



# Dapivirine Vaginal Ring and Oral PrEP: Simultaneous Use Discussion

SUMMARY OF EXPERT OPINIONS ON SAFETY AND  
MESSAGING

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**PROMISE** Preparing for Ring Opportunities through Market Introduction Support and Knowledge Exchange

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# Participating experts/advocates

Category	Names, affiliations
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Advocates	Cleopatra Makura, SayWhat, Zimbabwe; Shakirah Namwanje, UNASO, Uganda

**Topics covered:** why women would use oral pre-exposure prophylaxis (PrEP) and the dapivirine ring simultaneously; safety data on simultaneous use; expert opinions on safety and potential drug-drug interactions; questions women have about simultaneous use; messaging.

**MTN-025**

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

Objective:	<ul style="list-style-type: none"> <li>To provide former participants of ASPIRE (MTN-020) the opportunity to continue use of the dapivirine vaginal ring (DVR)</li> <li>To collect additional information on safety and how women would use the ring knowing that it was well-tolerated and reduced the risk of HIV in large clinical trials</li> </ul>
Study Design:	<ul style="list-style-type: none"> <li>Provided former Ring Study and ASPIRE participants access to the DVR for one year</li> <li>Women were free to accept the ring or not, and to change their minds during the study</li> <li>1456 women enrolled, attending visits monthly for 3 months and quarterly thereafter for a year</li> </ul>
Results:	<ul style="list-style-type: none"> <li>Most (92%) women who enrolled chose to accept the ring</li> <li>89% of returned rings had residual dapivirine amounts consistent with use during the previous month; the mean amount released was greater than in ASPIRE (by 0.21 mg; <math>p &lt; 0.001</math>)</li> <li>Modeling results suggest the ring reduced HIV risk; HIV incidence was 2.7/100 person years, compared with an expected incidence of 4.4/100 person years (3.2-5.8)</li> <li>No safety concerns were identified</li> </ul>

1. Baeten et.al. Lancet HIV, 2021

# Why would women use oral PrEP and the ring simultaneously?

- HOPE recorded low levels of simultaneous use, and TRIO (*a five-month prospective randomized, cross-over clinical study that examined acceptability, preference, choice and use of oral tablets, intra-muscular injections and vaginal rings*) found little overlap in preferences for oral PrEP and the ring; however, supply chain challenges and behavioral switching will likely lead to varied, intermittent, and at times overlapping, use.
- According to advocates, women want to cover their bases to achieve 100% protection and may want to:
  - Use both methods simultaneously in case they have to stop one method due to stockouts or family/partner influence, especially within the context of intimate partner or family violence.
  - Use the ring when initiating oral PrEP while waiting for oral PrEP to become protective.
  - Use the ring (as a less burdensome method) consistently but add oral PrEP during periods of high risk.

# Is it safe to use oral PrEP and the ring simultaneously?

- While there are few data available to provide evidence of safety, there was general consensus among experts that simultaneous use is likely safe for the following reasons:
  - The most commonly used oral PrEP regimen is emtricitabine combined with tenofovir disoproxil fumarate (FTC/TDF).
  - All three drugs (emtricitabine, tenofovir disoproxil fumarate, and dapivirine) have good safety profiles, and different side effect profiles and metabolic pathways.
  - The compartmental gradients for the drugs are reversed: e.g., high systemic, low topical concentration for oral PrEP; high topical, low systemic concentration for the ring.
  - The combination of FTC/TDF and a non-nucleoside reverse transcriptase inhibitor (NNRTI) is a first line recommendation for HIV treatment (similar to what would be the case for oral PrEP and the ring together).
  - There are no systemic toxicity or laboratory safety signals with the ring that would exacerbate FTC/TDF safety concerns.
- An area of potential concern, however, might be drug resistance among women who seroconvert.
- The current European Medicines Agency (EMA) opinion on the ring does not support simultaneous use, due to lack of safety data to make a determination.

***In summary, the EMA opinion does not support simultaneous use; however, there is little reason to suspect harm in using these drugs together. Monitoring drug resistance among any seroconverters using both methods would be important.***

# Ideas for future studies

- As the ring is rolled out, conduct studies on concurrent use, behavioral switching, switching due to access issues, and identify factors that lead to changes in use or methods.
- Potentially use animal studies to assess drug interactions and infectivity: infections detected during dual dosing (of oral PrEP and the ring) would signal reasons for concern, as none would be expected. Note: there are no currently validated animal models for ring efficacy.
- Assess use of DVR and simultaneous use, and interactions with hormonal contraception.
- Conduct direct observation studies with removal and re-insertion of the ring to assess the time it takes after removal to lose protective effect; consider adding dosing of oral PrEP to see if/how this changes topical concentrations.
- Given crossovers within MTN-034/REACH (*a phase 2a randomized, open-label crossover study of the ring and oral PrEP among adolescent girls and young women in Africa*) from oral PrEP to the DVR and vice versa without washout periods, this could potentially provide a platform to collect samples for pharmacokinetic and pharmacodynamic studies (explant and mucosal health [histology or flow cytometry as possible examples]).
- Conduct ongoing monitoring of HIV drug resistance with simultaneous use.

***Note: the suggested safety studies were not put forward as necessary to allow for simultaneous use, but as a “nice to have” to provide reassurance.***



# What questions do women have about simultaneous use?

- *When using oral PrEP and the ring together, is the drug concentration higher and is it safe? Are side effects worse?*
- *We are asked to use condoms with oral PrEP; can we now use the ring with oral PrEP instead?*
- *How does the use of the ring and oral PrEP together affect the efficacy of hormonal contraception, e.g., pills, IUD, depo, etc.?*
- *How do these methods work, e.g., what are the mechanisms, especially if used together?*
- *Given that neither oral PrEP nor the ring are 100% effective, if you use them at the same time, is protection improved?*
- *Can a woman who misses oral PrEP pills take post-exposure prophylaxis (PEP), then return to PrEP or go on the ring?*

# Key suggestions for messaging

- Women would like clarity on the safety of using oral PrEP and the ring (independently and simultaneously). Messaging should address:
  - Use during pregnancy and breastfeeding
  - Safety, efficacy and potential side effects of simultaneous use
  - Effectiveness of the DVR as a lead-in to oral PrEP
  - DVR and simultaneous use and potential interactions with hormonal contraception
- Some women might misunderstand prevention efficacy and assume that it is cumulative. There is a need for clear messaging that stresses that:
  - Both products reduce HIV risk and provide women with choices for different seasons of life.
  - All HIV prevention products must be used and adhered to as directed to reduce HIV risk.
  - Neither product protects against unintended pregnancy; therefore, dual use with contraception is recommended when pregnancy is not desired.
  - Neither product protects against sexually transmitted infections (STIs); therefore, dual use with condoms is recommended to prevent STIs.
  - The current European Medicines Agency (EMA) opinion on the ring does not support simultaneous use, due to lack of safety data to make a determination.

# Key suggestions for messaging

## In summary:

**Safety data on simultaneous use of oral PrEP and the dapivirine ring are very limited. Based on independent studies of how the drugs act in the body, simultaneous use is not likely to be less well-tolerated than when the drugs are used individually. No data are available on efficacy when both products are used together; however, it is possible that the ring may offer additional protection when oral PrEP is used intermittently/inconsistently and vice versa. More data are needed to confirm the safety and efficacy of simultaneous use of daily oral PrEP and the dapivirine ring. It will be important to monitor the potential of HIV drug resistance among seroconversions with simultaneous use.**



# Thank You!

For more information, please contact:

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