

PrEP Ring for Pregnant and Breastfeeding Women

Summary of research findings in eastern and southern Africa

RESEARCH BRIEF
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Recent studies have published critical new data on use of the dapivirine vaginal ring (PrEP ring or ring) among pregnant and breastfeeding people in eastern and southern Africa, offering evidence that the PrEP ring is a **safe and effective** HIV prevention method for a broader population than was initially recommended.

In 2021, the World Health Organization recommended the PrEP ring as an additional prevention option for women at substantial risk of HIV, noting the limited data on its use among pregnant and breastfeeding women (PBFW) available at the time. Since then, several African countries have updated their national HIV prevention guidelines to include the PrEP ring, but many maintain restrictions on use by PBFW. Recent studies on PrEP ring use during pregnancy or while breastfeeding provide evidence of the safety, efficacy, and acceptability of the ring. These studies could pave the way for the PrEP ring to be included in national guidelines and become a more accessible HIV prevention method for individuals during pregnancy or the postpartum period, which are times of increased risk of HIV acquisition.¹



What do we know about the PrEP ring?

Efficacy: The monthly PrEP ring reduced HIV-1 incidence by about 30 percent compared to placebo in two Phase 3 trials.^{2,3} Efficacy was lower among participants 18–21 years old 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 – DREAM and HOPE – found increased ring adherence compared to adherence during

¹ Thomson KA, Hughes J, Baeten JM, John-Stewart G, Celum C, Cohen CR, et al. Increased risk of HIV acquisition among women throughout pregnancy and during the postpartum period: a prospective per-coital-act analysis among women with HIV-infected partners. *J Infect Dis.* 2018 Jun 5;218(1):16–25.

² Baeten JM, Palanee-Phillips T, Brown ER, Schwartz K, Soto-Torres LE, Govender V, et al. Use of a vaginal ring containing dapivirine for HIV-1 prevention in women. *N Engl J Med.* 2016 Dec 1;375(22):2121–32.

³ Nel A, van Niekerk N, Kapiga S, Bekker L.-G, Gama C, Gill K, et al. Safety and efficacy of a dapivirine vaginal ring for HIV prevention in women. *N Engl J Med.* 2016 Dec;375(22):2133–43. doi: 10.1056/NEJMoa1602046

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clinical trials.^{4,5} Multiple efficacy analyses among participants who used the ring consistently suggest that the PrEP ring can reduce the likelihood of HIV acquisition during receptive vaginal intercourse by 50% or more with consistent use throughout the month.^{6,7} A recent secondary analysis suggests a 63% risk reduction per-sex-act when ring is used consistently.⁸

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.^{4,8} Fifteen safety studies of different ring formulations on multiple continents support the ring's tolerability profile, including one study of ring safety among users ages 15–17. An additional study with ring users ages 16–21 in Africa also confirmed tolerability in that age group.^{9,10} Safety studies of PrEP ring use during pregnancy have shown a favorable safety profile among pregnant women and their infants.^{11,12,13} Among those who used the PrEP ring during pregnancy, no differences in preterm labor, stillbirths, or pregnancy complications were seen during randomized control trials. Similarly, studies of PrEP ring and oral pre-exposure prophylaxis (oral PrEP) use during breastfeeding found favorable safety profiles among breastfeeding mother-infant pairs and low drug levels in breast milk and infant samples.¹⁴

Acceptability: Multiple acceptability studies were conducted to assess product preferences among women in Africa as well as acceptability data were in PrEP ring clinical studies. All of the studies found vaginal rings to be acceptable for HIV prevention, and nearly all participants expressed interest in using the ring if it were

⁴ Baeten JM, Palanee-Phillips T, Mgodini NM, Mayo AJ, Szydlo DW, Ramjee G, et al. Safety, uptake, and use of a dapivirine vaginal ring for HIV-1 prevention in African women (HOPE): an open-label, extension study. *Lancet HIV*. 2021 Feb;8(2): e87–e95.

⁵ Nel A, van Niekerk N, Van Baelen B, Malherbe M, Mans W, Carter A, et al. Safety, adherence, and HIV-1 seroconversion among women using the dapivirine vaginal ring (DREAM): an open-label, extension study. *Lancet HIV*. 2021 Feb;8(2):e77–e86.

⁶ Peebles K, Brown ER, Hendrix CW, Palanee-Phillips T, van der Straten A, Harkoo I, et al. Dapivirine ring HIV-1 prevention effectiveness for women engaged in vaginal and anal intercourse: insights from mathematical modeling. *J Acquir Immune Defic Syndr*. 2023;92(2):122–126. doi: 10.1097/QAI.0000000000003110.

⁷ Brown ER, Hendrix CW, van der Straten A, Kiweewa FM, Mgodini NM, Palanee-Phillips T, et al. Greater dapivirine release from the dapivirine vaginal ring is correlated with lower risk of HIV-1 acquisition: a secondary analysis from a randomized, placebo-controlled trial. *J Int AIDS Soc*. 2020 Nov;23(11): e25634.

⁸ Stalter RM, Dong TQ, Hendrix CW, Palanee-Phillips T, van der Straten A, Hillier SL, et al. Assessing per-sex-act HIV-1 risk reduction among women using the dapivirine vaginal ring. *J Infect Dis*. 2023 Dec 14;jiad550. doi: 10.1093/infdis/jiad550.

⁹ Nair G, Celum C, Szydlo D, Brown ER, Akello CA, Nakalega R, et al. Adherence, safety, and choice of the monthly dapivirine vaginal ring or oral emtricitabine plus tenofovir disoproxil fumarate for HIV pre-exposure prophylaxis among African adolescent girls and young women: a randomised, open-label, crossover trial. *Lancet HIV*. 2023 Dec;10(12):e779–e789. doi: 10.1016/S2352-3018(23)00227-8.

¹⁰ Bunge KE, Levy L, Szydlo D, Zhang J, Gaur AH, Reirden, et al. Brief report: Phase IIa safety study of a vaginal ring containing dapivirine in adolescent young women. *J Acquir Immune Defic Syndr*. 2020 Feb;83(2):135–139.

¹¹ Makanani B, Balkus JE, Jiao Y, Noguchi LM, Palanee-Phillips T, Mbilizi Y, et al. Pregnancy and infant outcomes among women using the dapivirine vaginal ring among early pregnancy. *J Acquir Immune Defic Syndr*. 2018 Dec 15;79(6):566–572.

¹² Bunge K, Balkus JE, Fairlie L, Mayo AJ, Nakabiito C, Mgodini N, et al. DELIVER: a safety study of a dapivirine vaginal ring and oral PrEP for the prevention of HIV during pregnancy. *J Acquir Immune Defic Syndr*. 2024 Jan 1;95(1):65–73. doi: 10.1097/QAI.0000000000003312.

¹³ Mhlanga F, Bunge KE, Fairlie L, Nakabiito C, Gadama L, Mgodini N, et al. Safety of dapivirine vaginal ring and oral PrEP for HIV prevention in the second trimester. *Conference on Retroviruses and Opportunistic Infections* 2024 Mar 3-6; Denver (CO).

¹⁴ Owor M, Noguchi L, Horne E, Matimbira M, Ssemambo PK, Madhlopa-Mandiwa V, et al. Dapivirine ring safety and drug detection in breastfeeding mother-infant pairs. *Conference on Retroviruses and Opportunistic Infections* 2023 Feb 19-22; Seattle (WA).

shown to be effective and made available.^{15,16} More than 90 percent of participants in Phase 3 trials of the PrEP 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.^{4,15} Studies of pregnant and breastfeeding women found acceptability and adherence of the PrEP ring to be generally high.^{15,17} Key findings amongst this population also included a high value placed on the ability to protect oneself and one's baby, the importance of counseling support especially around method side effects, and general sentiment on ease of use and acceptability.¹⁷ In one breastfeeding safety study, 97% of participants found the PrEP ring to be acceptable and adherence was generally high.¹⁸ Qualitative work from the same study showed participants found the ring to be acceptable and easy to use.¹⁹

“I like that the ring stays inside you and nobody can see it.... you don't have to disclose ring use to others if you want. My family doesn't know that I am using the ring. ...And the partner can't feel it as well.”

Trial participant MTN-020/ASPIRE

Some of the most recent studies regarding PrEP ring acceptability among PBFW were informed by a prior qualitative acceptability study that explored community attitudes toward the PrEP ring or oral PrEP during pregnancy and breastfeeding. The participants in that study valued choice for HIV prevention products for PBFW and agreed that healthcare providers' approval of the PrEP ring during pregnancy or breastfeeding was crucial for product acceptability.²⁰ The same study found that partners played the most important influencer role during pregnancy and breastfeeding and that health decisions, including those about medication use, were typically made jointly.^{20, 21}

Conclusion and recommendation

Research conducted with the PrEP ring in eastern 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 more than 8,700 participants, including women of reproductive age and pregnant and breastfeeding people. Further research examining quantitative and qualitative acceptability data is anticipated in 2024.

¹⁵ Montgomery ET, van der Straten A, Chitukuta M, Reddy K, Woeber K, Atujuna M, et al. Acceptability and use of a dapivirine vaginal ring in a phase III trial. *AIDS*. 2017 May;31(8):1159-1167.

¹⁶ Mayo AJ, Browne EN, Montgomery ET, Torgesen K, Palanee-Phillips T, Jeenaarain N, et al. Acceptability of the dapivirine vaginal ring for HIV-1 prevention and association with adherence in a phase III trial. *Aids Behav* 2021 Aug;25(8):2430-2440.

¹⁷ Montgomery ET, Hawley I, Fairlie L, Bunge K, Mathebula F, Etima J, et al. Acceptability of the dapivirine vaginal ring and oral Truvada among African users in late-stage pregnancy. *AIDS and Behavior*. 2023 Nov 1;28:963-973.

¹⁸ Noguchi L, Owor M, Mirembe B, Horne E, Mgodhi N, Taulo F, et al. Results of a multi-country, Phase 3B randomized trial of dapivirine vaginal ring and oral pre-exposure prophylaxis use for HIV prevention during breastfeeding [abstract]. In *International Journal of Gynecology & Obstetrics Volume 163: Abstracts of the XXIV FIGO World Congress of Gynecology & Obstetrics*. FIGO: 2023 Oct 9-11; Paris (FR).

¹⁹ Stoner MCD, Hawley I, Mathebula F, Horne E, Etima J, Kemigisha D, et al. Acceptability and use of the dapivirine vaginal ring and daily oral pre-exposure prophylaxis (PrEP) during breastfeeding in South Africa, Malawi, Zimbabwe, and Uganda. *AIDS Behav*. 2023 Dec;27(12):4114-4123.

²⁰ Van Der Straten A, Ryan JH, Reddy K, Etima J, Taulo F, Mutero P, et al. Influences on willingness to use vaginal or oral HIV PrEP during pregnancy and breastfeeding in Africa: the multisite MAMMA study. *J Intern AIDS Soc*. 2020 Jun;23(6):e25536.

²¹ Musara P, Hartmann M, Ryan JT, Reddy K, Ggita J, Mutero P, et al. Understanding the role of men in women's use of the vaginal ring and oral PrEP during pregnancy and breastfeeding: multi-stakeholder perspectives. *Afr J AIDS Res*. 2022 Dec;21(4):354-363.

Incident HIV infection during pregnancy and the postnatal period is high and associated with a higher likelihood of vertical transmission, and evidence emphasizes the following regarding PrEP use during pregnancy and breastfeeding:

- Pregnant and breastfeeding women need and deserve more options for prevention, including the PrEP ring.
- The PrEP ring has a favorable safety profile among pregnant and breastfeeding women and their infants.
- Pregnant and breastfeeding women found the ring to be highly acceptable and easy to use.
- Building an expansive body of evidence can inform updates to national PrEP guidelines on use of the PrEP ring by PBFW.

The evidence helps support a recommendation that PrEP ring should be made available to PBFW with appropriate risk/benefit counseling.

PrEP ring research among PBFW in eastern and southern Africa

Study	Description	Study locations	Participant sample	Status
MTN-016/EMBRACE	Prospective, observational cohort study of participants who became pregnant in microbicide trials, including the ASPIRE and HOPE studies. The study team 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 (1 site): 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: <i>Dapivirine ring use during early pregnancy was not associated with adverse effects on pregnancy or infant outcomes.</i>				
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 PBFW ages 18–40, male partners (MPs) of current or recent PBFW, key informants (KIs), and mothers/mothers-in-law of current or recent PBFW (grandmothers/GMs) Malawi: 51 (15 PBFW, 16 MPs, 10 GMs, 10 KIs) South Africa: 53 (15 PBFW, 12 MPs, 20 GMs, 6 KIs) Uganda: 68 (18 PBFW, 19 MPs, 21 GMs, 10 KIs) Zimbabwe: 60 (17 PBFW, 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. Primary manuscript on male partner perceptions completed. Results informed development of MTN-042 and MTN-043.
MTN-041 key takeaways: <i>Participants agreed that PBFW have an increased need for HIV prevention options, and new choices were welcomed for this population. Participants agreed that endorsement by health care providers and confirmation of safety for infants were key to product acceptance.</i>				

Study	Description	Study locations	Participant sample	Status
MTN-042/DELIVER	Phase 3b, open-label, randomized study to assess the safety and pharmacokinetics (PK) of the PrEP ring and oral PrEP when used during pregnancy. Participants are enrolled at different times during pregnancy to the ring or oral PrEP until delivery. The study is the first to be conducted of the ring during pregnancy.	4 sites in Zimbabwe, Uganda, Malawi, South Africa	<p>Total sample: 550 pregnant individuals</p> <p>Cohort 1 (36–37 weeks pregnant): 150 Malawi: 27 South Africa: 42 Uganda: 44 Zimbabwe: 37</p> <p>Cohort 2 (30–35 weeks pregnant): 157 Malawi: 40 South Africa: 28 Uganda: 42 Zimbabwe: 47</p> <p>Cohort 3 (12–29 weeks pregnant): 251 Malawi: 66 South Africa: 44 Uganda: 68 Zimbabwe: 73</p>	<p>Accrual took place from February 2020 to January 2023.</p> <p>Interim results from Cohort 1 presented at IAS 2021 and from Cohort 2 presented at CROI 2023 and Cohort 3 presented at CROI 2024.</p> <p>Safety paper from cohorts 1 and 2 published in JAIDS.</p> <p>Background rates of pregnancy outcomes and complications described in MTN-042B.</p>
<i>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 local communities.</i>				
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	<p>Total sample: 197 breastfeeding parent–infant pairs Malawi: 39 South Africa: 36 Uganda: 55 Zimbabwe: 67</p>	<p>Closed to follow-up November 2021. Interim results presented at AIDS 2022; final results presented at CROI 2023 and FIGO 2023.</p>
<i>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.</i>				

Study	Description	Study locations	Participant sample	Status
MTN-029/IPM 039	Phase I, open-label study to assess the presence of dapivirine in blood, breast milk, and cervicovaginal fluid when delivered via a PrEP ring used continuously for 14 days.	2 sites in the United States	Total sample: 16 breastfeeding parents	Closed to follow-up in March 2017. Primary results were presented at IAS in July 2017, with findings supporting MTN-043/B-PROTECTED. A final paper was published in Antimicrobial Agents and Chemotherapy in March 2019.

***MTN-029 key takeaway:** PrEP ring use was associated with low concentrations of detectable dapivirine in milk and plasma and had a favorable safety profile in lactating parents.*