

Safety, adherence, and HIV-1 seroconversion among women using the dapivirine vaginal ring (DREAM): an open-label, extension study



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Summary

Background The Ring Study, a phase 3 trial in 1959 sexually active women (randomised 2:1), showed a favourable safety profile and a 31% HIV-1 infection risk reduction for a vaginal ring containing 25 mg of dapivirine, compared with a placebo ring. We report here the DREAM study, which aimed to evaluate safety, adherence, and HIV-1 incidence in those using the dapivirine vaginal ring (DVR) in open-label use.

Methods The DREAM study is an open-label extension of The Ring Study, done at five research centres in South Africa and one research centre in Uganda. Former participants from The Ring Study, who remained HIV-negative and who did not discontinue the study due to an adverse event or safety concern that was considered to be related to the investigational product, were eligible. Women who were pregnant, planning to become pregnant, or breastfeeding at screening for DREAM were excluded. All participants received the DVR for insertion at the enrolment visit. Participants attended a 1-month follow-up visit and could either proceed with visits once every 3 months or attend monthly visits up to month 3 and then continue with visits once every 3 months. At each visit, HIV testing and safety evaluations were done, and residual dapivirine measured in used rings (approximately 4 mg is released from the DVR over 28 days of consistent use). HIV-1 incidence was compared descriptively with the simulated incidence rate obtained from bootstrap sampling of participants in the placebo group of The Ring Study, matched for research centre, age, and presence of sexually transmitted infections at enrolment. This study is registered with ClinicalTrials.gov, NCT02862171.

Findings Between July 12, 2016, and Jan 11, 2019, 1034 former participants from The Ring Study were screened, 941 were enrolled and 848 completed the trial. 616 (65.5%) of 941 participants reported treatment-emergent adverse events. Of these, six (0.6%) had events considered to be treatment-related. No treatment-related serious adverse events were reported. Measurements of monthly ring residual amounts in participants enrolled in both trials showed consistently lower mean values in DREAM than in The Ring Study. Arithmetic mean ring residual amounts of participants in The Ring Study DVR group who enrolled in DREAM were 0.25 mg lower (95% CI 0.03–0.47; $p=0.027$) than the mean ring residual amounts of these participants in The Ring Study. 18 (1.9%) HIV-1 infections were confirmed during DVR use, resulting in an incidence of 1.8 (95% CI 1.1–2.6) per 100 person-years, 62% lower than the simulated placebo rate.

Interpretation Although efficacy estimation is limited by the absence of a placebo group, the observed low HIV-1 incidence and improved adherence observed in DREAM support the hypothesis that increased efficacy due to improved adherence occurs when women know the demonstrated safety and efficacy of the DVR. The feasibility of a visit schedule of once every 3 months was shown, indicating that the DVR can be used in a real-world situation in usual clinical practice.

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Introduction

Epidemiological studies show that women in east Africa and southern Africa remain at high-risk of HIV infection.¹ A self-inserted vaginal ring, which provides sustained release of antiretroviral drugs over time, has the potential to offer a discreet, female-initiated, long-acting prevention option that does not require daily adherence or peri-coital

use.² A vaginal ring containing antiretroviral drugs could provide high vaginal drug concentrations and HIV-1 protection with limited systemic exposure to the active pharmaceutical ingredient, thereby reducing the risk of systemic toxicities.³

A silicone matrix vaginal ring containing 25 mg dapivirine (an HIV-1 non-nucleoside reverse transcriptase

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed from database inception up to Jan 31, 2020, with the search terms “HIV” AND “dapivirine” AND “vaginal” AND “ring”, as well as “HIV” AND “PrEP” and “HIV” AND “pre-exposure” AND “prophylaxis” (alone and combined with “adherence”). No language restrictions were used. Two randomised, double-blind, placebo-controlled, phase 3 clinical trials (The Ring Study and ASPIRE) showed that a 25 mg dapivirine vaginal ring (DVR), used for 28 days at a time, was well tolerated with a favourable safety profile and reduced HIV-1 incidence by 31% (95% CI 1–52) in The Ring Study and 27% (1–46) in ASPIRE, compared with placebo. A time-varying product adherence analysis (defined by a residual amount of ≤ 23.5 mg of dapivirine in used rings and a dapivirine plasma concentration of ≥ 95 pg/mL) of The Ring Study DVR group showed a 29% lower rate of HIV-1 infection during adherent intervals between visits than during non-adherent intervals between visits (hazard ratio 0.71 [95% CI 0.42–1.22]; $p=0.21$). In the ASPIRE trial, greater HIV-1 protection was observed among subgroups of women who had evidence of higher rates of adherence than among individuals with lower rates of adherence. Similar data were observed among African women in placebo-controlled trials of other new HIV prevention technologies such as daily oral tenofovir disoproxil fumarate-emtricitabine for pre-exposure prophylaxis (PrEP). Reported reasons for PrEP non-adherence included dosing regimen and uncertainty about an unproven product’s safety

and efficacy. Previous open-label PrEP studies showed increases in adherence during open-label studies after blinded randomised controlled trials—ie, when participants know that the trial product is safe and effective, they tend to be more adherent.

Added value of this study

This open-label trial among women who were HIV-1-negative who had previously participated in The Ring Study phase 3 trial, showed that use of the DVR under conditions approaching real-world scenarios such as visits once every 3 months and less frequent HIV testing is acceptable and results in a reduction in the risk of HIV-1 seroconversion. Objective measures using ring residual amounts of dapivirine indicated higher adherence than the phase 3 trial, despite less frequent visits. Overall, these findings provide support for improved adherence to the ring once women are aware of the efficacy and safety of the ring and support the feasibility of DVR use to reduce the risk of HIV-1 infection in women in sub-Saharan Africa.

Implications of all the available evidence

Consistent use in an open-label setting, with good tolerability of the dapivirine ring, suggest that an HIV-1 prevention method with modest efficacy, in which a new ring is used each month, is acceptable and feasible for women in sub-Saharan Africa. These results support continued regulatory assessment of the DVR as a potentially important option for women at high HIV risk and for implementation research to inform possible roll-out.

inhibitor [NNRTI], International Partnership for Microbicides, Silver Spring, MD, USA), was evaluated in two large, phase 3 clinical trials, which showed a significantly reduced risk of HIV-1 infection compared with placebo. In The Ring Study (protocol IPM 027), an overall risk reduction of 31% (95% CI 1–52) relative to placebo was observed,⁴ and a risk reduction of 27% (1–46) was seen in the ASPIRE trial (protocol MTN-020).³

In both phase 3 trials, participants had low systemic exposure to dapivirine and the dapivirine vaginal ring (DVR) was well tolerated with a favourable safety profile.^{3,4} Overall, there was no evidence of increased NNRTI resistance-associated mutations in the DVR groups in either trial;^{5,6} however, in The Ring Study, there were more participants with virus encoding Glu138Ala in the DVR group (11.0% vs 3.5%).⁵ No imbalance for virus encoding Glu138Ala was observed in the ASPIRE trial.⁶ The Glu138Ala variant, associated with potential or low-level resistance to some NNRTIs, is a common polymorphism in subtype C HIV-1 isolates from southern Africa.⁷

Imperfect adherence to DVR was likely to be a contributing factor to the modest HIV-1 risk reduction observed in The Ring Study and ASPIRE. Data from ASPIRE indicated that younger women (aged 18–21 years) had no reduction in HIV-1 infection risk and had

evidence of lower adherence.³ It is important to explore whether HIV risk reduction could be further improved when participants know a device is safe and effective, and they therefore show greater adherence. Increased HIV-1 risk reduction has been shown in oral pre-exposure prophylaxis (PrEP) open-label extension trials, compared with the earlier blinded randomised controlled trials.⁸ Similarly, data from oral PrEP implementation trials in Kenya and the PARTNERS-PrEP study have shown that increased effectiveness of oral PrEP is associated with high amounts of adherence.^{9,10} The Dapivirine Ring Extended Access and Monitoring trial (DREAM, protocol IPM 032) and the HIV Open-label Prevention Extension trial (HOPE, protocol MTN-025) were two open-label trials designed to assess safety and adherence to DVR in women who participated in The Ring Study and ASPIRE. Secondary trial objectives of DREAM were to assess incidence of HIV-1 seroconversion and frequency of HIV-1 drug resistance in women who acquired HIV-1 infection. The design included a visit once every 3 months and assessments that are closer to real-world settings to support implementation planning for potential DVR rollout programmes. Here, we aimed to establish the safety, adherence, and feasibility of a visit once every 3 months, and HIV-1 incidence data from DREAM.

Methods

Study design and participants

DREAM was a phase 3B, multicentre, follow-on, open-label extension trial of a DVR, inserted monthly, in healthy women who were HIV-negative and who participated in The Ring Study (a 2:1 randomised placebo-controlled trial) at five research centres in South Africa and one research centre in Uganda (appendix p 3).⁴ All formerly enrolled participants of The Ring Study who were HIV-negative and did not discontinue the study due to an adverse event or safety concern that was considered to be related to investigational product, were eligible for enrolment. Women who were pregnant, planning to become pregnant, or breastfeeding at screening for DREAM, were also excluded (for more details regarding inclusion and exclusion criteria see appendix p 5).

All participants received a DVR at enrolment and month 1 visits. A participant could either continue with monthly visits up to month 3, or proceed with a schedule of visits once every 3 months, at the investigator's discretion. At the month 3 visit, all participants were switched to a schedule of visits once every 3 months. Once the visit schedule commenced, three rings were dispensed at each visit; however, participants could choose to leave the rings at the research centre and collect a new ring once a month. Participants could also opt for a rapid HIV test at the research centre between the scheduled visits once every 3 months. Follow-up visits continued for a minimum of 12 months, after which a last product use visit (LPUV) occurred. The exit visit occurred approximately 1–2 months after the LPUV. At each visit, participants completed a questionnaire that included questions regarding the acceptability of a once every 3 months versus once a month follow-up visit at the research centre.

The trial was done in compliance with the Declaration of Helsinki and International Council for Harmonisation of Good Clinical Practice Guidelines. All local regulatory requirements were followed, and legal requirements complied with. The trial protocol was approved by independent ethics committees at all research centres (appendix p 3) and written informed consent was provided by all participants. The DREAM protocol is available online.

Procedures

Throughout the trial, all participants received pre-test and post-test HIV counselling, HIV and sexually transmitted infection (STI) risk reduction counselling, as well as contraceptive, condom, and DVR adherence counselling. Following unmasking in The Ring Study, efficacy and safety data were shared with the participants. Adherence counselling in DREAM included feedback on ring use adherence trends in The Ring Study and ASPIRE. Research centre staff also counselled participants to refrain from removing the ring and provided instructions to all participants in case of accidental ring expulsion. Participants were provided with diary cards on which the

date a new ring should be inserted was recorded. Instructions to the participants on how to store used and unused rings at home were also provided.

Participants were evaluated for the presence of STIs (*Trichomonas vaginalis*, *Neisseria gonorrhoeae*, and *Chlamydia trachomatis*) at screening and LPUV, and if clinically indicated, at other visits. Syphilis testing was done at screening. Treatment was provided for STIs using both syndromic and cause-based diagnosis. During follow-up, STIs were managed in accordance with local STI management guidelines.

HIV-1 seroconversion was evaluated at each visit with use of three rapid HIV test kits, according to a protocol-defined HIV testing algorithm (appendix pp 23–29). To estimate the timepoint of HIV-1 infection, HIV-1 RNA testing was done on stored plasma samples, with the Abbott RealTime HIV-1 assay (Des Plaines, IL, USA), in reverse sequential order until an undetectable result was obtained.

Only HIV-1 seroconversions with confirmed infections after enrolment, and until the LPUV were regarded as HIV-1 seroconversions on DVR.

The presence of resistance-associated mutations in participants who showed HIV-1 seroconversion was evaluated with a validated population-based genotyping assay done by the Bio Analytical Research Corporation South Africa (Johannesburg, South Africa). The Stanford HIV-1 Drug Resistance Database (version 8.4, dated June 16, 2017) was used to identify relevant NNRTI mutations.

Clinical and laboratory assessments (including pregnancy tests) were done according to the procedures described in the appendix (p 6). If a participant became pregnant, DVR use was discontinued, but the participant continued in the trial. If a participant subsequently had a negative pregnancy test, DVR use could be reinstated at the discretion of the investigator.

Outcomes

The primary objectives of DREAM were to assess the safety profile of the DVR and to assess adherence to the use of the DVR inserted at monthly intervals. Secondary objectives were the incidence of HIV-1 seroconversion and the frequency of HIV-1 drug resistance in women who acquired HIV-1 infection.

Safety of the DVR was evaluated through adverse event reporting, safety laboratory assessments, and physical and pelvic examinations. All adverse events and laboratory abnormalities were reported and graded according to the Division of Acquired Immunodeficiency Syndrome table for grading severity of adult and paediatric adverse events and female genital grading table for use in microbicide studies.^{11,12}

Adherence assessments included self-reported adherence and analysis of dapivirine residual amounts in used rings. Approximately 4 mg of the 25 mg dapivirine drug load in the ring is released over a month.¹³ A ring

For the Stanford HIV-1 Drug Resistance Database see <https://hivdb.stanford.edu/>

For DREAM protocol see https://www.ipmglobal.org/sites/default/files/ipm_032_prot_v2_0_amend_4_0_final_17oct2019.pdf

	DREAM overall (n=941)	The Ring Study overall (n=1959)	The Ring Study participants enrolled in DREAM (n=941)	The Ring Study participants not enrolled in DREAM (n=1018)	The Ring Study participants not enrolled in DREAM, HIV-negative (n=860)
Mean age, years	30.1 (20–50)	26.0 (18–45)	26.7 (18–45)	25.2 (18–45)	25.3 (18–45)
Race					
Black	931 (98.9%)	1941 (99.1%)	931 (98.9%)	1011 (99.3%)	853 (99.2%)
Other	10 (1.1%)	18 (0.9%)	10 (1.1%)	7 (0.7%)	7 (0.8%)
Highest education level					
Primary	277 (29.4%)	612 (31.2%)	300 (31.9%)	312 (30.6%)	263 (30.6%)
Secondary	498 (52.9%)	1146 (58.5%)	548 (58.2%)	598 (58.7%)	507 (59.0%)
Tertiary	103 (10.9%)	119 (6.1%)	43 (4.6%)	76 (7.5%)	65 (7.6%)
Marital status					
Married	126 (13.4%)	181 (9.2%)	111 (11.8%)	70 (6.9%)	67 (7.8%)
Never married	761 (80.9%)	1747 (89.2%)	812 (86.3%)	935 (91.8%)	784 (91.2%)
Has children	888 (94.4%)	1791 (91.4%)	880 (93.5%)	911 (89.5%)	765 (89.0%)
Has main sex partner	916 (97.3%)	1924 (98.2%)	920 (97.8%)	1004 (98.6%)	848 (98.6%)
Usual number of vaginal sex acts each month	8.8 (9.7)	8.2 (10.4)	8.6 (10.9)	7.8 (9.9)	7.8 (9.4)
≥2 male sexual partners	112 (11.9%)	297 (15.2%)	160 (17.0%)	137 (13.5%)	110 (12.8%)
Sexually transmitted infections identified	165 (17.5%)	536 (27.4%)	248 (26.4%)	288 (28.3%)	231 (26.9%)
Partner knowledge of ring use	716 (76.1%)	1066 (54.4%)	535 (56.9%)	531 (52.2%)	461 (53.6%)

Data are mean (range), n (%), or mean (SD).

Table 1: Baseline characteristics in The Ring Study and DREAM

residual value of more than 23.5 mg was considered to reflect very little ring use and was used to define non-adherence in this trial as well as in The Ring Study.³ This value was based on the lower limit of the 95% CI of dapivirine residual amounts in used rings (from a blinded analysis of all available dapivirine residual amounts up to the cutoff date of Oct 16, 2015, in The Ring Study), corresponding to dapivirine plasma amounts less than 95 pg/mL, which was determined as the amount below which a participant was most likely to not be adherent to DVR use over the intended 28 days, based on the population pharmacokinetic model for dapivirine. Ring acceptability was assessed through participant questionnaires completed at every trial visit after enrolment, until the LPUV.

Statistical analysis

The safety population included all participants who were enrolled and inserted at least one DVR. The analyses of safety, adherence, and HIV-1 resistance data were descriptive in nature and, when appropriate, were compared with data from The Ring Study. Arithmetic mean ring residual amounts computed over the entire study period (one value per participant for each study) were calculated and evaluated via a paired *t* test. A mixed model with repeated measures with age, research centre, centre-by-visit interaction, and presence of STI at baseline as fixed predictors for ring residual amounts and participant-specific intercepts and slopes for visit was fitted.

HIV-1 incidence was evaluated in the modified intention-to-treat (mITT) population, which excluded all participants who were HIV-1-positive at enrolment. The number of HIV-1 seroconversions, the HIV-1 seroconversion rate per 100 person-years of follow-up, and a 95% exact CI were presented. The HIV-1 incidence was compared descriptively with the incidence obtained from bootstrap sampling in the placebo group of The Ring Study: for the participants included in the mITT analysis in DREAM (appendix p 9 for baseline and demographic data), matching placebo participants were sampled in a 1:1 ratio, with replacement, based on research centre, age, and presence of STIs at enrolment. Age categories for the simulation (18–24 years, ≥25 years) were chosen to represent a sufficient number of participants in each combination of categories of age, research centre, and presence of STIs at enrolment. Analyses were done with SAS software, version 9.4. Safety data from the trial were evaluated by an independent data and safety monitoring board on an annual basis. Based on the review of the data, the board was required to provide recommendations about continuation, pausing, termination, or other modifications to the trial, including changes to the information provided to participants for obtaining their informed consent. This study is registered with ClinicalTrials.gov, NCT 02862171.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or

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 12, 2016, and Jan 11, 2019, of the former participants in The Ring Study ($n=1959$), 1567 (80.0%) were eligible for enrolment in DREAM. 1034 (66.0%) of 1567 were screened for DREAM, of whom 941 (91.0%) of 1034 were enrolled and received DVR (table 1). The most common reasons for screen failure were HIV-1 seropositivity (38 [40.9%] of 93); and pregnancy, planning to become pregnant, or breastfeeding (18 [19.4%] of 93). Of the 941 enrolled participants, 639 (67.9%) had been assigned to the DVR ring and 302 (32.1%) to the placebo ring in The Ring Study (figure 1). 150 participants were rolled over from The Ring Study to DREAM with no interruption in DVR use. For the remaining participants, the period between the two trials was variable, with a median time off investigational product (DVR or placebo ring) between The Ring Study and DREAM of 508 days (range 1–1884). The first participant's first visit was July 12, 2016, and the last participant's last visit was Jan 11, 2019.

The mean age of the participants was 30.1 years (range 20–50). Most participants (931 [98.9%]) were Black, never married (761 [80.9%]), and had secondary school education (601 [63.9%]). Most had a main partner (916 [97.3%]) and 76.1% reported that their partner had knowledge of their ring use (table 1). Long-acting injectable progestins were the most commonly used contraceptive method (649 [69.0%]) reported at screening, followed by oral contraceptives (106 [11.3%]). As would be expected from an extension study, the mean age of participants in the DREAM study had increased to 30 years, compared with a baseline mean age of 26 years in The Ring Study. Participants were also more likely to be married. The proportion of participants whose main partners were aware of ring use was higher in DREAM (76.1%), compared with The Ring Study (54.4%). At enrolment in DREAM, 165 (17.5%) participants presented with an STI, compared with 27.4% who had STIs identified at screening for The Ring Study (table 1).

Of the 941 participants, 848 (90.1%) completed the trial according to the protocol, while 93 (9.9%) discontinued early. The most common reasons for early discontinuation were HIV-1 seroconversion (18 [19.4%] of 93) and employment related (18 [19.4%] of 93; figure 1).

In total, 616 (65.5%) participants (table 2) reported treatment-emergent adverse events (defined as adverse events that occurred or worsened after the first insertion of the investigational product, up to 6 weeks after last ring use), compared with 1142 (87.4%) of 1306 who had a treatment-emergent adverse event in the DVR group in The Ring Study.⁴ The most frequently reported treatment-emergent adverse events (reported by more than 10% of

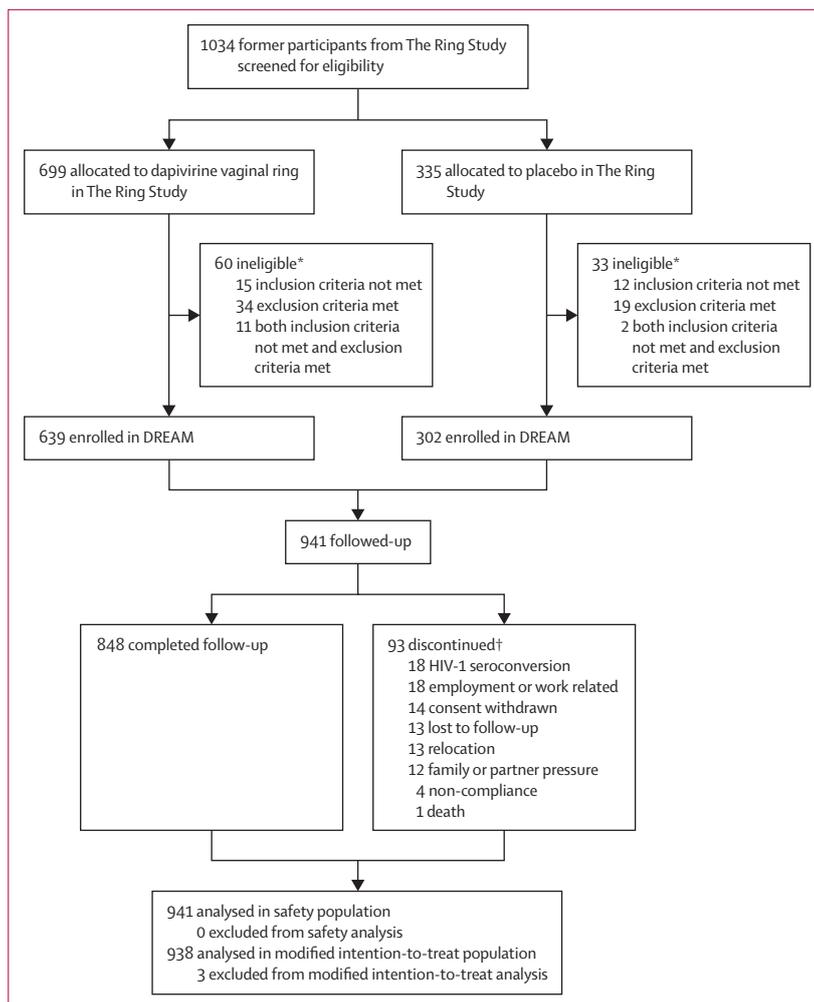


Figure 1: Trial profile

The modified intention-to-treat population excluded participants who had no detectable HIV-1 antibodies at enrolment but were identified as HIV-1-positive based on reverse sequential HIV-1 RNA testing. *A participant could have more than one reason for ineligibility. †Includes all participants who discontinued before completion of 12 months follow-up in DREAM.

participants) were upper respiratory tract infection (144 [12.1%]) and gynaecological chlamydia infection (109 [11.6%]). Other non-urogenital treatment-emergent adverse events reported by 2% or more of participants were headache (33 [3.5%]), gastritis (28 [3.0%]), back pain (26 [2.8%]), hypertension (19 [2.0%]), and viral upper respiratory tract infection (19 [2.0%]; appendix p 10). Most treatment-emergent adverse events were grade 1 (mild) or grade 2 (moderate) in severity and considered not related to DVR use by the investigator. Grade 3 (severe) or grade 4 (potentially life-threatening) treatment-emergent adverse events were reported in 37 (3.9%) participants (appendix p 12). All but six treatment-emergent adverse events were considered by the investigator as not related to DVR use (appendix p 14). The six treatment-emergent adverse events, all grade 1 (mild), considered as product-related, were

	The Ring Study participants allocated DVR enrolled in DREAM (n=639)	The Ring Study participants allocated placebo enrolled in DREAM (n=302)	DREAM overall (n=941)
Enrolled and received DVR	639 (100%)	302 (100%)	941 (100%)
At least one TEAE*	414 (65%)	202 (67%)	616 (65%)
At least one serious TEAE	10 (2%)	10 (3%)	20 (2%)
At least one DAIDS grade 3 or 4 TEAE	22 (3%)	15 (5%)	37 (4%)
At least one product-related TEAE	6 (1%)	0	6 (1%)
At least one serious product-related TEAE	0	0	0
TEAEs leading to death	1 (<1%)	0	1 (<1%)
TEAEs leading to permanent investigational product discontinuation	0	0	0
TEAEs leading to temporary investigational product discontinuation	2 (<1%)	0	2 (<1%)
TEAEs leading to trial discontinuation	0	0	0
Urogenital TEAEs	286 (45%)	124 (41%)	410 (44%)
Social harms reported as TEAEs	3 (<1%)	5 (2%)	8 (1%)
Confirmed pregnancies	17 (3%)	9 (3%)	26 (3%)

TEAEs were defined as adverse events that occurred or worsened after the first insertion of the investigational product, up to 6 weeks after last ring use. DVR=dapivirine vaginal ring. TEAE=treatment-emergent adverse event. DAIDS=Division of Acquired Immunodeficiency Syndrome. *See appendix (p 10).

Table 2: DREAM safety overview

ring application site pain, pelvic discomfort, pelvic pain, suprapubic pain, vulvovaginal discomfort, and vulvovaginal pain.

20 treatment-emergent serious adverse events were reported for 20 (2.1%) participants (table 2; appendix p 15). None of the serious adverse events were considered by the investigator or sponsor to be related to DVR use and most serious adverse events occurred as single, isolated events. The only system organ classes with more than two events recorded were injury, poisoning, and procedural complications with seven events related to trauma, and infections and infestations with four events related to infections (appendix p 15). The proportion of participants who had serious adverse events was similar to that reported in the DVR group in The Ring Study, in which serious adverse events were reported for 38 (2.9%) of 1306 participants.⁴ No adverse event, apart from one event with a fatal outcome (sudden death due to cardiomyopathy), resulted in early discontinuation from DREAM.

27 confirmed pregnancies were recorded in 26 participants (table 2). Pregnancy outcomes included 13 (48.0%) livebirths, seven (25.9%) spontaneous abortions (four individuals had known risk factors including maternal age >35 years, grand multiparity, cervical incompetence, and previous spontaneous abortion), and seven (25.9%) elective terminations of pregnancy. One pregnancy resulted in a twin birth; 13 of the 14 infants born were assessed as healthy at their last follow-up visit; a congenital umbilical hernia was reported in one newborn infant. One infant died

aged approximately 3 months after an unspecified febrile illness.

Overall, 410 (43.6%) participants reported any urogenital treatment-emergent adverse event (table 2). Urogenital treatment-emergent adverse events reported for 2% or more of participants were chlamydia infection, female genital infection, vulvovaginitis, gonococcal infection, trichomonas infection, vulvovaginal pruritus, bacterial vaginosis, dysmenorrhoea, vulvovaginal candidiasis, and pelvic pain. All events were grade 1 or 2 in severity (appendix p 17). All STIs identified at screening were treated either based on the organism identified, or according to the syndromic approach routinely used for management of suspected STIs in developing countries. Despite treatment and counseling received, at the LPUV, STIs were identified in 154 (16.4%) participants, resulting in an STI incidence of 15.3 (95% CI 12.9–17.7) per 100 person-years (appendix p 18).

Most participants (646 [68.7%] of 941) followed a schedule of visits once every 3 months from the start of DREAM. Of the remaining participants, 51 (5.4%) had visits at months 1 and 2, followed by a visit once every 3 months, while 230 (24.4%) had visits at months 1, 2, and 3, followed by a visit once every 3 months. Few participants (86 [9.1%]) opted to have HIV rapid tests at the research centre between the scheduled visits once every 3 months. At each scheduled follow-up visit, more than 95% of participants chose to take all three rings with them. The responses to the questionnaires indicated that although there was a tendency for monthly visits being preferred for the collection of new rings initially, the visits once every 3 months were clearly favoured from month 4 onwards. Similarly, from month 4 onwards, an HIV test once every 3 months was generally favoured.

More than 83% of participants self-reported at all visits that they were 90% or more adherent to ring use. Dapivirine residual amounts in used rings are depicted by visit in figure 2A (appendix p 19). At all timepoints, most participants had ring residual amounts of 23.5 mg or less, indicating at least some DVR use. On the basis of the mixed model with repeated measures, age and presence of STI at baseline were non-significant, and the estimates for the different centres were similar with the exception of centre 6, which had mean residual amounts that were 0.4 mg higher than the centre with the lowest ring residual amounts. In general, ring residual amounts did not significantly change over time for the different centres, with the exception of centre 2 for which ring residual amounts were estimated to increase 0.04 mg each month (appendix p 20).

A graphical comparison of dapivirine residual amounts in used rings for the same month of use from The Ring Study for those participants that enrolled in DREAM (including only those participants who had residual amounts available), showed that ring residual amounts in DREAM were lower at all timepoints (figure 2B). Arithmetic mean ring residual amounts computed over

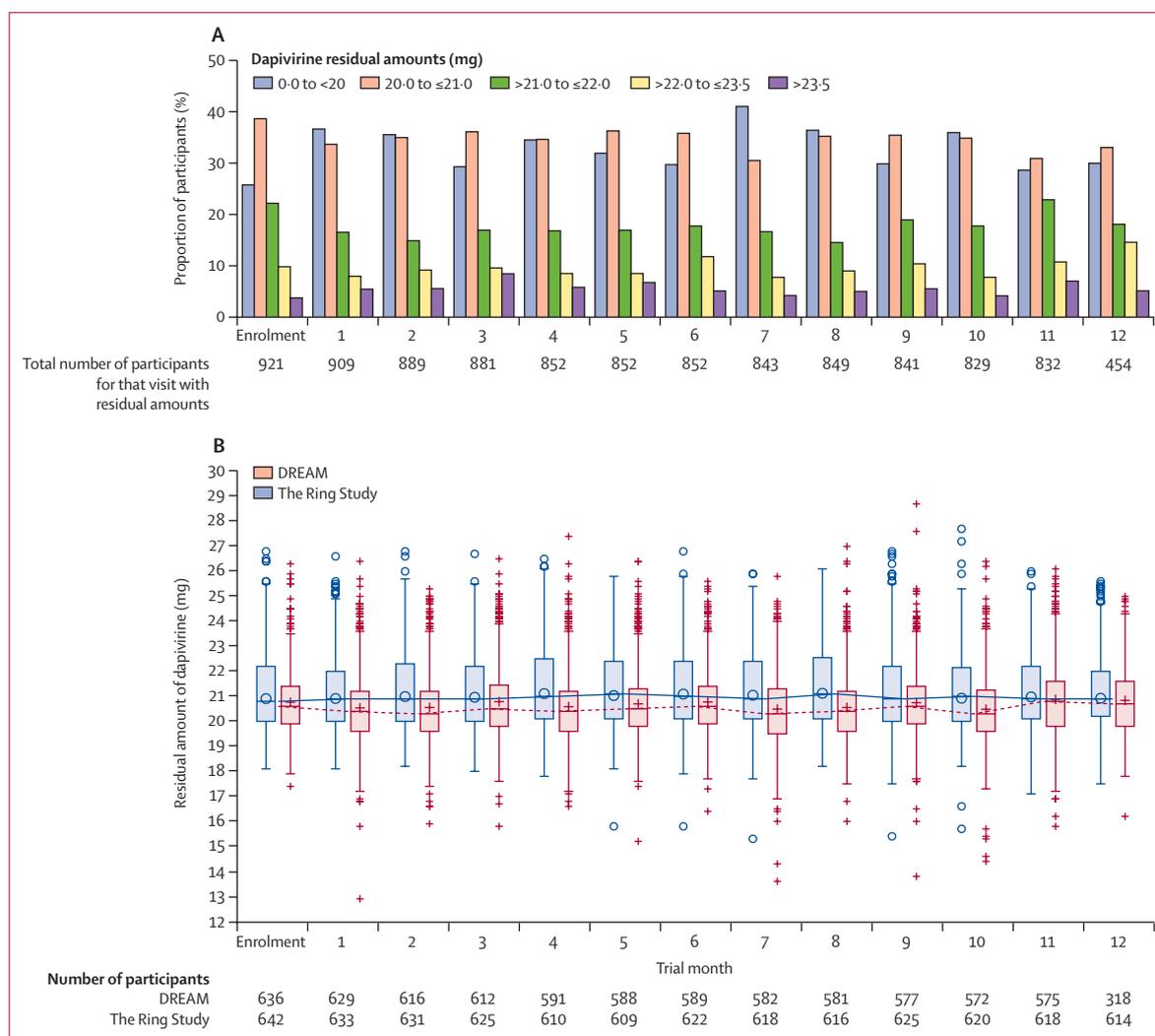


Figure 2: Residual amounts of dapivirine

Dapivirine residual amounts, by trial month and residual amount category. The visit label refers to the visit at which the DVR was dispensed, thus the DVR used in month 1 is labelled enrolment (A). Dapivirine residual amounts (mg) by month of ring use for The Ring Study and DREAM (B). Lines connect median values. Whiskers extend 1.5-times the IQR above the upper quartile and below the lower quartile; observed values outside this range are indicated by o; and + and are considered outliers. Ring residual values of more than 25 mg can occasionally be obtained due to variability in drug loading or assay variability. Participants in DREAM were limited to those who also had residual amounts in The Ring Study. DVR=dapivirine vaginal ring.

the entire study period (one value per participant for each study) for participants in The Ring Study DVR group who enrolled in DREAM were 0.25 mg lower (95% CI 0.03–0.47; $p=0.027$) than the mean ring residual amounts of these participants in The Ring Study.

For participants who seroconverted while using the DVR, the last three rings returned before HIV-1 seroconversion were evaluated and showed that the mean dapivirine residual amount (20.8 mg) was similar to the mean dapivirine residual amount (20.7 mg) in participants who were not HIV-positive. These data should be interpreted with caution due to the small number of individuals who seroconverted. For some participants who seroconverted, the residual amounts of dapivirine varied greatly for the last three returned

used rings, which might be indicative of inconsistent ring use (appendix p 30).

Self-reported ring acceptability was high, with responses from the LPUV indicating that 860 (91.4%) of 941 women responded they could use the ring effectively without having to remove it and 896 (95.2%) reporting that women would want to use the DVR if it was available.

Of the 941 participants enrolled in DREAM, 26 (2.8%) showed HIV seroconversion. Three of these participants had detectable HIV-1 RNA at enrolment, resulting in the mITT population of 938 participants. 23 participants became infected after enrolment; of these, 18 (1.9%) of 938 infections occurred while the participant was using DVR and were included in the HIV-1 seroconversion analysis. Of the remaining five individuals who

	The Ring Study participants allocated DVR enrolled in DREAM (n=638*)	The Ring Study participants allocated placebo enrolled in DREAM (n=300*)	DREAM overall (n=938*)
Number of confirmed HIV seroconversions on DVR†	13 (2%)	5 (2%)	18 (2%)
Number of person-years	681.4	314.4	995.8
Seroconversion rate, per 100 person-years	1.9 (0.9–2.9)	1.6 (0.2–3.0)	1.8 (1.0–2.6)

Data are n, n (%), or rate (95% CI). DVR=dapivirine vaginal ring. *Modified intention-to-treat population, which included all participants who were enrolled and were HIV-negative at enrolment. †Two participants are included in these results for whom HIV-1 RNA was first detected at the last product use visit.

Table 3: HIV-1 seroconversion rate in the modified intention-to-treat population

seroconverted, three had positive HIV-1 antibody tests at the exit visit but were HIV-1 RNA negative at the LPUV and were therefore considered to have become infected after DVR use was discontinued. One participant with HIV-1 seroconversion at the exit visit had an HIV-1 RNA result below the limit of detection (<40 copies per mL) at the LPUV, and an undetectable result when retested. The remaining participant had evidence of seroconversion at a scheduled visit following a period of 5 months of non-use of the DVR. The baseline data for participants who seroconverted during DVR use was similar to the overall population, apart from a slightly younger mean age (27.2 years vs 30.1 years; appendix p 21).

Participants in the mITT population had 995.8 person-years of follow-up in DREAM. On the basis of 18 confirmed HIV-1 seroconversion endpoints, the incidence was 1.8 (95% CI 1.0–2.6) per 100 person-years (table 3). Based on simulations with placebo group data in The Ring Study, an incidence of 4.7 (95% CI 3.7–5.8) per 100 person-years would be expected in the absence of DVR use. Thus, the observed HIV-1 incidence in DREAM was approximately 62% lower than would be expected based on the data from the placebo group in The Ring Study.

In a sensitivity analysis, the participant who seroconverted after a prolonged period of non-DVR use, and the participant who had an HIV-1 RNA result less than the limit of detection at LPUV were included as endpoints. By including these participants, the total number of HIV-1 infections during DVR use was 20, resulting in an incidence of 2.0 (95% CI 1.1–2.9) per 100 person-years, which is 57% lower than the expected rate in the absence of access to DVR.

Of the 18 participants included in the primary seroconversion analysis, 17 had a successful population-based HIV-1 genotyping assessment (appendix p 22). In five (29.4%) participants (all from the DVR group in The Ring Study), diverse NNRTI resistance-associated mutations (including Ala98Gly, Glu138Ala, and Lys101Glu in one participant each, and Lys103Asn in two participants) were identified, with no favoured pathway.

No participant had nucleoside reverse transcriptase inhibitor or major protease inhibitor resistance-associated mutations at seroconversion; however, one participant had a major protease inhibitor resistance-associated mutation (Met46Leu) at the exit visit.

Discussion

The data from DREAM showed that the DVR was well tolerated and had a safety profile analogous to what was observed in The Ring Study,⁴ with a similar nature and severity of adverse events, incidence of serious adverse events, but fewer treatment-emergent adverse events reported. No serious adverse events were considered product-related, no safety concerns were identified, and the DVR was well tolerated. Despite the less frequent trial visits, and fewer opportunities for adherence counselling, median residual dapivirine amounts in used rings were consistently lower in DREAM than in The Ring Study across visits, indicating improved adherence to DVR use throughout DREAM, and no adverse effect associated with a visit schedule of once every 3 months compared with visits once a month. Additionally, adherence remained consistent and did not decline over time, indicating that women continued to use the DVR throughout the study.

Quantification of the relationship between adherence markers for the DVR and efficacy for an individual is complex, as residual dapivirine amounts in used rings measure adherence over a period of time, but does not provide information on ring use at a specific point in time, such as during a high-risk sexual exposure event. However, the relationship between adherence to product use and efficacy has been clearly shown for oral PrEP. Although oral PrEP is highly effective for the prevention of HIV,^{10,14–16} poor adherence in two trials in women from sub-Saharan Africa did not show effectiveness.^{17,18} In DREAM, centre was the only covariate significantly associated with adherence (ie, centre 6 had higher ring residual amounts than other centres and in centre 2, ring residual amounts increased slightly over time); this finding could be due to cultural differences, and how participants were counselled regarding the importance of adherence and the relationship between research centre staff and participants.

An HIV-1 incidence of 1.8 (95% CI 1.0–2.6) per 100 person-years was observed in DREAM. This result is 62% lower than would be expected based on simulations with placebo group data of The Ring Study (4.7 per 100 person-years). One limitation of this analysis is the time lag between The Ring Study and DREAM; the background HIV transmission rates might have been different when the studies took place. In the ECHO trial, which evaluated HIV incidence from 2015 to 2018 (compared with the DREAM study period from 2016 to 2019) in women using different methods of contraception in southern Africa,¹⁹ an incidence of 4.5 per 100 person-years was observed at South African research centres.²⁰ Although the age of participants in the ECHO trial (median age of 23 years with 63% aged <25 years) was lower than the DREAM study

population, the fact that the observed incidence was almost identical to the estimated HIV-1 seroconversion rate using the placebo group from The Ring Study, supports the analysis for DREAM presented in this paper.⁴ It also highlights the high HIV infection risk that women, particularly in southern Africa, continue to face.

Of the 17 individuals who showed HIV-1 seroconversion in DREAM with a genotypic resistance test result, five (29.4%) of 17 had an NNRTI resistance-associated mutation identified, compared with 23 (17.3%) of 133 individuals who showed seroconversion in The Ring Study.³ It should be noted that these data are based on a small number of observations in DREAM and should be interpreted with caution, particularly because data for the transmitting partners' virological profile is unknown. Furthermore, in both The Ring Study and ASPIRE, no imbalance in NNRTI resistance-associated mutations overall was observed in the DVR groups compared with the placebo ring groups.^{5,6} NNRTI resistance pre-treatment is common in South Africa, with levels between 7.4% and 13.5% reported in five separate studies.^{18,21–25} The incidence of transmitted resistance has been shown to increase year on year.^{26,27} A meta-analysis showed an increase of 23% per year (95% CI 7–42; $p=0.0049$) for NNRTI resistance over time in southern Africa and 36% (21–52; $p<0.0001$) in eastern Africa since roll-out of anti-retroviral treatment programmes.²⁸ An increase in background NNRTI resistance in the time period that elapsed since The Ring Study might, therefore, at least partly explain the higher proportion of NNRTI resistance-associated mutations observed in DREAM. All individual NNRTI mutations identified in DREAM participants were also observed in The Ring Study. Although numbers were small, the proportion of participants with NNRTI mutations (five [29%]) was slightly higher than the observed prevalence of any NNRTI mutation in either treatment group in The Ring Study (13 [15.9%] of 82 in the DVR group *vs* eight [14.0%] of 57 in the placebo group).^{4,5} Additionally, most analyses of this type are based on the WHO drug resistance mutations for surveillance of transmitted HIV-1 drug-resistance.²⁹ This list of mutations does not include Glu138 or Ala98 variants and so might underestimate the prevalence and changes in prevalence over time of circulating resistance relevant to the current analysis. Indeed, due to the high rate of background NNRTI resistance in sub-Saharan Africa, WHO updated their treatment guidelines to recommend integrase inhibitor-based regimens as first-line treatment for HIV-1 infection.³⁰ This update should reduce concerns regarding NNRTI mutations and the potential effect on treatment options in women who seroconvert during DVR use.

The finding of NNRTI resistance-associated mutations only in the group of participants who previously had received DVR in The Ring Study is likely to be due to chance, given the small numbers and the 2:1 randomisation in The Ring Study, leading to more participants previously receiving DVR enrolling in DREAM. There

is no scientific rationale for use of the DVR several months earlier (in The Ring Study) while remaining HIV-1-negative, leading to an increased risk of NNRTI resistance-associated mutations developing following HIV-1 infection in DREAM.

A limitation of the DREAM trial is that only women who remained seronegative in The Ring Study could be enrolled. This design could have introduced selection bias, as women who remained HIV-1 seronegative throughout participation in The Ring Study might have a lower risk of HIV-1 infection or have been more adherent to ring use. The fact that the incidence of HIV-1 infection in The Ring Study did not diminish over time, would indicate that selection bias is unlikely. A further limitation of DREAM is that participants were older (mean age of 30 years *vs* 26 years in The Ring Study), which might have contributed to the increased adherence observed in DREAM, as better adherence in older women was observed in ASPIRE.^{3,4} Additionally, STI rates at enrolment as well as STI incidence (15.3 per 100 person-years) in DREAM were lower than that observed in The Ring Study (approximately 31.5 per 100 person-years).⁴ This result might indicate less high-risk sexual behaviour. However, as participants from The Ring Study placebo group that were used in the bootstrap sampling were chosen based on research centre, age, and presence of STIs at enrolment, these factors should be mitigated.

In conclusion, the results from DREAM provide support that the DVR was acceptable to women, and well tolerated with a similar safety profile to The Ring Study. The feasibility of a visit schedule of once every 3 months was shown, indicating that the DVR can be used in a real-world situation. Although estimation of reduction of HIV-1 risk is limited by the absence of a placebo group, the observed HIV-1 incidence and improved adherence, indicated by lower residual dapivirine amounts, support the hypothesis that increased efficacy will be seen when women are aware of the demonstrated safety and efficacy of the DVR.

Contributors

The principal investigators (KG, TG, PK, SK, CL, RM, and HT) were responsible for the conduct of the trial at the research centres. ZM provided research centre coordination at research centre 2. L-GB acted as the national principal investigator for South Africa. The International Partnership for Microbicides was responsible for development of the dapivirine vaginal ring (supported by BD), trial design, implementation and data interpretation (supported by AN, NvN, and ZR), trial project management and trial monitoring (supported by MM), clinical data monitoring (supported by WM), and safety data monitoring (supported by AC and JS). The DREAM clinical affairs team (AN and MM) was responsible for recruitment processes with community engagement, laboratory process standardisation, and public and media engagement. BVB supported the statistical analysis. Interpretation of the virology data was supported by CC and EvdR. AN, NvN, JS, CC, and EvdR accessed and verified the data. AN and EvdR prepared the manuscript, and all authors critically reviewed the manuscript for important intellectual content.

Declaration of interests

The International Partnership for Microbicides provided the candidate microbicide vaginal rings used in this trial. The dapivirine vaginal rings were manufactured by QPharma AB, Sweden. ZR, AN, NvN, BD, AC, MM, and JS were at the time of conduct of the trial employees of the International Partnership for Microbicides. EvdR, WM, AN,

and CC provided consulting services to International Partnership for Microbicides. All other authors declare no competing interests.

Data sharing

De-identified individual participant trial data from DREAM will be available to researchers with a methodologically sound proposal. Data requestors will need to sign a data access agreement. Publication concept proposal forms should be directed to publication@iprnglobal.org to gain access.

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