

WHO IMPLEMENTATION TOOL FOR PRE-EXPOSURE PROPHYLAXIS (PrEP) OF HIV INFECTION



JULY 2017



World Health
Organization

WHO/HIV/2017.17

© **World Health Organization 2017**

Some rights reserved. This work is available under the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 IGO licence (CC BY-NC-SA 3.0 IGO; <https://creativecommons.org/licenses/by-nc-sa/3.0/igo>).

Under the terms of this licence, you may copy, redistribute and adapt the work for non-commercial purposes, provided the work is appropriately cited, as indicated below. In any use of this work, there should be no suggestion that WHO endorses any specific organization, products or services. The use of the WHO logo is not permitted. If you adapt the work, then you must license your work under the same or equivalent Creative Commons licence. If you create a translation of this work, you should add the following disclaimer along with the suggested citation: "This translation was not created by the World Health Organization (WHO). WHO is not responsible for the content or accuracy of this translation. The original English edition shall be the binding and authentic edition".

Any mediation relating to disputes arising under the licence shall be conducted in accordance with the mediation rules of the World Intellectual Property Organization.

Suggested citation. WHO Implementation tool for pre-exposure prophylaxis (PrEP) of HIV infection. Module 1: Clinical. Geneva: World Health Organization; 2017 (WHO/HIV/2017.17). Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at <http://apps.who.int/iris>.

Sales, rights and licensing. To purchase WHO publications, see <http://apps.who.int/bookorders>. To submit requests for commercial use and queries on rights and licensing, see <http://www.who.int/about/licensing>.

Third-party materials. If you wish to reuse material from this work that is attributed to a third party, such as tables, figures or images, it is your responsibility to determine whether permission is needed for that reuse and to obtain permission from the copyright holder. The risk of claims resulting from infringement of any third-party-owned component in the work rests solely with the user.

General disclaimers. The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by WHO in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by WHO to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall WHO be liable for damages arising from its use.

Layout by L'IV Com Sàrl, Villars-sous-Yens, Switzerland.

Cover photos: ©prepster.info; © John Rae, NYC; © Innovation: Africa

Contents

INTRODUCTION	2
THE CLINICAL MODULE	4
Example of a pocket card for PrEP providers	4
Eligibility for PrEP	5
Practical screening questions	6
A sample of a record form for PrEP and PEP screening	7
Contraindications to PrEP	8
PrEP regimens containing tenofovir disoproxil fumarate (TDF)	9
PrEP usage	10
Suggested clinical procedure schedule	10
Management of creatinine elevation	12
Management of seroconversion	13
Key counselling regarding PrEP efficacy	13
Key counselling regarding PrEP safety	15
Special situations	16
Minimizing PrEP stigma	17
Gaps in clinical knowledge about PrEP	18
FURTHER READING	20
REFERENCES	21

Introduction

Following the WHO recommendation in September 2015 that “oral pre-exposure prophylaxis (PrEP) should be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination HIV prevention approaches”, partners in countries expressed the need for practical advice on how to consider the introduction of PrEP and start implementation. In response, WHO has developed this series of modules to support the implementation of PrEP among a range of populations in different settings.

Although there is growing acknowledgement of PrEP’s potential as an additional HIV prevention option and countries are beginning to consider how PrEP might be most effectively implemented, there has been limited experience with providing PrEP outside research and demonstration projects in low- and middle-income countries. Consequently, there is often uncertainty around many implementation issues. The modules in this tool provide initial suggestions for the introduction and implementation of PrEP based on currently available evidence and experience. However, it is recognized that this evidence may evolve following wider PrEP use; therefore, it is likely that this tool will require regular updating.

PrEP should not replace or compete with effective and well-established HIV prevention interventions, such as comprehensive condom programming for sex workers and men who have sex with men and harm reduction for people who inject drugs. Many people who could benefit most from PrEP belong to key population groups that may face legal and social barriers to accessing health services. This needs to be considered when developing PrEP services. Although the public health approach underpins the WHO guidance on PrEP, the decision to use PrEP should always be made by the individual concerned.

Target audience and scope of tool

This PrEP tool contains modules for a range of stakeholders to support them in the consideration, planning, introduction and implementation of oral PrEP. The modules can be used on their own or in combination. In addition, there is a module for individuals interested in or already taking PrEP. (See Summary of modules below.)

This tool is the product of collaboration between many experts, community organizations and networks, implementers, researchers and partners from all regions. The information presented is aligned with WHO’s 2016 consolidated guidelines on the use of antiretroviral drugs for HIV treatment and prevention.

All modules make reference to the evidence-based 2015 WHO recommendation on PrEP. They do not make any new recommendations on PrEP, focusing instead on suggested implementation approaches.

Guiding principles

It is important to adopt a public health, human rights and people-centred approach when offering PrEP to those at substantial risk of HIV. Similar to other HIV prevention and treatment interventions, a human rights-based approach gives priority to issues concerning universal health coverage, gender equality and health-related rights including accessibility, availability, acceptability and quality of PrEP services.

SUMMARY OF MODULES



Module 1: Clinical. This module is for clinicians, including physicians, nurses and clinical officers. It gives an overview of how to provide PrEP safely and effectively, including: screening for substantial risk of HIV; performing appropriate testing before initiating someone on PrEP and while the person is taking PrEP; and how to follow up PrEP users and offer counselling on issues such as adherence.



Module 2: Community educators and advocates. For PrEP services to reach populations in an effective and acceptable way, community educators and advocates are needed to increase awareness about PrEP in their communities. This module provides up-to-date information on PrEP that should be considered in community-led activities that aim to increase knowledge about PrEP and generate demand and access.



Module 3: Counsellors. This module is for staff who counsel people as they consider PrEP or start taking PrEP and support them in addressing issues around coping with side-effects and adherence strategies. Those who counsel PrEP users may be lay, peer or professional counsellors and healthcare workers, including nurses, clinical officers and doctors.



Module 4: Leaders. This module aims to inform and update leaders and decision-makers about PrEP. It provides information on the benefits and limitations of PrEP so that they can consider how PrEP could be most effectively implemented in their own settings. It also contains a series of frequently asked questions about PrEP, with related answers.



Module 5: Monitoring and evaluation. This module is for people responsible for monitoring PrEP programmes at the national and site levels. It provides information on how to monitor PrEP for safety and effectiveness, suggesting core and additional indicators for site-level, national and global reporting.



Module 6: Pharmacists. This module is for pharmacists and people working in pharmacies under a pharmacist's supervision. It provides information on the medicines used in PrEP, including the optimal storage conditions. It also gives suggestions for how pharmacists and pharmacy staff can monitor PrEP adherence and support PrEP users to take their medication regularly.



Module 7: Regulatory officials. This module is for national authorities in charge of authorizing the manufacturing, importation, marketing and/or control of antiretroviral medicines used for HIV prevention. It provides information on the safety and efficacy of PrEP medicines.



Module 8: Site planning. This module is for people involved in organizing PrEP services at specific sites. It outlines the steps to be taken in planning a PrEP service and gives suggestions for personnel, infrastructure and commodities that could be considered when implementing PrEP.



Module 9: Strategic planning. As WHO recommends offering PrEP to people at substantial HIV risk, this module offers public health guidance for policy-makers on how to prioritize services, in order to reach those who could benefit most from PrEP, and in which settings PrEP services could be most cost-effective.



Module 10: Testing providers. This module is for people who are responsible for providing testing services at PrEP sites and associated laboratories. It offers guidance in selecting relevant testing services, including appropriate screening of individuals before PrEP is initiated and monitoring while they are taking PrEP. Information is provided on testing for HIV, creatinine, hepatitis B and C virus, pregnancy and sexually transmitted infections.



Module 11: PrEP users. This module provides information for people who are interested in taking PrEP to reduce their risk of acquiring HIV and people who are already taking PrEP – to support them in their choice and use of PrEP. This module gives ideas for countries and organizations implementing PrEP to help them develop their own tools.

ANNEXES

Review of evidence. A wide range of evidence including the following two systematic reviews informed the 2015 WHO recommendation on PrEP for people at substantial risk of HIV infection: (i) Fonner VA et al. *Oral tenofovir-based HIV pre-exposure prophylaxis (PrEP) for all populations: a systematic review and meta-analysis of effectiveness, safety, behavioural and reproductive health outcomes*; (ii) Koechlin FM et al. *Values and preferences on the use of oral pre-exposure prophylaxis (PrEP) for HIV prevention among multiple populations: a systematic review of the literature*.

Annotated Internet resources. This list highlights some of the web-based resources on PrEP currently available together with the stakeholder groups they are catering to. WHO will continue to provide updates on new resources.

The clinical module

This module seeks to provide an overview of relevant information for clinicians, including physicians, nurses and clinical officers, who are providing PrEP in clinical settings. It describes important considerations when starting PrEP in an individual and monitoring PrEP use.

The following two-sided pocket card summarizes this module.

Example of a pocket card for PrEP providers

WHO CLINICAL PREP BASICS

Indications for PrEP (by history over the past 6 months):

HIV-negative AND

Sexual partner with HIV who is not virally suppressed, OR

Sexually active in a high HIV incidence/prevalence population AND any of the following:

- Vaginal or anal sexual intercourse without condoms with more than one partner, OR
- A sexual partner with one or more HIV risk factors, OR
- A history of a sexually transmitted infection (STI) by lab testing or self-report or syndromic STI treatment, OR
- Use of post-exposure prophylaxis (PEP), OR
- Requesting PrEP.

Contraindications:

- HIV-positive
- Estimated creatinine clearance <60 ml/min
- Signs/symptoms of acute HIV infection, probable recent exposure to HIV
- Allergy or contraindication to any medicine in the PrEP regimen.



#OfferPrEP

Rx (example): TDF 300 mg + FTC 200 mg PO daily #90 tablets.

Counselling: Link tablet use with a daily routine.

Develop a plan for contraception or safer conception and for STI prevention.

Key effectiveness messages:

PrEP is highly effective for preventing HIV infection when used as prescribed.

PrEP does not prevent pregnancy or STIs.

Side-effects:

1 in 10 PrEP users may have side-effects such as nausea, abdominal cramps, headache; these are usually mild and resolve over the first month of taking PrEP.

1 in 200 may have creatinine elevation (typically reversible if stop PrEP).

1% average loss of bone mineral density; recovers after stopping PrEP.

Initial tests:

HIV test; suggest Cr, HBsAg, STIs screening (e.g. syphilis, gonorrhoea, chlamydia); consider HCV for MSM.

Every 3 months: HIV test, suggest check STIs, assess PrEP indications and use.

Every 6 months: Suggest Cr.

Special situations:

- Exposure to HIV in the past 72 hours: use PEP for 28 days, then start PrEP.
- Acute viral syndrome: consider re-testing in 1 month before PrEP initiation.
- Pregnancy and breastfeeding: PrEP can be offered and continued.
- If HBsAg *negative*: consider vaccination; if HBsAg *positive*: assess HBV treatment indications; consider risk of flare if PrEP stopped.
- Adolescents: may benefit from more frequent appointments e.g. monthly visits.

#OfferPrEP

More information: <http://who.int/hiv/pub/prep/implementation-tool>

Eligibility for PrEP

PrEP providers should educate and counsel potential PrEP users about the risks and benefits of PrEP and may conduct an individualized risk-benefit assessment to assess eligibility.

Eligibility criteria include:

- HIV-negative
- no suspicion of acute HIV infection
- substantial risk of HIV infection
- no contraindications to PrEP medicines (e.g. TDF/FTC)
- willingness to use PrEP as prescribed, including periodic HIV testing.

The sexual partner of someone with HIV who is not on suppressive ART

PrEP can protect the HIV-negative partner in a serodiscordant relationship when the HIV-positive partner is either not on antiretroviral therapy (ART) or has not yet achieved viral suppression.

ART that suppresses viral load is highly effective for preventing HIV transmission to others (1). Still, PrEP may provide additional protection to serodiscordant couples in a number of situations:

1. ART may take up to six months to suppress viral load; in studies of serodiscordant couples, PrEP has provided a useful bridge to full viral suppression by the partner during that time (2).
2. The HIV-negative partner has doubts about the effectiveness of the partner's treatment or has other partners besides the HIV-positive partner on treatment.
3. There have been gaps in the partner's treatment adherence or the couple is not communicating openly about treatment adherence and viral load test results.

In addition, any sign of intimate partner violence, controlling behaviour, or anger or fear in response to questions about HIV treatment may prompt a discussion about the risks and benefits of PrEP as a possible way to control the risk of HIV transmission. This would also be an opportunity to refer the person to prevention and treatment services for intimate partner violence.

Screening for “substantial risk of HIV infection”

PrEP should be considered for other people who are at substantial risk of acquiring HIV (3). This could include someone in a **high HIV prevalence population or geographical location** who has had any of the following risk factors in the past six months:

- vaginal or anal sexual intercourse without a condom with more than one partner, OR
- a recent history (in the last six months) of a sexually transmitted infection (STI) by laboratory testing or self-report or syndromic STI treatment, OR
- has used post-exposure prophylaxis (PEP) for sexual exposure in the past six months.

Indicators of substantial risk of HIV infection vary depending on local HIV epidemiology and population group (see module on strategic planning).

Inconsistent use of condoms (male or female), including an intention to use condoms during sex with some occasional omissions or accidents, increases HIV risk (4). Social desirability bias in reporting condom use may occur, so PrEP could be considered for people reporting any intercourse without a condom or concerns about their future use of condoms. For example, someone who reports a desire to stop using condoms may be already having sex without condoms.

Recently diagnosed STIs are often indicators of risk of sexual acquisition of HIV. The predictive value of STI indicators varies by region, the type of STI and a person's demographic characteristics. A new diagnosis of syphilis or genital herpes is a strong predictor of HIV risk among men who have sex with men in most settings and among heterosexual men and women in areas of high HIV prevalence. PrEP services should be prioritized; local epidemiology will be essential to guide decisions about when to offer PrEP and to which populations.

Requesting PrEP has been shown to be an indicator of substantial risk (5–8). HIV incidence among people requesting PrEP has been higher than expected from observational studies in the same locality (6–8). People at high risk of acquiring HIV infection who request PrEP tend to have greater PrEP uptake, adherence and retention. Clinicians should consider any request for PrEP seriously (8), especially for individuals in settings where the local epidemiology indicates likely substantial HIV risk in their population group.

People who use and/or inject drugs are often at substantial HIV risk. WHO recommends a package of effective HIV services be provided for all people who inject drugs, including harm reduction (in particular opioid substitution therapy and needle syringe programmes). When these interventions are available, the risk of HIV transmission is significantly reduced. Providing these services should be a priority.

People who use and/or inject drugs may also be at risk of sexual transmission of HIV. In particular, this may be the case among people who use amphetamine type stimulants and engage in higher risk sexual practices (including among some subgroups of men who have sex with men in some settings). There may also be a link with sex work and not being empowered to use condoms consistently with all clients or with intimate partners.

Access to harm reduction remains the mainstay of HIV prevention for people who inject drugs. However, this population should not be excluded from PrEP services. PrEP can be considered for people who use drugs for whom harm reduction services – sterile injecting equipment and opioid substitution therapy – are not relevant, such as people using amphetamine type stimulants who are at substantial risk of HIV infection.

Practical screening questions

PrEP should be provided to individuals who want to use PrEP *if local criteria for PrEP use are met*. Easy and practical questions could be developed for screening individuals for PrEP. However, asking questions should not be seen as a way of rationing PrEP or excluding people from PrEP services. In PrEP demonstration projects and clinical services, people who asked for PrEP were likely to have made this choice based on a careful assessment of their own personal circumstances, risk and desire for additional HIV prevention.

Screening questions should be framed in terms of people's behaviour.

Screening questions can be used to introduce the consideration and offer of PrEP to people who are attending services but had not presented specifically to access PrEP. Preferably, screening questions should be framed in terms of people's behaviour rather than their sexual identity and should refer to a defined time period. It is important for PrEP providers to be sensitive, inclusive and non-

judgemental, and support people who want and would benefit from PrEP rather than develop a screening process that would discourage PrEP use.

For example, some of the following questions could be used to identify individuals who may benefit from PrEP.

1. General screening questions. Any "yes" answer from a person presenting in a high HIV incidence setting should prompt a discussion of the risks and benefits of PrEP.

In the past six months,

- "Have you had sex with more than one person?"
- "Have you had sex without a condom?"
- "Have you had sex with anyone whose HIV status you do not know?"
- "Have you injected drugs and shared injecting equipment?"
- "Are any of your partners at risk of HIV, through sexual or drug using behaviour?"
- "Do you have sex with a person who has HIV?"

- "Have you received a new diagnosis of a sexually transmitted infection?"
- "Do you desire pregnancy?"
- "Have you used or wanted to use PrEP or PEP for sexual or drug using exposure to HIV?"

2. For people who have a sex partner with HIV, the following questions will help to ascertain whether that person might benefit from PrEP:

- "Is your partner taking ART for HIV?"
- "Has your partner been on ART for more than six months?"
- "At least once a month, do you discuss whether your partner is taking HIV medication daily?"
- "If you know, when was your partner's last HIV viral load test? What was the result?"
- "Do you desire pregnancy with your partner?"
- "Do you use condoms every time you have sex?"

3. Additional factors to ask about, which may indicate situations that confer increased vulnerability to HIV and help to identify someone who may benefit from PrEP:

Are there aspects of your situation that may indicate higher risk of HIV? Have you...

- "Started having sex with a new partner?"
- "Ended a long-term relationship and are looking for a new partner?"
- "Received money, housing, food or gifts in exchange for sex?"
- "Been forced to have sex against your will?"
- "Been physically assaulted, including assault by a sexual partner?"
- "Injected drugs or hormones using shared equipment?"
- "Used recreational or psychoactive drugs?"
- "Been forced to leave your home (especially if due to sexual orientation or violence)?"
- "Moved to a new place (possibly having a higher prevalence of HIV exposure)?"
- "Lost a source of income (such that you may need to exchange sex for shelter, food or income)?"
- "Left school earlier than you planned?"

A sample of a record form for PrEP and PEP screening

The form in Figure 1 could be used and adapted to record key elements in a sexual and drug using history that suggest the need to screen before offering PrEP or PEP and for acute HIV infection. The asterisks used in the form indicate which responses should prompt which considerations. Use of standard medical record questions can expedite the monitoring and evaluation of PrEP services at the country level, and globally. If similar questions are asked on existing medical forms, updating the form to include PrEP- and PEP-related questions will be easier for staff than implementing an additional, duplicative form. The form also includes questions about current and recent PrEP or PEP use, which is helpful for tracking new versus continuing users of PrEP and PEP.

FIGURE 1. EXAMPLE OF A RECORD FORM FOR PREP AND PEP SCREENING

RECORD FORM FOR PREP AND PEP SCREENING				
What was your sex at birth?	Male	Female	Other	
What is your current gender?	Male	Female	Other	
What is your current age?	years			
In the past 6 months:				
With how many people did you have vaginal or anal sex?	0	1	2*	3+* men 3+* women
Did you use a condom every time you had sex?	Yes	No*	Don't Know*	
Did you have a sexually transmitted infection?	Yes*	No	Don't Know*	
Do you have a sexual partner who has HIV?	Yes	No	Don't Know*	
If "Yes," has he or she been on antiretroviral therapy for 6 or more months?	Yes	No*	Don't Know*	
If "Yes," has the therapy suppressed viral load?	Yes	No*	Don't Know*	
In the past 3 days:				
Have you had sex without a condom with someone with HIV who is not on treatment?	Yes**	No	Don't Know**	
Have you had a "cold" or "flu" such as sore throat, fevers, sweats, swollen glands, mouth ulcers, headache or rash?	Yes***	No	Don't Know	
*Consider offering PrEP; **Consider offering PEP; ***Consider acute HIV.				

Contraindications to PrEP

The contraindications for PrEP are:

- HIV infection
- signs/symptoms of acute HIV infection, probable recent exposure to HIV
- estimated creatinine clearance of less than 60 ml/min (if known)
- allergy or contraindication to any medicine in the PrEP regimen.

Ruling out current HIV infection when starting PrEP

HIV infection should be ruled out by testing.

Existing HIV infection should be ruled out by testing. HIV testing should be performed the same day that PrEP is started, using a point-of-care rapid HIV test. HIV testing will often follow the national HIV testing algorithm. The first test in the testing strategy should be the most sensitive test available. (See testing providers module of this implementation tool). If there are signs or

symptoms of an acute viral syndrome, including a flu-like illness, the possibility that acute HIV infection could be the cause should be considered. In such circumstances consider deferring PrEP for four weeks and having the person tested for HIV again. This allows time for possible seroconversion to be detected (9).

Creatinine and estimated creatinine clearance

Blood creatinine measured before beginning PrEP and every six months after the start of PrEP was sufficient to assure renal safety in an African demonstration project (10); more frequent creatinine monitoring may be warranted if there are co-morbid conditions that can affect renal function, such as diabetes mellitus and uncontrolled hypertension. Clinically significant creatinine elevations were extremely rare in people less than 45 years of age who had a baseline estimated creatinine clearance more than 90 ml/min and who weighed more than 55 kg (10, 11). Whether monitoring renal function is essential to assure safe use of PrEP is not yet known. Most PrEP studies monitored renal function with blood creatinine every three to six months (10, 12–14); creatinine elevations were mild, mostly self-limited, and reversible (15).

The laboratory should calculate estimated creatinine clearance and report this with the creatinine result. If the laboratory does not have the capacity to estimate creatinine clearance, the provider can use the Cockcroft–Gault equation to calculate estimated creatinine clearance based on measured serum creatinine, the client's sex at birth, age and estimated lean body weight¹.

COCKCROFT–GAULT EQUATION:

$$\text{Estimated Cr Clearance} = \text{Sex} * ((140 - \text{Age}) / (\text{SerumCreat})) * (\text{Weight} / 72)$$

Notes:

- For "sex", use 1 for a male, 0.85 for a female
- Give "age" in years
- Provide "serum creatinine" in mg/dL
- Give "weight" in kilograms

The Cockcroft–Gault equation gives appropriate estimates of creatinine clearance in people over the age of 12 years (16). For transgender populations, the sex at birth is used in the Cockcroft–Gault equation if the person is not using hormone therapy (17); among transgender populations using hormone therapy for more than three months, the current gender can be used (18). If Cockcroft–Gault calculations are not feasible, the clinician may consider excluding people with serum creatinine levels that are higher than the upper limit of normal as established in the laboratory that is reporting the result.

Creatinine measurements vary from day to day, depending on hydration, exercise, diet, creatine use (used by body builders) and other factors. Therefore, *if a single creatinine measurement is above the normal range, the measurement should be repeated before excluding that person from PrEP services.*

PrEP regimens containing tenofovir disoproxil fumarate (TDF)

WHO recommends oral PrEP regimens containing TDF (3). Selection of a PrEP regimen containing TDF depends on which combinations of medicines are available in the country, relative costs, regulatory status, and in-country normative guidance from professional societies or public health officials. The following regimens can be considered for use as PrEP.

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

TDF/FTC has proved safe and effective for adult men who have sex with men (19), transgender women (20) and heterosexual men and women (21, 22). As of September 2016, this regimen has been approved for use as PrEP by the United States Food and Drug Administration, and regulatory authorities in Australia, Canada, France, Kenya, Peru and South Africa. Approval is pending in other countries across Africa, Asia, Europe, and South America.

¹ See, for example, <http://reference.medscape.com/calculator/creatinine-clearance-cockcroft-gault>

Single-agent tenofovir disoproxil fumarate (TDF) 300 mg PO daily #90

A WHO meta-analysis (23) and the Partners PrEP trial (24) found that TDF alone and TDF/FTC are comparably safe and effective for heterosexual men and women (see appendix on evidence to decision). Single-agent TDF PrEP is also effective for people who inject drugs (25). In the WHO meta-analysis, risk of drug resistance during PrEP was low overall (23) and still lower among serodiscordant couples randomized to receive single-agent TDF compared with those randomized to receive TDF/FTC (26). There is limited evidence on the use of TDF alone for PrEP among men who have sex with men (27), and two cases have been recently reported of men who acquired HIV infection while taking TDF monotherapy for hepatitis B virus (HBV) infection (28). If available, single-agent TDF may be considered for use as PrEP for the prevention of heterosexual HIV transmission.

PrEP usage

PrEP should be used daily during periods of substantial risk of HIV acquisition, and can be stopped during periods of low or no risk. Events that herald the beginning or end of periods of risk will vary by region, demographic group, sociocultural practices and individual factors. For example, entering sex work, moving to a region that has a high HIV prevalence, or visiting home after work in the mining industry (29) may represent readily identified periods of substantial risk. Learning how best to guide PrEP users on how to start and stop PrEP is an emerging topic for implementation research.

On-demand/event-driven PrEP

Comparisons of daily and event-driven PrEP regimens are limited by the size and diversity of the studies. The effectiveness of event-driven oral PrEP regimens among women and heterosexual men has not yet been evaluated. Daily dose is the current WHO-recommended option.

Medicines supply

The optimal number of tablets to be dispensed has not been determined, and will likely vary by setting and population. PrEP discontinuation rates are often higher in the first four weeks (30), so some clinics may opt to dispense a one month supply at the first visit and then a three to four month supply at subsequent visits. If available, providing an extra month's supply of medicine at the first visit assures an adequate supply for daily dosing until the next clinic visit. For example, if clinic visits are planned for every three months, sufficient medicine for four months might be provided at the first visit. This is important in case the visit is delayed for any reason. Users who have some medicine supply in reserve may have better adherence (30). Also, a reserve supply may help users avoid rationing tablets as their next clinic visit approaches.

The optimal time to start PrEP has not been determined to date. Whether to start PrEP at the first visit will depend on the individual circumstances. Same-day start may be considered, for example when a potential user is requesting PrEP, reflecting a decision-making process has already taken place. As discussed above, requesting PrEP has been shown to be an indicator of substantial risk, which may lead to greater PrEP uptake, adherence and retention. If, however, the person is considering PrEP for the first time, it may be beneficial for them to be given the opportunity to return for another clinic visit after having had time to consider whether PrEP is something that they want and are motivated to take.

Suggested clinical procedure schedule

Initial visit

Table 1 shows investigations and interventions suggested to be undertaken at the first PrEP clinic visit. HIV-negative antibody status should be verified before PrEP is started. Some PrEP services routinely start PrEP the same day that people present for services, provided that specimens for suggested laboratory tests other than HIV testing (including creatinine, hepatitis B surface antigen (HBsAg) and STIs) are collected and sent to the laboratory and the PrEP user can be contacted if test results require additional action, confirmation or treatment.

TABLE 1. SUGGESTED PROCEDURES WHEN PREP IS STARTED (FIRST VISIT)

INVESTIGATION/INTERVENTION	RATIONALE
HIV test (using algorithm in national HIV testing services guidelines)	To assess HIV infection status. If recent exposure (in the past 72 hours), consider PEP and re-test after 28 days. To complete a symptom checklist for possible acute HIV infection.
Serum creatinine	To identify pre-existing renal disease (estimated creatinine clearance less than 60 ml/min).
Hepatitis B surface antigen	If negative, consider vaccination against hepatitis B. If positive, suggest further testing and assessment for hepatitis B treatment.
Hepatitis C antibody	Consider for MSM populations If positive, consider referral for assessment and treatment for hepatitis C infection.
Rapid plasma reagin	To diagnose and treat syphilis infection.
Other screening for sexually transmitted infection (STI)	To diagnose and treat STI (syndromic or diagnostic STI testing, depending on local guidelines).
Pregnancy testing	To guide antenatal care, contraceptive and safer conception counselling, and to assess risk of mother to child transmission. Pregnancy is not a contraindication for PrEP use (see section below).
Review vaccination history	Depending on local guidelines, epidemiology and populations, consider vaccination for hepatitis A (e.g. MSM) (31), human papilloma virus, tetanus and meningitis.
Counselling	To assess whether the client is at substantial risk of HIV. To discuss prevention needs and provide condoms and lubricants. To discuss desire for PrEP and willingness to take PrEP. To develop a plan for effective PrEP use, sexual and reproductive health. To assess fertility intentions and offer contraception or safer conception counselling. To assess intimate partner violence and gender-based violence. To assess substance use and mental health issues.

Follow-up visits

It is suggested that a person starting PrEP should have an HIV test every 3 months.

The optimal frequency for monitoring PrEP use has not been established, but it is suggested that a person starting PrEP should have an HIV test every three months. Other suggested follow-up tests are summarized in Table 2.

TABLE 2. SUGGESTED PREP FOLLOW-UP PROCEDURES

INTERVENTION	SCHEDULE FOLLOWING PREP INITIATION
Confirmation of HIV-negative status	Every 3 months. Consider also testing at 1 month.
Address side-effects	Every visit.
Brief adherence counselling	Every visit.
Estimated creatinine clearance	Every 6 months. Consider more frequently if there is a history of conditions affecting the kidney, such as diabetes or hypertension; consider less frequently if age is less than 45, baseline estimated creatinine clearance more than 90 ml/min, and weight more than 55 kg.
Hepatitis C antibody	Consider testing MSM every 12 months.
Provide screening for sexually transmitted infections (STI), condoms, contraception or safer conception services as needed. Note: frequency of STI screening may be every 3 or 6 months depending on population and national policy. Provide counselling regarding effective PrEP use (adherence), prevention of STIs, recognition of symptoms of STIs, and issues related to mental health, intimate partner violence and substance use.	

Adolescents and young adults (24 years old or less) may benefit from more frequent clinic visits to address their changing routines and multiple needs. Young people also benefit from clinical services that other young people have helped to design, access to social services, non-judgmental and approachable clinic staff and flexible clinic schedules. People with multiple sexual partners may benefit from screening for STIs every three to six months. Additional interactions with health workers can take place by telephone, for example to discuss laboratory results.

HIV testing following the WHO testing strategy must be performed before PrEP is started. Additional HIV testing conducted after one month of PrEP use can detect acute infection that may have been incubating when PrEP was started. HIV testing should also take place when PrEP is restarted. The optimum frequency of HIV testing to minimize resistance has not been established. Based on the frequency of testing performed in PrEP demonstration projects, testing for HIV should occur every three months while on PrEP (5, 32, 33).

HIV self-testing can be acceptable, reliable and convenient, and could be considered as part of demand creation activities for PrEP. However, clinic-based testing is always required before PrEP initiation. HIV self-testing has also been shown to be beneficial and acceptable for clients between clinic visits (34, 35). However, oral fluid tests used for HIV self-testing may be associated with a delay in detection of seroconversion during PrEP use (22) and should not replace clinic-based testing every three months while taking PrEP.

Management of creatinine elevation

Approximately one in every 200 PrEP users will have an elevation of serum creatinine during PrEP use. Participants randomized to the TDF-containing arms of PrEP trials had creatinine elevations (defined as a 50% increase above baseline or an elevation above the normal range) 36% more frequently than participants randomized to the placebo arms, although the absolute risk increase was small in this analysis (pooled risk increase 0.6%; 95% CI 0.1–1.2) (15). Approximately 80% of creatinine elevations are self-limiting (without stopping PrEP) and resolve when a separate specimen, collected on a different day, is tested (12). Such transient creatinine elevations are often due to dehydration, exercise or diet, or they could reflect a false positive creatinine test result. Creatinine elevations associated with starting PrEP usually reverse after stopping PrEP and do not reoccur when restarting PrEP (12–14).

The clinician should consider discontinuing PrEP if a creatinine elevation is confirmed on a separate specimen and if the estimated creatinine clearance decreases to less than 60 ml/min. Once PrEP is stopped, creatinine levels can be rechecked one to three months later and PrEP restarted if renal function, as measured by estimated creatinine clearance, has returned to more than 60 ml/min.

Stopping TDF-containing PrEP is typically sufficient to restore baseline renal function. Additional causes and management of creatinine elevations can be considered, especially if any of the following are present:

- creatinine elevations are more than 1.5 fold the upper limit of normal;
- renal function or creatinine elevations do not return to normal levels within three months of stopping PrEP;
- creatinine elevations progress at one month or more after stopping PrEP.

Common causes of chronic or severe renal insufficiency are diabetes mellitus, uncontrolled systemic hypertension, hepatitis C virus (HCV) infection, liver failure from any cause and pre-eclampsia during pregnancy.

Management of seroconversion

HIV seroconversion may occur after receiving PrEP. In clinical trials and demonstration projects, such seroconversions after receiving PrEP were due to pre-existing HIV infection or to no or inconsistent use of PrEP (36, 37).

ART can be offered as soon as possible after a confirmed positive HIV test result (seroconversion).² National guidelines vary depending on local practices and capacity. PrEP providers who do not feel comfortable treating HIV infection should receive additional training or identify HIV treatment services they can refer clients with positive test results to.

If a PrEP user tests positive for HIV, therapy for HIV infection can be started without a gap after PrEP is discontinued.

If a client using PrEP tests positive for HIV, therapy for HIV infection can be started without a gap after PrEP is discontinued. WHO recommends confirming reactive rapid test results by retesting a second sample (according to the national testing algorithm). When confirmation of a positive test result is delayed more than a few hours, transition to fully suppressive therapy can be considered while confirmatory testing is underway. Such transitions from PrEP to treatment without a gap may avoid the risk of resurgence in viral load and secondary transmissions.

Only 3% of seroconverters who have received PrEP in studies have shown any resistance to TDF or FTC (see appendix on evidence to decision) (23, 33). However, long-term outcomes for successful ART in seroconverters on PrEP is not known. Ongoing surveillance of drug resistance in PrEP user populations could be considered. The use of second-line regimens for those who seroconvert on PrEP is not usually required.

Key counselling regarding PrEP efficacy

• Effectiveness

Message: PrEP is highly effective if you take it as prescribed.

[In clinical trials overall, the reduction in risk of acquiring HIV was more than 90% when PrEP was used consistently. Several large demonstration projects have observed no new HIV infections during PrEP use (38, 39), while others have reported seroconversions associated with the use of fewer than four tablets per week among men who have sex with men and transgender women (5) or fewer than six tablets per week among women (40).]

• Ways to support adherence

Message: Taking PrEP each day is easiest if you make taking the tablets a daily habit, linked to something else that you do every day without fail.

[There are many ways to support adherence. For example, considering daily habits that could be linked with taking PrEP tablets, such as brushing teeth, after the evening meal, watching a daily television programme. Other ways to facilitate adherence include disclosing PrEP use to a partner or trusted person; using reminder devices, such as mobile phone alarms, can also be considered.]

² See <http://www.who.int/hiv/pub/guidelines/earlyrelease-arv/en/>

Message: If you forget to take a tablet, take it as soon as you remember.

[Occasional use of two tablets of TDF/FTC a day is safe (6, 41). Do not take more than two tablets per day.]

Message: PrEP tablets can be taken any time of day, with food or without food.

[PrEP can be taken with alcohol, although excess alcohol can be harmful to health and make people forget to take the PrEP tablets (42).]

Message: Taking PrEP is a responsible choice.

[PrEP is a responsible way to protect oneself, one's sex partners and one's community. It is important to help the PrEP client cope with the fact that not everyone will understand their decision to use PrEP. Seeking support from their friends and other people who use PrEP can be helpful.]

Message: PrEP is safe and effective even if you are taking hormonal contraceptives, sex hormones or non-prescription medications.

[There are no drug interactions between the PrEP medicines and hormonal contraception or sex hormones so they can be safely taken together (43).]

- **Starting PrEP**

Message: Additional HIV prevention measures should be taken for seven days after starting PrEP.

[PrEP provides high levels of protection in people who take PrEP medicines regularly. Time is needed to build up protective levels of the drug in the blood and other tissues. Additional HIV prevention should be taken for seven days (5, 6, 40, 44, 45). Ways to lower risk during this period include: adopting safer sexual practices, such as not having vaginal or anal intercourse, or using condoms for all vaginal and anal intercourse.]

- **Stopping PrEP**

Message: You can stop PrEP 28 days after your last possible HIV exposure.

[PrEP can be stopped 28 days after the last possible exposure to HIV. People can consider stopping PrEP if they are no longer at substantial risk of acquiring HIV infection. Ways to lower risk include: adopting safer sexual practices, such as not having vaginal or anal intercourse, or using condoms for all vaginal and anal intercourse; changing circumstances such as leaving sex work or stopping injecting drug use; or, moving to a place that has a low prevalence of HIV infection. For people in a serodiscordant relationship, HIV transmission risk is very low when the HIV-positive partner is virally suppressed on ART.]

- **No PrEP interactions with recreational drugs or alcohol**

Message: Taking alcohol or using recreational drugs such as heroin and other opioids, cocaine or methamphetamine will not reduce the effectiveness of PrEP.

[PrEP drug concentrations were comparable among users of cocaine and methamphetamine and people who denied the use of stimulants in a PrEP demonstration project (46).]

- **No STI protection (other than HIV infection)**

Message: PrEP does not prevent most sexually transmitted infections other than HIV. Condoms used in every act of sexual intercourse provide some protection against many of these infections.

[PrEP does not prevent syphilis, gonorrhoea, chlamydia, trichomonas or chancroid. PrEP provides some protection against acquisition of herpes in heterosexual populations (47) and has decreased the incidence of genital ulcers in men who have sex with men and herpes infections in transgender women (48). Consistent use of condoms provides protection against many STIs, especially gonorrhoea and chlamydia, which are transmitted through the exchange of fluids rather than by skin-to-skin contact.]

- **No contraceptive effect**

Message: PrEP does not prevent pregnancy.

[The client should be encouraged to use effective contraception unless pregnancy is desired. PrEP medicines can be taken safely with all contraception methods. If a client wants to become pregnant, ways to become pregnant safely should be considered. PrEP can be used in pregnancy and during breastfeeding if HIV risk continues to be substantial during this time (49).]

Message: Oral, injectable or implant hormonal contraceptives do not significantly change the effectiveness of PrEP medicines, and PrEP medicines do not make hormonal contraceptives less effective (50).

Key counselling regarding PrEP safety

- Testing

Message: Get an HIV test before starting PrEP or restarting PrEP after you have stopped.

[PrEP is not sufficient for the treatment of HIV infection. HIV testing before starting or restarting PrEP is essential to detect infections that require treatment. If PrEP is stopped, an HIV test should be obtained before restarting it. Use of PrEP in people who already have HIV infection can lead to development of resistance to PrEP medicines.]

- Overall safety

Message: PrEP is very safe, with no side-effects for 90% of users (19, 21, 22).

- Minor side-effects

Message: About 10% of people who start PrEP will have some short-term, mild side-effects.

[Side-effects may include gastrointestinal symptoms (diarrhoea, nausea, decreased appetite, abdominal cramping or flatulence). Dizziness or headaches have also been experienced. Such side-effects are usually mild and resolve without stopping PrEP. Typically, these symptoms start in the first few days or weeks of PrEP use and last a few days, and almost always less than one month.]

- Kidney side-effects

Message: A very small percentage of people will not be able to take PrEP because they have problems with their kidneys.

[Blood testing for kidney function can be performed when clients start PrEP and while they are taking PrEP. Usually, a creatinine test is used. One-time elevations in serum creatinine are seen in approximately one in every 200 PrEP users, but usually levels return to normal on a second test.]

- Hepatitis B and hepatitis C

Message: You can have a blood test to see if you have hepatitis B infection.

[If a screening test for hepatitis B is negative, the client could benefit from a hepatitis B vaccination (51); if the test result is positive, the client can have further blood tests to see if he/she would benefit from treating the HBV infection (52, 53). If a PrEP user has HBV infection and stops taking PrEP, the liver infection may get worse. Current HBV infection is indicated by the detection of HBsAg. Not everyone with detected HBsAg requires treatment. Treatment indications can be assessed in a variety of ways depending on which laboratory tests are available. TDF is recommended for treatment of HBV (52); therefore, oral PrEP containing TDF can benefit people whose HBV infection warrants treatment. People who stop treatment for HBV infection are at risk of virological and clinical rebound of their HBV infection. This risk is higher in people who have liver fibrosis before starting treatment (54). Clinical rebound after stopping PrEP was not observed in the limited data available from people with HBV infection who stopped oral PrEP containing TDF in trials (55, 56).]

Consideration could be given to testing for evidence of HCV infection in men who have sex with men and people who inject drugs prior to initiation of PrEP and every 12 months thereafter. Testing for evidence of HCV infection is typically conducted by using a serological assay to detect antibodies to HCV (anti-HCV).]

- Bone mineral density

Message: A slight decrease in the hardness of bones has been seen in people taking PrEP containing TDF.

[PrEP has been associated with a small decrease in bone mineral density (0.5-1.5%) in the spine and hip in the first six months. It does not progress after that (57, 58). In studies, there has been no increase in bone fractures (57). Bone mineral density returns to normal when PrEP use ends (57). People with a history of pathological bone fracture were excluded from PrEP trials; people with this kind of history who are considering PrEP should also consider treatment for low bone mineral density.]

- PrEP during pregnancy and breastfeeding

Message: You can use PrEP throughout pregnancy and breastfeeding.

[HIV infection can occur at high rates during pregnancy and breastfeeding. The risk of passing HIV infection onto a baby is higher if the mother becomes infected while she is pregnant. The existing safety data support the use of PrEP in pregnant and breastfeeding women who are at continuing substantial risk of HIV infection (49).]

Special situations

Hormonal contraception

PrEP does not affect the efficacy of hormonal contraceptives (43, 50), and hormonal contraceptives do not affect PrEP efficacy (59). PrEP medicines are processed in the kidneys, while contraceptive hormones are processed in the liver. There are no known drug interactions between TDF and FTC, on the one hand, and oral, injectable or implanted hormonal contraceptives, on the other.

Pregnancy

PrEP may be offered or continued during pregnancy in women at substantial risk of HIV acquisition.

Many serodiscordant couples desire pregnancy and PrEP can be considered as a strategy for safer conception (60). In Sub-Saharan Africa, some HIV-negative women continue to be at high risk of HIV infection during pregnancy and breastfeeding (61, 62). HIV infection acquired during pregnancy is more likely to be transmitted to the infant (3, 63). There were no differences in pregnancy outcomes, infant birth weight or congenital malformations in PrEP users compared to placebo users among serodiscordant couples in the Partners PrEP

study (50). TDF, in combination with other medicines, is frequently used for HIV treatment. Use of TDF for hepatitis B treatment has not been associated with adverse pregnancy outcomes (50). Therefore, PrEP may be offered or continued during pregnancy if the pregnant woman remains at substantial HIV risk.

Breastfeeding

PrEP may be offered or continued during breastfeeding in women at substantial risk of HIV acquisition.

Although experience with PrEP during breastfeeding is still lacking, there is substantial experience with TDF/FTC during breastfeeding by women with HIV on ART. TDF and FTC are secreted in breast milk at very low concentrations (0.3–2% of the levels required for treatment of HIV infection in infants) (64, 65). If a woman becomes infected with HIV during breastfeeding, the risk of transmission to her infant may be higher than if she is already infected because of high viral load soon after seroconversion (3, 63). Therefore, PrEP may be continued or offered during breastfeeding.

Hepatitis B infection

Hepatitis B vaccination is appropriate for people at substantial risk of HBV or HIV infection (51). Vaccination is warranted if there is no documented history of a completed vaccine series for HBV. PrEP can be provided whether or not HBV vaccination is available.

HBV infection is endemic in many regions where HIV is transmitted at high rates. TDF is active against HBV infection at the same dose used for PrEP. WHO recommends TDF for treatment of HBV infection in people for whom treatment is indicated. Not all people with chronic HBV infection have treatment indications. Indications for treatment of HBV can be assessed in a variety of ways depending on which laboratory tests are available.

When HBV treatment is stopped, occasionally HBV infection can flare in the following one to three months. Such flares are often limited to elevations in serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST), although decompensation of liver function can occur (54). Flares in HBV infection are treated by restarting treatment. The risk of hepatitis flares after stopping HBV treatment is higher in people with liver fibrosis (54). Hepatitis flares were not observed in two PrEP trials that enrolled participants with HBV infection (iPrEx and West Africa PrEP studies) (55, 56). These trials limited enrolment to people with normal (55) or near normal (less than two times the upper limit of normal) liver function tests (that is, AST or ALT) and no clinical signs of liver cirrhosis (56). Therefore, additional assessment can be considered for people with HBV infection who are considering PrEP.

Management of recent HIV exposure with PEP

People who have been exposed to HIV in the preceding 72 hours should be offered PEP. PEP should be offered as soon as possible after exposure. WHO recommends PEP consisting of TDF/3TC (or FTC), preferably combined with a boosted protease inhibitor, for 28 days. After 28 days of PEP, PrEP can be started without a gap if the HIV test remains negative and there is substantial ongoing risk of HIV acquisition (9). In people with ongoing potential exposure to HIV, there should be no gap between finishing PEP and starting PrEP.

WHO PEP GUIDANCE³

TDF + 3TC (or FTC) is recommended as the preferred backbone regimen for HIV post-exposure prophylaxis for adults and adolescents. (*Strong recommendation, low-quality evidence*)

Lopinavir/ritonavir (LPV/r) or atazanavir/ritonavir (ATV/r) is recommended as the preferred third drug for HIV post-exposure prophylaxis for adults and adolescents. (*Conditional recommendation, very low quality evidence*)

Where available, raltegravir (RAL), darunavir/ritonavir (DRV/r) or efavirenz (EFV) can be considered as alternative options.

Signs and symptoms of acute HIV infection

Acute HIV infection is often symptomatic, including signs and symptoms of fever, sore throat, aches and pains, lymphadenopathy (swollen glands), mouth sores, headache or rash. The signs and symptoms of acute HIV infection are not specific, and the majority of people with acute viral syndromes will have infections other than HIV (5, 33). Nonetheless, if an acute viral syndrome is present in someone reporting condomless sex in the past 14 days, acute HIV infection should be suspected. Starting PrEP in the setting of acute infection involves a risk of drug resistance, even if the seroconversion is detected within four weeks of starting PrEP (23).

Optimal diagnosis and management of suspected acute HIV infection depends on the resources available. The benefits of providing PrEP to prevent HIV infection typically outweigh the risks of drug resistance because: (i) most suspected acute HIV infections are not confirmed to be 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 (33, 66). Screening for baseline HIV infection using commonly available third generation point-of-care tests is sufficient to provide a highly favourable balance of benefits to risks. If resources allow, nucleic acid testing could be considered among people with clinical signs and symptoms of acute HIV infection (9). Another option for people with suspected acute HIV infection 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.

Minimizing PrEP stigma

People may face stigma if their use of PrEP becomes known. They may already find themselves judged or excluded based on their sexual practices, their sexual orientation, their partnerships with HIV-positive people, their drug use or their age. PrEP use can exacerbate stigma if others mistakenly consider PrEP use to be evidence of irresponsible behaviour or think that PrEP is HIV treatment. Such stigma may decrease PrEP uptake and adherence among people who would otherwise benefit most from it.

Presenting PrEP to communities as a responsible choice that protects both partners will increase the impact of PrEP, preventing more infections.

Presenting PrEP to communities as a responsible choice, which protects both the PrEP user and his or her sexual and/or drug using partner(s), will increase the impact of PrEP and save healthcare costs by preventing more HIV infections. Community education should also help people distinguish PrEP from treatment.

³ Source: Guidelines on post-exposure prophylaxis for HIV and the use of co-trimoxazole prophylaxis for HIV-related infections among adults, adolescents and children: recommendations for a public health approach: December 2014 supplement to the 2013 Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Geneva: WHO; 2014 http://apps.who.int/iris/bitstream/10665/145719/1/9789241508193_eng.pdf?ua=1&ua=1

Community advisory boards and linkages between health services and social support programmes in communities should be used to ensure that messaging about PrEP is respectful, helps people recognize their risk of acquiring HIV without shame and motivates people to use PrEP and other protective methods whenever needed. Health service providers should receive training in providing culturally competent care that applies user-centred perspectives.

Gaps in clinical knowledge about PrEP

As there has been limited experience to date in providing PrEP outside research and demonstration projects in low- and middle-income settings there are multiple gaps in knowledge related to the implementation of PrEP. Implementation research among diverse populations, including adolescents and transgender populations, and in varying clinical settings is warranted. Such research should include:

Demand creation and ways to increase awareness about PrEP. Research is needed into how best to engage populations who will benefit the most from PrEP, especially among adolescents, young adults, transgender men and women, and sex workers.

Service delivery issues. Research should consider variations in visit frequency, clinic staffing and the package of services tailored for different populations.

PrEP issues for transgender populations. Current information suggests that there are no significant drug-drug interactions between PrEP medicines and hormone therapy. However, there have been limited studies and demonstration projects among transgender men and women to inform acceptable and effective PrEP delivery.

PrEP issues for people who use and/or inject drugs. WHO recommends a package of effective HIV services be provided for all people who inject drugs including harm reduction (such as opioid substitution therapy and needle syringe programmes). However, people who use and/or inject drugs should not be excluded from PrEP services if they have substantial HIV risk. Acceptable ways to include and deliver PrEP for people who use drugs within comprehensive services for their other health and social needs could be explored.

Renal safety. The extent to which renal function monitoring is required for the safe use of PrEP is not known. The renal safety of TDF/FTC PrEP in people with diabetes mellitus and uncontrolled systemic hypertension has not yet been evaluated.

PrEP medicine choice. Although 3TC is equivalent to FTC for HIV treatment (67), the use of 3TC for PrEP has not been studied in clinical trials except in one Phase I study (51). Information from clinical services that utilize TDF/3TC PrEP would be helpful.

Other PrEP formulations. Other formulations and delivery modes (e.g. long-acting injectable, vaginal ring) are currently being evaluated.

Event-driven PrEP. Comparisons of daily and event-driven PrEP regimens are limited by the size and diversity of the studies. Event-driven PrEP has been shown to be highly effective and acceptable among men who have sex with men in high-income settings. However, the effectiveness of event-driven PrEP among women and heterosexual men has not yet been evaluated.

PrEP use in people co-infected with HBV. Although cases of HBV rebound when stopping TDF/FTC PrEP have not been observed among people with current HBV infection in clinical trials, most trials excluded such people from enrolment.

PrEP use during pregnancy and breastfeeding. Although all available data is reassuring regarding the safety of PrEP during pregnancy and breastfeeding, surveillance of mother and infant outcomes during PrEP use in pregnancy and breastfeeding should be prioritized.

Surveillance for HIV drug resistance and drug concentrations among PrEP users who acquire HIV.

Research in this area would contribute to monitoring the causes and consequences of PrEP failure, and ensuring that such failure continues to be rare as PrEP extends from clinical research to clinical practice.

PrEP use in adolescents. There is limited data from clinical or implementation research on the use of PrEP in adolescent boys and girls. As adherence is a key predictor of PrEP's effectiveness, models of enhancing PrEP adherence in adolescents need to be investigated further.

Impact of PrEP on performance of HIV testing assays. There is uncertainty over the potential of ARV medicines, including TDF/FTC, on delaying the ability of certain assays in detecting HIV infection. Further evaluation of how PrEP medicines can affect certain types of HIV tests, including rapid oral and blood-based tests, are warranted.

Further reading

WHO guidelines for the treatment of *Neisseria gonorrhoeae*. Geneva: World Health Organization; 2016 <http://apps.who.int/iris/bitstream/10665/246114/1/9789241549691-eng.pdf?ua=1>

WHO guidelines for the treatment of *Chlamydia trachomatis*. Geneva: World Health Organization; 2016 <http://apps.who.int/iris/bitstream/10665/246165/1/9789241549714-eng.pdf?ua=1>

WHO guidelines for the treatment of *Treponema pallidum* (syphilis). Geneva: World Health Organization; 2016 <http://apps.who.int/iris/bitstream/10665/249572/1/9789241549806-eng.pdf?ua=1>

Ensuring human rights in the provision of contraceptive information and services, Guidance and recommendations. Geneva: World Health Organization; 2014 http://apps.who.int/iris/bitstream/10665/102539/1/9789241506748_eng.pdf?ua=1

Guidelines for the screening, care and treatment of persons with chronic hepatitis C infection. Geneva: World Health Organization; 2016 http://apps.who.int/iris/bitstream/10665/205035/1/9789241549615_eng.pdf?ua=1

Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. Geneva: World Health Organization; 2015 http://apps.who.int/iris/bitstream/10665/154590/1/9789241549059_eng.pdf

References

1. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med*. 2011;365(6):493-505.
2. Baeten J, Heffron R, Kidoguchi L, Mugo N, Katabira E, Bukusi E, et al., editors. Near elimination of HIV transmission in a demonstration project of PrEP and ART. Presented at: CROI February 23 to 26, 2015; 2015; Seattle, WA 2015.
3. Humphrey JH, Marinda E, Mutasa K, Moulton LH, Iliff PJ, Ntozini R, et al. Mother to child transmission of HIV among Zimbabwean women who seroconverted postnatally: prospective cohort study. *BMJ*. 2010;341:c6580.
4. Smith DK, Herbst JH, Zhang X, Rose CE. Condom effectiveness for HIV prevention by consistency of use among men who have sex with men in the United States. *J Acquir Immune Defic Syndr*. 2015;68(3):337-44.
5. Grant RM, Anderson PL, McMahan V, Liu A, Amico KR, Mehrotra M, et al. Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study. *The Lancet Infectious Diseases*. 2014;14(9):820-9.
6. Molina JM, Capitant C, Spire B, Pialoux G, Cotte L, Charreau I, et al. On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection. *N Engl J Med*. 2015;373(23):2237-46.
7. McCormack S, Dunn DT, Desai M, Dolling DI, Gafos M, Gilson R, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. *Lancet*. 2015.
8. Grant RM, Glidden DV. HIV moments and pre-exposure prophylaxis. *Lancet*. 2016;387(10027):1507-8.
9. Grant RM, Smith DK. Integrating Antiretroviral Strategies for Human Immunodeficiency Virus Prevention: Post- and Pre-Exposure Prophylaxis and Early Treatment. *Open Forum Infect Dis*. 2015;2(4):ofv126.
10. Mugwanya K, Heffron R, Wyatt C, Mugo N, Celum C, Kiarie J, et al., editors. Optimizing the frequency of kidney safety monitoring in HIV-uninfected persons using daily oral tenofovir disoproxil fumarate pre-exposure prophylaxis. Presented at: AIDS 2016; 2016; Durban, South Africa.
11. Gandhi M, Glidden DV, Liu A, Anderson PL, Horng H, Defechereuz P, et al. Strong Correlation Between Concentrations of Tenofovir (TFV) Emtricitabine (FTC) in Hair and TFV Diphosphate and FTC Triphosphate in Dried Blood Spots in the iPrEx Open Label Extension: Implications for Pre-exposure Prophylaxis Adherence Monitoring. *J Infect Dis*. 2015.
12. Solomon MM, Lama JR, Glidden DV, Mulligan K, McMahan V, Liu AY, et al. Changes in renal function associated with oral emtricitabine/tenofovir disoproxil fumarate use for HIV pre-exposure prophylaxis. *AIDS*. 2014;28(6):851-9.
13. Mugwanya KK, Wyatt C, Celum C, Donnell D, Kiarie J, Ronald A, et al. Reversibility of Glomerular Renal Function Decline in HIV-Uninfected Men and Women Discontinuing Emtricitabine-Tenofovir Disoproxil Fumarate Pre-Exposure Prophylaxis. *J Acquir Immune Defic Syndr*. 2016;71(4):374-80.
14. Mandala J, Nanda K, Wang M, De Baetselier I, Deese J, Lombaard J, et al. Liver and renal safety of tenofovir disoproxil fumarate in combination with emtricitabine among African women in a pre-exposure prophylaxis trial. *BMC Pharmacol Toxicol*. 2014;15(1):77.
15. Yacoub R, Nadkarni GN, Weikum D, Konstantinidis I, Boueilh A, Grant RM, et al. Elevations in Serum Creatinine With Tenofovir-Based HIV Pre-Exposure Prophylaxis: A Meta-Analysis of Randomized Placebo-Controlled Trials. *J Acquir Immune Defic Syndr*. 2016;71(4):e115-8.
16. Pierrat A, Gravier E, Saunders C, Caira MV, Ait-Djafer Z, Legras B, et al. Predicting GFR in children and adults: a comparison of the Cockcroft-Gault, Schwartz, and modification of diet in renal disease formulas. *Kidney Int*. 2003;64(4):1425-36.
17. Bishop BM. Pharmacotherapy Considerations in the Management of Transgender Patients: A Brief Review. *Pharmacotherapy*. 2015;35(12):1130-9.
18. Leach C, Bishop B. Pharmacotherapy Considerations in the Management of Transgender Patients: An Alternative Viewpoint. *Pharmacotherapy*. 2016;36(4):e28-9.
19. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *New England Journal of Medicine*. 2010;363(27):2587-99.

20. Deutsch MB, Glidden DV, Sevelius J, Keatley J, McMahan V, Guanira J, et al. HIV pre-exposure prophylaxis in transgender women: a subgroup analysis of the iPrEx trial. *Lancet HIV*. 2015;2(12):e512-9.
21. Baeten JM, Donnell D, Ndase P, Mugo NR, Campbell JD, Wangisi J, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N Engl J Med*. 2012;367(5):399-410.
22. Thigpen MC, Kebaabetswe PM, Paxton LA, Smith DK, Rose CE, Segolodi TM, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. *N Engl J Med*. 2012;367(5):423-34.
23. Fonner VA, Dalglish SL, Kennedy CE, Baggaley R, O'Reilly K R, Koechlin FM, et al. Effectiveness and safety of oral HIV pre-exposure prophylaxis (PrEP) for all populations: A systematic review and meta-analysis. *AIDS*. 2016.
24. Baeten JM, Donnell D, Mugo NR, Ndase P, Thomas KK, Campbell JD, et al. Single-agent tenofovir versus combination emtricitabine plus tenofovir for pre-exposure prophylaxis for HIV-1 acquisition: an update of data from a randomised, double-blind, phase 3 trial. *Lancet Infect Dis*. 2014;14(11):1055-64.
25. Choopanya K, Martin M, Suntharasamai P, Sangkum U, Mock PA, Leethochawalit M, et al. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2013;381(9883):2083-90.
26. Lehman DA, Baeten JM, McCoy CO, Weis JF, Peterson D, Mbara G, et al. Risk of Drug Resistance Among Persons Acquiring HIV Within a Randomized Clinical Trial of Single- or Dual-Agent Preexposure Prophylaxis. *J Infect Dis*. 2015;211(8):1211-8.
27. Grohskopf LA, Chillag KL, Gvetadze R, Liu AY, Thompson M, Mayer KH, et al. Randomized trial of clinical safety of daily oral tenofovir disoproxil fumarate among HIV-uninfected men who have sex with men in the United States. *J Acquir Immune Defic Syndr*. 2013;64(1):79-86.
28. Fox J, Brady M, Alexander H, Davies O, Robinson N, Pace M, et al. Tenofovir Disoproxil Fumarate Fails to Prevent HIV Acquisition or the Establishment of a Viral Reservoir: Two Case Reports. *Infect Dis Ther*. 2016.
29. Cremin I, Morales F, Jewell BL, O'Reilly KR, Hallett TB. Seasonal PrEP for partners of migrant miners in southern Mozambique: a highly focused PrEP intervention. *J Int AIDS Soc*. 2015;18(4 Suppl 3):19946.
30. Grant RM, Anderson PL, McMahan V, Liu A, Amico KR, Mehrotra M, et al. Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study. *Lancet Infect Dis*. 2014;14(9):820-9.
31. WHO position paper on hepatitis A vaccines. Geneva: World Health Organization; 2012 http://www.who.int/wer/2012/wer8728_29.pdf?ua=1.
32. Liu AY, Cohen SE, Vittinghoff E, Anderson PL, Doblecki-Lewis S, Bacon O, et al. Preexposure Prophylaxis for HIV Infection Integrated With Municipal- and Community-Based Sexual Health Services. *JAMA Intern Med*. 2015;1-11.
33. Grant R, Fonner V, Rodolph M, Liegler T, Glidden D, Baggaley R, editors. Benefits of pre-exposure prophylaxis relative to drug resistance risk. Presented at: AIDS 2016; 2016; Durban, South Africa.
34. Johnson C, Baggaley R, Forsythe S, van Rooyen H, Ford N, Napierala Mavedzenge S, et al. Realizing the potential for HIV self-testing. *AIDS Behav*. 2014;18 Suppl 4:S391-5.
35. Wong V, Johnson C, Cowan E, Rosenthal M, Peeling R, Miralles M, et al. HIV self-testing in resource-limited settings: regulatory and policy considerations. *AIDS Behav*. 2014;18 Suppl 4:S415-21.
36. Anderson PL, Glidden DV, Liu A, Buchbinder S, Lama JR, Guanira JV, et al. Emtricitabine-Tenofovir Concentrations and Pre-Exposure Prophylaxis Efficacy in Men Who Have Sex with Men. *Sci Transl Med*. 2012;4(151):151ra25.
37. Donnell D, Baeten JM, Bumpus NN, Brantley J, Bangsberg DR, Haberer JE, et al. HIV Protective Efficacy and Correlates of Tenofovir Blood Concentrations in a Clinical Trial of PrEP for HIV Prevention. *J Acquir Immune Defic Syndr*. 2014.
38. Marcus JL, Hurley LB, Hare CB, Nguyen DP, Phengrasamy T, Silverberg MJ, et al. Preexposure Prophylaxis for HIV Prevention in a Large Integrated Health Care System: Adherence, Renal Safety, and Discontinuation. *J Acquir Immune Defic Syndr*. 2016;73(5):540-6.
39. Volk JE, Marcus JL, Phengrasamy T, Blechinger D, Nguyen DP, Follansbee S, et al. No New HIV Infections With Increasing Use of HIV Preexposure Prophylaxis in a Clinical Practice Setting. *Clin Infect Dis*. 2015;61(10):1601-3.

40. Grant RM, Liegler T, Defechereux P, Kashuba AD, Taylor D, Abdel-Mohsen M, et al. Drug resistance and plasma viral RNA level after ineffective use of oral pre-exposure prophylaxis in women. *AIDS*. 2015;29(3):331-7.
41. Barditch-Crovo P, Deeks SG, Collier A, Safrin S, Coakley DF, Miller M, et al. Phase I/II trial of the pharmacokinetics, safety, and antiretroviral activity of tenofovir disoproxil fumarate in human immunodeficiency virus-infected adults. *Antimicrobial Agents and Chemotherapy*. 2001;45(10):2733-9.
42. Van der Elst EM, Mbogua J, Operario D, Mutua G, Kuo C, Mugo P, et al. High acceptability of HIV pre-exposure prophylaxis but challenges in adherence and use: qualitative insights from a phase I trial of intermittent and daily PrEP in at-risk populations in Kenya. *AIDS Behav*. 2013;17(6):2162-72.
43. Nanda K, Stuart GS, Robinson J, Gray AL, Tepper NK, Gaffield ME. Drug interactions between hormonal contraceptives and antiretrovirals. *AIDS*. 2017;31(7):917-52.
44. Seifert SM, Glidden DV, Meditz AL, Castillo-Mancilla JR, Gardner EM, Predhomme JA, et al. Dose response for starting and stopping HIV preexposure prophylaxis for men who have sex with men. *Clin Infect Dis*. 2015;60(5):804-10.
45. Cottrell M, Yang K, Prince H, Sykes C, White N, Malone S, et al. A Translational Pharmacology Approach to Predicting HIV Pre-Exposure Prophylaxis Outcomes in Men and Women Using Tenofovir Disoproxil Fumarate ± Emtricitabine. *J Infect Dis*. 2016.
46. Grant RM, Anderson PL, McMahan V, Liu A, Amico KR, Mehrotra M, et al. Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study. *Lancet Infect Dis*. 2014.
47. Celum C, Morrow RA, Donnell D, Hong T, Hendrix CW, Thomas KK, et al. Daily oral tenofovir and emtricitabine-tenofovir preexposure prophylaxis reduces herpes simplex virus type 2 acquisition among heterosexual HIV-1-uninfected men and women: a subgroup analysis of a randomized trial. *Ann Intern Med*. 2014;161(1):11-9.
48. Marcus JL, Glidden DV, McMahan V, Lama JR, Mayer KH, Liu AY, et al. Daily oral emtricitabine/tenofovir preexposure prophylaxis and herpes simplex virus type 2 among men who have sex with men. *PLoS One*. 2014;9(3):e91513.
49. Mofenson LM, Baggaley RC, Mameletzi I. Tenofovir disoproxil fumarate safety for women and their infants during pregnancy and breastfeeding. *AIDS*. 2017;31(2):213-32.
50. Mugo NR, Hong T, Celum C, Donnell D, Bukusi EA, John-Stewart G, et al. Pregnancy incidence and outcomes among women receiving preexposure prophylaxis for HIV prevention: a randomized clinical trial. *JAMA*. 2014;312(4):362-71.
51. Mancuzo, A.V. Avaliação da Profilaxia Oral Pre-Exposição em homens que fazem sexo com homens: estudo clínico de fase 1 (Evaluation of oral pre-exposure prophylaxis in a cohort of MSM: a phase 1 clinical trial). MSc Dissertation, School of Medicine, Federal University of Minas Gerais, Brazil. 2017.
52. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. Geneva: World Health Organization; 2015 http://apps.who.int/iris/bitstream/10665/154590/1/9789241549059_eng.pdf
53. Guidelines on hepatitis B and C testing. Geneva: World Health Organization; 2017 <http://apps.who.int/iris/bitstream/10665/254621/1/9789241549981-eng.pdf?ua=1>.
54. Mondou E, Sorbel J, Anderson J, Mommeja-Marin H, Rigney A, Rousseau F. Posttreatment exacerbation of hepatitis B virus (HBV) infection in long-term HBV trials of emtricitabine. *Clin Infect Dis*. 2005;41(5):e45-7.
55. Peterson L, Taylor D, Roddy R, Belai G, Phillips P, Nanda K, et al. Tenofovir disoproxil fumarate for prevention of HIV infection in women: a phase 2, double-blind, randomized, placebo-controlled trial. *PLoS Clin Trials*. 2007;2(5):e27.
56. Solomon MM, Schechter M, Liu AY, McMahan VM, Guanira JV, Hance RJ, et al. The safety of tenofovir-emtricitabine for HIV pre-exposure prophylaxis (PrEP) in individuals with active hepatitis B. *J Acquir Immune Defic Syndr*. 2015.
57. Mulligan K, Glidden DV, Anderson PL, Liu A, McMahan V, Gonzales P, et al. Effects of Emtricitabine/Tenofovir on Bone Mineral Density in HIV-Negative Persons in a Randomized, Double-Blind, Placebo-Controlled Trial. *Clin Infect Dis*. 2015;61(4):572-80.
58. Liu AY, Vittinghoff E, Sellmeyer DE, Irvin R, Mulligan K, Mayer K, et al. Bone mineral density in HIV-negative men participating in a tenofovir pre-exposure prophylaxis randomized clinical trial in San Francisco. *PLoS one*. 2011;6(8):e23688.

59. Murnane PM, Celum C, Mugo N, Campbell JD, Donnell D, Bukusi E, et al. Efficacy of preexposure prophylaxis for HIV-1 prevention among high-risk heterosexuals: subgroup analyses from a randomized trial. *AIDS*. 2013;27(13):2155-60.
60. Vernazza PL, Graf I, Sonnenberg-Schwan U, Geit M, Meurer A. Preexposure prophylaxis and timed intercourse for HIV-discordant couples willing to conceive a child. *AIDS*. 2011;25(16):2005-8.
61. Drake AL, Wagner A, Richardson B, John-Stewart G. Incident HIV during pregnancy and postpartum and risk of mother-to-child HIV transmission: a systematic review and meta-analysis. *PLoS Med*. 2014;11(2):e1001608.
62. Mugo NR, Heffron R, Donnell D, Wald A, Were EO, Rees H, et al. Increased risk of HIV-1 transmission in pregnancy: a prospective study among African HIV-1-serodiscordant couples. *AIDS*. 2011;25(15):1887-95.
63. Singh, editor HIV seroconversion during pregnancy and mother-to-child HIV transmission: data from the enhanced perinatal surveillance projects, United States, 2005–2010. Presented at: CROI; 2013; Atlanta, GA.
64. Benaboud S, Pruvost A, Coffie PA, Ekouevi DK, Urien S, Arrive E, et al. Concentrations of tenofovir and emtricitabine in breast milk of HIV-1-infected women in Abidjan, Cote d'Ivoire, in the ANRS 12109 TEmAA Study, Step 2. *Antimicrob Agents Chemother*. 2011;55(3):1315-7.
65. Mugwanya KK, Hendrix CW, Mugo NR, Marzinke M, Katabira ET, Ngure K, et al. Pre-exposure Prophylaxis Use by Breastfeeding HIV-Uninfected Women: A Prospective Short-Term Study of Antiretroviral Excretion in Breast Milk and Infant Absorption. *PLoS Med*. 2016;13(9):e1002132.
66. Abbas UL, Glaubius R, Mubayi A, Hood G, Mellors JW. Antiretroviral therapy and pre-exposure prophylaxis: combined impact on HIV transmission and drug resistance in South Africa. *J Infect Dis*. 2013;208(2):224-34.
67. Ford N, Shubber Z, Hill A, Vitoria M, Doherty M, Mills EJ, et al. Comparative efficacy of Lamivudine and emtricitabine: a systematic review and meta-analysis of randomized trials. *PLoS One*. 2013;8(11):e79981.

For more information, contact:

World Health Organization
Department of HIV/AIDS
20, avenue Appia
1211 Geneva 27
Switzerland

E-mail: hiv-aids@who.int

www.who.int/hiv