Clinical Practice Guidelines for Dapivirine Ring Use in Pregnant and Breastfeeding Populations

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List of Acronyms

AFAB	Assigned Female Sex at Birth
AHI	Acute HIV Infection
ANC	Antenatal Care
ART	Antiretroviral Therapy
ARV	Antiretroviral
CHOICE	Collaboration for HIV Prevention Options to Control the Epidemic
FP	Family Planning
IPV	Intimate Partner Violence
MOSAIC	Maximizing Options to Advance Informed Choice for HIV Prevention
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitors
PBFP	Pregnant Breastfeeding Populations
PEPFAR	U.S. President's Emergency Plan for AIDS Relief
PNC	Postnatal Care
PPFP	Postpartum Family Planning
USAID	U.S. Agency for International Development
UTI	Urinary Tract Infections

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The Clinical Practice Guidelines for Providing Dapivirine Ring for Pregnant and Breastfeeding Populations have been designed as a supplement to the Clinical Practice Guidelines for Providing PrEP for Pregnant and Breastfeeding Populations, which were originally developed as part of the Collaboration for HIV Prevention Options to Control the Epidemic (CHOICE) project. CHOICE was a 24-month collaboration funded by USAID, in partnership with PEPFAR, through EpiC and RISE. The goal of this partnership was to address technical gaps and support national scale-up of pre-exposure prophylaxis in PEPFAR countries through catalytic evidence generation, translation, and research utilization. CHOICE was led by FHI 360 and Jhpiego. CHOICE was funded by PEPFAR) through USAID cooperative agreements 7200AA19CA00002 and 7200AA19CA00003.

Background

This clinical practice guideline, which is a supplement to the *Clinical Practice Guidelines for Providing PrEP for Pregnant and Breastfeeding Populations*, aims to assist health workers to offer the dapivirine vaginal ring as an additional HIV prevention option for pregnant and breastfeeding clients in settings where the dapivirine vaginal ring is an approved option for HIV prevention. The guidance here assumes that local national guidance is either permissive of, or specifically includes the dapivirine vaginal ring as a recommended HIV prevention option for pregnant and/or breastfeeding individuals, or that health workers will need to know how to care for those who become pregnant while using the dapivirine vaginal ring. Evidence on the safety and acceptability of the dapivirine vaginal ring for pregnant and breastfeeding populations (PBFP) continues to evolve. As such, updates to this document are anticipated as new data become available.

The dapivirine ring is a vaginal ring that used for HIV prevention. Other vaginal rings containing contraceptive hormones are available for family planning in some countries. Additional types of vaginal rings are under development for HIV prevention. Individual countries and programs may use different terms to refer to the dapivirine vaginal ring (e.g., the PrEP ring). In general, this document will refer to the dapivirine vaginal ring as the "ring" or the "dapivirine ring", but individual countries and programs should adapt to local preferences, as needed.

The dapivirine ring

The monthly dapivirine ring is a safe and effective additional HIV prevention choice for women at substantial risk of HIV infection as part of combination prevention approaches. The ring could be particularly useful for clients who are unable or do not want to take oral PrEP or when oral PrEP is not available. The ring has been studied for prevention of HIV only among those assigned female sex at birth (AFAB) during receptive vaginal sex and does not prevent HIV acquisition through any other mode of transmission. This protection against HIV infection is only for the person wearing the ring in the vagina and not their sexual partner. The dapivirine ring does not protect against other sexually transmitted infections or pregnancy.

The ring is available in one size and made of a flexible silicone material containing 25 mg of an ARV drug used only for HIV prevention called dapivirine. Silicone elastomer has been shown to be safe when used to make many medical devices, such as contact lenses, catheters, and other types of vaginal rings (e.g., contraceptive rings).[1] The ring is inserted into the vagina and should remain in place for one month to ensure maximum effectiveness during periods of exposure to HIV. Dapivirine belongs to a class of antiretrovirals (ARVs) called non-nucleoside reverse transcriptase inhibitors (NNRTI) that reduce the ability of HIV to make more copies of

itself inside a healthy cell. The ring delivers the drug continuously over the course of one month to the genital area, the site of potential infection during vaginal sex, with low absorption elsewhere in the body, lowering the likelihood of systemic side effects. Clients can insert, remove, and replace the ring themselves each month, or with the assistance of a health care provider if desired.

Dapivirine ring research on safety and effectiveness

Overall, the dapivirine ring has been shown to confer about 30% protection against HIV-1 acquisition through vaginal sex in clinical trials, with few adverse events and no safety concerns with long-term use. Results from two open-label extension studies — DREAM and HOPE —found similar safety results but somewhat higher levels of effectiveness at about 50% with consistent use.[2, 3] However, these studies did not show efficacy among the sub-group of participants aged 18–21 years old, who were also shown to have low adherence to the ring during the trials. Further analyses exploring the safety and acceptability of the dapivirine ring among people AFAB ages 15–21 have demonstrated that the ring is very acceptable to younger users, with a favorable safety profile among younger and older users, and can be used effectively by younger users with proper adherence support.[4]

World Health Organization Guidelines

In January 2021, WHO made a conditional recommendation to offer the dapivirine ring as a safe and effective additional prevention choice for women at substantial risk of HIV infection as part of combination prevention approaches. This recommendation was based on the cost–effectiveness of the ring, acceptability, demonstrated feasibility, and the potential to increase equity as an additional prevention choice, noting some variability in effectiveness in younger age groups and limited data regarding use among pregnant and breastfeeding populations.[5] The WHO also acknowledged the need for further information on safety in pregnancy and breastfeeding, with data expected to be provided from two studies known as DELIVER and B-PROTECTED, carried out in Malawi, Uganda, South Africa, and Zimbabwe.

Evidence for dapivirine ring safety during pregnancy and breastfeeding

Pregnancy

The dapivirine ring has been studied for safety during pregnancy in several ways, and studies are ongoing to further assess safety during pregnancy. These studies have not identified any negative pregnancy or infant outcomes associated with using the ring during pregnancy. Data are limited on the use of the ring by people who are pregnant, but results of a pregnancy registry study found that people who became pregnant while using the ring did not have increased risk of health problems for themselves or their infants.[6] One clinical trial

to further assess the safety of the dapivirine ring and oral PrEP use during pregnancy (the DELIVER study) is ongoing.[7] Interim results from the DELIVER study indicate that adverse pregnancy outcomes and complications were uncommon among ring users during late pregnancy (more than 36 weeks' gestation) and generally similar to rates observed in the surrounding study community.[8] Furthermore, studies of dapivirine have not shown adverse effects on pregnancy or offspring for animals. Providers and clients should weigh client preferences and ability to use HIV prevention methods effectively when considering whether the ring or another HIV prevention method, such as oral PrEP, should be used during pregnancy.

Breastfeeding

An observational study suggests that small amounts of dapivirine are present in breastmilk for those who use the ring while lactating, but dapivirine levels are so low that they are difficult to measure. These results suggest that the amount of dapivirine that would pass from milk to infants would also be extremely low. A clinical trial of ring and oral PrEP use while breastfeeding (the B-PROTECTED study) showed reassuring safety results for breastfeeding mothers and their infants.[9]

Counseling clients who become pregnant while using the dapivirine ring

Even in settings where ring use may not be approved for use in pregnancy, clients may present to family planning, antenatal care (ANC), or other healthcare settings with a history of dapivirine ring use in the periconception or pregnancy periods, including pregnant clients who have the dapivirine ring currently in place. Such clients should be provided with the following interventions, including appropriate counseling messages:

- If presenting to ANC setting, all routine ANC interventions, including HIV counseling and testing
- Counseling should include the following:
    - Options for HIV prevention including continuing the dapivirine ring or changing to another method, e.g., oral PrEP, and a balanced review of risks and benefits associated with product use, and where to access these options
    - Pregnancy management options counseling according to the local standard of care
    - Reassurance regarding dapivirine ring use in early pregnancy, which has not been associated with a negative impact on pregnancy or infant outcomes
- If client is experiencing potential side effects, evaluate these according to guidance in this document (see section on *Managing side effects during pregnancy and postnatal period*)

Before initiating a new prescription for the dapivirine ring

Identifying and screening pregnant and breastfeeding clients

When clients live in settings where HIV is common, all HIV-negative pregnant and breastfeeding persons should be considered candidates for oral PrEP, unless individual clinical contraindications exist. All ANC and postnatal care (PNC) clients are at increased risk for acquiring HIV during pregnancy and breastfeeding, due to a range of factors, including biologic factors, the possibility of their own or their partners' undisclosed multiple partners, changes in condom use patterns, sexual violence, and transactional sex. All HIV prevention methods that are available to PBFP should be reviewed with clients. The dapivirine ring may be a preferred option for people who wish to prevent HIV acquisition through receptive vaginal sex and are unable or do not want to take oral PrEP, or when oral PrEP is not available. At present, oral PrEP is the most efficacious self-controlled HIV prevention method for people, including pregnant and breastfeeding individuals, who wish to prevent HIV infection due to receptive anal sex.

Comprehensive application of this recommendation includes all of the following types of clients:

- Routine ANC and PNC clients
- Clients who are using the dapivirine ring and then subsequently become pregnant
- Clients seeking pregnancy, currently pregnant, or currently breastfeeding, with partner(s) who may:
    - Have unknown HIV status
    - Be living with HIV, but not on HIV treatment
    - Be living with HIV, but on treatment less than 6 months, not virally suppressed, or viral suppression status unknown
- Clients who may access the ring through facility- or community-based PrEP delivery programs, including adolescent girls and young women

Contraindications for dapivirine ring use

Contraindications for dapivirine ring use in pregnancy and breastfeeding are listed below:

- Some contraindications are the same as for non-pregnant, non-breastfeeding individuals

- An HIV-positive test result according to the national HIV testing algorithm
- Known recent exposure to HIV (because such clients may derive more benefit from post-exposure prophylaxis (PEP) if the potential for HIV exposure was high)
- Signs/symptoms of acute HIV infection (AHI) and potential exposure within the past 14 days
- Inability to commit to using the dapivirine ring effectively and attend scheduled follow-up visits
- Allergy or hypersensitivity to active substance or other substances listed in the product information sheet

- During pregnancy
  - Active labor at any gestational age
  - Vaginal bleeding
  - Suspected or confirmed rupture of the amniotic membranes (bag of waters)
  - Cervical cerclage (treatment for increased risk of preterm birth in those with history of cervical weakness)
  - Suspected or confirmed intrauterine infection, i.e., chorioamnionitis
- During the postnatal period
  - Unresolved postnatal vaginal bleeding (intermittent spotting during the postnatal period can be normal)
    - Unresolved vaginal bleeding may be due to infection or retained products of pregnancy/placenta
  - Uterus not yet returned to near pre-pregnancy size through normal involution
- Following spontaneous or therapeutic abortion
  - Suspected or confirmed intrauterine infection
    - In addition, it may be prudent to defer dapivirine ring start for some participants who require but have not yet completed treatment for **symptomatic** sexually transmitted infection, urinary tract infection, vaginitis, or pelvic inflammatory disease, due to potential discomfort and challenges understanding and managing side effects from different causes

SIGNS AND SYMPTOMS OF ACUTE HIV INFECTION

Acute HIV infection may include signs and symptoms of fever, sore throat, aches and pains, lymphadenopathy (swollen glands), mouth sores, headache, or rash. If the client has any of these signs or symptoms, the health provider should consider the possibility that acute HIV is present. In such circumstances, consider deferring PrEP or dapivirine ring start for 4 weeks and having the person tested for HIV again, which will allow time for possible HIV seroconversion to be detected.

- However, it should be noted that presence of sexually transmitted infection may increase risk for getting HIV, and these individuals may be especially important candidates for prompt start of an effective HIV prevention method

Laboratory testing

Before prescribing the dapivirine ring, HIV counseling and testing should be provided for PBFP. Blood tests for kidney function and hepatitis B virus infection are **not** needed before starting the ring, but should be ordered if other clinical indications are present. Optimally, all clients will also be evaluated for sexually transmitted infections as this is the preferred standard of care. Laboratory evidence of hepatitis B, syphilis, gonorrhea, or chlamydia should prompt evaluation for complications of these conditions, as well as appropriate treatment according to local standard of care. Results from these tests do not inform the decision to start the ring. Clients can start the ring while waiting for results.

Ruling out current HIV infection

As with clients who are not pregnant or breastfeeding, HIV should be ruled out by testing before initiation of dapivirine ring use. HIV testing should be performed the same day that the ring is started, using a point-of-care rapid HIV test, with additional testing according to the national HIV testing algorithm. The first test in the testing strategy should be the most sensitive test available.

Assess for PEP Indication

Clients exposed to HIV in the past 72 hours: If a client reports an exposure to HIV in the past 72 hours, screen for PEP indication instead of PrEP. Educate clients on the difference between PEP, PrEP, and antiretroviral therapy (ART) and offer HIV exposure reduction counseling. After 28 days of PEP, a client may be transitioned from PEP to PrEP or the ring without a gap if they are HIV-negative and meet other criteria for PrEP or ring use.

Assess for Acute HIV Infection

Clients suspected to have AHI: If client presents with signs and symptoms of AHI and possible exposure to HIV in the previous 14 days, the client is suspected to have AHI. If available, AHI can be diagnosed using “direct” viral tests such as HIV RNA or HIV antigen testing. In the absence of HIV RNA and HIV antigen testing, if the client has symptoms of AHI AND has been exposed to HIV in the 14 days prior to the test, defer ring start for four weeks and provide HIV exposure reduction counseling, as well as STI screening, diagnosis, and management, if available. Repeat HIV testing after four weeks; if the client is HIV-negative and meets other criteria for PrEP use, the client can start the dapivirine ring.

The purpose of this screening is to make sure: 1) PEP is prescribed instead of PrEP or ring for clients with potential exposure within 72 hours; 2) the client is not in the HIV testing window period, as evidenced by signs/symptoms and a potential exposure greater than 72 hours ago, since PrEP or ring should not be started for such clients because AHI would be suspected; 3) the client is requesting or indicated for PrEP or ring use; and 4) the client is free of contraindications for use of their chosen HIV prevention method. Figure 1 outlines the algorithm for ruling out PEP indication and possible AHI before starting oral PrEP or dapivirine ring.

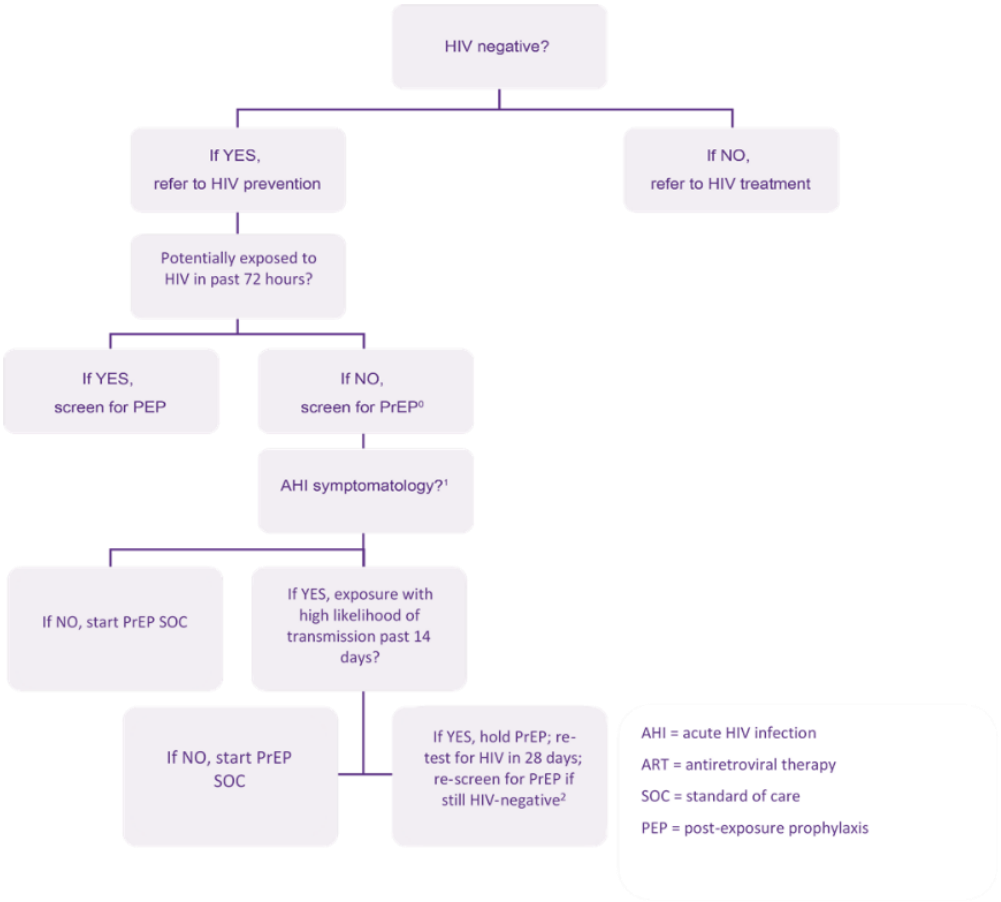

Figure 1. Ruling out PEP indication and possible acute HIV infection

[0] An answer of "NO" to question "Potentially exposed to HIV in past 72 hours?" means no potential past exposure to HIV at all or potential HIV exposure that was 73+ hours ago.
[1] Signs/symptoms mimicking AHI (sore throat, fever, sweats, swollen glands, mouth ulcers, headache, rash, muscle aches) are commonly due to illnesses other than HIV; providers need to use discretion in determining whether the symptomatology is consistent with HIV or may be explained by an alternative cause.
[2] PrEP/ring standard of care

Bringing up the topic of HIV prevention

The topics of oral PrEP and ring use for PBFP may be introduced in a variety of different community- and facility-based contexts. At any entry point to care, discuss the options of oral PrEP and ring use for PBFP (Figure 2).

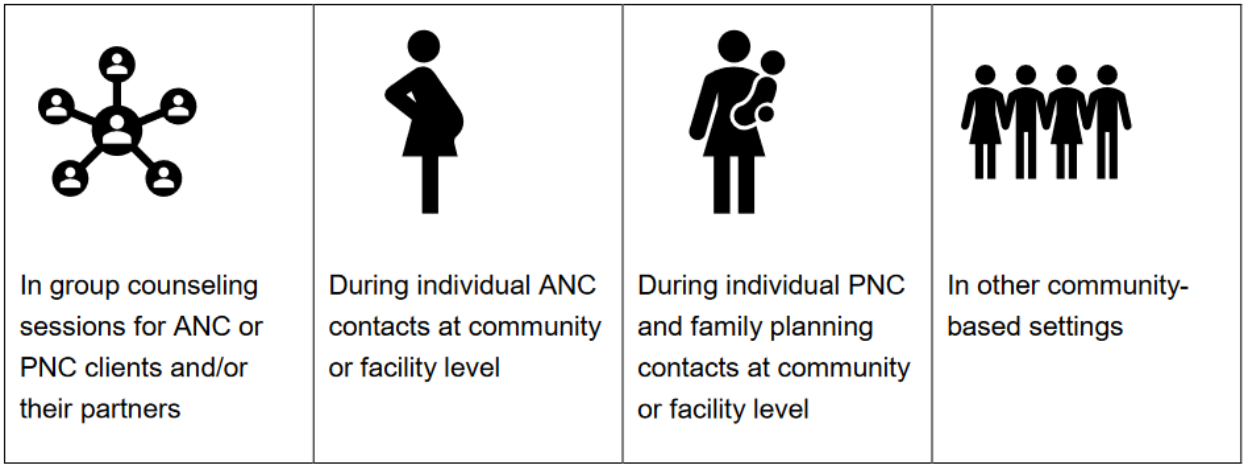

Figure 2. Opportunities to discuss PrEP and the ring with PBFP

All HIV prevention methods that are available to PBFP should be reviewed with clients. If introducing the topic at an individual ANC or PNC contact, it may be helpful to bring up oral PrEP and ring use whenever discussing other preventive interventions that protect the mother and baby, such as taking daily iron and folic acid tablets. This helps to normalize HIV prevention as care available to every pregnant person. One option is to start by asking the client if they have heard of the ring or oral PrEP before, and then counsel the client on what these options are, their safety during pregnancy and breastfeeding, as well as other key counseling messages, and as prompted by the client's individual questions. If clients decline oral PrEP or the ring, providers may remind clients that if their situation or preferences change, these options may be available to them in the future. Inviting PBFP to ask questions about the ring, oral PrEP, and other aspects of ANC and PNC builds trust and increases the value of the visit to the client, which also encourages them to engage with the health system and continue their HIV prevention regimen. In the context of serodifferent (also called serodiscordant) relationships, it is especially critical that ANC clients feel safe to ask questions about oral PrEP and ring use. Due to potential stigma, many clients in this situation may plan conception and become pregnant without consulting health care providers.

Clients interested in using the dapivirine ring should be counseled that it must be inserted into the vagina and worn for one month without removal. The ring must be in place for at least 24 hours before it is maximally effective. If a client wishes to discontinue use of the ring, they can remove it themselves. It is not known how

long the ring must remain in place after a potential exposure to be maximally effective. Ideally, clients who are discontinuing PrEP use will alert their providers and receive support to switch to other HIV prevention practices if they are still needed. An English language video that explains the dapivirine ring is available by scanning the QR code in Figure 3.

Figure 3. Video - A long-acting and woman-controlled HIV prevention option

Initial counseling

Shared decision-making between the client and provider is a successful approach used in family planning (FP) counseling, and a recommended approach when counseling pregnant and breastfeeding clients regarding oral PrEP and the dapivirine ring. Using this approach, the client reviews their potential vulnerabilities to HIV. The PrEP provider shares evidence-based information about the client's options for HIV prevention and invites the client to share their experiences, values, and preferences about HIV prevention options. Discussion topics can include evidence of safety, levels of effectiveness, side effect profiles, and how clients feel about taking a daily medicine and/or using a vaginal product. Other aspects of HIV prevention methods may be important to clients, and these should also be discussed. The health care worker can help the client weigh their competing priorities before making their choice.

In addition to routine counseling messages related to HIV prevention included in the *WHO Implementation tool for pre-exposure prophylaxis (PrEP) of HIV infection*, health care providers should integrate the following counseling messages into other routine counseling messages for PBFP, as appropriate:

- In general, people are at higher risk for acquiring HIV when they are pregnant or breastfeeding compared to times when they are not
- For most healthy people who live in areas where HIV is common, the potential benefits of oral PrEP and dapivirine ring use to mothers and infants outweigh potential risks; acquiring HIV is a greater risk to the mother and her baby's health, compared to potential risks of using either oral PrEP or the ring

- There is no evidence that either oral PrEP or the ring increase the chance of birth defects, miscarriage, or other complications during pregnancy, birth, or after the birth for the mother or the baby
- Oral PrEP and the ring do not have any known negative interactions with the medications and supplements most commonly prescribed for women in pregnancy and during breastfeeding
- Research has shown that PrEP and the ring are generally safe for mother and baby and well tolerated when used during breastfeeding
- The amount of medication that may pass to the baby with oral PrEP or dapivirine ring use during pregnancy and breastfeeding is very small, and has not been shown to cause any serious health problems for babies
- Oral PrEP and vaginal ring use during pregnancy and breastfeeding have not been shown to cause the baby to be too big or too small
- Oral PrEP and vaginal ring use have not been shown to have any impact on a person's ability to become pregnant in the future
- Some people using oral PrEP or the ring experience side effects, with some side effects (such as nausea) that may be similar to pregnancy discomforts; these side effects are generally mild, not dangerous, and resolve quickly
- The ring rests at the top of the vagina, right below the opening to the cervix, and in this position, it does not enter the uterus or touch the baby
- The ring should be removed before delivering the baby, ideally when contractions start or when arriving to the hospital for delivery of baby
- The ring can be restarted after delivering the baby, ideally after the mother's uterus has returned to its pre-pregnancy size and bleeding has diminished
- Neither oral PrEP nor the ring have been shown to affect a mother's milk production or the taste or quality of breast milk
- For breastfeeding mothers taking oral PrEP or the ring, exclusive breastfeeding for the first 6 months of life is still the recommended way of feeding infants, followed by continued breastfeeding with appropriate complementary foods for up to 2 years or beyond
- The health care provider should explore whether the mother is experiencing violence, and if so, discuss ways they can help them and their baby stay safe*

* The WHO LIVES (Listen, Inquire, Validate, Enhance safety and Support) curriculum is designed to provide health workers with a foundation for responding to domestic and intimate partner violence and sexual violence against women. Participants learn how to provide client-centered clinical care, including identifying clients experiencing violence, providing first-line support

If a client declines both oral PrEP and the ring, the provider should counsel on other safe and effective approaches for HIV prevention such as condoms, the availability of PEP, and the option to start either (or a different) prevention method in the future. Those providers offering ANC, PNC, and PrEP services for PBFP must be familiar with and comfortable providing PEP, due to the time-sensitive nature of eligibility (i.e., within 72 hours of exposure). Clients who decline any type of PrEP still need to know about their HIV prevention options for testing of partner(s), treatment of partner(s) living with HIV as prevention, condom use, use of safer sexual practices, and sexually transmitted infection (STI) testing and treatment.

Possible side effects

Health care providers should let clients know about possible side effects, so that these may be expected. At this time, few studies have assessed side effects among PBFP, but information on the side effects among those who are not pregnant and not breastfeeding, should be discussed with the client. The possible side effects of the ring are typically mild and include urinary tract infections (UTIs – experienced by about 15% of users), vaginal discharge (experienced by about 7% of users), vulvar itching (experienced by about 6% of users), and pelvic and lower abdominal pain (experienced by about 6% of users).[10] Side effects usually occur during the first month of use and resolve without the need to remove the ring. Ring users should be counseled to contact their health care provider if they experience any urinary or reproductive tract changes, because these could be a sign of a STI or UTI needing treatment.

Using and taking care of the dapivirine ring

All clients who are prescribed the ring should be counseled regarding its routine use and care. See Table 1 for counseling messages.

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though the LIVES approach, providing essential care for survivors, and identifying local support resources. The curriculum emphasizes compassionate, empathic provider–patient communication.

Table 1. Counseling messages on routine use and care of the dapivirine ring

Supporting effective use	The dapivirine ring is designed to be in place for a full month without being removed. After insertion, nothing needs to be done for the full month to be protected. However, if you decide to remove the ring, it is important to rinse it using clean water and insert it again as soon as possible. Setting a reminder may help you remember when to replace your ring. For example, an alert on your phone or a note in your diary, if you have one. If the ring is removed for a brief period and kept somewhere clean, it can be rinsed and reinserted. If it has been more than one month since the dapivirine ring was first inserted, you should instead get a new ring. *PROVIDER NOTE: Walk through insertion and removal instructions with the client. What strategies do you think will help you be successful with the ring? What challenges do you anticipate? *Providers should explore and emphasize continuous use and ring replacement reminder. This may be an appropriate time to explore gender and intimate partner violence (IPV). Providers may reference the CHARISMA toolkit for resources on discussing partner relationships and PrEP use. The CHARISMA toolkit aims to empower the client in their relationship and to use PrEP. It includes a counselling job aid with four modules on healthy and unhealthy relationship dynamics, including responding to IPV. The CHARISMA Standard Operating Procedure and Job Aid for Addressing Partner Relationships and Intimate Partner Violence in Pre-exposure Prophylaxis (PrEP) Services may also be referenced to support providers in identifying clients who are experiencing IPV and providing appropriate violence response services.
Cleaning the ring	The ring should stay in place inside the vagina for the full month. It does not need to be removed and cleaned for any reason. However, if desired, it is acceptable to remove the ring, rinse it in clean water only, and then reinsert it immediately.
Ring reinsertion	Although it is unlikely, it is possible that the ring may move out of place or fall out. If this happens in a clean location, the ring should be rinsed in clean water and reinserted. If the ring falls out in a dirty location, the ring should be replaced with a new ring. If the ring moves, feels out of place, or feels uncomfortable in the vagina, it is okay to insert a clean finger and push it up so it is again placed in a comfortable spot inside the vagina.
Ring use during sex	The ring does not interfere with sexual intercourse and should be worn during sex. It can be used with condoms (internal and external) and condom-compatible lubricant. Inserting substances to dry out the vagina is not good for vaginal health and should be avoided. Moreover, it is not well understood yet, but these practices could also affect how well the ring works to reduce your chance of getting HIV-1 infection. Although it is unlikely, it is possible that your partner may feel the ring during sex. If this happens, you may need to confirm ring placement, as it may mean that the ring should be pushed further into the vagina. The ring does not cause harm to your partner, but it does not prevent your partner from acquiring HIV.
The ring and menses (for non-pregnant clients)	The ring should be worn for one month, including during menses, to be most effective. The ring does not cover the cervix and does not interrupt the flow of menstrual fluids. There are no safety concerns related to the use of tampons, menstrual pads, menstrual cups, or other menstrual hygiene products while using the ring. If using a tampon, be careful not to accidentally remove the ring when removing the tampon. Should the ring fall out, following the instructions for reinserting the ring.
Sharing the ring	The ring should not be shared with others. If other people you know are interested in using the ring, they can come here.
The ring and douching	Flushing the vagina with water to clean it, or douching, is not recommended as it is not good for vaginal health and should be avoided. Moreover, it is not well understood yet, but douching could also affect how well the ring works to reduce your change of getting HIV-1 infection.
Ring storage	Store rings in their original packaging in a cool, dry place, away from children and direct sunlight, and secured from any pets or animals. The ring does not need to be refrigerated and can be safely stored at or around 25°C or 77°F for up to five years.
Ring disposal	Used rings can be placed inside the original wrapper provided with the ring or wrapped in tissue or toilet paper and disposed of in a trash bin out of reach of children. If you prefer, you can return your used ring to your health care provider/service provision point for disposal.

Inserting and removing the ring

Clients may need initial guidance and support to learn how to use the ring and, once confident, can continue to use the ring on their own. Some clients are comfortable inserting and using the ring on their own with minimal support from their first use. However, for clients who prefer support, a health care provider can help insert the ring or confirm placement. The ring is inserted with fingers; there is no need to use a speculum or other tools to insert the ring. Clear visual instructions should be offered with the ring. Step-by-step guidance is included in Figure 4.

Assisting client with first ring use

After providing ring insertion instructions and answering any questions the client may have, the health care provider should ask the client if they are ready to try inserting the ring. Staff should be sensitive to the fact that those later in pregnancy may not feel comfortable inserting the ring themselves or may find the task physically challenging. In these cases, the health care provider should offer to assist. Any issues or problems raised by the client should be addressed by the health care provider and documented in the chart so the information is easily available for reference at follow-up visits. After correct placement is confirmed, the clinician may ask the client if they would like to feel the position of the ring. This will help ensure an understanding of what correct placement feels like, should the client need to check this at any time.

Checking ring placement

1. Checking for ring placement is not typically required. If the client expresses discomfort after inserting the ring and wants reassurance that is has been placed correctly, the provider can offer to check ring placement. After ring placement, the participant should walk around prior to verification of correct ring placement.
2. The participant should then lie comfortably on the examination couch in supine position (on her back).
3. Upon genital inspection, the ring must not be visible on the external genitalia. If the ring is visible, the placement is not correct.
4. The ring should not press on the urethra.
5. On digital examination, the ring must be placed at least 2 cm above the introitus beyond the levator ani muscle.
6. If, on inspection, the ring is found to be inserted incorrectly, the ring should be removed and reinserted correctly by the client or the clinician.

Ring insertion steps for clients

Get into a position that is comfortable for inserting the ring, such as squatting, one leg lifted, or lying down. If a health care provider is assisting you, you should be in a reclining position.

With clean hands, squeeze the ring between the thumb and forefinger, pressing both sides of the ring together so that the ring forms a "figure 8" shape.

Use the other hand to open the folds of skin around the vagina.

Place the tip of the ring into the vaginal opening and use your fingers to push the folded ring gently up into the vagina.

Push the ring as far toward the lower back as possible. If the ring feels uncomfortable, it is probably not inserted far enough into the vagina. Use a finger to push it as far up into the vagina as is comfortable.

Ring insertion should be painless. If you have any bleeding or discomfort upon insertion, contact your health care provider.

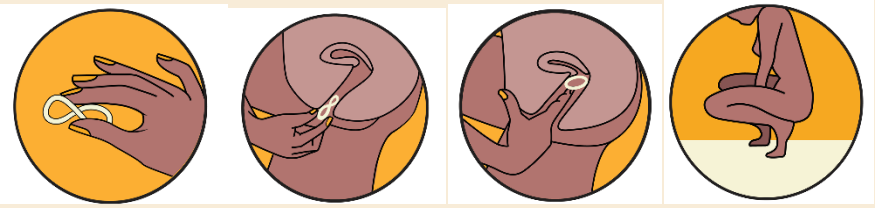

Figure 4. Ring insertion steps for clients

Removing the dapivirine ring

Clients can remove the ring without the help of a health care provider. However, for clients who prefer support, a health care provider can help remove the ring. The ring is removed with fingers; there is no need to use a speculum or other tools to remove the ring. If a client is being assisted by a health care provider, they should be in a reclining position during removal. Removal steps for clients are listed in Figure 5.

The ring should be removed before delivering the baby, ideally when contractions start or when arriving to the hospital for delivery of the baby.

Get into a position that is comfortable for removal, such as squatting, one leg lifted, or lying down.

With clean hands, insert one finger into the vagina and hook it around the edge of the ring.

Gently pull the ring out of the vagina.

Ring removal should be painless. If you have any bleeding or discomfort upon removal, contact your health care provider.

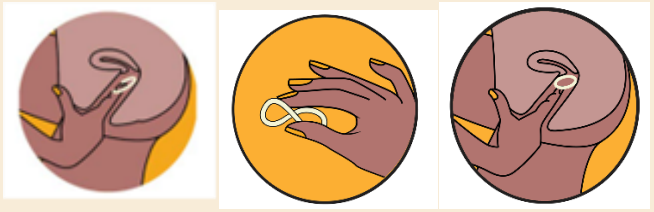

Figure 5. Ring removal steps for clients

Documentation in the client's clinical record

Normally, all prescriptions would be documented on the client's handheld ANC record (if this is used) as well as any relevant ANC, PNC, family planning, or PrEP-specific facility-based client records and registers. All clinical care related to oral PrEP or ring use should be documented in facility-based records. However, providers should consult with the client before documenting oral PrEP or ring use on handheld records. Providers may wish to use more discreet strategies for documentation related to oral PrEP or ring on handheld records carried by clients, so as to avoid unintentional disclosure to partners, family, or other household members, given the potential for stigmatization and related social harm.

Scheduling follow-up contacts and promoting ring continuation

If the client is receiving the ring through an ANC, PNC, or FP service delivery site, try to align visits to minimize trips to the clinic, as frequent visits may discourage some clients from continuing the ring. Follow national guidance on the timing of ANC, PNC, and family planning contacts.

To optimize chances for continuation, try to do the following:

- Understand motivations for using the ring
- Ask about potential barriers that may be faced in returning to the clinic and continuing ring use, as well as ways to overcome these barriers
- Ask about the potential for return at one month after initiation for assessment and confirmation of HIV-negative test status, assessment for early side effects and discussion of any difficulties with effective use or any other client concerns
- Consider providing a supply of rings that will last beyond the time of the next recommended visit, particularly if the client is not sure they will make it back
- After the one-month visit, follow-up visits are recommended every three months
- Ask about partner reactions and strategies to communicate about ring use with partners who are not supportive
- Provide anticipatory counseling to help manage any side effects, as these have been shown to impact motivation to continue medications in pregnancy
- Help identify a system (e.g., phone reminder, diary, etc.) to remember the appropriate time to insert a new ring

Client-centered care

Integration of dapivirine ring services into care for pregnant and breastfeeding clients

After the pregnant or breastfeeding client starts the ring, the health provider has several important roles:

- If ring provision is in the context of ANC or PNC, continue providing high-quality ANC or PNC (including family planning services) to the client to address their needs, and integrate PrEP care into the client's routine ANC or PNC services
- Monitor how the client is doing with ring use
- Help the client be an active partner in care, whether that means support for continuation of oral PrEP or ring use or transitioning to other strategies for protection of the mother and baby's health

- At each follow-up visit, the health provider needs to integrate information from history-taking, targeted physical examination, and any laboratory data to help the client reach their goals for a healthy pregnancy or postnatal experience and protection from HIV
- Counsel the client on the need to remove the ring in case of suspected or confirmed rupture of amniotic membranes, vaginal bleeding, uterine infection, cervical cerclage, or labor at any gestation

Medications prescribed in pregnancy and postpartum periods

Dapivirine has no known interactions with the medications most commonly prescribed in pregnancy, including but not limited to the following:

- Vaccines used for protection against COVID-19 infection
- Tetanus toxoid or pertussis vaccines
- Iron and folic acid tablets, multiple micronutrient supplements, or prenatal vitamins
- Penicillin injection for treatment of syphilis or other antibiotics used for treatment of STIs
- Antibiotics for asymptomatic bacteriuria, UTI, respiratory infection, or other suspected bacterial infections
- Intermittent prophylactic treatment of malaria in pregnancy with sulfadoxine-pyrimethamine (in settings where this is used)
- Preventive chemotherapy (deworming), using single-dose albendazole (400 mg) or mebendazole (500 mg) (in settings where this is used)
- Multiple micronutrient supplements, balanced energy and protein supplements, calcium supplements, or vitamin A
- Stool softeners such as docusate sodium
- Vaginally administered miconazole nitrate
- Medications and supplements recommended in the 2016 WHO ANC guidelines for treatment of common physiologic symptoms of pregnancy, such as the following:
    - Ginger, chamomile, and vitamin B6 for nausea and vomiting
    - Antacid preparations for women with troublesome symptoms of heartburn that are not relieved by lifestyle modification
    - Wheat bran or other fiber supplements to relieve constipation in pregnancy if the condition fails to respond to dietary modification

A drug-drug interaction study between the ring and miconazole nitrate (1200-mg vaginal capsule, commonly used for treatment of candidiasis or vaginal yeast infection) found that using both of these drugs at the same

time caused changes to levels of both drugs in the body; however, such these changes are not likely to alter how well either drug works. Potential interactions with other vaginal medications have not been studied. Therefore, if other vaginal medications are indicated for treatment, clients should be counseled regarding the unknown impact on ring effectiveness. Clients may wish to use a back-up method of HIV prevention during this period.

Dapivirine has no known interactions with the medications most commonly prescribed to women in the postnatal period, including but not limited to the following:

- Medications commonly used for fever and pain (e.g., paracetamol)
- Antibiotics

The ring can be used safely at the same time as most family planning methods, such as oral contraceptive pills, injectable progestin methods, sub-dermal implants, intrauterine devices, and barrier methods. However, the dapivirine ring should not be used together with a second vaginal ring, such as one formulated for contraception (available in some settings).

Family planning settings and breastfeeding clients

In general, clinical guidance is the same for breastfeeding clients receiving ring services in PNC and FP settings. As mentioned previously, the dapivirine ring has no known adverse interaction with most family planning methods (with the exception of avoiding dual vaginal ring use). Clinical priorities include the following:

- Providing counseling that assists clients to meet their personal family planning and HIV prevention goals
- Providing comprehensive clinical assessment and management to support safe continuation of family planning and HIV prevention methods, as well as breastfeeding according to WHO recommendations

Additional recommendations for improved integration of HIV prevention and family planning services are available in a WHO technical brief (*Actions for improved clinical and prevention services and choices: preventing HIV and other sexually transmitted infections among women and girls using contraceptive services in contexts with high HIV incidence*).

Managing ring side effects during pregnancy and postnatal period

Dapivirine ring use is generally well tolerated outside of and during pregnancy and the postnatal periods. Some side effects are possible, although they are typically mild. To provide high-quality care, PrEP providers should address client concerns with a thoughtful and systematic approach that includes history-taking, targeted physical examination, diagnosis, suggested measures to alleviate side effects, appropriate counseling, and a plan for future evaluation.

Separating some ring side effects from common pregnancy complaints and effects from other causes may be challenging. Most ring side effects are mild, temporary, and resolve without safety concerns. Table 2 provides more details on specific symptoms and potential causes. Any provider decision to discontinue the ring based on side effects should be discussed with the client, including careful consideration of potential risks (including risk of acquiring HIV in the absence of ring use), benefits, and alternatives, such as oral PrEP.

Table 2. Evaluation of possible ring side effects during pregnancy and breastfeeding

Sign or symptom	Possible finding in pregnancy	Possible finding in postnatal period	Expected with some family planning methods	May be related to ring use	May be related to another condition
Urinary tract infection	Urinary tract infections are more common during pregnancy compared to when someone is not pregnant	May occur during the postnatal period	Diaphragm, cervical cap	Experienced by about 15% of non-pregnant ring users	Urinary frequency and pain may also be seen for some sexually transmitted infections
Vaginal discharge	Normal during pregnancy (see section on vaginal discharge in the pregnant ring user)	Normal during the postnatal period, especially the early postnatal period		Experienced by about 7% of non-pregnant ring users	Vaginitis, either non-sexually transmitted or sexually transmitted
Vulvar itching				Experienced by about 6% of non-pregnant ring users	Vulvar yeast infection (candidiasis)
Pelvic and lower abdominal pain	Stretching of the round ligaments on either side of the pelvis may cause mild, benign pelvic pain			Experienced by about 6% of non-pregnant ring users	Preterm contractions, foodborne illness

Vaginal discharge in the pregnant ring user

Increased vaginal discharge is a normal occurrence in pregnancy. Physiologic discharge of pregnancy is typically clear to white and homogenous and increases in amount with advancing gestational age. Determining whether a client's report of increased vaginal discharge merits evaluation is at the discretion of the clinician. If the discharge is associated with pruritis, irritation, or odor, it may be worthwhile to assess for symptomatic bacterial vaginosis and/or yeast infection. If the description is consistent with physiologic discharge associated with pregnancy, further evaluation need not be done. When a participant reports increased vaginal discharge, it is incumbent on the clinician to ascertain through history whether the discharge might be amniotic fluid in a woman whose amniotic sac spontaneously ruptured.

Signs and symptoms which raise the possibility of ruptured membranes rather than physiologic discharge include the following:

- Colorless to slightly yellow thin watery discharge (the consistency of urine)
- An associated gushing or "pop" sensation
- Significant volume to saturate undergarments and clothes

If rupture of membranes is suspected, clinical evaluation is indicated. In general, the number of manual vaginal examinations should be minimized after rupture of membranes, especially in the absence of active labor, to avoid possible increased risk of chorioamnionitis.

Deciding whether to pause or stop dapivirine ring use for pregnant and breastfeeding clients

When a client presents with a sign or symptom that they associate with ring use, it is helpful to get more information to determine if it may be caused by the ring. Before deciding to pause or stop ring use, it is important to consider whether or not there is reasonable suspicion that a complaint was caused by ring use. To help determine this, clinicians can consider the guiding questions included in the Clinical Practice Guidelines for Providing PrEP for Pregnant and Breastfeeding Populations, as these questions are the same whether health providers are evaluating potential decisions to pause or stop oral PrEP or ring use.

If the health care provider and client decide that she may safely continue oral PrEP or ring use (e.g., because symptoms are mild and expected), the provider should offer reassurance and suggest strategies that may help to alleviate or improve coping with symptoms. The provider should also create a plan with the client to re-evaluate symptoms on a specified date, either by phone or in person. Showing the client that the health

care provider cares about the acceptability and safety of oral PrEP and the ring experience is an important way to build trust and provide client-centered care.

Several situations should prompt removal of the ring during pregnancy, including the following:

- Active labor at any gestation
- Vaginal bleeding
- Spontaneous or therapeutic abortion
- Suspected or confirmed rupture of the amniotic membranes (bag of waters)
- Cervical cerclage (treatment for cervical insufficiency)
- Suspected or confirmed intrauterine infection

Removal of the ring may be performed by a health care provider or the ring user. However, in some situations, (e.g., vaginal bleeding, suspected or confirmed ruptured membranes, intrauterine infection), it may be prudent for removal to be carried out by a health care provider wearing sterile gloves.

Pregnant and breastfeeding persons can consider stopping the ring at any time if their life circumstances or behaviors have changed and they no longer feel the need to protect themselves from HIV. However, pregnancy and breastfeeding place individuals at significant risk for acquiring HIV, even in the absence of other known risks. Several different strategies may lower a person's risk for acquiring HIV, whether they are using oral PrEP, the ring, or neither; however, it should be acknowledged that such strategies may be very difficult for clients to implement if they are living with challenges caused by poverty and/or abusive relationships. Ways to lower risk include the following:

- Adopting safer sexual practices, such as not having vaginal or anal intercourse, or using condoms for all vaginal and anal intercourse
- Changing circumstances, such as leaving sex work or getting treatment for drug or alcohol abuse; or, moving to a place that has a low prevalence of HIV
- For people in a serodifferent relationship, HIV transmission risk is very low when the HIV-positive partner is virally suppressed on antiretroviral therapy

Stopping dapivirine ring use due to HIV seroconversion

A positive HIV test is a reason to stop ring use. Clients who seroconvert while using the ring should be linked to care and initiated on ART urgently, in line with national guidelines for PBFP. When HIV infection happens during pregnancy or breastfeeding, the baby is at high risk of HIV infection, and the client needs ART for their

own health. Previous research has not shown an increased risk for development of HIV drug resistance among those who seroconvert while using the ring, compared to those who seroconvert while not using the ring.

Evaluating potential problems in breastfeeding infants

The level of dapivirine observed in breast milk of lactating ring users is so low that it is very difficult to detect or measure it. Because of this, it is unlikely for dapivirine ring use by the mother to impact breastfeeding infants. Severe abnormal signs or symptoms in an infant are unlikely to be related to maternal use of the dapivirine ring, but should be evaluated promptly according to the *WHO Paediatric emergency triage, assessment and treatment: care of critically-ill children* or other national guidance, as appropriate.[11]

When assessing whether a finding might be related to the mother's ring use, providers can consider the guiding questions included in the Clinical Practice Guidelines for Providing PrEP for Pregnant and Breastfeeding Populations.

Any provider decision to discontinue either oral PrEP or the ring based on side effects in a breastfeeding infant should be discussed with the client, including careful consideration of potential risks (including risk of mother and infant acquiring HIV in the absence of oral PrEP or the ring), benefits, and alternatives.

Transitioning between clinical contexts or service delivery settings

As with oral PrEP, there is no single best place to manage dapivirine ring use for PBFP who are transitioning from one care setting to another, or who may be eligible to receive services from multiple settings at once (e.g., key population program and ANC). Determining the best (or multiple locations) for clients to receive services should consider the following:

- Client needs and preferences
- Capacity of each service delivery setting to meet the individual needs of the client (as related to both PrEP and maternal newborn health care)

Thus, clients should be supported to continue dapivirine ring use (or another HIV prevention method, such as oral PrEP) as they transition between different clinical contexts and service delivery settings. Examples of such transitions may include the following:

- From safer conception to ANC
- From programs for key populations or adolescent girls and young women to ANC

- From FP to ANC
- From ANC to PNC
- From ANC to FP services, following delivery, if client does not access PNC
- From PNC to FP or other facility- or community-based PrEP provider, if client wishes to continue PrEP due to ongoing behavioral, social, and/or structural risk

In the absence of any contraindications, clients do not need a "break" from ring use, which may only serve to increase their risk for acquiring HIV.

Starting or restarting the dapivirine ring after childbirth

Following delivery, ring use should continue to pause while the uterus returns to its pre-pregnant size (uterine involution). Clients may experience pain from uterine contractions, called afterpains, and notice a discharge called lochia in the weeks following delivery. Both are normal signs of uterine involution, which may take up to approximately six weeks. Local cultural and clinical norms often advise an abstinence period of approximately 6 weeks following childbirth before resuming penetrative vaginal intercourse. Previous research on postpartum use of the dapivirine ring did not include those who were less than 6 weeks postpartum. However, the risk of unplanned exposure to HIV via sexual intercourse should be considered and discussed with the client. If the client wishes to restart ring use following delivery, it is prudent to wait until vaginal bleeding has diminished, noting that some intermittent vaginal spotting may be normal in the postnatal period, especially if clients are using progestin-only methods of family planning, such as DMPA-IM, DMPA-SC, norethisterone enanthate (NET-EN), or progestin-only oral contraceptive pills. Refer to eligibility guidelines when restarting the dapivirine ring in the postnatal period, and provide information on where to access the appropriate services. Try to ensure continuity of ring supply. When possible, facilitate a "warm hand-off" (e.g., personal introduction to next provider) when client is switching from one service delivery setting to another.

Transitioning between HIV prevention methods

Clients may switch between the ring and oral PrEP. Safety data on simultaneous use of oral PrEP and the ring are limited, and no data are available on this for PBFP. Although use of both methods is not likely to be less well-tolerated than use of each individually, more data are needed to confirm the safety and efficacy of simultaneous use of oral PrEP and the ring. No evidence indicates that using them together will result in any advantage. Whatever the choice, adherence is important to optimize effectiveness of either method. Inconsistent use of either or both would be ineffective for HIV prevention.

Other important services for pregnant and breastfeeding people

Other HIV prevention and family planning/reproductive health services

Within ANC and PNC settings, a range of additional HIV, family planning, and reproductive health services should be provided, in addition to PrEP. Health workers are reminded to review guidance on these services found in "Other HIV prevention and family planning/reproductive health services" in the Clinical Practice Guidelines for Providing PrEP for Pregnant and Breastfeeding Populations.

Those who are considering the ring should also have access to these services. Additional clinical considerations for postpartum family planning (PPFP) are applicable for clients who opt to use the ring.

- The ring can be used simultaneously with male condoms
- The ring should not be used simultaneously with other vaginal rings that may be available for contraception; however, other forms of contraception are acceptable, including intrauterine devices
- No interactions have been noted between dapivirine and contraceptive hormones

When providing other sexual and reproductive health services to dapivirine ring users during the antenatal or postnatal period, it is important to keep these points in mind:

- The ring does not prevent or treat STIs, including those transmitted during anal sex
- It is okay to keep the ring in place during treatment for a STI

For a person experiencing symptomatic vaginitis or primary herpes virus infection, it may be prudent to defer ring insertion until after any painful symptoms have resolved. However, it should be noted that STIs can increase risk for HIV acquisition; thus, prompt start of an effective method of HIV prevention is advised.

Screening for intimate partner violence

New, continued, or increased IPV may be experienced during pregnancy and the postnatal period. Health workers should also be aware that IPV has been associated with increased vulnerability to HIV. People who are considering the ring should also be screened for intimate partner violence. Health workers are reminded to review the detailed guidance on this screening found in "Screening for intimate partner violence" within the Clinical Practice Guidelines for Providing PrEP for Pregnant and Breastfeeding Populations.

Appendix 1. Sample Checklist for Ring Start-up for Pregnant and Breastfeeding Clients

Instructions: Complete checklist and file in individual's clinical record.

Screening Checklist Questions	Yes	No
1. Does client have a positive HIV test immediately prior to initiating PrEP?		
2. Does client have any signs or symptoms of acute HIV infection? Acute HIV infection may include signs and symptoms of fever, sore throat, aches and pains, lymphadenopathy (swollen glands), mouth sores, headache, or rash. If the client has any of these signs or symptoms, the health provider should consider the possibility that acute HIV infection is present. In such circumstances, consider deferring PrEP start for 4 weeks and having the person tested for HIV again, which will allow time for possible HIV seroconversion to be detected.		
3. Does client have any probable recent exposure to HIV? Clients with possible HIV exposure in the previous 72 hours should not be offered PrEP but instead be offered PEP. Then, retest the client for HIV after 28 days. PrEP may be offered to clients who test negative at this point. However, PrEP does not need to be held while waiting for the 28-day test; there should be no gap in medication provision as individuals transition from PEP to PrEP.		
4. Does client have a confirmed allergy or contraindication to any medicine in the PrEP regimen?		
5. Does client have any abnormal vaginal bleeding?		

If the answer to any of the above questions is "Yes", do not start dapivirine ring use. Clients whose exclusionary conditions have resolved may be able to start ring use at a later date (see Clinical Practice Guidelines for additional guidance). The list above is specific to dapivirine ring start-up and is not exhaustive of all appropriate assessment that clients may require. Other recommended assessments (e.g., in the context of antenatal care, postnatal care, and routine enquiry for intimate partner violence, etc.) should also occur.[12]

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