Safety, uptake, and use of a dapivirine vaginal ring for HIV-1 prevention in African women (HOPE): an open-label, extension study

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Summary

Background Two phase 3 clinical trials showed that use of a monthly vaginal ring containing 25 mg dapivirine was well tolerated and reduced HIV-1 incidence in women by approximately 30% compared with placebo. We aimed to evaluate use and safety of the dapivirine vaginal ring (DVR) in open-label settings with high background rates of HIV-1 infection, an important step for future implementation.

Methods We did a phase 3B open-label extension trial of the DVR (MTN-025/HIV Open-label Prevention Extension [HOPE]). Women who were HIV-1-negative and had participated in the MTN-020/ASPIRE phase 3 trial were offered 12 months of access to the DVR at 14 clinical research centres in Malawi, South Africa, Uganda, and Zimbabwe. At each visit (monthly for 3 months, then once every 3 months), women chose whether or not to accept the offer of the ring. Used, returned rings were tested for residual amounts of dapivirine as a surrogate marker for adherence. HIV-1 serological testing was done at each visit. Dapivirine amounts in returned rings and HIV-1 incidence were compared with data from the ASPIRE trial, and safety was assessed. This study is registered with ClinicalTrials.gov, NCT02858037.

Findings Between July 16, 2016, and Oct 10, 2018, of 1756 women assessed for eligibility, 1456 were enrolled and participated in the study. Median age was 31 years (IQR 27–37). At baseline, 1342 (92·2%) women chose to take the DVR; ring acceptance was more than 79% at each visit up until 12 months and 936 (73·2%) of 1279 chose to take the ring at all visits. 12 530 (89·3%) of 14 034 returned rings had residual dapivirine amounts consistent with some use during the previous month (>0·9 mg released) and the mean dapivirine amount released was greater than in the ASPIRE trial (by 0·21 mg; p<0·0001). HIV-1 incidence was 2·7 per 100 person-years (95% CI 1·9–3·8, 35 infections), compared with an expected incidence of 4·4 per 100 person-years (3·2–5·8) among a population matched on age, site, and presence of a sexually transmitted infection from the placebo group of ASPIRE. No serious adverse events or grade 3 or higher adverse events observed were assessed as related to the DVR.

Interpretation High uptake and persistent use in this open-label extension study support the DVR as an HIV-1 prevention option for women. With an increasing number of HIV-1 prophylaxis choices on the horizon, these results suggest that the DVR will be an acceptable and practical option for women in Africa.

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Introduction

More than half of the 1·7 million people who newly aquire HIV-1 each year are women, and women in some African settings (mostly in southern and eastern Africa) have among the highest rates of HIV-1 in any population worldwide.[1,2] The use of antiretroviral medications as pre-exposure prophylaxis (PrEP) by people who do not have HIV-1 has been shown to be effective for preventing HIV-1 acquisition.[3,4] Oral tablets taken daily containing the antiretroviral tenofovir disoproxil fumarate, alone or in combination with emtricitabine, was the first PrEP approach to show HIV-1 prevention efficacy and gain normative guidance. In settings in which PrEP with tenofovir disoproxil fumarate plus emtricitabine has been scaled up, declines in the rate of new HIV-1 infections have been seen at the population level, showing the importance of PrEP in curtailing the global HIV-1 epidemic.[5,6]

Although global implementation of PrEP with tenofovir disoproxil fumarate plus emtricitabine is expanding, it is

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Research in context

Evidence before this study

We searched PubMed between Jan 1, 2000, and Oct 15, 2020, for articles and relevant conference abstracts in any language with the term "dapivirine". We included publications if they reported results of phase 3 clinical trials. Two randomised, double-blind, placebo-controlled phase 3 clinical trials showed that a vaginal ring containing 25 mg dapivirine, worn for a month at a time, was well tolerated and reduced HIV-1 incidence. Specifically, HIV-1 incidence in the two trials was 3·3 versus 4·5 per 100 person-years in one trial and 4·1 versus 6·1 per 100 person-years in the second trial among those assigned the dapivirine vaginal ring (DVR). Adherence was modest in those trials and other clinical trials of pre-exposure prophylaxis (PrEP) against HIV-1 among African women. Reported reasons for non-adherence included uncertainty about the safety of an unproven product. Previous studies of oral PrEP with tenofovir disoproxil fumarate plus emtricitabine found greater adherence in open-label contexts (ie, trials occurring after demonstration of efficacy and without the potential to be assigned placebo) than in the initial placebo-controlled trials.

Added value of this study

We did a phase 3B open-label extension trial of the DVR among women who were HIV-1-negative who had participated in the completed ASPIRE phase 3 trial. These results provide an example of open-label access to the DVR. Ring use adherence was assessed objectively by testing for residual amounts of dapivirine in returned rings.

Implications of all the available evidence

High uptake and persistent use of the DVR in this study, coupled with high tolerability, suggest that the DVR is an acceptable and practical HIV-1 prevention option for women in Africa. These results support continued regulatory evaluation that might lead to widespread introduction of the DVR.

not at a sufficient pace to meet the goal set by UNAIDS of 3 million people taking oral PrEP by 2020.[1] Furthermore, in clinical trials, demonstration projects, and implementation settings worldwide, a sizable proportion of individuals offered the drug combination decline to initiate, discontinue soon after starting, or do not adhere sufficiently to gain HIV-1 protection.[7] In both clinical trials and in real-world settings, many African women have not shown high adherence to PrEP with tenofovir disoproxil fumarate plus emtricitabine.[8] Alternatives to daily oral PrEP are required and multiple options are needed to address users' preferences and needs.[9,10] Additional alternative PrEP options to tenofovir disoproxil fumarate plus emtricitabine pills are under development; particularly attractive are approaches not requiring daily use, with topical, injectable, implantable, and pill forms in clinical studies.[11–13]

Vaginal rings are a well accepted delivery method that have been developed to provide controlled and sustained release of medications;[14] vaginal ring products containing exogenous hormones are licensed for contraception and oestrogen replacement.[15] For HIV-1 prevention, a vaginal ring containing the antiretroviral non-nucleoside HIV-1 reverse transcriptase inhibitor dapivirine, designed to be used for 1 month at a time, was shown in two phase 3 clinical trials to be well tolerated and to reduce HIV-1 acquisition risk in women by approximately 30% compared with placebo (HIV-1 incidence 3·3 *vs* 4·5 per 100 person-years in one trial and 4·1 *vs* 6·1 per 100 person-years in the second trial).[16,17] For PrEP with tenofovir disoproxil fumarate plus emtricitabine, the transition from placebo-controlled trials to implementation settings was bridged by open-label studies (ie, trials occurring after demonstration of efficacy, with all participants having access to the active product, and without the potential to be assigned placebo), including extension trials among populations that had previously participated in the phase 3 trials.[18,19] Here, we report the results of an open-label extension trial of ASPIRE, in which we aimed to assess the uptake and use of the dapivirine vaginal ring (DVR).

Methods

Study design and participants

MTN-025/HIV Open-label Prevention Extension (HOPE) was a phase 3B, open-label extension trial of the DVR at 14 clinical research centres in Malawi (Blantyre, Lilongwe), South Africa (Cape Town, Durban [six sites], Johannesburg), Uganda (Kampala), and Zimbabwe (Chitungwiza [two sites], Harare). The primary objectives were to assess adherence to and safety of the DVR (25 mg), to be inserted continuously for 1 month at a time (QPharma, Malmö, Sweden) when used in an open-label setting. The population consisted of women who had previously participated in the phase 3, placebo-controlled MTN-020/ASPIRE trial and who remained HIV-1-negative. Those who enrolled in HOPE were offered 12 months of access to the DVR and could join the study and choose whether or not to accept the ring at each follow-up visit. ASPIRE concluded follow-up on June 25, 2015, and reported results on Feb 22, 2016. HOPE initiated enrolment on Aug 15, 2016, concluded enrolment on May 24, 2018, and completed follow-up on Oct 10, 2018. Participants did not have access to the DVR between completing ASPIRE and initiating HOPE but were referred to local services for HIV-1 testing and prevention.

All women who remained HIV-1-negative at the conclusion of ASPIRE were offered screening for participation in HOPE. In addition to negative HIV-1 serological status, women were required to be using an effective method of contraception at the time of entry into HOPE, to not be pregnant or breastfeeding, and to otherwise be healthy, with no contraindications to use of the DVR,

including no safety concern requiring permanent product discontinuation while participating in ASPIRE.

An extensive scientific and community consultation process was done before initiation of HOPE, including participation of community representatives from each study site, to consider the key next steps for the DVR and to plan the study design and conduct of the trial. The study protocol was approved by ethics review committees at each study site, which also approved participant reimbursement for study visit time and travel. All participants provided written informed consent.

Procedures

Study visits occurred at enrolment, monthly for 3 months, then once every 3 months for 12 months, transitioning towards the type of visit schedule that would be more applicable to real-world implementation settings. At each visit, women were counselled that they could choose to accept or decline the DVR at any point and still continue in the study;[20] participants choosing to accept were provided with a sufficient number of DVRs to last until their next scheduled visit (ie, one per visit during the first 3 months and three per visit thereafter). Women were taught how to insert and remove the vaginal ring and counselled to keep the ring inserted for the entire month. At visits once every 3 months, three rings were provided and women were instructed to change the ring monthly. Used rings were returned at each scheduled follow-up visit. Counselling about the ring as an HIV-1 prevention option was provided in the context of comprehensive counselling on HIV-1 prevention, including behavioural change for risk reduction, partner HIV-1 testing, testing and treatment of sexually transmitted infections (STIs) in participants and partners, and offer of free condoms; referrals were provided to access oral PrEP with tenofovir disoproxil fumarate plus emtricitabine at local clinics, at enrolment, or at any time during follow-up.

Follow-up visits included HIV-1 serological testing, safety monitoring, and individualised adherence counselling. Women were tested for pregnancy at each visit and the study ring was withheld from women who became pregnant; they resumed use of the ring when no longer pregnant or breastfeeding. The study protocol mandated temporary product holds for clinical safety reasons such as genital ulceration, severe genital erythema, cervicitis, grade 3 adverse events that study clinicians considered related to the investigational product, and all grade 4 adverse events.

Testing for residual dapivirine in returned rings was done with acetone extraction and high-pressure liquid chromatography (Parexel, Bloemfontein, South Africa). Results of residual dapivirine tests were provided to participants at the subsequent visit. Initially, testing for dapivirine in plasma was planned, but evidence emerged suggesting that residual amounts of dapivirine in returned rings was a better adherence measure and possibly related to better HIV-1 protection than plasma concentrations.[21]

HIV-1 diagnostic testing was done with a standard algorithm, beginning with two different HIV-1 rapid tests (generally one third and one fourth generation) done in parallel, followed by a confirmatory test (Bio-Rad HIV-1/2 Geenius, Hercules, CA, USA) if either or both rapid tests were positive. The study ring was temporarily withheld while confirmatory testing was pending and was permanently discontinued if testing confirmed HIV-1 acquisition. Participants completed a final study visit 4 weeks after the last study product use visit to assess for delayed HIV-1 seroconversion. Resistance testing was done with standard population genotyping.[22] Archived plasma samples from visits before HIV-1 seroconversion were tested by HIV-1 RNA PCR, and participants with detectable HIV-1 RNA at enrolment were excluded as primary study endpoints because HIV-1 infection occurred before trial entry. Women who tested positive for HIV-1 at the visit 4 weeks after the last study product use visit and who had detectable HIV-1 RNA at the last product use visit were included as primary study endpoints because HIV-1 infection occurred during the product use period. HIV-1 seroconversions that were unclear according to the HIV-1 testing algorithm defined in the trial protocol were evaluated by an endpoint committee that did not participate in the day-to-day oversight of the study.

Outcomes

The primary adherence endpoint was residual ring dapivirine amounts, an objective measure of use of the DVR.[21] The primary safety endpoint for the study was defined as a composite of any serious adverse event, any grade 3 and 4 adverse events, and those grade 2 adverse events assessed by the study clinicians as related to the study product. Additional outcomes included uptake and acceptance of the DVR at enrolment and during follow-up, as well as incident HIV-1 acquisition.

Statistical analysis

The percentage of women accepting the ring overall and at scheduled visits was calculated. The proportion of women accepting the ring throughout all 12 months of follow-up was calculated, limited to those eligible to choose the ring for all 12 months (eg, excluding those who could not receive a ring for all months, such as during pregnancy). Adherence was reported according to the amount of dapivirine released from returned rings and categorised as 0·9 mg or less, more than 0·9 mg to 4·0 mg, and more than 4·0 mg, all normalised to account for the number of days between ring dispensation and return. The first category corresponds to zero plus one SD of measurement error, thus likely to reflect no use.[22] The third corresponds to the amount of drug expected to be released from the ring with high certainty with 28 days of continuous use.[17] The middle category thus reflected at least some use and probably encompassed both incomplete or inconsistent use as

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See **Online** for appendix

For **study protocol** see https://mtnstopshiv.org/research/studies/mtn-025/mtn-025-protocols

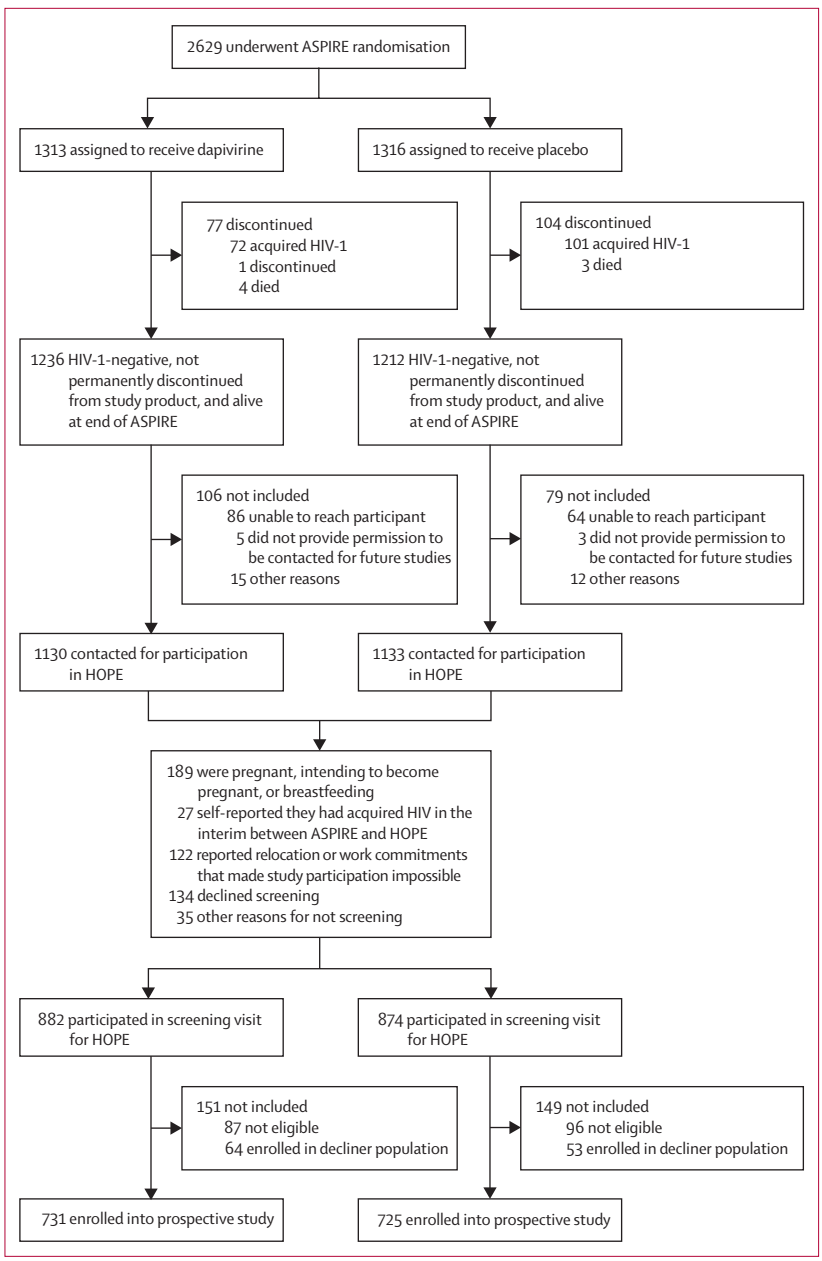

Figure 1: **Study profile**
507 participants were contacted but not screened. Study sites collated information on reasons based on their recruitment logs, but as these participants had not provided informed consent these reasons could not be captured in the database and are only available overall, not by ASPIRE randomisation group.

well as near-consistent use. Adherence data were assessed over time, including assessment of consistent use (defined as ≥0·9 mg dapivirine released from all three rings in 3 months) and persistent use (defined as ≥0·9 mg dapivirine released from all three rings in 3 months for all 12 months of follow-up). Factors associated with persistent use were evaluated with logistic regression adjusted for site. Finally, adherence was compared among women accepting the ring throughout follow-up to those not accepting the ring at all visits using linear mixed effects models with random intercepts adjusted for site and age. Residual amounts of dapivirine in returned, used rings were compared between those observed in HOPE and those measured in ASPIRE; data were restricted to women who participated in both studies and who were assigned to the active DVR group (as opposed to placebo) in ASPIRE. Data were compared with generalised estimating equations with exchangeable correlation and identity link function. In ASPIRE, testing for residual dapivirine in used rings was initiated after the first year of the trial; increased HIV-1 prevention efficacy was observed in subgroups of women with evidence of greater adherence.[22]

Safety was evaluated in the subset of participants who ever received a DVR during the study. The number and proportion of participants who had an adverse event in this subset are reported by severity and grade.

HIV-1 incidence was calculated as the number of participants with incident HIV-1 infection divided by the total number of person-years, with an exact CI for a Poisson event rate. HIV-1 incidence observed in the study was compared with an expected counterfactual HIV-1 incidence in a simulated similar population at risk, analogous to approaches used in other open-label studies of HIV-1 prevention interventions.[23] For the counterfactual model, a bootstrap resampling study was done, in which for each simulation we constructed a bootstrap sample of women from the placebo group of ASPIRE, with a distribution of HIV-1 risk characteristics (study site, age, presence of a curable STI at baseline) and duration of follow-up to match those of the present study. This resampling approach then estimated the incidence of HIV-1 infection in the absence of an intervention. Specifically, we used a weighted resampling approach to sample participants from the placebo group in ASPIRE in proportion to the prevalence of risk factors in HOPE. In both studies, we created cells according to age group (in 5-year increments from 20 to 49 years), site, and curable STI status. We calculated the proportion of participants within each cell in HOPE and then sampled participants with replacement from the cells in the ASPIRE placebo group according to the HOPE proportions. We repeated this process 10 000 times, each time calculating the incidence within the first year of ASPIRE; a 95% CI was defined by the 2·5th and 97·5th quantiles.

Analyses were done with SAS, version 9.4, and R, version 2.15.1, and all p values were two-sided. This study is registered with ClinicalTrials.gov, NCT02858037.

Role of the funding source

Representatives from both the funder and the regulatory sponsor were members of the study team, participated in trial design and execution, and contributed to data interpretation and writing of the report. All authors

had full access to all the data in the study and the corresponding author had final responsibility for the decision to submit for publication.

Results

Between July 16, 2016, and Oct 10, 2018, women were enrolled and participated in the study. Of 2629 women who participated in ASPIRE (figure 1), 2448 remained HIV-1-negative, not permanently discontinued from product, and alive at its conclusion, and 2263 (92·4%) were approached for potential participation in HOPE; of the remainder, 150 were unable to be contacted, eight did not provide permission for contact for future studies, one had been permanently discontinued from the study product during ASPIRE, and 27 were not approached for other reasons. Of the 2263 approached, 507 (22·4%) were not screened: 189 were pregnant, intending to become pregnant, or breastfeeding and were thus ineligible, 27 self-reported they had acquired HIV in the interim between ASPIRE and HOPE, 122 reported relocation or work commitments that made study participation impossible, 134 declined screening, and 35 had other unspecified reasons. Thus, in total, 1756 were screened, of whom 183 (10·4%) were ineligible (45 HIV-1-positive, 69 were pregnant or breastfeeding, 69 had other reasons), 117 (6·7%) declined study participation, and 1456 (82·9%) were enrolled into the prospective study (1456 [59·5%] of 2448 of those who were HIV-1-negative at the completion of ASPIRE).

Of 1456 enrolled, 157 (10·8%) were from Malawi, 707 (48·6%) from South Africa, 172 (11·8%) from Uganda, and 420 (28·8%) from Zimbabwe, a similar distribution across countries as was seen in ASPIRE. Median age was 31 years (IQR 27–37) and 181 (12·4%) of 1456 were younger than 25 years (table 1). Less than half (686 [47·1%] of 1456) of participants were married, 630 (43·3%) reported use of a condom with the last sex act, and 230 (15·8%) had a curable STI at study screening. In general, these characteristics, except age (given that HOPE enrolled only women who had previously completed ASPIRE and thus all had aged), were generally similar to those among the full population of women at baseline in ASPIRE. Oral PrEP with tenofovir disoproxil fumarate plus emtricitabine was reported by 16 women (at 36 visits) during HOPE.

Participants completed 8436 (97·9%) of 8621 expected follow-up visits. At enrolment, 1342 (92·2%) of 1456 women accepted the DVR and acceptance of the ring remained high throughout follow-up: 90·1% (1287 of 1428) at month 1, 88·5% (1259 of 1422) at month 2, 86·9% (1240 of 1427) at month 3, 83·3% (1169 of 1404) at month 6, and 79·3% (1093 of 1379) at month 9. Excluding women who acquired HIV-1 or who had a medical reason for not using the ring (eg, for incident pregnancy), 936 (73·2%) of 1279 women accepted the ring for all 12 months of follow-up. The most common reasons for not accepting the ring at a visit (total 975 visits at which the participant opted to not accept) were: the participant prefers alternative HIV-1 prevention strategies (415 [42·6%] visits), participant not interested in receiving the ring (199 [20·4%] visits), participant not ready to receive the ring (134 [13·7%] visits), partner unsupportive of ring use (106 [10·9%] visits), and other reasons (139 [14·3%] visits); side-effects were rarely reported as a reason to decline the ring (36 [3·7%] visits) as was feeling the ring was less effective than the participant wanted (21 [2·2%] visits), intending to fall pregnant (seven [0·7%] visits), and family unsupportive (two [0·2%] visits).

	HOPE (n=1456)	ASPIRE (n=2629)
Age, years	32·0 (6·5)	27·2 (6·2)
Median age (range)	31 (20–49)	26 (18–45)
Secondary school education or higher	1196 (82·1%)	2225 (84·6%)
Earns own income	889 (61·1%)	1186 (45·1%)
Currently married	686 (47·1%)	1074 (40·9%)
≥2 male sexual partners in the past 3 months	272 (18·7%)	436 (16·6%)
Episodes of vaginal intercourse in the past 3 months	23·6 (22·8)	26·5 (24·6)
Condom use during last vaginal intercourse	630 (43·3%)	1508 (57·4%)
Transactional sexual intercourse in past year	107/1447 (7·4%)	162/2618 (6·2%)
Contraception method		
Intrauterine device	265 (18·2%)	325 (12·4%)
Oral contraceptive pills	214 (14·7%)	287 (10·9%)
Depot medroxyprogesterone acetate	466 (32·0%)	1070 (40·7%)
Norethisterone enanthate	103 (7·1%)	381 (14·5%)
Hormonal implant	345 (23·7%)	501 (19·1%)
Sexually transmitted infections		
Chlamydia trachomatis	129 (8·9%)	316 (12·0%)
Neisseria gonorrhoeae	27 (1·9%)	109 (4·1%)
Treponema pallidum	22 (1·5%)	39 (1·5%)
Trichomonas vaginalis	80 (5·5%)	181 (6·9%)

Data are mean (SD) or n (%), unless specified.

Table 1: **Baseline characteristics**

Of 14463 rings dispensed, 14270 (99·7%) were returned and 14034 (97·0%) were tested for residual amounts of dapivirine. Overall, 12530 (89·3%) of 14034 rings had more than 0·9 mg of dapivirine released, indicating at least some use. The median amount of dapivirine released was 3·2 mg (IQR 2·4–4·3) and was relatively unchanged throughout the 12-month follow-up period (figure 2, appendix p 8). The mean amount released was greater (p<0·0001) in the open-label HOPE study than in the placebo-controlled ASPIRE study (figure 3); returned rings from HOPE had a mean of 0·21 mg more dapivirine released (95% CI 0·18–0·25; p<0·0001) than ASPIRE.

Consistent and persistent use was evaluated in 1277 participants with 4595 evaluations once every 3 months of which 3536 (77·0%) had evidence of use throughout the 3 months (ie, all three rings each with ≥0·9 mg of dapivirine released): 77·0% (983 of 1276) in months 1–3, 79·9% (936 of 1172) in months 4–6, 78·3% (866 of 1106) in months 7–9, and 72·1% (751 of 1041) in months 10–12. Overall, 562 (44·0%) of

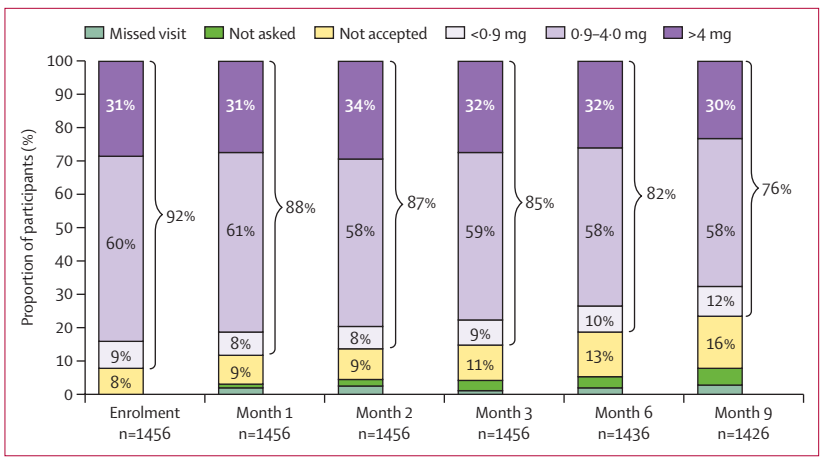

Figure 2: **Dapivirine released, by study visit**

Residual amounts of dapivirine in returned, used rings, by study visit of ring dispensing, showing amount of use of the dapivirine vaginal ring over 12 months of follow-up. Percentages in purple represent the proportion of tested rings dispensed at that visit in each category of adherence; the black bar to the right of each column represents the proportion of women accepting rings at each visit. Reasons for not being dispensed a ring are shown in line with the key.

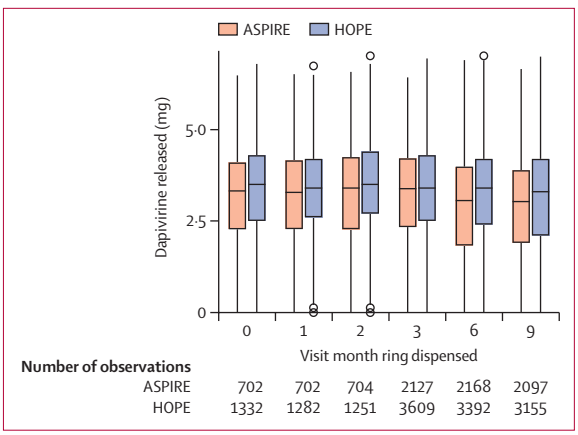

Figure 3: **Comparison of dapivirine released between the HOPE and ASPIRE studies**

Residual amounts of dapivirine in returned, used rings were compared between the phase 3B, open-label MTN-025/HOPE study and the phase 3, placebo-controlled MTN-020/ASPIRE study. Data are restricted to women who participated in both studies and who were assigned to the active dapivirine vaginal ring group as opposed to placebo in MTN-020/ASPIRE. Data were compared using generalised estimating equations: p<0·0001. Boxes represent median and IQR, whiskers represent 1·5 × IQR, and circles represent any observed values outside the range covered by the whiskers.

1277 women were classified as having persistent use through all 12 months of follow-up. Younger age (<25 years *vs* ≥25 years) was not associated with poorer use, nor were self-reported behavioural risk factors for HIV-1 acquisition—ie, condom use, number of partners, and frequency of intercourse (table 2). Consistent use in the previous 3 months strongly predicted subsequent consistent use. For months 4–6, the adjusted odds ratio (OR) was 7·18 (95% CI 5·05–10·27); for months 7–9, the adjusted OR was 6·10 (4·25–8·79); and for months 10–12, the adjusted OR was 8·92 (6·16–13·06). Women who chose to accept the ring at all visits during follow-up had greater amounts of dapivirine released from used rings than those who accepted the ring only at some visits (3·4 mg [IQR 2·5–4·3] *vs* 3·1 mg [1·5–4·1]). Adjusted for site and age, those who always accepted the ring had a mean of 0·72 mg (95% CI 0·57–0·88; p<0·0001) more dapivirine released from rings than women who inconsistently accepted the rings.

The frequency, severity, and type of adverse events observed were similar to those seen in the phase 3 trials of the DVR (table 3), with no new safety signal observed. No serious adverse event or grade 3 or worse adverse event was assessed by study clinicians to be related to the use of the DVR. Serious adverse events occurred in 19 participants, across 22 events (appendix p 9). One participant died due to pneumonia.

Grade 4 adverse events occurred in four participants (appendix p 9). Grade 3 adverse events occurred in 50 participants over 55 events (appendix p 9). Grade 2 adverse events assessed as related to investigational product occurred in two participants (abdominal pain [n=1] and pelvic pain with DVR insertion [n=1]).

35 incident HIV-1 infections occurred, at an incidence of 2·7 per 100 person-years (95% CI 1·9–3·8) two among participants from Malawi, 24 from South Africa, zero from Uganda, and nine from Zimbabwe). Counterfactual simulations based on data from the placebo group of ASPIRE predicted a median incidence of 4·4 per 100 person-years (95% CI 3·2–5·8) and thus the reduction in HIV-1 incidence in HOPE was estimated at 39% (95% CI 14–65); an incidence of 2·7 or less per 100 person-years would occur in less than 33 of 10 000 bootstrap samplings. Among the 35 infections, seven had non-nucleoside reverse transcriptase mutations (four Lys103Asn, one Ala98Gly, one Glu138Ala and Val179Asp, one Val106Met and Val179Asp), none of which suggest a dapivirine-specific resistance pattern.

Discussion

This multicentre, open-label extension trial of the DVR across four different countries found high uptake, evidence of good adherence and persistence throughout 12 months of access, a well tolerated safety profile consistent with that seen in the previous phase 3 studies, and lower HIV-1 incidence than expected in the absence of the ring. These results show that the DVR is an HIV-1 prevention option that women living in settings with high background risk of HIV-1 can use effectively.

In this study, women were offered the choice to accept or not accept the DVR, and the vast majority initially accepted the ring and most continued throughout 12 months. Testing of returned rings for residual amounts of dapivirine was used as an objective measure of adherence[21] and most rings had amounts consistent with at least some use. As has been seen in open-label studies of oral PrEP, adherence was greater in the open-label setting than in the blinded, placebo-controlled phase 3

	Odds ratio	95% CI	p value
Aged <25 years (*vs* ≥25 years)	0·83	0·54–1·25	0·37
Currently married (*vs* not married)	1·33	0·97–1·84	0·078
Number of livebirths (*vs* 0–1)			
2	1·40	0·99–1·99	0·058
3	1·68	1·14–2·49	0·0090
≥4	2·02	1·31–3·12	0·0016
Hormonal contraceptive use (*vs* intrauterine device)			
Oral contraceptive pills	0·77	0·50–1·20	0·25
Depot medroxyprogesterone acetate	1·55	1·08–2·21	0·014
Norethisterone enanthate	1·25	0·72–2·17	0·43
Hormonal implant	1·05	0·73–1·50	0·79
Any sexually transmitted infection (*vs* none)	0·77	0·56–1·06	0·11

Persistence defined as 0·9 mg or more dapivirine released from all three rings in 3 months or for all 12 months of follow-up. Analyses done with logistic regression, adjusted for site. Factors included in the table were associated (p<0·1) with persistence in univariate analysis and then included in the multivariable model. Factors not associated (at p<0·1) in univariate analysis included education, income, distance to clinic, whether or not participant had a primary sexual partner, partner aware of ring use, partner living with HIV, any non-primary partners, number of vaginal or anal sexual acts, any practice of transactional sexual intercourse, alcohol use, and randomisation group (active *vs* placebo) in ASPIRE.

Table 2: **Participant characteristics and association with persistent use of the dapivirine vaginal ring**

	Primary safety endpoint events (n=1368)
Primary safety endpoint*	54 participants (3·9%)
Any serious adverse event	19 participants (1·4%)
Death	1 (0·1%)
Any grade 4 event	4 (0·3%)
Any grade 3 event	50 (3·7%)
Any grade 2 event	2 (0·1%)

Data are n (%) unless specified. *The primary safety endpoint of the study was defined as any serious adverse event, any grade 3 or 4 adverse events, and any grade 2 adverse event assessed by the treating clinician as related to the study product.

Table 3: **Primary safety endpoint events among those who received the dapivirine vaginal ring**

trials, probably reflecting greater participant confidence in a product that had been shown to be well tolerated and efficacious for HIV-1 protection and also the ability to choose to use the product.[19,23] Similarly, not all participants in open-label PrEP studies used the product with high adherence, and some rings in this study appeared not to have been used (although <10%). Notably, the level of uptake of, adherence to, and persistence of use of the DVR observed in this study compares very favourably to uptake, adherence, and persistence to PrEP with tenofovir disoproxil fumarate plus emtricitabine in demonstration and implementation studies among African women, for whom 6-month to 12-month persistence to the drug combination has been 20–50% or less.[7]

Phase 3 trials showed that the DVR reduced HIV-1 incidence by approximately 30% compared with placebo and by 50% or more among subgroups with evidence of greater adherence to ring use.[16,17] The relationship between adherence and the reduction in HIV-1 acquisition has been shown across studies of HIV-1 PrEP.[24–27] The present study observed an overall HIV-1 incidence that was lower than anticipated when considering factors related to HIV-1 risk. Comparing HIV-1 incidence in the overall population to a counterfactual situation found a 39% reduction across the population, considering both those accepting and not accepting and using and not using the DVR. Although this counterfactual estimate adjusted for key risk characteristics (ie, age, study site, and presence of an STI at screening) and is informative, our results for HIV-1 incidence are limited by the absence of a placebo group and that women who enrolled in HOPE had not acquired HIV-1 during ASPIRE or in the intervening period between studies. Notably, other studies among populations of women from southern and eastern Africa done at the same time as HOPE found HIV-1 incidence similar to that seen in the placebo group during ASPIRE (ie, >4% per year), indicating little decline in HIV-1 risk at the population level.[2] Several factors limited robust analyses of the HOPE data to associate use of an individual dapivirine ring with HIV-1 protection, including the modest number of HIV-1 infections observed in HOPE, the frequency of study visits once every 3 months—which results in imprecision in correlating timing of ring use and timing of HIV-1 infection—and the finding that factors likely to be associated with HIV-1 acquisition such as sexual behaviour were not associated with ring use. However, more robust analyses from one of the two phase 3 trials of the DVR, in which rings were dispensed and returned monthly and were coupled to monthly HIV-1 testing and were able to be compared against the placebo group, found that HIV-1 protection could be as high as 75% or more among women who used the ring most consistently.[21]

There are additional limitations to this study. In the ASPIRE phase 3 trial of the DVR, objective measures of adherence and HIV-1 risk reduction were lowest among women aged 18–21 years. Because the present study enrolled only women who had participated in ASPIRE, very few women were still in that age group at the time of study entry. However, other studies of the DVR among adolescent girls and young adult women have been completed or are ongoing, and results to date suggest high interest and use of the DVR,[28] perhaps reflecting greater comfort after demonstration of tolerability and risk reduction of approximately 30% in the phase 3 trials. In addition, all women in HOPE had previously participated in ASPIRE; real-world studies among individuals without experience with the DVR are needed to increase generalisability of knowledge related to uptake and adherence to this new prevention product. Also,

although use of PrEP with tenofovir disoproxil fumarate plus emtricitabine was permitted in the present study, it was generally not available in public sector settings; as its availability expands, understanding how women choose between these options and additional future PrEP options is a priority. An ongoing study among adolescent and young adult women is directly examining their choices of daily oral tenofovir disoproxil fumarate plus emtricitabine and monthly DVR (NCT03593655), and two studies are exploring the DVR as a prevention option for women who are pregnant or breastfeeding (NCT03965923 and NCT04140266).

Women in Africa continue to bear a disproportionate burden of the global HIV-1 epidemic. These results suggest interest in, adherence to, and the potential for HIV-1 risk reduction when the DVR is used in an open-label setting, making the DVR a possible HIV-1 prevention option for women. In July, 2020, the European Medicines Agency adopted a positive opinion for the DVR,[29] facilitating further review by WHO and African regulatory authorities. The results presented here support continued regulatory evaluation that might lead to widespread introduction of the DVR.

Contributors

JMB, TP-P, NMM, JJ, AN, ZR, LES-T, SLH, and ERB designed the trial, with contributions from all authors. DWS, YJ, and, ERB did the data analyses. All authors contributed to the execution of the trial and critically reviewed and approved the final manuscript.

Declaration of interests

JMB reports personal fees from Gilead Sciences, Janssen, and Merck, outside the submitted work. JWM reports grants from Gilead Sciences and Janssen; personal fees from Accelevir DX, Gilead Sciences, ID Connect, Merck, and Xi'an Yufan Biotechnologies; and share options from Abound Bio, Cocrystal Pharma, and ID Connect, all outside the submitted work. CWH reports grants from Gilead Sciences, Merck, and ViiV-GSK; personal fees from Merck and ViiV-GSK; and non-financial support from Gilead, all outside the submitted work, as well as being a co-inventor on a patent for microbicide formulations issued to Johns Hopkins University. ZR reports grants from the governments of Denmark, Ireland, the Netherlands, the UK, and the USA, and the Bill & Melinda Gates Foundation, during the course of the study. SLH reports personal fees from Merck, outside of the submitted work. All other authors declare no competing interests.

Data sharing

Individual participant data that underlie the results reported in this Article, after de-identification, are available, beginning after publication, as well as the study protocol, data dictionary, statistical analysis plan, and informed consent. Data are available for researchers who provide a methodologically sound proposal in accordance with policies of the Microbicide Trials Network (MTN).

For the **Microbicide Trials Network** see https://www.mtnstopshiv.org/

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