Characteristics of Women Enrolled into a Randomized Clinical Trial of Dapivirine Vaginal Ring for HIV-1 Prevention

Thesla Palanee-Phillips, PhD

Wits Reproductive Health and HIV Institute, Johannesburg, Gauteng, South Africa

On behalf of K Schwartz, ER Brown, V Govender, N Mgodi, FM Kiweewa, G Nair, F Mhlanga, S Siva, L-G Bekker, N Jeenarain, Z Gaffoor, F Martinson, B Makanani , S Naidoo, A Pather, J Phillip, MJ Husnik, A van der Straten, L Soto-Torres, JM Baeten for the MTN-020/ASPIRE Study Team

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Outline

- Background and rationale
- Protocol overview : Design and objectives
- Baseline Characteristics of ASPIRE participants
- Questions

Background & Rationale

- Developing HIV-1 prevention options women can use remains a global priority
- Clinical trials among young women using daily or coitally-dependent products have found low adherence
- Coitally-independent, antiretroviral-containing vaginal microbicide rings which release medication over a month or longer may :
  - reduce adherence challenges and
  - may help maintain effective vaginal microbicide concentrations over a specified period

Developing dapivirine ring for HIV prevention

- Dapivirine is a non-nucleoside reverse transcriptase inhibitor of HIV
  - has shown safety and acceptability in phase I and phase II trials (in oral, gel, and ring form) *but its large-scale safety and its effectiveness for HIV protection are unknown*
- Formulated into a flexible silicone ring, it could provide a reliable, long-lasting, woman-initiated method to protect against HIV acquisition
- MTN-020 : designed as a pivotal clinical trial to provide strength of evidence to support licensure of dapivirine ring for HIV prevention, along with complementary studies:
  - IPM 027 (efficacy & safety), >25 completed phase I/II studies
  - ongoing/planned work in adolescents/post-menopausal women, drug-drug interactions

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Study Design and Objectives

MTN-020 / ASPIRE

A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Phase III Safety and Effectiveness Trial of a Vaginal Matrix Ring Containing Dapivirine for the Prevention of HIV-1 Infection in Women (ClinicalTrials.gov number NCT01617096).

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The study protocol can be found at http://www.mtnstopshiv.org/studies/3614.

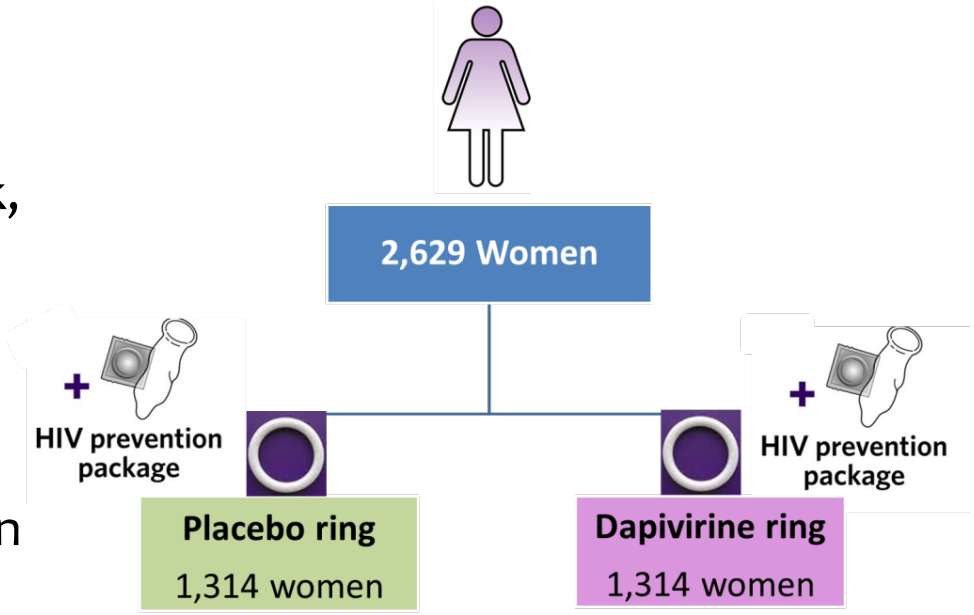
MTN-020 Objectives

- Primary Objective
  - To determine the ***effectiveness*** and ***safety*** of dapivirine (25 mg) administered in a silicone elastomer vaginal matrix ring, when inserted once every 4 weeks, in preventing HIV-1 infection among healthy sexually active HIV-1 uninfected women

- Secondary Objectives
  - To assess the ***acceptability*** of and ***adherence*** to the dapivirine vaginal ring, the frequency of ***drug resistance***, and the ***relationship between drug concentrations and HIV-1 seroconversion***

MTN-020 Design

- Randomized (1:1 active:placebo), double-blind, phase III trial
- Statistical design: 90% power to detect a 60% reduction in HIV-1 risk, ruling out a 25% reduction in risk, with a two-sided alpha of 0.05, including adequately powered analyses related to adherence
- Women use the ring for at least 1 year, with subjects enrolled early in the trial using >2 years.
- All participants receive a comprehensive HIV-1 prevention package, including risk-reduction, condoms, treatment of STIs, and partner testing and referral services



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MTN-020
Population and Procedures

- Population
  - Sexually active HIV-1 uninfected women who are non-pregnant, contracepting, and between 18-45 years of age
- Procedures
  - Monthly follow-up
    - HIV-1 testing, risk-reduction, contraceptive provision on-site, clinical and laboratory safety monitoring, product provision and counseling, and referral for pregnancy and HIV-1 care
- Data Collection
  - Paper based CRFs-Faxed using DataFax software (DF/Net Software ULC) and received at Statistical and Data Management Center located in Seattle, Washington, USA.
  - ACASI for some behavioural data collection

Data analyses conducted using SAS version 9.2 (SAS Institute, Cary, NC)

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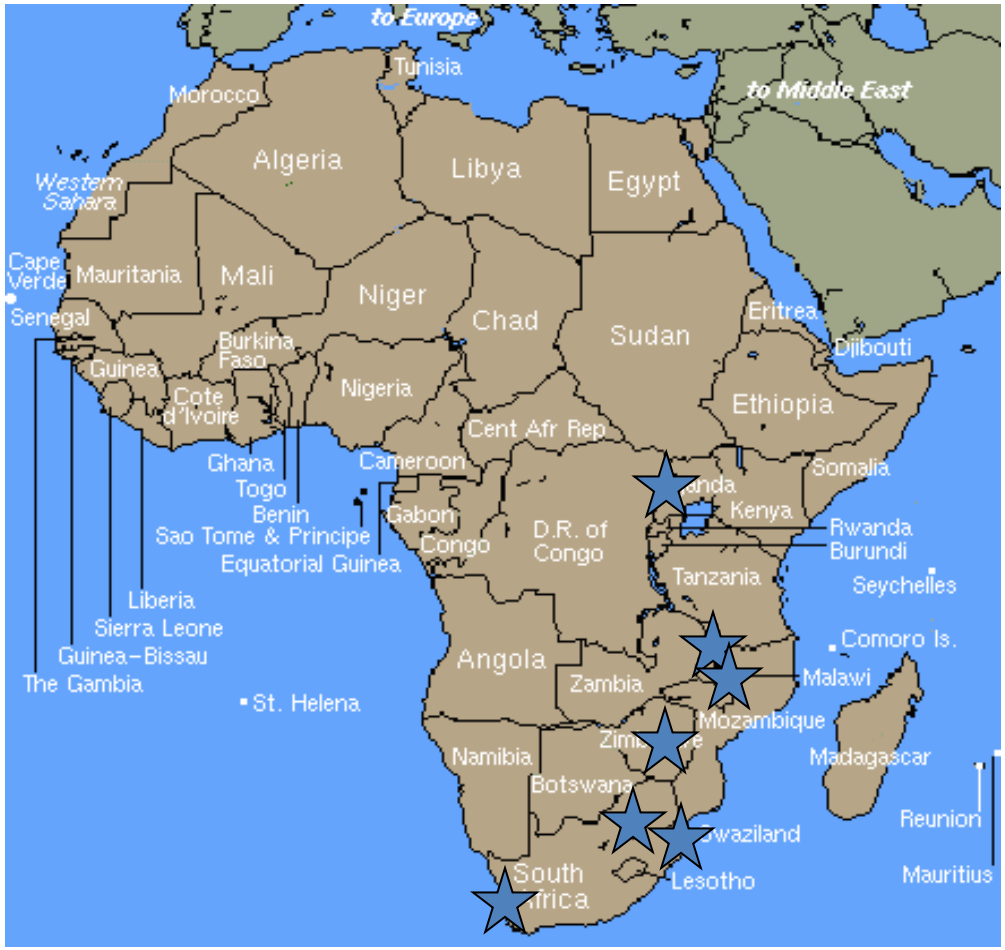
RESULTS

ASPIRE: 2,629/5516 women, 15 sites, 4 countries



Blantyre
Lilongwe
Malawi (272 women)

Cape Town
Durban (7 sites)
Johannesburg
South Africa (1,426 women)

Kampala
Uganda (253 women)

Harare/Chitungwiza (3 sites)
Zimbabwe (678 women)

54% from SA, 10% MA and UG, 26% ZIM

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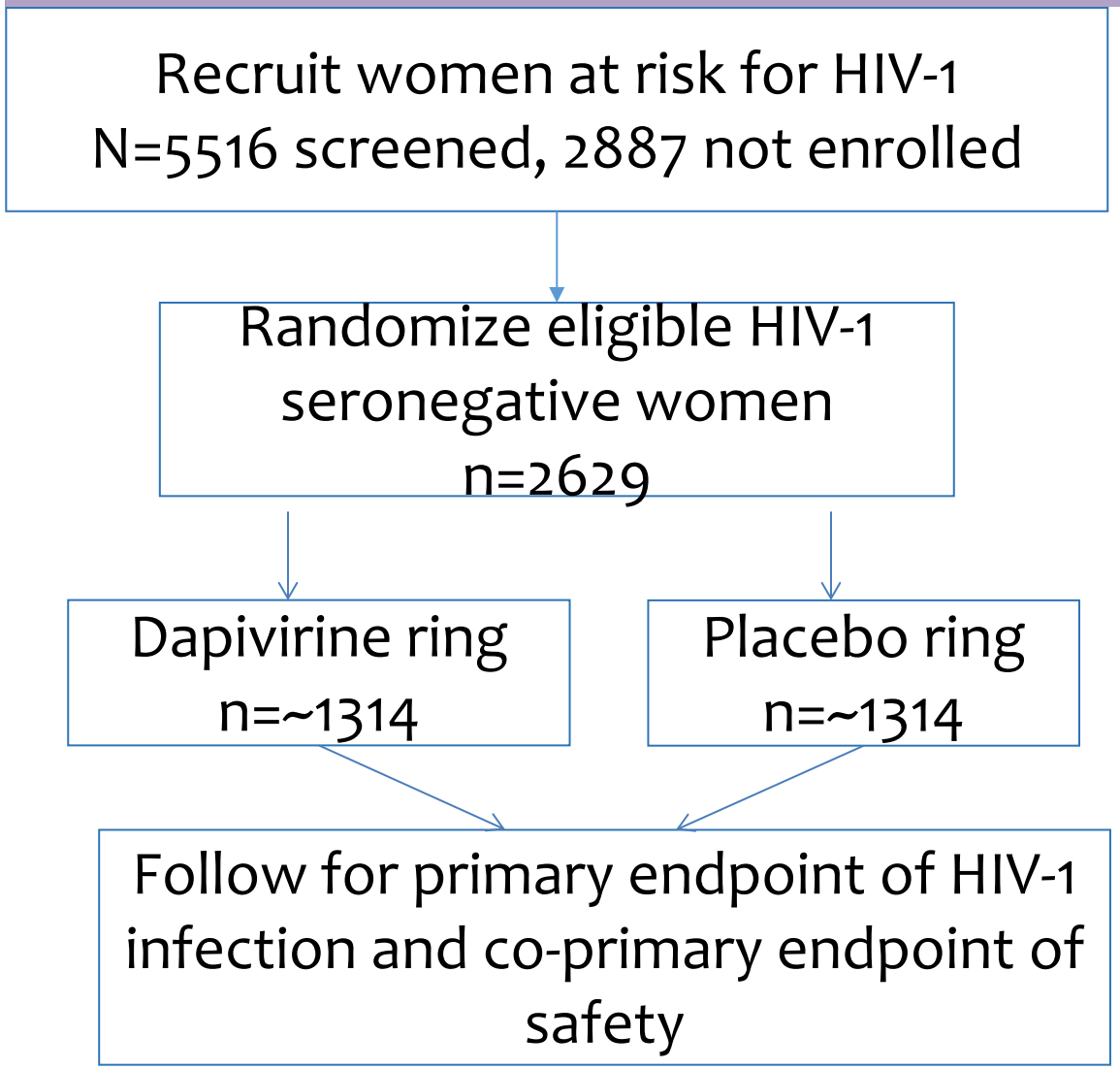
Figure 1. Study Schema



Baseline Participant Characteristics

- Age range 18-45, median 26, 39% <25, 14% 35+
- 59% unmarried, particularly SA (92%) followed by UG (34%), ZIM (17%), MW (15%)
- 85% had partial or complete secondary schooling or higher - mainly SA (96%) and ZIM (88%)

Participant characteristics

In the 3 months prior to screening and enrolment

- Nearly 100% of participants reported having a primary sex partner
  - 17% reported additional partners in this period
- Median number of sex acts : 20 (IQR 7-36)
- 57% reported male or female condom use with last vaginal sex act
- Anal sex : reported by 2% of those enrolled (n=54)

Partners of Participants

- Of 2616 participants reporting a primary sex partner in the past 3 months
  - 1.3% (n=35) knew their primary partner was HIV-1 infected
  - 43% (n=1137) did not know their primary partner's HIV-1 serostatus
- 75% reported that their primary partner was aware of their participation in a research study
- 64% reported that their primary partner knew that they would be using a vaginal ring

Table 1. STIs detected at Screening

STIs detected at the screening visit	Malawi	South Africa	Uganda	Zimbabwe	All
Trichomonas vaginalis	28 (10%)	88 (6%)	13 (5%)	51 (8%)	180 (7%)
Neisseria gonorrhoeae	13 (5%)	55 (4%)	15 (6%)	26 (4%)	109 (4%)
Chlamydia trachomatis	6 (2%)	237 (17%)	25 (10%)	48 (7%)	316 (12%)
Syphilis	11 (4%)	7 (0.5%)	6 (2%)	15 (2%)	39 (1%)

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Reasons for ineligibility

Of 5516 women screened, 2887 (52%) did not enroll

- Screen: enrol ratio of 2.1:1
- 2454 completed screening but were not eligible
- 378 did not complete screening
- 55 women (1% of those screened) were eligible but declined enrollment.

Reasons for ineligibility

- Of 2454 ineligible women:
  - seropositivity for HIV-1 (35%, 854 women)
  - pregnancy or planning to become pregnant (8%, 203 women),
  - breastfeeding (1%, 31 women),
  - not meeting laboratory eligibility criteria (8%, 203 women),
  - not meeting other clinical eligibility criteria (12%, 295 women).
  - 58 (2%) ineligible based on a grade 2 or higher pelvic examination finding.

Reasons for ineligibility

- IoR discretion to not enroll was exercised for 753 women (31% of those screened and not enrolled),
  - whom in opinion of site investigator enrollment of the subject would make
    - study participation unsafe,
    - complicate interpretation of study outcome data, or
    - otherwise interfere with achieving the study objectives.
- Most often, this discretion was used to enroll women committed to the study objectives and its intensive, longitudinal follow-up schedule.

Discussion

- African HIV-1 seronegative women at risk of HIV-1 acquisition from general population were successfully enrolled
- Participants were sexually active, with an important minority reporting >1 partner during the prior 3 months, and curable STI prevalence was high
- ~ 40% of participants were less than 25 years of age at the time of enrollment, more than half were unmarried (59%), and over 40% reported recent sex unprotected by condoms
  - In the VOICE trial of HIV-1 seronegative heterosexual women, these baseline characteristics predicted higher HIV-1 incidence as well as lower product adherence

Male partner involvement

- Defining characteristic of microbicides – potential for clandestine use or without explicit acquiescence of partner
  - majority of women in ASPIRE report telling their male partners about their planned study participation/ring use
- Additional work during trial to explore :
  - disclosure of ring use,
  - male partners' perceived attitudes and reactions, and
  - the influence of male partners on women's adherence to ring use.

Risk Reduction

- Comprehensive package of HIV-1 risk reduction services
  - self-reported condom use for last vaginal sex act at baseline was high in our cohort (57%)
  - women may have over-reported condom use as a result of social desirability bias

- High HIV-1 prevalence at screening across sites - some as high as 40% - underscores urgency around identification of interventions for women to protect themselves from HIV-1 acquisition

Motivation For Joining Trial

- HIV Risk
- access to quality health services including HCT
- health education, transportation reimbursement, peer pressure and altruism

- Commitment to visit schedules - explored in advance of enrolment in context of life plans (e.g., potential future employment, education or marriage)

- Careful assessment of all women presenting for enrolment by site investigators executed across ASPIRE sites
  - attempt to recruit individuals committed for duration of trial

Screen out rates

- ~20% of women who screened out were due to clinical and laboratory related eligibility criteria
- If dapivirine-based PrEP is shown to be safe and efficacious in ongoing trials, its safety will subsequently need to be
  - assessed in HIV-1 susceptible persons who are less optimally healthy than those selected for this trial, as well as pregnant and lactating women.
- Bridging studies are already being planned for lactating women to respond to these questions

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Conclusion

- Women in HIV prevention research face social and psychological risks, especially marginalized and vulnerable populations
- 2629 African heterosexual women at risk of HIV-1 transmission were successfully recruited
- Long-acting microbicide-based PrEP products, if well tolerated and effective, could simplify dosing regimens, thereby reducing user- dependent adherence challenges

Conclusion

- Given high risk of HIV-1 transmission among women, microbicides could be a cost-effective intervention
  - If demonstrated to be safe and effective in ASPIRE and the IPM Ring Study, implementation could be targeted to at-risk women in an effort to curb the HIV epidemic
  - Maximum PrEP benefits, at both individual and population levels, will likely be achieved by combining PrEP with other effective HIV-1 prevention interventions

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Thank You

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