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Uptake and use of a vaginal ring containing dapivirine for HIV-1 prevention in African women: an open-label extension study

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

Data sharing

Individual participant data that underlie the results reported in this article, after deidentification, are available, beginning following article 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 Microbicides Trials Network (www.mtnstopshiv.org).

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MTN-025/HOPE (HIV Open-label Prevention Extension) Study Team

Abstract

Background: Two Phase III 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 to placebo (3.3 and 4.1 versus 4.5 and 6.1 per 100 person-years). Understanding use of the dapivirine vaginal ring in open-label settings with high background rates of HIV-1 infection is the next step to bridge to implementation.

Methods: MTN-025/HOPE was a Phase IIIb open-label extension trial of the dapivirine vaginal ring (ClinicalTrials.gov number NCT02858037). HIV-1 uninfected women who had participated in the MTN-020/ASPIRE Phase III trial were offered 12 months of access to the dapivirine vaginal ring at 14 sites in Malawi, South Africa, Uganda, and Zimbabwe between July 2016 and August 2018. At each visit (monthly for 3 months, then quarterly), women chose whether or not to accept the offer of the ring. Used, returned rings were tested for residual levels of dapivirine as a surrogate marker for adherence. HIV-1 serologic testing was done at each visit. Dapivirine levels in returned rings and HIV-1 incidence were compared to data from the ASPIRE trial.

Results: A total of 1456 women enrolled. The median age was 31 years. At baseline, 1342 (92%) chose the dapivirine vaginal ring; ring acceptance was >79% at each visit through 12 months and 73% (936/1279) chose the ring at all visits. 89% (12,530/14,034) of returned rings had residual dapivirine levels consistent with some use during the prior month (>0.9 mg released) and the average dapivirine released was greater than in the ASPIRE trial (by 0.21 mg, $p<0.001$). No serious adverse events or Grade 3 or higher adverse events observed were assessed as related to the dapivirine vaginal ring. HIV-1 incidence was 2.7 per 100 person-years (95% CI 1.9–3.8, n=35 infections), compared to an expected incidence of 4.4 per 100 person-years (95% CI 3.2–5.8) among a population matched on age, site, and presence of a sexually transmitted infection from the placebo group of ASPIRE.

Conclusions: High uptake and persistent use in this open-label extension trial support the dapivirine vaginal ring as an HIV-1 prevention option for women. (Funded by the US National Institutes of Health)

Keywords

dapivirine vaginal ring; HIV-1 prevention; women; pre-exposure prophylaxis; microbicide; open-label extension; Africa

Introduction

Over half of the 1.7 million persons newly infected with HIV-1 each year are women, and women in some African settings 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 HIV-1 uninfected persons has been demonstrated to be effective for preventing HIV-1 acquisition.[3,4] Oral tablets taken daily containing the antiretroviral tenofovir disoproxil fumarate (TDF), alone or in combination with emtricitabine (FTC), was the first PrEP approach to demonstrate HIV-1 prevention efficacy and gain normative guidance. In settings where TDF/FTC PrEP has been brought to scale, declines in the rate of new HIV-1 infections have been seen at the population level, demonstrating the importance of PrEP to curtailing the global HIV-1 epidemic.[5,6]

While global implementation of TDF/FTC PrEP is expanding, it is currently not at a sufficient pace to meet the goal set by the Joint United Nations Programme on HIV/AIDS (UNAIDS) of three million persons taking oral PrEP by 2020.[1] Furthermore, in clinical trials, demonstration projects, and implementation settings worldwide, a sizable proportion of individuals offered TDF/FTC decline to initiate, discontinue relatively soon after starting, or do not adhere sufficiently to gain HIV-1 protection.[7] In both clinical trials and demonstration settings, many African women have struggled to achieve high adherence to TDF/FTC PrEP. [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 TDF/FTC pills are under development; particularly attractive are approaches not requiring daily use, with topical, injectable, implantable, and pill forms in clinical studies currently.[11–13]

Vaginal rings are a highly acceptable delivery method that have been developed to provide controlled and sustained release of medications;[14] for example, vaginal ring products containing exogenous hormones are licensed for contraception and estrogen 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 a month at a time, was demonstrated in two Phase III clinical trials to be well-tolerated and to reduce HIV-1 acquisition risk in women by approximately 30% compared to placebo (HIV-1 incidence 3.3 and 4.1 versus 4.5 and 6.1 per 100 person-years, respectively in the two trials).[16,17] For TDF/FTC PrEP, the transition from placebo-controlled trials to implementation settings was bridged by open-label studies (i.e., trials occurring after demonstration of efficacy, with all participants having access to active product, and without the potential to be assigned placebo), including extension trials among populations that had previously participated in the Phase III trials.[18,19] Here, we report the results of an open-label extension trial of the dapivirine vaginal ring.

Methods

Study design and participants.

MTN-025/HOPE was a Phase IIIb, open-label extension trial of the dapivirine vaginal ring, conducted at 14 sites in Malawi (Blantyre, Lilongwe), South Africa (Cape Town, Durban [six sites], Johannesburg), Uganda (Kampala), and Zimbabwe (Chitungwiza [two sites], Harare) (ClinicalTrials.gov number NCT02858037). The primary objectives were to assess adherence to and safety of the dapivirine vaginal ring (25 mg), to be inserted continuously for a month at a time (manufactured by QPharma, Malmö, Sweden) when used in an open-label setting. The population was women who had previously participated in the Phase III, placebo-controlled MTN-020/ASPIRE trial and who remained HIV-1 uninfected. Those who enrolled in HOPE were offered 12 months of access to the dapivirine vaginal ring and could join the study and choose whether or not to accept the dapivirine vaginal ring at each follow-up visit. ASPIRE concluded follow-up in June 2015 and reported results in February 2016. HOPE initiated enrollment in August 2016, concluded enrollment in September 2017, and completed follow-up in October 2018. Participants did not have access to the dapivirine vaginal ring between completing ASPIRE and initiating HOPE but were referred to local services for HIV-1 testing and prevention.

An extensive scientific and community consultation process was conducted prior to initiation of HOPE, including participation of community representatives from each study site, to consider the key next steps for the dapivirine vaginal ring and to plan the study design and conduct of the trial. The study protocol (available at https://mtnstopshiv.org/research/studies/mtn-025/mtn-025-protocols) was approved by ethics review committees at each study site, who also approved participant reimbursement for study visit time and/or travel, and all participants provided written informed consent.

All women who had remained HIV-1 uninfected at the conclusion of ASPIRE were offered screening for participation in HOPE. In addition to negative HIV-1 serologic 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 a child, and to otherwise be healthy, with no contraindications to use of the dapivirine vaginal ring, including no safety concern requiring permanent product discontinuation while participating in ASPIRE.

Procedures.

Study visits occurred at enrollment, monthly for three months, then quarterly 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 counseled that they could choose to accept or decline the dapivirine vaginal ring at any point and still continue in the study;[20] participants choosing to accept were provided with a sufficient number of dapivirine vaginal rings to last until their next scheduled visit (i.e., one monthly during the first three months and three monthly thereafter). Women were taught how to insert and remove the vaginal ring and counseled to keep the ring inserted for the entire month. At quarterly visits, three rings were provided and women were instructed to change the ring monthly. Used rings were returned at each scheduled follow-up visit. Counseling about the ring as an HIV-1 prevention

option was provided in the context of comprehensive counseling on HIV-1 prevention, including behavioural change for risk reduction, partner HIV-1 testing, testing and treatment of sexually transmitted infections in participants and partners, and offer of free condoms; referrals were provided to access oral TDF/FTC PrEP at local clinics, at enrollment or at any time during follow-up.

Follow-up visits included HIV-1 serologic testing, safety monitoring, and individualized adherence counseling. Women were tested for pregnancy at each visit and the study ring was withheld from women who became pregnant; they resumed use of the dapivirine ring when no longer pregnant or lactating. 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 study product, and all grade 4 adverse events.

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

HIV-1 diagnostic testing was performed using a standard algorithm, beginning with two different HIV-1 rapid tests (generally one 3rd- and one 4th-generation) conducted in parallel, followed by a confirmatory test (Bio-Rad HIV-1/2 Geenius) if either or both rapid tests was 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 four weeks after the last study product-use visit to assess for delayed HIV-1 seroconversion. Resistance testing was performed using standard population genotyping.[22] Archived plasma samples from visits prior to HIV-1 seroconversion were tested by HIV-1 RNA PCR, and participants with detectable HIV-1 RNA at enrollment were excluded as primary study endpoints because HIV-1 infection occurred prior to trial entry. Women who tested positive for HIV-1 at the visit four 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 levels, an objective measure of use of the dapivirine vaginal ring. 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 dapivirine vaginal ring at enrollment 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 (e.g., excluding those who could not receive a ring for all months, such as for pregnancy). Adherence was reported according to the amount of dapivirine released from returned rings and categorized as ≤0.9 mg, >0.9–4 mg and >4mg, all normalized to account for the number of days between ring dispensation and return. The first category corresponds to zero plus one standard deviation of measurement error, thus likely reflecting 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 likely encompassed both incomplete or inconsistent use as 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 a quarter) and persistent use (defined as ≥0.9 mg dapivirine released from all three rings in a quarter for all four quarters of follow-up). Factors associated with persistent use were evaluated using 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 levels 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 dapivirine vaginal ring arm (as opposed to placebo) in ASPIRE. Data were compared using generalized 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 dapivirine vaginal ring during the study. The number and proportion of participants who experienced 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 confidence interval for a Poisson event rate. HIV-1 incidence observed in the study was compared to an expected counterfactual HIV-1 incidence in a simulated comparable at-risk population, similar to approaches used in other open-label studies of HIV-1 prevention interventions.[23] For the counterfactual model, a bootstrap resampling study was conducted, where in each simulation we constructed a bootstrap sample of women from the placebo arm of ASPIRE, with a distribution of HIV-1 risk characteristics (study site, age, presence of a curable sexually transmitted infection at baseline) and duration of follow-up to match those of the present study. This resampling approach then estimates the incidence of HIV-1 infection in the absence of an intervention. Specifically, we employed a weighted resampling approach to sample participants from the placebo arm in ASPIRE in proportion to the prevalence of risk factors in HOPE. In both studies, we created cells according to age group (in five-year increments from 20 through 49), site and curable sexually transmitted infection status. We

calculated the proportion of participants within each cell in HOPE then sampled participants with replacement from the cells in the ASPIRE placebo arm 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% confidence interval was defined by the 2.5th and 97.5th quantiles.

Analyses were conducted using SAS version 9.4 (SAS Institute) and R version 2.15.1 (R Project for Statistical Computing) and all p-values are two-sided.

Role of the funding source.

The US National Institutes of Health funded the study. The International Partnership for Microbicides (Silver Spring, USA) is the ring's developer and regulatory sponsor and supplied the study rings. 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. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of 2629 women who participated in ASPIRE (Figure 1), 2449 were HIV-1 uninfected, not permanently discontinued from product, and alive at its conclusion, and 2263 (92%) were approached for potential participation in HOPE; of the remainder, 150 were unable to be contacted, 8 did not provide permission for contact for future studies, 1 had been permanently discontinued from study product during ASPIRE, and 27 were not approached for other reasons. Of the 2263 approached, 507 were not screened: 189 were pregnant/intending to become pregnant or lactating 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 reasons for not screening. Thus, in total, 1756 were screened, of whom 183 were ineligible (45 HIV-1 infected, 69 were pregnant or lactating, remainder other reasons), 117 declined study participation and 1456 were enrolled into the prospective study (59% [1456/2449] of those HIV-1 uninfected at the completion of ASPIRE).

Of 1456 enrolled, 157 (11%) were from Malawi, 707 (49%) from South Africa, 172 (12%) from Uganda, and 420 (29%) from Zimbabwe, a similar distribution across countries as had been seen in ASPIRE. The median age was 31 years (interquartile range [IQR] 27–37) and 12% (181/1456) were <25 years of age (Table 1). Less than half (47%, 686/1456) were married, 43% (630/1456) reported use of a condom with the last sex act, and 16% (230/1456) had a curable sexually transmitted infection 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 FTC/TDF PrEP was reported by 16 women (at a total of 36 visits) during HOPE.

Women completed 98% (8436/8621) of expected follow-up visits. At enrollment, 1342/1456 women (92%) accepted the dapivirine vaginal ring and acceptance of the ring remained high throughout follow-up: 90% (1287/1428) at Month 1, 89% (1259/1422) at Month 2, 87% (1240/1427) at Month 3, 83% (1169/1404) at Month 6, and 79% (1093/1379) at Month 9. Excluding women who acquired HIV-1 or who had a medical reason for not using the ring (e.g., for incident pregnancy), 73% of women (936/1279) 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 visits, 43%), participant not interested in receiving the ring (199 visits, 20%), participant not ready to receive the ring (134 visits, 14%), partner unsupportive of ring use (106 visits, 11%), and other reasons (139 visits, 14%); side effects were rarely reported as a reason to decline the ring (36 visits, 4%) as was feeling the ring was less effective than the participant wanted (21 visits, 2%), intending to fall pregnant (7 visits, 0.7%), and family unsupportive (2 visits, 0.2%).

Of 14,463 rings dispensed, 14,270 (99%) were returned and 14,034 (97%) were tested for residual levels of dapivirine. Overall, 89% of rings (12,530/14,034) had >0.9 mg of dapivirine released, indicating at least some use. The median amount of dapivirine released was 3.2 mg (interquartile range 2.4–4.3) and was relatively unchanged throughout the 12-month follow-up period (Figure 2 and Supplementary Figure S1, page 8). The average amount released was greater ($p<0.001$) in the open-label HOPE study than in the prior placebo-controlled ASPIRE study (Figure 3); returned rings from HOPE had on average 0.21 mg more dapivirine released (95% confidence interval [CI] 0.18–0.25, $p<0.001$) than ASPIRE.

Consistent and persistent use was evaluated in 1277 participants with 4595 quarterly evaluations of which 3536 (77%) had evidence of use throughout the quarter (i.e., all three rings each with ≥0.9 mg of dapivirine released): 77% (983/1276) in Months 1–3, 80% (936/1172) in Months 4–6, 78% (866/1106) in Months 7–9, and 72% (751/1041) in Months 10–12. Overall, 562/1277 (44%) women were classified as having persistent use through all four quarters of follow-up. Younger age (<25 vs. ≥25 years) was not associated with poorer use, nor were self-reported behavioral risk factors for HIV-1 acquisition: condom use, number of partners and frequency of intercourse (Table 2). Consistent use in the prior quarter strongly predicted subsequent consistent use: for Months 4–6 adjusted odds ratio (aOR) 7.18 (95% CI 5.05–10.27), Months 7–9 aOR 6.10 (95% CI 4.25–8.79), and Months 10–12 aOR 8.92 (95% CI 6.16–13.06). Women who chose to accept the ring at all visits during follow-up had greater dapivirine released from used rings than those who chose the ring only at some visits: 3.4 mg (IQR 2.5–4.3) vs. 3.1 mg (IQR 1.5–4.1); adjusted for site and age, those who always chose the ring had 0.72 mg (95% CI 0.57–0.88; $p<0.001$) more dapivirine released from rings than women who were inconsistent acceptors.

The frequency, severity, and type of adverse events observed were similar to that observed in the Phase III trials of the dapivirine vaginal ring (Table 3) – i.e., no new safety signal was observed. No serious adverse event or Grade 3 or greater adverse event was assessed by study clinicians to be related to the use of the dapivirine vaginal ring.

A total of 35 incident HIV-1 infections occurred, at an incidence 2.7 per 100 person-years (two among participants from Malawi, 24 South Africa, zero Uganda, and nine Zimbabwe). Counterfactual simulations based on data from the placebo arm of ASPIRE predicted a median incidence of 4.4 per 100 person-years and thus the reduction in HIV-1 incidence in HOPE was estimated at 39% (95% confidence interval 14–65%); an incidence of ≤2.7 per 100 person-years would occur in <33 out of 10,000 bootstrap samplings. Among the 35 infections, 7 had non-nucleoside reverse transcriptase mutations (four K103N, one A98G, one E138A/V179D, one V106M/V179D), none of which suggest a dapivirine-specific resistance pattern.

Discussion

This multi-country open-label extension trial of the dapivirine vaginal ring found high uptake, evidence of good adherence and persistence through 12 months of access, a well-tolerated safety profile consistent with that seen in the prior Phase III studies, and lower HIV-1 incidence than expected in the absence of the ring. These results demonstrate that the dapivirine vaginal ring is an HIV-1 prevention option that women living in settings with high background risk of HIV-1 can use.

In this study, women were offered the choice to accept or not accept the dapivirine vaginal ring, and the vast majority initially accepted the ring and most continued throughout 12 months. Testing of returned rings for residual levels of dapivirine was used as an objective measure of adherence and most rings had levels consistent with at least some use. As has been seen in prior open-label studies of oral PrEP, adherence was greater in the open-label setting than in the blinded, placebo-controlled Phase III trials, likely reflecting greater participant confidence in a product that had been demonstrated 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 (although <10%) in this study appeared not to have been used. Notably, the level of uptake of, adherence to, and persistence of use of the dapivirine vaginal ring observed in this study compares very favorably to uptake, adherence, and persistence to TDF/FTC PrEP in demonstration and implementation studies among African women, for whom 6 to 12-month persistence to TDF/FTC PrEP has been 20–50% or less.[7]

Phase III trials showed that the dapivirine vaginal ring reduced HIV-1 incidence by approximately 30% compared to 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 of HIV-1 acquisition has been demonstrated 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 dapivirine vaginal ring. While this counterfactual estimate adjusted for key risk characteristics (age, study site, and presence of a sexually transmitted infection at screening) and is informative, our results for HIV-1 incidence are limited by the lack of a contemporaneous 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 conducted at the same time as HOPE found HIV-1 incidence similar to that seen in the placebo group during ASPIRE (i.e., >4% per year), indicating little decline in HIV-1 risk at the population level.[2] Several factors limit 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 quarterly frequency of study visits which results in imprecision in correlating timing of ring use and timing of HIV-1 infection, and the finding that factors likely associated with HIV-1 acquisition such as sexual behavior were not associated with ring use. However, more robust analyses from one of the two Phase III trials of the dapivirine vaginal ring, where 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 III trial of the dapivirine vaginal ring, objective measures of adherence and HIV-1 risk reduction were lowest among women aged 18–21. 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 dapivirine vaginal ring among adolescent girls and young adult women have been completed or are ongoing, and results to date suggest high interest and use of the dapivirine vaginal ring,[28] perhaps reflecting greater comfort after demonstration of tolerability and risk reduction of approximately 30% in the Phase III trials. In addition, all women in HOPE had previously participated in ASPIRE; demonstration studies among persons without experience with the dapivirine vaginal ring are needed to increase generalizability of knowledge related to uptake and adherence to this new prevention product. Also, while TDF/FTC PrEP use was permitted in the present study, it was generally not available in public sector settings; as TDF/FTC availability expands, understanding how women choose among 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 TDF/FTC and monthly dapivirine vaginal ring (Clinicaltrials.gov NCT03593655), and two studies are exploring the dapivirine vaginal ring as a prevention option for pregnant and lactating women (Clinicaltrials.gov 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 dapivirine vaginal ring is used in an open-label setting, making the dapivirine vaginal ring a possible HIV-1 prevention option for women. In July 2020, the European Medicines Agency adopted a positive opinion for the dapivirine vaginal ring,[29] facilitating further review by the World Health Organization and African regulatory authorities. The results presented here support continued regulatory evaluation that may lead to widespread introduction of the dapivirine vaginal ring.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Declaration of competing 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, ID Connect, all outside the submitted work; CWH reports grants from Gilead Sciences, Merck, and ViiV/GSK, personal fees from Merck and ViiV/GSK, 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 the US, UK, Ireland, Netherlands, and Denmark and the Bill and Melinda Gates Foundation, during the course of the study; SLH reports personal fees from Merck, outside of the submitted work; all other authors report no conflicts of interest.

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Research in Context

Evidence before this study

Evidence from PubMed and relevant conference abstracts was reviewed, searching on the term “dapivirine.” Two randomized, double-blind, placebo-controlled Phase III 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 and 4.1 cases per 100 person-years among those assigned the dapivirine vaginal ring compared with 4.5 and 6.1 HIV-1 cases per 100 person-years, respectively. Adherence was modest in those trials and other clinical trials of pre-exposure prophylaxis (PrEP) against HIV-1 among African women. Reported reasons for nonadherence included uncertainty about the safety of an unproven product. Prior studies of oral tenofovir disoproxil fumarate/emtricitabine as PrEP found greater adherence in open-label contexts (i.e., 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 conducted a Phase IIIb open-label extension trial of the dapivirine vaginal ring among HIV-1 uninfected women who had participated in the previously-completed ASPIRE Phase III trial. These results provide an example of open-label access to the dapivirine vaginal ring. Ring use adherence was assessed objectively by testing for residual levels of dapivirine in returned rings.

Implications

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

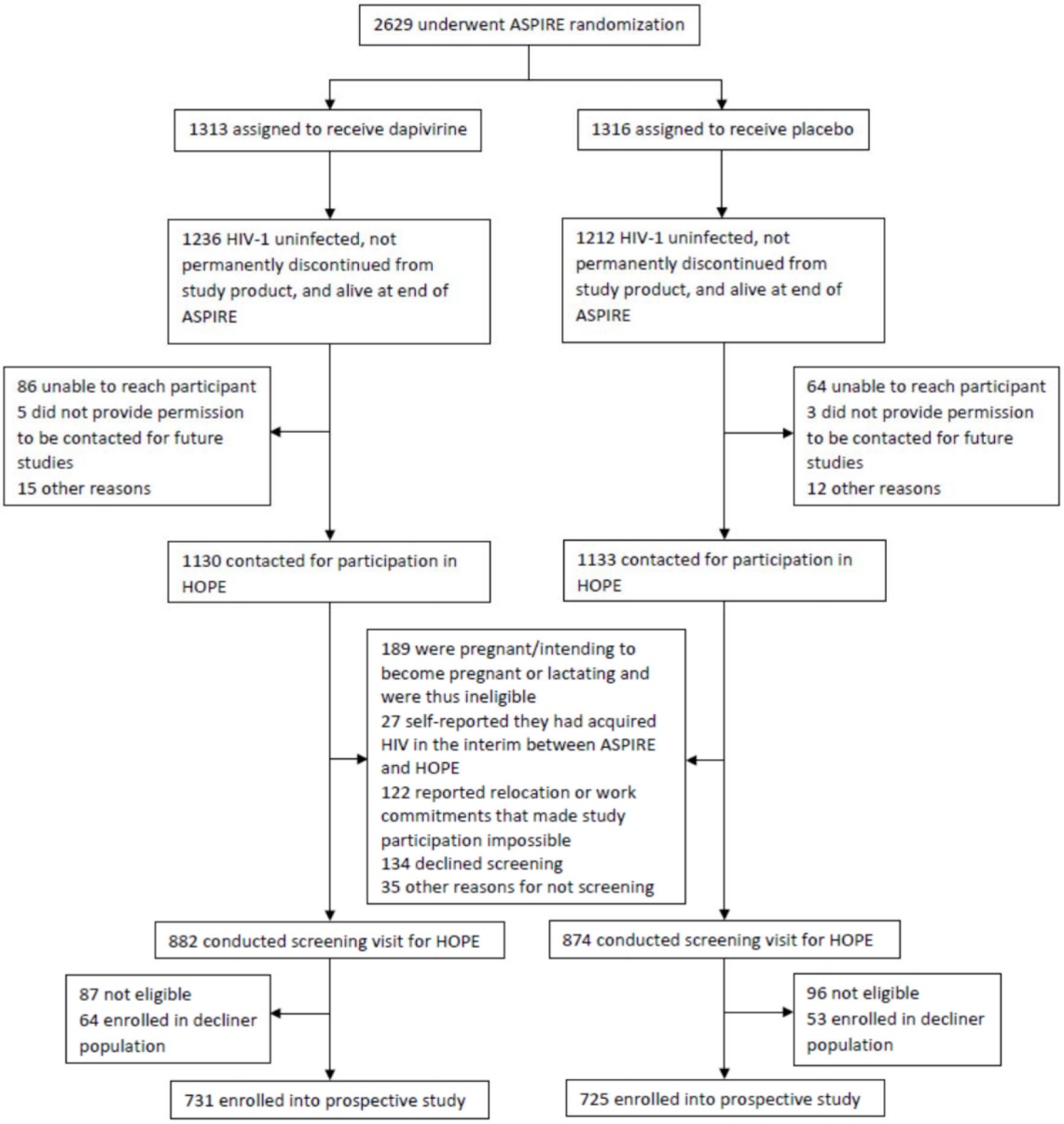

Figure 1.
Participant enrollment.

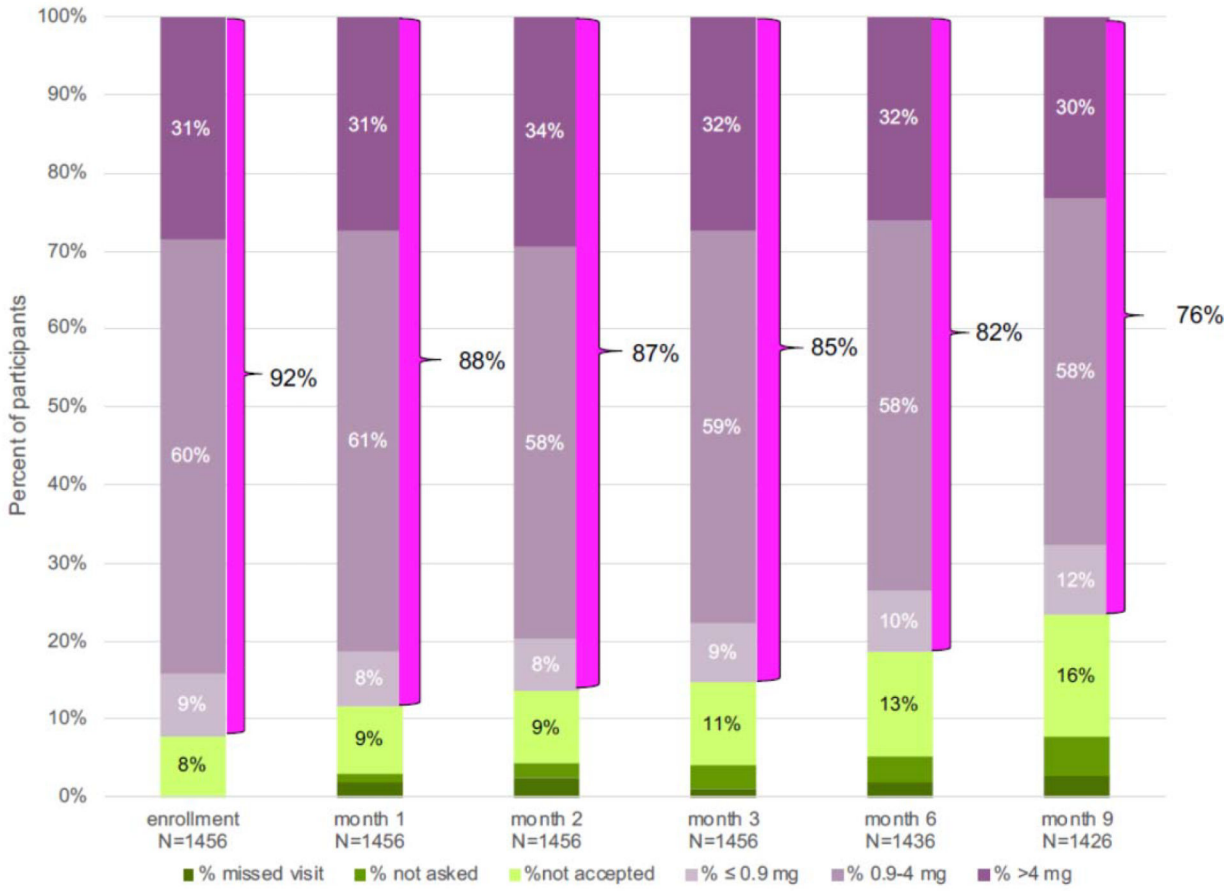

Figure 2. Dapivirine released, by study visit.

Residual levels of dapivirine in returned, used rings, by study visit of dispense of the ring, demonstrating level of use of the dapivirine vaginal ring over 12 months of follow-up. Percentages in purple representing the proportion of tested rings dispensed at that visit in each category of adherence; the dark pink bar to the right each column represents the proportion of women accepting rings at each visit. Green bars represent reasons for not being dispensed a ring: missed visit, not able to dispense (e.g., pregnancy, HIV-1 seroconversion), not accepted.

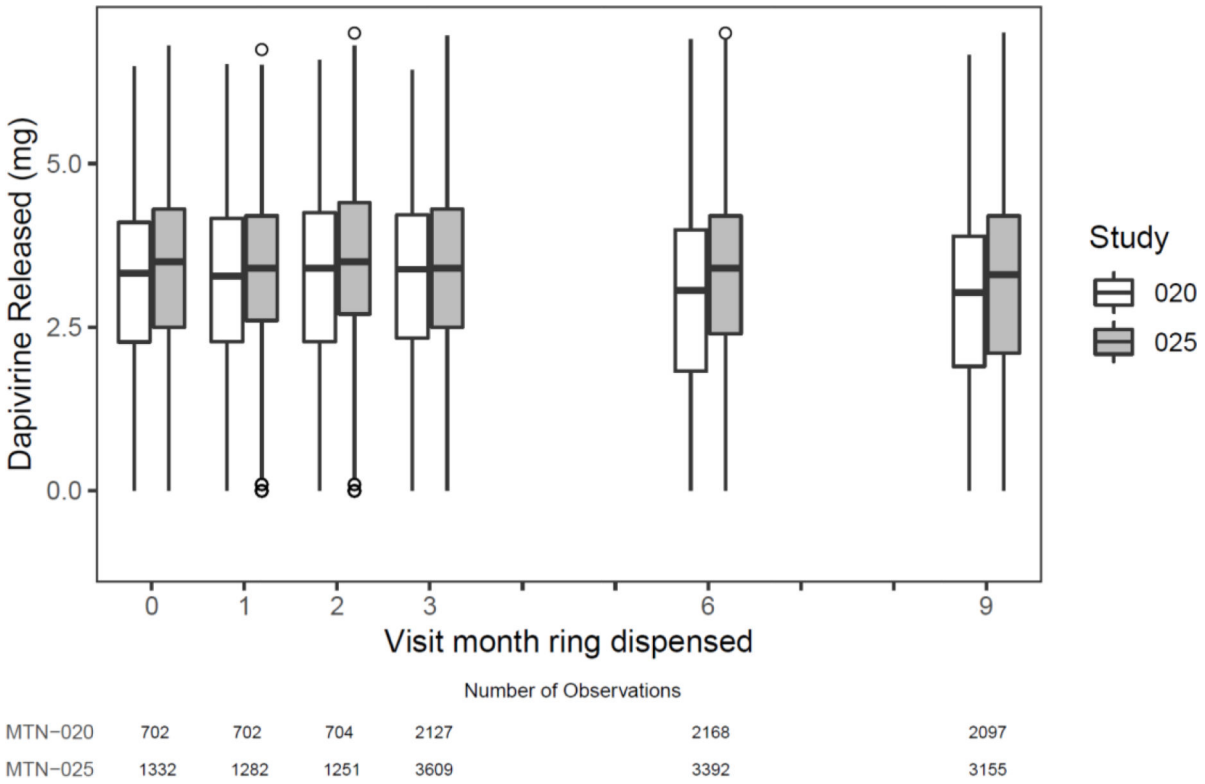

Figure 3. Comparison of dapivirine released, MTN-025/HOPE and MTN-020/ASPIRE.

Residual levels of dapivirine in returned, used rings were compared between the phase IIIb, open-label MTN-025/HOPE study and the phase III, 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 arm (as opposed to placebo) in MTN-020/ASPIRE. Data were compared using generalized estimating equations: $p<0.001$.

Table 1.

Enrollment characteristics.

	Mean (standard deviation) or number (%)	
Characteristic	**MTN-025/HOPE (n=1456)**	**MTN-020/ASPIRE (n=2629)**
Age, years	32.0 (6.5)	27.2 (6.2)
Median (range)	31 (20, 49)	26 (18, 45)
Secondary school education or higher	1196 (82)	2225 (85)
Earns own income	889 (61)	1186 (45)
Currently married	686 (47)	1074 (41)
≥2 male sex partners in the past 3 months	272 (19)	436 (17)
Episodes of vaginal intercourse in the past 3 months	23.6 (22.8)	26.5 (24.6)
Condom use during last vaginal sex	630 (43)	1508 (57)
Transactional sex in past year	107/1447 (7)	162/2618 (6)
Contraception method		
Intrauterine device	265 (18)	325 (12)
Oral contraceptive pills	214 (15)	287 (11)
Depot medroxyprogesterone acetate	466 (32)	1070 (41)
Norethisterone enanthate	103 (7)	381 (14)
Hormonal implant	345 (24)	501 (19)
Sexually transmitted infections		
Chlamydia trachomatis	129 (9)	316 (12)
Neisseria gonorrhoeae	27 (2)	109 (4)
Treponema pallidum	22 (2)	39 (1)
Trichomonas vaginalis	80 (6)	181 (7)

Table 2.

Participant characteristics and association with persistent use of the dapivirine vaginal ring.

Characteristic	OR	95% CI	p-value
Age <25 years (vs. ≥25)	0.83	0.54–1.25	0.37
Currently married (vs. not married)	1.33	0.97–1.84	0.08
Number of live births (vs. 0–1)			
2	1.40	0.99–1.99	0.06
3	1.68	1.14–2.49	0.009
≥4	2.02	1.31–3.12	0.002
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	0.01
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 dapivirine released from all three rings in a quarter for all four quarters of follow-up. Analyses performed using 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 sex acts, any practice of transactional sex, alcohol use, and randomization group (active vs. placebo) in ASPIRE.

Table 3.

Safety.

	Number of participants experiencing primary safety endpoint events, among those ever receiving the dapivirine vaginal ring, and number of events (n=1368)
Primary safety endpoint *	54 participants (4%)
Any serious adverse event	19 participants (1%)
Death	1 (0.07%)
Any Grade 4 event	4 (0.3%)
Any Grade 3 event	50 (4%)
Any Grade 2 event assessed as related	2 (0.2%), 2 events

* 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.

Serious adverse events (n=19 participants, experiencing 22 events): acute kidney injury (1), animal bite (1), asthma (1), endometriosis (1), gastritis (1), head injury (1), headache (1), hypertension (1), optic neuritis (1), pelvic inflammatory disease (1), pelvic pain (2), pneumonia (2), premature labor (1), psychotic disorder (1), respiratory tract infection (1), skin abscess (1), spontaneous abortion (1), traumatic contusion (1), trauma multiple (1), traumatic tendon injury of left arm (1)

Death (n=1 participants): pneumonia (1)

Grade 4 (n=4 participants): acute kidney injury (1), alanine aminotransferase increased (1), gastritis (1), pneumonia (1).

Grade 3 (n=50 participants, experiencing 55 events): allergic hypersensitivity (1), anal abscess (1), animal bite (1), aspartate aminotransferase increased (2), asthma (1), cephalopelvic disproportion (1), cervical carcinoma in situ (3), contusion (1), creatinine increased (7), diabetes mellitus type 2 (1), diarrhea (2), endometriosis (1), gastroenteritis (2), head injury (1), headache (1), hypertension (5), hypoesthesia of right upper limb (1), loss of consciousness (1), nausea (1), optic neuritis (1), pelvic inflammatory disease (1), pelvic pain (2), platelet count decreased (1), polytrauma (1), premature labor (1), pyelonephritis (1), psychotic disorder (1), respiratory tract infection (1), skin abscess (1), spontaneous abortion (1), tendon injury (1), tonsillitis (1), typhoid fever (1), vaginal bleeding after abortion (3), vaginal bleeding in pregnancy (1), weight loss abnormal (1), wrist fracture (1)

Grade 2 assessed as related (n=2 participants): abdominal pain (1), pelvic pain with dapivirine vaginal ring insertion (1)