ORIGINAL ARTICLE

Safety and Efficacy of a Dapivirine Vaginal Ring for HIV Prevention in Women

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ABSTRACT

BACKGROUND

The incidence of human immunodeficiency virus (HIV) infection remains high among women in sub-Saharan Africa. We evaluated the safety and efficacy of extended use of a vaginal ring containing dapivirine for the prevention of HIV infection in 1959 healthy, sexually active women, 18 to 45 years of age, from seven communities in South Africa and Uganda.

METHODS

In this randomized, double-blind, placebo-controlled, phase 3 trial, we randomly assigned participants in a 2:1 ratio to receive vaginal rings containing either 25 mg of dapivirine or placebo. Participants inserted the rings themselves every 4 weeks for up to 24 months. The primary efficacy end point was the rate of HIV type 1 (HIV-1) seroconversion.

RESULTS

A total of 77 participants in the dapivirine group underwent HIV-1 seroconversion during 1888 person-years of follow-up (4.1 seroconversions per 100 person-years), as compared with 56 in the placebo group who underwent HIV-1 seroconversion during 917 person-years of follow-up (6.1 seroconversions per 100 person-years). The incidence of HIV-1 infection was 31% lower in the dapivirine group than in the placebo group (hazard ratio, 0.69; 95% confidence interval [CI], 0.49 to 0.99; P=0.04). There was no significant difference in efficacy of the dapivirine ring among women older than 21 years of age (hazard ratio for infection, 0.63; 95% CI, 0.41 to 0.97) and those 21 years of age or younger (hazard ratio, 0.85; 95% CI, 0.45 to 1.60; P=0.43 for treatment-by-age interaction). Among participants with HIV-1 infection, nonnucleoside reverse-transcriptase inhibitor resistance mutations were detected in 14 of 77 participants in the dapivirine group (18.2%) and in 9 of 56 (16.1%) in the placebo group. Serious adverse events occurred more often in the dapivirine group (in 38 participants [2.9%]) than in the placebo group (in 6 [0.9%]). However, no clear pattern was identified.

CONCLUSIONS

Among women in sub-Saharan Africa, the dapivirine ring was not associated with any safety concerns and was associated with a rate of acquisition of HIV-1 infection that was lower than the rate with placebo. (Funded by the International Partnership for Microbicides; ClinicalTrials.gov number, NCT01539226.)

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In 2014, approximately 36.9 million people worldwide were living with human immunodeficiency virus (HIV) infection.[1] Rates of new HIV infection among adolescent girls and young women remain high in Eastern and Southern Africa,[2] which underscores the need for the development of safe and effective tools against HIV infection that women initiate themselves.[3-5]

A Quick Take is available at NEJM.org

Self-inserted vaginal rings, which provide a sustained release of antiretroviral drugs over time, have the potential to offer women a prevention option that does not require daily or pericoital use.[6] The International Partnership for Microbicides (IPM) developed a monthly self-administered vaginal ring that contains the nonnucleoside reverse-transcriptase inhibitor (NNRTI) dapivirine, which has antiviral activity against HIV type 1 (HIV-1).

In the Ring Study, we assessed the safety and efficacy of a dapivirine-containing vaginal ring (DVR-004), which was replaced every 4 weeks, for up to 24 months. Secondary trial objectives were to assess the incidence rate of curable sexually transmitted infections, adherence to ring use, and incidence of pregnancy. HIV-1 drug-resistance mutations were assessed in women who were infected with HIV-1 during the trial.

Methods

Trial Population, Design, and Oversight

This multicenter, randomized, double-blind, placebo-controlled, phase 3 trial involved healthy, HIV-negative, sexually active women who were enrolled at seven research centers in South Africa and Uganda (Fig. 1). Participants were assigned, in a 2:1 ratio, to receive either the dapivirine vaginal ring, which contains 25 mg of dapivirine dispersed in a platinum-catalyzed silicone matrix, or a matched placebo ring. Randomization was stratified according to research center. The dapivirine vaginal rings contained, on average, 24.4 mg of dapivirine (nonweighted average of eight batches [NK513, OB517, OC519, OF528, OK537, PA540, PB543, and PK574] used in the trial, with a relative standard deviation of ≤1.4%). IPM donated the vaginal rings (dapivirine and placebo) used in the trial, which were manufactured by QPharma (Sweden). QPharma had no other role in the trial. The authors vouch for the accuracy and completeness of the data and analyses presented and for the fidelity of the study to the protocol, available with the full text of this article at NEJM.org.

Participants could be enrolled in the trial if they fulfilled all the eligibility criteria (see the protocol and Table S1 in the Supplementary Appendix, available at NEJM.org). During the subsequent visits to the research center every 4 weeks, the participant removed the used ring and replaced it with a newly dispensed ring. Used rings were to be returned to the trial personnel. Counseling regarding adherence to ring use was provided.

Clinical and laboratory assessments after enrollment were performed according to the procedures described in Tables S2 and S3 in the Supplementary Appendix. Participants who received a diagnosis of a curable sexually transmitted infection (or other genital infection) were treated.

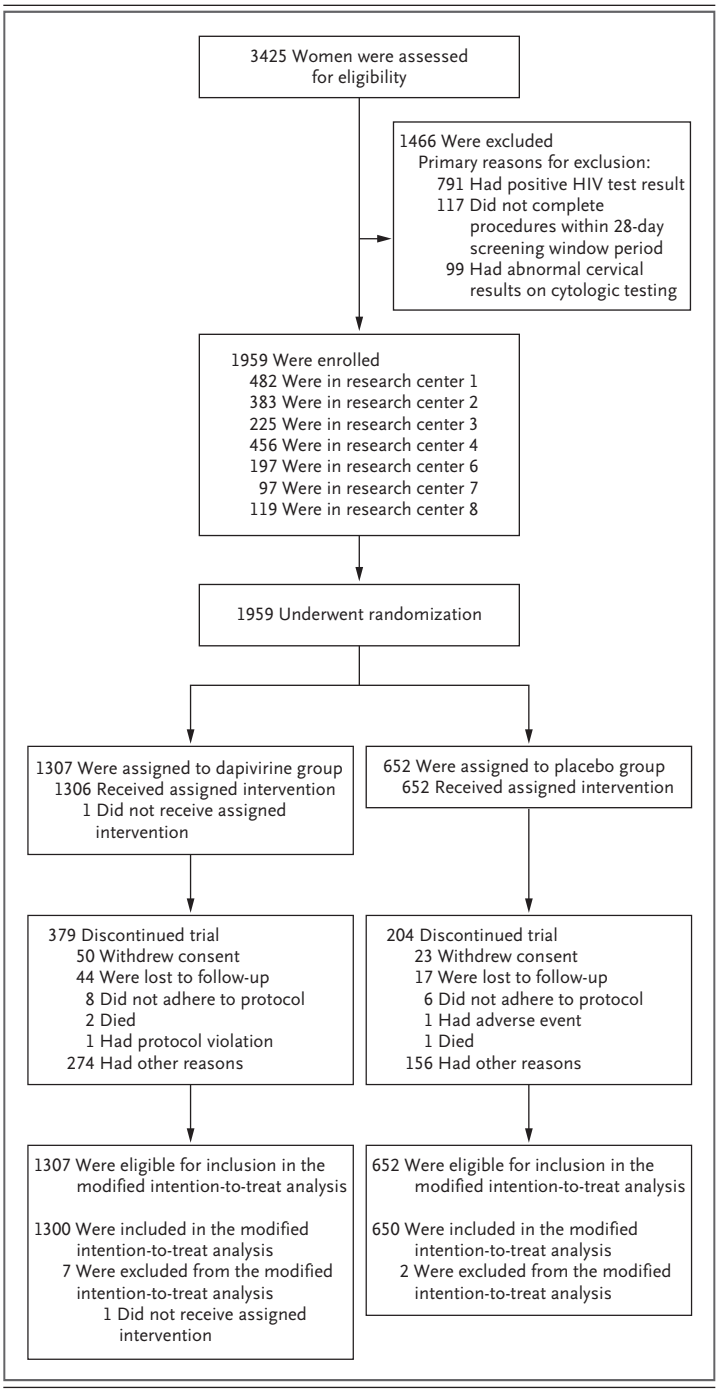
Participants received counseling regarding HIV before and after rapid and confirmatory HIV testing (HIV-1 testing algorithms are shown in Figs. S1 through S5 in the Supplementary Appendix) and received counseling with regard to reduction of the risk of HIV infection and other sexually transmitted infections and adherence to contraceptive use. Participants were provided with nonspermicidal condoms for male partners. Women who were confirmed to be pregnant or to have HIV infection discontinued the use of the investigational product immediately and were referred for prenatal support services, medical treatment, and social support, as appropriate.

The trial protocol was approved by the ethics committees for each site, and all the participants provided written informed consent before trial-related procedures were initiated at screening and enrollment. The trial was conducted according to the International Conference on Harmonisation Good Clinical Practice guidelines and other applicable local regulatory requirements. Safety data and other data collected during the trial were monitored by an independent data and safety monitoring board approximately every 6 months.

Analyses of Plasma Samples and Returned Rings

Plasma samples were obtained and the returned used rings were collected at all trial visits. HIV-1 RNA testing by means of polymerase-chain-reaction (PCR) assay and HIV-1 genotype resis-

Figure 1. Randomization and Enrollment of the Participants.
Ethics and regulatory approvals for the clinical-trial protocol and its amendments were obtained from the relevant ethics committees and regulatory authorities for the seven research centers in South Africa (centers 1, 2, 3, 4, 7, and 8) and Uganda (center 6). One participant in the dapivirine group did not receive the assigned intervention because she was menstruating at the time of ring administration, so she was not, per protocol, permitted to start use of the product; this participant was one of the seven who were not included in the modified intention-to-treat analysis. The modified intention-to-treat analysis included participants who underwent randomization to the dapivirine group or the placebo group (in a 2:1 ratio) and were negative for the human immunodeficiency virus (HIV) at enrollment.



tance testing were performed on stored plasma samples that were obtained from participants who underwent seroconversion to HIV-1. All the plasma samples that were obtained in the dapivirine group were analyzed for dapivirine with the use of high-performance liquid chromatography–tandem mass spectrometry.[7] Residual levels of dapivirine were determined in all used active rings and in a subgroup of placebo rings with the use of high-performance liquid chromatography–ultraviolet testing.[8]

PRIMARY EFFICACY AND SAFETY END-POINT MEASURES

The primary efficacy end point was the rate of HIV-1 seroconversion. All seroconversions were reviewed by an independent seroconversion-monitoring committee, and only HIV-1 seroconversions that were confirmed by the committee to be infections that occurred after enrollment and before the final visit at which the product was used (as assessed on the basis of PCR assay for HIV RNA on stored samples in reverse sequential order) were regarded as trial end points. The null hypothesis of the primary efficacy analysis was that the rate of HIV-1 seroconversion would not differ between participants assigned to receive the dapivirine ring and those assigned to receive the placebo ring. The primary safety end point was the determination of all adverse events as measured by self-reports, physical examinations, gynecologic assessments (including pelvic examination with the use of a speculum), laboratory tests, and other indicated investigations.

STATISTICAL ANALYSIS

The trial was designed with a planned sample of 1650 women. This number was increased to 1950 participants to mitigate the potential negative effect of nonadherence to the assigned product as observed at one research center (center 3).

The revised number allowed for a 95% probability of detecting an adverse event occurring at a rate of 0.3% or higher. Assuming an estimated annual incidence of seroconversion in the placebo group of 4%, we calculated that this sample size would provide the trial with 81% power to detect a 50% lower rate of HIV-1 seroconversion in the dapivirine group than in the placebo group. The formal statistical test that was used to evaluate the efficacy of dapivirine was the two-sided log-rank test, stratified according to research center; an adjusted two-sided significance level of 0.0466 was used to account for an interim efficacy analysis performed at the point when approximately 50% of the expected number of end points had been observed.

The primary analysis was performed in the modified intention-to-treat population, which included the participants with HIV-1 seroconversion that was confirmed by the independent seroconversion-monitoring committee to be a trial end point. Three complementary analyses of the primary efficacy end point were prespecified in the statistical analysis plan (see the protocol): an analysis in which data were excluded from one research center (center 3) at which widespread nonadherence to the product was observed; an analysis in which data were censored from participants who did not adhere to ring use according to a prespecified definition that was based on missed trial visits, nonreturn of used rings, and self-reports that the ring was removed from the vagina for 12 hours or more; and a time-varying product-adherence analysis, in which adherence (defined as a residual level of ≤23.5 mg of dapivirine in the ring and a plasma concentration of ≥95 pg of dapivirine per milliliter) was a time-varying covariate.

A subgroup analysis that was based on two age groups (≤21 years and >21 years) was prespecified in the statistical analysis plan. Owing to the observation of higher-than-expected numbers of HIV-1 end points and based on a recommendation from the independent data and safety monitoring board, the final safety and efficacy analyses were performed before the planned completion of the trial, which was to include a fixed 2-year follow-up for each participant. This article reports the final results of the Ring Study at the data cutoff point of October 16, 2015.

RESULTS

TRIAL PARTICIPANTS

A total of 1959 participants were enrolled in the trial; 1307 participants were randomly assigned to the dapivirine group and 652 to the placebo group (Fig. 1). At the data cutoff point, 615 participants (31.4%) were still in the trial, 761 (38.8%) had completed the trial, and 583 (29.8%) had discontinued early. A total of 61 of 1959 participants (3.1%) were lost to follow-up. One reason for the high rate of early discontinuation was a decision by the sponsor, before unblinding, to withdraw all the participants enrolled at research center 3 because of the high rates of noncompliance with the protocol and nonadherence to the product that were observed among enrolled women. This decision was made in consultation with national and local regulatory authorities. Other reasons for early discontinuation included HIV-1 seroconversion, withdrawal of consent, relocation, and pregnancy.

The two trial groups were well matched with respect to demographic characteristics (Table 1). The mean age of the participants in the trial was 26.0 years (range, 18 to 45). Most of the participants were single (89.2%), and almost all (98.2%) reported having a single main sex partner.

EFFICACY

HIV-1 Incidence Rate

HIV-1 incidence rates that were based on seroconversions (confirmed trial end points) are shown in Table 2 and in Figure S6 in the Supplementary Appendix. The overall incidence rate was 4.1 seroconversions per 100 person-years in the dapivirine group and 6.1 seroconversions per 100 person-years in the placebo group. The incidence of HIV-1 infection was 31% lower in the dapivirine group than in the placebo group (hazard ratio, 0.69, 95% confidence interval [CI], 0.49 to 0.99; P=0.04). A Kaplan–Meier plot of the time to seroconversion is shown in Figure 2.

Results of the three prespecified complementary efficacy analyses are presented in Table 2. The first complementary analysis, which excluded participants from research center 3, showed an HIV-1 incidence rate of 3.6 seroconversions per 100 person-years in the dapivirine group and 5.4 seroconversions per 100 person-years in the placebo group. The rate of HIV-1 infection was

30% lower in the dapivirine group than in the placebo group (hazard ratio, 0.70; 95% CI, 0.47 to 1.05; P=0.08).

In the analysis that censored data from participants in each group who had three or more events of prespecified nonadherence in 1 year, the HIV-1 incidence rate was 3.3 seroconversions per 100 person-years in the dapivirine group and 4.3 seroconversions per 100 person-years in the placebo group (hazard ratio, 0.74; 95% CI, 0.49 to 1.14; P=0.16) (Table 2). The analysis that was based on time-varying product adherence in the dapivirine group (defined by a residual level of ≤23.5 mg of dapivirine in used rings and a plasma concentration of ≥95 pg of dapivirine per milliliter) showed a 29% lower rate of HIV-1 infection during adherent intervals between visits than during nonadherent intervals between visits (hazard ratio, 0.71; 95% CI, 0.42 to 1.22; P=0.21) (Table 2).

Results from a prespecified subgroup analysis that was based on two age groups (≤21 years and >21 years) showed an HIV-1 incidence rate among participants 21 years of age or younger of 6.4 seroconversions per 100 person-years in the dapivirine group, as compared with 8.2 seroconversions per 100 person-years in the placebo group (hazard ratio, 0.85; 95% CI, 0.45 to 1.60) (Table 2). The HIV-1 incidence rate among participants older than 21 years of age was 3.4 seroconversions per 100 person-years in the dapivirine group as compared with 5.5 seroconversions per 100 person-years in the placebo group (hazard ratio, 0.63; 95% CI, 0.41 to 0.97; P=0.43 for treatment-by-age interaction), indicating no significant difference in efficacy of the dapivirine ring between the two age groups.

Dapivirine Resistance Mutations among Participants with HIV-1 Seroconversion

NNRTI resistance mutations occurred in 14 of 77 participants (18.2%) with HIV-1 seroconversion in the dapivirine group and in 9 of 56 (16.1%) with HIV-1 seroconversion in the placebo group (Table S4 in the Supplementary Appendix). The NNRTI mutation E138A was detected more frequently in participants in the dapivirine group than in those in the placebo group (11.7% vs. 1.8%). Other NNRTI mutations occurred with similar or lower frequency in the dapivirine group than in the placebo group.

Table 1. Characteristics of the Participants at Baseline.*

Characteristic	Dapivirine (N=1307)	Placebo (N=652)
Age — yr		
Mean	25.9±5.8	26.1±5.9
Range	18–45	18–45
Race — no. (%)†		
Black	1299 (99.4)	642 (98.5)
Other	8 (0.6)	10 (1.5)
Education completed — no. (%)		
None	58 (4.4)	24 (3.7)
Primary education	384 (29.4)	228 (35.0)
Secondary education	775 (59.3)	371 (56.9)
University degree	90 (6.9)	29 (4.4)
Marital status — no. (%)		
Divorced	2 (0.2)	1 (0.2)
Married	118 (9.0)	63 (9.7)
Separated	13 (1.0)	7 (1.1)
Single	1166 (89.2)	581 (89.1)
Widowed	8 (0.6)	0
Has a main sex partner — no. (%)		
No	23 (1.8)	12 (1.8)
Yes	1284 (98.2)	640 (98.2)
Currently residing with main sex partner — no./total no. (%)		
No	907/1284 (70.6)	447/640 (69.8)
Yes	377/1284 (29.4)	193/640 (30.2)
Had vaginal sex ≥1 time per week in previous 3 mo — no. (%)		
No	59 (4.5)	27 (4.1)
Yes	1248 (95.5)	625 (95.9)
Usual no. of vaginal sex acts each month		
No. of participants with data	1248	625
Mean	8.1±10.3	8.4±10.5
Range	1–180	1–120

* Plus–minus values are means ±SD. There were no significant between-group differences at baseline.
† Race was self-reported.

Dapivirine Levels in Returned Rings and Dapivirine Plasma Concentrations

Through October 16, 2015, a total of 35,706 rings were returned of the 36,720 rings that had been dispensed (97.2%). A total of 83% of the returned used rings contained 23.5 mg or less of

Table 2. Overall HIV-1 Seroconversion Rate and Additional Analyses in the Modified Intention-to-Treat Population.*

Variable	Dapivirine	Placebo	Hazard Ratio (95% CI)	Percent Difference (95% CI)
Primary efficacy analysis				
Total no. of participants	1300	650		
No. of participants with confirmed seroconversion	77	56		
No. of participants with censored value	1223	594		
Total person-yr of follow-up	1888	917		
Rate of confirmed seroconversion (per 100 person-yr)	4.1	6.1	0.69 (0.49 to 0.99)†	−30.67 (−51.50 to −0.90)†
Complementary analyses‡				
Analysis excluding research center 3				
Total no. of participants	1150	577		
No. of participants with confirmed seroconversion	63	46		
No. of participants with censored value	1087	531		
Total person-yr of follow-up	1745	852		
Rate of confirmed seroconversion (per 100 person-yr)	3.6	5.4	0.70 (0.47 to 1.05)	−29.68 (−52.70 to 4.53)
Product-adherence analysis				
Total no. of participants	1300	650		
No. of participants with confirmed seroconversion	56	36		
No. of participants with censored value	1244	614		
Total person-yr of follow-up	1708	836		
Rate of confirmed seroconversion (per 100 person-yr)	3.3	4.3	0.74 (0.49 to 1.14)	−25.67 (−51.45 to 13.81)
Time-varying product-adherence analysis for adherence vs. nonadherence in the dapivirine group§				
Rate (per 100 person-yr)	—	—	0.71 (0.42 to 1.22)	−28.77 (−58.33 to 21.78)
Subgroup analysis according to age¶				
≤21 yr				
No. of participants	312	156		
Rate of confirmed seroconversion (per 100 person-yr)	6.4	8.2	0.85 (0.45 to 1.60)	−15.15 (−54.91 to 59.70)
>21 yr				
No. of participants	988	494		
Rate of confirmed seroconversion (per 100 person-yr)	3.4	5.5	0.63 (0.41 to 0.97)	−37.47 (−59.49 to −3.49)

* The modified intention-to-treat population included participants who underwent randomization (in a 2:1 ratio) and were negative for the human immunodeficiency virus (HIV) at enrollment. Data from participants who did not undergo seroconversion to HIV type 1 (HIV-1) were censored at the date of the last negative HIV-1 test result. Person-years are based on the cumulative follow-up time (i.e., time to HIV-1 seroconversion or time to censoring of data at the date of the last negative HIV-1 test result). Hazard ratios and 95% confidence intervals were estimated on the basis of a Cox proportional-hazards model stratified according to research center, except as otherwise noted. Efficacy was evaluated with the use of a log-rank test, stratified according to research center, with a hazard ratio of 1 for the null hypothesis at a two-sided significance level of 0.0466 (to account for superiority evaluation at the interim analysis).

† P=0.04.

‡ We conducted three prespecified complementary analyses of the primary efficacy end point: an analysis that excluded data from one research center (center 3) at which widespread product nonadherence was observed; a product-adherence analysis that censored data of participants who did not adhere to ring use according to a prespecified definition that was based on missed trial visits, nonreturn of used rings, and self-reports that the ring was removed from the vagina for 12 hours or more; and a time-varying product-adherence analysis, in which adherence was included as a time-varying covariate.

§ In this analysis, the definition of adherence (residual level of dapivirine in the ring ≤23.5 mg and plasma concentration of dapivirine ≥95 pg per milliliter if both assessments were available; otherwise based on the available assessment) was used to categorize time periods as adherent or nonadherent. Last-observation-carried-forward imputation was used for time points at which no residual levels in the ring or plasma concentrations were available and for which sampling was scheduled. The same woman could contribute observation time to both periods. The total amount of follow-up time in the adherent periods was 1460 person-years; 50 participants underwent HIV-1 seroconversion during these adherent periods. The total follow-up time in nonadherent periods was 424 person-years; 27 participants underwent HIV-1 seroconversion during these nonadherent periods. A total of 3 person-years of follow-up was associated with missing data before a first measurement (for which no imputation could be performed).

¶ Hazard ratio and 95% confidence intervals for the subgroup analyses were estimated on the basis of a Cox proportional-hazards model including treatment, age, and treatment-by-age interaction, stratified according to research center. Neither the age effect (P=0.07) nor the treatment-by-age interaction (P=0.43) was significant.

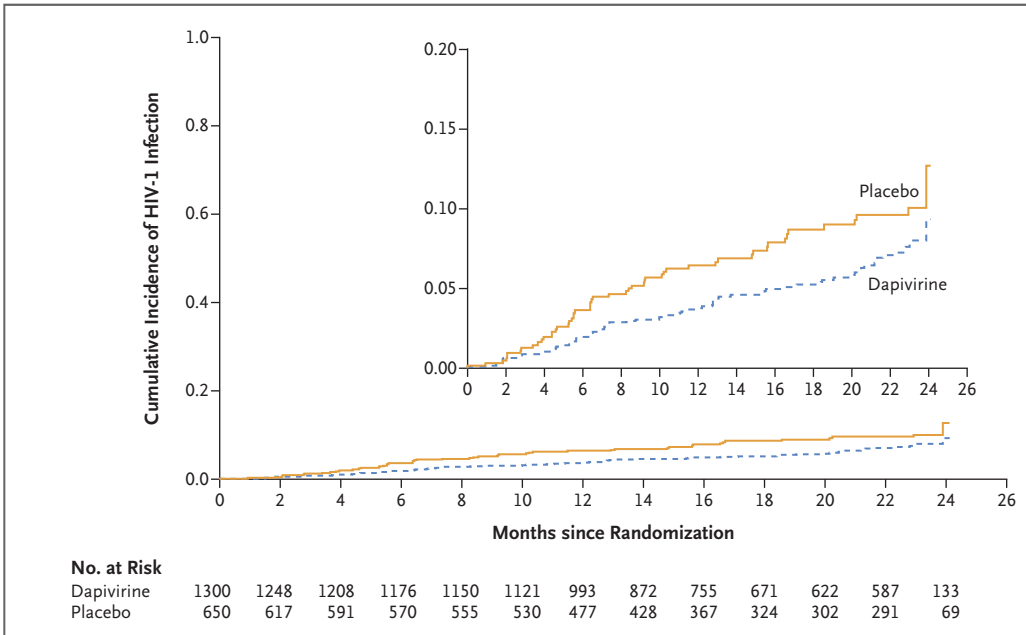


Figure 2. Time to Seroconversion, on the Basis of Confirmed Trial End Points, in the Modified Intention-to-Treat Population.

Shown are data in the analysis window up to the end of the week 104 (last product-use visit). Eight participants in the dapivirine group and nine in the placebo group had longer follow-up time, including one participant in the dapivirine group and four in the placebo group who had seroconversion at the exit visit. The inset shows the same data on an enlarged y axis. HIV-1 denotes human immunodeficiency virus type 1.

dapivirine. The overall median residual level of dapivirine in the rings was 21 mg. Dapivirine was detected at levels of 95 pg or more per milliliter of plasma in 84% of the samples obtained every 4 weeks. Overall, the median plasma concentration of dapivirine was 264 pg per milliliter. At all visits, at least 73% of the participants had a residual level of 23.5 mg or less of dapivirine in the ring and a plasma concentration of at least 95 pg of dapivirine per milliliter (Table S5 in the Supplementary Appendix).

SAFETY

Adverse Events

The cumulative incidence of adverse events during the trial was similar in the dapivirine group (1142 of 1306 participants [87.4%]) and the placebo group (559 of 652 [85.7%]). A total of 63 participants (4.8%) in the dapivirine group and 19 (2.9%) in the placebo group had an adverse event of grade 3 or 4 during the trial (Table 3, and Table S6 in the Supplementary Appendix). The difference between the trial groups was not significant, and none of these adverse events were assessed by the investigators as being product-related. Three deaths (grade 5 events) were reported. All other adverse events during the trial were of grade 1 or 2 (Table S7 in the Supplementary Appendix).

Overall, 44 participants (38 [2.9%] in the dapivirine group and 6 [0.9%] in the placebo group) had at least one serious adverse event (Table 3, and Table S8 in the Supplementary Appendix). The difference between the groups was significant ($P=0.008$), but no patterns were identified to indicate clinical relevance. The investigators considered none of the serious adverse events to be product-related, and no serious adverse events resulted in the withdrawal of participants from the trial. Two participants in the dapivirine group died (one from multiple injuries sustained in a motor vehicle accident and one from a gunshot wound), and one participant in the placebo group died (from circulatory collapse during substance abuse).

Product-related events were reported in five participants (0.4%) in the dapivirine group and in three (0.5%) in the placebo group (Table 3,

Table 3. Adverse Events during the Trial.*

Event	Dapivirine (N=1306)	Placebo (N=652)
	no. of participants (%)	
Any event	1142 (87.4)	559 (85.7)
Serious adverse event†	38 (2.9)	6 (0.9)
Grade 3 or 4 adverse event‡	63 (4.8)	19 (2.9)
Product-related adverse event§	5 (0.4)	3 (0.5)
Event leading to death¶	2 (0.2)	1 (0.2)
Event leading to premature discontinuation of product	0	1 (0.2)

* Grading of events was performed according to criteria of the Division of AIDS, National Institute of Allergy and Infectious Diseases.[9]
† P=0.01 for the comparison of serious adverse events by a continuity-adjusted chi-square test.
‡ P=0.06 for the comparison of grade 3 or 4 adverse events by a continuity-adjusted chi-square test.
§ Included in this category were events that were assessed by the investigators as being related to the product or events for which as assessment of product-relatedness was missing. There were no grade 2 or serious product-related adverse events.
¶ Two participants in the dapivirine group died (one from multiple injuries sustained in a motor vehicle accident and one from a gunshot wound), and one participant in the placebo group died (from circulatory collapse during substance abuse).

and Table S9 in the Supplementary Appendix). All the events that were considered by the investigators to be product-related were mild in severity. One participant who was assigned to receive the placebo ring discontinued the trial early owing to grade 2 cervical dysplasia, which required further evaluation and treatment.

Safety Laboratory Findings

No relevant differences between the two trial groups were observed in the incidence of laboratory abnormalities during the trial. Most laboratory abnormalities were not clinically relevant and were either mild (grade 1) or did not meet the criteria for grade 1 (in 1001 participants [76.6%] in the dapivirine group and 505 [77.5%] in the placebo group).

Sexually Transmitted Infections and Other Genital Infections

The overall incidence rates of sexually transmitted infections were similar in the two trial groups. We observed 32.0 infections (95% CI, 29.6 to 34.5) per 100 person-years in the dapivirine group and 31.1 infections (95% CI, 27.7 to 34.6) per 100 person-years in the placebo group (Table S10 in the Supplementary Appendix).

Pregnancy Incidence Rate

The incidence of pregnancy during the trial was similar in the two groups. We observed 1.6 pregnancies (95% CI, 1.1 to 2.2) per 100 person-years in the dapivirine group and 2.0 pregnancies (95% CI, 1.2 to 2.9) per 100 person-years in the placebo group.

DISCUSSION

In the Ring Study, the insertion of a dapivirine vaginal ring every 4 weeks was associated with a 31% lower risk of HIV-1 acquisition than was a placebo ring among women at high risk for HIV infection in two countries in sub-Saharan Africa. The cumulative probability curves of the incidence of HIV-1 infection indicated that the prevention benefit of the dapivirine vaginal ring was achieved early in the trial and was sustained. Divergence in the trial groups did not, however, increase over time. This result is in contrast to that observed in the ASPIRE trial (A Study to Prevent Infection with a Ring for Extended Use),[10] a multicenter, randomized, double-blind, placebo-controlled, phase 3 safety and effectiveness trial of a vaginal matrix ring containing dapivirine for the prevention of HIV-1 infection in women, in which the benefit from the dapivirine vaginal ring was apparent only after the first 12 months — a finding that was attributed to participants needing time to become comfortable with using the ring.

Analysis according to age group showed a 37% lower rate of HIV-1 acquisition with the dapivirine ring than with the placebo ring among women older than 21 years of age and a 15% lower rate among those 21 years of age or younger (the age effect was not significant). In the ASPIRE trial,[10] age was shown to be significantly related to protection against HIV-1 infection, with no protection observed among participants 18 to 21 years of age and with a 56% lower rate observed among participants older than 21 years of age. The lower level of protection that was observed among younger women may be due to physiologic differences in the genital tract of younger women, lower adherence to ring use,

more frequent vaginal or anal sex, or a combination of these factors. Further analyses of the data from our trial may shed light on the reasons for the lower rate of protection in this younger cohort.

Measurements of dapivirine in monthly plasma samples and in used rings indicate that most women in the trial used the ring at some time during each month. Although the overall protective effect that was observed with the dapivirine vaginal ring was significant, prespecified adherence analyses that were based on a cutoff of 23.5 mg or less in the residual level of dapivirine in used rings and a concentration of 95 pg or more of dapivirine per milliliter of plasma did not show increased protection. Previous trials investigating HIV prevention have shown relationships between adherence to the regimen and HIV-1 protection,[11-13] and a similar outcome was anticipated in this trial. However, the prespecified criteria that were based on plasma concentrations and residual levels of dapivirine in the used rings may not be the most appropriate criteria for assessment of adherence. Both criteria have substantial limitations.

Pharmacokinetic studies have shown that plasma levels rise rapidly after insertion of the dapivirine vaginal ring, because the initial release of dapivirine from the ring follows first-order kinetics. Dapivirine is detectable in plasma as early as 1 hour after insertion of the ring, and average concentrations exceed 100 pg per milliliter within 8 hours.[14] Thus, women who may have used the ring intermittently or just before a clinic visit would have a plasma concentration of more than 95 pg of dapivirine per milliliter. Indeed, the requirement of the trial that women remove the used ring at the clinic before inserting a new ring probably contributed to an overestimation of adherence in participants.

The prespecified residual level of more than 23.5 mg of dapivirine in the ring, which was based on data from a phase 1–2 study conducted in sub-Saharan Africa,[15] was used during the trial to identify the proportion of participants in the dapivirine group who were more than 95% likely to be completely nonadherent to the regimen. However, the median residual level of dapivirine that was observed in the phase 1–2 trial and in two phase 1 trials[15,16] as well as in the Ring Study was 21 mg and is, therefore, probably a better indicator of sustained adherence to ring use. An exploratory time-varying product-adherence analysis in which adherence was defined as a residual level of 21 mg or less of dapivirine in the ring showed a rate of HIV-1 acquisition that was 44% (95% CI, 7 to 67) lower during adherent periods than during nonadherent periods. Further analyses of the data from our trial may assist in determining a more appropriate definition of adherence on the basis of objective measures.

Mutations that were associated with resistance to NNRTIs were generally observed with similar frequency in the dapivirine group and the placebo group, with the exception of the mutation E138A, which was observed more frequently in the dapivirine group. The E138A substitution is a polymorphism of HIV-1 subtype C, and although it is associated with rilpivirine and etravirine, two close analogues of dapivirine,[17] it is not associated with nevirapine and efavirenz, which are the more widely used NNRTIs in sub-Saharan Africa. The data are consistent with the data from the ASPIRE trial,[10] which also showed no significant difference between the dapivirine group and the placebo group in the numbers of participants with NNRTI mutations suggesting antiviral resistance.

No significant differences in the percentage of patients with serious adverse events were seen between the dapivirine group and the placebo group in the ASPIRE trial. Close monitoring for safety in future studies will help clarify these findings.

The incidence rate of 6.1 seroconversions per 100 person-years that we observed in the placebo group occurred in the context of a clinical trial in which all the participants received regular HIV testing and counseling, treatment for sexually transmitted infections, and free condoms. In addition, participants in this trial live in communities in which male circumcision by medical personnel and HIV treatment are widely available.[18] Continued high rates of HIV transmission underscore the need for new HIV prevention approaches for women. The protection that was observed in this trial among high-risk women is lower than that shown with once-daily tenofovir or combination tenofovir–emtricitabine oral prophylaxis in men who have sex with men[19] and in heterosexual HIV-1–discordant couples.[20]

However, in two clinical trials of tenofovir and of tenofovir or tenofovir–emtricitabine oral prophylaxis in participants who are similar to those enrolled in our trial, no protection against HIV-1 infection was observed, because of poor adherence to the daily use of the trial drugs.[11,12] Similarly, in studies that evaluated microbicides, one study of a vaginal gel containing tenofovir showed evidence of protection from HIV-1 infection,[21] but this result was not confirmed in subsequent studies.[12,13]

The dapivirine vaginal ring was developed to provide discreet, self-initiated, monthly use with the potential for high adherence. Most participants were able to use the ring for some time of each month, as shown by the residual levels in the used rings and by the plasma concentrations. Several studies have identified reasons for nonadherence among female participants in HIV-prevention trials, including concerns about the potential side effects of the product.[22-24] Increases in adherence to oral preexposure prophylaxis have been shown in open-label studies,[25-27] and similar trials with the dapivirine vaginal ring are ongoing.

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APPENDIX

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