Dapivirine Vaginal Ring (PrEP ring or ring)

Summary of research findings in East and Southern Africa

RESEARCH BRIEF
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What do we know about the PrEP ring?

Efficacy: The monthly dapivirine vaginal ring (PrEP ring or ring) reduced HIV-1 incidence by about 30% compared to placebo in two Phase 3 trials. Efficacy was lower among participants under age 21 due to low adherence, and greater among participants who used the ring at least some of the time. Results from two subsequent open-label extension studies showed increases in ring use, with modeling data from these and other studies suggesting greater risk reduction – by about 50% or more with consistent use – compared to the Phase 3 trials.

Safety profile: The ring was well-tolerated with long-term use, with no statistical difference between the active dapivirine group and the placebo group in the Phase 3 trials. Fifteen safety studies of different ring formulations on multiple continents support the ring's tolerability profile, including one study of ring safety among users aged 15-17. An additional study with ring users aged 16-21 in Africa has also confirmed tolerability in this age group. Safety studies of PrEP ring use during pregnancy and breastfeeding have shown a favorable safety profile among pregnant and breastfeeding people and their infants.

Acceptability: Multiple acceptability studies were conducted to assess product preferences among women in Africa, and acceptability data was also collected in clinical studies of the ring. All these studies found vaginal rings to be acceptable for HIV prevention, and nearly all participants expressed interest in using the ring if shown to be effective and made available. More than 90% of participants in Phase 3 trials of the ring reported that the ring was comfortable to wear on a daily basis, and many noted that neither they nor their partner could feel it during sex.

Research conducted with the ring in East and Southern Africa is expansive, including clinical trials, open-label studies, acceptability studies, and qualitative/behavioral research. Ring research carried out in this region to date has included over 8,700 participants – including women of reproductive age, pregnant and breastfeeding people, adolescent girls and young women, male partners, and key stakeholders.

Breaking news from the DELIVER Study

DELIVER/MTN-042 enrolled approximately 550 pregnant individuals from South Africa, Uganda, Malawi, and Zimbabwe from February 2020 to January 2023. The study was conducted in three cohorts beginning with later gestational ages when risks of drug exposure are less. Participants were randomized to use either the PrEP ring or oral PrEP for the duration of their pregnancy and followed until 6 weeks after delivery. Infants continued in follow-up to one year.

The PrEP ring has a favorable safety profile among pregnant people and their infants.

- Both products were well-tolerated with no serious adverse events associated with either product when used during the third trimester of pregnancy.
- Adverse pregnancy outcomes, pregnancy complications, and adverse infant outcomes were uncommon and similar to background rates observed in the communities where the study was conducted.
- These results, along with safety data during early pregnancy from MTN-016, support PrEP ring use for pregnant people at risk of HIV.
- Results from the final cohort, which enrolled those 12-29 weeks pregnant, are anticipated early 2024.

Breaking news from the B-PROTECTED Study

B-PROTECTED/MTN-043 enrolled approximately 200 breastfeeding individuals from South Africa, Uganda, Malawi, and Zimbabwe from September 2020 to July 2021. Parent-infant pairs were enrolled 6-12 weeks after delivery, randomized to use either the PrEP ring or oral PrEP for 12 weeks, and followed until 2 weeks after stopping product.

The PrEP ring has a favorable safety profile among breastfeeding people and their infants.

- Both products were well-tolerated with no serious adverse events associated with either product.
- Drug levels in breast milk and infant samples were very low.
- Adherence and acceptability were generally high.

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PrEP ring research conducted in East and Southern Africa

Study	Description	Study location(s)	Participant sample	Status
IPM-007	An observational, long-term follow-up study for participants who acquired HIV during IPM 027 and IPM 032. The study assessed the impact of exposure to an antiretroviral microbicide at the time of HIV acquisition.	7 sites in South Africa and Uganda	**Total sample: 151** South Africa: 139 (6 sites) Uganda: 12	Completed August 2019. Results presented at SA AIDS 2019.
IPM-007 key takeaway: *No notable difference in HIV-1 disease progression was observed in participants who seroconverted while using the ring, as compared to the placebo group.*				
IPM-011	An open-label crossover study designed to assess the safety and acceptability of a placebo vaginal ring (containing no drug) when inserted for a 12-week period in healthy, sexually active women.	4 sites in South Africa and Tanzania	**Total sample: 170** South Africa (3 sites): 120 Tanzania: 50	Closed to follow-up March 2010. Primary safety manuscript and primary acceptability manuscript completed.
IPM-011 key takeaways: *No safety concerns were identified for any safety variables assessed during the trial. The ring appeared to be highly acceptable for women and men.*				
IPM-015	A Phase 1/2 trial designed to assess and compare the safety of a dapivirine vaginal ring against a placebo vaginal ring when inserted once every 28 days over a 12-week period.	10 sites in Kenya, Malawi, South Africa, Tanzania	**Total sample: 280** Kenya: 20 Malawi: 16 South Africa (7 sites): 235 Tanzania: 9	Closed to follow-up May 2011. Primary manuscript completed.
IPM-015 key takeaways: *No safety concerns or clinically relevant differences were observed between the dapivirine ring and placebo groups. At trial end, 96% of participants reported that the ring was usually comfortable.*				
MTN-015	Prospective, observational cohort study of participants who acquired HIV-1 in microbicide trials,	PrEP ring cohort: 15 sites in Zimbabwe, South Africa,	**Total cohort: 158 across the 15 sites**	Closed to follow-up June 2019. Manuscript on ASPIRE

	including the ASPIRE and HOPE studies. The study provides data on HIV disease progression, virologic responses following initiation of ART, and HIV-drug resistance.	Uganda, Malawi		cohort completed.
MTN-015 key takeaways: *The acquisition of HIV-1 during dapivirine or placebo ring use in ASPIRE did not lead to differences in HIV-1 disease progression. NNRTI-based ART regimens remained effective among those who acquired HIV-1 while using the ring.*				
MTN-016/ EMBRACE	Prospective, observational cohort study of participants who became pregnant in microbicide trials, including the ASPIRE and HOPE studies. The protocol monitored for adverse pregnancy outcomes and monitored babies for their first year of life.	PrEP ring cohort: 15 sites in Zimbabwe, South Africa, Uganda, Malawi	**Total cohort: 143 adults, 133 infants** South Africa (9 sites): 65 adults, 63 infants Uganda: 19 adults, 18 infants Zimbabwe (3 sites): 47 adults, 40 infants Malawi (2 sites): 12 adults, 10 infants	Closed to follow-up May 2020. Manuscript on ASPIRE cohort completed.
MTN-016 key takeaway: *Dapivirine ring use during early pregnancy was not associated with adverse effects on pregnancy or infant outcomes.*				
MTN-020/ ASPIRE	Phase 3, randomized, double-blind, placebo-controlled clinical trial designed to evaluate the safety and efficacy of the PrEP ring.	15 sites in Zimbabwe, South Africa, Uganda, Malawi	**Total sample: 2,629** Zimbabwe (3 sites): 678 South Africa (9 sites): 1,426 Uganda: 253 Malawi (2 sites): 272	Closed to follow-up June 2015. Primary manuscript completed. Further manuscripts addressing adherence and effectiveness, and acceptability and adherence are also available.
MTN-020 key takeaways: *The ring was associated with 27% HIV-1 risk reduction, with increased efficacy in subgroups with evidence of increased adherence. No safety concerns were identified. At trial exit, 66% of participants reported being "very likely" to use the ring in the future. Participants who minded wearing the ring during sex or menses, or reported a negative change in the vaginal environment, were more likely to have periods of nonadherence.*				
IPM-027/	Phase 3, randomized, double-blind, placebo-controlled	7 sites in South Africa and Uganda	**Total sample: 1,959** Uganda: 197	Closed to follow-up December 2016. Primary

The Ring Study	clinical trial designed to evaluate the safety and efficacy of the PrEP ring.		South Africa (6 sites): 1,762	manuscript completed.
IPM-027 key takeaways: *The ring was associated with 35% HIV-1 risk reduction. No safety concerns were identified.*				
MTN-025/ HOPE	Phase 3B, open-label, randomized, trial open to participants previously enrolled in MTN-020/ASPIRE. HOPE participants could choose to use the ring – or not – for 1 year of participation. The study gained more information on the safety of and adherence to the PrEP ring.	14 sites in Zimbabwe, South Africa, Uganda, Malawi	**Total sample: 1,456** Zimbabwe (3 sites): 420 South Africa (8 sites): 707 Uganda: 172 Malawi (2 sites): 157	Closed to follow-up October 2018. Primary manuscript completed.
MTN-025 key takeaways: *More than 73% of participants chose to accept the ring at all study visits, with 89.3% of returned rings showing some use, reflecting an overall increase in adherence over the ASPIRE trial. Modeling data suggests HIV-1 risk reduction of approximately 39%. No safety concerns were identified.*				
IPM-032/ DREAM	Open-label follow-on trial to IPM-027 to collect additional safety data and establish adherence to ring use of the PrEP ring monthly for 12 months.	6 sites in South Africa and Uganda	**Total sample: 941** Uganda: 121 South Africa (5 sites): 820	Closed to follow-up December 2018. Primary manuscript completed.
IPM-032 key takeaways: *Residual dapivirine levels in returned rings were 0.25mg lower, on average, than in DREAM, reflecting an overall increase in adherence. Modeling data suggests HIV-1 risk reduction of approximately 63%. No safety concerns were identified.*				
MTN-032 / AHA	Qualitative sub-study of the ASPIRE and HOPE trials that examined socio-contextual and trial-specific issues impacting participant adherence to the PrEP ring, and male partner attitudes about the ring.	7 sites in Zimbabwe, Malawi, South Africa, and Uganda	**Total sample: 227 former ASPIRE and HOPE participants (FPs), 54 male partners (MPs)** Zimbabwe (2 sites): 41 FPs, 13 MPs Malawi: 44 FPs, 11 MPs South Africa (3 sites): 103 FPs, 22 MPs Uganda: 39 FPs, 8 MPs	Data collection completed in October 2016. ASPIRE cohort manuscript, HOPE cohort manuscript, and male partner manuscript completed.
MTN-032 key takeaways: *Former ASPIRE and HOPE participants reported multiple reasons for ring removal, including fear of male partner reactions or ring interference with sex, or dislike of wearing the ring during*				

menses. More than half (59%) of male partners reported never feeling the ring. Among those who did feel it, few reported sexual problems or changes as a result.				
MTN-034/ REACH	Phase 2a, randomized, open-label, crossover study. Participants use the PrEP ring monthly for 6 months, oral PrEP (Truvada) for 6 months, and then choose the ring, Truvada, or neither for final 6 months. The study will evaluate safety, adherence, and acceptability of the ring and oral PrEP in users aged 16-21.	4 sites in Zimbabwe, Uganda, South Africa	**Total sample: 247 adolescent and young women aged 16-21 (inclusive)** Zimbabwe: 60 (28 age 16-17) Uganda: 60 (20 age 16-17) South Africa (2 sites): 127 (37 age 16-17)	Data collection completed in September 2021. Interim results presented at IAS 2021. Final results presented at CROI 2022 and final manuscript published in 2023.
MTN-034 key takeaways: *Most (88% and 64%) of participants reported that the ring and oral PrEP were acceptable, respectively. More than 50% of participants had high adherence levels to both products. About 2/3 of participants chose the ring in the choice period, with those who had high adherence to oral PrEP in the randomization period more likely to select oral PrEP in the choice period.*				
MTN-041/MAMMA	Qualitative acceptability study to explore attitudes of community members and key informants from the community about the use of the PrEP ring or oral PrEP during pregnancy and breastfeeding.	4 sites in Malawi, South Africa, Uganda, Zimbabwe,	**Total sample: 232 pregnant or breastfeeding people (PBFP) aged 18-40, male partners (MPs) of current or recent PBFP, key informants (KIs), and mothers/mothers-in-law of current or recent PBFP (grandmothers/GMs)** Malawi: 51 (15 PBFP, 16 MPs, 10 GMs, 10 KIs) South Africa: 53 (15 PBFP, 12 MPs, 20 GMs, 6 KIs) Uganda: 68 (18 PBFP, 19 MPs, 21 GMs, 10 KIs) Zimbabwe: 60 (17 PBFP, 16 MPs, 17 GMs, 10 KIs)	Closed to follow-up November 2018. Results presented at IAS 2019. Primary manuscript on willingness to use PrEP during pregnancy and breastfeeding completed. Results informed development of MTN-042/DELIVER and MTN-043/B-PROTECTED.

MTN-041 key takeaways: *Participants agreed that PBFP have an increased need for HIV prevention options, and new choices were welcomed for this population. Participants agreed that endorsement by healthcare providers and confirmation of safety for infants were key to product acceptance.*				
MTN-042/ DELIVER	Phase 3b, open label, randomized study designed to assess the safety and pharmacokinetics (PK) of the PrEP ring and oral PrEP when used during pregnancy. Participants will enroll at different times during pregnancy and will use either the monthly ring or Truvada as daily PrEP until the time they deliver. The study is the first to be conducted of the ring during pregnancy.	4 sites in Zimbabwe, Uganda, Malawi, South Africa	**Total sample: 550 pregnant individuals** **Cohort 1 (36-37 weeks pregnant): 150** Malawi: 27 South Africa: 42 Uganda: 44 Zimbabwe: 37 **Cohort 2 (30-35 weeks pregnant): 157** Malawi: 40 South Africa: 28 Uganda: 42 Zimbabwe: 47 **Cohort 3 (12-29 weeks pregnant): 251** Malawi: 66 South Africa: 44 Uganda: 68 Zimbabwe: 73	Accrual took place from February 2020 to January 2023. Interim results from Cohort 1 presented at IAS 2021, and Cohort 2 presented at CROI 2023. Safety paper from Cohorts 1 and 2 published in JAIDS. Note: Background rates of pregnancy outcomes and complications described in MTN-042B.
MTN-042 key takeaway: *Adverse pregnancy outcomes and complications were uncommon among ring and oral PrEP users and were generally similar to rates observed in study communities.*				
MTN-043/ B-PROTECTED	Phase 3b, open-label, randomized study designed to assess the safety and PK of the PrEP ring and oral PrEP when used during breastfeeding. The study is the first to be conducted of the ring during breastfeeding.	4 sites in Zimbabwe, Uganda, Malawi, South Africa	**Total Sample: 197 breastfeeding parent/infant pairs** Malawi: 39 South Africa: 36 Uganda: 55 Zengeza: 67	Closed to follow-up November 2021. Interim results presented at AIDS 2002 and final results presented at CROI 2023 and FIGO 2023.
MTN-043 key takeaway: *Both PrEP ring and oral PrEP have a favorable safety profile among breastfeeding parent-infant pairs. Drug levels in breast milk and infant samples were very low. Acceptability and adherence were generally high.*				