

Belgian 2024 Guidance on the use of Pre-Exposure Prophylaxis

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Abstract

Objectives: We aimed to develop a guidance on the use of pre-exposure prophylaxis (PrEP) for HIV tailored to the Belgian context.

Methods: Different aspects of PrEP care were judged by an expert group of 9 Belgian clinicians, seeking consensus for areas of controversies.

Results: PrEP should be considered in HIV negative patients at high risk of acquiring HIV.

Currently, only oral tenofovir/emtricitabine is available in Belgium for PrEP, which can be used daily, or also event-driven in cisgender men and trans women who are not taking exogenous estradiol-based hormones. Personal counselling directed at medication adherence and sexual health should have a central role in PrEP care. At the initial assessment clinicians should give attention to symptoms of an acute HIV infection, the patients' immunization status and renal function. A regular follow-up must be set up to diagnose HIV seroconversion, treat sexually transmitted infections and manage side effects of PrEP.

Conclusion: The Belgian guidance on the use of PrEP provides a point of reference for standard PrEP care in Belgium and will be periodically updated.

Keywords: HIV, pre-exposure prophylaxis, guidance

Main text

Introduction

This is a revision of the first Belgian Pre-Exposure Prophylaxis (PrEP) guidelines, which were developed at the introduction of PrEP in 2017. Meanwhile, new evidence became available and PrEP has evolved, with new challenges emerging. These relate to scaling-up PrEP coverage; increasing access to PrEP for vulnerable populations, such as migrants and sex workers; preparing the introduction of novel PrEP formulations, such as long-acting injectable PrEP; and advancing collaborative PrEP care, which extends PrEP delivery to e.g. general practitioners (GP), nurses and community organizations, while reducing capacity constraints of HIV clinics with a growing population of PrEP users.

The need for new guidelines was expressed in the Belgian PrEP Network and a specific Working Group on PrEP Guidelines has been set up to conduct the revision. In addition to updating the evidence on PrEP and recent evolutions, these new guidelines take some different points of view:

- National PrEP guidelines may provide a point of reference for standard PrEP care. However, they should not be regarded as strictly normative, imposing a uniform way of working. Rather, they guide clinical practice, especially to less experienced professionals engaging with PrEP, and should be regarded as *guidance* instead of guidelines.
- This new PrEP guidance is not restricted to medical aspects, but also includes psychosocial ones. More emphasis is put on counselling and sexual health.
- This guidance is not limited to use by physicians within an HIV reference centre (HRC) but should extend to all healthcare providers involved or confronted with aspects of PrEP care, such as GPs and nurses. To date, PrEP services in Belgium are mainly provided through the HRCs. To optimize PrEP uptake and retention in care, we require the help of nurses within HRCs as well as the involvement of GPs for the 3-month follow-up. As of May 2023, two follow-up visits per year can be organized by the GP. Therefore, we recommend a differentiated PrEP service delivery approach, including involving GPs, to make PrEP care

more client-centered. These recommendations are based on a recent Belgian publication focusing on PrEP services delivery [1].

Evidence of PrEP effectiveness

Since 2010, HIV PrEP has proved its effectiveness as a novel prevention tool through several studies all over the world. The IPREX study was the first to show that the use of PrEP among men who have sex with men (MSM) significantly reduced the level of HIV transmission (44% compared to the placebo group) [2]. Later, large-scale randomized controlled trials, such as IPERGAY [3] and PROUD [4], using event-driven (also known as “2+1+1”) and daily PrEP dosing regimen respectively, have both shown a reduction of HIV transmission among MSM of 86% to 90% compared to placebo. Since, studies have repeatedly confirmed the high rate of efficacy and safety of PrEP among MSM and also the heterosexual population at high risk of HIV infection [5,6].

Methodology

A first draft of this guidance was written by an expert group, all of which are clinicians involved in the care for PrEP users in Belgium. A consensus was sought between the members of the Working Group for areas of controversies. Thereafter, the text was sent for feedback to all Belgian HRCs, which endorsed the final version of this guidance.

General considerations

- PrEP should be used during periods of substantial risk for HIV acquisition and can be stopped during periods of low or no risk.
- PrEP care should be initiated in an HRC.
- Personal counselling should have a central role in PrEP care.
- Community involvement in different steps of the PrEP care continuum (e.g. from raising

awareness to supporting service delivery) is essential to ensure broad access and coverage, especially for more vulnerable populations.

Eligibility for PrEP

To judge eligibility for PrEP, we advise health care providers to perform an individualized risk-benefit assessment based on a detailed sexual and drug use history. PrEP should be considered in HIV negative patients older than 16 years at high risk of acquiring HIV. Patients who are eligible for PrEP commencement based on the following criteria should be referred to an HRC. These patients include:

1. MSM and transgender individuals at high risk of acquiring HIV
 - a. Reporting unprotected anal sex with one or more partners
 - b. Acquisition of multiple sexually transmitted infection (STI) during the last year, including syphilis, chlamydia, gonorrhea, or acute hepatitis B or C
 - c. Use of psychotropic substances during sexual activity (“Chemsex”)
 - d. Treatment with HIV post-exposure prophylaxis
2. Other persons with a high individual risk
 - a. People who inject drugs (PWID) sharing needles
 - b. Sex workers exposed to unprotected sex, particularly anal sex
 - c. People exposed to unprotected sexual activities, at high risk of HIV acquisition*
 - d. Sexual partners of a seropositive individual with a detectable viral load

* These include persons originating from a country with a high HIV prevalence (e.g., in sub-Saharan Africa) regularly visiting their country of origin and heterosexual women who engage in unprotected sex with male partners who are at high risk of HIV acquisition (e.g. bisexual male partners or male partners from areas with a high prevalence).

A PrEP request should always be taken seriously, even if the abovementioned criteria are not strictly

fulfilled. Clinicians with limited PrEP experience are therefore encouraged to refer persons whose HIV risk is unclear, or who still request PrEP despite not fitting the criteria above. HIV is not transmissible through sexual contacts with partners living with HIV who have an undetectable viral load, and thus PrEP is not indicated in these cases.

Initial assessment and follow-up

First medical consultation

During the first medical consultation, we advise to perform a thorough anamnesis to determine whether the patient fits the eligibility criteria (as stated above), to assess comorbidities and to record current medications and prior immunizations. Attention should be given to symptoms of an acute HIV infection. A physical examination should be performed if deemed necessary (e.g. suspicion of acute HIV infection or STI). Counselling and sources of patients' information, as specified in the next sections, should be provided. We advise to discuss immunization against hepatitis A and B, Mpox, meningitis B and human papilloma virus (HPV), although this may be postponed to the first follow-up consultation in case serological results are not available. According to the Superior Health Counsel, hepatitis A and B vaccination is advised for all MSM and hepatitis B vaccination for PWID [7,8]. Vaccination against HPV can be proposed to all MSM up to the age of 26 years [9]. Vaccination against Mpox should be considered according to the epidemic situation and recommendations in Belgium. Recent evidence suggests that complete vaccination against meningitis B with the 4CMenB vaccine protects between 33-44% against infections with *N. gonorrhoeae* (NG) [10,11]. In contrast, the preliminary results of an ongoing RCT (DoxyVAC) in MSM on PrEP showed only limited clinical benefit. Pending the results of further studies, immunization with the 4CMenB vaccine should only be considered in cases of recurrent symptomatic NG infections.

As baseline laboratory tests, we advise to perform a 4th generation HIV test, hepatitis B virus (HBV) serology (HB surface antigen (HBsAg), anti-HB core (HBc) and anti-HBs antibodies), anti-hepatitis A IgG, hepatitis C antibodies and a syphilis test. A HIV-PCR should be considered if there is a high

clinical suspicion of HIV with a negative HIV test. In that case, PrEP should not be started until the result of the HIV-RNA is available or a second HIV test is performed 4 weeks later. In cis women, a pregnancy test should be performed. Furthermore, the serum creatinine and eGFR, serum phosphate, ALT/GPT and urinary protein/creatinine ratio should be determined.

If there are no symptoms of recent seroconversion, PrEP can be started as soon as contraindications have been ruled out. In practice, a prescription is given when results are available or a prescription can be offered to the patient directly which should be used later, allowing the clinician to check the results and timely contact the patient in case of a formal contra-indication.

First follow-up consultation

A follow-up consultation after 4-6 weeks should be planned in case of recent risk of HIV acquisition before starting PrEP or risk of misunderstanding of PrEP usage. This should be specifically applied for cases of PrEP initiated right after PEP. For other patients, the first follow-up can be planned after 3 months. Furthermore, adherence should be assessed, and potential adverse effects should be discussed.

Three-month follow-up consultations

The proposed laboratory tests during follow-up are summarized in Table 1. Parameters of renal function should be determined at least annually (including serum creatinine and eGFR, serum phosphate and urine protein/creatinine ratio). More frequent screenings (3-6 monthly) should be considered in individuals over 50 years of age, with chronic kidney disease (CKD) or risk factors for CKD (e.g. diabetes and hypertension) or who use nephrotoxic medications. Preferably these patients are followed up in an HRC.

We advise to test for HIV and syphilis every 3 months and hepatitis C every 6 months. We also advise to determine ALT/GPT every 3 months for early diagnosis of hepatitis C virus (HCV) infection especially if HCV serology is known to be positive. If ALT/GPT are elevated and if there was a substantial risk for HCV acquisition, we recommend determining HCV-RNA. Based various

types of evidence, which are described in detail in the Supplementary Data, we recommend only testing MSM who use PrEP for NG or Chlamydia trachomatis (CT) if:

- they have symptoms compatible with these infections
- a partner has a symptomatic infection, to avoid a symptomatic reinfection in that partner
- they have sex with women as well as men
- they express a strong desire for asymptomatic screening

The working group acknowledges that this recommendation contrasts with general recommendations from some international guidelines, including ECDC and CDC. Our recommendation, however, applies to the strict population of MSM who use PrEP, for which uncertainties remain with regard to the benefits and harm of asymptomatic screening. As such, this recommendation might be revised in the future as new evidence emerges.

For women, transmen and men who have sex with women and men, NG/CT should be tested intermittently according to risk. Indeed, untreated chlamydia and gonococcal infections can lead to pelvic inflammatory disease among women and associated long-term sequelae, including infertility, ectopic pregnancy and preterm delivery [12]. If screening is performed this should be done via 3-site testing (pharynx, urine and anorectum) in all risk groups. These samples can be pooled for testing if this service is available at one's local laboratory.

PrEP counselling

Counselling on sexual health and medication adherence should be provided at the initiation of PrEP and during the follow-up consultation if deemed necessary. Box 1 provides an overview of the key components of counselling. Overall, a space of trust and confidentiality should be created, free of stigma, to talk about sexual behaviour and practices.

PrEP regimen and dosage

Both daily and event-driven PrEP with tenofovir disoproxil/emtricitabine (TDF/FTC) 245mg/200 mg

has shown to be effective in the prevention of HIV acquisition. However, the event-driven regimen has only been studied in cisgender men, transgender and gender diverse people assigned male at birth who are not taking exogenous estradiol-based hormones (for example, gender-affirming hormones). This population can opt for daily or event-driven use of PrEP, depending on the person's circumstances and preferences. As an exception, patients treated for chronic hepatitis B should use daily PrEP (see paragraph under 'Special situations'). All other populations should use a daily dosing regimen. An overview of how to start and stop PrEP in different populations is provided in Table 2.

If PrEP is used on daily basis, medication must be taken within a window of 2 hours. For cisgender men and transgender diverse people assigned male at birth who are not taking exogenous estradiol-based hormones, protection is effective 2 hours after a loading dose of 2 pills. For other individuals, TDF/FTC one dose per day for seven consecutive days is needed to achieve protective concentration. Alternative HIV prevention methods should be used during this time. After loading doses, continue daily oral PrEP by taking one dose per day. Expect for cisgender men and transgender diverse people assigned male at birth who are not taking exogenous estradiol-based hormones, PrEP should be stopped seven days after the last potential exposure to HIV.

If PrEP is used event-driven, a loading dose of 2 pills should be taken 2-24 hours before sexual exposure. Ideally, this loading dose should be taken closer to 24 hours before potential exposure. PrEP should be continued as 1 pill per day until 2 days after the day of the last sexual exposure.

The Discovery trial has shown that tenofovir alafenamide(TAF)/FTC was comparable to TDF/FTC in terms of effectiveness and safety for PrEP [13]. However, TAF/FTC is currently not available in Belgium. Cabotegravir intramuscular once every 2 months has proven to be effective and safe as PrEP for MSM and transgender woman and cisgender women [14,15]. At the time of redaction of this guidance, no reimbursement was available in Belgium, but reimbursement submission is expected in 2024.

Special situations

Woman who are pregnant or trying to conceive

Pregnancy is a period of elevated risk of HIV acquisition and the infection is more often spread to the infant when it occurs during pregnancy [16,17]. Providers should offer PrEP to pregnant women whose sexual partner has HIV, especially when their current partner's viral load is unknown, is detectable, or cannot be documented as undetectable [18]. Data on pregnancy outcomes in the Antiretroviral Pregnancy Registry provide no evidence of adverse effects among fetuses exposed to TDF/FTC, used for either HIV treatment or prevention of HIV acquisition during pregnancy [19,20].

Breastfeeding

If a woman becomes infected during breastfeeding, the risk of transmission of HIV to her infant is appreciable because of high viral load soon after seroconversion. Data from studies of infants born to HIV-infected mothers and exposed to TDF or FTC through breast milk suggest limited drug exposure [21,22]. TDF and FTC are secreted in breast milk at very low concentrations (0.3–2% of the levels required for infant treatment). Thus, the risk/benefit ratio of PrEP during breastfeeding should be evaluated case by case.

Chronic hepatitis B infection

TDF and FTC are also used to treat patients with a chronic HBV infection, i.e. individuals positive for the HBsAg more than 6 months. When these drugs are discontinued, patients with an HBV infection may experience clinically significant hepatitis flares. We advised not to use event-driven PrEP in this population. Daily PrEP with TDF/FTC can be considered even if HBV treatment is not required at the moment of PrEP initiation. However, when treatment with PrEP is discontinued, the need for ongoing therapy for HBV should be assessed and monitoring for a flare is advised, especially if liver fibrosis was present before starting PrEP [23]. Nevertheless, flares were not observed in 2 PrEP trials limited to participants with normal liver function tests and no clinical signs of cirrhosis [24,25].

Chronic kidney disease

TDF is associated with Fanconi syndrome and progression of CKD. In patients with CKD stage 3 or higher (estimated glomerular filtration (eGFR) rate <60 mL/min/1.73m²) the initiation of event-driven PrEP (TDF/FTC) can be considered if the benefit is deemed higher than the risk of progressive kidney disease.

Recent PEP exposure - switching directly from PEP to PrEP

For patients who required the prescription of post-exposition prophylaxis (PEP), the initiation of PrEP should be discussed at the end of the PEP treatment. A large gap between the termination of the PEP treatment and initiation of PrEP is deemed unnecessary given the sensitivity of current HIV tests [26] and the efficacy of PEP reported in observational trials [27]. The PrEP baseline laboratory tests should be performed 1-2 weeks after the end of the 28-day PEP treatment and PrEP can be initiated in case this test is negative [28].

Transgender persons

In the iPrEx subgroup analysis, trans women taking PrEP were reported to have a higher risk of HIV acquisition as compared to MSM [29]. Daily PrEP with TDF/FTC had lower effectiveness in trans women than in MSM, primarily linked to lower adherence as measured by drug concentrations. Some studies have reported that the high doses of feminizing hormones prescribed to trans women result in lowering of activated tenofovir diphosphate levels in rectal tissue [30]. There are no studies in trans women on intermittent dosing. We therefore advise to only prescribe event-driven PrEP to trans and gender diverse people assigned male at birth who are not taking exogenous oestradiol-based hormones, given the potential reduction of TDF at the site of exposure due to hormone usage.

Bariatric surgery

Individuals taking PrEP who have gastrointestinal disorders (including sleeve gastrectomy, gastrointestinal bypass surgery, terminal ileitis, celiac disease and chronic diarrhoea) may have lower than expected TDF plasma concentrations despite high adherence [31]. In these cases, we advise to

use daily PrEP. Furthermore, these PrEP users need closer follow-up and should be encouraged to adhere to other recommended prophylactic measures. Although therapeutic drug monitoring with determination of TDF and FTC trough levels is possible in abroad laboratories, its cost prohibits the implementation in daily clinical practice [32].

Missed medication and indications for PEP

If a person forgot to take his pill within 12 hours, the next pill should be taken as soon as possible, and PrEP continued at the same hour as usual. If a person forgot to take his pill later than 12 hours, only the next pill should be taken at the same hour as usual.

In case of a risk contact and suboptimal medication adherence, the HRC should be contacted to evaluate the need for PEP. Low adherence is defined as [28]:

- For men and women on daily regimen: less than 4 pills a week, regardless of the distribution
- For men on even-driven PrEP: at least 1 pill before and 1 pill after sexual intercourse have to be taken.

Side effects

PrEP is very safe with no side effects in 90% of users [2,5,6]. Reported side effects include:

- Gastrointestinal symptoms: diarrhea, nausea, vomiting, flatulence, ... Typically, these symptoms start in the first few days or weeks of PrEP use and last almost always less than 1 month.
- General symptoms: dizziness, headache and fatigue.
- Renal failure: One-time elevations in serum creatinine are seen in approximately 1 in every 200 PrEP users but are self-limiting and resolve in 80% of cases without stopping PrEP when a separate specimen is tested [33-36]. The Fanconi syndrome is a seldom side effect of TDF usage, which has been described in patients living with HIV taking the drug daily for at least several months [37]. In patients on PrEP with worsening of kidney function, we proposed to

confirm this on a separate specimen. If eGFR drops below $<60 \text{ mL/min/1.73m}^2$, we advise to refer the patient to the HRC. Also, if eGFR decreases over 20% without recovery, the patients should be referred to HRC for further work-up including determination of urinary protein/creatinine ratio, glucosuria, fractional phosphate excretion, measurement of urine pH and plasma bicarbonate.

- Reduction of bone density: Oral PrEP with TDF/FTC has been associated with a small decrease in bone mineral density (0,5 - 1,5%) at the spine and hip in the first 6 months, without further progression afterwards [38]. Studies have found no increase in risk of bone fracture and bone mineral density returns to normal when PrEP is discontinued [39]. Thus, no screening for bone mineral density recommended. For people with a history of bone fracture who are considering PrEP should be referred to exclude osteoporosis that needs treatment.

Seroconversion and resistance

HIV seroconversion while using PrEP might occur. In clinical trials, seroconversion was related to either pre-existing HIV infection or inconsistent use of PrEP [40,41]. Only 3% of seroconverters who have received PrEP in studies have shown any resistance to FTC or TDF [42]. Recently, a case of HIV acquisition with multidrug resistance was reported despite long term adherence to TDF/FTC, but this case remain the only one described until now [43]. Thus, in case of seroconversion, a drug resistance testing should be performed and the patient needs to be refer to an HRC as soon as possible to start an adapted treatment.

Doxycycline to prevent STIs ('doxy-PEP')

Doxycycline PEP, which refers to the intake of 200 mg within 24 to 72h after sexual intercourse [44], proved to be effective in preventing bacterial STIs in MSM with the caveat of the unknown long-term effects on microbiota and STIs resistance. Given these uncertainties, there is currently no recommendation for its widespread use.

Patient information

These are the main message which should be shared with the patient:

- PrEP is highly effective against HIV acquisition, if you take it correctly.
- Adherence (correctly taking pills) and regular testing for HIV (every 3 months) are essential.
- PrEP does not protect against other STIs. Condom use does.
- PrEP has no contraceptive effect.
- PrEP does not affect the efficacy of hormonal contraceptive and hormonal contraceptive does not affect PrEP.
- If vomiting occurs at least 30 minutes after intake, there is no need to retake a second tablet. If one tablet is missed, take it as soon as you remember.
- In case of missed/incorrect pill intake, contact a health professional (a PEP treatment might be needed).
- For event-driven PrEP, pay attention to correctly starting (2-24h before; 2 pills) and stopping (2 days after last sex).
- There are no interactions of PrEP with recreational drugs or alcohol. However, chemsex may cause impaired adherence to PrEP and other health problems.

Reliable patient information can be found on the following websites:

- [Myprep.be](http://myprep.be) (French only, a patient information leaflet is available)
- [Sensoa](http://sensoa.be) (Dutch only)
- [PrEPster](http://prepster.be)
- <https://www.itg.be/nl/clinics/service/hiv-prep-pre-expositie-profylaxe>

Information to be collected by the HRCs

Sciensano collects aggregated data of the HRCs on PrEP usage on yearly basis. The following data need to be reported:

1. The number of individuals starting PrEP in the last year, including their sex, age group, risk category, presence of specific circumstances (sex work and start after PEP usage) and regimen chosen at the start.
2. The number of individuals taking PrEP in the last year, including the number with a new diagnosis of a specific STI (HIV, syphilis, NG, CT, lymphogranuloma venereum, hepatitis A, hepatitis B, hepatitis C, Mpox and HIV), the number reporting chemsex usage and the regimen at the last consultation of the year.
3. The number of individuals who interrupted PrEP and the reasons for this interruption.

Conclusion

In conclusion, we recommend the use of PrEP for a selected population. A regular follow-up has to be set up to diagnose HIV seroconversion, to treat other STIs, to prevent side effects and to avoid resistance occurrence. We recommend that patients should be counselled regarding the use of PrEP as part of a combination approach to HIV prevention.

Conflict of interest: none.

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Box 1: Key components of counselling

<ul style="list-style-type: none"> • Risk reduction <ul style="list-style-type: none"> - Assess the risk: type of sexual intercourse, use of alcohol/“chemsex” (i.e. sexualised drug use), use of sextoys and discuss risk reduction - Chemsex: educate for individual tools, lubricant use, interactions between drugs (see chemsex.be, application “knowdrugs”) - Review STI transmission mode and remind that condom use is the only measure that protect against all STI (refer to depistage.be and for doctors www.ist.kce.be) - Reinforce the need for immunization (e.g. HPV and hepatitis) - Assess potential sexual health and wellbeing issues: discuss the role of chemsex and mental health in relation to sexual behaviour. Refer to sexologist, mental health specialist, addiction specialist or community associations if needed.
<ul style="list-style-type: none"> • Educate for STI screening when symptoms are present and partner notification
<ul style="list-style-type: none"> • Medication adherence <ul style="list-style-type: none"> - Test the understanding of the chosen regimen of PrEP, e.g. using a real life case study - Provide pill box, mobile applications (e.g. myprep and AT-PrEP) and websites (see below under ‘Patient information’) - Discuss strategies to adopt in case of discontinuation: out of stock situation, unexpected travel, etc. - Discuss the indication of PEP - Ensure low-threshold contact with caregivers: offer a list with telephone numbers, e-mail addresses and emergency hotline

Table 1: Laboratory tests at follow up visits

	After 1 month (optional)	3 monthly	6 monthly	12 monthly
HIV 4 th generation (Ag/Ab) test	x	x		
Syphilis		x		
ALT/GPT		x		
HCV*			x	
Serum creatinine, eGFR and serum phosphate***	x			x
Urinary protein/creatinine ratio**				x

*HCV via testing for antibodies or combo-test (antigen/antibody) unless previous HCV infection when HCV-RNA test is required

** cut-off is <0.15

*** every 3 to 6 months in individuals over 50 years of age, with CKD or risk factors for CKD (e.g. diabetes and hypertension) or who use of nephrotoxic medications

Table 2. How to start and stop oral PrEP

Population	Starting oral PrEP	Using oral PrEP	Stopping oral PrEP
Cisgender men and trans and gender diverse people assigned male at birth who are not taking exogenous oestradiol-based hormones*	Take a double dose 2–24 hours before potential sexual exposure	Take 1 dose per day	Take 1 dose per day until 2 days after the day of the last potential sexual exposure**
Cisgender women and trans and gender diverse people assigned female at birth*	Take 1 dose daily for 7 days before potential exposure	Take 1 dose per day	Take 1 dose daily for 7 days after last potential exposure
Cisgender men and trans and gender diverse people assigned male at birth who are taking exogenous oestradiol-based hormones*	Take 1 dose daily for 7 days before potential exposure	Take 1 dose per day	Take 1 dose daily for 7 days after last potential exposure
People using oral PrEP to prevent HIV acquisition from injecting practices*	Take 1 dose daily for 7 days before potential exposure	Take 1 dose per day	Take 1 dose daily for 7 days after last potential exposure

*Patients in need of chronic hepatitis B treatment should take daily PrEP. Stopping PrEP should be discussed with physician and monitoring is recommended after stopping TDF-based PrEP to detect relapse and manage HBV.

**Some event-driven PrEP studies (2) showed effectiveness by taking 2 doses daily after potential exposure, even if the first of the 2 last doses is on the same day of the last exposure for it is after the exposure. Sources like WHO recommend taking 2 daily doses after the last potential exposure.