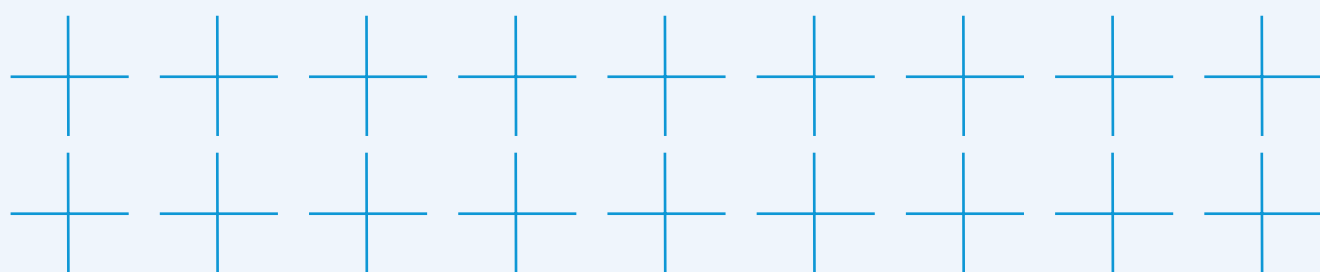

Differentiated and simplified pre-exposure prophylaxis for HIV prevention

Update to WHO implementation guidance

TECHNICAL BRIEF



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Technical Brief

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Contents

Acknowledgements	iv
Abbreviations	vi
Overview	vii
Introduction	1
Background	1
Target audience and scope	2
Guiding principle and methodology	2
Starting, using and stopping oral PrEP	3
Oral event-driven PrEP (ED-PrEP)	3
Starting and stopping oral PrEP	3
Rationale	5
PrEP and hepatitis B and C	6
Hepatitis B virus	6
Hepatitis C virus	7
Rationale	8
PrEP and kidney function	9
Rationale	11
HIV self-testing (HIVST) for PrEP	12
What is HIVST?	12
HIVST and PrEP	12
Rationale	14
Differentiated PrEP service delivery: When, where, who and what to deliver	15
Building blocks of differentiated PrEP service delivery	15
Where to deliver PrEP	16
PrEP in fixed and mobile community settings	18
Telehealth for PrEP	20
PrEP delivery in pharmacies	22
Who to deliver PrEP	23
When and what services to deliver	24
Research gaps	26
References	27
Annex 1: Summary of mathematical modelling of HIVST for PrEP in Kenya	33
Annex 2: Background and methods on the global PrEP provider study	34
Annex 3: Summary of a review of PrEP services for people who inject drugs	36

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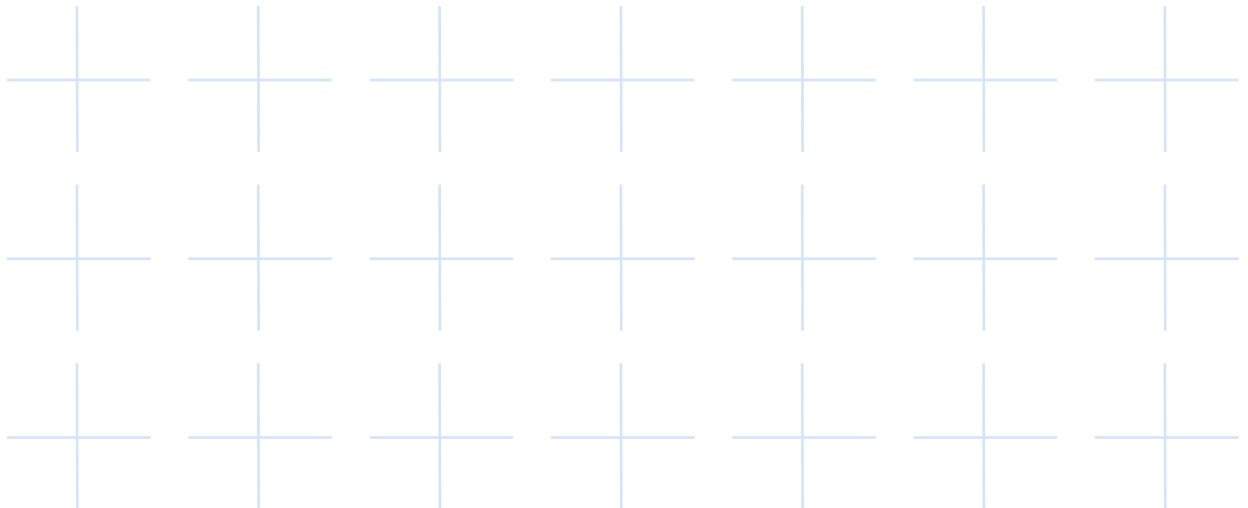
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Abbreviations

ART	antiretroviral therapy
CAB-LA	long-acting injectable cabotegravir
DVR	dapivirine vaginal ring
ED-PrEP	event-driven PrEP
eGFR	estimated glomerular filtration rate
FTC	emtricitabine
GFR	glomerular filtration rate
HBsAg	HBV surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HIVST	HIV self-testing
MMD	multi-month dispensing
NRTI	nucleoside reverse transcriptase inhibitor
PEP	post-exposure prophylaxis
PrEP	pre-exposure prophylaxis
RCT	randomized controlled trial
RDT	rapid diagnostic test
STI	sexually transmitted infection
TDF	tenofovir disoproxil fumarate
3TC	lamivudine
WHO	World Health Organization

Overview

What is this technical brief?

This technical brief by the World Health Organization (WHO) updates and supplements previous WHO guidelines and guidance on pre-exposure prophylaxis (PrEP) for HIV prevention. The brief aims to support differentiated, simplified, demedicalized and comprehensive PrEP services. This can support PrEP uptake, persistence and effective use and assist efforts to achieve global goals set out in the 2022–2030 Global Health Sector Strategies on HIV, viral hepatitis and sexually transmitted infections. Further updates to WHO PrEP implementation guidance are expected in the second half of 2022 and 2023.

Key points

Starting, using and stopping oral PrEP

- Oral event-driven PrEP (ED-PrEP) can be used to prevent sexual acquisition of HIV by cisgender men and trans and gender diverse people assigned male at birth who are not taking exogenous estradiol-based hormones.
- Hepatitis B virus (HBV) infection is not a contraindication for ED-PrEP.
- Individuals eligible for oral ED-PrEP can start oral PrEP by taking two doses 2–24 hours prior to potential exposure, regardless of whether they intend to use an oral daily or ED-PrEP dosing regimen, and continue to take one dose per day until two days after the day of the last potential sexual exposure.
- All other individuals should start daily oral PrEP by taking one dose per day for seven days prior to potential exposure to HIV and can stop taking daily PrEP seven days after the last potential exposure.

PrEP and hepatitis B and C

- Individuals at substantial risk of HIV infection may also be at a higher risk for HBV and hepatitis C virus (HCV) infection. PrEP services provide an important opportunity to screen for HBV and HCV infection and provide linkages to care.
- Testing PrEP users for HBV surface antigen (HBsAg) once, at or within one to three months of PrEP initiation, is strongly encouraged where feasible, particularly in highly endemic countries.
- HCV antibody testing is strongly encouraged at or within one to three months of PrEP initiation and every 12 months thereafter where PrEP services are provided to populations at high risk of HCV infection.
- TDF-based daily or event-driven oral PrEP and the dapivirine vaginal ring (DVR) can be safely offered to people with HBV or HCV infection.
- Lack of HBV and HCV testing should not be a barrier to PrEP initiation or use. PrEP can be initiated before HBV and HCV test results are available. HBV or HCV testing are not a requirement for PrEP use (see this section for specific considerations for long-acting injectable cabotegravir (CAB-LA)).

PrEP and kidney function

- Impaired kidney function (estimated glomerular filtration rate [eGFR] <60 mL/min per 1.73 m²) is a contraindication for tenofovir disoproxil fumarate (TDF)-based oral PrEP.
- Measuring kidney function is optional for those aged under 30 years without kidney-related comorbidities. *(Continues on next page)*

PrEP and kidney function (continued)

- Individuals aged 30 years and older without comorbidities may be screened once, at or within one to three months of oral PrEP initiation. Depending on available resources, this can be considered optional for those aged 30–49 years, 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 (eGFR <90 mL/min per 1.73 m²).
- Waiting for kidney function test results should not delay initiation or continuation of oral PrEP.

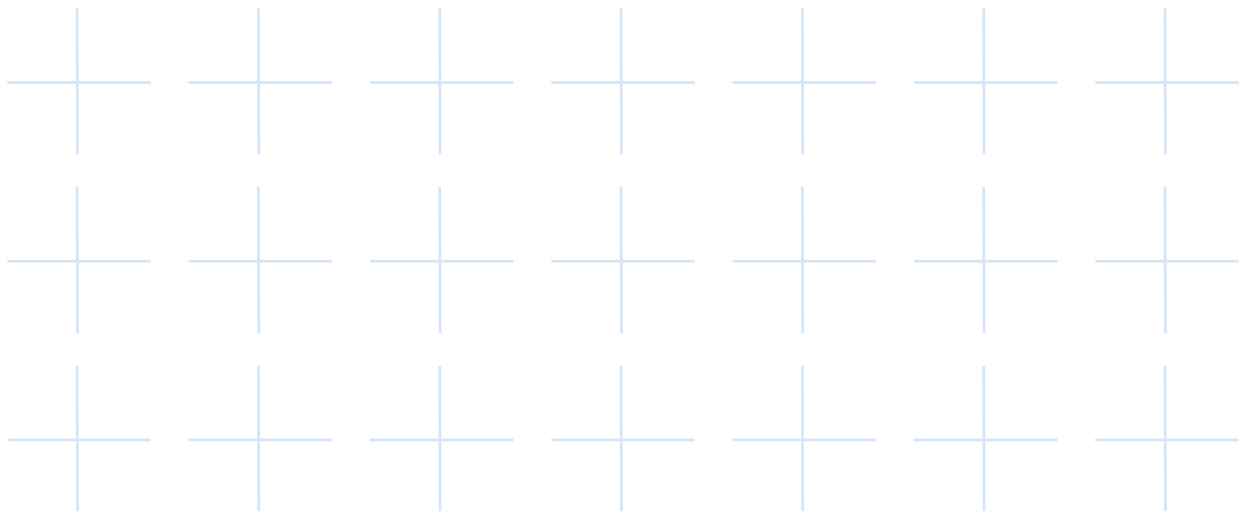
HIV self-testing (HIVST) for PrEP

- Differentiated service delivery models have the potential to remove barriers to accessing PrEP and increase uptake, persistence and effective use.
- HIVST can complement existing HIV testing strategies for PrEP to support differentiated service delivery approaches for oral PrEP and the DVR to reduce clinic visits, and it may increase PrEP use and frequency of HIV testing.
- HIVST provides an additional testing choice to PrEP users when starting, restarting or continuing PrEP, which may be preferred for convenience, privacy and self-managed care.

- Clear and concise messaging for clients and regular HIV testing while taking PrEP are critical.
- HIVST-supported PrEP delivery models that reduce clinic visits should be balanced with the benefits of provision of comprehensive services to address the diverse needs of PrEP users.
- Operational research on HIVST-supported PrEP delivery remains important, particularly for optimizing delivery, understanding impact and assessing the costs of different models.

Differentiated PrEP service delivery: When, where, who and what to deliver

- A differentiated PrEP service delivery approach is person- and community-centred and adapts services to the needs and preferences of 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.
- A common framework for differentiated PrEP service delivery utilizes the four building blocks of where (service location), who (service provider), when (service frequency), and what (service package). These building blocks can be different for PrEP initiation, continuation and re-initiation, and for different PrEP products.



Introduction

Background

Pre-exposure prophylaxis (PrEP) for HIV prevention is the use of antiretroviral drugs by HIV-negative individuals to reduce the risk of acquisition of HIV. The World Health Organization (WHO) has recommended multiple PrEP options as part of combination prevention approaches (Box 1). When WHO recommended offering TDF-based oral PrEP to people at substantial risk for HIV in 2015 (Box 2), implementation of PrEP services was largely limited to small-scale studies and projects and high-income settings. Given the limited experience, WHO followed a cautious “do no harm” principle when developing guidance that was primarily based on practice in clinical trials and expert consensus. Since 2015, there has been a global uptake of PrEP into national guidelines and widespread implementation of PrEP services (1). In many countries, services have been demedicalized, simplified, differentiated, digitalized and integrated to increase uptake and effective use of PrEP. This WHO technical brief aims to support these trends, accelerated by the COVID-19 pandemic, which required innovative approaches to maintain PrEP services and improve PrEP uptake, persistence and effective use¹ by providing implementation guidance for differentiated and simplified service delivery. This will support efforts to achieve the target adopted by the United Nations General Assembly to reduce the number of new HIV infections to less than 370 000 by 2025 (2) and the goals set out in the 2022–2030 Global Health Sector Strategies on HIV, Viral Hepatitis and Sexually Transmitted Infections (3),² which recognizes implementation of PrEP services as a key action.

Box 1. WHO recommendations on PrEP for HIV prevention

2015: Oral PrEP containing TDF should be offered as an additional prevention choice for people at substantial risk of HIV infection^a as part of combination HIV prevention approaches (*strong recommendation, high certainty evidence*) (4).

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

2022: Long-acting injectable cabotegravir (CAB-LA) may be offered as an additional prevention choice for people at substantial risk of HIV infection^a as part of combination prevention approaches (*conditional recommendation; moderate-certainty evidence*) (5).

^a See Box 2 for reflections on substantial risk of HIV infection.

^b For the recommendation on the DVR, the term “women” applies to cisgender women, meaning women assigned female at birth. There is currently no research to support the DVR for other populations.

¹ PrEP persistence (sometimes called continuation) 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.

² In 2022, the 75th World Health Assembly renewed WHO’s mandate to work with countries on HIV, viral hepatitis and sexually transmitted infections until 2030. See here for details: <https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/strategies/global-health-sector-strategies>.

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 given priority to be offered PrEP since requesting PrEP indicates that there is likely to be a risk of acquiring HIV. When PrEP use is risk informed (taken during periods of risk of HIV acquisition), PrEP can be cost-effective. Cost-effectiveness 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.

Target audience and scope

This technical brief aims to support a range of stakeholders in planning and implementing PrEP services. It provides guidance on PrEP implementation and is meant to supplement and update guidance previously published in the WHO Consolidated HIV Guidelines (4) and the WHO PrEP Implementation Tool.³ The guidance in this document relates primarily to TDF-based oral PrEP (including TDF in combination with emtricitabine [FTC] or lamivudine [3TC]) as most of the implementation experience and evidence available is for oral PrEP. Key principles of the guidance will also be applicable to other PrEP products, including the DVR and CAB-LA, although CAB-LA has properties that may require different implementation from oral PrEP and the DVR. Throughout this document, specialized considerations for the DVR and CAB-LA are made explicit as relevant. Updates to the WHO PrEP Implementation Tool modules are expected from late 2022, including comprehensive considerations on implementation of different PrEP products.

Guiding principle and methodology

This technical brief follows a public health, human rights and people-centred approach to provide evidence-based guidance on PrEP service delivery. Such an approach puts the people and communities who could benefit from PrEP services at the centre of service delivery, adapting services to their preferences and needs while maximizing impact and health system efficiency.

The development of this brief was led by a core group of staff members and consultants of the Testing, Prevention and Populations unit of the Global HIV, Hepatitis and Sexually Transmitted Infections Programmes of WHO. It was supported by an informal working group of internal and external experts comprising researchers, programme managers, implementers and community representatives. All external contributors to the working group meetings completed a WHO declaration of interests form in accordance with WHO policy for experts. External contributors also completed confidentiality undertaking forms to ensure confidential discussions. Declarations of interest forms were reviewed and assessed by the WHO core group and where necessary discussed with the WHO Ethics Team. The WHO core group identified no case where exclusion from the discussion was necessary based on the declared interests. Further external experts were consulted as needed to provide additional peer review. Individuals who contributed to this document are listed in the acknowledgements.

³ Access WHO publications on PrEP, including the WHO PrEP Implementation Tool, online at <https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/hiv-prevention/pre-exposure-prophylaxis>.



Starting, using and stopping oral PrEP

Oral event-driven PrEP (ED-PrEP)

Key points

- Oral ED-PrEP can be used to prevent sexual acquisition of HIV by cisgender men and trans and gender diverse people assigned male at birth³ who are **not** taking exogenous estradiol-based hormones.
- HBV infection is not a contraindication for ED-PrEP.

To reduce the risk of HIV acquisition through sexual exposure, cisgender men and trans and gender diverse people assigned male at birth⁴ who are not taking exogenous estradiol-based hormones (for example, gender-affirming hormones) may be offered oral ED-PrEP (also known as “2+1+1”) or daily oral PrEP as options. The choice can be based on the person’s circumstances and preferences. All other individuals wanting to use oral PrEP should use a daily dosing regimen. While testing for HBV is strongly encouraged (see next section), chronic HBV infection is not a contraindication for TDF-based daily oral or oral ED-PrEP.

Starting and stopping oral PrEP

Key points

- Individuals eligible for oral ED-PrEP can start oral PrEP by taking two doses 2–24 hours prior to potential exposure, regardless of whether they intend to use an oral daily or ED-PrEP dosing regimen, and continue to take one dose per day until two days after the day of the last potential sexual exposure.
- All other individuals should start daily oral PrEP by taking one dose per day for seven days prior to potential exposure to HIV and can stop taking daily PrEP seven days after the last potential exposure.

To reduce the risk of HIV acquisition through sexual exposure, cisgender men and trans and gender diverse people assigned male at birth⁴ who are not taking exogenous estradiol-based hormones may be offered oral daily PrEP or ED-PrEP as options (Table 1 and Figure 1). Whether the intention is to use oral daily PrEP or ED-PrEP, people eligible for ED-PrEP can start and stop PrEP using the same strategy:

- Start PrEP with two doses (loading dose) of TDF-based oral PrEP taken between 2 and 24 hours before sexual exposure. Ideally, this loading dose should be taken closer to 24 hours before potential exposure.
- Continue to take one dose per day until two days after the day of the last potential sexual exposure.

All other groups (cisgender women, trans and gender diverse people assigned female at birth,⁴ people with potential exposure through injecting practices, and people taking exogenous estradiol-based hormones) may use daily oral PrEP.

- Start PrEP with one dose of TDF-based oral PrEP per day for seven consecutive days to achieve protective concentrations. Alternative HIV prevention methods should be used during this time.
- Continue daily oral PrEP by taking one dose per day and stop seven days after the last potential exposure to HIV.

Guidance in this section applies to TDF-based oral PrEP. For guidance on starting and stopping the DVR and CAB-LA, please consult the relevant WHO guidelines (4,5).

⁴ “Trans and gender diverse people” is an umbrella term for those whose gender identity, roles and expression does not conform to the norms and expectations traditionally associated with the sex assigned to them at birth; it includes people who are transsexual, transgender, or otherwise gender nonconforming or gender incongruent. Transgender people may self-identify as transgender, female, male, transwoman or transman, transsexual or one of many other gender nonconforming identities.

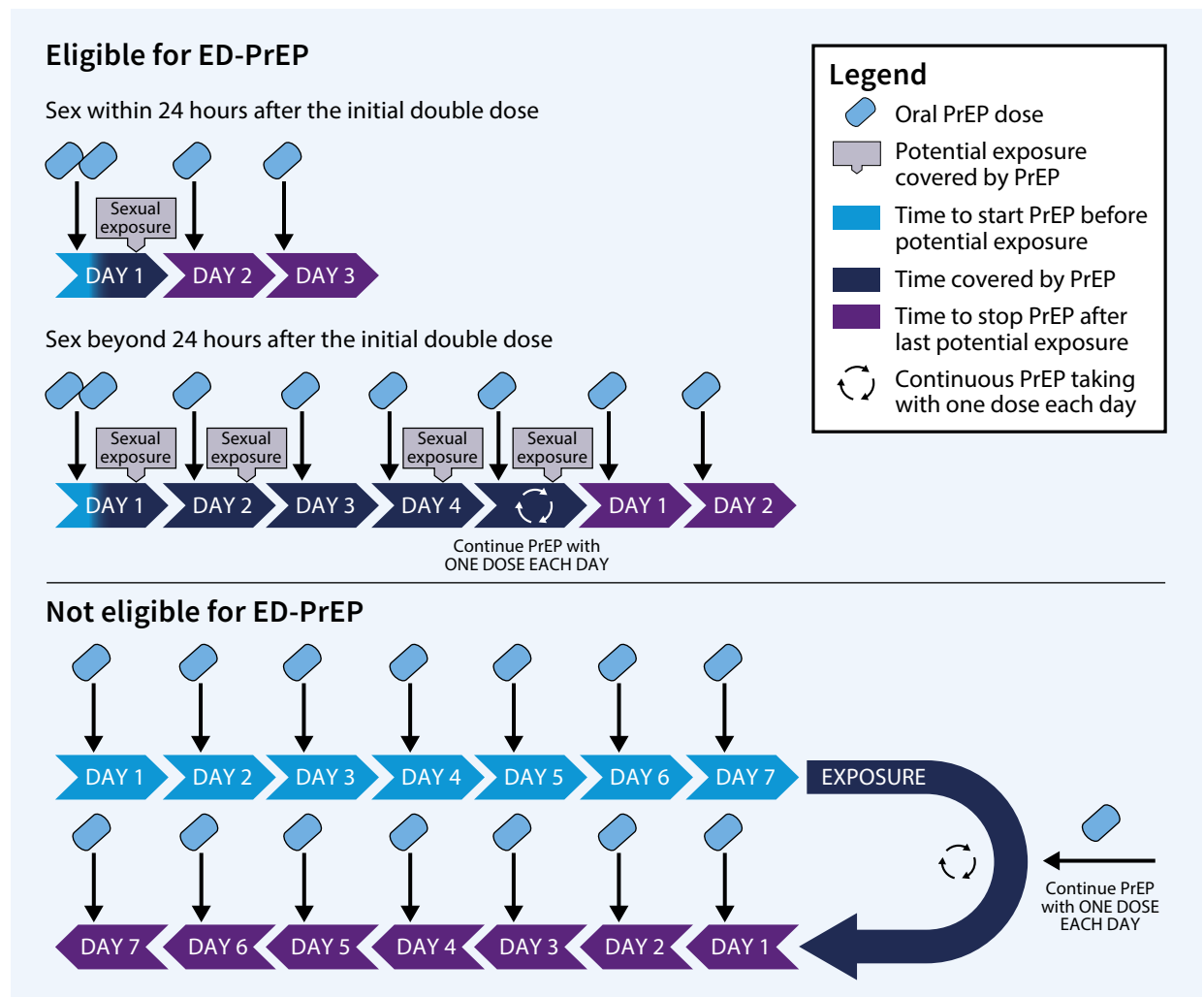
Table 1. Starting, using and stopping TDF-based oral PrEP safely

Population	Starting oral PrEP	Using oral PrEP	Stopping oral PrEP
Cisgender men and trans and gender diverse people assigned male at birth ^a who: <ul style="list-style-type: none"> • have sexual exposure AND • are not taking exogenous estradiol-based hormones 	Take a double dose 2–24 hours before potential sexual exposure (ideally closer to 24 hours before potential exposure)	Take one dose per day	Take one dose per day until two days after the day of the last potential sexual exposure
Cisgender women and trans and gender diverse people assigned female at birth ^a Cisgender men and trans and gender diverse people assigned male at birth ^a who are taking exogenous estradiol-based hormones People using oral PrEP to prevent HIV acquisition from injecting practices	Take one dose daily for seven days before potential exposure	Take one dose per day	Take one dose daily for seven days after last potential exposure

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

^a “Trans and gender diverse people” is an umbrella term for those whose gender identity, roles and expression does not conform to the norms and expectations traditionally associated with the sex assigned to them at birth; it includes people who are transsexual, transgender, or otherwise gender nonconforming or gender incongruent. Transgender people may self-identify as transgender, female, male, transwoman or transman, trans-sexual or one of many other gender nonconforming identities.

Fig. 1. How to start and stop oral PrEP for those eligible for ED-PrEP and those not eligible



Rationale

Data from trials, open label extension studies and demonstration studies have shown that oral PrEP using the ED-PrEP dosing regimen is as effective in preventing HIV infection as daily PrEP in cisgender men who have sex with men (6–8). As a result, WHO recommended that an ED-PrEP regimen is safe and highly effective in reducing risk of HIV acquisition through receptive and/or insertive sex between cisgender men and can be offered as an alternative to daily dosing for men who have sex with men (6). Importantly, ED-PrEP is effective for all positioning (insertive and/or receptive). It is reasonable to extrapolate that the risk of HIV associated with cisgender men having sex with cisgender men should not be lower than for cisgender men having sex with individuals from other populations. Similarly, for trans and gender diverse people assigned male at birth who are not taking exogenous estradiol-based hormones, the risk of HIV acquisition from anal sex should be similar to cisgender men.

While much of the discussion about the pharmacokinetics of oral PrEP has focused on rectal concentrations and exposures, oral PrEP is protective for insertive positioning and it is unlikely that the efficacy or pharmacodynamics should differ between insertive positioning adopted for anal sex and for vaginal sex. As such, ED-PrEP should be suitable as an option for all individuals with sexual exposure who were assigned male at birth and are not taking exogenous hormones (for example, gender-affirming hormones). There is insufficient evidence to support the efficacy of ED-PrEP dosing regimens for other groups, including people with injecting exposure, people assigned female at birth, and people assigned male at birth who are taking estradiol-based hormones. Small studies have suggested that the use of gender-affirming hormones may reduce the concentrations of TDF and FTC among transgender women by 12–27% (9,10), although this has been questioned (11). While the lower

PrEP concentration is unlikely to affect the efficacy of daily oral PrEP, effects on ED-PrEP dosing efficacy are unclear and further studies are needed. Furthermore, more research is needed on risks of HIV acquisition and efficacy of ED-PrEP associated with neovaginal sex (involving a person assigned male at birth who underwent vaginoplasty).

For populations not eligible for ED-PrEP, modelling of observed pharmacokinetics with both TDF and FTC, the most common drug combination for oral PrEP, support a shorter stopping regimen of 7–10 days (12–14). TDF and FTC work synergistically (12,15) and have different pharmacokinetic profiles in tissue (16–18). For sexual exposure, while FTC-triphosphate declines quickly in vaginal and rectal tissues, TDF-diphosphate has a longer half-life (16,19). TDF-FTC and TDF-3TC are modelled to remain $\geq 50\%$ effective for about 10 days after discontinuation (19). Population pharmacokinetic models suggest that the combination of TDF-FTC may provide quick, durable (up to 84 hours) and high protection and could completely protect against parenteral exposure for people who inject drugs with as little as two doses per week (13).

Limited evidence available for post-exposure prophylaxis (PEP) suggests low completion rates for a 28-day regimen (20). This may be similar for oral PrEP, and, as reports suggest, clients who stop using PrEP often do not return to a clinic to receive a final oral PrEP prescription. Anecdotal evidence suggests that needing to continue oral PrEP for 28 days after the last exposure may serve as a barrier to prescribing or supporting daily oral PrEP initiation and re-initiation. Recommendations for a seven-day stopping regimen for daily PrEP have been made in several guidelines, including by the International Antiviral Society–USA (21), British HIV Association and British Association for Sexual Health and HIV (22) and European AIDS Clinical Society (23), and 7–10 days by the US Centers for Disease Control and Prevention (24).



PrEP and hepatitis B and C

Key points

- Individuals at substantial risk of HIV infection may also be at a higher risk for HBV and HCV infection. PrEP services provide an important opportunity to screen for HBV and HCV infection and provide linkages to care.
- Testing PrEP users for HBV surface antigen (HBsAg) once, at or within one to three months of PrEP initiation, is strongly encouraged where feasible, particularly in highly endemic countries.
- HCV antibody testing is strongly encouraged at or within one to three months of PrEP initiation and every 12 months thereafter where PrEP services are provided to populations at high risk of HCV infection.
- TDF-based daily or event-driven oral PrEP and the DVR can be safely offered to people with HBV or HCV infection.
- Lack of HBV and HCV testing should not be a barrier to PrEP initiation or use. PrEP can be initiated before HBV and HCV test results are available. HBV or HCV testing are not a requirement for PrEP use (see Box 3 for specific considerations for CAB-LA).

Hepatitis B virus

Testing PrEP users for HBsAg once, at or within one to three months of PrEP initiation (or later if not available around initiation), is strongly encouraged, particularly in highly endemic countries. TDF-based daily or event-driven oral PrEP and the DVR can be safely offered to persons with HBV infection. There are specific considerations regarding offering CAB-LA to people with HBV (Box 3). HBV testing is not a requirement for PrEP use. Therefore, lack of HBV testing should not be a barrier to PrEP initiation or use. Where HBV testing is conducted, PrEP can be initiated before results are available. Rapid point-of-care tests are available for HBsAg, and WHO has prequalified several rapid diagnostic tests (RDTs).

▶ **HBsAg test is non-reactive:** WHO recommends HBV vaccination for people at risk of acquiring HBV (25).⁵

▶ **HBsAg test is reactive:** Further assessment for HBV treatment eligibility.

- Eligibility for long-term therapy for HBV infection as per WHO guidance (26):
 - People with detectable HBsAg and clinical evidence of compensated or decompensated cirrhosis.
 - People older than 30 years with persistently abnormal alanine aminotransferase (ALT) levels and evidence of high-level HBV replication (who do not have clinical evidence of cirrhosis).
- WHO recommends TDF or entecavir to suppress HBV. TDF-based oral PrEP is active against HBV. For people who require HBV treatment and request HIV PrEP, TDF-based oral PrEP should be considered, as it will suppress HBV and prevent HIV. These people will, in most cases, need to take TDF as a life-long therapy, and they can be switched to a TDF-only regimen when the PrEP user and the provider decide that HIV PrEP is not needed or desired anymore. PrEP and HBV treatment providers should (where possible) jointly manage these cases.
- TDF-based oral PrEP can be considered even if HBV treatment is not required at the moment of PrEP initiation. There is a small risk of HBV relapse after daily or event-driven use of TDF-containing oral PrEP. Risks and benefits of oral PrEP use should be evaluated on a case-by-case basis. Regular monitoring after stopping TDF-based PrEP is important to detect relapse and manage HBV (including treatment, when eligible).

⁵ 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 (25).

Hepatitis C virus

HCV antibody testing is strongly encouraged at or within one to three months of PrEP initiation (or later if not available around initiation), and every 12 months thereafter, where PrEP services are provided to populations at high risk of HCV infection. Risks of HCV vary across settings, and populations at high risk of HCV include, but are not limited to, cisgender men and transgender women who have sex with men, people who use drugs, and people in prisons and other closed settings. TDF-based daily or event-driven oral PrEP and the DVR can be safely offered to persons with HCV infection. There are specific considerations regarding offering CAB-LA to people with HCV (Box 3).

HCV testing is not a requirement for PrEP use. Therefore, lack of HCV testing should not be a barrier to PrEP initiation or use. Where testing is conducted, PrEP can be initiated before test results are available. Rapid point-of-care tests are available for HCV serology and WHO has prequalified several RDTs.

Individuals with reactive serology test results should receive further assessment (on-site or by referral) for presence of active HCV infection and be offered treatment as per WHO recommendations (27). Further guidance on HCV retesting and treatment of recently acquired infection in people with ongoing risk are provided in the updated 2022 WHO key populations guidelines (28). New guidance regarding decentralization, integration, task-shifting and point-of-care confirmatory diagnosis of HCV care are highlighted in the updated WHO guidelines on HCV care and service delivery (27).

WHO recommends that HCV self-testing should be offered as an additional approach to HCV testing services and has released guidance on implementation considerations (29). HCV self-testing can be used in PrEP programmes as an additional choice for HCV testing. Secondary distribution of HCV self-tests through social, sexual and drug-injecting networks of PrEP users may also reach people who do not otherwise test. There is limited experience of using HCV self-testing in PrEP programmes and additional implementation research is needed on how to optimally integrate different HCV testing options.

Box 3. CAB-LA for people with HBV and HCV

To date, clinical trial data on or implementation experience with CAB-LA for people with HBV or HCV infection are limited. CAB-LA may be inappropriate for those with advanced liver disease and acute viral hepatitis, and those requiring treatment for HBV. For CAB-LA implementation, testing for HBV and HCV and further assessment for those with reactive test results is strongly encouraged. More research is needed on implementation of CAB-LA for people with HBV or HCV.

- **HBsAg test is reactive:** HIV prevention and HBV treatment needs should be evaluated on a case-by-case basis, and PrEP and HBV treatment providers should (where possible) jointly manage these cases. CAB-LA is not active against HBV. For people eligible for HBV treatment as per WHO guidance (26), TDF-based oral PrEP should be offered as the preferred PrEP option. Even where there is no indication for treatment for HBV, TDF-based oral PrEP should be strongly considered as it will suppress HBV and prevent HIV.
- **HCV serology test is reactive:** HCV treatment should be offered as per WHO guidelines (30), and PrEP and HCV treatment providers should (where possible) jointly manage these cases. CAB-LA is not active against HCV. There are no known drug–drug interactions between CAB-LA and treatment drugs for HCV, but data are scarce. Alternative PrEP and HIV prevention options should be considered.



Rationale

WHO estimates that in 2019, there were 296 million people living with chronic HBV infection and 58 million people living with HCV infection worldwide (31). An estimated 1.1 million deaths in 2019 were due to HBV and HCV infection. The Global Health Sector Strategy on Viral Hepatitis, approved by the World Health Assembly in 2016, set the goal to eliminate viral hepatitis as a major public health threat by 2030 (32). HBV and HCV are endemic in many parts of the world where there is also a high burden of HIV, and many key and vulnerable populations are affected by both HIV and viral hepatitis. PrEP services for HIV prevention offer an important opportunity to screen for HBV and HCV infection and provide linkages to care, addressing multiple public health issues and providing improved person-centred health care.

HBV infection is not a contraindication for TDF-based oral daily PrEP or ED-PrEP. Previous WHO guidance (6) suggested that event-driven oral PrEP is not appropriate for individuals with HBV infection due to small risks of virological and clinical relapse when withdrawing active therapy against HBV. However, clinical relapse did not occur during or after PrEP use in clinical oral PrEP trials that included people with chronic HBV infection (33–35), and it is considered rare. Most cases of relapse are asymptomatic but can, in rare cases, lead to hepatic decompensation (36).

The risk of HBV relapse is related to the length of exposure to treatment and viral suppression. Duration of TDF exposure is likely to be limited with oral PrEP use, although risk of HBV relapse exists for both oral daily PrEP and ED-PrEP. This further underscores the benefits of HBV testing within three months of PrEP initiation. 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. TDF has a high genetic barrier to drug resistance, and HBV drug resistance against TDF is considered very rare (37–39).

Use of the DVR does not affect the risk of virological and clinical relapse of HBV (4). However, in HBV-endemic areas, PrEP services, including for the DVR, provide an opportunity to screen for HBV and provide linkage to care. This would also contribute to efforts to prevent vertical transmission of HBV during pregnancy. To prevent vertical transmission of HBV, WHO recommends that all newborns receive a timely birth-dose of HBV vaccination, and that those who tested HBSAg-positive during pregnancy and are at high risk of transmitting the virus to their infants receive TDF prophylaxis from the 28th week of pregnancy until at least delivery (40). Different PrEP options and risks and benefits for both the individual and infant should be discussed with those who are pregnant, living with HBV and attending PrEP services.



PrEP and kidney function

Key points

- Impaired kidney function (estimated glomerular filtration rate [eGFR] <60 mL/min per 1.73 m²) is a contraindication for TDF-based oral PrEP.
- Measuring kidney function is optional for those aged under 30 years without kidney-related comorbidities.
- Individuals aged 30 years and older without comorbidities may be screened once, at or within one to three months of oral PrEP initiation. Depending on available resources, this can be considered optional for those aged 30–49 years, 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 (eGFR <90 mL/min per 1.73 m²).
- Waiting for kidney function test results should not delay initiation or continuation of oral PrEP.

Impaired kidney function, indicated by an eGFR of <60 mL/min per 1.73 m² or an estimated creatinine clearance of <60 mL/min, is a contraindication for the use of TDF-based oral PrEP. Measuring kidney function in potential PrEP users at initiation and during PrEP continuation is suggested for some populations. Table 2 outlines suggested procedures (applicable to oral daily PrEP or ED-PrEP). Box 4 provides suggestions on estimating kidney function.

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. Before stopping oral PrEP due to reduced kidney function, the kidney function test should be repeated on another day. Kidney function usually returns to normal levels after stopping oral PrEP. Other HIV prevention options should be discussed with clients when stopping PrEP. Oral PrEP can be restarted if eGFR is confirmed ≥ 60 mL/min per 1.73 m² (or creatinine clearance ≥ 60 mL/min) 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. Kidney function measurement is not necessary for use of the DVR. No kidney toxicity is anticipated during use of CAB-LA.



Table 2. 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 ^a	Optional	If no initiation test conducted or if initiation test is normal, ^b follow-up is optional If initiation test result suggests at least mild loss of kidney function, ^c follow-up measurements every 6–12 months are suggested
Individuals aged 30–49 years and no kidney-related comorbidities ^a	Optional/conduct once, at or within 1–3 months of initiation ^d	If initiation test is normal, ^b follow-up is optional If initiation test result suggests at least mild loss of kidney function, ^c follow-up measurements every 6–12 months are suggested
Individuals aged 50+ years and no kidney-related comorbidities ^a Individuals of any age with kidney-related comorbidities ^a Individuals with previous measurement of kidney function suggesting at least mild loss of kidney function ^c	Conduct once, at or within 1–3 months of initiation	Follow-up measurements every 6–12 months

eGFR: estimated glomerular filtration rate; PrEP: pre-exposure prophylaxis; TDF: tenofovir disoproxil fumarate.

^a 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.

^b eGFR ≥ 90 mL/min per 1.73 m² or creatinine clearance of ≥ 90 mL/min.

^c eGFR < 90 mL/min per 1.73 m² or creatinine clearance of < 90 mL/min.

^d 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.



Box 4. Measuring kidney function

Glomerular filtration rate (GFR) is a measure of kidney function. A GFR of ≥ 90 mL/min per 1.73 m^2 suggests normal kidney function. Urinary inulin clearance measurement is the gold standard for measuring GFR but difficult to implement routinely. Alternative measures use serum creatinine to determine estimated GFR (eGFR). National guidelines should be considered on preferred estimation methods and eGFR should be calculated using an equation that has been validated for the specific population. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation is commonly used to determine eGFR (41) and considered a more accurate measure of GFR than Cockcroft-Gault-estimated creatinine clearance. The 2021 version of the equation (42) is:

For people assigned female at birth^{a,b} with serum creatinine ≤ 0.7 mg/dL:

$$\text{eGFR} = 142 \times \left(\frac{S_{cr}}{0.7}\right)^{-0.241} \times 0.9938^{\text{age}} \times 1.012$$

For people assigned female at birth^{a,b} with serum creatinine > 0.7 mg/dL:

$$\text{eGFR} = 142 \times \left(\frac{S_{cr}}{0.7}\right)^{-1.2} \times 0.9938^{\text{age}} \times 1.012$$

For people assigned male at birth^{a,b} with serum creatinine ≤ 0.7 mg/dL:

$$\text{eGFR} = 142 \times \left(\frac{S_{cr}}{0.9}\right)^{-0.302} \times 0.9938^{\text{age}}$$

For people assigned male at birth^{a,b} with serum creatinine > 0.7 mg/dL:

$$\text{eGFR} = 142 \times \left(\frac{S_{cr}}{0.9}\right)^{-1.2} \times 0.9938^{\text{age}}$$

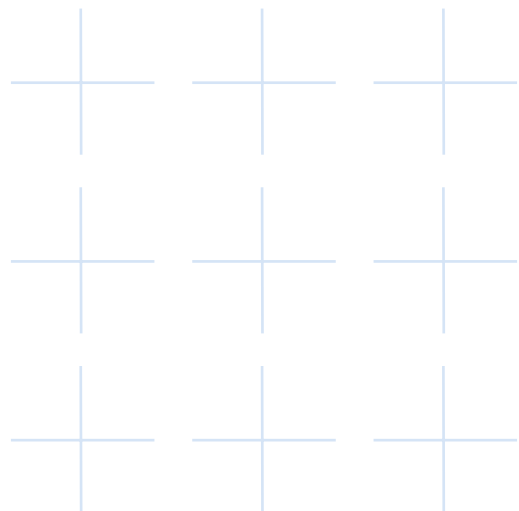
Where S_{cr} is serum creatinine given in mg/dL and age is in years.

^a Exposure to gender-affirming hormones may influence eGFR estimates and eligibility for oral PrEP (43). Gender identity, rather than sex assigned at birth, may be more appropriate for individuals who have been in hormone therapy for over six months (44). However, more research is needed on estimating eGFR in trans and gender diverse populations, and optimal equations to estimate eGFR in individuals who have been receiving gender-affirming hormones should be considered on a case-by-case basis.

^b Equations to calculate eGFR may be inaccurate during pregnancy and underestimate eGFR at lower values (45). National guidelines should be considered for preferred methods on estimating kidney function during pregnancy.

Rationale

Multiple systematic reviews and meta-analyses of randomized controlled trials (RCTs) found that individuals taking TDF-based oral PrEP have, on average, a higher risk of experiencing kidney-related adverse events compared with individuals taking placebos (46–48), but these adverse events tend to be mild, nonprogressive, and reversible after PrEP discontinuation. Severe kidney-related adverse events are very rare. An analysis of data from 17 implementation projects and two clinical trials from 15 countries found that less than 1% of over 18 000 individuals screened for PrEP had abnormal estimated creatinine clearance levels of < 60 mL/min (46). Proportions of individuals with < 60 mL/min baseline creatinine clearance increased with age (from 0.09% among those aged 15–19 years to 1.83% among those aged 50+). Less than 3% of over 14 000 individuals who initiated oral PrEP had a measurement of < 60 mL/min creatinine clearance after initiation. Older individuals, particularly those over 50 years, and individuals with a baseline creatinine clearance of < 90 mL/min had a higher probability of declining to < 60 mL/min creatinine clearance. The median age of those experiencing < 60 mL/min creatinine clearance after PrEP initiation was 40 years, and less than 1% of oral PrEP users younger than 30 years experienced abnormal creatinine clearance. Among those with a decline in creatinine clearance to < 60 mL/min who had a subsequent measurement, 83% had a creatinine clearance of ≥ 60 mL/min at the subsequent measurement. Optional or reduced kidney function measurements for some populations may remove barriers to PrEP implementation and uptake.



HIV self-testing (HIVST) for PrEP

Key points

- Differentiated service delivery models have the potential to remove barriers to accessing PrEP and increase uptake, persistence and effective use.
- HIVST can complement existing HIV testing strategies for PrEP to support differentiated service delivery approaches for oral PrEP and the dapivirine vaginal ring (DVR) to reduce clinic visits, and it may increase PrEP use and frequency of HIV testing.
- HIVST provides an additional testing choice to PrEP users when starting, restarting or continuing PrEP, which may be preferred for convenience, privacy and self-managed care.
- Clear and concise messaging for clients and regular HIV testing while taking PrEP are critical.
- HIVST-supported PrEP delivery models that reduce clinic visits should be balanced with the benefits of provision of comprehensive services to address the diverse needs of PrEP users.
- Operational research on HIVST-supported PrEP delivery remains important, particularly for optimizing delivery, understanding impact and assessing the costs of different models.

What is HIVST?

In HIVST, people collect their own specimen (generally oral fluid or fingerprick whole blood) using a simple rapid HIV test and then perform the test and interpret their result, often in private or with someone they trust. WHO has recommended HIVST as an approach to HIV testing services since 2016 (4), and the approach has been scaled up globally with nearly 100 countries reporting national policies.⁶ Currently, there are five WHO prequalified HIVST products available,⁷ all of which have been shown to be highly accurate and achieve good performance (49). In field settings, HIVST has been shown to be safe, reliable and accurate, especially following an in-person demonstration (50).

HIVST and PrEP

HIVST could be an important tool to enable countries to increase access to PrEP and uptake, persistence and effective use. Since the beginning of the COVID-19 pandemic, WHO has supported HIVST to maintain PrEP services (51), and several countries have integrated HIVST into their PrEP programming to initiate and continue clients on PrEP (see Box 6 and 10 in next section). A literature review found evidence that HIVST can reduce clinic visits for oral PrEP continuation and support HIV testing between clinic visits, and may increase PrEP use in some groups (52). Experience during COVID-19 and published evidence suggest that HIVST can complement existing HIV testing strategies for oral PrEP services and enable differentiated service delivery approaches for PrEP to reduce clinic visits, such as delivery outside of health facilities, including through virtual interventions. Differentiated models have the potential to remove barriers to access and increase use of PrEP (see next section).

There are three key approaches where HIVST can be considered as part of PrEP delivery:

1. Demand generation and linkage to PrEP
2. PrEP initiation
3. PrEP continuation, re-initiation, and effective use

HIVST for demand generation and linkage to PrEP

HIVST can be an important tool to generate demand for PrEP by reaching individuals who may not otherwise test or access health facilities (53). Many programmes already use HIVST to deliver messages about PrEP and facilitate linkage among those who could benefit from PrEP. However, it is important that these programmes engage with local communities to develop appropriate strategies and messaging (54,55).

⁶ Data on HIVST policy adoption into national guidelines can be found online: <https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/hiv/strategic-information/hiv-data-and-statistics>

⁷ Reports on WHO prequalified HIVST can be found online: https://extranet.who.int/pqweb/vitro-diagnostics/prequalification-reports/whopr?field_whopr_category=60

HIVST for PrEP initiation

HIVST could be considered for PrEP initiation outside of clinics, although current evidence is limited. Some programmes may prefer provider-delivered HIV testing over HIVST when initiating first-time oral PrEP users or re-initiating less experienced oral PrEP users, partly due to concerns about initiating PrEP during acute HIV infection, which may result in HIV drug resistance (56). However, risks of initiating a person on PrEP while acutely HIV infected are low (57) and likely similar for HIVST and provider-administered RDTs (58). Mathematical modelling suggests that, while HIVST may miss some cases of acute and chronic HIV infection compared with provider-delivered testing, the overall differences are small and unlikely to result in increased population-level HIV drug resistance (Sharma et al., unpublished data; see Annex 1).

HIVST for PrEP continuation and re-initiation and to support effective use

HIVST may be particularly appropriate to support PrEP continuation and reduce follow-up clinic visits and for re-initiation of more experienced PrEP users. In some populations, HIVST between clinic visits has also been shown to increase PrEP use and frequency of HIV testing among PrEP users and their partners.

Clear and concise messages are critical

Where HIVST is used for PrEP initiation or continuation, regular interactions between PrEP providers and clients are important to ensure that PrEP users have adequate counselling and can raise any issues or concerns with providers. Clear and concise messages are critical, including:

- For initiation, following a reactive HIVST, individuals should not initiate PrEP and seek further testing by a trained provider.
- For continuation, following a reactive HIVST, PrEP users should not discontinue PrEP and seek further testing by a trained provider.
- Regular HIV testing is important while taking PrEP to identify an HIV infection as soon as possible.

The importance of regular HIV testing and comprehensive services

A one-month follow-up test after PrEP initiation is often appropriate to detect HIV infection that may have been missed at initiation. While risks of HIV acquisition are low when taking PrEP as prescribed, there may be a

delayed antibody response when a person exposed to TDF-based oral PrEP acquires HIV. Regular HIV testing while taking PrEP is suggested (such as every three months). An HIV diagnosis is never based on a single test. Therefore, after a reactive HIVST, PrEP users should not discontinue PrEP, and they should seek further testing by a trained provider, using the full national HIV testing algorithm. Further testing following a reactive test is consistent with WHO guidance for HIV testing in all situations (59).

PrEP services should be integrated to address the diverse needs of PrEP users (such as contraception, STIs, and mental health; see next section). HIVST-supported PrEP delivery models that reduce clinic visits should be balanced with the benefits of provision of comprehensive services. Alternative approaches to provide services outside of clinic settings should be considered (for example, STI self-sampling, HCV self-testing and virtual interventions including telehealth models).

HIVST for different PrEP products

HIVST approaches similar to those for oral PrEP can likely be applied to the DVR. HIVST may be particularly appropriate to support continuation of the DVR, as there is no systemic absorption of PrEP that could impact the sensitivity of HIVST. However, evidence and experience of HIVST for the DVR is more limited. For CAB-LA, there are specific considerations regarding HIV testing; see WHO guidelines for details (5).

Key research gaps for HIVST for PrEP

HIVST can complement existing HIV testing strategies for PrEP to support differentiated service delivery approaches and provides an additional choice to users that may be preferred for convenience, privacy and self-managed care. The potential public health impact of HIVST for PrEP will depend on a range of factors (for example, PrEP product options, availability of quality-assured tests, needs of PrEP user populations and gaps in service delivery). Training of PrEP providers and engagement with communities and PrEP users on the role of HIVST and its safe and effective use to enhance PrEP programming will be important. WHO will publish additional guidance on HIVST for PrEP in 2023. Further implementation research is needed to optimize HIVST-supported PrEP delivery approaches and understand more broadly the acceptability, feasibility, effectiveness, costs and impact of different models (Box 5).



Box 5. Key research questions for HIVST for PrEP

- How **feasible** and **effective** are HIVST-supported PrEP delivery models for initiation and continuation across settings and populations and for different PrEP products (oral PrEP and the DVR)?
- What are the **benefits** (for example, increased PrEP uptake, more acceptable service provision) and **harms** (for example, HIV drug resistance, missed opportunities for integrated services) of HIVST-supported PrEP services? How do these benefits and harms balance on a population level?
- What are the **costs** of HIVST-supported PrEP delivery models, and how **cost-effective** are they?
- How can providers offer **comprehensive and integrated services** that address PrEP users' multiple health needs in HIVST-supported PrEP delivery models?
- What are the **values** and **preferences** of all stakeholders (PrEP users, providers, policymakers, etc.)?
- What **training** and **information** do PrEP providers need to effectively implement HIVST-supported PrEP services?
- How can services **capture data** from HIVST and incorporate HIVST used for PrEP into national **monitoring and evaluation** systems?

who received six-month PrEP with HIVST. An RCT in Uganda found that sex workers provided with HIVST between quarterly clinic visits had similar PrEP use and persistence after 12 months compared with those who did not use HIVST, and nearly all participants in the HIVST study group used at least one HIVST kit. In South Africa, an RCT among postpartum women and their male partners evaluated HIVST in combination with enhanced adherence feedback through urine TDF testing and found higher levels of PrEP use and higher levels of partner HIV testing compared with standard counselling without HIVST. The trials did not identify any adverse events or social harms.

Five studies were identified that assessed values and preferences of PrEP users around HIVST for PrEP delivery in Brazil, Kenya, Uganda and Zambia. These found that HIVST-supported models of PrEP delivery were acceptable and often preferred, although no study was identified that evaluated preferences around initiation of PrEP through HIVST. About 18% of over 1000 PrEP providers in a global survey indicated that they used HIVST as part of their HIV testing algorithm for PrEP initiation. In 30 in-depth interviews, PrEP providers noted that HIVST was primarily used as a screening tool to link individuals to PrEP services. PrEP providers generally supported the use of HIVST for PrEP continuation, particularly for clients who are stable on PrEP with no complex health issues, while support for using HIVST for initiation was limited due to concerns about missing acute HIV infection. At the same time, many providers emphasized the importance of opportunities for regular contact between PrEP clients and service providers to discuss challenges with use of PrEP and other health concerns (see Annex 2 for details on the survey and interviews).

Rationale

A systematic review on HIVST for PrEP initiation and continuation (52) identified three completed RCTs that evaluated PrEP continuation after initiation in health care facilities, while no studies evaluated HIVST-based PrEP initiation. All studies evaluated oral PrEP. An RCT in Kenya that evaluated six-month PrEP dispensing supported with HIVST between clinic visits found that PrEP clinic visits were halved, while PrEP persistence and use were similar to standard-of-care three-month PrEP dispensing and clinic-based HIV testing. PrEP use was significantly higher among women not in serodifferent relationships

A mathematical modelling study of PrEP use in sub-Saharan Africa found that reduced HIV testing sensitivity had little effect on the prevalence of HIV among PrEP users (58). Preliminary findings by a mathematical modelling study of HIVST for PrEP in Kenya similarly found no difference in the number of acute-stage PrEP initiations by test modality (HIVST vs. facility-based RDT) (Sharma et al., unpublished data, see Annex 1). This modelling also found that population prevalence of nucleoside reverse transcriptase inhibitor (NRTI) drug resistance was similar across scenarios, largely due to the reduction in HIV (and therefore HIV-related drug resistance) in the PrEP scenarios compared with the counterfactual of no PrEP.

Differentiated PrEP service delivery: When, where, who and what to deliver

Key points

- A differentiated PrEP service delivery approach is person- and community-centred and adapts services to the needs and preferences of 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.
- A common framework for differentiated PrEP service delivery utilizes the four building blocks of where (service location), who (service provider), when (service frequency), and what (service package). These building blocks can be different for PrEP initiation, continuation and re-initiation, and for different PrEP products.

A differentiated PrEP service delivery approach is person- and community-centred and adapts services to the needs and preferences of the people who are interested in and could benefit from PrEP. Differentiated PrEP service delivery may also support more efficient and cost-effective use of health care resources. WHO recommends differentiated service delivery for HIV testing and antiretroviral therapy (ART) (4). 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 differentiated service delivery is recognized as a key action (3).

This section provides guidance on differentiated service delivery for PrEP, utilizing the four building blocks of differentiated service delivery (Table 3). These building blocks can be different for PrEP initiation, continuation and re-initiation. For example, a person may be initiated on PrEP at a health care facility and offered follow-up visits in a community setting. The building blocks may also be different for the various PrEP products. Although the primary focus of this section is oral PrEP delivery, many of the principles could be applied to the DVR. However, for CAB-LA there are different safety and clinical considerations, and there has been very limited implementation of CAB-LA outside of clinical trial settings.

Building blocks of differentiated PrEP service delivery

In many countries, individuals interested in PrEP must go to a health care facility (often an HIV clinic) to obtain a prescription from a medical provider (often a physician). In recent years, and particularly during the COVID-19 pandemic (60), the shift towards differentiated PrEP service delivery has accelerated.



Table 3. The building blocks of differentiated PrEP service delivery

Building block	PrEP initiation, initial follow-up (0–3 months), and re-initiation			PrEP continuation (3+ months)	
	Initiation	Initial follow-up (0–3 months) (if required)	Re-initiation after discontinuation	PrEP refill	Follow-up
Where? Service location (e.g., primary health care facility, community setting, virtual setting)	Locations for PrEP assessment and initiation	Locations for initial follow-up	Locations for PrEP re-initiation	Locations where PrEP refills can be collected	Locations where follow-up services will be provided
Who? Service provider (e.g., physician, nurse, pharmacist, peer)	Service provider/s authorized to assess for and initiate PrEP	Service providers who can carry out initial follow-up visit/s	Service provider/s authorized to re-initiate PrEP	Service provider/s who can dispense PrEP refills	Service provider/s who conduct follow-up
When? Service frequency (e.g., monthly, every 3 months)	Timing of PrEP assessment and initiation	Timing of initial follow-up	Timing of PrEP re-initiation	Frequency of PrEP refill visits (length of supply)	Frequency of follow-up services
What? Service package (including HIV testing, clinical monitoring, PrEP prescription and dispensing, and comprehensive services)	Service package for PrEP assessment and initiation	Service package at initial follow-up	Service package for PrEP re-initiation	Service package with PrEP refill	Service package with follow-up

PrEP: pre-exposure prophylaxis.

Source: Adapted from the International AIDS Society framework for differentiated service delivery (61).

Where to deliver PrEP

There are a range of barriers to PrEP access, uptake, persistence and effective use associated with service delivery in health care facilities. These include actual or perceived lack of privacy, stigma and discrimination, negative attitudes of health care providers, travel distance, direct and opportunity costs for clients, frequency of required clinic visits for continuation, lengthy waiting times and inconvenient operating hours. Provider-level barriers include policy and legal barriers (for example, policies restricting eligibility), lack of training, understaffing, limited time for interactions with clients, and stockouts of

drugs and supplies. Delivery of oral PrEP and the DVR has relatively few necessary components, including HIV testing, counselling, and PrEP prescribing and dispensing, although additional laboratory tests may be indicated for some individuals. Therefore, it can be feasible and appropriate to deliver oral PrEP and the DVR in community settings and outside of health care facilities, which could overcome some barriers to accessing and using PrEP. Diversifying where PrEP is delivered also expands choice and increases convenience, so individuals can select their preferred location and service type. More implementation science is needed on the feasibility of delivering CAB-LA outside of health care facilities.

WHO already recommends community-based and lay provider-delivered HIV testing services and HIV self-testing as well as ART initiation and refills outside of health care facilities (4). WHO also recognizes the benefits of decentralized and community-based services for key populations (28). A range of differentiated oral PrEP service delivery models outside of health care settings has been implemented, including in fixed and mobile community sites, pharmacies and telehealth models. Some of these models provide PrEP services outside of health care facilities for initiation and continuation, while others provide initiation at health care facilities and continuation in community settings. Research suggests that community-based PrEP delivery models are acceptable to PrEP providers and are recognized to improve uptake of services (Box 6). Key considerations for any community-based PrEP service delivery model include:

- Community-based delivery sites should ensure adequate community sensitization and community involvement in service design, planning, community mobilization, recruitment, service delivery and evaluation (28).
- Government support and policy are needed to legitimize service delivery approaches and ensure nationally defined standards and procedures (for example, for training and supervision and accreditation of providers).
- Logistics systems at national and subnational level must integrate community-based service delivery to ensure sustainability of supplies.
- Community-based delivery sites need adequate infrastructure for PrEP delivery, including HIV testing and laboratory testing as necessary (on- or off-site) and space to ensure privacy and confidentiality.
- Clinical oversight or partnerships and referral pathways are needed, particularly for clients with complex needs (such as those with more severe side effects (62)) or those who require additional services.
- Data need to be captured and fed into national reporting systems (including for donor reporting, where applicable).
- PrEP services should be person-centred and integrated with other relevant services, such as screening and treatment for STIs and provision of contraception.

Box 6. Provider perspectives on delivering PrEP outside of health care facilities

A global study of PrEP providers' practices and perspectives was conducted from November 2021 through February 2022, comprising an online survey and 30 in-depth interviews (see Annex 2). Of 747 survey respondents who completed questions on mobile PrEP services, 40% reported experience with mobile outreach services for PrEP initiation and 36% for follow-up visits. Telehealth models were used by 28% of respondents for initiation and by 34% for follow-up visits. Interview participants reported that PrEP delivery outside of clinic settings was commonly implemented in response to COVID-19. These adaptations have often been maintained, even as COVID-19 restrictions were lifted, as clients expressed preference for fewer clinic visits, noting convenience, privacy, perceived stigma and travel constraints due to social and political instability. Community-based delivery was viewed as vital for reaching individuals – particularly from highly marginalized populations – who are unable or unwilling to engage with facility-based services. Telehealth and online services were considered especially useful for follow-up consultations with clients who are stable on PrEP and have no challenges to effective use, allowing clinic staff to dedicate more time for clients initiating PrEP and for those with complex medical and psychosocial needs. Providers reported that HIVST and STI self-sampling support differentiated services such as home delivery and pharmacy pick-up of PrEP. Most providers emphasized the importance of regular in-person engagement with PrEP users for examinations and discussions about sexual health, although they also recognized the benefits of demedicalized and community-based PrEP delivery. Some providers expressed concerns that new PrEP products such as CAB-LA may lead to remedicalization of PrEP services.



PrEP in fixed and mobile community settings

Service models that deliver oral PrEP in fixed community sites (such as through nongovernmental organizations) and mobile and semimobile sites (for example, vans parked in community settings) have been implemented. A systematic review (Box 7) (63) identified diverse models demonstrating the feasibility of these approaches in a range of countries, but data on effectiveness were limited. In addition to considerations outlined above, studies highlighted the need for strong partnerships between mobile PrEP delivery sites and local community-based organizations.

Same-day PrEP initiation can be offered to maximize uptake, and clients should be offered the opportunity to return to fixed or mobile community sites for PrEP refills as needed. PrEP should be offered with other relevant services, and studies have demonstrated the feasibility of community-based PrEP delivery providing comprehensive and integrated services (Box 8), including sexual and reproductive health services (for example, STI and contraceptive services (64)), harm reduction for people who inject drugs (65), and noncommunicable disease services (such as blood pressure and blood glucose management (66)).

Box 7. Evidence on PrEP delivery in fixed and mobile community settings

A systematic review (63) identified 17 studies evaluating oral PrEP delivery in fixed community settings, although only two completed studies (SEARCH and Love O2O) included a comparison group. The SEARCH trial was conducted in Kenya and Uganda and compared home- or community-based PrEP delivery in a fixed setting to clinic-based PrEP delivery. Community-based delivery was associated with significantly higher PrEP persistence and resulted in lower HIV incidence among PrEP initiators. The Love O2O study in Thailand compared PrEP initiation at the Adam's Love clinic that focuses on men who have sex with men and transgender women, fixed community drop-in centres, and a Thai Red Cross clinic. Individuals were more likely to initiate PrEP at the Adam's Love clinic compared with the Red Cross clinic, but PrEP initiations did not differ between community drop-in centres and the Red Cross clinic. Although Adam's Love was a clinic setting, it adapted services specifically to men who have sex with men and transgender populations, including tailored social media promotions and virtual counselling support on a web platform. Several other studies evaluated PrEP delivery at fixed community sites and found high acceptability and feasibility of this model, including in community safe spaces and public spaces (N=5; Kenya, South Africa, Zimbabwe), family planning clinics (N=2; Kenya, South Africa), nongovernmental organizations (N=5; Kenya, Thailand, USA), syringe exchange programs (N=1; USA) and alcohol-serving

venues (N=1; South Africa). These studies included PrEP services delivered to adolescent girls and young women (N=4), adult men (N=2), female sex workers (N=3), men who have sex with men (N=4), transgender women (N=4) and people who inject drugs (N=2).

The systematic review identified 12 studies evaluating PrEP delivery at mobile community sites. Studies were conducted in the USA (N=4), South Africa (N=4), Kenya (N=3), and Viet Nam (N=1). PrEP initiations and persistence varied widely across studies. In general, people who use drugs and women who are unstably housed had the lowest proportions of PrEP initiations and PrEP persistence through the mobile model (three studies).

The systematic review identified 20 studies on values and preferences regarding PrEP service delivery. Most studies assessed perspectives from PrEP clients and included men who have sex with men (N=11), adolescent girls and young women (N=4), sex workers (N=3), transgender people (N=3), and adult men and women (N=1). One study evaluated perspectives of PrEP providers. These studies found that community-based services were acceptable but preferences about service delivery locations (clinic vs. community) varied, emphasizing the benefits of offering a choice of delivery locations. Study participants underscored the importance of offering PrEP together with comprehensive services during convenient hours.

Box 8. Bringing PrEP closer to home in Viet Nam

Viet Nam has introduced mobile PrEP and STI services to complement existing services and better meet the needs of underserved populations who may experience barriers to accessing services. The teams include physicians, nurses, counsellors, laboratorians, pharmacists and peers. Services include HIV and STI testing, counselling, and assessment for and provision of PrEP, as well as STI treatment and referral to other services. Mobile PrEP clinics were launched in four provinces in 2021. In Binh Duong, Hai Phong, and Bà Rịa-Vung Tau, three mobile clinics conducted 61 visits for 501 clients (67% sex workers and 23% men who have sex with men). In Dong Nai, the PrEP on Wheels program

is led by Dong Nai Center for Disease Control and G-link clinic (Figure 2). PrEP on Wheels delivers PrEP to men who have sex with men in peri-urban and industrial zones, where accessing HIV clinic services can be difficult. Between January and May 2021, 71 clients were enrolled on PrEP, and one client was newly diagnosed with HIV and linked to HIV treatment services. High persistence on PrEP was observed, with over 90% of new PrEP clients continuing at month three and returning for a health check. The programme successfully supported an increase in PrEP uptake in the province and will soon be expanded further with models called PrEP Bus and PrEP Bike (PrEP delivered via motorbike).

Fig. 2. PrEP on Wheels in Dong Nai province, Viet Nam (January 2021)



Photo credit: PATH.



Telehealth for PrEP

The use of information and telecommunication technologies to create virtual platforms for delivering PrEP services has the potential to remove barriers to PrEP uptake and persistence and support effective use of PrEP. WHO recommends that online delivery of HIV, viral hepatitis and STI services to key populations may be offered as an additional option, while ensuring that data security and confidentiality are protected (28). In many countries, telehealth for PrEP has addressed access challenges during the COVID-19 pandemic.⁸ A systematic review identified a range of case studies of PrEP service delivery via telehealth platforms, including telehealth counselling and prescription with PrEP initiation and refills via home delivery, or pharmacy or clinic pick-up, although data on effectiveness were lacking (Box 9) (63). Several RCTs of home- and telehealth-based PrEP delivery are underway in the USA, and preliminary analyses suggest that telehealth models are associated with higher self-reported effective use of PrEP than clinic-based models. Telehealth services may be preferred for individuals who are stable on PrEP and have few challenges to effective use. Telehealth platforms need to ensure confidentiality and privacy, and staff need to be trained to maintain data security. Telehealth and digital service delivery models can support or replace many aspects of PrEP service delivery, including:

- Assessment of whether a person could benefit from PrEP and linkage to services (locally or virtually).
- HIV testing and any other relevant laboratory tests. During COVID-19, WHO has supported the use of HIVST to maintain PrEP services (51), and several programmes have implemented telehealth PrEP services that delivered HIVST kits to clients' homes, both for PrEP initiation and continuation (Box 10). Home delivery of HIVST kits (and STI self-sampling kits) should include detailed instructions (and easy methods for returning samples, if applicable). Other models include referral to local laboratories.
- Counselling before or after laboratory testing conducted via phone, video or other digital platforms. This could also be conducted on an as-needed basis, for instance, after a brief assessment through an electronic survey indicates a need for counselling.

- PrEP delivery offered through a range of platforms, including home delivery or pick-up at pharmacies or clinics.
- Comprehensive and integrated services, providing person-centred services, for example, through self-sampling for STIs.

Box 9. Evidence on telehealth for PrEP delivery

A systematic review (63) identified 18 studies evaluating oral PrEP service delivery via telehealth platforms, which includes telehealth counselling and prescription with PrEP initiations and refills via home delivery or pharmacy or clinic pick-up. Studies were conducted in the USA (N=7), Brazil (N=3), the United Kingdom (N=2), South Africa (N=1), Zimbabwe (N=1), Kenya (N=1), the Philippines (N=1), Thailand (N=1), and Viet Nam (N=1). None of these studies were RCTs or quasi-experimental studies with a comparison group. PrEP initiations and persistence varied widely across studies. Only one study reported PrEP persistence below 50%, but this study looked at PrEP persistence through 18 months, while four other studies reported high PrEP persistence of 59–90% through 12 months using a telehealth model. Several studies found that the telehealth model was most feasible for supporting PrEP initiations and refills when there were community health workers or peer navigators from the target population who were available to manage client questions and provide optional in-person support (N=6, with men who have sex with men, transgender women and adolescent girls and young women). Studies suggest that telehealth models were acceptable as an approach to conveniently offer PrEP and reduce stigma and wait time during clinic visits. However, some clients reported concerns with the security of telehealth platforms.

⁸ Webinar by the PrEP Learning Network: Going Virtual for Provider PrEP Training, 25 June 2020 https://www.prepwatch.org/wp-content/uploads/2020/06/May28_2020_PrEPLearningNetwork_GoingVirtualServiceDelivery.pdf (accessed 5 May 2022).

Box 10. Telehealth for PrEP during COVID-19 in Brazil

In Brazil, telehealth approaches were implemented during COVID-19 to maintain PrEP services for both adolescent and adult men who have sex with men and transgender women. In the ImPrEP project for adults, PrEP teleconsultations were used and 120-day PrEP supplies together with HIVST kits were dispensed, with HIVST results sent by clients via digital photos (67). Similar levels of PrEP persistence were maintained during COVID-19 compared with fully clinic-based approaches before COVID-19, while reducing the average time spent at PrEP services by clients. The PrEP1519 project adapted PrEP services for adolescents during COVID-19 using digital recruitment and phone-based service navigation by peers, and PrEP continuation appointments via telehealth (68). Refills of PrEP for 120-day and HIVST kits, together with condoms and lubricants,

were mailed to participants in discreet packages (Figure 3), and additional social and mental health support as needed was provided via telehealth. The need for regular HIVST was emphasized to clients. High levels of acceptability of the telehealth services and willingness to continue them were reported for ImPrEP (69) and PrEP1519 (70). These measures helped to mitigate impacts of COVID-19 on PrEP initiations and persistence and contributed to a growth in PrEP uptake in Brazil (71). Staff training and supportive regulatory frameworks were key for the implementation of these services. These adaptations during COVID-19 demonstrate how digital and home-based PrEP services could improve access to and persistence on PrEP. However, some clients prefer in-person services, so telehealth approaches should be offered alongside facility-based services.

Fig. 3. A PrEP1519 participant receives an HIV prevention kit with an HIVST at home, Brazil



Photo credit: Project1519.



PrEP delivery in pharmacies

Pharmacies can be more accessible, acceptable and convenient for clients than health care facilities. In resource-limited settings, individuals commonly first seek health care services from pharmacies before going to clinics (72,73). The WHO Guideline on Self-Care Interventions for Health and Well-Being (74) notes that providing PrEP through pharmacies may present an opportunity to expand access to PrEP. However, feasibility has only been demonstrated in a limited number of settings, and the effectiveness and cost-effectiveness of this model are unknown (Boxes 11 and 12). To create a pharmacy-based PrEP delivery system, pharmacists need the legal authority to implement PrEP services and have access to the necessary infrastructure (such as for HIV testing and counselling). They also need to be trained and willing to provide PrEP and able to allocate time to PrEP provision, and they need adequate physical space to ensure privacy for clients.

Box 11. Evidence about PrEP delivery in pharmacies

A systematic review identified six case studies of oral PrEP delivery in pharmacies (75), although no study evaluated the effectiveness of this delivery model with a comparison group. All case studies were implemented in the USA and most PrEP users were men who have sex with men. One case study in Seattle enrolled 695 clients on PrEP, while all other case studies enrolled 50–69 clients each. Eleven studies reported on values and preferences around delivering PrEP in pharmacies (eight in the USA, two in Kenya, and one in South Africa). These found that potential PrEP users and pharmacists generally supported PrEP delivery in pharmacies, although some PrEP clients preferred access through clinics. Another scoping review identified nine studies in the USA that evaluated different pharmacy PrEP-related interventions (76), noting high acceptability of pharmacy PrEP models among clients but emphasized the need for appropriate provider training.

Box 12. Oral PrEP initiation and continuation in private pharmacies in Kenya

A pilot study of initiating and continuing PrEP services was implemented at five private retail pharmacies in Kenya. Trained pharmacists engaged clients who were purchasing services that suggested that they could benefit from PrEP (for example, emergency contraception or STI treatment). Pharmacists provided counselling, used HIVST to determine HIV status, and prescribed and dispensed PrEP. A remote clinician was available for further consultation as needed. No additional staff were employed to provide PrEP services in the pharmacies. From November 2020 to October 2021, 575 pharmacy clients were screened and 287 were initiated on PrEP. Among clients initiating PrEP, the median age was 26 years, 43% were female, 38% were married, 84% reported partners of unknown HIV status and 53% reported multiple sexual partners. Most clients learned of pharmacy PrEP from the pharmacy provider (42%) or via informal word-of-mouth referral (42%). PrEP continuation among PrEP clients was 54% one month following initiation and 36% four months following initiation. This pilot demonstrated that clients with characteristics suggesting that they may benefit from PrEP frequently visit retail pharmacies and can be initiated by pharmacists. Comparisons with data from Ministry of Health clinics in Kenya suggest that uptake and persistence were similar, but more research is needed on the effectiveness and cost-effectiveness of this model. Further scale-up of this model requires changes to regulatory and legal frameworks to allow pharmacists to prescribe PrEP.

Fig. 4. PrEP delivery in a pharmacy, Kenya



Photo credit: Fred Hutch/Katrina Ortblad.

Who to deliver PrEP

For HIV treatment, WHO recommends (4) that 1) trained nonphysician clinicians, nurses and midwives can initiate and maintain ART, and 2) trained and supervised community health workers can dispense ART and lay providers can distribute ART. For PrEP, in most countries a clinician prescribes PrEP, while other health care providers (for example, lay providers) may deliver other aspects of PrEP services, such as assessing whether individuals could benefit from PrEP or conducting HIV testing. Task sharing to enable PrEP delivery by a range of health workers, including peer and community health workers, may generate health system efficiencies. It may also support models of service provision that are more acceptable to users (for example, where services are provided by community members). For CAB-LA, implementation science is needed to understand potential service delivery models involving different health worker cadres, although regulatory frameworks (including for the administration of injections) may present barriers to task sharing.

Task sharing with nurses

In nurse-led PrEP services, trained nurses are the central providers, including prescribing PrEP. Nurse-led PrEP services are feasible in a range of settings (77), and WHO recognizes that task sharing with trained nurses can support the expansion of person-centred PrEP services, similar to the way nurse-led services have expanded ART provision (78). Enabling policy environments are needed to allow for nurse-led PrEP services, including changes to prescribing regulations and the endorsement of the role of nurses in PrEP provision in national guidelines. Additional key considerations to support sustained task sharing for nurse-led PrEP include: training for both service providers and supervisors to maintain competence and confidence (including preservice training and integration into curricula), adequate supplies of drugs and other commodities to support decentralization, clear protocols and referral lines for clients in need of additional care, addressing nurse staffing levels and workloads within the service, and remuneration reflecting changes in scope of practice. These principles also apply to task sharing with other health cadres, such as midwives.

Key population- and community-led services

WHO recognizes the central role of community-led services to increase access and acceptability of services for HIV, viral hepatitis and STIs (28). In key population-led PrEP services, community health workers or lay providers who are members of communities at significant risk of HIV infection are trained to deliver PrEP services, expanding their traditional roles of providing linkage to care and outreach. In Thailand, trained key population community health workers conduct HIV testing, assess suitability for PrEP, provide counselling and dispense oral PrEP on the same day. This model has been shown to be feasible and acceptable and has significantly contributed to the scale-up of PrEP services in Thailand (79,80). In Viet Nam, key population leaders have established social enterprise clinics that are staffed by providers from the community, including counsellors, nurses, doctors, pharmacists and technicians approved by local authorities to deliver oral PrEP and other health services (81). In Zimbabwe, the Sisters with a Voice programme for female sex workers provides differentiated PrEP services led by sex worker communities, supporting significant scale-up of PrEP (82).

However, criminalization, discrimination and stigmatization of key populations in many countries are important barriers to wider implementation of this model. To scale up peer-led models, structural and legal barriers to access PrEP and other health services by key populations must be addressed. Equally important is the endorsement of key population-led services in national guidelines, establishment of systems to accredit the services, funding and integration into national health systems. To ensure high-quality services, training (including certification) and mentoring of staff, effective quality assurance systems, clear protocols, linkage and support from health care facilities (including clinical oversight) and adequate remuneration are needed.



When and what services to deliver

Multi-month dispensing (MMD)

WHO recommends that people living with HIV established on ART should be offered three-to-six-month ART refills, preferably lasting six months (4). MMD of ART has been found to be feasible and cost-saving for providers and clients in a range of countries, and COVID-19 has accelerated adoption of ART MMD (83). For oral PrEP, a one-month supply is commonly provided at initiation, requiring a one-month follow-up visit. This is often appropriate, as it allows PrEP users to check in with their provider, review laboratory results as relevant, discuss issues or concerns such as side effects when starting PrEP, and detect HIV infection that may have been missed at initiation. After the first month of PrEP use, prescription lengths and supply amounts vary, and even multi-month prescriptions may still require monthly dispensing. Frequent follow-up visits create costs for the health system and barriers to uptake and persistence among users (for example, due to time and costs associated with frequent travel to pick up PrEP). WHO guidance to maintain essential health services during COVID-19 suggested MMD for oral PrEP users who are well established on PrEP (51). Several countries have implemented MMD of oral PrEP as part of differentiated service adaptations. For instance, in Viet Nam, after the first PrEP visit, a one-month PrEP supply is dispensed, a two-month supply is dispensed on the second visit, followed by three-month supplies thereafter (84). Guidance on HIV service delivery in Zimbabwe during COVID-19 suggested three-month dispensing of PrEP supplies (85). The Sisters with a Voice programme for female sex workers in Zimbabwe provided three-month supplies of oral PrEP during COVID-19 and reported a considerable increase in uptake of PrEP (82). An RCT in Kenya found that six-month oral PrEP dispensing with interim HIV self-testing halved the number of clinic visits compared with three-month PrEP supply and clinic visits, while PrEP persistence and use were similar (86) (PrEP use was significantly higher among women not in serodifferent relationships who received six-month PrEP with HIVST kits). Similar principles of MMD could be applied to the DVR, although implementation science is needed.

Regular follow-up visits are suggested for PrEP users to ensure HIV testing and the provision of other services, including testing for STIs, although different PrEP service components may be delivered at different frequencies. Aligning PrEP supplies with visit schedules is likely to make PrEP services more acceptable for clients and reduce health system costs. As differentiated service

delivery is person-centred, choice is critical; multi-month supplies of PrEP or less frequent contact with health care workers may be preferred for some but not all PrEP users. Younger PrEP users and PrEP users with other health, mental, emotional and social needs may benefit from more frequent contact with PrEP providers. Differentiated PrEP service delivery can also provide additional support separately from multi-month PrEP refills, such as through virtual or telehealth platforms. PrEP users who start, stop and restart PrEP may need less support for PrEP re-initiation, and longer supplies of PrEP drugs may be appropriate for these more experienced PrEP users, although all users should have the opportunity to return to PrEP services when needed or desired.

Integrated services

Differentiated PrEP services use a person-centred approach to address a client's multiple health needs appropriately. PrEP provision should not depend on receiving other services; however, integration of multiple services can lead to more convenient and acceptable service provision, thus supporting initiation, persistence and effective use of PrEP. It also supports engagement with care for other health needs unrelated to PrEP and may improve multiple health outcomes (87). Similarly, integrating PrEP into other services, such as HIV testing and counselling and primary health care services, can support the provision of holistic and integrated care. A status-neutral framework has also been proposed to provide holistic services in which individuals enter services through HIV testing and, depending on their status, are immediately engaged in HIV treatment or PrEP or PEP (88,89).

Integration of services depends on the context and unique needs of PrEP user populations. This may include peer support, mental health and social services (90), gender-based violence services, and PEP (including in the context of, but not limited to, sexual violence). For trans and gender diverse people seeking gender affirmation, integrating PrEP with gender-affirming services may make services more acceptable and has been shown to be feasible (91–93). Substance use and harm reduction services are critical for people who use drugs (including related to chemsex). A review of PrEP delivery for people who inject drugs (Shaw et al., unpublished review, see Annex 3) found that integrated PrEP services with comprehensive community-based harm reduction programmes are likely to be most effective in reaching people who inject drugs, and harm reduction services are key to increasing awareness of and linkage to PrEP services (Box 13).

Integration of PrEP into antenatal, postnatal and family planning services offers opportunities to improve uptake and persistence of PrEP in populations characterized by high HIV incidence, such as adolescent girls and young women in eastern and southern Africa. In many countries, clinic visits for contraception and PrEP follow similar schedules. WHO has provided guidance on integrating HIV and STI prevention services, including PrEP, within family planning services (94). Such an integrated model has been found feasible in Kenya (95,96) and South Africa (64), for instance. A framework has been proposed to support successful integration of PrEP and family planning services, including plans and policies, resource management, service delivery, and monitoring and reporting (97). Integration of PrEP and contraceptive services also supports potential future introduction of multipurpose PrEP–contraceptive technologies. There may be particular potential of integration of CAB-LA with family planning services for injectable contraception, but implementation science is needed on the feasibility of this model.

Integrating STIs with PrEP, and PrEP with STIs

High prevalence and incidence of curable STIs – particularly syphilis, gonorrhoea and chlamydia, including in extragenital sites – have been observed among PrEP users (98). These STIs can have severe reproductive and sexual health consequences and have broader public health consequences when

untreated, including contributing to gonococcal antimicrobial resistance. As people who could benefit from PrEP are also at increased risk of other STIs, PrEP services are an opportunity to provide comprehensive sexual and reproductive health services, including STI testing and treatment and effective strategies to assist with partner services (99). Similarly, those accessing STI services could likely benefit from being offered PrEP. PrEP services also offer an opportunity to integrate human papillomavirus (HPV) screening, which would contribute to preventing cervical cancer (100). Testing for STIs among PrEP users, with or without symptoms, is suggested at initiation and regularly thereafter (such as every three to six months). The frequency of screening for different STIs may vary (101), and some populations may benefit from more or less frequent screening. WHO suggests that dual HIV/syphilis RDTs can be used as the first test in antenatal care (ANC), as these tests are cost-saving compared with standard testing in ANC (102,103), and the dual HIV/syphilis test may be considered for use among key populations (28). Screening for STI symptoms could be beneficial where testing is not available (104). STI self-collection of samples is recommended by WHO (105), and some countries started implementation of self-collection during the COVID-19 pandemic (106,107). WHO will publish more detailed guidance on STI services for PrEP users, including frequency of testing, in the second half of 2022.

Box 13. PrEP for people who inject drugs in Glasgow

An outreach PrEP service was initiated in response to an HIV outbreak which began in 2015 in Glasgow, Scotland (108). Despite high coverage of harm reduction interventions, HIV prevalence among people who inject drugs reached 11%, associated with homelessness, incarceration and a shift to injection of cocaine (109,110). Qualitative research with people who inject drugs demonstrated willingness to engage with PrEP but recognized that this group requires service model adaptations (111). A small team of sexual health nurses trained in PrEP delivery worked in conjunction with an HIV physician. The team was based at a multiagency service for homeless people and embedded themselves in settings frequented by people who inject drugs. They formed close working relationships with allied service providers, educated them about the outbreak, and encouraged referral of clients for oral PrEP assessment. Consultations and blood tests were provided at various locations tailored to individual needs, such as addiction and rehabilitation services. During COVID-19, the team provided consultations in a mobile clinical van. Oral PrEP was predominantly sent to community

pharmacies already used by clients and dispensed (usually daily) alongside supervised opioid agonist therapy. This model incorporated PrEP delivery within services already used by people who inject drugs and facilitated adherence monitoring. Community pharmacists reported any breaks in PrEP use to the outreach team, who then actively followed up clients. This also helped to direct additional HIV tests following adherence breaks. On average, approximately 10 people who inject drugs were enrolled on PrEP each month. High levels of effective use and persistence were observed (108). Clients appreciated this service, with one saying, “Sometimes I have so much going on that I forget to care about myself. PrEP was definitely a positive thing for me. I was putting myself at risk of HIV. The nurses helped me to get on it and then came to see me every couple of weeks to make sure I was ok, getting tested all the time and being negative made me feel happier”. Implementation was supported by relationships between the PrEP team and the agencies supporting people who inject drugs in Glasgow, but service expansion is limited by the intensity of staffing required.

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Research gaps

While the feasibility of a range of differentiated PrEP service delivery models has been demonstrated, additional evidence of effectiveness of PrEP-related outcomes (uptake, persistence and effective use) is needed. Implementation science and quasi-experimental approaches, such as difference-in-differences methods for pre-post evaluations of interventions, could provide robust evidence on effectiveness, particularly since RCTs are often not feasible and do not necessarily provide insight into real-world implementation of services. Moreover, evidence on feasibility of community-based approaches and task sharing for PrEP disproportionately represents cisgender men who have sex with men and adolescent girls and young women from a few countries, highlighting the need for additional evidence across multiple geographies and populations. Evidence is

also needed on the costs and cost-effectiveness of differentiated PrEP service delivery approaches, from both the perspective of the client and the health-care system. Additional data on acceptability across populations are needed to understand the diverse needs of people who could benefit from PrEP services. For instance, community-based services may not be preferred or acceptable for all individuals, and it is important to ensure that those individuals are not disadvantaged where resources are shifted towards community-based services. Research on providers' perspectives on PrEP service delivery can support identification of barriers to implementing differentiated PrEP services and access, particularly for stigmatized and marginalized populations. Experience with differentiated service delivery is largely limited to oral PrEP and implementation science is needed on diverse service delivery models for the DVR and CAB-LA.



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Annex 1: Summary of mathematical modelling of HIVST for PrEP in Kenya

Background

Community-based oral PrEP provision has the potential to expand PrEP access. HIVST can facilitate community-based PrEP delivery by enabling non-health-care providers to conduct HIV testing for PrEP initiation and continuation. However, HIVST can have lower test sensitivity than facility-based RDTs, potentially leading to inappropriate PrEP provision to persons living with HIV. The overall health impact of HIVST for PrEP delivery is not well understood.

Methods

We parameterized an agent-based network model, EMOD-HIV, to project the impact of rapid scale-up of PrEP in western Kenya using either provider-administered RDTs, blood-based HIVST or oral HIVST, compared with a counterfactual of no PrEP. Individuals aged 18–49 years entering a partnership were assumed to have a 50% probability of initiating PrEP; those who initiate have a 50% probability of continuing PrEP after one month (and 75% probability of continuation every three months thereafter). We assumed 75% PrEP efficacy and assessed HIV infections, deaths, numbers of persons with HIV inappropriately initiated on PrEP and cases of NRTI drug resistance in each scenario over a 20-year time horizon.

Findings

Our model resulted in an average PrEP coverage of 28.2% of adults aged 18–49 years. This PrEP coverage was projected to avert 49% of HIV infections and 16% of HIV-related deaths over 20 years; health impacts were similar across HIV testing modalities. Out of an estimated 150 million PrEP initiations over 20 years, the number of individuals with acute HIV infection

who were inappropriately initiated on PrEP was 12,001 and 13,471 in the blood-based HIVST and oral HIVST scenario, respectively, compared with 11,839 in the provider-administered HIV testing scenario. The number of individuals with chronic HIV inappropriately initiated on PrEP was 26,664 and 56,755 in the blood-based HIVST and oral HIVST scenario, respectively, compared with 18,595 in the provider-administered HIV testing scenario. The percentage of HIV infections with PrEP-associated drug resistance was 4.8% and 7.6% in the blood-based HIVST and oral HIVST scenario, respectively, compared with 4.1% in the provider-administered testing scenario. Accounting for background NRTI resistance, we found similar proportions of resistance across scenarios (including the No PrEP scenario).

Conclusions

Increasing PrEP coverage among sexually active individuals has the potential to avert nearly half of new HIV infections over 20 years; community-based PrEP implementation using HIVST could be an effective strategy for scaling up PrEP. We projected that a low number of persons with acute HIV would be inappropriately initiated on PrEP, which was similar across testing modalities. This reflects the universally low sensitivity of HIV tests to detect early HIV infection and the small number of acutely infected individuals in the population. The number of chronic stage PrEP initiations was higher in HIVST scenarios, highlighting the importance of continued monitoring with scale-up of PrEP using HIVST. The population prevalence of NRTI resistance was similar across scenarios, largely due to the reduction in HIV (and therefore HIV-related drug resistance) in the PrEP scenarios compared with the counterfactual of No PrEP.

Annex 2: Background and methods on the global PrEP provider study

WHO supported a global study of PrEP providers, comprising an online survey and in-depth interviews, from November 2021 through February 2022. The survey aimed to understand current service delivery practices as well as perspectives on new PrEP products. Follow-up interviews with survey participants were conducted to gain additional insights and to offer an opportunity for providers to raise other issues of concern. An independent consultant in collaboration with technical experts of WHO HHS led a consultative, iterative process to formulate survey questions and the interview guide. WHO technical experts provided content and reviewed draft questions to ensure

accuracy and clarity; interviews were tailored to each participant based on their survey responses. The survey was translated into French and Spanish and was distributed through WHO regional offices and partner networks. Interviews were conducted in English.

The online survey was implemented from November through December 2021. A total of 1353 individuals participated in the survey, of which 849 completed all sections (63% completion rate). Survey respondents practised in 84 countries, and 73% of respondents were from low- and middle-income countries (Table A2.1).

Table A2.1. Regional and country income level distribution of online survey participants^{a,b}

WHO region	Countries represented by respondents (#)		Respondents from regions (#)		Proportion of survey respondents from regions	
	LMIC	HIC	LMIC	HIC	LMIC	HIC
Africa	27	–	805	–	59.5%	–
Americas	14	5	50	52	3.7%	3.8%
Eastern Mediterranean	4	–	4	–	0.3%	–
Europe	6	13	10	273	0.7%	20.2%
South-East Asia	8	–	54	–	4.0%	–
Western Pacific	5	2	69	36	5.1%	2.7%
TOTAL	64	20	992	361	73.3%	26.7%

HIC: high-income country; LMIC: low- and middle-income country.

^a Country income level data source: <https://data.worldbank.org/>

Nearly half (47.6%) of respondents identified as male, 50.8% as female, 0.74% as nonbinary and 0.89% preferred not to answer this question. Most respondents were physicians (25%), nurses (24%) or clinical officers (13%), and most worked with nongovernmental and community-based organizations (48.6%) and publicly funded health services (42.35%). The survey was primarily intended for direct providers of PrEP services. In some cases, respondents included programme managers, researchers and PrEP navigators, all of whom have extensive knowledge of PrEP delivery in their setting; in a few other cases, survey respondents reported functions that suggest limited engagement with PrEP clients or knowledge of PrEP provision.

Of those who completed the survey, 556 provided contact information to participate in interviews (65% of completed surveys). Of these, 150 survey

respondents were randomly selected for screening as possible interview participants, and 67 of those were invited for interviews. Selection criteria for interview participation included geographic representation, provider type, gender balance, experience with non-clinic-based service delivery and familiarity with new PrEP products. Thirty in-depth interviews were conducted with providers from the African (7), Americas (8), Eastern Mediterranean (1), European (6), South-East Asian (5) and Western Pacific (3) regions (Table A2.2). Participants included 17 physicians, eight nurses, one researcher, one PrEP navigator, one counsellor, one clinical psychologist and one pharmacist/clinician/researcher. Fourteen participants identified as cisgender male, 10 as cisgender female, and six participants who had not completed a survey were not asked how they identified.

Table A2.2. Geographic representation of participants in in-depth interviews on PrEP provider perspectives

WHO region	Number of participants	Countries
Africa	7	Mali, Namibia, Nigeria, Uganda (2), Zambia, Zimbabwe
Americas	8	Brazil, Dominican Republic, Guatemala, Mexico, USA (4)
Eastern Mediterranean	1	Lebanon
Europe	6	Poland, Spain, Switzerland, United Kingdom, Ukraine (2)
South-East Asia	5	Indonesia, Myanmar, Nepal, Sri Lanka, Thailand
Western Pacific	3	Australia (2), Thailand

PrEP: pre-exposure prophylaxis. Numbers refer to multiple PrEP providers who participated for listed countries.

Annex 3: Summary of a review of PrEP services for people who inject drugs

Background

Since 2015, WHO has recommended offering TDF-based oral PrEP to all people at substantial risk of HIV as part of combination HIV prevention, but little is known about the extent to which this recommendation has been implemented for people who inject drugs. The objectives of this study were to review literature on perspectives on and use of PrEP by people who inject drugs and map global service delivery for this group.

Methods

PubMed and Google Scholar databases were searched for studies published between 2010 and 2021. Relevant data were extracted using standardized questions. Information on delivery of PrEP services for people who inject drugs was also sought from 1) drug user-led networks and groups; 2) HIV/AIDS, sexual and reproductive health rights, harm reduction, and human rights stakeholders and networks; and 3) websites of organizations involved in HIV prevention studies or services for people who inject drugs.

Findings

A total of 225 studies were identified and 22 included in the study. Of these, 21 reported on the perspectives of PrEP and nine on PrEP use by people who inject drugs. Nearly all studies were conducted in the USA. Individual-level barriers, negative prior experience with other health care interventions, and persistent stigma and discrimination by health care providers were the main types of barriers to accessing PrEP by people who

inject drugs. PrEP awareness by people who inject drugs was associated with HIV testing within the previous six months, sexual minority status, the sharing of drug use paraphernalia, having had a conversation about HIV prevention at a needle/syringe programme, and having undertaken drug treatment. A greater willingness by people who inject drugs to take PrEP was associated with higher perceived HIV risk, including the sharing of drug use paraphernalia and being injected by another person who injects drugs, the number of HIV tests conducted; cost, and side effects. The global mapping exercise identified PrEP services in 25 countries (17 high-income). Models of PrEP service delivery to people who inject drugs were largely based around who is authorised to provide PrEP and the provider's location. PrEP services for people who inject drugs included stand-alone clinics, those with a direct link with drug treatment services, community-based services, peer-led outreach services, online services, and a hybrid model comprising community outreach and referral to health care facilities and PrEP dispensed at community pharmacies.

Conclusion

This study indicates limited PrEP service availability for and use by people who inject drugs. There is a need to expand PrEP services for people who inject drugs within existing harm reduction programmes, preferably through community-based and peer-led services. While PrEP should be offered as an additional HIV prevention choice for people who inject drugs, support for PrEP must not result in a reduction in funding for any other component of a comprehensive harm reduction programme.

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