Chapter 3
Clinical and Laboratory Information on PrEP

PrEP, short for pre-exposure prophylaxis, is the provision of ARV drugs to people who are presumed to be HIV-negative before they anticipate being unintentionally exposed to HIV infection. Currently, the predominant PrEP drug regimens in Thailand are tenofovir disoproxil fumarate (TDF) 300 mg and emtricitabine (FTC) 200 mg combined in the same tablet, and referred to as TDF/FTC. This formulation is to be taken once a day and as long as the exposure to infection lasts. TDF/FTC is currently listed on the Thai National Essential Medicines List (List A). It is indicated for pre-exposure prophylaxis in HIV-negative people. The Thai Government Pharmaceutical Organization (GPO) can now produce generic TDF/FTC drugs which have been registered with the Thai Food and Drug Administration (FDA).

In Thailand, daily PrEP is recommended for all populations due to ease of administration, and especially for those who are at frequent risk. On-demand PrEP is recommended for men who have sex with men (MSM). Both daily and on-demand PrEP can use the TDF/FTC formulation.

PrEP is under continuous research and investigation, and there are other formulations which have been proven effective. In 2019, the US FDA approved TAF/FTC (tenofovir alafenamide/emtricitabine) for HIV prevention in adults and adolescents weighing 35 kg or more, and for all forms of sexually-transmitted risk, except for the receptive partner in vaginal intercourse.

3.1 Effectiveness of PrEP

The current use of oral PrEP is based on systematic research into its effectiveness and safety. It was found that if taken regularly, the effectiveness in preventing HIV infection was almost 100 percent.

3.1.1 Effectiveness of daily PrEP

iPrEx project

iPrEx (Pre-exposure Prophylaxis Initiative) is a phase 3 randomized, double-blind, placebo-controlled, multi-center trial conducted in Peru, Ecuador, Brazil, Thailand, South Africa, and the United States. The study followed a total of 3,324 MSM and transgender women (TGW) subjects. PrEP TDF/FTC was forty-four percent effective in preventing HIV infection (95% confidence interval [95% CI]: 15 to 63). But when considering only those with detected TDF blood levels, the effectiveness was ninety-two percent (95% CI: 40 to 99).

PROUD PROJECT

PROUD is a phase 3, randomized, open-label, multi-center trial in the UK among 544 MSM participants. Daily PrEP was found to be eighty-six percent (95% CI: 64 to 96) effective in preventing HIV infection.

Bangkok Tenofovir Study Project

The Bangkok Tenofovir Study (BTS) is a phase 3 randomized, double-blind, placebo-controlled trial conducted in Bangkok. A total of 2,413 persons who inject drugs (PWID) were studied, and the analysis found that PrEP TDF was forty-nine percent effective in preventing HIV infection by (95% CI: 10 to 72). However, when considering only those who completed at least seventy-one percent of their drug regimen and had serum TDF levels detected, TDF blood level was associated with a seventy-four percent reduction in HIV risk (95% CI: 17 to 94).

iPrEx-OLE Project

iPrEx-OLE (iPrEx Open-label Extension) is a follow-up to iPrEx using 1,603 MSM and 339 TGW volunteers from the iPrEx, ATN 082/Project PrEPare and the US CDC MSM Safety Trial to follow-up for TDF/FTC dosing on the open-label. This study found that PrEP TDF/FTC was forty-nine percent effective in preventing HIV infection (95% CI: -1 to 74). However, when considering only those whose blood levels of TDF were found to be equivalent to taking four or more tablets of TDF/FTC per week, the PrEP efficacy reached 100 percent (i.e., no incidence of HIV infection at all).

Partners PrEP Program

Partners PrEP is a phase 3 randomized, double-blind, placebo-controlled, multi-center trial conducted in Uganda and Kenya with 4,758 heterosexual discordant couples. This study found that TDF alone was sixty-seven percent effective in preventing HIV infection (95% CI: 44 to 81), while TDF/FTC was seventy-five percent effective in preventing HIV infection (95% CI: 55 to 87). When considering only those with detectable TDF blood levels, TDF/FTC was ninety percent effective (95% CI: 58 to 98).

Project Prévenir

Prévenir is an exploratory research study conducted in France. Preliminary results were published in 2021. A total of 3,067 volunteers were followed, yielding a total of 5,633 subject-years. Nearly all (99%) of the volunteers were MSM. About half chose daily PrEP and half chose on-demand PrEP. The incidence of HIV infection was 0.11 (95% CI: 0.01 to 0.23) per 100 person-years. Among the volunteers in the daily TDF/FTC group, there were three new HIV infections, or an incidence of 0.12 (95% CI: 0.01 to 0.34) per 100 person-years. In the on-demand group, there were also three new HIV infections, representing an incidence of 0.12 (95% CI: 0.01 to 0.34) per 100 person-years. However, all of the cases of HIV infection had discontinued PrEP at least two weeks before engaging in risk behavior.

DISCOVER PROJECT

DISCOVER is a phase 3, randomized, double-blind, active-controlled, multi-center trial conducted in the North America and Europe. The study compared daily TAF/FTC intake with TDF/FTC in a total of 5,387 MSM and TGW subjects after a total follow-up of 8,756 person-years. The study found that TAF/FTC was not inferior to TDF/FTC in preventing HIV. There were twenty-two cases of new HIV infection among those who received seven TAF/FTC doses (0.16 percent per year) and fifteen TDF/FTC doses (0.34 percent per year). This translates into an incidence of 0.47 (95% CI: 0.19 to

1.15). Twenty of the twenty-two infections were explained by the fact that the subjects took insufficient medication during the program, or were HIV-infected prior to participating in the program.

3.1.2 Efficacy of On-demand PrEP

IPERGAY and IPERGAY-OLE projects

IPERGAY is a Phase 3 double-blind, randomized, multi-center trial of 414 MSM (431 follow-up years) in France and Canada. In the study, the risk of HIV infection was reduced by eighty-six percent (95% CI: 40 to 98) with only two incidences of HIV infection. In the On-demand Prep group, two of the infected individuals stopped taking PrEP 1-3 months before infection. In a MSM-specific subgroup analysis of subjects who had infrequent sex (median of 5 monthly episodes or equivalent with a median dose of 9.5 tablets per month), the on-demand PrEP group had no cases of new HIV infection (compared to six infections in the placebo group). In other words, on-demand PrEP reduced HIV risk by 100 percent (95% CI: 20 to 100) in this sub-group, despite members having infrequent sex.

A subsequent open-label extension study of IPERGAY (IPERGAY-OLE), which collected 518 volunteer-years of data, found that on-demand PrEP reduced the rate of HIV infection by ninety-seven percent (95% CI: 81 to 100) compared to the placebo group. A single HIV-infected volunteer did not take PrEP.

Project Prévenir: This project was previously discussed in the section on Daily PrEP, and which found an HIV incidence of 0.12 (95% CI: 0.01 to 0.34) per 100 follow-up-years in the on-demand TDF/FTC group.

Table 3.1 Effectiveness of PrEP by Various Clinical Studies

Project	Target Group	PrEP	Efficacy (overall)	Adherence (%)	Efficacy(high adherence)
	MSM & TGW				
	MSM				
	MSM				
	Discordant couples				
	Heterosexual men and women				
	Women				
	Women				
	PWID				
	MSM & TGW				
	MSM				
	MSM & TGW				

[a]On-demand PrEP acceptors

[b]The PrEP was found to be ineffective because of the low adherence.

3.2 Indications for PrEP

PrEP is indicated for people at risk of contracting HIV and who are expected to be at risk for future HIV infection. Those who meet PrEP indications should receive standard PrEP counseling.

Table 3.2 Indications for PrEP

HIV-negative persons who meet at least one of the following criteria in the past six months:

- Had sex without condoms with a PLHIV who had failed to suppress the virus
- Had sex without a condom with someone whose HIV status was unknown
- Had an STI, e.g., gonorrhea, syphilis
- Took a mood-altering substance before or during sex
- Shared syringes with others to inject drugs
- Had ever received HIV post-exposure prophylaxis (nPEP)
- Wants PrEP

Persons under 18 years of age can receive PrEP if indicated (see Table 3.2). Medication adherence and side effects should be monitored closely. Healthcare professionals should take a history of sexual behavior and substance abuse to assess risks before initiating PrEP. That information will assist in behavioral assessment and the need for behavioral modifications to reduce the risk of HIV infection.

Case management

The practitioner should consider the context of risk behavior, e.g., if there is a history of sex or drug risk behavior. Although the service recipient may claim that they use condoms every time and have no risk, the PrEP provider should still make an independent judgment whether the client is at risk of HIV. The practitioner should always have a thorough discussion with the client before providing PrEP.

3.3 PrEP eligibility criteria

In addition to having a history of risk mentioned above, clients who wish to receive PrEP must meet the requirements listed below. They must

• not be infected with HIV;
• have no suspected symptoms of acute HIV infection;
• be at risk of contracting HIV; or should be counseled about PrEP;
• have no contraindications for PrEP (e.g., TAF/FTC requires CrCl > 30 ml/min, not allergic to PrEP); and
• consent to use PrEP as instructed, and agree to regularly test for HIV infection.

3.4 Current information about oral PrEP

The current oral formulation of PrEP is an easy-to-take medication with few side effects and few drug interactions. Providers should always be informed and advise their clients before starting PrEP.

3.4.1 PrEP regimen

Thailand recommends oral formulations as the PrEP of choice.

PrEP oral formulations

• TDF (300 mg)/FTC (200 mg) or TDF (300 mg)/3TC (300 mg)
• TAF (25 mg)/FTC (200 mg)

Combined TDF/FTC is generally recommended as the first formulation. PrEP is available to all groups except those with impaired renal function (creatinine clearance (CrCl) < 60 ml/min). Adolescents can use PrEP if their weight is thirty-five kg or more. This version of the guidelines addresses TDF/FTC, including TDF/3TC.

Other PrEP regimens

• The Dapivirine vaginal ring inserted vaginally, changed every twenty-eight days, can be used as an alternative if access to oral PrEP is not available.

• Long-acting Cabotegravir (600 mg) administered intramuscularly four weeks apart (double dose) after intramuscular injection every eight weeks.

Details of other formulations can be found in Appendix A under 'Other PrEP formulations' section.

3.4.2 Food and absorption

TDF/FTC and TAF/FTC do not interact with diet. Taking these formulations with food or on an empty stomach does not affect drug levels.

3.4.3 Adverse reactions

Common (more than 10%) side effects include nightmares, depression, diarrhea, dizziness, fatigue, headache, insomnia, nausea, rash, abnormal skin color on the palm and/or the soles of the feet (e.g., darker pigment), but these are not severe.

Rare (1-10%) side effects include nasopharyngitis, respiratory infections, or sinusitis.

3.4.4 Side effects from taking PrEP

In most cases PrEP has no serious side effects. If any, the side effects usually disappear in the first month after starting PrEP ("*start-up syndrome*").

• Some side effects, including nausea, bloating, and headache occur in approximately one in ten subjects, and symptoms improve to normal within three to four weeks of starting PrEP.

• The provider may recommend the use of a pain reliever, or medicine for nausea or flatulence. These OTC medications have no effect on PrEP absorption levels.

• Clients should be counseled about signs or symptoms that indicate the need for urgent evaluation, such as those indicating acute renal failure or acute HIV infection.

• A potentially serious side effect is kidney dysfunction. Most cases are found in people over forty years of age or with previously impaired renal function. Based on measuring an increase in creatinine, the incidence of this side effect was found to be approximately 1 in 200, and the condition was reversible after stopping PrEP.

• Bone mass may be thinner by one percent but this has no clinical significance and will return to the original state after stopping PrEP.

3.4.5 Storage of medicines

• Store at room temperature

• Clients often remove pills from pill containers because the label is an ARV drug for HIV treatment. It is recommended to store the pills in a dry place that is not too hot.

3.4.6 PrEP Interactions with other drugs

• PrEP often has no drug interactions with other drugs. Nevertheless, the service provider should advise the client about relevant details regarding the formulation.
• The key point is that TDF is excreted through the kidneys through glomerular filtration with active tubular secretion, which tends to produce side effects in people receiving nephrotoxic drugs such as non-steroidal anti-inflammatory drugs (NSAID). Taking PrEP with these types of drugs at high doses or for long periods of time requires monitoring of renal effects.
• TAF/FTC should not be used with anticonvulsants, carbamazepine, phenobarbital, phenytoin, etc., and the tuberculosis drug rifampicin, rifapentine, etc.
• PrEP is safe to use for TGW who are taking female hormones.
• PrEP is not a contraindication to any vaccination, including the Covid-19 vaccine. See Appendix B, PrEP and other drug interactions.

3.4.7 Drug use for patients with kidney disease
• TDF/FTC is contraindicated in those with CrCl < 60 ml/min.
• TAF/FTC should not be used in those with CrCl < 30 ml/min.

3.4.8 Drug use for patients with liver disease
• TDF/FTC does not require dose adjustment in patients with impaired liver function.
• TAF/FTC is not recommended in patients with Child-Pugh B and C liver disease.

3.5 Issues to consider when initiating PrEP and following up
Providers should spend time talking to their clients about lifestyle and risks. There are issues to consider in initiating PrEP and monitoring as noted in Table 3.3.

Table 3.3 Considerations for initiating PrEP and follow-up

Consideration	Explanation
Advice	● Providers should help clients decide when to take PrEP and when to stop, along with promoting safe sex and the use of clean syringes and equipment. • Advice should be given about the need for regular 3-month check-ups, and taking PrEP regularly for it to be effective. • Not being able to take PrEP regularly should not be a contraindication to administering PrEP, as each client tends to have different challenges in complying with the regimen. Providers should

	endeavor to encourage clients to cope with these obstacles rather than denying PrEP for those who cannot take PrEP regularly.
Risk during the window period	If the PrEP client is in a situation of constant, unavoidable risk (e.g., sex worker) and, thus, cannot have a window period long enough to be certain that a blood test is indeed HIV-negative, then take a history to ensure that there are no symptoms of acute HIV infection and that PrEP is resumed normally. Emphasize the importance of repeat HIV testing one month after PrEP initiation.
Duration of PrEP	This depends on how long the client is expected to be in a risk situation
Dispensing/prescribing PrEP	Provide PrEP for the first 30 days, then every 90 days. When dispensing for 90 days, PrEP may be dispensed before the latest HIV test results are known in order to maintain continuity of protection. The client must be contacted promptly if the blood results are abnormal.
Evaluating compliance with the PrEP regimen	At each follow-up appointment, the provider should give repeat education about regular and adequate PrEP intake, especially for those who report inadequate compliance, but who are still qualified to take it. Compliance is crucial to preventing PrEP drug resistance.
Regular Follow-up: At one month after initiating PrEP, and then quarterly thereafter (if still taking PrEP)	• Once PrEP is initiated, clients should be scheduled for a follow-up visit at one month, and then every three months thereafter to assess and confirm their HIV-negative status. Assess side effects early, discuss the challenges of taking adequate PrEP and troubleshoot solutions together if there are problems with compliance. To follow up with a service recipient who has not kept a regular appointment, the provider may consider contacting the service recipient in a way where they may not need to come to the service facility, e.g., remote service (telehealth).

	• Often, the service recipient is unable to attend a follow-up visit within the specified time period. The provider may prescribe medications and appointments for longer than routine. However, the client must be tested for HIV at another location every three months.
Receiving a PrEP client who initiated service with another provider	If the client is a continuing PrEP user who initiated service elsewhere, consider taking the history again, consider past blood test results, and consider prescribing additional tests before continuing PrEP.
Risk-reduction counseling	• The use of condoms is recommended to prevent other STIs, especially in the case of having multiple sexual partners. • In case of having anal sex, it is recommended to use a water-based lubricant along with condoms to prevent condoms from breaking. • It is recommended that clients receive vaccinations against other STIs, including hepatitis B, and HPV. • It is recommended to use a clean needle and syringe in case of injecting drugs, and seek drug addiction treatment.
Covid-19	• PrEP clients can be vaccinated against Covid-19 while using PrEP. • PrEP is not effective against Covid-19.

Assessing symptoms at every follow-up visit

• Assess risk behaviors and PrEP requirements, provide advice on risk reduction (e.g., using condoms and water-based lubricants), assess mental health problems, and mood-altering drug use since that can lead to risky behaviors for HIV and other STIs.

• Provide counseling to reinforce the importance of adequate medication intake, the need for follow-up and scheduled blood tests each time a client receives PrEP.

• Ask about side effects. If the client reports symptoms such as headache or nausea during the initial period, advise that these symptoms should fade within one month.

• Ask about concomitant use of other medications that may affect the kidneys, such as NSAIDs, or diseases affecting the kidneys.

• Ask about symptoms related to acute HIV infection.

3.6 Acute HIV infection

Screening for acute HIV infection is important because using PrEP while already infected with HIV can cause drug-resistant strains of HIV to emerge. Providers should not initiate PrEP for clients with a history of suspected acute HIV infection.

3.6.1 Acute HIV infection

Acute HIV infection refers to recent exposure to HIV, and the body has not yet produced antibodies to counter the HIV. If the standard HIV test is negative or inconclusive, but the qualitative HIV RNA or p24 antigen test is positive, then PrEP should not be prescribed to people with a history and suspected symptoms of acute HIV infection as it may lead to ARV drug resistance. The provider should always ask about suspected symptoms of acute HIV infection before prescribing PrEP.

• Forty to ninety percent of newly HIV-infected persons will show symptoms of acute retroviral syndrome two to six weeks after exposure. Most have non-specific symptoms, or symptoms similar to common viral infections. The most common symptoms are fever (96%), followed by enlarged lymph nodes (74%), and throat inflammation, rash, body aches, etc.

• Acute HIV infection has symptoms and signs similar to other viral infections, such as influenza. However, in many cases, acute HIV infection is asymptomatic. If infection can be diagnosed at this stage it will greatly help prevent transmission of HIV to others. That is because, during this acute infection period PLHIV have a high viral load (VL) (often more than 100,000 copies/ml), increasing their infectiousness many fold.

Table 3.4 Symptoms of acute HIV infection

Symptom	Prevalence (%)
Fever	
Enlarged lymph nodes	
Throat infection	
Erythematous maculopapular rash on the face and body Or ulcers on the mucous membranes such as the mouth, genitals	
General aches and pains; joint pain	
Diarrhea	
Headache	
Nausea, vomiting	
Enlarged liver or spleen	
Sudden weight loss	
Thrush	
Neurological symptoms such as aseptic meningitis, peripheral neuropathy, facial palsy, Guillain-Barré syndrome, brachial neuritis, cognitive impairment	

Table 3.5 Key points to remember about acute HIV infection and prescribing PrEP

Issue	Guideline

When should acute HIV infection be suspected?	- At every follow-up, take a history of acute HIV infection; if suspected, test for acute HIV infection immediately; and - individuals with high risk for HIV and who have been potentially exposed to HIV in the last 2-3 weeks.
Why is PrEP contraindicated for people suspected of acute HIV infection?	Initiating PrEP in individuals with acute HIV infection increases the risk of HIV strains that are resistant to tenofovir and FTC, especially to FTC
PrEP should not be initiated until it is confirmed that there is no acute HIV infection.	Persons with signs or symptoms consistent with acute HIV infection should not start PrEP until it is confirmed that they are not HIV-infected.
Concerns about resistance to tenofovir or FTC	- Overall, the risk of microbial resistance to TDF or FTC is low in PrEP users. - The development of drug-resistant infections can occur in people who use PrEP and who become infected with HIV. This is because, if PrEP is not taken as prescribed, and HIV infection occurs, then it is possible that strains of HIV will emerge which are resistant to the PrEP formulation. - For those who take PrEP irregularly, the blood level of the drug may not be high enough to prevent HIV infection, and that increases the risk of drug resistance. Consequently, regular PrEP intake and regular HIV testing are of the utmost importance to ensure that clients get the most protection from taking PrEP, and reduce the risk of drug-resistant strains of HIV from developing.

3.6.2 Diagnosing acute HIV infection in PrEP users

If there is a case of suspected symptoms of acute HIV infection, but the HIV test result was negative and the client insists that they continued to take PrEP as prescribed, then consider the following action:

- In cases where HIV infection can be confirmed quickly, have the client continue on PrEP, while applying a more sensitive diagnostic, such as a nucleic acid amplification test (NAT) or HIV RNA test as soon as possible.
    - If the HIV-negative status is confirmed, continue PrEP as prescribed.
    - If the client is HIV+, immediately switch to ART.
- In cases where HIV infection cannot be confirmed in a timely way, advise the PrEP client to avoid risky behavior (e.g., use condoms for all sex), and consider on a case-by-case basis, according to the provider's judgment, whether to stop PrEP and wait for a repeat HIV test. If the repeat blood test results are negative, PrEP can be continued as prescribed.

3.7 Laboratory Examinations

PrEP acceptors are to have laboratory tests at initiation, during, and post-PrEP on a regular basis to ensure they are not infected with HIV, and so that they can be screened and vaccinated against other related diseases in a timely manner.

3.7.1 Laboratory tests at inception and after PrEP initiation

PrEP acceptors receive laboratory tests at inception and after PrEP initiation as shown in Table 3.6.

Table 3.6 Summary of laboratory tests at initiation and after PrEP initiation

	Initiation	Month 1	3 months	6 months	Yearly	Pre-discontinuation	Remarks
HIV infection[a]							Check one month after starting the drug and every three months.
Kidney function[b] (creatinine, CrCl)							As per risk status
STIs[c]							Every 3-6 months as per risk status
Hepatitis B[d] (HBsAg, anti-HBs)							If HBsAg and anti-HBs are negative, recommend vaccination
Hepatitis C[e]							Ever 6-12 months as per risk status
Pregnancy[f]							Whenever suspected
Side effects[g]							If abnormal, consult with a physician and consider stopping

[a]Always screen for HIV infection before stopping PrEP

[b]People age < 30 years old do not need screening; People age ≥ 30 years old or have a pre-existing disease affecting the kidneys (eg diabetes, high blood pressure); people age ≥ 50 years, people with pre-existing disease affecting the kidneys, and those with CrCl < 90 mL/min should be monitored every 6-12 months.

[c]STIs: Recommend screening even without symptoms; blood test for syphilis, screening for gonorrhea and chlamydia (vaginal, urethral, anal, oral) – based on voluntary consent from the service recipient. Recommend screening for other STIs and vaccines (Hepatitis A, HPV).

[d]Do not test if there is a history of anti-HBs positive in the past. If both HBsAg and anti-HBs are negative, hepatitis B vaccination is recommended. If not vaccinated, HBsAg testing is recommended every year.

[e]It is highly recommended for MSM, TGW, and PWID.

[f]Examine only women of childbearing age.

[g]Take a history of acute HIV infection at every follow-up visit. Follow-up from the 1st month onwards. Providers may also use telehealth methods whereby the patient receives laboratory tests from a medical facility near their home.

In the case of testing limitations, or the laboratory test cannot be completed as recommended: At a minimum, HIV, kidney function (creatinine and CrCl, only those at risk of abnormal kidney values) and hepatitis B infection (HBsAg, only those who have never been anti-HBs positive) should be tested.

Table 3.7 Screening for liver function

Chronic condition which could affect the liver	Age	Test at PrEP initiation	Test at every 6 – 12 months
None	<30		
	30-49		Only those whose CrCl < 90 ml/min.
	50+		
Yes (e.g., diabetes, high blood pressure, chronic kidney disease)			

Table 3.8 Summary of Laboratory Tests at Initiation and After PrEP Initiation

Diagnosing HIV infection	
Test results before PrEP initiation	Results should be obtained within seven days before starting PrEP
HIV test results before starting PrEP must always be negative	• For the safety of the service recipient, a negative HIV test result must always be obtained and recorded at the time of evaluation for PrEP • Recommend the use of fourth-generation HIV test which detects infection as early as two weeks after infection • Test for HIV at one month after starting PrEP and quarterly thereafter
HIV test results are inconclusive	Standard laboratory tests should be repeated two weeks after the first test. If repeated results are inconclusive, report as negative, and PrEP can be initiated. If positive, initiate ART; try to start ART as soon as diagnosis is made.

HIV self-testing	Recommend use of self-testing HIV screening kits for follow-up in those cases who take PrEP as prescribed, but do not have easy access to more sensitive tests (such as the 4th generation tests). The self-test kits are 2nd and 3rd generation and, thus, could miss early HIV infection in the window period. HIV self-screening is not recommended at PrEP initiation.
Assessing liver function during PrEP	
Test results prior to PrEP initiation	Results should be obtained within six months before starting PrEP.
Measuring creatinine and creatinine clearance	• A creatinine test is recommended to calculate CrCl using the Cockcroft-Gault equation. (See Appendix C) • There is no need to wait for CrCl results before prescribing PrEP. Providers can look back on retrospective test results at the follow-up date. • Starting daily TDF/FTC is not recommended for people whose CrCl is less than 60 mL/min. • Those who have CrCl < 60 mL/min at the time of initiation are recommended to repeat the test for confirmation seven days later. If re-examination shows CrCl ≥ 60 mL/min, initiate the TDF/FTC PrEP regimen. • In those whose CrCl levels drop below 60 mL/min while taking TDF/FTC, repeat the test in seven days to confirm the results before deciding to discontinue the drug, and after at least one month after stopping the drug. If the CrCl returns to > 60 ml/min again, then consider resuming TDF/FTC. • For TGW who have been using sex hormones for more than three months: CrCl is calculated using their current gender. TGW who do not use sex hormones: Calculate CrCl using their gender.
Screening for STIs before PrEP	
Test results prior to PrEP initiation	Results should be obtained within three months before starting PrEP
Screening for STIs	• Providers should screen for STIs such as syphilis, gonorrhea, and chlamydia even if there are no symptoms, every 3-6 months depending on risk status • Gonorrhea and chlamydia should be screened by nucleic acid amplification test for Chlamydia trachomatis and Neisseria Gonorrhoeae (NAT CT/NG) in three channels: 1) oral, 2) urethra/vaginal, 3) anus – provided that there is voluntary consent of the service recipient. • If NAT CT/NG is unable to be examined, a Gram stain test should be performed only when symptoms are present. • PrEP can be started even if the client has an STI.
Hepatitis B and C Assessment	
Test results prior to PrEP initiation	Results should be obtained within one year before starting PrEP.
Hepatitis B	• Check for HBsAg and anti-HBs at initiation. • If there is a history of anti-HBs positive, no screening for hepatitis B is required. • If both HBsAg and anti-HBs are negative, vaccination against hepatitis B is recommended for all cases if not vaccinated. It is recommended that HBsAg be tested every year.
Hepatitis C	• Clients with hepatitis C can receive PrEP and should be enrolled in treatment for hepatitis C. • Screening should be intensive for high-risk groups, including MSM, TGW and PWID. • Screening with anti-HCV every 6-12 months. • People who have recovered from hepatitis C will not be able to be screened for re-infection with anti-HCV; they must be screened using HCV RNA or HCV cAg.
Pregnant and breastfeeding women	

For women of childbearing age, screen for pregnancy before starting PrEP; test for pregnancy whenever suspected	• PrEP TDF/FTC can be dispensed to pregnant and lactating women. There is no evidence that the drugs had any adverse effects on the unborn or breastfed infant whose mother was taking PrEP. • There have been no studies on the use of TAF/FTC as PrEP among women who had vaginal intercourse.

3.7.2 Knowledge of diseases at initiation and after the start of PrEP

3.7.2.1 Monitoring of renal function

It is safe to use TDF/FTC as a PrEP drug, but there should be periodic monitoring of kidney function.

• Use of TDF in HIV-positive people based on meta-analysis. Studies found that TDF may significantly impair renal function but has little clinical significance and was not found to be associated with bone fracture risk, low blood phosphate, or severe proteinuria. Proximal renal tubular dysfunction (including Fanconi syndrome) may occur with the use of TDF, but is rare.

However, with the use of TDF in HIV-negative individuals, systematic review and meta-analysis data showed that, among those starting PrEP, less than one percent had a CrCl lower than 60 mL/min. After taking PrEP, CrCl decreased to less than 60 mL/min in less than three percent of subjects, with a greater likelihood of CrCl reduction in those age over fifty years at initiation CrCl < 90 mL./min, and had congenital diseases affecting the kidneys, such as diabetes or high blood pressure. Conversely, in PrEP users under the age of thirty, less than one percent of CrCl abnormalities were found.

• The iPrEx study found that PrEP was associated with a significant reduction in CrCl, but the value returned to the original level after stopping the drug. The risk factors were age forty years or over, initial eGFR less than 90 ml/min/1.73 m2, and medication adherence.

• The IPERGAY study found that on-demand PrEP did not significantly affect renal function.

• The DISCOVER study found that TAF/FTC had a significantly lower effect on eGFR than TDF/FTC.

Therefore, these findings are the basis for changing the recommendations for screening and monitoring kidney values to screen and follow up only in groups of those who may be at risk of abnormal kidney values.

3.7.2.2 Examination and follow up of STIs

Providers should screen for STIs, including syphilis, gonorrhea, and chlamydia, even in cases without symptoms. Practitioners should use standardized examinations and procedures for the care and management of STIs according to the 2015 STIs Treatment Guidelines, the 2019 Guidelines for the Management of Gonorrhea, and the Syphilis Diagnostic and Follow-up Manual: Laboratory 2021. Screening should be conducted every three to six months and, if STIs are found, the client and their contact partners should be followed for treatment as well.

People taking PrEP should be advised about the following:

• Prevention of transmission and transmission of STIs

• Signs and symptoms of STIs

• The need for STI screening every three to six months

• The need for STI testing and treatment for both oneself and sexual partners

• Vaccination against other STIs: Hepatitis B (recommended for all genders); Hepatitis A (follow up for PWID and for STI cases among MSM); and HPV (recommended for all sexes)

Even if STIs are detected, PrEP can be continued. At the next follow-up appointment, the STI should be treated. This event should be used as a rationale to discuss prevention, with a focus on regular STI screening and receiving complete treatment, both for the client and their sexual partners. The practitioner should be careful not to blame or judge the client as being immoral because of an STI.

3.7.2.3 Hepatitis B virus testing and monitoring

Both TDF/FTC and TAF/FTC are effective against hepatitis B. For people who have hepatitis B and are taking PrEP: if PrEP is discontinued at some point, that change may cause hepatitis B virus to multiply, and hepatitis flare can occur within one to three months after discontinuation of the drug, with elevated AST and ALT values. However, the iPrEx and West Africa PrEP research programs studied cases of hepatitis B with normal or near-normal liver function values and without cirrhosis. No recurrent hepatitis symptoms were observed during PrEP discontinuation.

• People taking PrEP who are infected with the hepatitis B virus should be referred to a doctor for treatment, and to assess the case in conjunction with the “Guidelines for the c\Care of Chronic Hepatitis B and C in Thailand, 2015”.

• Patients with cirrhosis should continue hepatitis B therapy until HBsAg becomes negative, which should be supervised by the aforementioned physician, so that PrEP caregivers do not have to worry about hepatitis flare in these patients.

• Persons with hepatitis B should be counseled about the importance of adhering strictly to the Daily PrEP regimen to prevent exacerbation of hepatitis B. Intermittent PrEP is not to be taken, nor is on-demand PrEP, for the reasons above.

• Discontinuation of the drug in hepatitis B infection: If the attending physician determines that there is no need for TDF or TAF to continue treating hepatitis B, PrEP can be discontinued as usual.

For additional guidelines on hepatitis B screening and PrEP management in people with chronic hepatitis B infection, see Table 3.9

Table 3.9 Hepatitis B Screening and PrEP Management in Hepatitis B Infected Persons

Management guidelines	Details
HBsAg negative and anti-HBs negative	This means that hepatitis B infection has not been found and there is no immunity. Hepatitis B vaccination is recommended at the same time that PrEP is started.
HBsAg negative and anti-HBs positive	The client has immunity; PrEP can be initiated.
HBsAg positive	This indicates infection with hepatitis B virus. PrEP can be taken, but it must be taken every day, not at intervals, and in consultation with a physician for evaluation.

3.7.2.4 Hepatitis C screening and monitoring

Hepatitis C should be screened, especially in groups with a high incidence of HCV infection, e.g., MSM, PWID. Screening is also recommended for TGW because MSM and TGW may be at elevated risk of hepatitis C from using syringes, either for drugs, or beauty enhancements with others, or from injuries caused by anal intercourse. They should be screened every six to twelve months with anti-HCV. However, in other groups, if they have had high-risk sexual behaviors, such as rough sex, took mood-altering drugs before or during sex, or sold sex, then screening for hepatitis C may be considered appropriate at least once a year. If the results of the anti-HCV test is positive, PrEP can still be prescribed, but there should be consultation with a physician, and monitoring according to “Guidelines for the Treatment of Chronic Hepatitis C Patients in Thailand -- 2018”.

3.7.2.5 Bone Marrow Density Assessment

The iPrEx study found that ten percent of PrEP TDF/FTC participants had low bone density prior to PrEP. TDF/FTC was associated with a one percent decrease in bone mass, but not easily-fractured bones. The value returned to the same level after discontinuation of the drug. It was concluded that the lower bone mass was not permanent. However, a study by the Buddy CU Clinic found that thirty-nine percent of adolescents fifteen to twenty-four years old using PrEP had vitamin D deficiency, as the study found that 400 units of vitamin D3 given per day and elemental calcium 1,200 mg/day given two times had a significant benefit on bone mass. Between the age of fifteen to twenty-four is a time when bone mass is built, and there are additional recommendations for calcium and vitamin D supplementation for adolescents receiving PrEP as follows:

PrEP users aged fifteen to twenty-four years have the following recommended calcium and vitamin D supplementation:

• Routine bone mass measurements without indications are not recommended

• People with a history of osteoporosis, fractures, or prone to fracture: TAF/FTC should be prescribed instead of TDF/FTC because the DISCOVER study found that TAF/FTC did not have as negative an effect as TDF/FTC.

3.8 Taking PrEP

There are currently two major regimens for PrEP in Thailand: Daily PrEP and On-demand PrEP, both of which are equally effective.

3.8.1 Daily PrEP

Daily PrEP is defined as taking PrEP (either TDF/FTC or TAF/FTC) once daily, every day.

Key Points:

• Daily PrEP is suitable for all populations.

  - Exception: TAF/FTC is not recommended for at-birth females (women and transgender men) who engage in receptive vaginal intercourse, as there is insufficient data on safety.

• Recommended daily intake during periods of HIV risk. If, later on, the risk is reduced, PrEP may be discontinued in between periods of risk.

  - Exception: In cases of hepatitis B infection, PrEP must be taken continuously without interruption.

Selection of drug formulations

The recommended dosing regimen is TDF/FTC, preferably in a combination tablet. Consult with a physician to see when TDF/FTC is contraindicated.

Table 3.10 Selection of Daily PrEP regimens

TDF/FTC

- Suitable for all groups
- Contraindicated if CrCl < 60 ml/min.
- MSM should use the on-demand regimen

TAF/FTC

• Can be used by all groups except for at-birth females who have receptive vaginal sex

• Can be prescribed if CrCl > 30 ml/min

• Take daily only
• Safer for people with osteoporosis
• Contraindicated for clients with Child-Pugh B and C liver disease

Starting, maintaining efficacy, and stopping the drug

Lead-in Period

• All groups take one tablet of PrEP daily for seven days before sexual intercourse. That is to ensure that drug levels in the rectal and vaginal tissues are raised to levels that can prevent HIV.

- MSM can start taking two TDF/FTC tablets at the same time (double dose) to shorten the duration until drug onset of effectiveness to two hours
- Other high-risk groups should consider starting with two tablets at the same time (double dose)

Effective Use

• At least six tablets of TDF/FTC per week

- MSM take at least four tablets per week.

• If there is a risk during a period of insufficient medication intake, take more pills to reach the weekly minimum. For example, a woman who has taken five pills of PrEP daily should continue talking one more day's supply to complete the requirement of six daily doses in a week. If this is not possible, and the exposure to HIV has not been more than seventy-two hours, then take nPEP.

Stopping the PrEP drugs

• All groups take one tablet of PrEP daily for seven days after their last sexual intercourse.

- MSM take one pill a day for two days after their last sexual intercourse.

In case of forgetting to take a dose, then take the dose as soon as remembering. If it is almost time for the next dose (< 6 hours), skip the missed tablet and take the next scheduled dose -- no need to take twice the dose as compensation.

It can be seen that MSM have alternative medication options that reduce the time it takes for the drug to become effective, and that means that less discipline is required in taking the drug. This also shortens the duration until next dose after the last risk exposure. This flexibility is the application of knowledge from studies of On-demand PrEP. In addition, if a MSM wants to start a new course of PrEP within seven days of the last dose, PrEP can be started with one tablet instead of the double dose (optional).

Initiation of two PrEP tablets simultaneously as a loading dose in groups other than MSM may be recommended for people at high risk or for those who are expected to be unable to avoid risky behaviors within seven days of starting the drug. However, there is no data on how long it will reduce the time it takes for the drug to become effective. All groups starting with the double dose should be advised that side effects such as nausea and severe headache may occur.

TAF/FTC may take a shorter time to become effective when PrEP is initiated compared to TDF/FTC, and it may not be necessary to take the drug as regularly as TDF/FTC because the drug levels are retained in the target cells longer than the TDF/FTC. More studies are needed to clarify this possible difference.

The original PrEP prescribing guidelines recommended that Daily PrEP be continued for twenty-eight days after the last risk exposure, or the same estimated duration for taking nPEP. However, taking PrEP in the early stages eradicates HIV faster than nPEP, so it is thought to take a shorter time. Hence, the change in post-risk drug duration from twenty-eight days to seven days was made to be in line with the recommendations of the British HIV Association (BHIVA) and the European Association of AIDS Clinics (EACS).

3.8.2 On-demand PrEP

In these PrEP guidelines for Thailand, On-demand PrEP services refers to the “PrEP 2-1-1” notation. The World Health Organization (WHO) also refers to this as “ED-PrEP” (event-driven PrEP). Other academic literature may have different names (e.g., non-daily, event-based, periodical, intermittent) for On-demand PrEP, but the method is the same.

The On-demand PrEP drug formulation is the same as the Daily PrEP regimen, namely TDF/FTC. If clients have frequent sex or wish to continue taking PrEP, they can continue taking Daily PrEP. It is advised to alternate between Daily and On-demand regimens according to circumstances and needs, as long as there is no contraindication.

Key Content

• On-demand PrEP uses the drug TDF/FTC. TAF/FTC is not recommended due to insufficient studies.

• On-demand PrEP is used for MSM (either the insertive or receptive partner). There is still too little data about On-demand PrEP for other risk groups.

- Men who have sex with women have the same physiology as MSM. Thus, it is reasonable to expect the body to respond identically to On-demand PrEP. However, research data is insufficient to draw conclusions.
- The iFACT study found that estrogen use among TGW was associated with lower serum TDF levels. Therefore, the prescription of On-demand PrEP in this group should be done cautiously until further information becomes available.
- There is no evidence of the use of On-demand PrEP to prevent HIV infection through injection drug use.

• On-demand PrEP should not be used in cases with hepatitis B infection. That is because the use of PrEP may cause exacerbation of hepatitis symptoms during the periods of discontinuation.

The criteria for choosing between Daily PrEP and On-demand PrEP are summarized in Table 3.11.

Table 3.11 Choosing Daily PrEP or On-demand PrEP

Daily PrEP

• Applicable to all groups
• There is no need to plan the time for sex in advance
• Persons with hepatitis B virus can use this regimen

On-demand PrEP

• Only for MSM
• Must know when they will have sex in advance, or they can delay sex because the drug must be taken at least two hours in advance
• Suitable for those who have infrequent sex (less than two times a week)
• Uses less medication than Daily PrEP
• Must not be infected with hepatitis B virus

On-demand PrEP is taken differently from Daily PrEP, and the provider needs to educate the client on the difference.

How to use On-demand PrEP

• On-demand PrEP begins with two TDF/FTC tablets (double dose) two to twenty-four hours before sexual intercourse. After that, one tablet a day at the same time as the first dose. Continue taking it for two days after sex. This ends the 2-1-1 regimen.
• If the client has had sex for several days in a row, they should take one tablet daily for up to two days in a row after last sex.
• If the client wants to start On-demand PrEP within seven days after the last dose, they can start with one pill instead of a double dose (optional).

Figure 3.1 Diagram below showing how to take On-demand PrEP.

(1) When having sex once or on one day:

Sex at

1 a.m.

Wed.	Thur.	**Fri.**	Sat.	Sun.
	10 p.m	10 p.m	10 p.m.	
	PrEP	PrEP	PreP	
	PrEP			

(2) When having sex on consecutive days

Sex at 2 a.m.	**Sex at 11 p.m.**	**Sex at 11 p.m**	
Fri.	Sat.	Sun.	Mon.
Noon	noon	noon	noon
PrEP	PrEP	PrEP	PrEP
PrEP			

(3) When having sex over multiple days, but not necessarily consecutively

Sex at 11 p.m.	**Sex at 10 p.m**		**Sex at 1 p.m.**		
Fri.	Sat.	Sun.	Mon.	Tue.	Wed.
9 a.m.	9 a.m.	9 a.m.	9 a.m.	9 a.m.	9 a.m.
PrEP	PrEP	PrEP	PrEP	PrEP	PrEP
PrEP					

(4) Starting one PrEP tablet on-demand less than seven days after the last tablet of the previous dose

Sex at 9 p.m.	**Sex at 11 p.m**									
Fri.	Sat.	Sun.	Mon.	Tue.	Wed.	Thu.	Fri.	Sat.	Sun.	Mon.
7 p.m	7 p.m.	7 p.m.	7 p.m.				5 p.m.	5 p.m.	5 p.m.	5 p.m.
PrEP	PrEP	PrEP	PrEP				PrEP	PrEP	PrEP	PrEP
PrEP										

(5) Starting with two on-demand tablets if more than seven days have passed from the last tablet of the previous dose

Sex at 9 p.m.	**Sex at 11 p.m**								
Fri.	Sat.	Sun.	Mon.	Tu/W/Th/Fr/Sa/Su/Mo	Fri.	Sat.	Sun.	Mon.
7 p.m	7 p.m.	7 p.m.	7 p.m.		5 p.m.	5 p.m.	5 p.m.	5 p.m.
PrEP	PrEP	PrEP	PrEP		PrEP	PrEP	PrEP	PrEP
PrEP					PrEP			

Table 3.12: Summary of key content for counseling clients about On-demand PrEP

Issue	Explanation
Persons who are appropriate for On-demand PrEP	MSM who do not have hepatitis B
Starting and stopping On-demand PrEP	Start taking two pills at the same time 2-24 hours before sexual intercourse; take one pill a day until two days after the last sexual intercourse
Take PrEP less than two hours before sex (when the dose that the recipient ingested is not enough)	• Always use condoms and lubricants during sex • If you forget to use a condom, continue taking nPEP for four weeks and get tested for HIV as scheduled by your doctor.
Forgetting to take the full PrEP 2-1-1 regimen	If it's not more than 48 hours after the last pill, take the pill as soon as you remember. If it's more than 48 hours after the last pill, but not 72 hours after the risk, take nPEP.
Risk reduction	PrEP should be used in conjunction with a condom and a water-based lubricant for every episode of sex with a non-regular partner, or if one is not in a committed relationship

	with a single sexual partner. This is to reduce the risk of contracting STIs and help prevent HIV infection in cases where the level of the PrEP drug is incomplete.

3.9 Stopping PrEP

Some clients may have intermittent risk of HIV infection. Those who start taking PrEP can stop and restart at regular intervals. Knowing when and how to start and stop PrEP is important for PrEP to be effective. For example, the need for PrEP may end when the HIV+ positive partner in a discordant couple is able to suppress their viral load to an undetectable level, or when the client enters into a truly monogamous relationship with a non-infected partner.

Reasons for Stopping PrEP

- Client is no longer at risk of contracting HIV.
- Client enters a truly monogamous relationship with a non-infected partner.
- In case of discordant couples, PrEP can be stopped when the HIV+ partner has suppressed their viral load.
- Client experiences side effects from taking PrEP, or is allergic to PrEP.

Reasons for re-starting PrEP

The reasons for resumption of PrEP are the same as those for starting PrEP initially, such as:

- Having sex without a condom with a person of unknown serostatus;
- Initiating a new relationship with a PLHIV who is not receiving ART and/or cannot suppress the viral load;
- Using mood-altering drugs before and during sex;
- Having multiple sex partners;
- Having group sex; and
- Starting work as a sex worker.

Table 3.13 Discontinuation of PrEP

Stopping PrEP	
Indications for stopping PrEP	• There are side effects from taking PrEP • No risk behaviors from either unsafe sex or injecting drugs • The client has self-assessed that there is no risk of infection in the future
Steps in stopping PrEP	• Ask about the timing of the last risk behavior • All groups: Take one pill daily for seven days after last sex • MSM: Take one pill a day for two days after last sex • Always get tested for HIV before stopping PrEP ● If HIV+: Enroll immediately in ART ● If HIV-negative: Stop PrEP, but return for HIV testing if having a risk episode
Advice	Clients should be advised to return for a new PrEP consultation if they resume HIV risk behavior.
Risk reduction	• PrEP must still be used in conjunction with the promotion of harm reduction from sex and/or injecting drugs • Screening for HIV infection before and during PrEP is also very important in preventing the development of drug-resistant infections. Those who are taking PrEP must be HIV-negative. If a PrEP user develops an HIV infection, continued use of PrEP may cause drug-resistant strains of HIV to develop.

Recording the history of those who discontinue PrEP

When PrEP is discontinued for any reason, the following information should be recorded in the client's history:

- HIV status at the time of discontinuation of PrEP;
- Reasons for quitting PrEP;
- Consistency in recent PrEP intake and risky sexual behaviors;
- Persons who have stopped PrEP and want to re-start should be re-evaluated before starting a new PrEP course; and
- Providers should not reject anyone who wants to start PrEP again, regardless of the reason (other than HIV infection).

3.10 In the event that the client has chronic risk for HIV

If a person has continual exposure to risk for HIV, such as a sex worker, there will never be a window period that is long enough to be certain that a blood result was indeed negative. The provider should take a history of symptoms of acute HIV infection and if there are no such symptoms, PrEP can be started. That is because, if PrEP is not started, the client has increased risk of HIV infection. The client must realize the importance of repeating the HIV test at one month after starting PrEP.

If the client was exposed to HIV risk within seventy-two hours, a four-week nPEP may be considered in accordance with the Thai guidelines. If, at the fourth week after nPEP, the client tests HIV-negative, then continue PrEP immediately.

3.11 PrEP dosing after nPEP

Clients taking nPEP are those who have a history of HIV infection. If risk for infection is anticipated in the near future, it is advisable to continue taking PrEP.

- Service recipients who have been at risk for more than seventy-two hours should be given nPEP as soon as possible after exposure (within one to two hours if possible). nPEP must be taken for four weeks, and then the client should continue with PrEP. Provide PrEP counseling and laboratory testing as usual. PrEP can be administered immediately after nPEP, regardless of the risk while taking nPEP. Once PrEP is started, make an appointment 1 month after starting PrEP as usual.
- If the client does not want to continue taking PrEP after nPEP, and the client encounters risk in the first one to three weeks of nPEP, there is no need to prescribe additional nPEP to cover the seven days after the last risk. (MSM have two days after the last risk.)

3.12 Considerations for pregnant women

- PrEP TDF/FTC is safe for pregnant and lactating women.
- As yet, there have been no studies on the use of TAF/FTC as PrEP among women who had vaginal intercourse.
- If a woman has an HIV+ partner who has been able to adequately suppress their viral load, then the woman does not need to take PrEP.
- In the case of a pregnant woman with a gestational age of ≥ thirty-six weeks and having sex without using a condom with an HIV+ partner who is unable to suppress the virus, then provide ART instead of PrEP to prevent mother-to-child transmission just before delivery. Additional information on the provision of PrEP services among pregnant women can be found in Chapter 6.

3.13 In case of seroconversion while on PrEP

- If a person taking PrEP is later diagnosed with HIV, it is likely to have been caused by irregular or improper use of the drug or by exposure to HIV that is resistant to TDF or FTC. Sometimes drug resistance can occur after PrEP is continued despite being exposed to HIV. HIV resistance should be tested in all cases. HIV+ clients should be enrolled in ART as soon as possible -- within the same day as the infection is known. Consider integrase inhibitor or protease antiviral regimens, e.g., TDF/3TC/dolutegravir or other formulations as deemed appropriate while waiting for the results of the drug sensitivity tests.

• A history should be taken of signs or symptoms of acute HIV infection during the previous month or on the day of assessment. If diagnosed with HIV while taking PrEP, treatment for HIV infection should be considered the priority. The emphasis should not be on PrEP compliance or investigation of how HIV was acquired.

3.14 Considerations for Service Providers Initiating PrEP Services

• Consider the regimen of PrEP that is most suitable for the client;
• Prescribe a proven, safe and effective drug regimen for HIV-negative people which meets the criteria to reduce the risk of acquiring HIV;
• Educate PrEP recipients about medications and how to take them in the safest way;
• Provide support and counseling for PrEP compliance. This is to help the recipient achieve and maintain an adequate level of the drug in the body for protection;
• Provide support to reduce HIV risk behaviors, and refer for related services as needed;
• Provide effective contraception to women who are taking PrEP and do not want to become pregnant; and
• Follow up on for side effects of PrEP clients every three months, and screen for HIV/STIs and risk behaviors to modify strategies to promote good health for the client.