

What we know and don't know about PrEP and the Dapivirine Ring in Pregnant and Breastfeeding Women

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**Ensuring Safe HIV Prevention Methods for
Pregnant and Breastfeeding Women**

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Not enough

Remember:

- Pregnant and breastfeeding women were excluded from participation in Phase III trials of PrEP and the dapivirine ring
- If women got pregnant they stopped using the product right away

Does this mean we know nothing about PrEP and the ring in pregnant and breastfeeding women?

- We actually know a little bit ...
- But what we know about the safety of PrEP is not enough for some countries to decide whether to offer PrEP to pregnant and breastfeeding women
- What we know about the safety of the ring is not enough for regulatory authorities to consider expanding approval to include these populations (if the ring is approved in the first place)

What we need to know...

- Are PrEP and the dapivirine vaginal ring safe for mother?
- Are PrEP and the dapivirine vaginal ring safe for baby?
- How is the drug in each product taken up in the body in pregnant and breastfeeding women?
- Will pregnant and breastfeeding women use these products – and are they acceptable?

Truvada as Oral PrEP



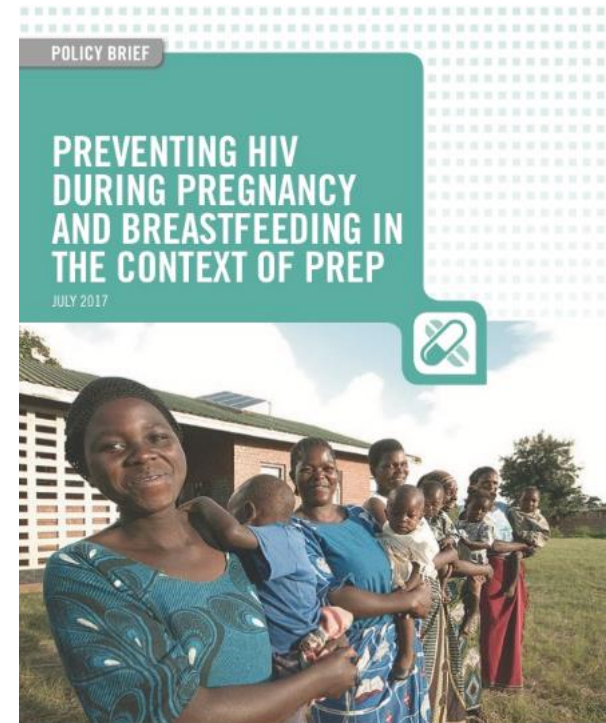
What is PrEP?



- PrEP is an HIV prevention method that involves daily use of an ARV tablet - Truvada
- Truvada contains two drugs – tenofovir (TDF) & emtricitabine (FTC)
 - This medication is used in combination with other medicines to treat HIV
- Several studies have shown that Truvada can reduce a person's risk of acquiring HIV
 - First approved for prevention (PrEP) by the US Food and Drug Administration in 2012
 - Now approved in more than 40 countries – but not for pregnant and breastfeeding women
- The World Health Organization (WHO) recommends its use by anyone who is at risk of HIV

PrEP in pregnancy and breastfeeding women

- The WHO recommends oral PrEP for women during pregnancy and breastfeeding
- Recommendations are based on a review of 33 studies – 26 of these involved HIV-infected women using Truvada (or tenofovir) for treatment of HIV or for prevention of mother to child transmission
- Only 2 studies were of PrEP -- women who became pregnant during the trial and stopped PrEP as soon as it was known she was pregnant



WHO: Truvada and Pregnancy

- ◆ The review of 33 studies of pregnant women who took Truvada, using Truvada did not increase a woman's risk of pregnancy loss, preterm delivery, low birthweight, small for gestational age, birth defects or fetal or maternal death
- Still, WHO recognizes that more information was needed about the use of Truvada as PrEP
- Of the 2 PrEP studies
 - In 1 of these trials women took the medication as directed
 - In the other trial, women did not take the medication well
 - In both trials, once a pregnancy was discovered, women stopped using the medication. This means they only tell us about the drug's safety in early pregnancy

We are learning more about safety of Truvada as PrEP

- In a small study comparing 30 women who chose to stay on PrEP during pregnancy to 96 women who stopped, babies born to women who took drug had smaller heads and less body length at one month. By one year, that difference was gone.
- In a larger study 246 women who reported PrEP use during pregnancy had similar rates of preterm birth and congenital malformations as well as birth measurements as 7515 women who reported that they had not used PrEP
- The implication is that Truvada is safe!

Key PrEP in pregnancy safety gaps

- ◆ **Few PrEP in pregnancy studies**
 - 3/5 from large clinical trials in which PrEP was stopped with pregnancy diagnosis so safety is limited to early pregnancy
- ◆ **Few studies quantify infant exposure**
 - Maternal adherence also not confirmed
- ◆ **No data on longer-term outcomes**
 - Only birth outcomes, growth up to 1 year

What about PrEP and breastfeeding?

- Some studies look at how much drug gets into breast milk, because if the drug level is low, the baby's exposure is low

Levels in the breastmilk were low
Tenofovir was not measurable in 94% of babies

- Researchers in Kenya and Uganda watched 50 women take PrEP every day so that they were certain that they were using the medicine as instructed. They measured:
 - Drug level in the mother's blood
 - Drug level in the breast milk
 - Drug levels in the baby's blood

Additional Research is underway

- IMPAACT 2009
 - Determining whether the standard dose for oral PrEP is adequate for a pregnant or breastfeeding woman
 - Assessing the safety of oral PrEP for mom and baby when the mom takes the medicine while pregnant and breastfeeding
- Being conducted here and at six other sites in Uganda, South Africa and Zimbabwe



The Dapivirine Ring



The Dapivirine Ring



- Made of flexible silicone, making it easy for women to insert and remove themselves
- Intended to be used for a month at a time
 - Women rarely feel it
 - Is discreet – their partners seldom feel during sex
- Slowly releases dapivirine into the vagina – most drug stays in the vagina, the potential site of infection
 - Dapivirine is a new drug only being used for prevention – it is not used in treatment of HIV
- Developed by the International Partnership for Microbicides (IPM) – a nonprofit group – that is seeking its approval

Two potential issues to consider

- The effects of the drug – dapivirine
- The effects of the ring itself

The drug

- Animal studies are reassuring
 - No effects on fetal development in rabbits despite really high levels of drug
 - Levels that are much much higher than expected levels in women using the ring
- The amount of drug detectable in the blood (systemic exposure) is minimal
 - For drug to reach the baby it must be filtered through the placenta

The ring itself

- Two major theoretical concerns with keeping a silicone product in the vagina during pregnancy



1. The normal balance of bacteria in the vagina might shift such that “bad” bacteria outnumber the “good” bacteria, leading to infection in the womb and preterm delivery
2. The presence of an object in the vagina might disrupt the cervix leading to preterm delivery

Concerns assessed

- In clinical trials of the dapivirine vaginal ring there were no changes in women's vaginal bacteria from using the ring
- While the dapivirine vaginal ring hasn't (yet) been studied in pregnancy, silicone devices have
- Pessaries (vaginal silicone products) are currently used during pregnancy (and have been used since the 1960s!) for prolapse and to prevent preterm delivery



What is known about the dapivirine ring during pregnancy so far?

- We have no reason to think the dapivirine ring would be unsafe in pregnancy
 - BUT, we have very little information
 - Unlike oral PrEP, dapivirine is not used in treatment so the amount of data is MUCH smaller
- Our experience is limited to the ASPIRE and The Ring Study which found that the ring was safe during conception and early pregnancy
 - About 250 women across both trials became pregnant
 - They stopped using the ring as soon as they learned of their pregnancy
- **The ring was safe!**



Pregnancy and Infant Outcomes Among Women Using the Dapivirine Vaginal Ring in Early Pregnancy

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Epidemiology

What about the dapivirine ring and breastfeeding?

- One study looking at the safety and take up of drug from the dapivirine ring in women who are producing milk: MTN 029/IPM 039
- 16 healthy women who had recently weaned their babies were enrolled
- They used the ring for 14 days and collected milk, blood, and fluid from the vagina to check for drug levels
- No infants were actually exposed to drug, but researchers were able to estimate infant exposure based on milk drug levels

The ring was safe and the drug levels low

- The vaginal ring was safe and well tolerated
- Dapivirine drug levels in the breast milk were double the level found in maternal blood but still very very low

If a baby breastfed everyday for the rest of its life, the amount of drug he would take in for the REST OF HIS LIFE would be smaller than a grain of rice





Conclusions

Summary

- The dapivirine ring and PrEP were safe and effective in trials– but pregnant and breastfeeding women not included
- PrEP – daily use of an ARV - is approved in many countries, but information about its safety in pregnant and breastfeeding women is still somewhat limited
- A monthly vaginal ring is a new product under regulatory review – much less is known about its safety in these populations
- Knowing whether these methods are safe during pregnancy and breastfeeding is vitally important

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