

Pooled Efficacy Analysis of Two Phase III Trials of Dapivirine Vaginal Ring for the Reduction of HIV-1 Infection Risk in HIV-Uninfected Women in Sub-Saharan Africa

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Background

The safety and efficacy of a Dapivirine Vaginal Ring (DVR) in reducing the risk of HIV-1 infection via vaginal intercourse in healthy, HIV-negative women was demonstrated in each of two independent, well-controlled Phase III trials: IPM 027 (The Ring Study) and MTN-020 (ASPIRE), conducted among 4588 women ages 18-45 years in Malawi, South Africa, Uganda and Zimbabwe. The DVR is designed to be replaced every month and intended for use in combination with safer sex practices. The pooled efficacy results of the two Phase III trials are presented.

Methods

Pooled Efficacy Analysis

- Endpoint Analysis: HIV-1 infection, as measured by:
 - HIV-1 seroconversion rate
 - Time of first detection of HIV-1 RNA
- Adherence to DVR use, using measures that indicate at least some DVR use during the prior 4 weeks defined as:
 - Dapivirine residual levels in used rings of ≤23,5 mg AND
 - Dapivirine plasma concentrations of ≥95 pg/mL

Results

- The rate of HIV-1 seroconversion was 3.7 (95% CI: 3.1 to 4.3) per 100 personyears in the DVR group and 5.0 (95% CI: 4.2 to 5.8) in the placebo group.
- The DVR reduced the risk of HIV-1 infection statistically significantly by 27.4% (95% CI: 8.6 to 42.3; p=0.0063) relative to placebo, based on HIV-1 seroconversion (Table 1).
- Using time of first detection of HIV-1 RNA, HIV-1 risk reduction was 29.9% with DVR use (95% CI: 11.8 to 44.3; p=0.0023).
- The cumulative risk of HIV-1 infection became higher in the placebo than DVR



group after approximately 5 months (Figure 1).

- HIV-1 risk reduction was statistically significantly higher in participants older than 21 years; no risk reduction was observed in participants 21 years or younger (Table 1).
- For periods in which participants were defined as adherent to at least some DVR use, HIV-1 infection risk reduction improved to 45.3% (Table 2).

Table 1	. HIV	-1 Se	eroconv	version	Rates	- Overall and by Age at Baseline	

(modified ITT population*)	
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Age at Baseline	% Reduction in HIV-1 seroconversion (95% CI)	p-value (main effect)	p-value (interaction effect)
Overall	27.41 (8.56; 42.30)	0.0063	-
≤ 21 years	-4.81 (-57.31; 30.17)	< 0.0001	0.0266
> 21 years	39.78 (20.19; 54.56)	-	-

* modified-ITT: All randomised participants who were HIV-negative at enrolment.

Figure 1. Time to HIV-1 Infection, based on HIV RNA Detection (modified ITT population)

Table 2. HIV-1 Infection Rate, based on time to HIV RNA Detection, Adjusted for Adherence* (reduced[#] and full ^{##} modified ITT population)

	Dapivirine Adhe	rent vs. Placebo	Dapivirine Non-adherent vs. Placebo		
Population	% Reduction in HIV-1 Infection (95% CI)	p-value for adherence effect vs. Placebo	% Reduction in HIV-1 Infection (95% CI)	p-value for adherence effect vs. Placebo	
Reduced m-ITT population	45.30 (27.44; 58.77)	< 0.0001	-2.69 (-45.68; 27.61)	0.8817	
Full m-ITT population	41.44 (23.97; 54.89)	< 0.0001	-5.88 (-45.93; 23.18)	0.7272	

* Adherence defined as ≤23.5 mg residual dapivirine in used rings and dapivirine plasma concentration ≥95 pg/mL.

Reduced m-ITT: For one trial, collection of used rings for determination of residual levels was only initiated one year after start of the trial; this population includes data from this trial collected after this time point.
Full m-ITT: All randomised participants who were HIV-negative at enrolment.
M-ITT – modified ITT

Conclusions

- The pooled results of two independent, well-controlled Phase III trials of a monthly DVR resulted in an overall HIV-1 risk reduction of 27.4%, a statistically significant result.
- Higher HIV-1 risk reduction was observed with increased adherence to product use.
- The maximum level of HIV-1 infection risk reduction from vaginal exposure with consistent ring use cannot be determined based on the available data.







PRESENTED AT THE 9TH IAS CONFERENCE ON HIV SCIENCE - PARIS, FRANCE

