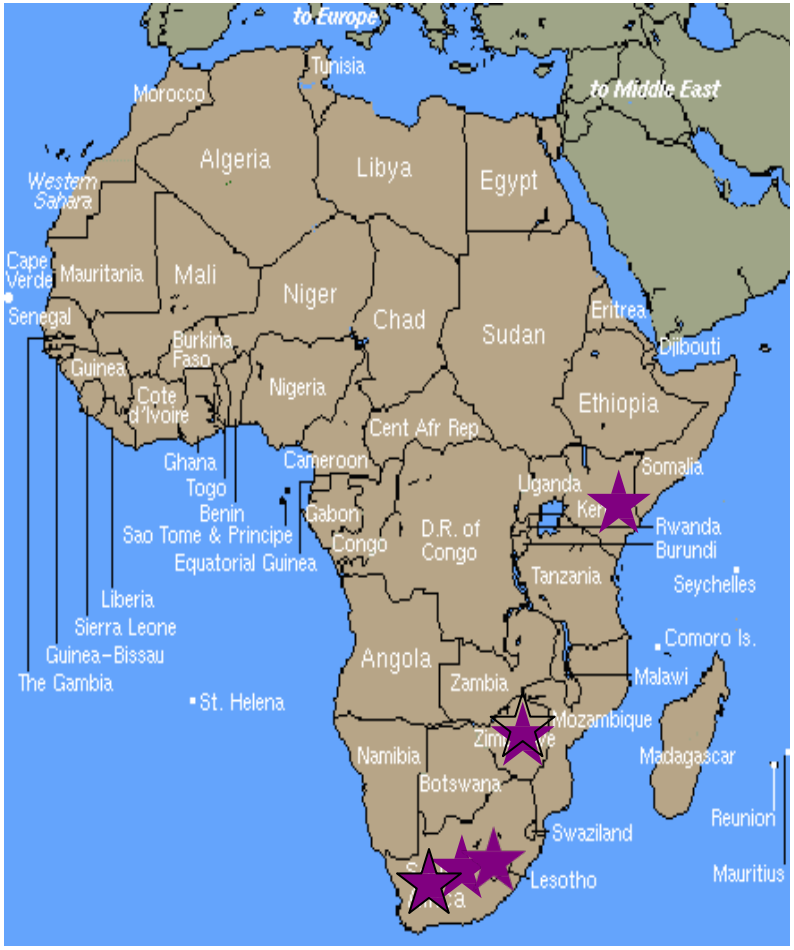
Participants

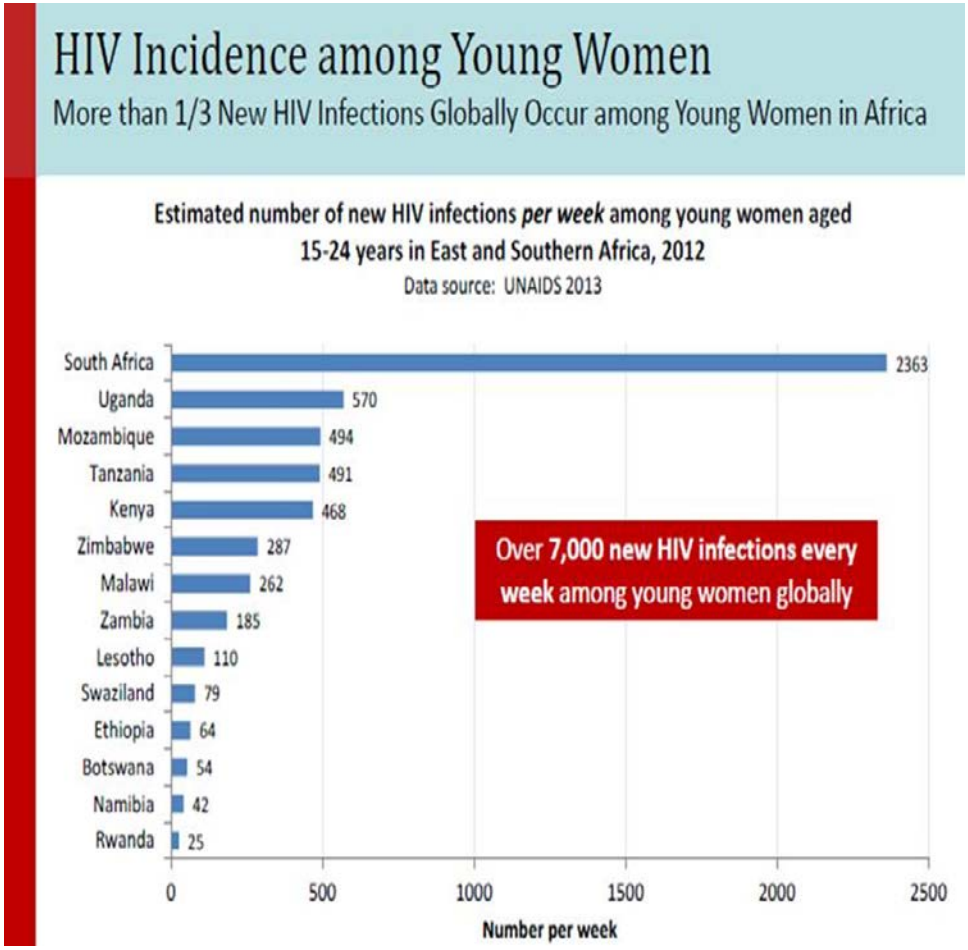
- **Sample Size:** 300 participants

- **Study Population:** Healthy, HIV-uninfected, adolescent females (16 - 17 years old) and young women (18-21 years old) on effective contraception

- **Study Duration:** 73 weeks of follow-up per participant with a projected accrual period of approximately 12 months at each site

5 Sites across 3 countries





South Africa/Zimbabwe/Kenya

Study Design: September 2016

- Protocol first reviewed by PSRC Dec 1, 2015, N = 300 adolescents ages 16-17
- Proposed changes based on ASPIRE results:
  - Include participants aged 18-21 (n 200)/adolescents 16-17 (n 100)
  - Add a third period during which young women will be allowed to select their preferred product

	Assigned Study Product Period 1 (24 Weeks)	Assigned Study Product Period 2 (24 Weeks)	Choice of product period 3 (24 Weeks)
Sequence A	Dapivirine VR	Oral FTC/ TDF	Oral FTC/TDF or Dapivirine VR
Sequence B	Oral FTC/ TDF	Dapivirine VR	

Study objectives

- Primary objectives
  - To compare the Safety profiles of oral Truvada and DPV VR
  - Compare adherence to TDF/FTC and the dapivirine VR by drug concentrations in blood
- Secondary objectives
  - Acceptability: to compare acceptability of oral Truvada and DPV VR
  - Adherence: Does adherence differ when women have a choice in comparison to when randomised?
  - Study product preference: choice during 3rd product use period and product preference ranking at PUEV

Study objectives

- Exploratory objectives
  - Characterize the vaginal microenviroment during product use
    - Changes in Microbiome
    - Biomarkers for safety and efficacy in mucosal secretions
      - Incident STIs
      - CCR5 and CD69 expression on cervical CD4 cells (subset)
      - Inflammation mediators
      - Cellular repair markers

How will MTN 034 meet its objectives?

- Enrol motivated young women
- Strong community engagement from the outset:
  - Establishment of youth CABs
  - Community engagement to include parents
- Youth engagement:
  - Addressing staff attitude to be non judgemental
- Encourage adherence:
  - Supportive, adolescent appropriate counselling approach
  - Drug level feedback at 2 time points in each study arm

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Behavioral Evaluations

Approach

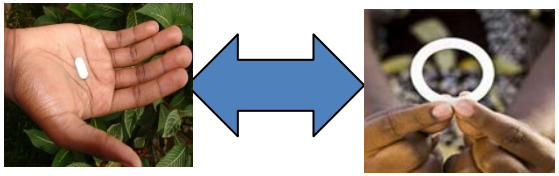
- **Design** - Prospective from baseline to exit
- **Quantitative** – all participants
  - CRF
  - ACASI
- **Qualitative** – subset of participants
  - IDIs + FGDs
- **Assessments:** Enrolment, Monthly/Quarterly (by study period) and exit

Qualitative Sample

- Total: N~50 women and ~70 IDIs
- Per site: N~10 and ~14 IDIs
- 2 FGDs per site

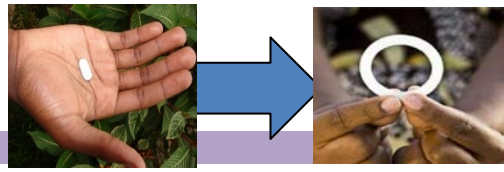
Type of Qualitative Data Collection	# of Women per Site	# of Interviews per Site	Timing of IDI
Serial IDI (TOTAL)	~4*	8	
Dapivirine IVR Arm	~2	~4 (2 per ppt)	(M2); (M12)
Oral FTC/TDF Arm	~2	~4(2 per ppt)	(M2); (M12)
Single IDI (interesting cases)	≥3**	≥3	When identified
Single IDI (Choice non-acceptor)	~3***	~3	At the Choice phase
Total Per Site	~10	~14	

Acceptability & Attitudes



- **Motivations and barriers**
- **Acceptability during sex and menses**
- **Correlates of continuation**
  - Behavioral risk and risk perception
  - Understanding of relative & partial effectiveness of oral TDF/FTC PrEP and dapivirine IVR
  - Stigma associated with oral ARVs
- **Product use concerns (Is there a change over the course of the study)**
  - Partner's knowledge & reaction
  - Side effects (e.g., GI and vaginal symptoms)
  - Concerns systemic vs topical exposure to ARVs

User experiences



- **Experiences during use of oral PrEP and dapivirine IVR**
  - Patterns of self-reported product use
  - Sexual activity including condom use, frequency, vaginal and anal, partners
  - Disclosure to partner, family, and friends
  - Vaginal hygiene practices
  - Contraceptive methods
  - Product storage
- **Dapivirine IVR specific experiences**
  - Ring insertion, circumstance for removal, ease of use
  - Frequency & context of IVR expulsion incidents
- **Oral PrEP specific experiences**
  - Size of tablets, ease of swallowing, when and how tablets were taken

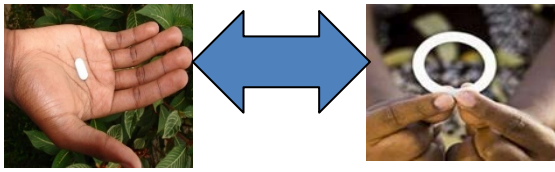
Measures - User Preferences

TDF/FTC
PrEP

dapivirine IVR

- Preference at beginning of study (after counseling & being shown TDF/FTC pill & dapivirine ring)
- Change in preference after each phase of oral PrEP or IVR
- Detailed assessment of factors that influenced product preference
- Preferences for future use at end of study after experience with oral PrEP and dapivirine IVR

Summary behavioral questions



Topic	Sample Questions
Acceptability	What motivated adolescents and young women accept the the product ? (Initiation and (dis)continuation rates)
Preferences	Which method if any do adolescents and young women prefer? Why? Switching? Are there differences in preferences according to participant characteristics and behavior?
Adherence	Do they use the methods as counseled ? Correlates, barriers & facilitators
User experiences	Use as relates to sexual behavior? Condom use? Contraceptive use? Vaginal hygiene practices?

Acknowledgements

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