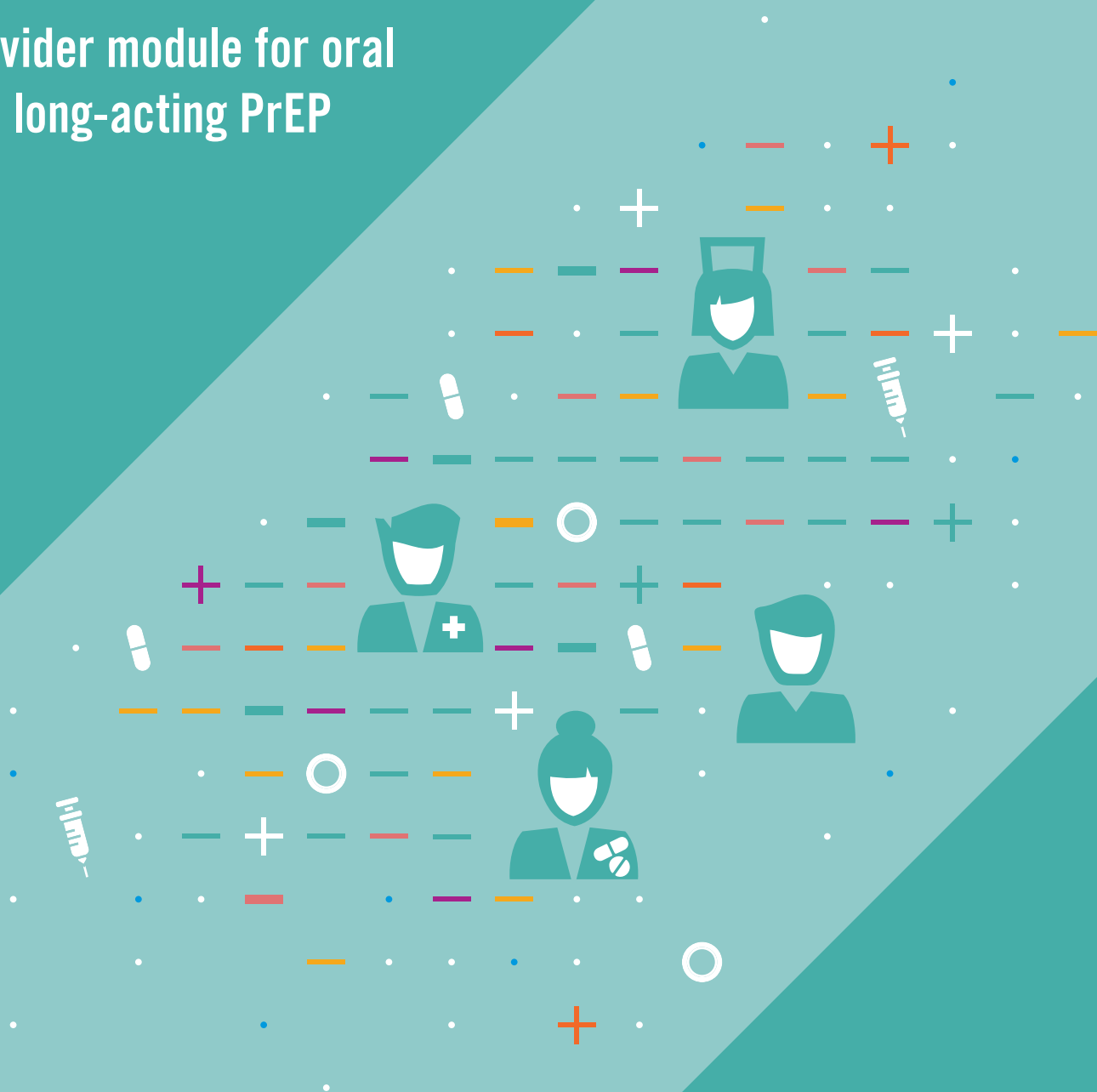


# WHO implementation tool for pre-exposure prophylaxis (PrEP) of HIV infection

Provider module for oral and long-acting PrEP





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**Provider module for oral  
and long-acting PrEP**

WHO implementation tool for pre-exposure prophylaxis (PrEP) of HIV infection: provider module for oral and long-acting PrEP

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## Abbreviations

AHI	acute HIV infection
ALT	alanine transaminase
ART	antiretroviral therapy
AST	aspartate transaminase
ARV	antiretroviral drugs
CAB	cabotegravir
CAB-LA	long-acting injectable cabotegravir
DSD	differentiated service delivery
DTG	dolutegravir
DVR	dapivirine vaginal ring
ED-PrEP	event-driven PrEP
eGFR	estimated glomerular filtration rate
EPT	expedited partner therapy
FTC	emtricitabine
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HIVST	HIV self-testing
INSTI	integrase strand-transfer inhibitor
MMD	multi-month dispensing
NAAT	nucleic acid amplification test
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
PEP	post-exposure prophylaxis
PrEP	pre-exposure prophylaxis
RCT	randomized controlled trial
RDT	rapid diagnostic test
SRH	sexual and reproductive health
STI	sexually transmitted infection
TB	tuberculosis
TDF	tenofovir disoproxil fumarate
TLD	tenofovir disoproxil fumarate, lamivudine, dolutegravir
VMMC	voluntary male circumcision
WHO	World Health Organization
3TC	lamivudine



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# Introduction to the WHO implementation tool for pre-exposure prophylaxis (PrEP) of HIV infection

WHO has developed the *WHO PrEP implementation tool*<sup>1</sup> as a series of modules in collaboration with community organizations, PrEP providers, implementers, researchers and other experts from all regions. The objective of the implementation tool is to support the implementation of oral and long-acting HIV PrEP for a range of populations and settings as an integral part of comprehensive HIV prevention approaches. The implementation tool can support PrEP uptake, persistence and effective use.<sup>2</sup> It can also assist efforts to achieve the global goals in the Global Health Sector Strategies on HIV, viral hepatitis and sexually transmitted infections for the period 2022–2030 (1) and global targets defined in the Political Declaration on HIV and AIDS, adopted by the United Nations General Assembly in 2021 (2).

Since the original publication of the WHO PrEP implementation tool modules in 2017 and 2018, WHO has released additional and amended guidance on PrEP and new WHO recommendations for long-acting injectable cabotegravir (CAB-LA) and the dapivirine vaginal ring (DVR). While some of the information in the previous modules may still be relevant, this Provider module for oral and long-acting PrEP is based on the latest WHO recommendations and evidence.

## Guiding principles

When offering PrEP, it is important to adopt an evidence-based, public health approach that is people-, community-, and human rights-centered.<sup>3</sup> Such an approach is aligned with principles of universal health coverage, gender equality and health-related rights; including accessibility, availability and quality of services for people who could benefit from PrEP.

PrEP should be promoted as a positive choice, in conjunction with other appropriate prevention interventions and services, including sexual and reproductive health (SRH) services. As an additional HIV prevention option, PrEP should not displace other effective and well-established HIV prevention interventions such as comprehensive condom programming, voluntary medical male circumcision (VMMC), and harm reduction for people who use drugs. Instead, it should be integrated into existing health services. Many people who could benefit from PrEP belong to key populations and often face legal, financial and social barriers to accessing health services. Legal environments in which the rights of people at substantial risk of HIV are violated may represent an important barrier to PrEP implementation. Efforts should address these barriers to ensure access to prevention, testing and care services for HIV and other STIs more broadly.

Placing the people and communities who could benefit from PrEP at the centre of design, planning and implementation allows services to be adapted to their preferences and sexual-health needs while maximizing impact and health system efficiency. The public health approach underpins WHO guidance on the provision of PrEP. However, the decision to use PrEP should always be made by the individual; and provision should follow national guidelines. Countries should ensure the relevant policies are in place to support rollout and scale-up of PrEP, accommodating the diverse preferences and needs of those who could benefit from it.

**PrEP should be promoted as a positive HIV prevention choice, in conjunction with other appropriate HIV prevention interventions and services.**

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<sup>1</sup> The WHO PrEP implementation tool modules are available at: <https://www.who.int/tools/prep-implementation-tool>

<sup>2</sup> Persistence refers to the consistency of taking PrEP over time after PrEP initiation. Effective use of PrEP refers to the appropriate use of PrEP during periods of HIV risk to achieve high levels of protection against HIV acquisition.

<sup>3</sup> People- or person-centered care is focused and organized around the health needs and expectations of people and communities rather than diseases. People-centered care is a principle of differentiated service delivery.

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# Introduction to the provider module for oral and long-acting PrEP

## Background and rationale

Since the first release of the *WHO PrEP implementation tool* in 2017, PrEP inclusion in national guidelines and PrEP service implementation have accelerated globally. Increasingly, countries have demedicalized, simplified, differentiated, digitalized and/or integrated PrEP services to increase uptake, persistence and effective use. Furthermore, WHO has recommended additional PrEP products – including long-acting formulations – as evidence of their safety and effectiveness has become available (see Box 1).

## Methods

This 2024 update of the *Provider module for oral and long-acting PrEP*, formerly the *Clinical module*, incorporates the recent WHO guidance on differentiated and simplified PrEP services (3), guidelines on services for key populations (4) and WHO recommendations on the DVR (5) and CAB-LA (6).

**Methodology for content development:** The internal working group and a small team of external experts reviewed the 2017 Clinical Module to identify outdated guidance, and evidence and guidance gaps. The document development was informed by the recent WHO guidance and recommendations, a literature review of relevant scientific publications in Pubmed was then performed, relevant conference abstracts sought, and recent clinical guidelines from national authorities and/or international technical organizations collected. Internal and external experts drafted the document and an external peer review process was conducted.

**Competing interests:** All external experts submitted to WHO a declaration of interest disclosing potential conflicts of interest that might affect, or might reasonably be perceived to affect, their objectivity and independence in relation to the subject matter of the guidance. WHO reviewed each of the declarations and concluded that none could give rise to a potential or reasonably perceived conflict of interest related to the subjects discussed at the meeting or covered by the guidance.

## Intended use

This module is intended to provide practical support to the range of people involved in providing PrEP, including physicians, nurses, clinical officers, community health workers, pharmacists and lay and peer providers, in either clinical or community settings. Countries and programs should adapt this guidance according to the individual setting, including relevant training materials for different types of providers involved in PrEP services.

The module outlines important considerations for the safe and effective provision of different PrEP products and dosing regimens for clients starting, continuing, stopping and restarting PrEP use. It also supports the provision of culturally competent, respectful and user-centric PrEP services. When PrEP providers consider the full range of health, social and emotional needs of those seeking and using PrEP, they can help to normalize PrEP as a responsible choice for sexual health, mental health and improved well-being. In this way, PrEP providers play an important role in reducing stigma and other barriers to equitable health services.

### Box 1. Key WHO recommendations on PrEP for HIV prevention

**2015:** Oral PrEP containing tenofovir disoproxil fumarate (TDF) should be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination HIV prevention approaches (strong recommendation, high certainty evidence (7)).

**2021:** The DVR may be offered as an additional prevention choice for women <sup>4</sup> at substantial risk of HIV infection as part of combination prevention approaches (conditional recommendation, moderate-certainty evidence) (5).

**2022:** CAB-LA may be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination prevention approaches (conditional recommendation; moderate-certainty evidence) (6).

Strength of recommendation and certainty of evidence as determined by the Guideline Development Group at the time when the recommendation was formed.

For WHO guidelines and guidance on PrEP, see list of suggested further reading.

PrEP: pre-exposure prophylaxis; TDF: tenofovir disoproxil fumarate; DVR: dapivirine vaginal ring; CAB-LA: long-acting injectable cabotegravir.

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<sup>4</sup> In the context of this recommendation, the term “women” applies to cisgender women, meaning individuals assigned female at birth. There is currently no research to support the DVR for other populations.

# Quick reference guide for PrEP providers

This section provides an overview of this provider module for oral and long-acting PrEP. Please refer to each section in the module for more information. PrEP providers can include physicians, nurses, clinical officers, community health workers, pharmacists, lay and peer providers and other cadres, in either clinical or community settings.

## WHO-recommended PrEP products



Oral PrEP (tenofovir disoproxil fumarate (TDF) 300 mg + emtricitabine (FTC) 200 mg OR TDF 300 mg + lamivudine (3TC) 300 mg tablets)



DVR (25 mg dapivirine impregnated silicone ring) – long-acting



CAB-LA (600 mg cabotegravir extended-release injectable suspension) – long-acting

PrEP should be offered to HIV-negative individuals who are at substantial risk of HIV acquisition as part of combination HIV prevention approaches. PrEP is not suitable (contraindicated) for:

- people living with HIV
- people indicated for post-exposure prophylaxis (PEP)
- people with suspected acute HIV infection (AHI) with a potential HIV exposure in the previous 14 days
- people with a contraindication, allergy or hypersensitivity to the PrEP product.



### Initial PrEP visit

**(most people can start the same day they come to the service)**

1. Identify individuals who could benefit from PrEP, for example:
  - a. Individuals who request PrEP; OR
  - b. Individuals with likely ongoing HIV exposure, which may include any of the following:
    - i. a sexual partner living with HIV who is not virally suppressed on HIV treatment;
    - ii. recent or probable future inconsistent use of condoms for vaginal or anal sex;
    - iii. a recent sexually transmitted infection (STI);
    - iv. recent PEP use for sexual exposure to HIV, especially for individuals who have used PEP more than once.
2. Test for HIV (only individuals who return a negative test result should be offered PrEP).
3. Assess for PEP (offer PEP if there is a probable exposure in the previous 72 hours).
4. Assess for AHI and probable recent exposure (assess any signs and symptoms in the context of probable exposures to HIV in the previous 14 days – decisions to initiate PrEP or defer should be made on a case-by-case basis).
5. Provide information on PrEP (for example, discuss client's concerns and goals, PrEP products and how to take them, side-effects, procedures for receiving PrEP and additional services that can be offered).
6. Assess for contraindications, allergies and hypersensitivities to PrEP.
7. Discuss PrEP products that are available.
8. Confirm willingness to use PrEP as directed and provide the chosen PrEP product.
9. Provide (or refer for) any of the suggested additional services appropriate to the PrEP product and client, for example STI screening. (Only the results of an HIV test are needed to start PrEP. Waiting for other tests should not delay starting PrEP as these may be performed and/or the results provided at a later visit).



## Follow-up PrEP visits (timing will depend on the PrEP product)

1. Test for HIV (only clients who have a negative test result should continue PrEP).
2. HIV self-testing (HIVST) may be appropriate for people using oral PrEP or the DVR to support effective use.
3. Check-in with the client (for example, discuss sexual health concerns and goals, key messages about PrEP, side-effects and intention to continue PrEP).
4. Assess for effective use of PrEP (assess for AHI and PEP if PrEP use was not effective).
5. Provide the chosen PrEP product.
6. Provide, or refer for, any of the suggested additional services appropriate to the PrEP product and client, for example, STI screening. (Only the results of an HIV test are required to continue PrEP. Waiting for other tests should not interrupt PrEP as these may be performed and/or the results provided at a later visit.)



## Key counselling messages

- All PrEP choices are effective HIV prevention options<sup>5</sup>.
- Effective use is important to prevent HIV acquisition (this means using PrEP according to the dosing schedule during periods of HIV risk).
- PrEP does not offer prevention against other STIs or pregnancy.
- PrEP products are generally safe and well tolerated. Side-effects are typically mild and resolve on their own and can be treated symptomatically. Severe side-effects should be reported to the PrEP provider without delay.
- Regular follow-up is important to support effective PrEP use and to provide other services including HIV testing. The follow-up visit schedule will depend on the PrEP product chosen.



## Key messages for PrEP providers

- Task sharing is a key component of differentiated service delivery (DSD) for PrEP and a variety of providers can safely and effectively deliver PrEP. More experienced or qualified PrEP providers have an important role in supporting other cadres.
- PrEP is not a lifelong commitment. People using PrEP can generally stop, start and restart PrEP as their needs and circumstances change. PrEP providers should empower clients to use PrEP effectively, including appropriate starting, stopping and restarting. PrEP providers should support clients who want to switch products and provide information about how to do this safely and effectively.
- Consider simplified and DSD options for PrEP to support persistent and effective use by increasing accessibility and acceptability for clients.
- Oral PrEP is safe during pregnancy and breastfeeding. Although there are limited data on the use of CAB-LA and DVR in pregnancy and breastfeeding, there has been no safety signal and neither product is contraindicated.
- Adopting a person-centered approach, where the PrEP service is tailored to the needs and preferences of the client, is important. Some people, such as adolescents and young people, may require additional support and benefit from more frequent contact with PrEP providers. Others could have additional considerations. For example, people who use drugs should be supported to receive harm reduction services alongside PrEP. Alternatively, some people may only want services directly related to PrEP. These needs and preferences may also change over time.

<sup>5</sup> Specific efficacy varies by PrEP product. Using PrEP as directed according to the dosing schedule for the specific PrEP product is important for high effectiveness.

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# Overview of PrEP

PrEP involves the use of antiretroviral drugs (ARV) by HIV-negative people to reduce the risk of acquisition of HIV. PrEP is recommended by WHO as an additional choice for people at substantial risk of HIV infection (see Box 2) as part of combination prevention approaches.<sup>6</sup>

The PrEP products currently recommended by WHO do not protect against other STIs or pregnancy<sup>7</sup>. However, PrEP services offer an opportunity to provide person-centred and comprehensive health services, addressing sexual and reproductive and other health needs of clients.

## Box 2. A note on substantial risk of HIV acquisition

HIV acquisition risk varies considerably within populations and geographical locations. Population-level HIV incidence is an important determinant of individual-level risk of HIV acquisition. However, when considering who could benefit from PrEP, it is important to consider the characteristics and behaviours of individuals and their partners that could lead to HIV exposure. Even in locations with a low overall HIV incidence, there may be individuals at substantial risk who could benefit from PrEP services.

Individuals requesting PrEP should be prioritized since requesting PrEP has been associated with a substantial risk of acquiring HIV (21, 59–61).

The cost-effectiveness of PrEP will vary across countries, populations and PrEP products. However, 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.

PrEP: pre-exposure prophylaxis; STI: sexually transmitted infection

DSD is key to a successful PrEP programme (see Box 3). Different types of providers can offer PrEP safely and effectively, including physicians, nurses, clinical officers, community health workers, pharmacists and lay and peer providers. PrEP can also be offered in a variety of settings - from traditional health care facilities to pharmacies and a variety of other community settings, such as drop-in centres and online and mobile settings.

## Box 3. DSD for PrEP

DSD is person- and community-centered. It is adapted to the needs and preferences of the people who are interested in and could benefit from PrEP. Differentiated PrEP services may make PrEP services more acceptable and accessible and support PrEP uptake, persistence and effective use. DSD for PrEP may also support more efficient and cost-effective use of health care resources. Delivery of person-centred health services is one of the key strategic directions of the global health sector strategies on HIV, viral hepatitis and STIs; and DSD is recognized as a key action (1).

WHO has published guidance to support differentiated PrEP services (3) using a framework of four building blocks of DSD: service location (“where”), frequency (“when”), package (“what”), and provider (“who”). Adaptations of the building blocks of service delivery may differ for PrEP initiation, continuation and re-initiation, as well as for various PrEP products. Examples of DSD adaptations include PrEP delivery that is community-, pharmacy-, and home-based (“where”), multi-month dispensing (MMD) to reduce follow-up visits (“when”), integrated services to address clients’ diverse health needs (“what”), and task sharing with various health worker cadres and lay providers, including key population- and community-led services (“who”) (3, 8–15). HIV self-testing for PrEP (HIVST) can support many of these differentiated PrEP service delivery models and allow fewer in-person visits (16, 17). Providers are also often supportive of DSD models for PrEP (18).

For further details, see WHO guidance on simplified and differentiated PrEP service delivery (3). WHO has also published guidance on integrating STI services into PrEP delivery (19).

PrEP: pre-exposure prophylaxis; DSD: differentiated service delivery; STI: sexually transmitted infection

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<sup>6</sup> Combination prevention refers to a combination of behavioural, biomedical and structural approaches to HIV prevention to achieve maximum impact on reducing HIV transmission and acquisition.

<sup>7</sup> Multipurpose PrEP products are in development, including combined PrEP and contraceptive.

## PrEP products and regimens

WHO has recommended three products for use as HIV PrEP (see Box 1): TDF-based oral PrEP, the DVR and CAB-LA. The choice of the product will depend on a range of factors including national guidelines, product availability and client preferences and characteristics.



### Oral PrEP containing TDF

TDF is a nucleoside reverse transcriptase inhibitor (NRTI) used in oral PrEP as well as for the treatment of both HIV (in combination with other drugs) and hepatitis B virus (HBV). TDF-based oral PrEP is safe and effective for the prevention of HIV acquisition from sexual exposure. When used as directed, oral PrEP can reduce the risk of HIV acquisition through sexual transmission by more than 90% (20–23) and pharmacological evidence suggests up to 99% (24, 25). Evidence is more limited of the efficacy of oral PrEP at preventing parenteral HIV acquisition, although pharmacokinetic/pharmacodynamic modelling suggests that oral PrEP could provide high levels of protection against HIV infection from injecting practices (26). TDF-based oral PrEP can therefore be an additional choice to complement comprehensive and evidence-based harm reduction for people who inject drugs (4).

### Antiretroviral regimens used for oral PrEP

The following regimens have been included under the WHO essential medicines list (27) and can be considered for use as oral PrEP:

#### Tenofovir disoproxil fumarate (TDF) 300 mg/ emtricitabine (FTC) 200 mg PO

TDF/FTC may be used to prevent HIV acquisition from either parenteral exposure or sexual exposures (vaginal and anal sex), including by those taking exogenous feminizing or masculinizing hormones. A fixed dose combination, where one pill contains both active drugs, simplifies oral PrEP use and reduces pill burden.

#### Tenofovir disoproxil fumarate (TDF) 300 mg/ lamivudine (3TC) 300 mg PO

WHO considers 3TC and FTC interchangeable, both for the prevention and treatment of HIV infection (27–29). This means that TDF/3TC or TDF/FTC may be used for PrEP. As with TDF/FTC, a fixed dose combination, where one pill contains both active drugs, simplifies PrEP use and reduces pill burden.

### Dosing regimens for oral PrEP

There are currently two dosing regimens for TDF-based oral PrEP. The dosing regimen to use depends on the person's characteristics, circumstances and the route of exposure.

**TDF/FTC and TDF/3TC are interchangeable for oral PrEP.**

#### Dosing regimen for most groups of people with sexual or injecting exposure

Fig. 1A depicts the dosing regimen for most groups of people including:

- cisgender women
- trans and gender diverse people assigned female at birth (including transgender men)
- trans and gender diverse people assigned male at birth (including transgender women) taking exogenous estradiol-based hormones
- people using oral PrEP to prevent HIV acquisition from injecting practices.

Whether the person intends to use PrEP for a short or long period of time, do as follows:

- Start PrEP with one dose of TDF-based oral PrEP per day for seven consecutive days prior to exposure to HIV. Alternative HIV prevention methods should be used during this time.
- Continue to take one dose per day for as long as taking oral PrEP is desired, and for at least seven days after the last potential exposure to HIV.

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This regimen is appropriate to reduce the risk of HIV acquisition through both sexual exposure and parenteral exposure.

**Dosing regimen for people assigned male at birth with sexual exposure and *not* taking estradiol-based hormones**

Fig. 1B depicts the dosing regimen for the following groups:

- cisgender men (including men who have sex with men and men who have sex with women) with sexual exposure to HIV
- trans and gender diverse people assigned male at birth (including transgender women) who are **not** taking exogenous estradiol-based (gender-affirming) hormones and with sexual exposure to HIV.

Whether the person intends to use oral PrEP for a one-off sexual exposure, or for a short or extended time, do as follows:

- Start by taking two doses 2–24 hours before sex. Ideally, this loading dose should be taken closer to 24 hours before sex to allow more time to absorb the PrEP.
- Continue taking one dose per day for as long as oral PrEP protection is desired AND for at least two days after the **last** potential sexual exposure.

This regimen is only appropriate to prevent the sexual acquisition of HIV.

Cisgender men and transgender women **not** taking gender-affirming hormones can adapt PrEP use to their HIV prevention needs and preferences. Some people may use PrEP for a single event (for example, sex on only one day), or for infrequent “single” events that are weeks or months apart. This is sometimes called event-driven PrEP (ED-PrEP) or 2+1+1.

If exposure to HIV continues for more than one day - or if an individual prefers to continue to take oral PrEP daily rather than stopping and restarting - they should take one dose of oral PrEP every day (sometimes called daily oral PrEP<sup>8</sup>) for as long as desired AND until at least two days after the last potential exposure. This means that ED-PrEP can become daily oral PrEP simply by extending the time a client takes PrEP; there is no difference in how to start or stop oral PrEP. There are several reasons why some individuals may prefer to take oral PrEP every day over a period of time rather than starting and stopping repeatedly. These include unpredictable exposures, finding a daily routine easier, or because taking oral PrEP every day will provide continuing protection, even if a dose is missed.

Irrespective of the dosing regimen, everyone should be empowered to safely start, continue, stop and restart oral PrEP in accordance with their preferences and likely exposures, to effectively prevent HIV acquisition. There is no time limit on how long a client can take oral PrEP, nor on the number of times a client can restart oral PrEP. If an individual stops taking PrEP (specifically, has more than two days without taking a dose), the next time they anticipate having sex or want to restart oral PrEP, they should their regimen again. If an individual misses a dose, they should take it as soon as they remember; but should **not** take more than two doses in one day.

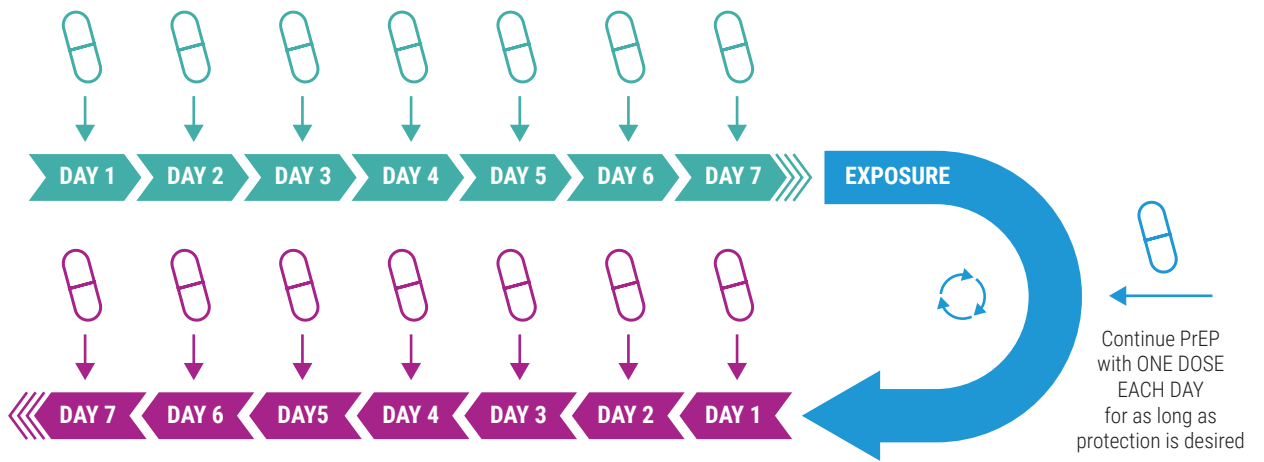
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<sup>8</sup> Daily oral PrEP, also called daily dosing, refers to taking one dose of oral PrEP every day over a period. For details on how to start or stop oral PrEP safely and effectively, refer to the population specific guidance outlined in this module.



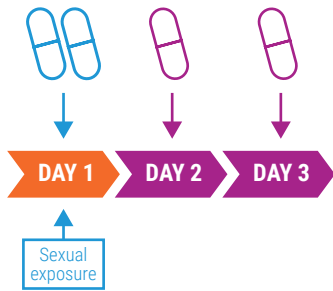
Fig. 1.

**A. Example oral PrEP dosing regimen for all other groups, including cisgender women, transgender women (taking gender affirming hormones) and people who inject drugs**

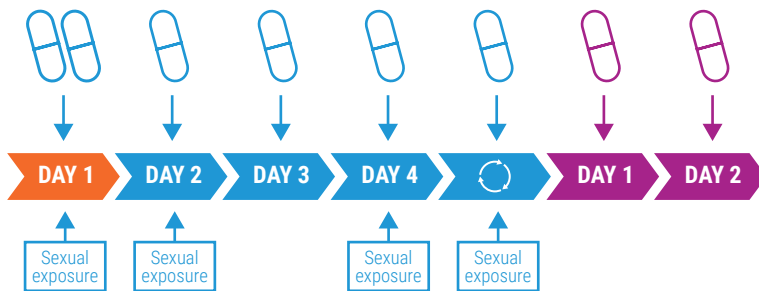


**B. Example oral PrEP dosing regimen for cisgender men and transgender women (not taking gender affirming hormones) with sexual exposure**

PrEP for a single event e.g. sex on 1 day



PrEP for multiple events or daily



Continue PrEP with ONE DOSE EACH DAY for as long as protection is desired

	Oral PrEP dose		Potential exposure covered by PrEP		Continuous PrEP taking with one dose each day
	Time to start PrEP before potential exposure		Time covered by PrEP		Time to stop PrEP after last potential exposure

Further details are available in the WHO technical brief *Differentiated and simplified pre-exposure prophylaxis for HIV prevention: update to WHO implementation guidance* (3).



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### **Possible side-effects**

Side-effects of oral PrEP are usually mild and may be experienced by 1 in 10 people in the first few weeks of use. The most common include:

- gastrointestinal symptoms (diarrhoea and nausea, decreased appetite, abdominal cramping and flatulence)
- dizziness
- headaches.

PrEP providers should advise a client considering PrEP that, in most cases, side-effects will resolve within the first month of use (where oral PrEP is continued daily) or will become milder over time (where PrEP is used periodically). Side effects can be managed symptomatically and usually resolve on their own without intervention or a need to discontinue PrEP. Clients should be advised to contact their PrEP provider if side-effects are severe, or if they become concerned. PrEP providers should refer to the product information leaflet for further information on side-effects.

### **Additional considerations, contraindications and drug-drug interactions**

Oral PrEP can be taken with or without food.

TDF, FTC and 3TC do not have any known interactions with contraceptive hormones and do not affect levels of estradiol-based exogenous (gender-affirming) hormones used by transgender individuals (30–32). There is some evidence that the use of estradiol-based gender affirming hormones may reduce oral PrEP drug levels (30, 31, 33). Therefore, individuals taking estradiol-based gender affirming hormones should take PrEP for seven days prior to exposure and continue with daily PrEP until seven days after the last exposure (as shown in Fig. 1B).

TDF, FTC and 3TC do not have interactions with most commonly used medicines and can be safely taken at the same time as antidepressants, tuberculosis (TB) and/or malaria medicines. There is no evidence that taking alcohol or recreational drugs such as heroin and other opioids, cocaine or methamphetamine concurrently with oral PrEP reduces the effectiveness of oral PrEP. For some people, excessive use of alcohol or recreational drugs may impede their ability to take oral PrEP as recommended, and PrEP providers should counsel and support people on effective use.

### **Oral PrEP and kidney function**

Known kidney impairment (indicated by an estimated glomerular filtration rate (eGFR) of under 60 mL/min per 1.73 m<sup>2</sup> or a creatinine clearance of less than 60 mL/min) is a contraindication for TDF-based oral PrEP (4). Evidence suggests that reduced kidney function is uncommon among PrEP users and particularly among people aged under 30 years. The likelihood of reduced kidney function increases with increasing age. While people taking TDF-based oral PrEP may have a higher risk of kidney related adverse events, these are typically mild, nonprogressive and reversible after stopping oral PrEP. Severe kidney related adverse events are rare.

Measuring kidney function is optional for those aged under 30 years without kidney-related comorbidities; and can be considered optional for people aged 30–49 years without comorbidities, particularly those aged 30–39, given the low risk of kidney impairment. More frequent screening (every 6–12 months) is suggested for individuals with comorbidities, those aged 50 years and older, and those with a previous kidney function test result suggesting at least a mild reduction in function (estimated glomerular filtration rate (eGFR) <90 mL/min per 1.73 m<sup>2</sup>).

Where required, kidney function tests can be performed within three months of initiation. Oral PrEP initiation should not be delayed while waiting for test results.

See Annex 1 and the WHO technical brief *Differentiated and simplified pre-exposure prophylaxis for HIV prevention: update to WHO implementation guidance* (3) for further details.



## The DVR

The DVR is a safe and effective option for cisgender women<sup>9</sup> to prevent HIV acquisition during vaginal sex. There is no evidence for the effectiveness of the DVR for any other transmission mode. Dapivirine is a non-nucleoside reverse transcriptase inhibitor (NNRTI). It is impregnated into a flexible silicone ring with an outer diameter of 56 mm and cross-sectional diameter of 7.7 mm. The DVR delivers dapivirine locally in the vagina and there is low systemic exposure (34). Evidence suggests that, when used correctly and consistently, the DVR reduces HIV risk by over 50% (35, 36), and some analyses have found a higher effectiveness (35, 37). As with oral PrEP, effective use of the DVR (consistent and continuous use during periods of potential HIV exposure) is critical for effectiveness.

### **Dosing regimen**

The DVR, which contains 25 mg of dapivirine, can be inserted and removed by the client or with provider assistance. PrEP providers should offer to help all clients for the first insertion. Some clients, particularly young women, may prefer assistance with additional insertions, and/or may benefit from assurance that the DVR has been inserted correctly, particularly early in use. Guidance on inserting and removing the DVR is outlined in the product information leaflet provided with the DVR. Training resources have also been produced (38) that may be helpful for PrEP providers.<sup>10</sup>

The DVR should be worn for 24 hours prior to exposure to HIV. The DVR is designed to be worn continuously in the vagina for one month<sup>11</sup> until it is replaced with a new ring. To maintain efficacy, a new DVR should be inserted immediately after a previous ring has been removed. The DVR should not be removed prior to, during, or immediately after vaginal sex. In the case of accidental expulsion or removal of the DVR, the DVR can be rinsed in clean water and immediately reinserted if the ring has not been exposed to an unhygienic environment, or the client can replace it with a new DVR. Levels of dapivirine in the vagina drop quickly and other prevention options should be used if another DVR is not inserted immediately.

### **Possible side-effects**

Side-effects of the DVR are usually mild and may be experienced by up to 1 in 10 people. The most common side-effects can include:

- urinary tract infections
- inflammation of the vagina, vulva or cervix
- vaginal discharge
- vaginal or vulvar itching
- pelvic or lower abdominal pain.

Clients should be advised that side-effects are uncommon. If they do occur, it is usually in the first month of use. Side-effects can be managed symptomatically and will usually resolve by themselves without the need to remove the ring. PrEP providers should counsel clients on possible side-effects and advise clients to contact their PrEP provider if severe or if they become concerned. PrEP providers should refer to the product information leaflet for further information on side-effects.

### **Additional considerations, contraindications and drug–drug interactions**

Given that there is low systemic exposure to dapivirine with use of the DVR, the risk of systemic medication interactions is considered low.

There are no known interactions between dapivirine and contraceptive hormones, alcohol or recreational drugs. There are no data on concurrent use of the DVR and other vaginal rings (such as contraceptive rings or diaphragms) and these vaginal products should **not** be used together. There is insufficient evidence from trials around interactions between the DVR and use of gender-affirming hormones; however, interaction is unlikely. The DVR can be used safely with both external (also called male) and internal (also called female) condoms.

<sup>9</sup> In the context of the 2021 WHO recommendation, the term “women” applies to cisgender women, meaning individuals assigned female at birth. There is currently no research to support the DVR for other populations.

<sup>10</sup> The “Dapivirine Vaginal Ring “PrEP Ring” Clinical Training for Providers” provides detailed information on how to deliver the DVR.

<sup>11</sup> A month is defined as approximately 28 days.

For clients with a known STI at the time of initiation, treat any STIs according to local guidelines. If only mild symptoms are present, offer the DVR. If there is severe ulceration, pain or discharge, delay providing the DVR until symptom resolution, and advise to use alternative HIV prevention methods. Once the DVR has been inserted, STIs can generally be diagnosed and treated without its removal. Due to a lack of data, concurrent use of the DVR and vaginally administered antimicrobial products, including vaginal metronidazole or clindamycin, should be avoided. Concurrent use of vaginally administered clotrimazole and the DVR has been reported to be safe and well tolerated (39), but data remain limited, and concurrent use should be undertaken with caution. Co-administration of vaginally administered miconazole with the DVR has been studied in one trial (40) and data are limited. Additional HIV prevention options, such as condoms, should be offered during co-administration. Consider if there are alternatives available for treatment of candida.

There is no evidence that taking alcohol or recreational drugs concurrently with the DVR reduces the DVR effectiveness. For some people, excessive use of alcohol and recreational drugs may impede their ability to use the DVR as recommended and PrEP providers should counsel and support clients with effective use.



### CAB-LA

CAB-LA is a safe and highly effective prevention option for the prevention of HIV acquisition through sexual exposure (41). Cabotegravir (CAB) is an integrase strand-transfer inhibitor (INSTI) used in the prevention and treatment of HIV infection. Evidence from clinical trials suggests that, when administered correctly and on schedule, CAB-LA may reduce the risk of HIV acquisition by 79% compared with use of oral PrEP (41).<sup>12</sup> It is important to note that oral PrEP when used as directed is already highly effective. The higher relative reduction in HIV risk infections in the CAB-LA arms compared with TDF/FTC is likely influenced by differences in adherence to the dosing schedule, as it is well documented that oral PrEP efficacy is highly dependent on adherence. In both trials >95% of the incident infections in the TDF/FTC arm occurred in people with poor or non-adherence to TDF/FTC. Modelling studies suggest an overall efficacy for CAB-LA of 93–94% (42), which is similar to the efficacy reported in oral PrEP trials.

**Both Oral PrEP and CAB-LA are highly effective in preventing HIV acquisition. The greater efficacy of CAB-LA in the randomized control trials (RCTs) is likely due largely to better adherence to the injectable CAB-LA than to the oral TDF/FTC.**

People who inject drugs were not explicitly included in the clinical trials on CAB-LA, but animal models suggest that CAB-LA may be effective for parenteral exposure (43). People who use drugs will also benefit from CAB-LA for sexual exposure as part of comprehensive harm reduction services.

### Dosing regimen

CAB-LA is a cabotegravir extended-release injectable suspension (3 ml) at a dose of 600 mg. CAB-LA is administered as a gluteal intramuscular injection (44).<sup>13</sup> Injections are administered one month apart for the first and second injections (sometimes called initiation injections) and every two months thereafter (sometimes called continuation injections) for as long as the client wants to remain on CAB-LA.<sup>14</sup>

Ideally, a client with ongoing HIV exposure who opts for CAB-LA would have the following injection schedule:

1. First injection: month 0.
2. Second injection: one month (+/- 7 days)<sup>15</sup> after the first injection.
3. Third and subsequent injections: two months (+/- 7 days)<sup>16</sup> after the previous injection.

PrEP providers should explain to clients the importance of following the injection schedule closely to maintain effective levels of CAB-LA. Although the time between the first injection and achieving maximal protection against HIV acquisition is not currently known, the available evidence suggests that most individuals will reach high levels of protection within 7 days.

<sup>12</sup> While both TDF-based oral PrEP and the DVR were compared to placebo to evaluate efficacy, phase 3 efficacy trials (HPTN 083 and HPTN 084) compared CAB-LA to oral TDF/FTC. As such the efficacy measures are not directly comparable.

<sup>13</sup> The *Provider training toolkit on use of CAB for PrEP* provides detailed information on how to administer CAB-LA: [www.jhpiego.org/HIVPrEPToolkit](http://www.jhpiego.org/HIVPrEPToolkit)

<sup>14</sup> A month is defined as approximately 28 days.

<sup>15</sup> Clients may be given CAB-LA up to seven days before or after the scheduled date for the injection.

<sup>16</sup> Ibid.

Individuals transitioning from oral PrEP or the DVR should continue using that method for the first 7 days after starting CAB-LA. All other individuals should use alternative HIV prevention methods during the first 7 days.

When a person stops CAB-LA, cabotegravir remains in the body for a prolonged period (up to one year) (45) with concentrations slowly declining. This is referred to as the “pharmacokinetic tail” or “tail period”. During the tail period, cabotegravir concentrations become gradually less protective against HIV acquisition, particularly after more than 2 months, and HIV infections may occur. Alternative HIV prevention options should be considered after CAB-LA is stopped.

There is currently no evidence to support an alternative dosing schedule for CAB-LA (46). Table 1 lists suggested procedures if a client misses a scheduled injection visit. Daily oral CAB (30 mg) lead-in was provided prior to the first injection during the clinical trials<sup>17</sup> to minimize the risk of allergy and severe adverse events. This became optional in the open label extension studies as there were no safety concerns and will likely not be required by national programs.

**Table 1. Suggested procedures for clients who miss a scheduled CAB-LA injection.**

Time since last injection	Suggested procedure
For second “initiation” injection	
≤2 months	Administer the CAB-LA injection as soon as possible and continue with injections every two months.
>2 months	<b>Restart the client on CAB-LA</b> by providing one injection followed by the next dose one month later. Subsequent injections are two months apart.
For third and subsequent injection(s):	
≤3 months	Administer the CAB-LA injection as soon as possible and continue with injections every two months.
>3 months	<b>Restart the client on CAB-LA</b> by providing one injection followed by the next dose one month later. Subsequent injections are two months apart.

CAB-LA: Long-acting injectable cabotegravir.

Adapted from (47). One month is approximately 28 days. Clients who have missed a CAB-LA injection and do not wish to restart CAB-LA should be counselled on other PrEP and HIV prevention options.

### **Possible side-effects**

Side-effects are usually only mild or moderate and are experienced by very few users. The most common side-effects of CAB-LA include:

- injection site reactions
- headache
- nausea
- diarrhoea
- tiredness.

<sup>17</sup> In the randomized controlled trials (RCTs), a daily oral cabotegravir lead-in for five weeks was provided prior to the first injection to minimize the risk of allergy and other severe adverse events. No allergic reactions occurred in the RCTs. The oral lead-in became optional in the open label extension studies as no safety concerns were observed. The oral lead-in may not be required by national programs offering CAB-LA. Research is ongoing on potential differences in the pharmacokinetics of CAB-LA without the oral lead-in period.

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Side-effects can be managed symptomatically and most will resolve within the first month of use. Mild or moderate injection site reactions (particularly pain, tenderness and swelling at the injection site) are more common than other side-effects but usually decrease over time. PrEP providers should counsel clients on possible side-effects and advise clients to contact their PrEP provider if they are severe or if the client becomes concerned. PrEP providers should refer to the product information leaflet for further information on side-effects.

### ***Additional contraindications and drug-drug interactions***

Based on the limited data available, cabotegravir may interact with some medicines used to treat TB (rifampicin and rifapentine), some anticonvulsants (carbamazepine, oxcarbazepine, phenobarbital and phenytoin) and may result in subtherapeutic concentrations of CAB-LA. These should not be co-administered with CAB-LA. If these medicines are started when someone has already taken CAB-LA (for example, a client who is diagnosed with TB) they should be advised of the drug-drug interaction and about additional HIV prevention methods.

There are no known interactions between CAB-LA and contraceptive hormones and, based on the limited evidence available (48), there are no expected interactions with gender-affirming hormones.

There are no known interactions between CAB-LA and alcohol or recreational drugs; though alcohol and drug use could impact the ability to attend necessary health appointments, potentially resulting in missed injections. PrEP providers should support clients to ensure adherence to the injection schedule as needed.

### ***CAB-LA, hepatitis and liver function***

Evidence for the use of CAB-LA among people with HBV or hepatitis C virus (HCV) is very limited.<sup>18</sup> CAB-LA should not be initiated in people with advanced liver disease or acute hepatitis. Clients with suspected hepatotoxicity should discontinue CAB-LA.<sup>19</sup>

Consistent with other PrEP products, testing for HBV and HCV and further assessment of clients with reactive test results, including appropriate treatment as clinically indicated and according to WHO guidance (53, 54), is strongly encouraged. CAB-LA is not active against HBV or HCV. Clients with HBV and/or HCV should be assessed on a case-by-case basis and, where possible, managed jointly with HBV and/or HCV specialized clinicians. In consultation with an HCV and/or HBV specialised clinician, consideration should be given to offering clients eligible for HBV treatment as per WHO guidance (54), TDF-based oral PrEP as the preferred PrEP product, given the dual role of HIV prevention and suppressing HBV infection.

The risks of hepatotoxicity due to CAB-LA are likely small. Liver function testing is not required for CAB-LA and may represent barriers to implementation of PrEP services offering CAB-LA. Where available, liver function testing – such as measuring alanine transaminase (ALT) – can be considered before and during CAB-LA use and may be limited to when liver impairment is suspected, such as in the context of high alcohol use. CAB-LA initiation should not be delayed while waiting for the test results.

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<sup>18</sup> In the HPTN 083 and HPTN 084 clinical trials, people with HBV and HCV were excluded from participation, and data for these populations are limited.

<sup>19</sup> In the HPTN 083 and HPTN 084 clinical trials, a small number of people receiving CAB-LA experienced severe adverse events involving elevated liver enzymes (aspartate transaminase (AST) and/or ALT) (49, 50). However, the incidence was similar to those receiving TDF/FTC. A similar incidence of liver-related adverse events was found among users of TDF-based oral PrEP (51). Hepatotoxicity is rare in people living with HIV taking INSTI class antiretrovirals, such as dolutegravir (52).



## Starting PrEP

*This section outlines how to provide the three currently available PrEP products. In general, the same steps are followed for all products. Where there are special considerations for a specific product, these have been highlighted.*

PrEP may be a suitable and preferred HIV prevention option for a variety of clients. Irrespective of the product chosen, PrEP providers should consider PrEP for clients who are:

- requesting PrEP OR identified by a PrEP provider as someone who could benefit from PrEP
- HIV-negative<sup>20</sup>
- not indicated for PEP
- not suspected of AHI with a probable recent HIV exposure in the previous 14 days<sup>21</sup>
- not contraindicated to the PrEP product or who do not have an allergy or hypersensitivity to any ingredient in the PrEP product<sup>22</sup>
- willing and able to use PrEP as directed.

Most clients can start PrEP on the same day (see Box 4). The suggested clinical procedures for oral PrEP, the DVR and CAB-LA are outlined in Table 3 and Table 4 respectively. Suggested additional procedures at PrEP initiation and follow-up are outlined in Table 5.

### Box 4. Same-day PrEP

Most people can start PrEP on the same day they come to the clinic or PrEP service (sometimes called same-day PrEP initiation). Offering same-day PrEP may increase uptake among people who could benefit from PrEP (55–58). People requesting PrEP – even if they do not disclose to the PrEP provider details about their potential risk – are likely to meet criteria for substantial risk (21, 59–61), and to have made a choice to use PrEP based on their personal circumstances, ongoing HIV risk and prevention preferences.

In some cases, delaying PrEP may be preferable or required. This can include where the individual is eligible for PEP or AHI is suspected. Alternatively, individuals not previously familiar with PrEP may want additional time to decide whether they want to use PrEP or another HIV prevention option and/or which PrEP product. PrEP providers should ensure mechanisms are in place to follow up and support such clients (for instance, using telehealth).

PrEP services offering same-day initiation must be able to test for HIV, or have the results of HIV testing, including through an HIVST, prior to the individual starting PrEP, and be able to prescribe PrEP drugs. In addition, at the time of the first visit, they should be able to perform or order any other tests indicated at initiation, and they must confirm that the client can be contacted, for example, via telephone, email or SMS, if test results require additional confirmation or treatment prior to the next scheduled visit.

PrEP: pre-exposure prophylaxis; STI: sexually transmitted infection



### Identifying clients who can benefit from PrEP

WHO recommends PrEP for people at substantial risk of HIV (see Box 2). Clients who can benefit from PrEP may present to services requesting PrEP or may be identified by a PrEP provider as someone who could benefit from PrEP.

PrEP providers can take a sexual and drug use history, which should be non-judgemental, for all clients requesting PrEP or HIV, STI and other sexual health or related services. A sexual and drug use history can also help identify people who could benefit from PrEP who did not specifically come to the service for PrEP.

<sup>20</sup> The ARVs used for PrEP are not sufficient for HIV treatment. People living with HIV should be started on ART as soon as possible.

<sup>21</sup> For the DVR, suspected AHI is not a contraindication given the low systemic absorption, and that there is no evidence of HIV drug resistance associated with DVR use.

<sup>22</sup> Consider a different PrEP product or prevention option for these clients.

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Questions or prompts should be used to facilitate a discussion to gather relevant information on sexual partners, sexual practices, use of and preferences for prevention, drug use (including chemsex<sup>23</sup>), STIs and sexual health concerns and goals. These types of questions should **not** be used to ration PrEP or exclude people from PrEP services, but instead used to support clients to make informed choices about HIV prevention. Providing details of past or current sexual behaviour or drug use is not required to access PrEP. PrEP providers should also consider whether recording stigmatized or criminalized behaviours may put clients in danger and, if so, take appropriate precautions.

As the risk of HIV acquisition varies substantially between individuals, all clients should be assessed on an individual basis. PrEP providers should place a stronger emphasis on possible future exposures to HIV than on a client's history when considering PrEP. Local epidemiology, including the incidence and prevalence of HIV within a geographic area and population, may also guide decisions about when to offer PrEP and to whom. PrEP providers should be particularly aware that people who could benefit from PrEP may include clients with:

**Risk-based assessment tools should never be used to exclude someone from HIV PrEP, especially if they have stated concerns about HIV and are motivated to use it.**

- inconsistent condom use (for example, within the last six months<sup>24</sup>) for vaginal or anal sex, intention to use condoms inconsistently, or anticipating that condoms may not be used consistently
- a recent<sup>25</sup> STI by laboratory testing, self-report or syndromic STI screening<sup>26</sup>
- recent<sup>26</sup> PEP use for a sexual exposure, especially individuals using PEP more than once
- a sexual partner(s) living with HIV who is not virally suppressed on ART.

Inconsistent use of condoms, including an intention to use condoms during sex but with some occasional omissions or accidents, increases HIV risk (62). PrEP providers should also be aware that biased reporting of condom use may occur. For example, someone may overestimate their condom use due to a fear of judgement from a provider, or someone who reports a desire to stop using condoms may already be having sex without condoms. PrEP should therefore be considered for people reporting any sex without a condom, anticipating sex without a condom or who are uncertain about future condom use. PrEP providers should also be aware that individuals may not always be able or willing to negotiate HIV or STI prevention with their partner/s, including condom use. This may be because of power imbalances with sexual partner/s, or could include reduced ability to negotiate while taking drugs or alcohol (including during chemsex).

**It is important for PrEP providers to be sensitive, inclusive and non-judgemental. Questions should always be framed in terms of people's behaviour, not in terms of their sexual identity or orientation, and should focus on specific timeframes, such as the previous three or six months.**

PrEP can protect an HIV-negative person in a serodiscordant relationship when the partner living with HIV is either not on ART or is not virally suppressed. ART that suppresses viral load is highly effective for preventing onward HIV transmission (63). However, PrEP may provide additional protection to serodiscordant couples in several situations.

- ART may take up to six months to suppress the viral load. In studies of serodiscordant couples, PrEP has provided a useful bridge for the HIV-negative partner until full viral suppression of the partner living with HIV is reached (64).
- The client has doubts about the effectiveness of their partner's HIV treatment or has additional sexual partners.
- The client suspects their partner has imperfect HIV treatment adherence or the couple is not communicating openly about treatment adherence and viral load test results.

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<sup>23</sup> In this document, chemsex is defined as when individuals engage in sexual activity while taking primarily stimulant drugs, typically involving multiple participants and over a prolonged period. Individuals engaging in chemsex may be at an increased risk of HIV and other STIs as it has been associated with condomless sex and unsafe injecting.

<sup>24</sup> The timeframe used should be based on local factors, which may include the recommended frequency of HIV testing and local epidemiology; however, timeframes longer than six months may be more likely to suffer from recall bias.

<sup>25</sup> Definitions of "recent" vary between local guidelines, with three and six months most common definition used. The timeframe used should be based on local factors, which may include the recommended frequency of HIV testing and local epidemiology; however, timeframes longer than six months may be more likely to suffer from recall bias.

<sup>26</sup> A new STI diagnosis (for example, syphilis, gonorrhoea, chlamydia or genital herpes) can indicate a higher risk of HIV acquisition among key populations in most settings, and among heterosexual adults and adolescents in areas of high HIV prevalence.



PrEP may also be beneficial during pregnancy or the postpartum period, including during breastfeeding due to the increased HIV risk (65–67). HIV acquisition during pregnancy or while breastfeeding also increases risk of vertical transmission to infants (67). The amount of safety data available varies depending on the PrEP product; as such, counselling on PrEP use during pregnancy and breastfeeding should include appropriate risk/benefit counselling (see Special considerations for specific situations and populations for more detail).

### Box 5. A note on risk-based assessment tools

Risk-based assessment tools can be effective in guiding a conversation between a PrEP provider and client about a possible HIV exposure, HIV and STI prevention and whether to consider PrEP (68). Self-assessment tools can also be used to help individuals decide whether PrEP is a beneficial HIV prevention choice. While tools have been developed and validated with strong results, many have only low to moderate ability to identify substantial HIV risk (69). Risk-based assessment tools should **not** be used to exclude people from PrEP services or discourage PrEP use. Some individuals may not feel comfortable discussing behaviours or experiences that increase their risk of HIV acquisition, especially where there is a risk of stigma, discrimination and/or criminalization. Therefore, PrEP should be offered as an additional HIV prevention choice to anyone who requests it and for whom it is suitable, regardless of the results of any assessment tool.

PrEP: pre-exposure prophylaxis; STI: sexually transmitted infection

**People requesting PrEP.** Requesting PrEP has been associated with a substantial risk for HIV and other STIs (21, 59–61, 70). PrEP providers should be aware that an individual requesting PrEP may not wish to disclose the reason for requesting it (i.e. the HIV risk), especially in settings where there is criminalization, stigma and/or discrimination. PrEP providers should consider any request for PrEP seriously (67), especially for people in settings where the local epidemiology indicates likely substantial HIV risk in their population group.

### HIV testing

Only individuals who are HIV-negative should use PrEP. To rule out existing HIV infection, a negative HIV test is required before starting or restarting any PrEP product.<sup>27</sup> Ideally, HIV testing should be performed and results provided on the same day that PrEP is offered to facilitate same-day initiation of PrEP.

HIV testing can be conducted according to the standard WHO testing strategy for HIV diagnosis (5) using the national testing algorithm, usually composed of quality-assured serology assays using the WHO serial three test strategy with rapid diagnostic tests (RDTs) (see the WHO *HIV testing services guidelines* (71). A non-reactive result for the first test in the national algorithm is sufficient to start PrEP for all products.

**HIV infection should be ruled out by testing.**



#### **HIVST for PrEP**

HIVST use can be considered with oral PrEP and the DVR to simplify and support DSD for PrEP. WHO recommends that HIVST can be used to support clients when first initiating PrEP, re-starting, or continuing PrEP (conditional recommendation, low certainty evidence) (71).



HIVST can be used to replace provider-administered testing in several scenarios (Figure 2). For example, to replace clinic-based testing for starting, restarting or during PrEP use (i.e. as prescribed), based on evolving needs including making decisions about stopping or restarting PrEP (i.e. as needed) and as desired by clients between PrEP visits to give reassurance and confidence, and/or support effective use (3). HIVST may be particularly useful for PrEP services outside health care facilities, such as in pharmacies or in the client's home (3, 71–74) and may be an important tool to reach underserved populations (71, 72).

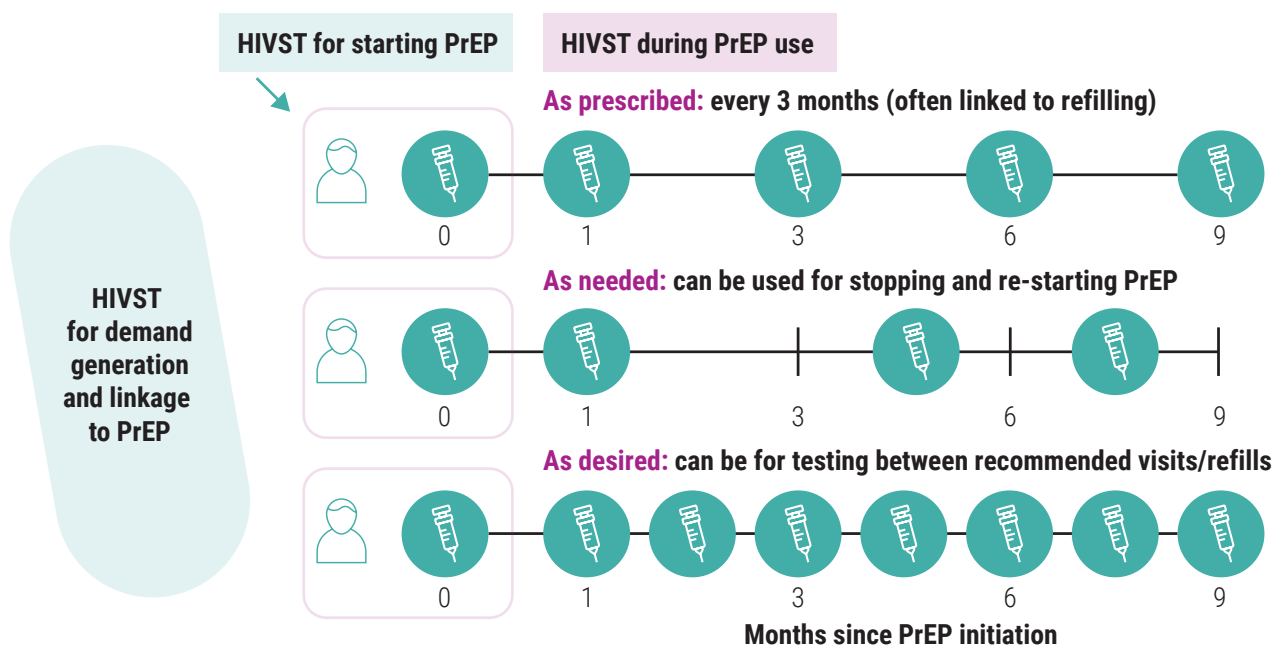
<sup>27</sup> Since oral PrEP use can be dynamic, and individuals may start, stop and restart oral PrEP in accordance with their HIV prevention needs, HIV testing should be done at each scheduled follow-up visit, regardless of whether the client takes PrEP for a single event, multiple events or every day. Additional HIV testing can be offered between visits based on individual client needs.



The use of HIVST should always be an individual's choice. HIVST may be preferred for convenience, privacy and self-managed prevention. Clients should also have the choice between oral fluid-based and blood-based kits if both are available.

HIVST is not currently recommended for CAB-LA and further research is needed.

Fig. 2.



### Assessing for PEP

PEP is the use of ARVs by HIV-negative individuals to prevent HIV acquisition **after** a possible HIV exposure. People who come to PrEP services may have had an exposure to HIV within the previous 72 hours (for example, condomless sex<sup>28</sup> or parenteral exposure). PrEP providers should assess the likelihood of exposure, offer standard HIV testing or an HIVST and, if negative, offer PEP without delay.<sup>29</sup>

PEP should be taken daily for 28 days. WHO recommends that a PEP regimen with two ARV drugs is effective, but the use of three drugs is preferred (conditional recommendation, low certainty evidence) (5). The preferred ARV regimen for adults and adolescents is TDF+3TC (or FTC) (strong recommendation, low certainty evidence) with dolutegravir (DTG) as the third drug (strong recommendation, low certainty evidence) (5).

Refer to the 2021 WHO consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring (5) and the WHO guidelines on PEP for further information.<sup>30</sup>

PrEP providers should also discuss whether the client may benefit from PrEP and options for transitioning from PEP to PrEP.

### PEP to PrEP transition

Individuals can start PrEP without a gap after completing a 28-day PEP regimen **if** they have a negative HIV test result and do not have any contraindications to the PrEP product chosen. Immediate transition to PrEP is preferable for individuals with ongoing exposure to HIV since PrEP is likely to be more effective and can avoid the need for repeat PEP use. Individuals transitioning from PEP to any PrEP product can be managed the same as any other client on PrEP.

PEP should be easily accessible to ensure quick initiation for those who could benefit from it.

Individuals who access PEP may benefit from PrEP and can be immediately transitioned to PrEP following a negative HIV test result at the end of the PEP course.

<sup>28</sup> PEP is not required for sex with a person living with HIV who has a confirmed undetectable viral load or where the client's sexual partner is confirmed to be HIV negative. The risk of HIV exposure should be assessed on a case-by-case basis. Refer to local guidelines for further details.

<sup>29</sup> PEP is most effective when taken within 24 hours after an exposure, and so should be started as soon as possible.

<sup>30</sup> WHO is updating the guidance on PEP in 2024.

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## Assessing for AHI

PrEP providers should take an appropriate symptom and exposure history to assess for AHI. AHI is often symptomatic, including fever, rash, sore throat, aches and pains, lymphadenopathy (swollen glands), mouth sores and/or headache. However, these symptoms are not specific to AHI and most individuals will have an infection other than HIV (59, 75). For this reason, PrEP providers should also assess the client for possible recent exposures to HIV (for example, sex without condoms) within the last 14 days.

Optimal diagnosis and management of AHI will depend on the resources available, and the PrEP provider will need to make a clinical judgement. If the PrEP provider judges the exposure as low risk, PrEP can be initiated. If AHI is suspected and a decision is made to defer PrEP, the client can be retested after four weeks, which is generally sufficient to detect seroconversion. It is critical to accurately establish HIV infection prior to starting a client on ART. Where a PrEP provider is inexperienced or non-clinical, they should consult with more experienced PrEP providers. Counselling the client is crucial to ensure that the client has a good understanding of the decision to defer PrEP and what it means for them; including the need to use other HIV prevention methods during this time to protect themselves and their partners.

The potential risks and benefits of offering PrEP should be evaluated on a case-by-case basis, taking into consideration a range of factors including the chosen PrEP product,<sup>31</sup> the risk of HIV acquisition if PrEP is deferred and the risk of HIV drug resistance if PrEP is started during AHI.

Typically, the benefits of providing PrEP to prevent HIV acquisition outweigh the risks of potential drug resistance because: (i) AHI is rare and most suspected AHIs are not due to HIV, and (ii) PrEP is highly effective in preventing HIV infection that would otherwise require life-long therapy, associated with an annual risk of virological failure and drug resistance (75–77).



Given that AHI is rare and that there is low systemic exposure to dapivirine while using the ring, the risk of HIV drug resistance is likely to be low. The DVR can be offered to individuals with suspected AHI, but the PrEP provider should schedule the next follow-up visit for one month (rather than three months) so that follow-up HIV testing can be performed. PrEP providers should emphasize the importance of attending this follow-up visit with the client.



The impact of starting CAB-LA with AHI on delayed diagnosis, drug resistance and future treatment options is not well understood, and a more cautious approach may be considered. Further data will become available as implementation studies involving CAB-LA are conducted. Currently WHO recommends programs use standard HIV testing strategies with RDTs. However, if resources allow, NAAT could be considered among people with clinical signs and symptoms of AHI (78). Another option for people with suspected AHI is to defer PrEP and repeat antibody testing after four weeks, which is sufficient time for seroconversion to be detected with the commonly available third generation tests. In case of potential HIV exposure, people should be advised to use another HIV prevention method, for example condoms, during this time.

## Assessing contraindications for the client's preferred PrEP product

For all PrEP products being considered by the client, PrEP providers must assess individuals for product-specific PrEP contraindications, including allergy or hypersensitivity to any active ingredient or other substance listed in the product information sheet. Clients may decide on their preferred product during the visit, so this assessment may take place before, during or after other counselling.

## Providing information on PrEP choices

PrEP providers should adapt their approach to counselling to the client's individual preferences and needs (see Box 6). Someone who is considering PrEP for the first time may require a more in-depth discussion than someone who has used PrEP previously. In general, the discussion should be positive, focusing on achieving the client's goals for health, well-being and HIV protection (this is sometimes referred to as "gain-framing" messaging) (79).

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<sup>31</sup> The benefits of starting PrEP are likely to outweigh the risks (for example, drug resistance) for oral PrEP and the DVR in most cases. As following injection of CAB-LA, cabotegravir remains within the body for a prolonged period, it will have a different risk-benefit profile, including regarding drug resistance. For further details refer to the WHO guideline on CAB-LA (6).

Counselling can include a focus on increasing awareness of PrEP as a HIV prevention option, including the different PrEP products available, as well as helping the client to decide whether PrEP is the right choice for them. For clients interested in PrEP, PrEP providers can provide appropriately detailed information on how to use the chosen PrEP product(s), as well as more general information on PrEP. Individuals should be willing and able to use PrEP as recommended, including periodic HIV testing.

### Box 6. Offering a choice in PrEP products

People accessing PrEP services should be counselled on all available PrEP and HIV prevention options and empowered to make an informed decision. Values and preferences research suggests that preferences for different PrEP options varies across geographies and populations (80). Offering a range of products has the potential to improve uptake, persistence and effective use of PrEP as people can choose the method that suits their needs, preferences and lifestyles at any given moment in time. The same has been found to be true regards contraceptives, where research suggests that increasing the number of available contraceptive options also increased contraceptive coverage (81). Information provided to individuals should include the potential benefits and limitations of the different PrEP products available, including effectiveness, how the products are used and potential side-effects (see Table 2). The best HIV prevention option for a client is one that they will use effectively. Moreover, a client's choice of product, and the availability of products, may change over time. Therefore, information about all available options should be part of an ongoing conversation – even among those already on PrEP.

PrEP: pre-exposure prophylaxis

Counselling should be adapted to the local context and a client's individual needs and concerns, and may address the following issues and services:

- sexual health concerns and goals
- overview of the different PrEP products available to the client (see Table 2 for key messages about each product)
- follow-up during PrEP, including importance of regular HIV and STI testing:
  - PrEP providers should book a follow-up visit with the client at a mutually convenient time
  - PrEP providers should consider DSD options for PrEP that might support the client to stay engaged with the service (see Box 3)
- management of side-effects
- strategies for effective use of PrEP and persistence (see Box 7), including what to do if PrEP is not used as recommended
- other services (as appropriate):
  - prevention and testing for STIs
  - sexual and reproductive health
  - testing for HBV and HCV and linkage to care
  - mental health, drug and alcohol use (including chemsex), gender-affirming care, and sexual and interpersonal violence (as appropriate) (see Box 8).

For further details, see WHO guidance for PrEP counsellors in *WHO PrEP implementation tool* (82).<sup>32</sup>

**WHO does not recommend counselling aimed only at changing behaviours to reduce the risk of HIV and STI transmission. Behaviour change counselling has not been shown to have an effect on HIV or STI incidence, nor to influence behaviours such as condom use and needle/syringe sharing (4). Counselling and information sharing that is not aimed at changing behaviours can be a key component of engagement and, when provided, should be done in a non-judgemental manner alongside other prevention interventions and with the involvement of peers.**

**People accessing PrEP services often have diverse health and social needs and are at risk of infection with HIV, STIs, HBV and HCV. PrEP services offer a unique opportunity to provide comprehensive and person-centered care.**

<sup>32</sup> The Counsellors module will be updated in 2024 to include new information including specific discussion points regarding the DVR and CAB-LA. The modules can be found at: <https://www.who.int/tools/prep-implementation-tool>

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### Box 7. Effective use of PrEP

Effective use of PrEP refers to using PrEP according to the recommended dosing schedule (sometimes called adherence to the dosing schedule<sup>33</sup>) during periods of HIV risk to reduce the risk of acquiring HIV.

PrEP is unlikely to be used for life. Any PrEP product can be discontinued if a person is no longer at risk or decides to use an alternative PrEP product or HIV prevention strategy. It is not unusual for people to start and stop PrEP repeatedly, depending on periods of higher and lower HIV risk (83, 84).

PrEP providers should emphasize the importance of effective use and assist individuals to recognise circumstances that may make PrEP use more challenging and/or involve substantial risk of HIV, such as changes in relationship status, alcohol and drug use, leaving school, leaving home, trauma, migration or other events. Some groups, such as young people, may require more support or more frequent check-ins. Support groups for PrEP users, including social media groups, may be helpful for peer-to-peer sharing of experience and challenges. HIVST may be useful for supporting effective use in some groups, such as adolescents (74).

PrEP: pre-exposure prophylaxis; HIVST: HIV self-testing

### Box 8. Addressing interpersonal violence in the context of PrEP

WHO estimates that almost one in three women have experienced physical and/or sexual violence by an intimate partner or sexual violence by someone other than their partner (85), and one in four adolescent girls (15–19 years) have experienced intimate partner violence at least once in their lifetime (86). The limited evidence available indicates that violence is also disproportionately high among transgender individuals (87) and those who engage in sex work.




HIV services are critical entry points for identifying survivors (88), and so PrEP providers can play a critical role in identifying and supporting individuals affected by interpersonal violence. Any sign of interpersonal violence, controlling behaviour, anger or fear, in response to interpreting PrEP as HIV treatment, could prompt discussion about the risk and benefits of PrEP as a possible way to control risk of HIV. Different PrEP products and PEP can also be explored. This would also be an opportunity to refer the client to prevention and treatment services for intimate partner violence. A safety assessment and plan, as well as counselling and support for disclosure, should be offered to those who agree to take PrEP and are identified as potentially experiencing interpersonal violence (89).

PrEP: pre-exposure prophylaxis; PEP: post-exposure prophylaxis

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<sup>33</sup> Adherence is an important part of effective use. Adherence refers to using PrEP as recommended and will depend on the PrEP product being used.

**Table 2. Summary of key messages to support counselling on PrEP product choice**

	 <b>Oral PrEP</b>	 <b>DVR</b>	 <b>CAB-LA</b>
<b>Type</b>	<b>Oral tablet</b>	<b>Flexible silicone vaginal ring</b>	<b>Injection</b>
<b>All PrEP products are effective HIV prevention options (when used as directed).<sup>a</sup></b>	At least 90% effective (possibly as high as 94–99%). <sup>b</sup>	At least 50% effective. <sup>b</sup>	At least 90% effective (possibly as high as 92–95%). <sup>b</sup>
<b>Effective use is important to prevent HIV acquisition (this means using PrEP according to the dosing regimen during periods of HIV risk).</b>	<p>For individuals assigned male at birth with sexual exposure and not taking gender-affirming hormones:</p> <ul style="list-style-type: none"> <li>take two doses 2–24 hours prior to exposure;</li> <li>take one dose per day during exposure; and</li> <li>continue with one dose per day, for two days, after the last exposure.</li> </ul> <p>For all other groups:</p> <ul style="list-style-type: none"> <li>take one dose per day for seven days prior to exposure;</li> <li>take one dose per day during exposure; and</li> <li>continue with one dose per day until seven days after the last exposure.</li> </ul> <p>(See “PrEP products &amp; regimens” for further details about starting, using and stopping.)</p>	<p>Wear in the vagina for one month (including during menstruation) before replacing with a new ring.</p> <p>(See “PrEP products &amp; regimens” for details on starting, stopping and using the DVR.)</p>	<p>To start,</p> <ul style="list-style-type: none"> <li>intramuscular gluteal injections are given at month 0 and month one.</li> </ul> <p>To continue,</p> <ul style="list-style-type: none"> <li>injections are then given every two months.</li> </ul> <p>(See “PrEP products &amp; regimens” for further details on starting, stopping and using CAB-LA.)</p>
<b>Use additional HIV protection until you’re protected by PrEP.</b>	<p>The time the client needs to use oral PrEP before exposure to HIV varies by population.</p> <ul style="list-style-type: none"> <li>For individuals assigned male at birth with sexual exposure and not taking gender-affirming hormones, the time to protection is estimated at 2–24 hours following a double dose.</li> <li>For all other groups, the time to protection is estimated at seven days following daily dosing.</li> </ul> <p>Individuals who stop oral PrEP are no longer protected.</p> <ul style="list-style-type: none"> <li>Individuals assigned male at birth with sexual exposure and not taking gender-affirming hormones should take one dose per day for two days after the last exposure.</li> <li>All other groups should take oral PrEP for seven days following their last exposure.</li> </ul>	<p>The DVR should be in place for 24 hours before vaginal sex. It does not protect against HIV acquisition during anal sex or injecting.</p> <p>Once removed, the DVR is not known to provide any protection.</p>	<p>The time the client needs to use CAB-LA before exposure to HIV is not currently known.</p> <p>The available data suggest that most individuals are likely to reach high levels of protection within seven days. Alternative HIV prevention methods should be used during this time.</p> <p>After the last injection, a client remains protected for two months.</p>



### Oral PrEP



### DVR



### CAB-LA

<b>PrEP is generally safe during pregnancy and breastfeeding.</b>	Safe during pregnancy and breastfeeding.	Evidence to date suggests DVR use is safe during pregnancy and breastfeeding (90–92).	Although evidence on safety during pregnancy and breastfeeding is limited, there are currently no safety signals and CAB-LA is not contraindicated. Risks and benefits should be evaluated on a case-by-case basis.
<b>PrEP is generally safe and well tolerated. Side-effects are usually mild and resolve by themselves.</b>	Usually mild and resolve within one month.	Typically, mild and resolves within one month.	Mild–moderate injection site (on the side or the back of the buttock) reactions may be experienced; other side-effects are usually mild or moderate and resolve within one month.
<b>Kidney function monitoring is only required for some individuals.</b>	Kidney function monitoring may be required for some individuals, such as those aged 50 years or older and those with kidney related comorbidities (3, 93). Monitoring for kidney function should not delay PrEP.	None	None
<b>People with viral hepatitis or impaired liver function can safely use oral PrEP and the DVR, but CAB-LA use may require further evaluation.</b>	HBV and HCV are not contraindications.	HBV and HCV are not contraindications. Individuals with HBV infection could consider TDF-based oral PrEP as an alternative given the dual effectiveness against HIV and HBV.	HBV and HCV may require further evaluation. CAB-LA may be inappropriate for those with advanced liver disease and acute hepatitis, and those requiring treatment for HBV. Liver function testing (e.g., ALT) may be considered but is not required to start CAB-LA. Individuals with HBV infection could consider TDF-based oral PrEP given the dual effectiveness against HIV and HBV.
<b>There are few drug–drug interactions and contraindications.</b>	Low risk of interaction with most medications. Can be taken safely with recreational drugs, alcohol and hormonal contraception. Oral PrEP does not affect levels of gender-affirming hormones, but estradiol-based exogenous hormones may reduce levels of tenofovir.  (See “PrEP products & regimens” for more details.)	Low risk of interaction with other medications. Can be taken safely with recreational drugs, alcohol and hormonal contraception.  (See “PrEP products & regimens” for more details.)	May interact with some anticonvulsant and TB medicines. Can be taken safely with recreational drugs, alcohol and hormonal contraception. No known interaction with gender-affirming hormone therapy.  (See “PrEP products & regimens” for more details.)



### Oral PrEP

**Follow-up is important to support effective PrEP use and to provide other services (see Table 5).**

Follow-up visits are generally every three months. (Additional visits at one month or longer intervals can be considered depending on the client's circumstances.)



### DVR

Follow-up visits are generally every three months. (Additional visits at one month or longer intervals can be considered depending on the client's circumstances.)



### CAB-LA

The first follow-up visit will be at one month. Subsequent follow-up visits are generally every two months.

#### **PrEP does not protect against other STIs or pregnancy**

**Individuals with STI symptoms who are using PrEP should be provided with or referred for diagnosis and treatment**

**Contraceptive services should be available for all cisgender women and other individuals assigned female at birth who are taking PrEP**

PrEP: pre-exposure prophylaxis; DVR: dapivirine ring; CAB-LA: long-acting injectable cabotegravir; TDF: tenofovir disoproxil fumarate; HBV: hepatitis B virus; HCV: hepatitis C virus; ALT: alanine transaminase

See the relevant sections in this module for more information on individual topics.

- <sup>a</sup> Effectiveness at preventing sexual acquisition of HIV. There is considerable uncertainty around the effectiveness of using PrEP to prevent parenteral HIV acquisition (see section on Special considerations below).
- <sup>b</sup> Methods to determine effectiveness and control groups in clinical trial varied across PrEP products. Clinical trials of oral PrEP and the DVR compared these against a placebo, while clinical trials of CAB-LA compared this against oral PrEP. For CAB-LA, mathematical modelling estimated placebo-controlled effectiveness.

## Providing the PrEP drugs



### Oral PrEP and the DVR

At the initial visit, individuals using oral PrEP or the DVR should ideally be prescribed or supplied with sufficient bottles or rings, respectively, to allow for daily use until the next scheduled visit, depending on the client's needs and preferences.

Rates of stopping oral PrEP and the DVR are likely to be higher in the month after starting PrEP (58, 59) and individuals using PrEP who have some medicine supply in reserve may have better effective use (59). Consideration should also be given to providing an extra bottle or ring in case the next scheduled follow-up visit should be delayed for any reason. Such a reserve supply may also prevent any rationing of PrEP as a follow-up visit approaches. While multi-month dispensing (MMD) should be used whenever possible, PrEP providers should be aware that some individuals may prefer single month prescriptions or supply due, for example, to difficulties storing additional bottles or rings.



### CAB-LA

Individuals using CAB-LA will be given the intramuscular gluteal injection at the scheduled visits by a trained PrEP provider. To start CAB-LA, injections are given at the initial visit (month 0) and month one, and then every two months thereafter for as long as the client remains on CAB-LA.





## PrEP follow-up

*This section outlines the follow-up for the three currently available PrEP products: oral PrEP, the DVR and CAB-LA. In general, the same steps are followed for all products. Where there are special considerations for a specific product, these have been highlighted.*


Follow-up visits for oral PrEP and the DVR are typically conducted every three months and can include an optional visit at month one.<sup>34</sup> However, these schedules can be adapted to the client's needs and preferences (3). For example, a client using oral PrEP may be travelling for extended periods of time (and so may not be able to meet a suggested visit schedule), or a client may not need three monthly visits (particularly for the more "PrEP-experienced" individuals). Conversely, adolescents and young people (aged 24-years-old or younger) may benefit from more frequent visits to address changing routines and multiple needs. In-person follow-up visits may not be required and could be replaced by telehealth or virtual visits, depending on the service resources and needs and preferences of the client (see Box 9).

For CAB-LA, following the two initiation injections/visits, which are provided at month 0 and month one, follow-up visits for continuation should be conducted every two months thereafter. For example, the first continuation visit is conducted two months after the second injection. Adherence to the injection schedule is important as the CAB-LA injection is provided at the follow-up visit (see Table 1).

All follow-up visits should include an appropriate package of services (see Table 3, Table 4 and Table 5), a check-in with the client and the provision of oral PrEP, DVR or CAB-LA. In addition, follow-up visits should also be coordinated with visits to other health services, such as contraception, to reduce the number of visits required.

### HIV testing

While using PrEP, regular HIV testing is needed to ensure that the client remains HIV negative – or to facilitate linkage to confirmatory testing and treatment. HIV testing can be completed in accordance with the WHO testing strategy for HIV diagnosis using the full national testing algorithm, which is usually composed of quality-assured serology assays (RDTs and enzyme immunoassays) (see WHO *HIV testing services guidelines* (71)).



As described earlier, HIVST can be considered as an additional HIV testing choice for oral PrEP and DVR (3). It can be used to replace provider-administered testing, as needed, for starting, continuing or restarting PrEP, and as desired by clients between PrEP visits to give reassurance and confidence (3). HIVST may also support longer intervals between in-person visits to a PrEP service (16).



HIVST is not currently recommended for CAB-LA and further research is needed (6).

### Check-in discussion

Follow-up visits can be an important opportunity for PrEP providers and clients using PrEP to check-in about sexual health goals and concerns, as well as PrEP-specific experiences including side-effects and effective use (see Box 7). All clients using PrEP should have the opportunity to check-in with a PrEP provider, to raise any questions or concerns they might have, or to discuss alternative HIV PrEP products or prevention methods should they wish to switch. However, PrEP providers should be aware that some clients, especially those who are experienced with PrEP, may prefer less frequent contact and/or more streamlined visits.

Similar to the initial visit, the check-in discussion should be non-judgemental and positive to encourage clients using PrEP to discuss successes and challenges in using PrEP, intention to continue PrEP and/or switch PrEP products, and to ask new questions about PrEP.

<sup>34</sup> An additional visit at month one for oral PrEP and DVR is optional, but can be considered depending on the client's needs and preferences, as well as the available resources. Discontinuation rates are highest in the one month after starting PrEP. An additional visit at one month can provide an early opportunity for providers to discuss with a client their experiences and to identify any challenges, such as side-effects, support insertion / removal of the DVR or support effective use of oral PrEP. It also provides an opportunity to test for HIV. For example, more frequent visits may be preferable for younger clients. However, frequent PrEP visits can be a barrier to continuing PrEP, and consideration should be given to DSD options such as home PrEP or virtual interventions, including telePrEP to increase convenience for the client.



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PrEP providers should adapt their approach to counselling to the client's individual preferences and needs, and counselling can address the following issues and services:

- sexual health concerns and goals
- key messages about the PrEP product being used (see Table 2), including how to stop PrEP
- managing of side-effects
- assessment of effective use (Box 7):
  - providers should discuss strategies for effective use of PrEP and persistence (see Box 6), including what to do if PrEP is not used as directed
- follow-up on PrEP, including importance of regular HIV and STI testing:
  - PrEP providers should book a follow-up visit with the client at a mutually convenient time
  - PrEP providers should consider DSD options for PrEP that might support the client to stay engaged with the service (see Box 3)
- intention to continue to use PrEP or desire to switch PrEP products
- other services (as appropriate):
  - prevention and testing for STIs
  - sexual and reproductive health
  - testing for HBV and HCV and linkage to care
  - mental health, drug and alcohol use, gender-affirming care, and sexual and interpersonal violence (as appropriate) (see Box 7).

### **Effective use**

PrEP providers can assess effective use at each visit by discussing possible HIV exposures and PrEP use (including any missed doses or DVR removal). To be effective, all possible exposures should be covered by PrEP. Clients should be assessed for PEP, and AHI considered, if there has been ineffective use of PrEP (specifically, missed doses or ring removal around the time of possible HIV exposure).

If a client reports challenges with effective use of PrEP, PrEP providers should help their clients to identify a range of strategies to make effective use easier.



For oral PrEP, this could include setting themselves a phone reminder, linking taking oral PrEP to a daily activity such as brushing teeth, or carrying at least two doses (such as a pill box on a keychain). Linking DVR replacement to menstruation for individuals with regular cycles could be considered. Social media and support groups may be able to provide a range of different support options to a client, irrespective of the PrEP product being used. Successful PrEP users often find their own solutions to support effective use.



For CAB-LA, clients may require support with developing strategies to ensure that scheduled injection visits are not missed. As there is currently little experience outside the trial setting for CAB-LA use, CAB-LA persistence<sup>35</sup> is not well understood. The available evidence from open label extension studies suggests that persistence on CAB-LA may vary between populations and individuals. As CAB-LA becomes more widely available, it will be important to understand and address factors that support effective CAB-LA use and any key barriers.

### **Assessment for AHI**

PrEP providers should be aware of the possibility for AHI among individuals who have stopped PrEP or not used PrEP effectively. If AHI is suspected in the context of ineffective use, PrEP providers should take a similar approach to the initial visit.

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<sup>35</sup> Persistence in the context of CAB-LA refers to continuing CAB-LA according to the injection schedule.

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### **PrEP to PEP**

People using PrEP as directed will rarely require PEP. However, if PrEP is not used as directed or is stopped, there can be a risk of acquiring HIV. Individuals may stop taking PrEP for many reasons, including believing that they no longer need it, using other HIV prevention methods or simply preferring to no longer continue taking it. Unfortunately, some people acquire HIV soon after stopping PrEP. For this reason, PrEP providers should discuss PEP use with all clients, including where to get PEP, where to get an HIV test (including HIVST). PrEP providers should also advise clients about the need to start PEP as soon as possible after a potential exposure (ideally within 24 hours).

PrEP providers should discuss with clients any possible exposures to HIV and their previous or current PrEP use, including the number of doses taken for oral PrEP, or for the DVR, any removal or exposure other than vaginal sex. Refer to the 2024 update to the WHO PEP guidelines for more detail on PrEP to PEP.

PrEP providers should discuss restarting PrEP with clients who stopped PrEP and have now come to a service for PEP if these clients may have ongoing HIV risk.



PEP is not required whilst the client is having CAB-LA injections as scheduled. PEP should be considered if the client has stopped CAB-LA and has a potential exposure to HIV more than one month after the first injection or two months after a follow-up injection. PEP could be a useful prevention option for people who do not want to switch to oral PrEP when they stop CAB-LA during the tail period (refer to the section on PrEP products and regimens: CAB-LA for more information).

## **Providing PrEP drugs**

### **Oral PrEP and the DVR**



At follow-up visits, people using oral PrEP or the DVR should ideally be provided with a multi-month supply, depending on the client's needs and preferences. While MMD should be used whenever possible, PrEP providers should be aware that some clients may prefer to have one bottle or one ring dispensed at a time. Such clients may have additional "refill" visits. Where possible, multiple locations for follow-up and refill visits should be offered so that clients can choose their preferred location (see Box 9). Clients not using PrEP every day may have some oral PrEP in reserve from their last refill. All clients should have a sufficient supply of oral PrEP drugs or rings for daily use until their next scheduled visit. Consideration should also be given to providing an extra bottle or ring in case the next scheduled follow-up visit should be delayed for any reason.

### **CAB-LA**



After the first two initiation visits, spaced one month apart, clients using CAB-LA will be given a continuation injection at the scheduled follow-up visits by a trained PrEP provider every two months thereafter, for as long as the client remains on CAB-LA.

# Suggested procedures for starting PrEP and follow-up

This section outlines the suggested procedures for starting and follow-up of the three currently available PrEP products.

Suggested procedures for oral PrEP and the DVR are listed in Table 3. These schedules can be adapted to the client's needs and preferences (3). Suggested procedures for CAB-LA are listed in Table 4.

For all PrEP products, additional services for clients can also be considered as part of a comprehensive PrEP package tailored to the local epidemiology and client needs and preferences (see Table 5). These may include periodic screening for STIs; testing for HBV and/or HCV (and linkage to HBV vaccination and treatment services, as appropriate); contraceptive services; and comprehensive harm reduction services for people who use drugs, including sterile needles and syringes and opioid agonist treatment. Other services that may be relevant include, but are not limited to, gender-affirming services, mental health services and/or services for survivors of sexual violence.

**Table 3. Suggested procedures for oral PrEP and the DVR**

Investigation	Rationale	Month <sup>a</sup>					
		0 (Initiation visit)	1 (Optional follow-up visit)	3	6	9	12
<b>Suggested minimum service package</b>							
<b>Identify individuals who could benefit from PrEP</b>	Requesting PrEP and/or could benefit from PrEP use according to national guidelines.						
<b>HIV test<sup>b</sup></b>	An HIV test result is required prior to initiation and regularly while using PrEP. This can include HIVST and dual HIV/syphilis tests.	X	X (optional)	X	X	X	X
<b>Assess for PEP</b>	Provide PEP if the client had a potential exposure within 72 hours <sup>c</sup> prior to starting PrEP, or if a client reports ineffective PrEP use within the previous 72 hours. Individuals can transition from PEP to PrEP after 28 days, if suitable. See section above on PEP.	X	X	X	X	X	X
<b>Assess for signs and symptoms of AHI</b>	To minimize the risk of drug resistance, the likelihood of AHI should be assessed for all individuals starting PrEP and individuals reporting ineffective use of PrEP, taking into consideration both the signs and symptoms of AHI, risk of HIV exposure and any PrEP use. The PrEP provider should weigh the risks and benefits of deferring or stopping PrEP on a case-by-case basis.	X	X	X	X	X	X
<b>Provide information on PrEP/ "check in"</b>	The information provided on PrEP, both topics and amount of information, should be tailored to the client's needs and preferences. A regular check-in provides an opportunity for providers to assess side-effects and effective use; to discuss with clients whether they want to continue PrEP (and/or switch products); discuss successes and challenges in using PrEP; and for clients to ask new questions.	X	X	X	X	X	X

Investigation	Rationale	Month <sup>a</sup>					
		0 (Initiation visit)	1 (Optional follow-up visit)	3	6	9	12
<b>Assess for contraindications</b>	If a client has a contraindication to an oral PrEP regimen or the DVR, including allergy or hypersensitivity, a different PrEP product or HIV prevention option should be offered.	X					
<b>Provide oral PrEP drugs or the DVR</b>	MMD should be used, except in exceptional circumstances or where single-month dispensing is preferred by clients.  Ensure the client has enough oral PrEP or DVR units to cover them for daily use until the next visit.	X	X	X	X	X	X

### **Suggested additional services for oral PrEP**

<b>Kidney function measurement<sup>d</sup></b>  (Only for individuals taking oral PrEP)	May be optional for individuals under 50 years of age without kidney-related comorbidities. <sup>e</sup>  For individuals aged 50 years or older and individuals of any age with kidney-related comorbidities, kidney-function monitoring may be done once at initiation or within three months of PrEP initiation and, if required, every 6–12 months thereafter.  See Annex 1 for suggested procedures.	X <sup>f</sup>					X
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PrEP: pre-exposure prophylaxis; HIVST: HIV self-testing; PEP: post-exposure prophylaxis; AHI: acute HIV infection; HBV: hepatitis B virus; HCV: hepatitis C virus; STI: sexually transmitted infection; DVR: dapivirine vaginal ring

- <sup>a</sup> There is currently no universal approach to scheduling follow-up visits. In some countries, follow-up is conducted at month three and then every three months thereafter. Some countries conduct follow-up at month one, month three and then every three months thereafter. Other countries conduct follow-up at month one, month four and then every three months thereafter. This schedule is a guide and can be adapted to the local context and needs and preferences of the client.
- <sup>b</sup> A non-reactive HIVST or negative first test following the approved national testing algorithm is sufficient to start PrEP. Testing schedule should follow national guidelines.
- <sup>c</sup> PEP should be started as early as possible, ideally within 24 hours but not later than 72 hours after a potential HIV exposure.
- <sup>d</sup> eGFR of <60 mL/min per 1.73 m<sup>2</sup> or an estimated creatinine clearance of <60 mL/min is a contraindication for oral PrEP. As kidney function may vary from day-to-day, dependent on a range of factors, a measurement that suggests reduced kidney function should be repeated on another day with a new sample before excluding a person from PrEP services or stopping oral PrEP. Oral PrEP can be restarted if kidney function returns to above the cut-off within one to three months after stopping oral PrEP. If kidney function does not return to normal levels after stopping PrEP, other causes of kidney insufficiency should be evaluated. See Annex 1 for details.
- <sup>e</sup> Kidney-related comorbidities include chronic kidney disease or risk factors such as diabetes or hypertension. There may be an increased risk of kidney-related adverse events during pregnancy, and conditions such as preeclampsia, may cause kidney impairment, so more frequent kidney function testing may be considered during pregnancy.
- <sup>f</sup> Where indicated, may be done within 3 months of starting PrEP.

**Where possible contraception services should be provided alongside PrEP for women to increase choice, access and impact.**

**Table 4. Suggested procedures for CAB-LA**

Investigation		Month 0 (Initiation injection #1)	Month one (Initiation injection #2)	Month three and every two months thereafter (Follow-up injections)
<b>Suggested minimum service package</b>				
<b>Identify individuals who could benefit from PrEP</b>	Requesting PrEP and/or could benefit from PrEP use according to national guidelines.	X		
<b>HIV test<sup>a</sup></b>	An HIV test result is required prior to initiation and regularly while using PrEP. This can include an HIV/syphilis dual test. HIVST is currently not considered sufficient for CAB-LA initiation and continuation (although clients may use HIVST between injections).	X	X	X
<b>Assess for PEP</b>	Provide PEP if the client had a potential exposure within 72 hours. <sup>b</sup> Clients can transition from PEP to PrEP after 28 days, if suitable. See section above on PEP.	X		
<b>Assess for signs and symptoms of AHI</b>	To minimize the risk of drug resistance, the likelihood of AHI should be assessed for all individuals starting CAB-LA, taking into consideration both the signs and symptoms of AHI and the risk of HIV exposure. The PrEP provider should weigh the risks and benefits of deferring or stopping PrEP on a case-by-case basis.	X		
<b>Provide information on PrEP/ “check in”</b>	The information provided on PrEP, both topics and amount of information, should be tailored to the client’s needs and preferences. A regular check-in provides an opportunity for providers to assess side-effects and effective use; to discuss with clients whether they want to continue PrEP (and/or switch products); discuss successes and challenges in using PrEP; and for clients to ask new questions.	X	X	X
<b>Assess for contraindications</b>	If a client has a contraindication to CAB-LA, including allergy or hypersensitivity, a different PrEP product or HIV prevention option should be offered.	X		
<b>Provide CAB-LA injection</b>	<b>Note:</b> There is a +/- 7-day window for receiving the initiation injection #2. Once initiation injections #1 and #2 are complete, follow-up visits should be scheduled beginning two months after initiation injection #2 and every two months thereafter. There is a +/- 7-day window for receiving follow-up injections. See Table 1 for information on delayed/missed doses.	X	X	X

Investigation	Month 0	Month one	Month three and every two months thereafter
	(Initiation injection #1)	(Initiation injection #2)	(Follow-up injections)

**Suggested additional services for CAB-LA**

<b>Liver function measurement</b> <sup>f</sup>	Optional. Where available, liver function measurement (such as measuring ALT) can be considered before and during CAB-LA use, as per national guidelines. Consider for people with evidence of viral hepatitis or other signs and symptoms of impaired hepatic functioning.	x
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PrEP: pre-exposure prophylaxis; HIVST: HIV self-testing; CAB-LA: long-acting injectable cabotegravir; HBV: hepatitis B virus; HCV: hepatitis C virus; ALT: alanine transaminase; STI: sexually transmitted infection

<sup>a</sup> A negative first test following the approved national testing algorithm is sufficient to start PrEP.

<sup>b</sup> PEP should be started as early as possible, ideally within 24 hours but not later than 72 hours after a potential HIV exposure.

<sup>c</sup> Data on the use of CAB-LA in people with HBV and HCV infection are scarce.

<sup>d</sup> WHO recognizes that people at risk of acquiring HIV, including people attending PrEP services, could be a possible target group for HBV catch-up vaccination, depending on the local HBV epidemiology and available resources. See (94) for details.

<sup>e</sup> Where indicated, may be done at PrEP initiation or within three months of initiation.

<sup>f</sup> CAB-LA should not be initiated in people with advanced liver disease or acute hepatitis and should be discontinued if hepatotoxicity is confirmed. CAB-LA injections should not be delayed while waiting for results of liver function tests.

**Table 5. Suggested additional procedures at PrEP initiation and follow-up, adapted to the local context and client's needs and preferences <sup>36</sup>**

<b>Hepatitis B surface antigen testing <sup>a</sup></b>	<p>Optional but strongly encouraged, particularly in highly endemic countries. May be done once within three months of starting PrEP.</p> <p>HBV infection is not a contraindication for oral PrEP or the DVR. Where oral PrEP is used by people with chronic HBV infection, regular monitoring to detect relapse and management of HBV after stopping TDF-based PrEP is important (3). Individuals with acute hepatitis should not start CAB-LA.</p> <p>If positive, refer for further testing and assessment for HBV treatment.</p> <p>CAB-LA is not effective against HBV and may be inappropriate for individuals with HBV infection. Individuals requiring treatment for HBV should be considered for oral PrEP instead. Even where there is no treatment indication for HBV, oral PrEP should be strongly considered as it will suppress HBV and prevent HIV.</p> <p>If negative, WHO recommends HBV vaccination for people at risk of acquiring HBV. <sup>b</sup></p>
<b>Hepatitis C antibody testing <sup>a</sup></b>	<p>Optional but strongly encouraged for individuals with potential exposure to HCV including, but not limited to, cisgender men and transgender women who have sex with men, people who inject drugs, and people in prisons and other closed settings. May be done once at PrEP within three months of starting PrEP, and every 12 months thereafter.</p> <p>HCV infection is not a contraindication for oral PrEP or the DVR. CAB-LA should not be started in individuals with acute hepatitis.</p> <p>WHO recommends HCV self-testing as an additional approach to complement facility-based HCV testing (95).</p> <p>If positive, refer for further assessment and treatment for HCV infection.</p>
<b>STI testing: syphilis, gonorrhoea, and chlamydia</b>	<p>Periodic testing for STIs is optional but strongly encouraged as PrEP does not protect against other STIs. Testing every 6–12 months is suggested (19), although frequency may vary according to national guidelines.</p> <p>Rapid tests for syphilis (standalone treponemal tests,<sup>37</sup> dual treponemal/non-treponemal test or combined with HIV) can expedite treatment initiation, decrease loss to follow-up and be cost-saving. Testing with treponemal test only will require further testing to confirm syphilis diagnosis and initiate treatment. Decision on treatment based only treponemal tests will depend on local epidemiology, past treatment history and national protocols. Provide treatment and/or referrals per national guidelines.</p> <p>Molecular tests for gonorrhoea and chlamydial infection, if available, should be performed with samples from all anatomical sites to minimize missed infections (WHO recommends that these samples can be pooled for testing (4, 96)). Self-collection of samples is also recommended (97). Provide treatment and/or referrals per national guidelines.</p> <p>Partner services, including provider-assisted referral and expedited partner therapy (EPT) of sexual partners is critical to avoid reinfection and to break the chain of transmission. When appropriate, EPT could be considered for gonorrhoea and chlamydia.</p> <p>For further details see WHO guidance on integrating STI services in PrEP delivery (19).</p>
<b>Screening for STI signs and symptoms</b>	<p>Assessing or self-assessment of STI signs and symptoms at every visit is strongly encouraged (19).</p> <p>STI symptom screening and management for individuals presenting for PrEP can identify those in need of STI care who otherwise might have been missed.</p>

<sup>36</sup> Where other services are not available at the same site as PrEP, robust client-centred referral systems must be in place to minimise loss to follow-up. PrEP should still be provided even if these additional services are not available.

<sup>37</sup> Treponemal only RDTs (single or combined with HIV) cannot differentiate between current (active) infection and previously treated infection.

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<b>Contraceptive services and pregnancy testing</b>	Assess reproductive intentions and offer or refer for pregnancy testing, if appropriate, and reliable contraceptive options.
<b>Other services</b>	<p>Prevention commodities, including condoms, should be offered to all clients at all visits. Harm reduction services should additionally be offered to people who use or inject drugs (4).</p> <p>Individuals using or interested in PrEP may also benefit from a range of other services, including:</p> <ul style="list-style-type: none"> <li>• gender-affirming care services</li> <li>• mental health services</li> <li>• other drug and alcohol services, including for chemsex</li> <li>• anal health</li> <li>• prevention, assessment and treatment of cervical cancer</li> <li>• HPV vaccination.</li> </ul> <p>The additional services offered should be tailored to the needs and preferences of the individual.</p>

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PrEP: pre-exposure prophylaxis; HIVST: HIV self-testing; CAB-LA: long-acting injectable cabotegravir; HBV: hepatitis B virus; HCV: hepatitis C virus; ALT: alanine transaminase; STI: sexually transmitted infection

<sup>a</sup> Data on the use of CAB-LA in people with HBV and HCV infection are scarce.

<sup>b</sup> WHO recognizes that people at risk of acquiring HIV, including individuals attending PrEP services, could be a possible target group for HBV catch-up vaccination, depending on the local HBV epidemiology and available resources. See (94) for details.

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# Stopping and restarting PrEP use

*This section outlines how to stop and restart the three currently available PrEP products. In general, the same steps are followed for all products. Where there are special considerations for a specific product, these have been highlighted.*

## Stopping PrEP

Clients may choose to stop PrEP for a variety of reasons. For example, they may have chosen to use an alternative HIV prevention method or no longer perceive themselves at risk of HIV. PrEP providers have a role in helping clients assess their prevention needs and exposure to HIV, but clients should not be required to return to a PrEP provider to stop PrEP.

Clients should be informed about how to safely stop PrEP, emphasizing the need to continue PrEP for the recommended time after their last potential HIV exposure. PrEP providers should also discuss where clients can get PEP and HIVST if they have an exposure after stopping PrEP. The approach to stopping PrEP varies between PrEP products (see Table 2 for further information).



As CAB-LA is a long-acting product, quarterly monitoring for one year after CAB-LA has been stopped<sup>38</sup> is suggested, including HIV testing.

## Restarting PrEP

Individuals who have stopped oral PrEP, the DVR or CAB-LA can restart PrEP using their preferred product and/or dosing regimen.<sup>39</sup> When restarting the same PrEP choice, PrEP providers should use a similar approach as was used when they first initiated the product. Individuals should **always** be tested for HIV prior to starting PrEP using WHO standard testing strategies, or a HIVST for oral PrEP or the DVR, even if the last test was less than three months earlier, and assessed for contraindications. The procedures and counselling should be tailored; for example, some testing may have been conducted within an appropriate timeframe and may not need to be repeated if results are available.

**PrEP is not a lifelong commitment. People may choose to start, stop and restart PrEP multiple times throughout their life, in accordance with their needs and preferences for HIV prevention, and their personal circumstances.**

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<sup>38</sup> When a person stops CAB-LA, concentrations in the body slowly decline. This is called the tail period or pharmacokinetic tail. During the pharmacokinetic tail, cabotegravir concentrations become gradually less protective against HIV acquisition, and HIV infections may occur. While there is a risk of drug resistance if individuals acquire HIV soon after stopping CAB-LA, the limited available data do not indicate that drug resistance is likely.

<sup>39</sup> Restarting PrEP refers to using the same PrEP product. Whether a client is restarting PrEP will take into consideration the duration since PrEP was last used, any potential exposures during that time and the PrEP product. For oral PrEP, a client should restart if there has been a break in taking oral PrEP of at least one week AND there has been a possible exposure, or a break of more than three months with or without an exposure. For the DVR, if it is not used continuously a client should restart PrEP. For CAB-LA, a client should restart CAB-LA if there is a break of more than two months between the first and second injection, or if there is a break of three months or more for the third or any later injection (see Table 1 for further details).

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# Special considerations for specific situations and populations

*This section outlines special considerations for the three currently available PrEP products. In general, the same steps are followed for all products. Where there are special considerations for a specific product, these have been highlighted.*

## Switching between PrEP products

Clients may choose to switch between PrEP products. This may happen when different products become available or as their needs or preferences change. The best strategy for switching between PrEP products, including any overlapping use of PrEP products, is not well understood. PrEP providers should use their best clinical judgement to support clients to switch between products safely. There may be simultaneous use of different PrEP products as clients switch between them, particularly to cover the start-up or tail periods and ensure no gap in protection. While no serious concerns are anticipated, there are limited data on the safety of using more than one PrEP product at a time. There is no evidence to suggest that using multiple PrEP products at the same time results in any advantage in terms of reduced risk of HIV acquisition (beyond the advantages of each PrEP product individually).

It is important that PrEP providers continue to ensure that clients are aware of the range of options available; and support clients to choose the one that best fits their needs. PrEP providers should counsel clients on these PrEP options by explaining the key messages for each product (see Table 2) so that clients can make informed decisions.

## Management of seroconversion

While all PrEP products can provide a high level of protection when used effectively, HIV seroconversion can occur after starting PrEP. In most cases, this is because the client had a pre-existing HIV infection that was undetected when starting PrEP,<sup>40</sup> or HIV was acquired after starting PrEP due to ineffective use. Continued use of PrEP by someone with HIV may lead to the development of HIV drug resistance. This is rare but has been observed for users of oral PrEP and CAB-LA (98).

After an HIV diagnosis is made, the client should stop PrEP and ART should be offered as soon as possible. If a PrEP service doesn't provide ART services, clients should be referred immediately to an ART site. Transition from PrEP to ART without a gap will decrease the risk of secondary transmission.

Clients who have been using oral PrEP or the DVR prior to seroconversion can be offered first line regimens according to local guidelines, as the risk of developing HIV drug resistance when using oral PrEP or the DVR is likely to be low (98, 99).

**If a PrEP user has a confirmed HIV diagnosis, ART for HIV infection can be started without a gap after PrEP is discontinued.**



HIV drug resistance is a particular concern for CAB-LA, as integrase strand-transfer inhibitor (INSTI) resistance may compromise the efficacy of DTG, part of WHO-recommended first-line treatment (5). Currently there are limited data on INSTI resistance after CAB-LA exposure and the subsequent effect on the clinical efficacy of treatment regimens containing DTG. One source of data is the HPTN 083 trial. Among the small number of participants who acquired HIV after CAB-LA exposure within six months of their first positive HIV test in the HPTN 083 trial, major INSTI resistance-associated mutations were observed in 10 of 18 cases (100). INSTI resistance was not observed among participants who acquired HIV but did not have recent CAB-LA exposure. Of the 10 participants with CAB resistance, all had DTG cross resistance; additional studies are ongoing to evaluate the clinical effectiveness of using INSTI-containing ART regimens among people who acquire HIV after exposure to CAB-LA for PrEP. Population-level monitoring of drug resistance in populations using PrEP, and particularly for CAB-LA during its initial rollout, remains important.<sup>41</sup> PrEP providers should be aware of national policies on drug resistance.

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<sup>40</sup> WHO guidance for oral PrEP, the DVR and CAB-LA is that the national testing algorithm may be used. However, it should be noted that there remains uncertainty around the possible harms of drug resistance and the optimal HIV testing strategy. This is an area of ongoing research. See the WHO guidelines on long-acting injectable cabotegravir for HIV prevention for further details (6).

<sup>41</sup> Monitoring drug resistance in populations using PrEP can be accomplished through the implementation of WHO-recommended surveys of HIV drug resistance in populations using PrEP and generally consists of drug resistance testing of remnant specimens from all people testing positive for HIV in a defined survey period (i.e., one year) (100, 101).

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## Management of clients taking hormonal contraception



**Oral PrEP.** TDF-based oral PrEP does not affect the efficacy of hormonal contraceptives and hormonal contraceptives do not affect oral PrEP efficacy (20, 102).



**DVR.** As there is limited systemic drug absorption from the DVR, limited potential for interaction with hormonal contraceptives is expected, and no effect on contraceptive efficacy has been observed in one trial (103).



**CAB-LA.** The limited evidence to date suggests that CAB-LA efficacy is not affected by hormonal contraceptives (49, 104), and there is no evidence that oral cabotegravir affects the pharmacokinetics of oral contraceptives (105).

## PrEP in pregnancy and postpartum

Pregnancy and postpartum periods are times of increased risk of HIV acquisition (65, 67), and those who are pregnant or breastfeeding could often benefit from PrEP for themselves and their infants.



**Oral PrEP.** TDF-based oral PrEP is safe during pregnancy and breastfeeding (106, 107). WHO has published guidance on offering oral PrEP during pregnancy and breastfeeding (108, 109). Integrated delivery of oral PrEP in ante- and postnatal care settings is feasible (110, 111). Pregnant and breastfeeding PrEP clients may experience challenges to effective use (111, 112). This includes experiencing side-effects like nausea and vomiting, which may resemble or worsen existing pregnancy symptoms. Additional counselling, particularly on the transient nature of PrEP-related side-effects, may be important.



**DVR.** Evidence from studies to date show a favourable safety profile of the DVR during pregnancy and breastfeeding (90–92). Adverse pregnancy outcomes, complications and adverse events were uncommon among study participants, and generally similar to the rates observed in the surrounding community (91, 92). Only a small amount of dapivirine can be detected in human milk (90, 113), and minimal drug was detected in breastfeeding infants, with no safety concerns noted (90). Results from the final cohort in the DELIVER study, which enrolled participants who were 12–29 weeks pregnant, are expected in 2024.



**CAB-LA.** To date there is limited data on use of CAB-LA during pregnancy and breastfeeding. Among the small number of pregnant or breastfeeding people exposed to CAB-LA, CAB-LA was found to be well tolerated (114), and no congenital anomalies were reported (115). However, more research and safety surveillance in pregnancy are needed to monitor adverse pregnancy and infant outcomes, particularly rare adverse events, through the surveillance of PrEP within larger surveillance programmes or antiretroviral pregnancy registries. Although more data is expected to become available in 2024, there are currently no data on the level of cabotegravir is present in breast milk, any impact on breast milk production, or effects on breastfeeding infants among clients exposed to CAB-LA. Given these uncertainties, the risks and benefits of using CAB-LA during pregnancy and/or breastfeeding should be considered on a case-by-case basis, and clients should be counselled that CAB-LA systemic circulation continues after CAB-LA discontinuation. Clients should be supported to make their own decisions about continuing CAB-LA during the pregnancy and breastfeeding period by weighing up the benefits and potential risks.

In addition to HIV prevention considerations, additional services suggested for pregnant clients include HBV testing (contributing to efforts to prevent mother-to-child transmission) and STI services, when relevant. WHO recommends syphilis testing at the first antenatal care visit due to the high risk of adverse pregnancy outcomes (116). Rapid syphilis testing can be used (standalone or combined with HIV) and, if reactive, treatment should be immediately initiated, as per national guidelines.

## PrEP for trans and gender diverse people

Globally, transgender women are estimated to be 14 times more likely to acquire HIV than the general population (117). Other trans and gender diverse people are also at higher risk of HIV infection (118, 119). This population could often benefit from PrEP, but commonly faces structural barriers to accessing health services (4). Additionally, they also carry a disproportionate burden of other STIs and viral hepatitis (119, 120). Gender-affirming care is often a priority for the trans and gender diverse community, and integration of PrEP services with such services has been shown to be feasible, which can increase the acceptability of PrEP services for this population (3).



**Oral PrEP.** Trans and gender diverse people who use estradiol-based gender-affirming hormones can start PrEP with one dose per day for seven consecutive days and continue daily oral PrEP by taking one dose per day until seven days after the last potential exposure to HIV. Anyone assigned male at birth (including transgender women) not taking estradiol-based hormones and with sexual exposure can start by taking two doses 2–24 hours prior to any potential sexual exposure and continue to take one dose per day until two days after the last potential sexual exposure (see Fig. 1B). The limited evidence available suggests that estradiol-based gender-affirming hormones may reduce concentrations of oral PrEP (30, 31) although this is uncertain (121, 122). While the lower PrEP concentration is unlikely to affect oral PrEP efficacy when used daily, the efficacy of other dosing approaches is unclear and further studies are needed. Research is also needed given the lack of data for oral PrEP use in the context of gender-affirming masculinizing hormones among transgender men and other individuals assigned female at birth.



**DVR.** To date the DVR has not been studied in trans and gender diverse populations. This means that there are no data for trans men using gender-affirming hormones and the DVR. However, no interactions are expected. There are also no data for trans women using DVR with a neovagina. Additional research is needed. However, trans men and other gender diverse individuals assigned female at birth who are not using gender-affirming hormones could use the DVR for frontal (vaginal) sex. The DVR will not be protective for clients who have frontal *and* anal sex.



**CAB-LA.** The limited available data available suggest that use of gender-affirming estradiol-based hormones do not reduce CAB-LA concentrations (123, 124). Similarly, CAB-LA is not expected to have a clinically significant impact on gender-affirming hormone levels given the metabolic pathways. There is currently no evidence for alternative CAB-LA injection sites for individuals with gluteal implants. More research is needed on delivering CAB-LA for trans and gender diverse populations, including integration with gender-affirming care services and alternative injection sites.

## PrEP for people who inject or use drugs

There is limited evidence for effectiveness of PrEP for the prevention of parenteral HIV acquisition. Pharmacokinetic/ pharmacodynamic modelling suggests that oral PrEP could provide high levels of protection against HIV infection from injecting behaviours (26); however, implementation of PrEP services for people who inject drugs is limited to date (125). The DVR and CAB-LA have not been specifically studied among people who inject drugs. As the DVR releases dapivirine locally in the vagina, it is not expected to offer systemic protection against HIV acquisition, including through parenteral exposure.

People who use and/or inject drugs may also benefit from any PrEP option for the prevention of sexual acquisition of HIV.

PrEP services should not replace comprehensive harm reduction programmes, including needle and syringe programmes. Rather, PrEP should be offered as an additional HIV prevention choice as part of comprehensive harm reduction programmes.

## PrEP for sex workers

While sex workers are often at an increased risk of HIV acquisition, PrEP programmes have often not-prioritised services for sex workers. Sex workers also commonly face barriers to PrEP uptake and use, including stigmatization, discrimination and criminalization. PrEP providers can play an important role in creating services that are acceptable and accessible to sex workers, and that provide HIV PrEP and prevention choices. Collecting and acting on evidence about sex workers' values and preferences, and on barriers and ways to provide acceptable services will be important.

Trials for DVR and CAB-LA did not specifically include sex workers although some participants may have been sex workers; therefore, there is a lack of implementation evidence for this group. Implementation research is needed to understand how to provide acceptable, accessible and effective PrEP services for the DVR and CAB-LA for sex workers. However, some initial evidence may be drawn from oral PrEP studies that support the role of DSD approaches – including peer-led models – as effective strategies for increasing access and uptake among sex workers (126).

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## PrEP for adolescents and young people

In some settings, adolescents and young people under 25 years of age, including young members of key populations, are at increased risk of HIV acquisition and may benefit from PrEP (117). PrEP is generally safe and well tolerated by adolescents and young people. Young key populations in most settings may also benefit from PrEP.

However, TDF-based oral PrEP and CAB-LA may be inappropriate for individuals under a certain weight, and national regulatory authorities may include a minimum weight in approvals (such as 35 kg, as in the case of the United States Food and Drug Administration (US FDA) approval of oral PrEP and CAB-LA (47, 127).

PrEP providers should facilitate access to PrEP for adolescents and young people who may benefit from it. PrEP providers can play a pivotal role in overcoming any age-related legal, policy, regulatory and social barriers to accessing PrEP, and health services more broadly, faced by adolescents, as well as overcoming challenges with logistics and expenses for attending services. For example, age of consent laws that limit access to HIV testing and/or HIVST can be a barrier to PrEP, given that testing is an entry point for PrEP and is required to provide PrEP safely.

PrEP providers can also play a central role in helping to overcome challenges to effective use and persistence. Adolescents and young people often face challenges to use PrEP effectively, including oral PrEP (20, 58) and, in some studies, the DVR (128). Evidence from the REACH (MTN -034) study highlights that the DVR may be highly acceptable among adolescents aged 15–17 years in South Africa, Uganda and Zimbabwe, with a similar favourable safety profile as among adult women (129). Tailored interventions to facilitate adherence among adolescents and young people may be needed, including more regular follow-up and support groups for clients using PrEP, such as social media groups for peer-to-peer sharing of experiences and challenges. Adolescents and young people benefit from clinical services that young people have helped to design, access to social services, non-judgemental and approachable staff, and flexible visit schedules. The use of newer approaches, including virtual visits and HIVST, can be used. Integration of PrEP with other services, especially those that specifically meet the needs of adolescents and young people, such as sexual and reproductive health and mental health services, can also support uptake, persistence and effective use of PrEP by these populations.

## Minimizing PrEP-related stigma

People who could benefit from PrEP, particularly members of key populations, commonly face structural barriers to accessing health care, including stigma and discrimination. Therefore, it is critical that all PrEP services are not only inclusive, compassionate and of high quality, but are also accompanied by enabling interventions that reduce structural barriers to equitable access to health services. See the WHO *Consolidated guidelines on HIV, viral hepatitis and STI prevention, diagnosis, treatment and care for key populations* for further details (4).

PrEP use can be a source of stigma, for example, where PrEP use is associated with behaviours considered socially “undesirable” (such as having casual or multiple sexual partners) or with stigmatized and criminalized behaviours (such as sex work, injecting drug use and same sex relationships) (130, 131). PrEP use can also be stigmatized due to associations with HIV, for example, if others think that PrEP is HIV treatment. Such stigma may decrease PrEP uptake, persistence and effective use.

Normalizing PrEP as a health intervention by presenting PrEP as a responsible choice, situating PrEP within broader sexual health - including improved well-being and mental health, and positive messaging - can reduce PrEP-associated stigma (referred to as “gain-framing” messaging).

Meeting the needs of people who could benefit from PrEP requires the involvement of communities in designing and delivering PrEP services. PrEP providers should receive training in providing culturally competent, respectful and user-centric services. For example, when taking sexual and drug use histories, PrEP providers should be sensitive and non-judgemental, should not require disclosure for clients to access PrEP, and should consider whether recording stigmatized or criminalized behaviours may put clients in danger. DSD approaches for PrEP can also make services acceptable and accessible, for instance by providing community- and home-based services, and by involving communities and peers in service delivery. See WHO guidance on simplified and differentiated PrEP services (3) and the *Consolidated guidelines on HIV, viral hepatitis and STI prevention, diagnosis, treatment and care for key populations* for further details (4).

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# Gaps in clinical knowledge about PrEP

While there has been a significant global scale-up of PrEP programmes delivering oral PrEP (132), experience with delivering the DVR and CAB-LA is largely restricted to clinical trials and other research projects, and significant gaps in clinical knowledge about delivering multiple PrEP products remain. Implementation research among diverse populations across geographies is warranted.



## Knowledge gaps across PrEP products

**Switching between PrEP products and simultaneous use.** Clients may choose to switch between PrEP products. The ideal strategy for transitioning between different PrEP products, including overlapping use of PrEP products, is not currently known. There are also limited data on the safety of using more than one PrEP product at a time. There is no evidence suggesting that using multiple PrEP products at the same time results in any advantage in terms of reduced risk of HIV acquisition (beyond the advantages of each PrEP product individually).

**Efficacy of PrEP for prevention of HIV acquisition through parenteral exposure.** Evidence on the efficacy of oral PrEP at preventing parenteral HIV acquisition is scarce and there is limited implementation of PrEP services for people who inject drugs (125). The DVR and CAB-LA have not been specifically studied among people who inject drugs. As the DVR releases dapivirine locally, it is not expected to offer systemic protection against HIV acquisition, including through parenteral exposure.

People who use and/or inject drugs may benefit from any PrEP option for the prevention of sexual acquisition of HIV. PrEP services should not replace comprehensive harm reduction programmes, including needle and syringe programmes. Rather, PrEP should be offered as an additional HIV prevention choice as part of comprehensive harm reduction programmes.



## Knowledge gaps for TDF-based oral PrEP

**Measuring kidney function for oral PrEP among trans and gender diverse populations taking gender-affirming hormones.** Where kidney function measurement for oral PrEP delivery is implemented (see Table 3 and Annex 1), there are special considerations for trans and gender diverse populations in the context of gender-affirming hormones. Exposure to gender-affirming hormones may influence eGFR estimates and eligibility for oral PrEP (133). Using gender identity rather than sex assigned at birth may be more appropriate in formulas to calculate eGFR for individuals who have been in hormone therapy for over six months (134). However, more research is needed on estimating eGFR in trans and gender diverse populations using gender-affirming hormones, and optimal equations to estimate eGFR in individuals who have been receiving gender-affirming hormones should be considered on a case-by-case basis.

**Oral PrEP dosing for cisgender women.** The evidence is evolving on the relationship between PrEP adherence and efficacy for different routes of exposure and groups, including recent studies suggested more forgiveness in dosing for oral PrEP for cisgender women (25, 135, 136). WHO will continue to review the data as it becomes available.



## Knowledge gaps for the DVR

**Forgetting to remove the ring.** It is not fully known what happens if a user forgets to remove the ring, but limited data from a small study suggest no safety concerns with extended use of the PrEP ring (beyond one month). However, after one month of continuous use, the amount of dapivirine released from the PrEP ring may not be sufficient to effectively protect the user from HIV.

**Pregnancy and breastfeeding.** Data are limited on the use of the ring by pregnant women. Interim results from an ongoing safety trial of ring use during pregnancy indicate that adverse pregnancy outcomes and complications were uncommon among participants using the ring and were generally similar to the rates observed in the surrounding study community (92, 137). One study showed that only a small amount of dapivirine can be detected in human milk (90, 113), suggesting minimal exposure of the drug to the baby from breastfeeding (113, 138).

**DVR and antimicrobial or vaginal antibiotic products.** There are currently no data on concurrent use of the DVR and vaginally administered antimicrobial products, such as metronidazole or clindamycin. Such concurrent use is therefore not suggested and alternative HIV prevention options should be considered.





## Knowledge gaps for CAB-LA

**Time to protection for CAB-LA.** Concentrations of CAB-LA associated with high levels of protection against HIV acquisition are likely reached for most individuals within seven days of the first injection (139). However, further research is needed to better characterize the time to protection and any differences between populations.

**Length of protection after last CAB-LA injection.** Cabotegravir remains at effective levels for two months after the last injection. After stopping CAB-LA, cabotegravir may remain in the body for a prolonged period (12 months or longer for about half of individuals), but at levels that may not prevent HIV (sometimes referred to as the “tail period”) (45).<sup>42</sup> There is currently no evidence to support an alternative dosing schedule for CAB-LA (46).

**CAB-LA during pregnancy and breastfeeding.** Data are limited on the use of CAB-LA during pregnancy and breastfeeding. Among the small number of pregnant or breastfeeding women exposed to CAB-LA, CAB-LA was found to be well tolerated (114) and no congenital anomalies were reported (115). However, more research and safety surveillance in pregnancy are needed to monitor adverse pregnancy and infant outcomes, particularly rare adverse events, through the surveillance of PrEP within larger surveillance programs or antiretroviral pregnancy registries. There are no data yet on whether cabotegravir is present at any significant levels in human milk, impacts human milk production, or affects breastfeeding infants among women exposed to CAB-LA. Given these uncertainties, the risks and benefits of using CAB-LA during pregnancy and/or breastfeeding should be considered on a case-by-case basis, and clients should be counselled that CAB-LA systemic circulation continues after CAB-LA discontinuation.

**CAB-LA and HIV drug resistance.** There are risks of delayed diagnosis and HIV drug resistance when an individual with a pre-existing HIV infection initiates CAB-LA, an individual acquires HIV while using CAB-LA, or an individual acquires HIV within 6 months of stopping CAB-LA. Across the published clinical trials, the number of people who started CAB-LA with AHI or who acquired HIV while taking CAB-LA was small (41, 50, 140–142). Although some individuals had INSTI-resistance associated mutations detected at the time of HIV diagnosis, the clinical effectiveness of first-line ART regimens containing DTG, for example, tenofovir disoproxil fumarate, lamivudine, dolutegravir (TLD), among those with CAB resistance is currently unknown. To date, the emergence of these drug-resistance mutations has only been observed in individuals who received CAB-LA within the 6 months prior to their HIV diagnosis (140, 143). INSTI-associated resistance mutations have not been detected in people who received CAB-LA PrEP more than 6 months before their diagnosis. Further research, as well as monitoring and evaluation of PrEP programs are needed to quantify the risks of HIV drug resistance after CAB-LA exposure, identify the factors associated with INSTI drug resistance, and determine the clinical impact of CAB-related INSTI drug resistance mutations on ART regimens containing DTG.

Although earlier diagnosis of breakthrough HIV infections may be possible with the use of molecular tests, these are expensive and often not readily available at the point-of-care in many low- and middle-income countries. WHO and several regulatory authorities do not require molecular testing, for example, NAAT, for CAB-LA delivery. Research on the role of HIVST in implementing long-acting injectable PrEP options, such as CAB-LA, is also needed. Further implementation research and monitoring of different testing approaches will be important to establish the optimal testing strategy for safe and effective CAB-LA delivery.

**CAB-LA for trans and gender diverse people.** Limited available data from the HPTN 083 clinical trial suggest CAB-LA drug concentrations were similar among transgender women using gender-affirming hormones compared with those not taking gender-affirming hormones (123, 124). Although no impact is expected based on metabolism, research is needed on the impact of CAB-LA on gender-affirming hormones. Moreover, there is currently limited evidence for alternative CAB-LA injection sites for individuals with gluteal implants, although evidence on cabotegravir/rilpivirine for HIV treatment suggests similar pharmacokinetics after thigh injections compared to gluteal injections (144). More research is needed on delivering CAB-LA for trans and gender diverse populations, including integration with gender-affirming care services and alternative injection sites.

<sup>42</sup> The HPTN 077 study found that the time to the lower limit of quantification of CAB-LA after the last injection was 43.7 weeks for those assigned male at birth (range: 20.4–152.5 weeks) and 67.3 weeks for those assigned female at birth (range: 17.7–225.5 weeks).

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## Suggested further reading

Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: Recommendations for a public health approach. Geneva: World Health Organization; 2021. (<https://iris.who.int/handle/10665/342899>)

Consolidated guidelines on HIV viral hepatitis and STI prevention, diagnosis, treatment and care for key populations. Geneva: World Health Organization; 2022. (<https://iris.who.int/handle/10665/360601>)

Differentiated and simplified pre-exposure prophylaxis for HIV prevention: update to WHO implementation guidance. Geneva: World Health Organization; 2022. (<https://iris.who.int/bitstream/handle/10665/360861/9789240053694-eng.pdf>)

Global health sector strategies on, respectively, HIV, viral hepatitis and sexually transmitted infections for the period 2022–2030. Geneva: World Health Organization; 2022 (<https://iris.who.int/bitstream/handle/10665/360348/9789240053779-eng.pdf>)

Guidelines on long-acting injectable cabotegravir for HIV prevention. Geneva: World Health Organization; 2022. (<https://iris.who.int/bitstream/handle/10665/360869/9789240054097-eng.pdf>)

WHO implementation tool for pre-exposure prophylaxis (PrEP) of HIV infection. Module 13. Integrating STI services. Geneva: World Health Organization; 2022. (<https://iris.who.int/bitstream/handle/10665/362227/9789240057425-eng.pdf>)



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# Annex. Suggested procedures for measuring kidney function for TDF-containing oral PrEP

## Suggested procedures

Impaired kidney function, indicated by an estimated glomerular filtration rate (eGFR) of <60 mL/min per 1.73 m<sup>2</sup> or an estimated creatinine clearance of <60 mL/min, is a contraindication for TDF-based oral PrEP. Table A1 outlines suggested procedures for measuring kidney function for PrEP initiation and continuation for different populations. Where required, kidney function can be measured within three months of PrEP initiation. Waiting for a kidney function test result should not delay initiation or continuation of oral PrEP, as results can be reviewed at follow-up visits.

**Table A1. Suggested procedures for measuring kidney function for TDF-containing oral PrEP.**

Population	Measurement of kidney function	
	At initiation	At follow-up
Individuals aged under 30 years and no kidney-related comorbidities <sup>a</sup>	Optional	If no initiation test conducted or if initiation test is normal, <sup>b</sup> follow-up is optional.  If initiation test result suggests at least mild loss of kidney function, <sup>c</sup> follow-up measurements every 6–12 months are suggested.
Individuals aged 30–49 years and no kidney-related comorbidities <sup>a</sup>	Optional/conduct once, at, or within three months of initiation <sup>d</sup>	If initiation test is normal, <sup>b</sup> follow-up is optional.  If initiation test result suggests at least mild loss of kidney function, <sup>c</sup> follow-up measurements every 6–12 months are suggested.
Individuals aged 50+ years and with no kidney-related comorbidities <sup>a</sup> Individuals of any age with kidney-related comorbidities <sup>a</sup> Individuals with previous measurement of kidney function suggesting at least mild loss of kidney function	Conduct once, at or within three months of initiation	Follow-up measurements every 6–12 months.

PrEP: pre-exposure prophylaxis; TDF: tenofovir disoproxil fumarate.

<sup>a</sup> Kidney-related comorbidities include chronic kidney disease or risk factors such as diabetes or hypertension. There may be an increased risk of kidney-related adverse events during pregnancy, and conditions such as preeclampsia may cause kidney impairment, so more frequent kidney function testing may be considered during pregnancy.

<sup>b</sup> eGFR ≥90 mL/min per 1.73 m<sup>2</sup> or creatinine clearance of ≥90 mL/min.

<sup>c</sup> eGFR <90 mL/min per 1.73 m<sup>2</sup> or creatinine clearance of <90 mL/min.

<sup>d</sup> Risks of kidney impairment and kidney-related adverse events remain low among those aged 30–49 years without kidney-related comorbidities, particularly those aged 30–39, so kidney function monitoring can be considered optional in this group too, depending on available resources.





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