National Dapivirine Vaginal Ring Implementation Guidelines

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Updated

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FOREWORD

In 2016, the National Health Council approved the implementation of the National Policy on HIV Pre-Exposure Prophylaxis (PrEP) and Test and Treat (T&T) for populations at risk. The use of antiretroviral (ARV) treatment as oral PrEP to prevent persons at risk from acquiring HIV, is an important milestone in our quest to reduce and curtail new HIV infections.

Oral PrEP, first introduced in South Africa in June 2016 and now available at most public Primary Health Care facilities, has been a game changer for HIV prevention. The approval of the Dapivirine Ring by the South African Health Products Regulator (SAHPRA) in March 2022, has further expanded the ARV-based HIV prevention options available. The Dapivirine Ring provides an additional HIV PrEP option from which individuals can make a choice.

The development of these guidelines was a collaborative effort with contributions from researchers, professional bodies, donor agencies, implementing partners, international agencies, civil society and health care users. I am grateful to all stakeholders who actively contributed to and made resources available for the development of these guidelines.

I want to acknowledge and extend my gratitude and appreciation to the over 600,000 individuals, from all walks of life from across the country, who have opted to embrace the use of ARVs a protection against an HIV infection. These individuals access services at over 3,000 public health facilities, university campus health clinics and special clinics, which are currently offering this important intervention. Together, these PrEP users and health facilities have offered valuable insights that have contributed to an in-depth understanding and evidence for the delivery of HIV PrEP.

There is no doubt that our nurses, doctors, counsellors and health promoters and researchers will find these guidelines invaluable in their quest to offer quality HIV prevention services to the South African public.

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DIRECTOR-GENERAL: HEALTH
DATE: 02/12/2022

Abbreviations and Acronyms

AGYW	Adolescent girls and young women
AHI	Acute HIV infection
ANC	Antenatal care
ART	Antiretroviral treatment
ARV	Antiretroviral
CAB-LA	Long acting cabotegravir
DVR	Dapivirine vaginal ring
EDL	Essential drugs list
EMA	European Medical Agency
FTC	Emtricitabine
GBV	Gender based violence
HIV	Human Immunodeficiency Virus
IEC	Information, education, and communication
IPM	International Partnership for Microbicides
IPV	Intimate partner violence
IUD	Intra-uterine device
MSM	Men who have sex with men
MTN	Microbicides Trial Network
NDOH	National Department of Health
NNRTI	Non-nucleoside reverse transcriptase inhibitor
PEP	Post exposure prophylaxis
PID	Pelvic inflammatory Disease
PMTCT	Prevention of mother to child transmission
PrEP	Pre-exposure Prophylaxis
PWID	People who inject drugs
SAHPRA	South African Health Products Regulatory Authority
SRH	Sexual reproductive health
STI	Sexually transmitted infection
T&T	Test and Treat
TB	Tuberculosis
TDF	Tenofovir disoproxil fumarate
TDF/FTC	Tenofovir disoproxil fumarate/Emtricitabine
TG	Transgender persons
VMMC	Voluntary medical male circumcision
WHO	World Health Organization

Glossary: Working definitions of terms

Note on gender related terminology: A lot of the Ring material refers to the Ring being a method for "women" and use the pronouns "she" and "her". This document is committed to using gender-neutral and gender-sensitive language in recognition of people's right to define their own gender identity. To this end, potential Ring users are described as individual's assigned female at birth, for protection when having vaginal sex – because the Ring only provides HIV protection locally in the vagina. Where possible and appropriate, gender-neutral terminology is used throughout the document.

Bio-medical HIV prevention: Biomedical HIV prevention refers to medical interventions used for the prevention of HIV. This includes, for example, antiretroviral based pre-exposure prophylaxis, post exposure prophylaxis, barrier methods such as male and female condoms, and procedures such as voluntary medical male circumcision.

Microbicides: The Ring belongs to a category of biomedical products known as microbicides. Microbicides are undergoing continuous research and development and refer to a product used in the vagina and/or rectum to help prevent HIV infection during sex. Microbicides provide localised protection in the area directly where it is inserted (vagina or rectum), as opposed to pills or injectables, which act systemically. Most microbicides contain an antiretroviral (ARV) to provide protection against HIV infection.

Systemic: Systemic refers to medicines or interventions that affect the whole body, rather than a specific part of a body.

Vaginal rings: Vaginal contraceptive rings have been safely used for over two decades. These methods of contraception, for example, the contraceptive NuvaRing, act through a slow release of hormones over a 28-day cycle. The dapivirine ring uses a microbicide with an ARV (dapivirine), delivered in the form of a vaginal ring, developed for HIV prevention as pre-exposure prophylaxis.

Receptive vaginal sex: This is used to clarify that the Ring is only of benefit to the person being penetrated when having vaginal sex (receptive) and not of benefit to the insertive partner (in other words - the partner inserting their penis).

1. Background

In 2015, the World Health Organization (WHO) recommended that HIV-negative people who are at a substantial risk of acquiring an HIV infection should be offered daily oral HIV pre-exposure prophylaxis (PrEP) as part of a combined HIV prevention strategy, thereby expanding the biomedical HIV prevention options available. Recommendations emphasised that oral PrEP should form part of a comprehensive package of prevention services that includes HIV testing, risk reduction counselling, male and female condoms, lubricants, ARV treatment for partners with HIV infection, and voluntary medical male circumcision (VMMC). South Africa introduced oral PrEP as part of its expanded HIV prevention strategy in 2016 [1]. Since then, the provision of oral PrEP has expanded from specific targeted populations and sites: sex workers, men who have sex with men (MSM), universities and institutions of higher learning, adolescent girls and young women (AGYW), transgender persons (TG), and people who inject drugs (PWID), to include any client who is at substantial risk of HIV or who requests PrEP at public sector primary healthcare clinics. As of July 2022, there were 658 885 oral PrEP initiations at 3 034 health facilities. The national oral PrEP implementation guidelines [2] were revised to ensure alignment with updated global evidence and WHO guidelines [3].

Increasing ARV-based prevention options expands choice and increases access, acceptability, and coverage of effective HIV prevention

Whilst oral PrEP has been an important game changer in HIV prevention there have been barriers to scaling up provision. These have included issues relating to uptake, continuation, effective use, challenges with taking a daily pill, side effects, and stigma. Additionally, unpredictable sexual patterns require further understanding of people's sexual risk periods and the associated complexities relating to cycling on and off oral PrEP. These barriers all point to the need for additional PrEP options, including those that are more discreet, do not rely on daily adherence, and have no systemic side effects [3]. This is supported by studies looking at women's needs and preferences, which endorse the necessity for long-acting, woman-controlled options. Research for long-acting PrEP products has been ongoing and includes implementation studies looking at the dapivirine vaginal ring (hereafter referred to as "the Ring", see Box 1), long acting injectable Cabotegravir (CAB-LA), and trials related to the dual-purpose (HIV and contraceptive) vaginal ring [3–8].

In recognition of the necessity to expand HIV prevention options, the Ring was approved by the South African Health Products Regulatory Authority (SAHPRA) in March 2022. These guidelines provide guidance for Ring provision and service delivery as part of a comprehensive combination HIV prevention package.

Box 1. What is the dapivirine vaginal ring?

The Ring is a long-acting HIV prevention product developed to expand the biomedical HIV prevention options available to women. It is *recommended for clients who are unable or do not want to take oral PrEP or when oral PrEP is not available*. The Ring has only been studied in those assigned female sex at birth, during receptive vaginal intercourse, and does not prevent HIV acquisition through any other mode of transmission. The Ring is made of a flexible silicone material containing 25mg of the antiretroviral (ARV) drug dapivirine. The Ring is inserted into the vagina and should remain in place for 28 days. Dapivirine belongs to a class of ARVs called non-nucleoside reverse transcriptase inhibitors (NNRTI), which reduce the ability of HIV to replicate itself inside a healthy cell. The Ring slowly releases dapivirine directly around the site of potential infection (the vagina) over the course of 28 days, with low absorption elsewhere in the body, lowering the likelihood of systemic side effects and drug interactions with systemically administered drugs. Clients can insert, remove, and replace the Ring themselves each month, or with the assistance of a healthcare provider if preferred.

2. Regulatory approval of the Ring

The Ring was developed by International Partnership for Microbicides (IPM) and early feasibility research began in 2004 [9]. In July 2020, the European Medicines Agency (EMA) provided positive scientific opinion on the Ring as an HIV prevention option for women aged 18 and older. WHO recommended the dapivirine vaginal ring as a new choice for HIV prevention for women at substantial risk of HIV infection and the Ring was included in the WHO pre-qualification list in January 2021. IPM has made submissions to several African countries' regulatory authorities, including South Africa. The Ring was submitted to SAHPRA by IPM and was approved on 8 March 2022. It is registered under the name **DapiRing**. The Ring is classified as a Schedule 4 drug.

Regulatory approval for the Ring makes provision for its use to reduce the risk of HIV-1 infection via insertive vaginal intercourse in:

- HIV uninfected individuals assigned female at birth
- aged 18 years and older

The Ring should be offered alongside oral PrEP and other safer sexual practices, so women can choose an option which is most suitable for them. The Ring may be an attractive option for women who do not want or are unable to take daily oral PrEP.

3. ARV based HIV prevention and treatment

It is important to understand the difference between pre-exposure prophylaxis (PrEP), post exposure prophylaxis (PEP), and antiretroviral treatment (ART), as described in Table 1 below:

Table 1. ARV based HIV prevention and treatment

Pre-Exposure Prophylaxis (PrEP)	Post-Exposure Prophylaxis (PEP)	Anti-retroviral treatment (ART)
The use of ARVs by HIV-negative individuals *before* potential exposure to HIV to prevent HIV acquisition. Current PrEP options in South Africa include oral PrEP (oral TDF/FTC as a fixed-dose combination) and now, the dapivirine ring. There are other methods in the pipeline, including the two monthly long-acting injectable cabotegravir (CAB-LA), which is currently under SAHPRA review.	ARV medication taken within 72 hours *after* exposure to HIV and continued for 28 days to prevent HIV acquisition.	Lifelong treatment with a combination of ARV drugs for people with HIV to minimise the effect of HIV by increasing the CD4 count and reducing the viral load*. Prevention of mother to child transmission (PMTCT) effectively reduces transmission from a pregnant woman to her infant.

* For further information see: https://www.who.int/news/item/20-07-2018-viral-suppression-for-hiv-treatment-success-and-prevention-of-sexual-transmission-of-hiv

4. Dapivirine Vaginal Ring ("the Ring") – key features

The key features of the Ring are summarised in Table 2 below:

Table 2. Key features of the Ring

Key feature	Dapivirine Vaginal Ring (the Ring)
Registered name	Registered in South Africa under the name – the "DapiRing vaginal delivery system".
Description	A flexible, off white, vaginal ring, made of silicone, with an outer diameter of 56 mm and a cross-sectional diameter of 7,7 mm (there is only one size).
Formulation	Contains 25 mg of the non-nucleoside reverse transcriptase inhibitor (NNRTI) ARV dapivirine and releases approximately 4 mg of dapivirine over a period of 28 days.
How does it work?	Slowly releases dapivirine into the vagina (at the site of potential HIV infection) and prevents HIV from making copies of itself inside healthy cells around the vaginal area; it reduces the risk of HIV infection acquired during vaginal sex.
Schedule classification	Classified as Schedule 4 (an appropriately trained healthcare provider authorised to assess, diagnose, prescribe, and dispense).
Lead in period	The Ring needs to be in place for 24 hours before providing protection – use other prevention measures for the first 24 hours.
Shelf life and storage	The Ring can be stored for up to 60 months from date of manufacture; storage at or below 30°C (room temperature).
Indication	Recommended to reduce the risk of HIV-1 infection via vaginal sex in individuals assigned female sex at birth who are HIV-negative, aged 18 years and older, when clients are unable or do not want to use oral PrEP, or when oral PrEP is not available. It is recommended that the Ring is used together with other safer sex options for additional protection from HIV. The Ring does not protect against pregnancy and STIs.
Mechanism for insertion and removal	The Ring is inserted into and removed from the vagina – either with the assistance of a healthcare provider OR by the Ring user on their own.
Duration of effectiveness	The Ring should be worn continuously for 28 day – it can then be removed (with the help of a healthcare provider or the Ring users themselves) and a new Ring inserted. *Note:* The Ring is only effective when inserted in the vagina and provides no residual protection once removed.
Efficacy	Studies demonstrated that the Ring reduced HIV acquisition by about 35% overall[†] (**Error! Reference source not found.**).

[†] Two Phase III safety and efficacy studies (The Ring Study and ASPIRE). In addition, two Phase III open label extension (OLE) studies (DREAM and HOPE), final results of HOPE and DREAM differed (31% to 62%) - for more detailed information, see Appendix 2.

Safety	Across multiple studies, the Ring was well tolerated with no significant safety concerns identified, and with low potential for the development of NNRTI resistance associated with long term use of the Ring. The Ring is recommended by EMA and WHO and has WHO pre-qualification status. The Ring is approved by SAHPRA, which considers the safety profile of health products.
Side effects	The most reported side effects in Ring studies include urinary tract infections, vaginal discharge or itching, and pelvic or lower abdominal pain. Most side effects were mild to moderate [10]. Side effects were usually of short duration and resolved without the need to remove the Ring. Serious side effects were very rare.
Benefits to Ring users	- Does not require safety laboratory monitoring - Client-controlled, and can be self-removed and/or inserted - Can remain in place for 28 days without being removed - Reduces risk of HIV, especially if used in combination with other prevention methods, such as condoms - Easy to store, does not require refrigeration - Can be used discreetly - Does not interfere with sex or menses - Minimal side effects
The Ring and HIV, STI, and pregnancy prevention	Due to its modest efficacy (Box 2), it is recommended that, where possible, the Ring is used with other HIV prevention methods (Box 3), and as part of an integrated HIV/sexual reproductive health (SRH) package of care (**Box 4**). The Ring only provides protection against HIV during receptive vaginal sex. It does not provide protection through any other mode of transmission i.e., anal or oral sex, from occupational exposure (needle stick injuries, blood spill), or sharing needles (people who inject drugs). The Ring does not protect against sexually transmitted infections (STI) or pregnancy – therefore consistent and correct condom use and use of reliable contraceptive methods are recommended.

Box 2. A note on research results and efficacy

Two Phase 3 safety and efficacy studies (The Ring Study and ASPIRE) in Eastern and Southern Africa demonstrated that the dapivirine vaginal ring reduced HIV acquisition by about 30% overall with no significant safety concerns associated with long-term use.

- The Ring Study, led by IPM, found that the Ring reduced overall risk by 35%
- ASPIRE, led by the US National Institutes of Health, funded by the Microbicide Trials Network (MTN), found that the Ring reduced overall risk by 27% [25]

In these trials, HIV acquisition reduction was greater among participants who used the Ring more consistently.

Two subsequent open-label Phase 3b studies (DREAM and HOPE) appeared to increase adherence and effectiveness up to 62% (DREAM). This is likely because participants knew the Ring offered some reduction in the likelihood of HIV acquisition and were able to use it as directed. The open-label modelling estimates for the Ring use the same statistical modelling method used in oral PrEP open-label studies, and they indicate a similar, promising trend of increased effectiveness with correct and consistent use. As with oral PrEP, we anticipate similar improvements in Ring effectiveness based on increased access and more consistent real-world use [26].

Across multiple studies, there have been no significant safety concerns reported and it has been determined that there is a low potential for the development of HIV drug resistance with long term use of the Ring.

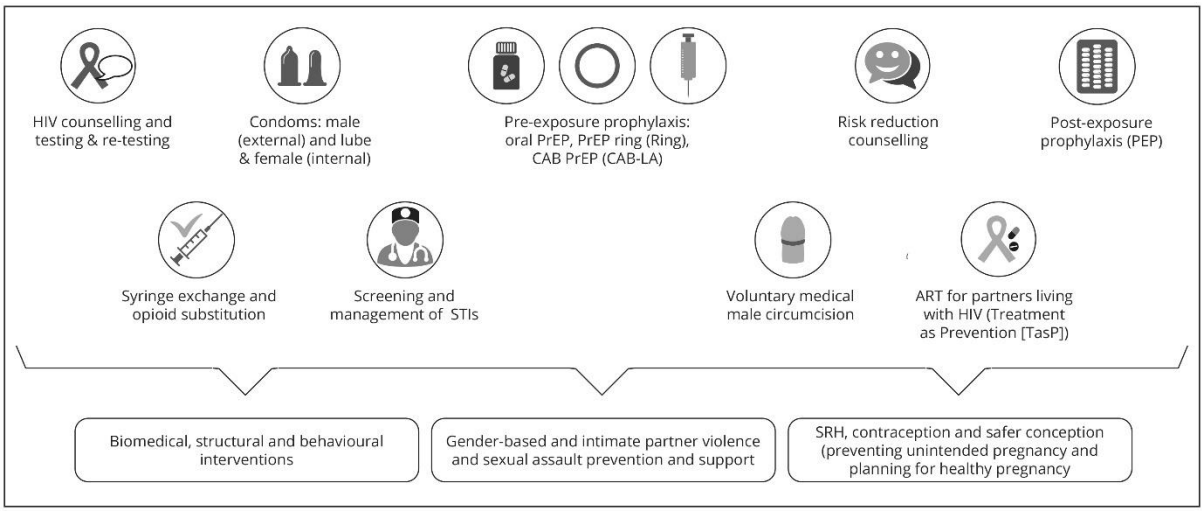
For more information, refer to Appendix 2

5. Important themes underpinning service delivery

Several key themes guide the provision of ARV-based HIV prevention methods, including the Ring, in South Africa. These include:

Integration: All PrEP methods need to be provided as part of comprehensive SRH and HIV combination prevention services. The Ring forms an additional option within the HIV combination prevention package (Box 3).

Box 3. Combination Prevention



Note: The concurrent use of oral PrEP and the Ring has not yet been researched, and there is insufficient evidence to recommend this as an option.

Core services such as HIV testing, condom provision, contraception counselling and provision, and STI screening and management need to accompany PrEP services. An integrated minimum service package is summarised in

Box 4.

Box 4. Minimum package of services

- HIV testing services‡ (including partner notification)
- Risk reduction counselling
- Treatment for HIV-positive individuals (including linking partners with HIV to ART)
- PrEP
- PEP
- STI screening and management (including partner notification)
- Condoms and lubricants
- Pregnancy screening
- Contraception
- Termination of pregnancy
- GBV and IPV assessment and response
- TB screening
- Voluntary male medical circumcision
- Mental health counselling and referral

Important

- Provide referral when services not available at point of care
- Ensure referral service points are **operational** and **accessible**

Choice and informed decision: Up until now there has only been one option for an ARV-based biomedical prevention method – oral PrEP. The Ring provides an additional option. It is intended that the Ring is offered as a choice to individuals who wish to prevent HIV acquisition through receptive vaginal intercourse and who cannot or do not want to take oral PrEP. Potential Ring users need accurate, user-friendly information and unbiased counselling to make an informed decision on their preferred prevention method. Several factors may influence their decision, including:

- medical contraindications
- mode of administration (daily oral pill, or vaginal insertion)
- side effects
- ability to remember to take daily pills
- partners' attitudes
- efficacy and the respective methods' protection during different sexual activities (e.g., vaginal and/or anal sex).

This requires access to and availability of information, education, and communication (IEC) materials and nuanced counselling, which speaks to informed decision making and choice.

Job Aid 3 provides guidance on client support in selecting their preferred method of HIV prevention.

Access: It is important that people wanting to prevent HIV have full access to all HIV prevention options, including oral PrEP and the Ring, alongside quality SRH services. Further work is needed to improve access and reach, including identifying differentiated service delivery models, which are easily accessible for those who would benefit from these options. Initiatives to decentralise and de-medicalise services need to be encouraged and supported.

‡ Includes provider-initiated HIV testing as per NDOH national guidelines and HIV self-testing as per national guidelines

Quality of care: Services need to be provided within the framework of quality healthcare. This embraces the core national quality standards[§], as well as Batho Pele principles.

A rights-based approach: All services should be provided in an environment that respects clients' rights, including those relating to SRH and HIV. In addition, South Africa has a Patient's Rights Charter [11] emanating from its constitutional framework. This framework articulates the rights every person should have when using public health facilities. Important rights pertaining to PrEP service delivery include inter alia, confidentiality, respect, access to non-discriminatory and conveniently located services, privacy, choice, informed decision-making, and accurate, evidence-guided information. Adolescent and youth friendly services are particularly important to ensure services meet and are responsive to the needs of young people.

Defining HIV risk and eligibility for PrEP: There has been a shift in paradigms describing priority populations for PrEP programmes – from groups and populations at substantial risk of HIV, to all individuals at risk [2,3].

> *"…individual risk varies considerably within populations depending on individual behaviour and the characteristics of sexual partners. In locations with a low overall incidence of HIV infection, there may be individuals at substantial risk who should be offered PrEP services. PrEP programmes should consider local context and heterogeneity in risk. Individual characteristics and behaviour that could lead to exposure to HIV, rather than population-level HIV incidence, are most important when considering those who might benefit from PrEP. Individuals requesting PrEP should be given priority to be offered PrEP, since requesting PrEP likely indicates there is a risk of acquiring HIV. Cost–effectiveness should not be the only consideration when implementing PrEP programmes, since remaining HIV negative and having control over HIV risk has intangible value to people and communities."* - WHO 2021 [3]

[§] For example, the NDOH National Core Standards for Health Establishments in South Africa (2011), and its six priority areas: Improving staff values and attitudes, waiting times, cleanliness, patient safety and security, infection prevention and control, and availability of medicines and supplies; and the Ideal Clinic programme, NDOH Ideal Clinic™ Manual Version 19 Updated May 2021.

6. Ring service delivery

6.1 Who can provide the Ring?

The Ring is classified as a Schedule 4 drug. It can be provided by authorised prescribers such as doctors, professional nurses, and pharmacists authorised to prescribe.

6.2 Clients who may benefit from the Ring

Potential clients who may benefit from the Ring include HIV-negative people at substantial risk of HIV **OR** any individual who requests PrEP, **AND** are:

- assigned female sex at birth and understand that the Ring provides protection against HIV infection acquired during receptive vaginal sex (in other words, there is no benefit for the insertive partner)
- 18 years and older
- unable or unwilling to take oral PrEP, perceive themselves to be at risk
- able to make an informed decision that they would like to use the Ring

Note on Ring use with adolescents: Limited evidence of Ring use with adolescents shows similar side effects to adults, with no new safety concerns [12–14]. Efficacy has not yet been established [3].

6.3 Considerations for PrEP in pregnant and breastfeeding women

HIV-negative pregnant and breastfeeding women at risk of HIV, must be counselled and offered HIV prevention interventions, including PrEP, together with acute HIV infection screening, adherence counselling, assessment for HIV exposure, safety monitoring, and three-monthly HIV testing and antenatal care. There is insufficient data on how the Ring affects pregnancy outcomes and infants of breastfeeding women. Currently the Ring is not recommended for pregnant and breastfeeding women in South Africa.

The Deliver and B-Protected studies [15,16] will provide evidence on the Ring and oral PrEP safety and acceptability in breastfeeding and pregnant women.

6.4 Considerations for transwomen

The Ring has been studied so far only among individuals assigned female at birth. There have been no studies of the Ring's use in people who have undergone gender-affirming surgery (with a neo-vagina), so its efficacy, safety, side effects, and acceptability among these individuals is not known. Transgender women with neo-vaginas should be encouraged to consider oral PrEP, especially for those who engage in both vaginal and anal sex, since oral PrEP covers both routes of HIV transmission. Women should consult with their healthcare providers to determine what approach may work best.

7. Clinical management of the Ring

All clients testing HIV-negative and at high risk of HIV, or requesting PrEP, must be counselled and offered HIV prevention interventions, including counselling on their choice of PrEP options. Job Aid 1 provides an algorithm for PrEP provision.

The Ring is optimally effective when left correctly inserted in the vagina for the full 28 days[**], after which it needs to be removed and replaced.

7.1 Initiation

As with oral PrEP, the Ring can be initiated on the same day for most clients. Initiation visit steps for clients beginning use of the Ring are outlined below, with a summary provided in Job Aid 2.

7.2 Eligibility for the Ring

- HIV-negative by routine rapid antibody test
- Absence of symptoms of acute HIV infection (Box 5)
- Willing and able to use the Ring as prescribed
- Age ≥18 years
- Not currently pregnant or breastfeeding or intends to become pregnant or breastfeed

Box 5. Signs and symptoms of acute infection (AHI)

- Fever
- Swollen lymph glands
- Skin rash
- Headache
- Sore throat
- Aches and pains
- Mouth sores

7.3 Baseline investigations

- HIV test (if possible recent exposure within 72 hours, recommend PEP)
- Pregnancy test/screening and assessing whether breastfeeding (Note: currently the Ring is not recommended for use by pregnant or breast-feeding women)
- STI screening
- Assess for contraindications (Box 6)

[**] Note on clients late for 28 days: There is an estimated 6-day window period where the ring will still be effective.

Box 6. Contraindications for the Ring [10]

- The Ring does not require blood tests
- There are no systemic drug to drug contraindications
- The Ring should **NOT** be provided to people with:
  - HIV-positive test result using the national HIV testing algorithm
  - Known exposure to HIV in the past 72 hours (defer PrEP and consider PEP counselling/initiation for clients, even in the absence of symptoms of acute HIV infection (AHI))
  - Signs of AHI (Box 5) AND potential exposure within the past 14 days
  - Inability to commit to effectively using the ring and attend scheduled follow-up visits
  - Allergy or hypersensitivity to active substance or other substances listed in the product information sheet

Note:

- No baseline blood tests (e.g. Hepatitis B surface Antigen or Creatinine) are required prior to Ring use
- A pelvic examination may be considered at initiation or at any follow-up visit, if clinically indicated, as per national guidelines

Ensure an integrated package of HIV and SRH services are provided, as summarised in

Box **4**. these include risk reduction counselling, STI screening and management, provision and education about condoms use and lubricants, contraceptive services, and GBV and IPV assessment and response.

Pregnancy testing is available at all public health facilities [17]. Where a pregnancy test is not available, the following pregnancy checklist should be used (Box 7).

Box 7. Pregnancy testing and screening

Pregnancy checklist [27]

Ask the client questions 1-6. As soon as the client answers "yes" to any of the questions, stop and follow the instructions below.

No		Yes
	1. Did your last monthly bleeding start within the last 7 days?	
	2. Have you abstained from sexual intercourse since your last monthly bleeding, delivery, abortion, or miscarriage?	
	3. Have you been using a reliable contraceptive method consistently and correctly since your last monthly bleeding, delivery, abortion, or miscarriage?	
	4. Have you had a baby in the last 4 weeks?	
	5. Did you have a baby less that 6 months ago, are you fully or nearly-fully breastfeeding, and have you had no monthly bleeding since then?	
	6. Have you had a miscarriage or abortion in the last 7 days (if planning to use a copper IUD, the 7-day window is expanded to 12 days)	

If the client answers **NO** to all of the questions, pregnancy *cannot* be rules out using the checklist. Rule out pregnancy with other means	If the clients answers **YES** to *at least one of the questions,* you can be reasonably sure she is not pregnant.

7.4 Drug to drug interactions

- There are no known interactions between dapivirine and contraceptive hormones, alcohol, or recreational drugs. If a Ring user thinks that their use of alcohol or other substances may interfere with their effective use of the Ring, the provider should discuss and support behaviour change and offer additional prevention options, including condoms/lubricants.
- When using the Ring in someone with vaginal candidiasis, preference is to use an oral anti-fungal, such as a stat dose of fluconazole. If a cream or pessary is to be used, such as clotrimazole and miconazole, reinforce safer sex practices until symptoms have subsided and treatment completed.

7.5 Key counselling points prior to initiation

Below is a summary of key points prior to initiation (additional information in Job Aids 2 and 3):

- **Understanding of the difference between HIV prevention and treatment:** Check for understanding about PrEP, PEP, and ART.
- **HIV risk discussion and HIV prevention needs and options:** Explore options and choices (Job Aid 3); willingness to use the Ring; discuss choice of PrEP together with other prevention options – information and discussion for the client to make an informed decision. (*Note:* the concurrent use of oral PrEP and the Ring has not yet been researched and there is insufficient evidence to recommend this as an option)
- **HIV prevention effectiveness:** Emphasise the point that the Ring is not completely effective on its own and needs to be used with other HIV prevention methods, such as consistent and correct use of condoms.
- **Using the Ring:** Using Job Aids 4, 5, and 7, explain the basics about the Ring. Emphasise that the Ring only works for receptive vaginal sex, and for the Ring to work optimally, **it must be kept in place in the vagina and worn for the full 28 days.** Removal or sporadic use compromises its efficacy. Job Aid 4 provides useful pictures of the pelvic area and how the Ring is situated in the body. Box 8 provides pictures and instructions on Ring insertion and removal (also see Job Aid 5).
- **Fertility intentions:** Discuss whether the client is planning to become pregnant and is currently breastfeeding and/or planning to breastfeed. Explain why this is not recommended with the Ring.
- **Use of the Ring during menstruation:** There is evidence that menstruation and use of tampons may result in a decrease of dapivirine levels and therefore women should be advised to use additional HIV preventive measures during menses [18]. (The clinical relevance of the reduced vaginal dapivirine levels during menses and tampon use is unclear, hence the advice to use additional HIV prevention methods during menses) (See 10.7 and Box 9).
- **Use of other vaginal products:** Discuss the use of other vaginal products, such as contraceptive vaginal rings and menstrual cups, and explain that these cannot be used with the Ring [10]. Discuss vaginal cleaning practices, such as, but not limited to douching, and why this not advised when using the Ring.
- **Condom use:** Both male and female condoms, as well as water-based lubricants, can be used with the Ring.
- **STIs and pregnancy:** Note that the Ring does not protect against STI and pregnancy – therefore consistent and correct condom use (male or female) and the use of reliable contraceptive methods are recommended.
- **Gender based violence (GBV) and Intimate Partner Violence (IPV) assessment and response:** Provide appropriate response, including first-line support and referral where necessary.

Important Counselling Message

- The Ring is not completely effective on its own and needs to be used with other HIV prevention methods, such as consistent and correct use of condoms
- The Ring only works for receptive vaginal sex
- The Ring must be kept in place in the vagina and worn for the full 28 days

7.6 Method of administration of the Ring - insertion, removal, disposal

- Before you begin demonstrating the insertion of the Ring, explain to the person the structure of the pelvic area, where the vagina is, where the Ring is placed when inserted, and how it sits snugly in place (Job Aid 4).
- Some clients may initially prefer a healthcare provider to insert the Ring and confirm its placement. Once comfortable with the process, they can remove and insert the Ring themselves. This requires sensitive guidance, practice, and building the clients comfort with their bodies and confidence.

Guidance for Ring insertion, removal, and disposal are provided in Box 8 and Job Aid 5).

In addition, a demonstration video is available from the following link and QR code:
https://vimeo.com/707699170

Key points for demonstrating Ring insertion and use

- Many women are not familiar with their pelvic area. Provide guidance (Job Aid 4) and/or use a pelvic model, where available.
- Encourage the woman to understand how safe the Ring is. Provide reassurance that it cannot travel and demonstrate how it sits snugly in place. Mention that tampon, contraceptive vaginal ring, and female condoms all are placed in the vagina.
- Let the woman hold and feel the flexibility of the Ring.
- Demonstrate use of the Ring by inserting it for the woman, then remove it, and let the woman try on her own. Be relaxed and reassuring.
- Explain, that in all the research to date, most partners were not aware of the Ring during sex (unless their partners disclosed Ring use), and if they were, it did not decrease pleasure.

Table 3. Summary: PrEP Ring initiation visit schedule and readiness assessment[††]

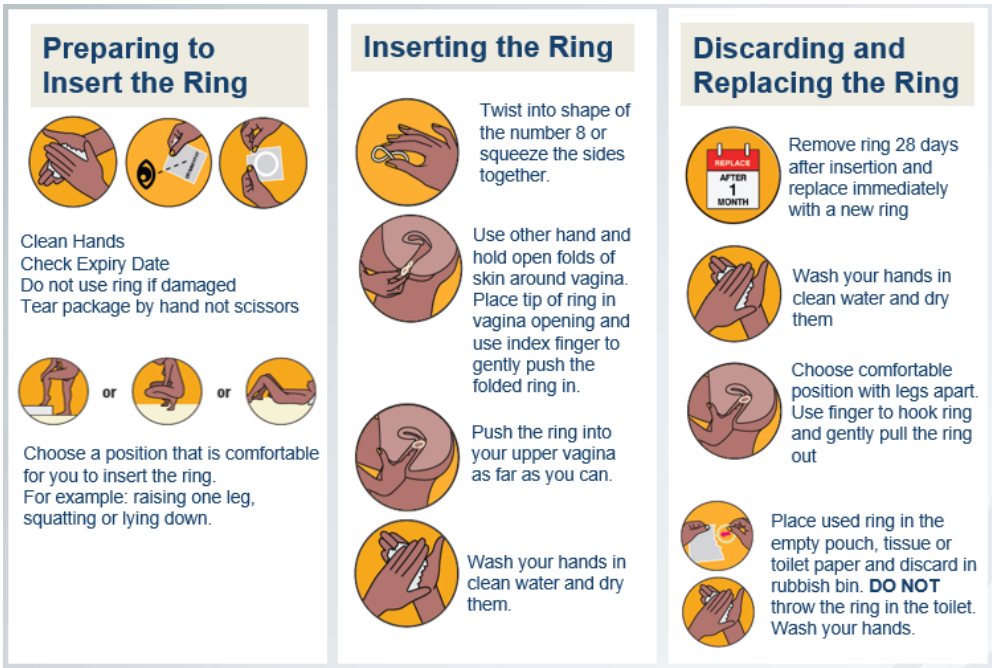
(See Job Aid 2)

Required Initiation Steps	Action
HIV test (per national HIV testing guidelines)	**Same-day HIV testing is suggested:** • If HIV-positive - client must not be initiated on PrEP and should be immediately referred for ART. • If inconclusive, defer use of PrEP and follow the national algorithm until a definitive HIV test result has been obtained. Provide counseling on how to prevent/reduce potential exposures to HIV.
Assessment for recent exposure to HIV	**Clients exposed to HIV in the past 72 hours:** If a client reports an exposure to HIV in the past 72 hours, screen for possible eligibility for PEP instead of the Ring. • Educate clients on the difference between PEP, PrEP, and ART and offer counseling on how to prevent/reduce potential exposures to HIV. • After 28 days of PEP, client may be transitioned from PEP to PrEP (oral PrEP or Ring) without a gap, if HIV-negative and free of other contraindications. **Clients with possible acute HIV infection** (**Box 5**)**:** If client presents with signs and symptoms of HIV infection and has had possible exposure to HIV in the previous two weeks: • Defer use of PrEP. Provide counseling on how to reduce or minimize potential exposures to HIV, as well as STI screening, diagnosis, and management. • Repeat HIV testing after four weeks. If negative, initiate use of PrEP (oral PrEP or Ring) if free of other contraindications.
Counselling	Assess whether the client perceives themselves to be at risk of HIV. Discuss prevention needs and provide condoms/lubricants and provide counseling on how to prevent/reduce potential exposures to HIV. Discuss desire for HIV prevention methods, explore choices (see Job Aid 3). The healthcare provider and client should determine together whether oral PrEP or the Ring may be appropriate for the client by discussing the client's potential exposures to HIV, their experience with oral PrEP, and their willingness and ability to use either method effectively. Include a discussion in relation to the practice of anal receptive intercourse emphasising that the Ring only offers protection in the vagina.

[††] Adapted from: PROMISE PrEP Ring Guideline Template Aug 2021

	Assess if the client may be pregnant, breastfeeding, or intends to become pregnant or breastfeed in the near future. If the client wants to use the Ring, deliver and discuss any remaining education and counseling messages about the Ring (see Job Aids 7 and 8). Explain Ring insertion and removal (Job Aid 5).
Assessment for contraindications for Ring use	Assess for contraindications of the Ring (Box 6). If no contraindications, provide a single or multi-month supply of the Ring per client preference.
Screening, testing, and treatment of STIs	See Section 10.3
Pregnancy testing	Regular pregnancy testing is recommended, where indicated, for clients using the Ring (Job Aid 2). The Ring is not currently recommended for pregnant and breastfeeding women (no safety concerns to date but limited data available). If pregnant, explore alternative HIV prevention options, such as oral PrEP and condoms, link to antenatal care, provide pregnancy options counseling.
Contraception	Can use all methods except the contraceptive vaginal ring (NuvaRing) - explore alternative methods if in use.
Integrated SRH and HIV service package	This includes: • Risk reduction counselling • STI screening and management • Provision and education about condom use and lubricants • Contraceptive services • Mental health • GBV and IPV assessment and response
GBV/IPV inquiry and response	Assess client's experience of GBV, including IPV. Provide appropriate GBV/IPV response, including first-line support and referral where necessary, and support clients to identify ways to effectively initiate and continue with Ring use. Although the Ring may be an option for clients concerned about IPV due to its discreet nature, clients who wish to keep their Ring use private from their sexual partner(s) should be counseled on the possibility that a partner may feel the Ring during sex and be assisted with a plan to implement should this occur. *Clients experiencing GBV or IPV should not be prohibited from receiving the Ring if they can effectively use it.*

Box 8. Guidance for Ring insertion, removal, and disposal



7.7 Follow up visits

Follow up visits include:

- HIV screening:
  - Assess for acute HIV infection (Box 5).
  - HIV testing: It is recommended that HIV testing should be done every three months, or more frequently where the Ring has not been used consistently. HIV testing is provided as per NDOH policy and guidelines [19,20].
  - Ask about consistent Ring use and if there is possible recent exposure within 72 hours, recommend PEP.
- Pregnancy testing/screening, when indicated (**Error! Reference source not found.**). (Currently the Ring is not recommended for use by pregnant or breastfeeding women)
- Support for Ring use:
  - Support should be provided on effective Ring use, challenges, side effect management, and use of additional prevention options, including for example, condom or switching to oral PrEP
- An integrated service package (

- **Box 4**):
    - Risk reduction counselling
    - STI screening and management (see Section 10.3)
    - Provision and education about condoms use and lubricants
    - Contraceptive services
    - GBV and IPV assessment and response

Important

- Provide referral when services not available at point of care
- Ensure referral service points are operational and accessible

7.8 Frequency of follow up visits

There is no definitive period for Ring dispensing or return visits. This will depend on the client's needs, confidence with self-insertion, and convenience for the client.

- Rings can be dispensed with an optional follow up visit after one month, followed by a three-monthly visit, with multi-ring dispensing, aligned with HIV testing. Clients wanting assistance with removal and re-insertion may wish to return every 28 days - this needs to be discussed with the client.
- Where possible, visits should be aligned with other clinic appointments, for example contraception services or other chronic medication visits, to reduce the number of times a client needs to return to the clinic.

8. Stopping and restarting the Ring[‡‡]

Clients may choose to stop and restart using the Ring for a number of reasons, which may include changes in relationship status or sexual practice(s), re-locating, planning to get pregnant, or their preferred HIV prevention option changes.

Important points about stopping and restarting the Ring:

- As soon as the Ring is removed, there is no residual protection.
- Clients need to be counselled about risk and HIV prevention options.
- Clients who have previously used the Ring and decide to reinitiate Ring use should go through the same procedures for an initiation visit as outlined above.

[‡‡] Adapted from: PROMISE PrEP Ring Guideline Template Aug 2021

9. Ring use - Intermittent use and discontinuation

9.1 Intermittent use

- The Ring is designed to be used continuously to get optimal protection; therefore, **intermittent use is not recommended**. There is insufficient research done, but what is known is that local levels of dapivirine drop quickly after the Ring is removed. It is not necessary to clean or remove the Ring during or after menses or sex. STIs can be diagnosed and treated without removing the Ring [10] (see Section 10.3 for further information on STI management).
- Should there be intermittent Ring use, and there is concern about possible HIV exposure, the woman can transition straight onto post exposure prophylaxis (PEP), following NDOH guidelines [21], within 72 hours after exposure.
- If the Ring comes out or is removed (although extremely rare), it should be re-inserted, considering the following:
    - If this occurred in a clean place (such as in a bed or in clothes), the Ring should be rinsed in clean, cool water and immediately reinserted
    - If this occurred in a place that is not clean (e.g., falls in the toilet or the floor), the Ring should be thrown away and a new Ring should be inserted immediately or as soon as possible

9.2 Removal and re-insertion in the middle of the 28 days

When the Ring is removed, and re-inserted, it takes 24 hours for the it to be effective. Emphasise the importance of not removing the Ring, but if it is removed and re-inserted within the 28 days, advise condom use or abstinence for 24 hours.

9.3 Discontinuing Ring use and switching between PEP or PrEP

As with oral PrEP, a woman may choose to stop using the Ring.

- When stopping Ring use, it is important to emphasise that the level of dapivirine drops quickly after removal from the vagina, and there is no residual effect, so it is important to use another method of HIV prevention immediately after removing the Ring, such as oral PrEP and/or condoms.
- Switching between the Ring and oral PrEP or PEP:
    - *Women transitioning from oral PrEP to the Ring*: Continue to take daily oral PrEP for 7 days after potential exposure, as per SA guidelines [2]. On completion, insert the Ring. Ensure the client is aware that the Ring takes 24 hours to be effective, and reinforce the importance of using additional HV prevention, such as condoms.
    - *Women transitioning from Ring to oral PrEP*: Remove the Ring and follow the steps for initiation outlined in the oral PrEP guidelines [2] - including the 7-day

lead in period. Reinforce the importance of using additional HIV prevention, such as condoms during the lead in period.

- *Women transitioning from the Ring to PEP:* Remove the Ring and transition immediately onto PEP if there is anxiety about HIV transmission. PEP can be provided within 72 hours as per national guidelines [21].

Note on the simultaneous use of oral PrEP and the Ring

Safety data on simultaneous use of oral PrEP and the Ring are limited. Although use of both products is not likely to be less well-tolerated than when the drugs are used individually, more data are needed to confirm the safety and efficacy of simultaneous use of oral PrEP and the Ring.
Currently, there is insufficient evidence to recommend this as an option.

10. Additional precautions – key points

10.1 Risk of HIV resistance with undetected HIV-1 infection

It is important to test for HIV when screening for eligibility for Ring use, as the Ring should only be used by women who are HIV-negative. HIV testing should be done at frequent intervals (every three months) [18].

Continued use of the Ring in the presence of HIV infection could result in viral mutations associated with NNRTI resistance. If there are clinical symptoms indicating possible HIV infection, and recent exposure (< 1 month) is suspected, use of the Ring should be delayed or stopped for at least a month, until a negative status is confirmed [22].

10.2 Pelvic inflammatory Disease (PID) and genital infections including non-sexually transmitted vulvovaginal infections

Although no increased risk was observed in clinical trials, it is not yet known whether the use of the Ring in someone with an unrecognised STI could increase the risk of PID. The prescriber should consider this possibility in anyone presenting with symptoms consistent with PID.

10.3 STI and genital infection management

- Health providers should ask about presence of STIs prior to starting the Ring and these should be treated according to national guidelines.
    - If only mild symptoms are present, offer the Ring. If severe ulceration, pain, or discharge, delay providing the Ring until symptom resolution and advise condom use.
- STIs can be diagnosed and treated without removing the Ring during follow up visits.
- Early detection and treatment (as per STI guidelines) during Ring use is recommended.
- The simultaneous use of vaginally administered antimicrobial products to treat STIs has not yet been studied, and therefore is not recommended [22].
- When using the Ring in someone with vaginal candidiasis, preference is to use an oral anti-fungal like a stat dose of fluconazole. If a cream or pessary is to be used, such as clotrimazole and miconazole, reinforce safer sex practices until symptoms have subsided and treatment completed. Return to clinic if symptoms do not resolve within a week.

10.4 Alcohol and substance use

If clients think that alcohol or recreational drug use may interfere with effective use of the Ring, the healthcare provider should discuss additional HIV prevention options, as well as discuss support for behaviour change.

10.5 Use with contraception

The Ring can be used with all methods of contraception, except the contraceptive vaginal ring (e.g. NuvaRing), cervical caps, or diaphragms.

10.6 Use with condoms

Studies have shown that the Ring can be used with both male and female condoms, as well as water-based lubricants.

10.7 Use during menstruation and with tampons

- The Ring can be used during menstruation, and should not be removed at any point during the 28 days
- The Ring does not cover the cervix and does not interfere with menstrual flow
- Tampons and the Ring can be used together, the Ring should not be removed when using a tampon
- The Ring should not be used with menstrual cups

Note: There is evidence that menstruation and use of tampons may result in a decrease of dapivirine levels and therefore women should be advised to use additional HIV preventive measures during menses (Box 9).

Box 9. A note on menstruation, use of tampons, and Ring use

The IPM package insert warns that menstruation and the use of tampons may decrease the level of dapivirine, and advises use of extra prevention.

According to professional package insert [18]:
"Dapivirine vaginal fluid concentrations decreased up to 4-fold during menses but increased again thereafter and achieved concentrations consistent with the 'no menses' group in a clinical trial by end of menses. The use of tampons generally resulted in a 2-fold decrease of dapivirine in vaginal fluid concentrations during menses. As the clinical relevance of the reduced vaginal dapivirine levels during menses and tampon use is unclear, women should be advised to use additional preventive measures against HIV during menses"

11. Management of side effects and adverse reactions

The most reported side effects are minimal and need to be managed as per standard guidelines. These include urinary tract infection, vaginal discharge, vulvovaginal pruritus, vulvovaginitis, and pelvic pain. (See Appendix 2 for research results concerning the occurrence of side effects)

12. Reporting of adverse events

Reporting suspected adverse reactions is important. It allows further monitoring and analysis of the adverse events. Suspected adverse reactions need to be recorded in the client's clinical record and reported to SAHPRA via the *6.04 Adverse Drug Reactions Reporting Form.* This can be found on the following link: https://www.sahpra.org.za/Publications/Index/8

13. Ring clients who test HIV-positive

- It is important to test frequently for HIV (at least 3 monthly) when using the Ring
- Clients who test HIV-positive must stop and remove the Ring immediately and be initiated on ART or referred for ART as soon as possible, regardless of CD4 count. They must be linked to HIV care, treatment, and support. Where possible, their partners should be encouraged to test for HIV.
- HIV seroconversion after initiating PrEP can occur and may be due to:
    - Inconsistent use: Women who use the Ring inconsistently, and remove or stop without using another prevention method
    - Breakthrough infections: As the Ring is not 100% effective in preventing HIV, regular HIV testing is recommended to detect any breakthrough infections and enable women to start ART if they test positive
    - Exposures not covered by the Ring: This could include for example, anal sex and shared injection needles, where Ring use is not protective
- All persons using the Ring that have seroconverted must be reported on the PrEP seroconversion form (refer to Job Aid 10)

14. Counselling and education for Ring use

The following highlights three important counselling and education messages underpinning Ring provision – risk reduction counselling, choice and informed decision-making, and supporting effective use of the Ring. An expanded list of key counselling and education messages are provided in Job Aid 7.

Risk reduction counselling

- It is important to discuss the person's risk in term of HIV, STI, pregnancy, and GBV.
- A simple risk assessment is provided as a tool for individuals to explore their own risk and options for prevention.
- Self-understanding of risk encourages ownership and motivation to use HIV prevention methods effectively.

Choice and informed decision-making

- Although HIV prevention programmes have encouraged combination prevention, this is the first time that there is more than one biomedical PrEP option available: oral PrEP and the Ring. Therefore, it is important to provide evidence-based, accurate and clearly understandable counselling and information for clients to explore the choices available to them and the possible implications of such choices.
- The relative benefits and drawbacks of respective methods need to be provided and weighed up by the client. Both the healthcare provider and IEC materials need to assist the client in making an informed decision (see Job Aid 3).
- Given that clinical trials indicate that the Ring is 35% effective[§§] (see Appendix 1), the need for additional protection needs to be emphasised. Consistent and correct condom use (male or female condoms) provide the most effective protection when using all PrEP HIV prevention methods, including the Ring.
- STI and pregnancy prevention and the need for condom use, STI management, and the use of effective contraceptive methods, needs to be continuously reinforced.
- The client can also choose to discontinue or switch prevention methods at any time.

NB: If there has been recent possible HIV exposure (within 72 hours), always consider PEP.

[§§] Summary of Product Characteristics (SmPC) for IPM 027

Supporting effective use:

- It is important to explain to women how the Ring is inserted and where it fits for the 28 days. The use of videos, pelvic models, and pictures are essential for this process.
- Demonstration insertion and removal of the Ring is helpful, coupled with encouraging the client to practice themselves. Support and guidance instil confidence for women to be able to insert and replace the Ring on their own.
- Time between insertion and achieving high drug concentrations in vaginal fluid that is expected to reduce the risk of HIV infection is 24 hours, so additional prevention methods should be used within this time.
- Studies show that consistent use increases effectiveness. The Ring is only effective when in place in the vagina, once removed it is no longer effective. Local levels of dapivirine drop when the Ring is removed, and it therefore needs to be replaced immediately to be effective.
- The Ring should not be removed prior to, during, or after vaginal intercourse, nor during menstruation. Additional prevention is particularly important during menstruation and if using a tampon (see Box 9).
- The Frequently Asked Questions Job Aid are useful for addressing anxieties and concerns (Job Aid 8).

Effective use key points [10]**:**

The effectiveness of the Ring is correlated with correct use:

- Use the Ring continuously over the 28 days
- Immediately replace by inserting a new Ring at the end of the 28 days
- Keep the Ring in before, during and after vaginal intercourse, and during menstruation

Note: Emphasise that the Ring is most effective when correctly inserted and kept in place for 28 days. The Ring is only effective when in place in the vagina and once removed it is no longer effective.

15. Monitoring and reporting

Routine monitoring of the Ring programme is essential to monitor, evaluate, and learn more about the implementation of this new product. The data collected will also assist with forecasting demand to ensure sufficient and an uninterrupted supply of the Ring.

To facilitate standardised and systematic monitoring of the programme, all PrEP service points must use the updated **PrEP Clinical Form** to collect client data. A copy of the PrEP clinical form can be found in Job Aid 11. PrEP providers must ensure that the form is completed in detail and kept in the client file at the healthcare facility. The information contained in the clinical form must then be used for entry into TIER.Net after each clinical visit or if there is a change in the client's status as PrEP user.

Introducing additional PrEP options, such as the Ring, is intended to provide choice and thereby support more women at substantial HIV risk to access ARV–based prevention. Monitoring the total number of people using PrEP, by option, will also be important.

The following data elements (*Table x*) will be used for the routine monitoring of Ring implementation to assess uptake, safety, and continued use

Initiated age continuation

Data elements	Definition	Source document	Point of collection
D-Ring Uptake	Number of individuals (disaggregated by age) who received Dapivirine Ring for the first time in the reporting period.	PrEP Clinical form	At D-Ring initiation
Continuation on D-Ring	Number of individuals (disaggregated by age), inclusive of those newly enrolled, that received D-Ring in the reporting period.	PrEP Clinical form	At monthly follow-up visit

Appendix 1. Effectiveness of the Ring in reducing HIV infection – summary of evidence

The following is a summary of overarching Ring findings in relation to efficacy, extracted from the WHO HIV guidelines [3].

At a glance

Summary of Product Characteristics (SmPC) final efficacy results:

- Ring Study (IPM 027): 35%
- HOPE: 31%
- DREAM: 62%.

Summary of review findings

A systematic review and meta-analysis of dapivirine vaginal ring trials demonstrated that the Ring is effective in reducing the risk of acquiring HIV infection. Two randomized controlled trials – the Ring Study (IPM-027) and ASPIRE (MTN-020) – reported that the dapivirine vaginal ring was approximately 31% effective in reducing HIV infection in intention-to-treat analysis. A subgroup analysis by age did not show efficacy among women 18–24 years old, who had lower adherence.

The results from two open-label extension studies – DREAM and HOPE – found increased efficacy, increased adherence, and increased retention, relative to the randomized controlled trials. The results from one of the open-label extension studies indicated a 62% reduction in HIV transmission, comparing study results to the simulated control.

Further studies are underway or planned to help understand whether this lack of effect among younger women results from non-adherence or other factors and to identify ways to support adherence for younger women who choose the dapivirine vaginal ring for HIV prevention.

Safety and acceptability are also being studied among adolescents 15–17 years old, who were not included in the trials. The dapivirine vaginal ring acts locally, and systemic absorption is low. The trials reported no notable difference, in the treatment and placebo ring groups, in respect of adverse pregnancy outcomes (spontaneous abortion, stillbirth, and ectopic pregnancy), or fetal and/or infant outcomes. However, since the number of pregnancies was small, ongoing trials are gathering further safety data during pregnancy and breastfeeding.

Reduction in HIV infection

The evidence for reduction in risk of HIV infection, measured as an outcome in five studies, was of moderate certainty. A meta-analysis of HIV infection reported in the two Phase III placebo-controlled randomized controlled trials (ASPIRE and the Ring Study) found a 29%

reduction in HIV risk (95% CI 11–43%). This was similar to a pooled analysis using time-to-event data conducted by investigators from both trials, which found a 27% relative reduction in HIV risk comparing the dapivirine vaginal ring to the placebo arms (95% CI 9–42%). Individually, ASPIRE found a 27% relative reduction in HIV risk (95% CI 1–46%), and the Ring Study found a 33% relative reduction in HIV risk (95% CI 5–53%) for active dapivirine vaginal ring versus placebo arms.

In the ASPIRE study, efficacy increased when observations from the two research sites with low adherence were dropped, yielding a 37% relative reduction in HIV risk (95% CI 12–56%). ASPIRE conducted an age-stratified analysis excluding the two sites with low adherence and found that the dapivirine vaginal ring did not significantly reduce the risk of acquiring HIV among women younger than 25 years (the reduction in HIV incidence was 10%, 95% CI −41% to +43%), whereas HIV incidence was 61% lower for the dapivirine vaginal ring versus placebo among women 25 years and older (95% CI 32–77%). A post hoc analysis showed no efficacy and lower adherence among women 18–21 years old.

The Ring Study also conducted an age-stratified analysis but found no significant difference in risk reduction for women 21 years and younger versus women older than 21 years. However, when the results across the two trials were pooled using individual-level data, the reduction in the risk of acquiring HIV-1 was significantly higher among participants older than 21 years; no risk reduction was observed for participants 21 years or younger.

The results from the two open-label extension studies, DREAM and HOPE, found increased efficacy, increased adherence, and increased retention relative to the randomized controlled trials. The results from DREAM indicated a 62% reduction in HIV risk compared with the simulated control, and the results from HOPE demonstrated a 39% relative reduction in HIV risk (95% CI 14–69%) compared to the simulated control. Of note, the participants in HOPE were given the choice of using the dapivirine vaginal ring at every study visit, whereas the participants in DREAM had to be willing to use the dapivirine vaginal ring as part of the study's eligibility criteria. In HOPE, 92% of the participants accepted the dapivirine vaginal ring at enrolment and 73% accepted the dapivirine vaginal ring for the duration of the study.

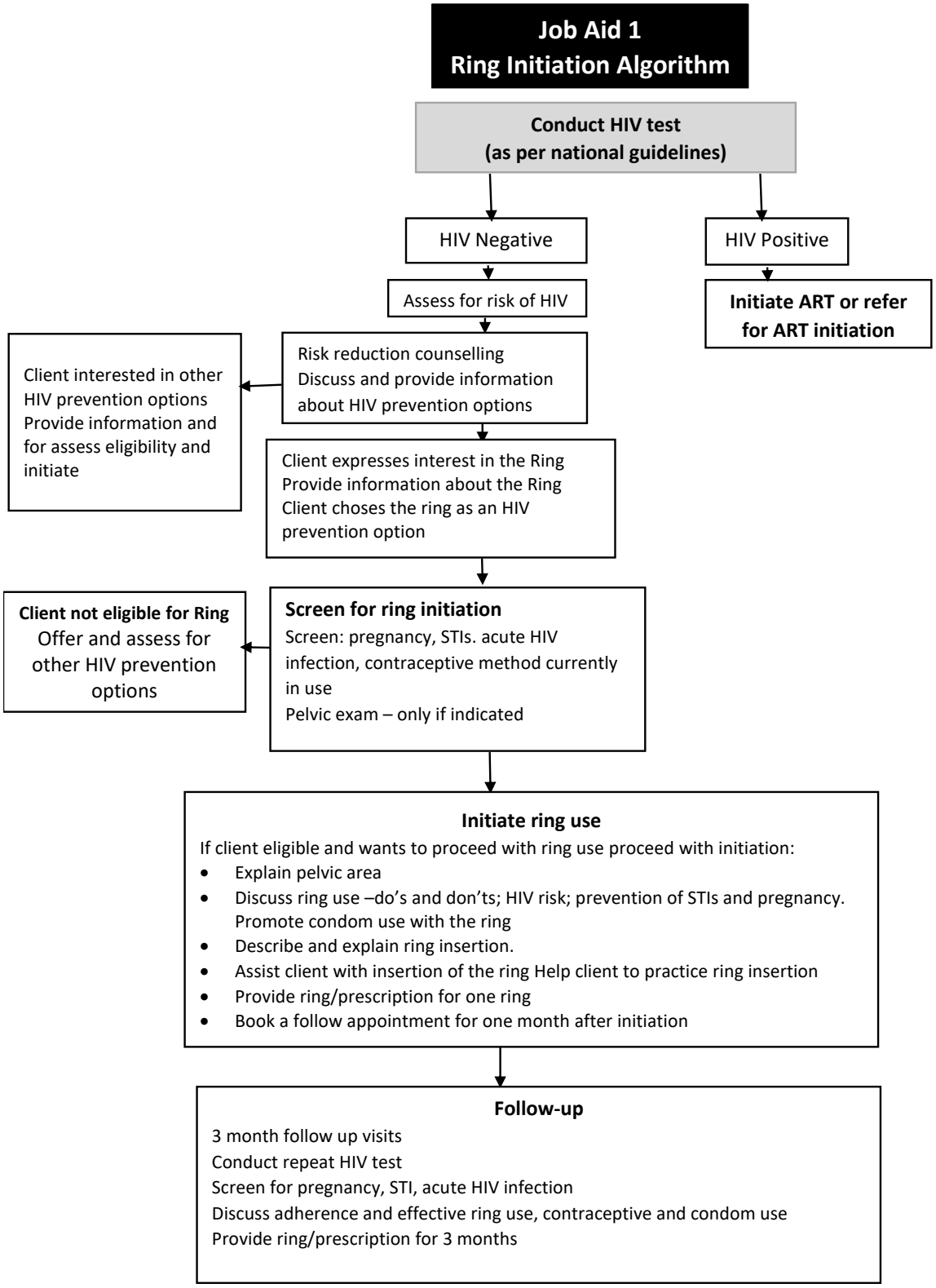
Appendix 2. Side effects and adverse events

The most reported adverse reactions reported by ≥ 5 % of participants in combined studies are summarised below.

Side effect reported	Ring	Placebo	Total
Urinary tract infection	15.3%	16.7%	15.2 %
Vaginal discharge	7.3%	9.2%	7.1 %
Vulvovaginal pruritus	6.6%	7.9%	6.5 %
Pelvic pain	6.8%	7.4%	6.2 %

- This data showed that there was no significant difference between the placebo and the Ring
- Side effects were generally mild to moderate and were treated with no interruption in Ring use
- There was no evidence of increased incidence/prevalence of urinary tract infections over time.
- Majority of events were Grade 1 or 2 in severity, with none leading to permanent product discontinuation
- All experienced side effects were managed with standard clinical guidelines or resolved on their own

Job Aid 1: Ring initiation algorithm



Job Aid 2: PrEP Ring initiation visit schedule and readiness assessment[***]

As with oral PrEP, the Ring can be initiated on the same day for most clients. Initiation visit steps for clients beginning use of the Ring are outlined in the table below.

Required Initiation Steps	Action
HIV test (per national HIV testing guidelines)	**Same-day HIV testing is suggested:** • If HIV-positive - client must not be initiated on PrEP and should be immediately referred for ART. • If inconclusive, defer use of PrEP and follow the national algorithm until a definitive HIV test result has been obtained. • Provide counseling on how to prevent/reduce potential exposures to HIV.
Assessment for recent exposure to HIV	**Clients exposed to HIV in the past 72 hours:** If a client reports an exposure to HIV in the past 72 hours, screen for possible eligibility for PEP instead of the Ring. • Educate clients on the difference between PEP, PrEP, and ART and offer counseling on how to prevent/reduce potential exposures to HIV. • After 28 days of PEP, client may be transitioned from PEP to PrEP (oral PrEP or Ring) without a gap, if HIV-negative and free of other contraindications. **Clients with possible acute HIV infection** (**Box 5**)**:** If client presents with signs and symptoms of HIV infection and has had possible exposure to HIV in the previous two weeks: • Defer use of PrEP. Provide counseling on how to reduce or minimize potential exposures to HIV, as well as STI screening, diagnosis, and management. • Repeat HIV testing after four weeks. If negative, initiate use of PrEP (oral PrEP or Ring) if free of other contraindications.
Counselling	**Encourage informed decision-making and choice:** • Assess whether the client perceives themselves to be at risk of HIV. • Discuss prevention needs and provide condoms and lubricants and provide counseling on how to reduce potential exposures to HIV. • Discuss desire for HIV prevention methods and explore choices (see Job Aid 3).

[***] Adapted from: PROMISE PrEP Ring Guideline Template Aug 2021

	○ The healthcare provider and client should determine together whether oral PrEP or the Ring may be appropriate for the client by discussing the client's potential exposures to HIV, their experience with oral PrEP, and their willingness and ability to use either method effectively. • Discuss the practice of anal receptive intercourse emphasising that the Ring only offers protection in the vagina. • Assess for eligibility and any contraindications which may influence clients choice. • Assess if the client may be pregnant (Job Aid 2), breastfeeding, or intends to become pregnant or breastfeed in the near future. • If the client wants to use the Ring, deliver and discuss any remaining education and counseling messages about the Ring (see Job Aid 7). • Explain Ring insertion and removal (Job Aid 5).
Integrated SRH and HIV service package	**Seek opportunities to discuss and provide SRH services:** • Risk reduction counselling • STI screening and management • Provision and education about condom use and lubricants • Contraceptive services • Mental health • GBV and IPV assessment and response

If client chooses the Ring…	
Assessment for contraindications for Ring use	Assess for contraindications of the Ring (Box 6). • If no contraindications, provide a single or multi-month supply of the Ring per client preference.
Menstruation and use of tampons and the Ring	• The Ring is most effective when left in place for 28 days, and does not need to be removed during menstruation. • Menstruation and the use of tampons have both been shown to possibly compromise the efficacy of the Ring – use of additional prevention is recommended. • The use of menstrual cups is not recommended with the Ring.

Management of STIs and the Ring	• Clients initiating the Ring should receive screening, testing, and treatment for STIs per national guidelines.
	• If testing is not possible, manage as per STI standard treatment guidelines (syndromic management) in South Africa.
	  ○ If only mild symptoms - offer the Ring.
	  ○ If severe ulceration, pain, or discharge delay providing the Ring until symptom resolution and advise condom use.
	• STIs can be diagnosed and treated without removing the Ring during follow up visits.
	• Early detection and treatment (as per STI guidelines) during Ring use is recommended.
	• The simultaneous use of vaginally administered antimicrobial products to treat STIs has not yet been studied, and therefore is not recommended [18].
	• When using the Ring in someone with vaginal candidiasis, preference is to use an oral anti-fungal (i.e. stat dose of fluconazole). If a cream or pessary is to be used, such as clotrimazole and miconazole, reinforce safer sex practices until symptoms have subsided and treatment has been completed. Advise client to return to the clinic if symptoms do not resolve within a week.

Pregnancy and the Ring	• Regular pregnancy testing is recommended, where indicated, for clients using the Ring (Job Aid 2). • The Ring is not currently recommended for pregnant and breastfeeding women (no safety concerns to date but limited data available). • If pregnant, explore alternative HIV prevention options, such as oral PrEP and condoms, link to antenatal care, provide pregnancy options counselling.
Contraception and the Ring	• Check if the client is using the contraceptive vaginal ring (NuvaRing) – and explore alternative methods if in use. • All other methods can be used with the Ring, including male and female condoms.

GBV/IPV and the Ring	• Assess client's experience of GBV, including IPV. Provide appropriate GBV/IPV response, including first-line support and referral where necessary, and support clients to identify ways to effectively initiate and continue with Ring use. • Although the Ring may be an option for clients concerned about IPV due to its discreet nature, clients who wish to keep their Ring use private from their sexual partner(s) should be counseled on the possibility that a partner may feel the Ring during sex and be assisted with a plan to implement should this occur. *Clients experiencing GBV or IPV should not be prohibited from receiving the Ring if they can effectively use it.*

Job Aid 3: Informed decision-making and choice

The Ring may be offered as an option for individuals who wish to prevent HIV acquisition through receptive vaginal intercourse, *in combination with other HIV prevention practices.*

There are several factors an individual needs to consider when deciding which prevention option to choose. These tools are provided to assist the healthcare provider encourage and support the client to understand the different options, and guided by information, decide on their preferred method.

Job Aid 3.1 provides a useful summary of the key features of the Ring, oral PrEP, and condoms, to assist the client in making an informed decision.

Job Aid 3.2 provides a range of considerations to reflect on when choosing a suitable HIV prevention method.

Job Aid 3.1 Summarising oral PrEP, the Ring, and condoms

	Ring	Oral PrEP	Condoms
Active ingredients	Dapivirine	Emtricitabine and tenofovir (TDF/FTC)	Latex; rubber; soft plastic nitrile
Frequency	Monthly vaginal ring	Daily pill	Each and every time having sex
Lead in period	24 hours	7 days (for cis-gender women)	None; needs to be put on prior to penetration. The female condom can be inserted 8 hours prior to intercourse.
Who is this option for?	Individual assigned female at birth, for protection with vaginal sex	All persons at risk according to guidelines and medical eligibility	All persons
Approval status in South Africa	SAHPRA; still needs to be registered on the essential drug list (EDL)	Approved by SAHPRA	Approved
Availability in South Africa	Selected demonstration and implementation science sites	Roll out at public health facilities, institutions of higher learning, AGYW and other key population project sites	Available at all facilities, public venues, private retail outlets, etc.
HIV prevention efficacy	35%[†††]	Over 90%	Highly effective: • 80% at population level [23] • 98% at individual level if used consistently and correctly
STI prevention	No	No	Yes
Pregnancy prevention	No	No	Yes, only if used consistently and correctly
Use when pregnant, breastfeeding	Not sufficient evidence	Yes, with the guidance of a healthcare provider	Yes
Note: It is highly recommended that condoms are used together with oral PrEP or the Ring. However, the simultaneous use of oral PrEP and the Ring is not recommended, as there is insufficient evidence to support this.			

[†††] SmPC/Prescribing information based on IPM 027 data including retrospective testing required by EMA. For more detailed information, see Appendix 1.

Job Aid 3.2: Considerations when selecting an HIV prevention method

As with contraception, women need to be able to choose which HIV prevention method best suits them. There are a number of personal factors that may influence their choice and all of these factors should be explored with the client as part of the decision making process.

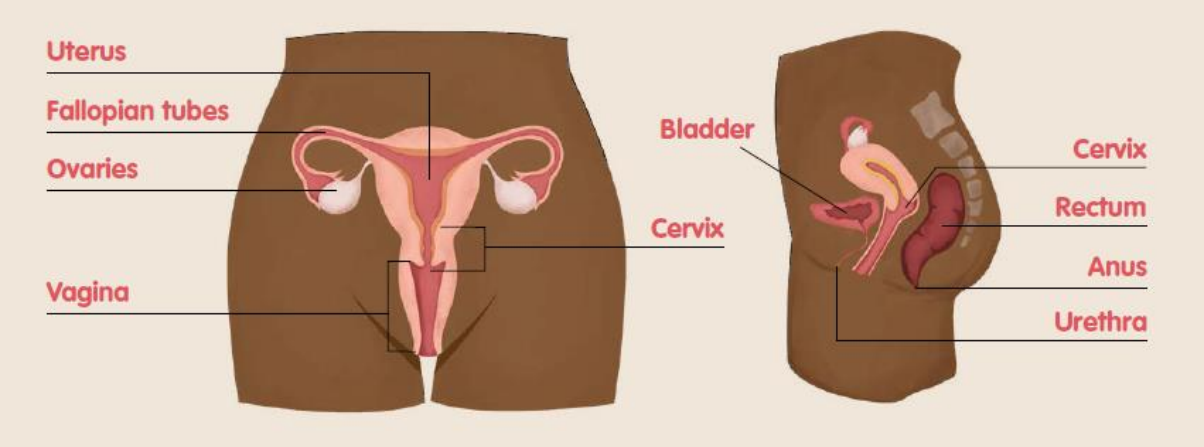
Issues to assist with decision-making	Explore with client:
Potential risk	Vulnerability to HIV: • Partners HIV status? • Are condoms used consistently and correctly, each and every time? • If partner is HIV-positive, are they taking their ART regularly?
Partner involvement	• Is their partners opinion about their choice of HIV prevention method important? • Whose decision is it - can the client make the decision on their own or do they need it to be a mutual decision? • Is the client fearful of their partner finding out?
Frequency/patterns of sex	• What is the frequency of sex: Regular? Unpredictable and unplanned? Limited to a specific time (e.g. holidays; a sexual partner visiting for a period of time)? • Anal and/or vaginal sex?
Availability and access	• What prevention methods are available and easy to access? • What are the possible costs: Is the product free? Money for transport to get to the place providing the method? • Is the client able to use the service in terms of times available, transport, distance, queue waiting times? How comfortable does the client feel about utilising the service?
HIV, STI, and pregnancy protection	Most HIV prevention products, such as oral PrEP and the Ring, do not protect against STIs and pregnancy. • Is the client able to use condoms consistently and correctly each and every time they have sex? • Are they using contraception, and if not what are the options? • Have they been assessed for STIs? • Can the HIV prevention method be used together with condoms?
Effectiveness	No HIV prevention method is 100% effective in preventing HIV: effectiveness varies. • How effective are the methods the client is interested in? And how important is this to the client? • How can the client get maximum protection? Are there any other issues which may affect the effectiveness of a method?

Personal commitment and preference for mode of use	• How does the client feel about how to use the method – e.g. daily pill, vaginal insertion, putting condoms on, etc.?
	• Is the client able to remember to take a daily pill? Does the client understand how to use the methods to ensure maximum protection, and are they willing to try?
	  ○ For oral PrEP: taking a daily pill, cycling on and off; complying with the lead in time of 7 days and use for 7 days after stopping.
	  ○ For the Ring: How does the client feel about inserting the Ring into their vagina and having the Ring in place for 28 days?
	• How easy is it to use condoms each and every time the client has sex?

Side effects	• Is this an important factor? • Does the client have prior experience with side effects?
Pregnant or breastfeeding	• How does the client best protect against HIV when pregnant or breastfeeding? • Is the method registered for use by pregnant and breastfeeding women?
Personal preference	Overall, the client may just have a preference because it suits them at this point in time, or they have tried a method before and want to try something different. **It is their decision**, as long as they are eligible.

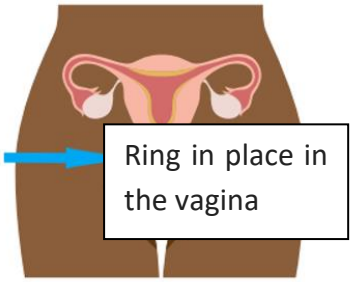
Job Aid 4: Pelvic area [24]

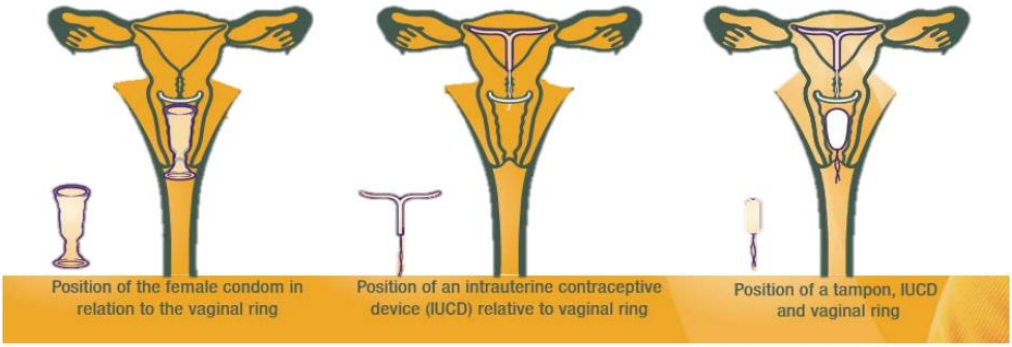
Understanding the pelvic area and where the Ring is inserted is important for clients wanting to use the Ring and learning how to use it.

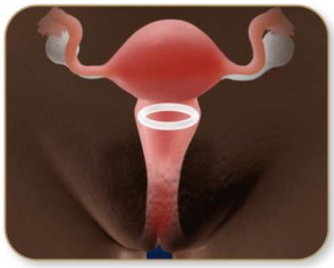


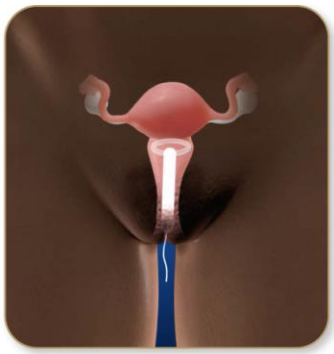
- **Vagina:** A tube that connects your vulva with your cervix and uterus. Babies and menstrual blood leave the body through the vagina. Some people put penises, fingers, sex toys, menstrual cups, and/or tampons here, and it is where the vaginal Ring sits.
- **Uterus:** A pear-shaped organ in the middle of the pelvis, above the vagina. Sometimes called the womb because the foetus grows here during pregnancy. The uterus is where tissue and blood build up before menses.
- **Cervix:** A muscular gateway where the uterus opens into the vagina. Your cervix separates your vagina from the rest of your body, so things like tampons or the vaginal Ring can't get "lost" inside of you.
- **Ovaries:** Oblong organs about the size of your thumbnail, where your eggs are stored. You have two of them, and they are attached to the uterus by the fallopian tubes. You are born with thousands of eggs in your ovaries and will not produce any more during your lifetime.
- **Fallopian tubes:** Tubes that connect each ovary to the uterus and provide a pathway for the egg to be released for fertilization by the sperm.
- **Anus:** Opening to the rectum, where the butt creases start behind the vulva. Stool/poop passes through the anus when you defecate (poo) and this is where the penis enters during anal sex.

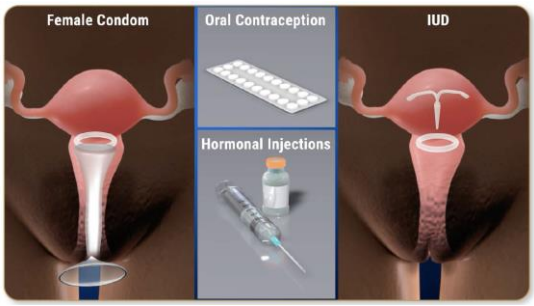
Picture of the Ring in place on its own, with a female condom, with an IUD, and with a tampon [10]











Job Aid 5: Ring insertion and removal[‡‡‡]

Please also refer to free IPM demonstration video link: https://vimeo.com/707699170

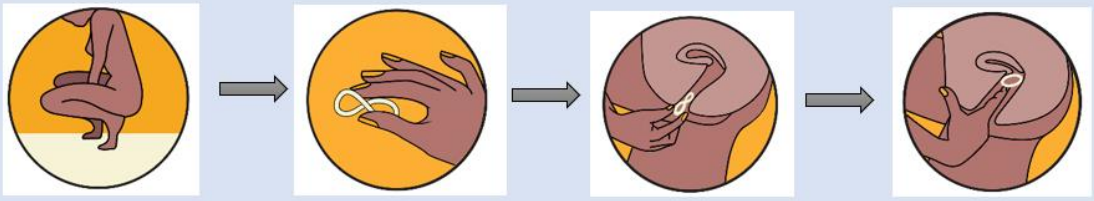
Inserting the PrEP Ring

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 using the Ring on their own with minimal support from their first use. However, for clients who prefer support, a healthcare provider can help insert the Ring or confirm placement. The Ring is inserted by hand; there is no need to use a speculum or other tools to insert the Ring. Clear visual instructions should be offered with the Ring.

Ring insertion steps for clients:

1. Get into a position that is comfortable for inserting the Ring, such as squatting, one leg lifted, or lying down. If a healthcare provider is assisting you, you should be in a reclining position.
2. 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.
3. Place the tip of the Ring into the vaginal opening and use your fingers to push the folded Ring gently up into the vagina.
4. 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 healthcare provider.*



1 2 3 4

[‡‡‡] Mosaic Template Guidelines for Oral Pre-Exposure Prophylaxis (PrEP), PrEP Ring, and CAB PrEP unpublished Nov 2022

Removing the PrEP Ring

Clients can remove the Ring without the help of a healthcare provider. However, for clients who prefer support, a healthcare care provider can help remove the Ring. The Ring is removed by hand; there is no need to use a speculum or other tools. If a client is being assisted by a healthcare provider, they should be in a reclining position during removal.

Ring removal steps for clients:

1. Get into a position that is comfortable for removing the Ring, such as squatting, one leg lifted, or lying down.
2. With clean hands, insert one finger into the vagina and hook it around the edge of the Ring.
3. Gently pull the Ring out of the vagina.

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

1 2 3

Job Aid 6: Follow up visits: Timing, processes, and procedures

- Clients using the Ring may wish to return after one month to have an HIV test, receive support, address side effects, discuss any difficulties with Ring adherence, and have assistance removing and inserting the new Ring.
- Clients not wishing to return after one month, can begin a three-monthly visit schedule at their initial visit (with three Rings provided).
- When possible, follow-up visits should be coordinated with visits for other services, to reduce the number times a client must return to receive services.

Follow up visits to include:

HIV testing and possible exposure	• Assess for acute HIV infection (Box 5) and possible exposure within the past 14 days • HIV testing: It is recommended that HIV testing should be done after one month and every three months thereafter. Recommend more frequently where the Ring has not been used consistently • HIV testing is provided as per NDOH policy and guidelines • If there is possible recent exposure within 72 hours, recommend PEP • Discuss Ring and condom use and ways to prevent/reduce risks to HIV
Pregnancy testing/screening, when indicated	Currently the Ring is not recommended for use by pregnant or breastfeeding women • Discuss contraception or plans to get pregnant • Pregnancy test or screening at visit (Box 7) • If pregnant, counsel on alternative prevention options and refer for antenatal care
Support for Ring use	Discuss and counsel on the following: • Whether the Ring has been in place for entire time and the importance of Ring adherence • How to reduce or minimise potential exposure to HIV • Challenges with Ring use • Side effect management • Use of additional prevention options, including condoms • Choice and options: desire to stop or switch to oral PrEP

An integrated HIV and SRH service package	Follow up services to include the integrated service package summarised in Box **4**. • STI screening and management (See section 10.3 in guidelines, and Job Aid 6) • Provision of condoms and lubricants and education about their use • Contraceptive services • Mental health and GBV/IPV assessment and response

Job Aid 7: Key counselling and education messages

Topic	Key Messages
Difference between PrEP, PEP, and ART	**Pre-exposure prophylaxis (PrEP):** • The use of ARVs by HIV-negative individuals *before* potential exposure to HIV to prevent HIV acquisition. • Current PrEP options in South Africa include oral PrEP (oral TDF/FTC as a fixed-dose combination) and now, the dapivirine ring. • There are other methods in the pipeline, including the two monthly long-acting injectable cabotegravir (CAB-LA). **Post exposure prophylaxis (PEP):** • ARV medication taken within 72 hours after exposure to HIV and continued for 28 days to prevent HIV acquisition. **Antiretroviral Treatment (ART):** • Lifelong treatment with a combination of ARV drugs for people with HIV to minimise the effect of HIV by increasing the CD4 count and reducing the viral load. • Prevention of mother to child transmission (PMTCT) effectively reduces transmission from a pregnant woman to her infant • Proper use of ART for HIV-positive persons effectively reduces HIV transmission.

Effective use of the Ring	• The Ring should remain in place for 28 days without removal and should be replaced with a new Ring at the end of the month. • The Ring must be in place for at least 24 hours before it is considered maximally effective. During this time, safer sex practices should be used, for example, abstinence or condoms/lubricants. • The Ring only prevents HIV acquisition through receptive vaginal intercourse. • Use the Ring if you think you may be at risk: Some people only need to use the Ring during certain times in their lives, while others may have an ongoing need. Continue using the Ring as long as you feel you have increased likelihood of acquiring HIV or until other methods for HIV prevention work for you and your life.
Sharing the Ring	• The Ring should not be shared with others. If other people are interested in using the Ring, encourage them to see a healthcare provider.
Ring use during sex	• The Ring does not interfere with sexual intercourse and should be worn during sex. • It can be used with condoms (male and female). • 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.
Ring use with contraceptives	• The Ring does not prevent pregnancy, so it is important that you use a reliable method of contraception as well. Almost all methods can be used with the Ring (hormonal contraceptives pills, injectables, implants, IUDs, and barrier methods, including condoms (male and female). However, use with the contraceptive vaginal ring (NuvaRing), diaphragm, and cervical cap is not recommended. • The Ring can be used with male or female condoms.
Ring use during pregnancy and breastfeeding	There is limited information about the safety of using the Ring during pregnancy or when breastfeeding (and it is not yet recommended in South African guidelines). If you are pregnant or breastfeeding or intend to be, discuss with your healthcare provider.

Side effects	There is a possibility of side effects with Ring use, such as urinary tract infections, vaginal discharge, vaginal and vulvar itching, and pelvic and lower abdominal pain. These side effects usually resolve without the need to remove the Ring. Urinary or reproductive tract changes may be signs of a urinary tract infection or a sexually transmitted infection, and you should seek medical advice as soon as possible.
The Ring and alcohol or other recreational drugs	Using the Ring while you are using alcohol or other recreational drugs will not hurt you. If you have concerns about this, discuss with your healthcare provider.
The Ring and STI prevention	• The Ring does not prevent any STIs other than HIV. • When possible, use a condom correctly whenever you have sex to prevent other STIs. The Ring can be used with male of female condoms.
The Ring and menses	• The Ring should be worn for 28 days, including during menses, to be most effective. The Ring does not cover the cervix and does not interrupt the flow of menstrual fluids. • The Ring should not be removed when menstruating. • The Ring should not be used with menstrual cups, but sanitary pads and tampons can be used. • If using a tampon, be careful not to accidentally remove the Ring when removing the tampon. NOTE: There is evidence that menstruation and use of tampons may result in a decrease of dapivirine levels and therefore women should be advised to use additional HIV preventive measures during menses such as condoms. Condoms should be used when using the Ring to add additional protection, but this is especially important when menstruating.
The Ring and douching	• Douching is not recommended at any time, including while using the Ring, because it may have a negative impact on the health of the vagina. • It is possible that flushing the vagina with water to clean it (or any form of douching) may dilute the concentration of dapivirine in the vagina.
Cleaning the Ring	• The Ring 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 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.

Ring storage	• Store Rings in their original packaging in a cool, dry place, away from children and direct sunlight, and secure from any pets or animals. • The Ring does not need to be refrigerated and can be safely stored at or around 30°C within 5 years from the manufacturing date on the package.
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 the trash bin out of reach of children. • You can return your used Ring to your healthcare provider/service provision point if you prefer.
Other ways to lower chances of getting HIV	To lower your chances of getting HIV: • Use oral PrEP • Adopt safer sexual practices, including consistent condom and lubricant use • Engage in non-penetrative sex, including mutual masturbation • Receive screening, diagnosis, and treatment for other STIs • Ensure the HIV-positive partner in a sero-different partnership has been on effective ART for at least six months, has an undetectable viral load, and remains adherent to ART • Males to have voluntary medical male circumcision • Reduce number of sexual partners • Access drug harm reduction and treatment services
Switching between HIV prevention options	• It is okay to start the Ring and decide later that you want to use another option to prevent HIV infection, like oral PrEP. • Many people switch between methods as their needs change. Discuss this with your healthcare provider.
The Ring and alcohol/substance use	• It is okay to use alcohol or other substances when using the Ring. It only is a problem if the use of alcohol or other substances interfere with the client's ability to use the Ring and this may decrease the protection the Ring provides against HIV.

Job Aid 8: Frequently asked questions

What if a woman wants to stop using the Ring?

The Ring is simply removed when a woman wants to stop using it. Once the Ring is removed, she is no longer protected. She can discuss prevention options with her healthcare provider.

Can a woman use contraception with a Ring?

The Ring can be used with the following: male and female condoms, oral contraception, and hormonal injections, IUD, and implants. The Ring should not be used with contraceptive vaginal rings, cervical caps, or diaphragms.

Can condoms be used when using the Ring?

Yes, male, and female condoms can both be used. Water-based lubricants can also be used with male condoms.

Does the Ring come in different sizes

There is only one size – one-size-fits-all

What do I do during menstruation?

- The Ring can be used during menstruation and should not be removed.
- Tampons can be used, but caution should be exercised not to dislodge the Ring when removing (See Job Aid 4, for a picture of the Ring and a tampon, the tampon can be comfortably removed).
- Menstrual cups should not be used when using the Ring.
- Menstruation and tampon use may reduce the level of dapivirine, and therefore Ring users are especially recommended to use additional prevention measures during menstruation – such as condoms.

What happens if the Ring comes out accidentally?

If the Ring comes out accidentally, or if removed, the following applies:

- If this happens in a clean environment and the Ring does not touch anything unhygienic (e.g. the toilet), then the Ring can be rinsed with clean water and re-inserted for the remaining time (until it has been used for the 28 days).
- If it touches something unhygienic, or if the woman is not sure, then discard that Ring, and re-insert a new Ring as per instructions.
- Remember that once the Ring is removed, and is re-inserted, or a new Ring is inserted, additional prevention methods should be used for 24 hours to build up the right level of protection.

How is the Ring disposed of when finished?
The Ring has a bag in which it can be wrapped and placed in the bin. Alternatively wrap in toilet paper or tissue and dispose in a bin, kept away from children.

Does the Ring provide protection against HIV when having anal or oral sex?
No, the Ring only provides protection when having receptive vaginal sex. It does not provide protection when having anal or oral sex. It is designed specifically for vaginal intercourse and should never be inserted rectally. Best to use oral PrEP and/or condoms (and lubrication (water-based)) when having anal sex.

Does the Ring provide protection for people who inject drugs?
No, the Ring only provides protection when having receptive vaginal sex. If individuals who inject drugs want HIV protection, then they need to use other strategies to reduce the likelihood of HIV acquisition when injecting drugs, such as oral PrEP and clean needle exchange services.

Does the Ring cause discomfort during sex? Can a sexual partner feel the Ring during sex?
Most participants in studies reported that they did not experience changes for themselves or their partners during sex, nor did it impact on sexual pleasure.

Does the Ring impact on a woman's fertility?
The Ring has no effect on a women's fertility. It does not contain hormones. Nor does it impact on hormonal levels or menstrual cycle. However, women are at risk of pregnancy when using the Ring and should use contraception to prevent pregnancy.

Is a woman still protected against HIV after removing the Ring? Does the dapivirine (ARV) build up in the system and if so, for how long does it provide protection after removal?
The Ring contains 25 mg of the ARV drug dapivirine, which it releases slowly and evenly throughout the 28 days. It protects the vaginal area from HIV with very little absorption elsewhere. Once the Ring is removed it is no longer effective.

What happens if a woman gets pregnant while using the Ring? Can the Ring be used by women who are breastfeeding?
There are limited data on the Ring's safety among pregnant and breastfeeding women. There are several ongoing studies researching the Ring's safety and use among pregnant and breastfeeding women (Deliver and B-Protected studies).

Job Aid 9: Ring provision – The basics: What do services need?

Ring readiness - The essentials
• Supply of commodities (the Ring) • Appropriate storage • Stock control systems in place • Reporting and M&E systems in place • Infection control measures/universal precaution, including COVID-19 • Availability of other HIV prevention options (oral PrEP, PEP, condoms (male and female), lubricant)

• Staff training:
  ○ Adapted according to the scope of work of selected staff – defined by regulatory provision, clinical and non-clinical positions, etc.
  ○ Training to include: Understanding the Ring, Ring safety and efficacy, providing the Ring, meeting HIV prevention needs of diverse user groups, raising awareness and communicating about the Ring, clinical management of clients on the Ring, counseling and supporting effective Ring use

• The Ring should be integrated into the following clinical services (*with operational and accessible referrals where necessary*):
  ○ HIV testing and counselling - HIV prevention counselling, discussion, and information: risk, HIV prevention options
  ○ Pregnancy test or screening
  ○ Pregnancy counselling, referral to ANC, ToP, and/or social services
  ○ Oral PrEP
  ○ PEP
  ○ ART
  ○ Contraception
  ○ STI screening
  ○ GBV/IPV/sexual assault services
  ○ TB screening
  ○ Covid screening

• Provision of the Ring: ○ Consultation: privacy, bed (if available, but can do insertion standing up), clean linen, screens, infection control measures

• Toolkit/resources to support Ring use:
  ○ For providers: Rings for demo; Q&A; pictures, model, and ability to demonstrate. Video a nice to have.
  ○ For clients: Pictures and info to take home, Q&A, IEC material to share with others. Reminders: calendar, diary, phone app, reminder for 28 days

Job Aid 10: PrEP sero conversion form (Combined)

health
Department: Health
REPUBLIC OF SOUTH AFRICA

First name				Folder #	
Surname				Phone #	
DOB	dd / mm / yy	Gender:	M / F / TG	Address	
ID Number		Date of visit:	dd / mm / yy		

Instructions: Please use the form to document the circumstances/factors/situations pertaining to the seroconversion of the PrEP client. The available fields should be completed with the relevant information available at the time of reporting. Please complete and affix a copy of the PrEP clinical form and/or any relevant documentation.

PrEP drugs exposure before positive HIV test

PrEP start date: dd / mm / yy **Date of HIV+ Test:** dd / mm / yy **Drug name (s):**

PrEP History

1. At the time of the positive test result, is the client still on PrEP?	Y Client is still on PrEP — Which PrEP method was used? Oral DVR CAB LA N Client is still on PrEP — (Specify date when the last PrEP dose was taken): dd / mm / yy
2. In the last 3 months, has the client been taking/using PrEP effectively? i.e. without missing a dose or intermittent DV ring use or missed a Cab LA injection	**Oral PrEP**: 0 Never missed; 1 Missed 1-6 days; 2 Missed >7 Days **DVR**: 0 Never missed; 1 Missed 1-6 days; 2 Missed >7 Days **CAB LA**: 0 Never missed; 1 Missed 1-28 days; 2 Missed > 1 month
3. What is the clients partner/s HIV status?	1 Partner/s is HIV negative; 2 Partner/s is HIV positive; 3 Don't know partner/s HIV status
4. Did client use a condom with partner/s?	1 Always 2 Sometimes 3 Never
5. Additional comments on circumstances relating to the seroconversion:	

Resistance Testing Results

Date	Comments:
dd / mm / yy	
dd / mm / yy	
dd / mm / yy	
Relevant medical history	

Job Aid 11: PrEP clinical form (Combined)

health
Department: Health
REPUBLIC OF SOUTH AFRICA

PrEP Clinical form (Initiation)

First name		Folder #	
Surname		Phone #	
DOB	dd / mm / yy **Gender:** M / F / TG	Address	
ID Number			

Instructions: Please use the below form to capture initiation, continuation, discontinuation, and re-initiation for **ALL** PrEP methods: Oral PrEP (TDF/FTC), Dapivirine ring (DVR), and Cabotegravir (CAB). If a client discontinues PrEP, continue the record with the corresponding date of discontinuation (section B). Should a client re-start or switch to another PrEP method, record with the corresponding date and PrEP method (section A), and all subsequent visits will be captured on this same form (section B). Additional clinical notes can be captured further below.

SECTION A: PrEP Initiation/Re-Initiation or Change of PrEP method

Date of Visit	HIV Test Result	PrEP Counselling Conducted?	PrEP Baseline Assessments					
			Weight (kg)	Pregnancy	Hepatitis B	STI Screening	Creatinine (eGFR/sCr)	PrEP method (*select one*):
/ /	+ / -	Y / N		+ / - / NA		+ / -		TDF/FTC: DVR: CAB
/ /	+ / -	Y / N		+ / - / NA		+ / -		TDF/FTC: DVR: CAB
/ /	+ / -	Y / N		+ / - / NA		+ / -		TDF/FTC: DVR: CAB
/ /	+ / -	Y / N		+ / - / NA		+ / -		TDF/FTC: DVR: CAB
/ /	+ / -	Y / N		+ / - / NA		+ / -		TDF/FTC: DVR: CAB
/ /	+ / -	Y / N		+ / - / NA		+ / -		TDF/FTC: DVR: CAB
/ /	+ / -	Y / N		+ / - / NA		+ / -		TDF/FTC: DVR: CAB

Original PrEP Initiation Date	/ /

Transfer in:	
Date: / /	**Clinic:**

SECTION B: PrEP continuation, monitoring and discontinuation

# of months on PrEP	Next visit date:	Actual visit date:	PrEP Method (*TDF/FTC, DVR, CAB*)	Test results (if applicable)						
				HIV Test	Weight (kg)	STI Screen	Pregnancy	Creatinine (eGFR/sCr)	Outcome (RIP, LTF, TFO, Sero, DNA, Disc)	Date of Outcome
0	/ /	/ /	TDF/FTC: DVR: CAB	+ / -		+ / -	+ / - / NA			/ /
1	/ /	/ /	TDF/FTC: DVR: CAB	+ / -		+ / -	+ / - / NA			/ /
2	/ /	/ /	TDF/FTC: DVR: CAB	+ / -		+ / -	+ / - / NA			/ /
3	/ /	/ /	TDF/FTC: DVR: CAB	+ / -		+ / -	+ / - / NA			/ /
4	/ /	/ /	TDF/FTC: DVR: CAB	+ / -		+ / -	+ / - / NA			/ /
5	/ /	/ /	TDF/FTC: DVR: CAB	+ / -		+ / -	+ / - / NA			/ /
6	/ /	/ /	TDF/FTC: DVR: CAB	+ / -		+ / -	+ / - / NA			/ /
7	/ /	/ /	TDF/FTC: DVR: CAB	+ / -		+ / -	+ / - / NA			/ /
8	/ /	/ /	TDF/FTC: DVR: CAB	+ / -		+ / -	+ / - / NA			/ /
9	/ /	/ /	TDF/FTC: DVR: CAB	+ / -		+ / -	+ / - / NA			/ /
10	/ /	/ /	TDF/FTC: DVR: CAB	+ / -		+ / -	+ / - / NA			/ /
11	/ /	/ /	TDF/FTC: DVR: CAB	+ / -		+ / -	+ / - / NA			/ /
12	/ /	/ /	TDF/FTC: DVR: CAB	+ / -		+ / -	+ / - / NA			/ /
13	/ /	/ /	TDF/FTC: DVR: CAB	+ / -		+ / -	+ / - / NA			/ /
14	/ /	/ /	TDF/FTC: DVR: CAB	+ / -		+ / -	+ / - / NA			/ /

Notes: Medical history/reason for discontinuation or change of PrEP method etc.

NB: Please affix any copies of additional notes or laboratory results that are necessary.

1

PrEP Clinical form

First name	
Surname	
DOB	dd / mm / yy **Gender:** M / F / TG
ID Number	

History:

Signature: _____ Date: _____

Name: _____

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