



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 Mgodhi, 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

MTN Annual Meeting, 16 March 2015

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



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).



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



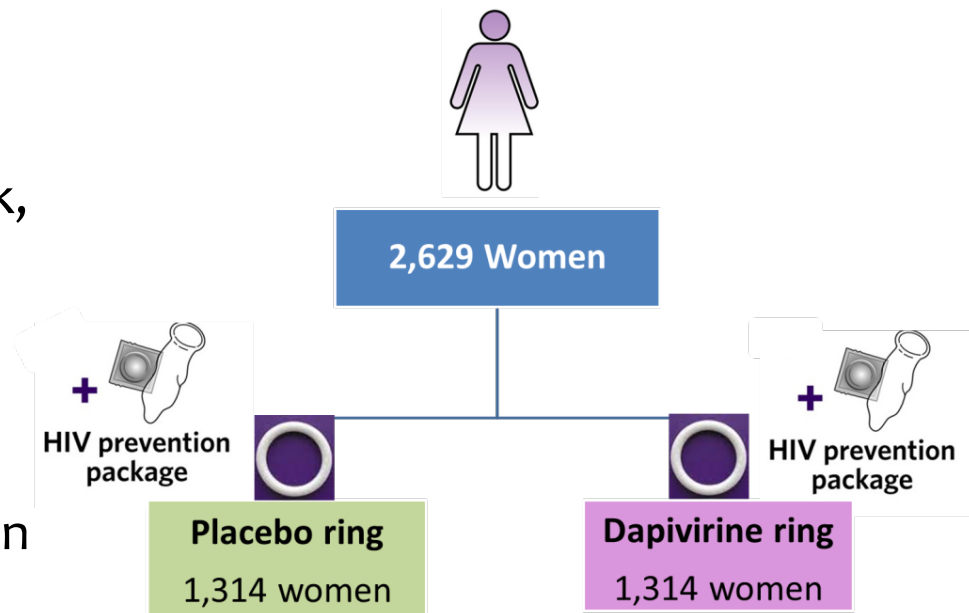
The study protocol can be found at <http://www.mtnstopshiv.org/studies/3614>.

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



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)



RESULTS



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



Blantyre
Lilongwe
Malawi (272 women)

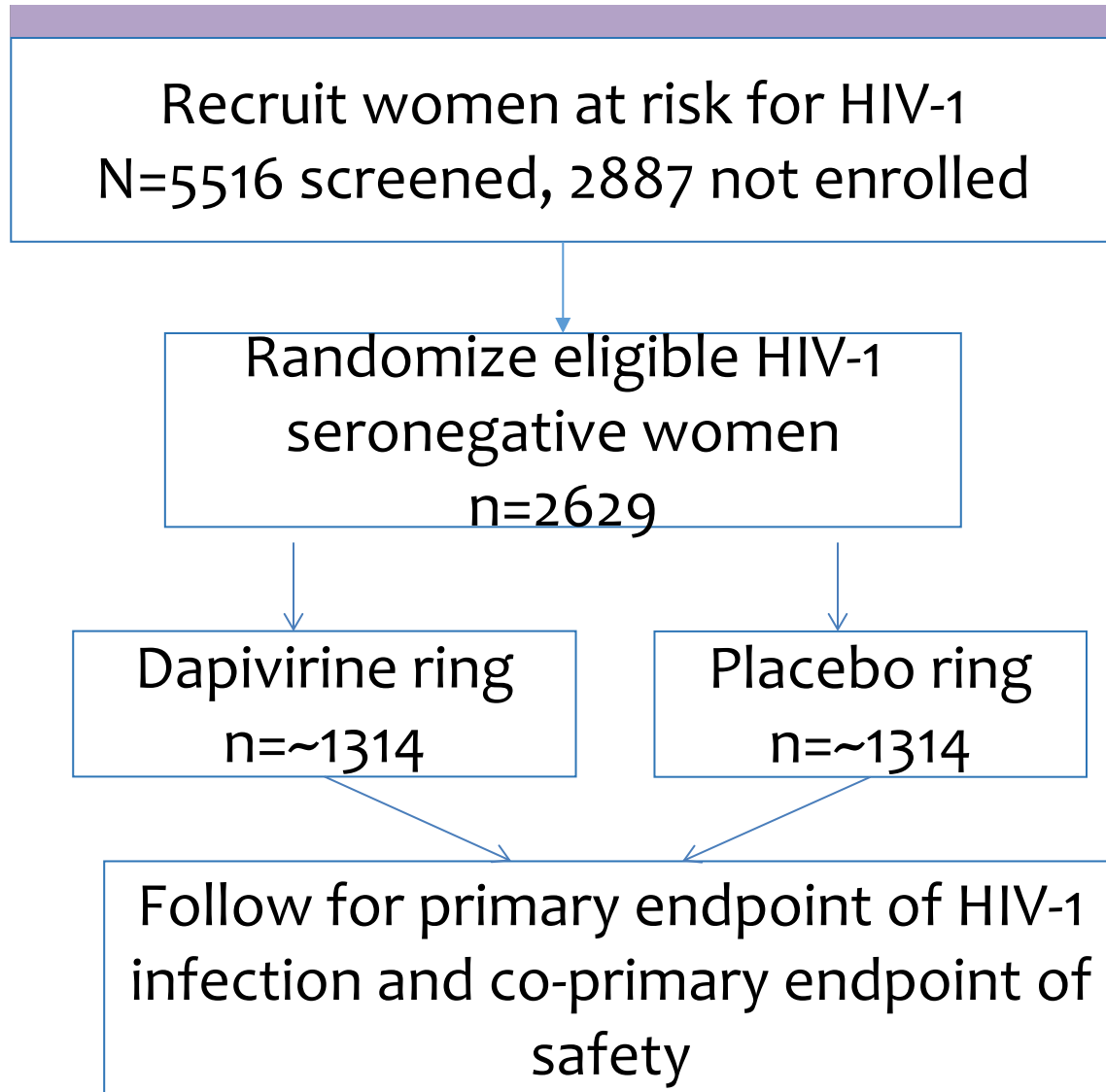
Cape Town
Durban (7 sites)
Johannesburg
South Africa (1,426 women)

Kampala
Uganda (253 women)

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

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

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
<i>Trichomonas vaginalis</i>	28 (10%)	88 (6%)	13 (5%)	51 (8%)	180 (7%)
<i>Neisseria gonorrhoeae</i>	13 (5%)	55 (4%)	15 (6%)	26 (4%)	109 (4%)
<i>Chlamydia trachomatis</i>	6 (2%)	237 (17%)	25 (10%)	48 (7%)	316 (12%)
<i>Syphilis</i>	11 (4%)	7 (0.5%)	6 (2%)	15 (2%)	39 (1%)

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

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

**THE
WORLD**



**IS
WATCHING**

ASPIRE

A Study to Prevent Infection
with a Ring for Extended Use

Acknowledgements

We are grateful to the study participants for their participation and dedication. We thank the study team members at the research sites, at the Protocol Management team and at the MTN Leadership Operations Center for their contributions to data collection.

MTN is funded by NIAID (5U01AI068633), NICHD and NIMH, all of the U.S. National Institutes of Health

MTN is funded by NIAID (UM1AI068633, UM1AI068615, UM1AI06707), NICHD and NIMH, all of the U.S. National Institutes of Health



Thank You



Malawi College of
Medicine – JHU
Research Project



INTERNATIONAL
PARTNERSHIP FOR
MICROBICIDES



Participants and communities

University of Zimbabwe,
School of Medicine