



Vaginal Ring Use in a Phase 3 Microbicide Trial: A Comparison of Objective Measures of Adherence in ASPIRE with Self-reports of Product Use

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Background

- Behavioral assessments are potentially useful for understanding trial outcomes
- Yet, accurate measurement of adherence to study products has been challenging in microbicide trials
- Participants are often reluctant to admit that they have not used product as directed; several trials (e.g. Fem-PrEP and VOICE) have shown substantial discrepancies between self-reports and biomarkers of adherence
- This “biological-behavioral adherence gap” appears to vary inversely with the level of adherence as measured by biological data (van der Straten et al. JIAS 2016:19)

MTN 020/ASPIRE

- MTN-020/ASPIRE: multi-center, randomized, double-blind, placebo-controlled phase III trial of a vaginal matrix ring containing the NNRTI dapivirine
- 2629 women enrolled —1313 in Dapivirine group and 1316 in the placebo group — and followed for 12-33 months
- Median follow-up was 1.6 years and maximum 2.6 years
- Effectiveness was found to be 27% ($p=0.046$)
- Adherence measured both by self report and via more objective measures: dapivirine levels in plasma samples and residual dapivirine in used rings

Research questions

- Is there an association between self-reports of ring use and more objective measures of adherence in ASPIRE?
- Based on objective measures of ring use, did non-adherent participants in ASPIRE over-report ring use?
- In the ASPIRE trial, might the ring have been less effective in younger women because they were more likely than older women to remove it?

Methods

Sample: active arm participants

Measures of dapivirine ring use:

- Dapivirine plasma concentrations
 - Measured quarterly
 - >95 pg/ml: level typically achieved within 8 hours of continuous use
- Residual dapivirine levels in used rings
 - Measured monthly beginning 12 months after study initiation
 - <23.5 mg : amount of drug released consistent with some use during the month

Methods (continued)

- Self-reports of product use
 - Measured monthly via CRF
 - Dichotomous measures based on two questions:
 - How many times in the past month has the participant had the vaginal ring out, in total? [ring ever out vs. ring never out]
 - How many of these times was the vaginal ring out for more than 12 hours continuously? [ring ever out >12 hours vs ring never out >12 hours]

Exclusion criteria

- Any visit reported to be on product hold
- Follow-up visits without self-report, plasma concentration and residual ring data*
- Follow-up visits with no access to ring
- Follow-up visits ≥ 32 days since last visit

* Dapivirine residual ring data were collected only after 12 months and thus exclude the first calendar year of follow-up. All analyses were also done with visits that included self-report and dapivirine plasma concentrations, for which there is a larger sample; several are shown here.

Characteristics of participants at baseline with self-report, plasma concentration, and residual-ring data N=1211

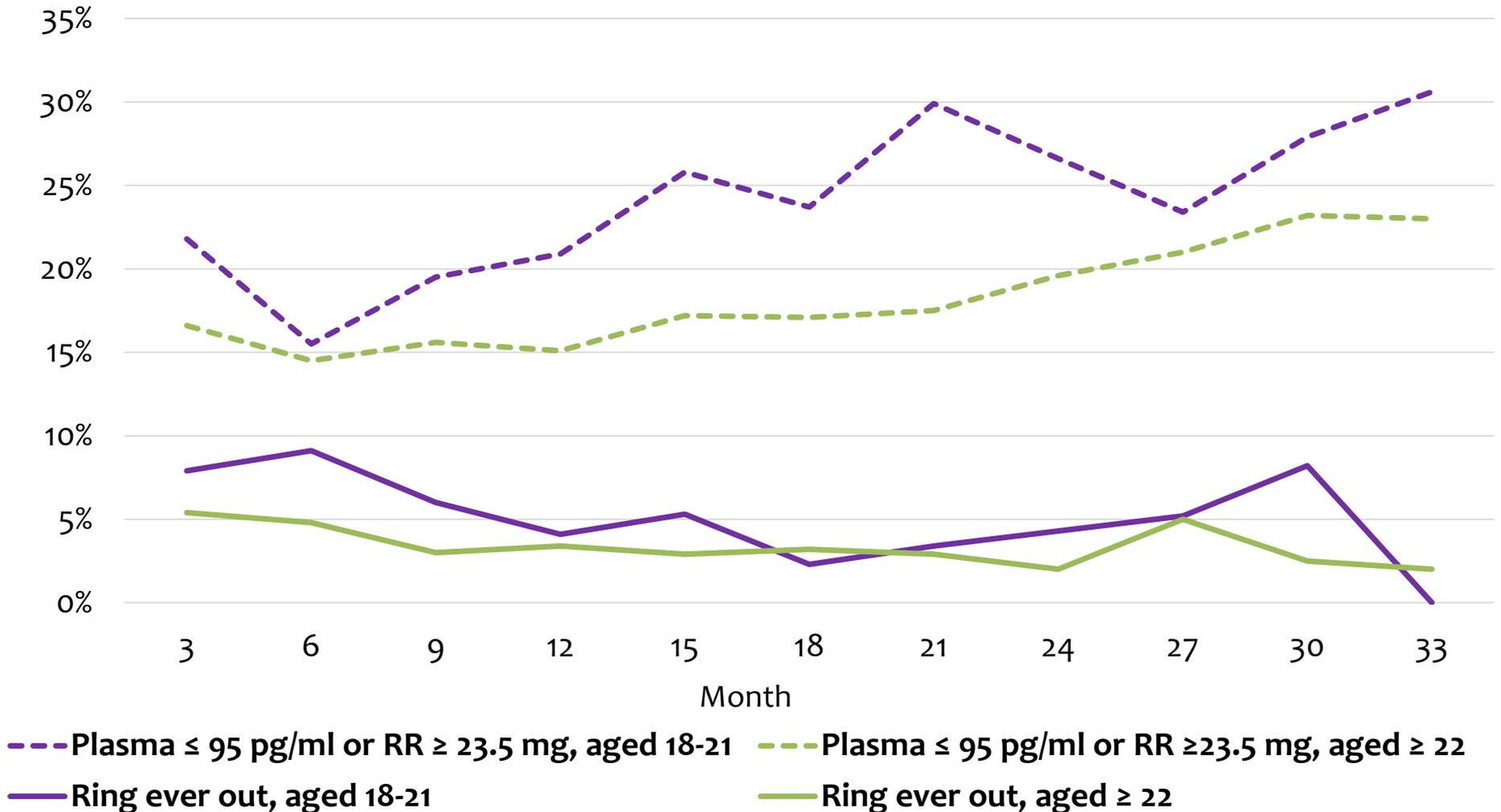
Age group	18-21	20.3%
	≥ 22	79.7%
Married		41.5%
# of partners in past 3 months	0	28.7%
	1	58.4%
	2+	12.9%
Country	Malawi	10.6%
	South Africa	52.6%
	Uganda	10.3%
	Zimbabwe	26.5%
Timing of first visit with self-report, plasma, and residual ring data	3 months	44.8%
	6 months	12.8%
	9 months	14.7%
	12 months	21.2%
	Other	6.5%

Ring non-adherence by age group aggregated over all visits*

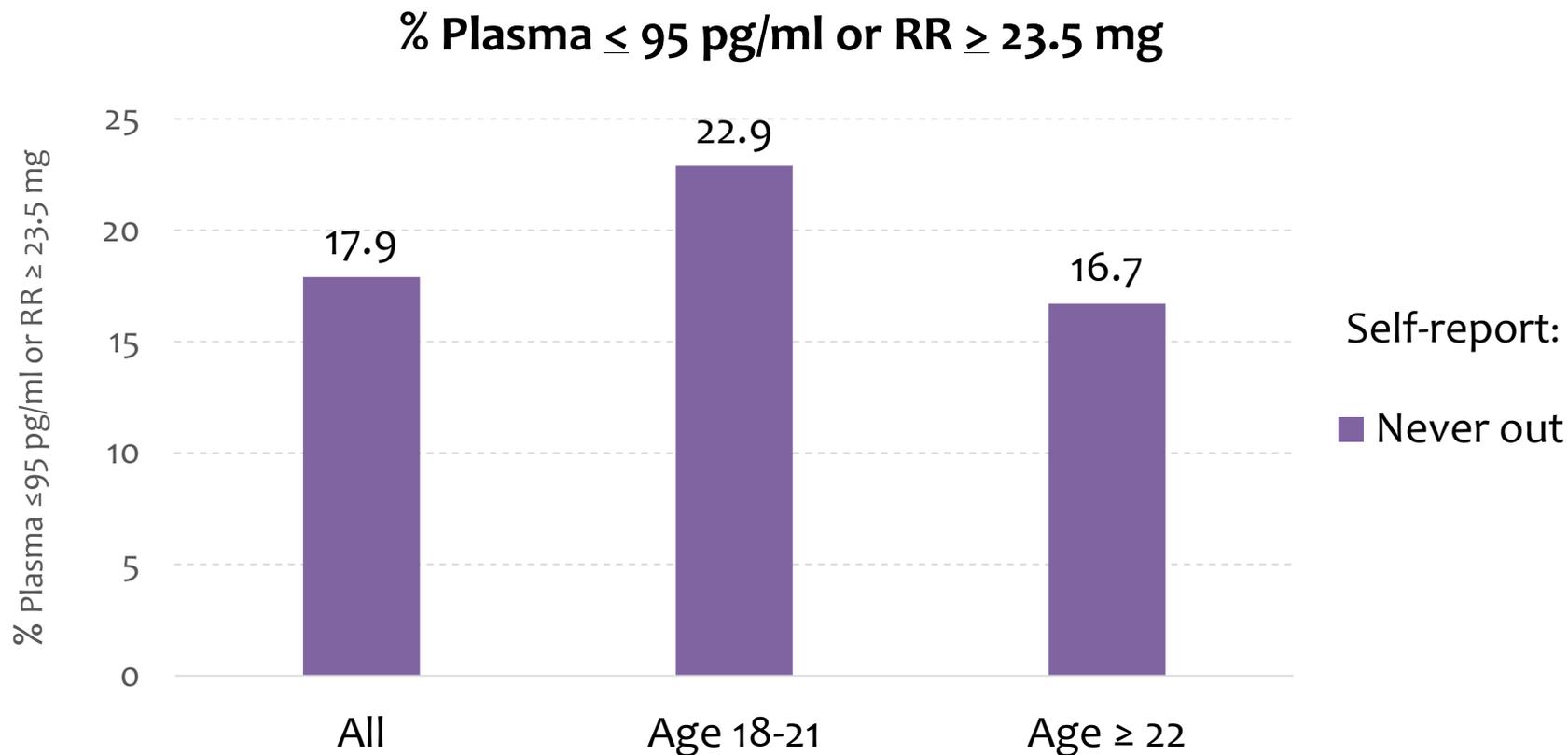
	18 – 21	≥ 22
Ring ever out	5.5%	3.8%
Plasma \leq 95 pg/ml or Residual ring \geq 23.5 mg	23.8%	17.4%
(# of visits)	(1208)	(5037)

*Limited to visits with self report data, plasma and residual ring data

Ring non-adherence assessed via self report and biological measure at quarterly visit, by age group



Biological measure of non-adherence among participants who report ring never out, aggregated over all visits



- Younger women were slightly more likely to underreport nonadherence

Are younger women more likely to report non-adherence?

Generalized Estimating Equations (GEE)* outcome: ring out; predictor: age

Visits with plasma, self-report, and residual ring data

	Variable	OR (95% CI)	p-value
Ring ever out	Age 18-21	1.48 (1.09, 2.02)	0.01
Ring ever out > 12 hours	Age 18-21	1.12 (0.65, 1.93)	0.7

Visits with plasma and self-report data

	Variable	OR (95% CI)	p-value
Ring ever out	Age 18-21	1.61 (1.26, 2.07)	<0.001
Ring ever out >12 hours	Age 18-21	1.69 (1.20, 2.39)	0.003

*GEE models account for within-participant correlation due to repeated outcome measures

Reasons* for ring being out by age

N=418 visits

Reason	18-21 (N=117)	≥22 (N=301)	OR (95%CI)**	P-value**
Physical/hygienic	17.1%	22.9%	0.69 (0.39, 1.23)	0.7
Study related procedures	36.8%	30.9%	1.30 (0.79, 2.13)	0.3
Social/sexual	13.7%	14.0%	0.98 (0.50, 1.91)	1.0
Came out on its own	8.5%	8.0%	1.08 (0.50, 2.34)	0.8

* Participants could report more than one reason

**From GEE models; limited to visits with plasma and self-report

Do self-reports of ring adherence predict biological measures?

Multivariable models of ring adherence:

- Outcome = composite biological measure of adherence: plasma >95 pg/ml and residual ring <23.5 mg
- Predictors = age group and self-report of adherence

Variable	OR (95% CI)	p-value	aOR (95% CI)*	p-value
Ring never out	2.54 (1.88, 3.43)	<0.001	2.22 (1.60, 3.08)	<0.001
Age 18-21	0.68 (0.52, 0.88)	0.004	0.79 (0.60, 1.05)	0.11

Research questions:

- Is there an association between self-reports of ring use and more objective measures of adherence in ASPIRE? **Yes**
- Based on objective measures of ring use, did non-adherent participants in ASPIRE over-report ring use? **Yes**
- In the ASPIRE trial, might the ring have been less effective in younger women because they were more likely than older women to remove it? **Yes**

Summary

- Ring removal underreported in ASPIRE among participants who were not adherent according to biological measures
- At nearly 1/5 of visits where women reported that the ring was never out, plasma or residual ring levels suggested very low or no use at all during the month
- Younger women were significantly more likely to report the ring out but age was not associated with plasma DPV level or residual DPV in ring in models with self-report of ring removal
- That age not significant in multivariable models suggests it was removal of ring that likely accounted, at least in part, for difference in the objective measure of adherence

MTN-020/ASPIRE Study Team

- **MTN-020/ASPIRE leadership:** Jared M. Baeten (protocol chair), Thesla Palanee-Phillips (protocol co-chair), Elizabeth R. Brown (protocol statistician), Katie Schwartz (FHI 360 senior clinical research manager), Lydia E. Soto-Torres (DAIDS medical officer)
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 - **Malawi: Lilongwe site (University of North Carolina Project):** Francis Martinson
 - **South Africa: Cape Town site (University of Cape Town):** Linda-Gail Bekker
 - **South Africa: Durban eThekweni site (Centre for AIDS Programme of Research in South Africa):** Gonasagrie Nair
 - **South Africa: Durban – Botha’s Hill, Chatsworth, Isipingo, Tongaat, Umkomaas, Verulam sites (South African Medical Research Council):** Vaneshree Govender, Samantha Siva, Nitesha Jeenarain, Zakir Gaffoor, Arendevi Pather, Logashvari Naidoo, Gita Ramjee
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- **International Partnership for Microbicides:** Zeda Rosenberg, Annalene Nel
- **MTN-020/ASPIRE participants and their communities; MTN-020 Community Working Group; MTN-020 Study Monitoring Committee; DAIDS MNDSMB**
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