Pre-Exposure Prophylaxis Clinical Guidelines (PrEP): Pakistan Country Guidelines

Developed for

National AIDS Control Program

Ministry of National Health Services, Regulation and Coordination, Government of Pakistan

Endorsed by the HIV Expert Group of Pakistan

1. Oral PrEP

Oral pre-exposure prophylaxis of HIV (PrEP) is the use of ARV drugs by HIV-uninfected people before exposure to prevent HIV acquisition.

Clinical trials of oral PrEP have shown evidence of effectiveness in sero-discordant couples, heterosexual men, women, men who have sex with men, people who inject drugs and transgender women. It is important to understand that PrEP is an additional HIV prevention choice and does not replace the biomedical and behavioral interventions mentioned above (in particular early treatment of an HIV positive partner in a sero-discordant partnership, condom use and safe needle practices for people who inject drugs). PrEP has been found to be safe across populations and has not been associated with population-level drug resistance.

1.1: Indications for PrEP

PrEP should be offered as **an additional prevention choice** for people at risk of HIV infection **as part of combination HIV prevention approaches. PrEP is recommended in people at a "substantial risk" of acquiring HIV.** In Pakistan, the highest incidences of HIV are among men who have sex with men, male sex workers, female sex workers and transgender women. There is also a high HIV prevalence among people who inject drugs. Individuals in sero-discordant relationships, where the HIV positive partner is not virally suppressed, may also be at substantial risk.

Eligibility criteria for PrEP

At a minimum, three eligibility criteria are universally necessary for offering PrEP:

1. Confirmed HIV-negative status and
2. No signs and symptoms of acute HIV infection and
3. Determined to be at substantial risk for HIV

Those at substantial risk include but are not limited to the following:

- HIV-negative sexual partners of a person living with HIV who is either not virally suppressed or for whom the results of viral load testing are unknown (e.g. sero-discordant couples).
- Individuals in key populations such as men who have sex with men, male sex workers, female sex workers, transgender women or people who inject drugs with individual behavioral risks.
- Individual behavioral risks include:
    - Having had condomless anal or vaginal sexual intercourse with more than one partner in the previous 6 months.

    - Having a new sexually transmissible infection (STI) in previous 12 months e.g. chlamydia, gonorrhoea or syphilis.
    - Receiving PEP in the previous 12 months for non-occupational exposure.
    - Using recreational drugs, such as methamphetamines, in the context of sex (chemsex).
    - Having a sexual partner with one or more risk factors with whom condoms are not consistently used.
- Individuals requesting PrEP.
- HIV-negative sexual partners of persons living with HIV:
    - While the HIV-positive partner is becoming established on ART i.e., has received less than 6 months of ART or has an unsuppressed viral load.
    - The HIV-positive partner does not want to engage in care or refuses ART.
    - Where the HIV-negative partner has concerns about the reliability of their HIV-positive partner's adherence to treatment.
    - Where VL monitoring is not available and there are concerns that the HIV-positive partner may not be virally suppressed due to known treatment interruptions to drug supply that are beyond the individual's control.
    - In any situation where the HIV-negative partner in a sero-discordant or sero-unknown relationship chooses, after counselling, to use PrEP because of personal preference.

Contra-indications to oral PrEP

- HIV infection or suspected acute HIV infection (i.e. flu-like symptoms in the last 4 weeks in combination with a preceding high-risk exposure for HIV)
- Adolescents <35 kg
- Impaired renal function (estimated creatinine clearance of <60 mL/min)
- Allergy or contraindication to any drug in the PrEP regime
- Refusal to attend at least one follow up appointment

Special considerations

Conception, pregnancy and breastfeeding

HIV-negative women who have HIV-positive sex partners may be at risk of HIV acquisition during attempts to conceive during condomless sex. There is an increased risk of HIV acquisition during pregnancy. There is a substantial risk for HIV for women during pregnancy and conception, whose partners are not taking antiretroviral treatment medication or women whose partners are treated but not virally suppressed. Women whose partners have documented sustained viral load suppression are at effectively no risk of sexual acquisition of HIV infection. The extent to which PrEP use further decreases

risk of HIV acquisition when the male partner has a documented recent undetectable viral load is unknown.

Providers offering pre-conception and pregnancy care to women who have HIV-positive sexual partners, may not be providing care to the male partner and may not have access to their medical records containing the most recent HIV viral load. When the HIV status of the male partner is unknown, the provider should perform an HIV test for the partner. When the male partner is reported to have HIV infection but his recent viral load is unknown, is detectable, or cannot be documented as undetectable, PrEP should be offered during the preconception period and pregnancy for the uninfected woman.

PrEP can be used in per-conception, pregnancy and during breastfeeding if HIV risk is substantial during this time. The existing safety data support the use of PrEP in pregnant and breastfeeding women who are at continuing substantial risk of HIV infection.

1.2: Monitoring prior to and while on PrEP

Before initiating PrEP, providers and counselors should educate individuals on the topics regarding PrEP, outlined in the appendix, in addition to other HIV prevention options.

Clients must be tested for HIV prior to starting PrEP, and retested at 1 month, 3 months and every 3 months thereafter while taking PrEP to ensure HIV seronegative status. Since PrEP contains tenofovir, serum creatinine must also be checked at initiation and then every 6 months thereafter. More frequent creatinine monitoring may be warranted if there are co-morbid conditions that can affect renal function, such as diabetes mellitus and uncontrolled hypertension.

Similarly, as tenofovir is active against hepatitis B, providing tenofovir to a person with hepatitis B infection may lead to virologic and clinical relapse. Therefore, hepatitis-B status, with hepatitis B surface antigen testing should be documented prior to PrEP.

Following confirmation of HIV-negative status, and no contraindications, PrEP can be prescribed and provided the same day while laboratory tests including creatinine, hepatitis B surface antigen and STIs are sent for testing. The PrEP user can be contacted if test results require additional confirmation or treatment.

Table 1: Summary of pre-exposure prophylaxis visits and procedures

Visit (visit number)	Recommended procedures

Screening and PrEP initiation (visit 1)	• Assess risk and eligibility - thorough history (sexual) and physical examination
	• Educate client about the risks and benefits of PrEP
	• Contraceptive counselling, pregnancy test, and offer services
	• **Tests**
	  ○ HIV
	  ○ Creatinine clearance using serum Cr*
	  ○ Hepatitis B surface antigen
	• Confirm eligibility with HIV test result
	• Follow up on other test results and creatinine clearance calculation (these results should not delay the prescribing of PrEP)
	• Hepatitis C testing where clinically warranted
	• Provide STI testing and treatment, if indicated
	• Provide condoms
	• Educate client about PrEP side-effects and management
	• Educate client about signs and symptoms of acute HIV infection
	• Provide one-month of TDF/3TC or TDF/FTC prescription and follow up date
	• Arrange follow up visit

1 month follow up (visit 2)	• Assess tolerability, side effects and effective use (adherence) • Actively manage side effects • Contraceptive counselling and offer services • **Tests** ○ HIV • Provide STI testing and treatment, if indicated • Provide condoms • Provide 2 month prescription • Arrange follow up visit

3 month follow up (visit 3)	• Assess tolerability, side effects and effective use (adherence)
	• Actively manage side effects
	• Contraceptive counselling and offer services
	• **Tests**
	  ○ HIV
	  ○ Creatinine clearance using serum Cr *
	• Provide STI testing and treatment, if indicated
	• Provide condoms
	• Provide 3 month prescription
	• Arrange follow up visit

6 month follow up
(visit 4)
	• Assess tolerability, side effects and effective use (adherence)
	• Actively manage side effects
	• Contraceptive counselling and offer services
	• **Tests**
	  ○ HIV
	  ○ Pregnancy test
	  ○ Hepatitis B surface antigen (at 7 months only)
	• Provide STI testing and treatment, if indicated
	• Provide condoms
	• Provide 3 month prescription
	• Arrange follow up visit

9 month follow up
(visit 5)
	• Assess tolerability, side effects and effective use (adherence)
	• Actively manage side effects
	• Contraceptive counselling and offer services
	• **Tests**
	  ○ HIV
	  ○ Creatinine clearance using serum Cr *
	• Provide STI testing and treatment, if indicated
	• Provide condoms
	• Provide 3-month prescription
	• Arrange follow up visit

12 month follow up
(visit 6)
	• Assess tolerability, side effects and effective use (adherence)
	• Actively manage side effects
	• Contraceptive counselling and offer services
	• **Tests**
	  ○ HIV
	  ○ Pregnancy test, if indicated
	• Provide STI testing and treatment, if indicated
	• Provide condoms
	• Provide 3-month prescription
	• Arrange follow up visit

*For creatinine clearance use the following formula

$$\text{CrCl} = \frac{(\text{age}-140) \times \text{weight}}{72 \times \text{Cr}}$$

For women multiply by 0.85

Table: 2 Managing clinical and laboratory results on pre-exposure prophylaxis initiation and follow up

Screening	Action
HIV-positive at initial evaluation	Do not start PrEP, counsel and link to immediate care and treatment
HIV-positive after initiation of PrEP	Discontinue PrEP, counsel and link to immediate care and treatment
STI symptoms	Provide STI treatment
Hepatitis B surface antigen - negative	Offer Hepatitis B virus vaccination
Hepatitis B surface antigen - positive	This is not a contraindication to PrEP. However, will require monitoring of liver function and referral for management of liver disease
Side effects of PrEP	Gastrointestinal - nausea, vomiting, weight loss: these are often mild, self-limiting and occur during the first 1-2 months. Provide supportive counselling, offer symptomatic treatment. Renal - transient increase in creatinine, and rarely proteinuria and Fanconi's syndrome (presenting as polyuria, bone pain and weakness) may occur. Measure creatinine (and calculate estimated creatinine clearance) at initiation of PrEP, at 3 months and every 6 months thereafter. If creatinine clearance (estimated glomerular filtration rate) <60 mL/min, then do not start PrEP, recheck after 2 weeks. Refer for evaluation of underlying renal disease. If the renal function returns to normal, reassess for PrEP and initiate/ continue PrEP. When restarting PrEP, optimum protection is reached after 7 doses of PrEP.
Pregnancy or breastfeeding	Pregnancy and breastfeeding are not contraindications to provision of PrEP. PrEP is also indicated for the HIV-negative partner in discordant partners who wish to conceive. PrEP in these situations can be prescribed during the pre-conception period and throughout pregnancy and breastfeeding to reduce risk of sexual HIV infection.

1.3: Drugs, dosing and duration of PrEP use

PrEP must always contain tenofovir ideally in combination with lamuvidine (3TC) or emtricitabine (FTC) in a fixed drug combination. As currently TDF/3TC is available, TDF/3TC (300mg/300mg) should be given in the standard once daily dosing. TDF/FTC is a suitable alternative should it be available in Pakistan.

PrEP should be used daily during periods of substantial risk of HIV acquisition, and can be stopped during periods of no risk. Events that herald the beginning or end of periods of risk will vary by region, demographic group, sociocultural practices and individual factors. For example, entering sex work, moving to a region that has a high HIV prevalence, or visiting home after work in the mining industry may represent readily identified periods of substantial risk.

For women, daily PrEP is recommended as tenofovir concentrates in the vaginal issue less than rectal tissue. Daily PrEP is also recommended for men engaging in insertive sex, transgender women having vaginal sex and transgender men having vaginal or frontal sex. For these populations, daily PrEP must be started at least 7 days before the exposure is likely to occur (e.g. in couples trying to conceive) to reach protective levels and continued until 28 days after exposure period ends.

For men engaging in infrequent receptive anal intercourse **only**, event-driven (ED) PrEP, also called on-demand PrEP, may be used. Given the clinical evidence for efficacy of ED-PrEP among MSM, and recent pharmacological modeling, MSM are suggested to take 2 tablets in the 2-24 hours before sex, then 1 tablet 24 hours later, and then 1 more tablet 24 hours after that (i.e., 4 tablets per sexual exposure where the last tablet is taken 48 hours after the sexual exposure).

Summary of TDF/3TC regimen used for PrEP

- For both men and women, PrEP should taken daily, ideally 7 days prior to the risk and continued for 28 days until the risk ends.
- During this period, other protective precautions must be used, such as condoms or abstinence.
- For men engaging in infrequent receptive **anal** intercourse **only** event-driven PrEP (ED-PrEP) may be used. The dose is 2 pills in the 2 to 24 hours before sex, then 1 pill every day until 24 hours after their last sex and 1 more pill 48 hours after their last sex.

1.4: Side effects

PrEP is usually safe, with no side effects for 90% of users. Minor side effects: About 10% of people who start PrEP will have some short-term mild side effects. These may include gastrointestinal symptoms (diarrhoea, nausea, decreased appetite, abdominal cramping, or flatulence). Dizziness or headaches have also been experienced. Such side effects are usually mild and resolve without stopping PrEP. Typically, these symptoms start in the first few days or weeks of PrEP use and last a few days and almost always less than 1 month.

Stopping PrEP

PrEP should be stopped when any of the following occurs:

- HIV test is positive
- Repeated and confirmed creatinine clearance <60 mL/min
- When an individual no longer has substantial HIV risk

1.5: Counseling Section

See table titled "Pre-exposure prophylaxis education checklist for providers or counselors" in the appendix for topics for counseling during the PrEP clinical visit or in the community

1.6: PrEP Implementation

In several countries, PrEP has been successfully implemented by counselors, nurses, peers from key populations and/or other healthcare providers. Task shifting to community-based programs should be used when possible.

Notes for Implementing PrEP

- Community-based organizations (CBO) should be utilized whereas possible in the implementation of PrEP. CBO paramedics and outreach workers can provide much of the required services, supplemented by counselors and physicians for prescribing. Medications can potentially be housed at CBOs for distribution to individuals who are in CBO PrEP programs.
- Medical officers, nurses, and the equivalent who are trained to provide ART can provide PrEP.
- Non-ART medical officers, nurses, and the equivalent should be prioritized to be trained to provide PrEP since ART centers can potentially provide stigma for individuals who are not HIV-infected.
- The PrEP initiation visit should preferably take place on the same day as HIV screening.
- Co-formulated TDF/FTC (300mg/200mg) is a suitable alternative to TDF/3TC (300mg/300mg) for use as PrEP.

List of settings to potentially deliver PrEP services

- Drop-in centers for key populations (including community and facility settings)
- HIV clinics (for HIV-negative partners before the HIV-positive partner achieves viral suppression)
- Antenatal care, Maternal, neonatal and child health, Reproductive Health and STI clinics

- Community settings meeting the criteria for initial client assessment and evaluation (e.g. integrated prevention centers and youth friendly outlets)
- Resupply of PrEP can be done in both community and facility settings

Appendix

Tables within the appendices include pre-exposure prophylaxis education checklist for providers or counselors, pre-exposure prophylaxis assessment checklist for providers or equivalent, and the summary of guidance of pre-exposure prophylaxis prescribing for providers or equivalent.

Pre-exposure prophylaxis education checklist for providers or counselors

How PrEP works as part of combination prevention
Limitations of PrEP • **Daily adherence required for efficacy** [note: that event-driven PrEP may be offered to men engaging in receptive anal sex **only]** • **PrEP does not prevent pregnancies and STIs**
PrEP use • **The medications used (show the client the pills)** • **How the medications are used (daily)** • **Number of daily doses required to achieve efficacy (2 doses for men having anal sex only, 7 doses for all other groups)** • **What to do when doses are missed (continue daily doses)** • **Discontinuation of PrEP (need to continue for 2 days for men having anal sex only or 28 days for all other groups from last potential exposure to HIV)** • **Side effects and what to do in case these are present (Consult the clinician)**
Risk reduction counselling and support • **Education (risk and safer sex practices)** • **Managing mental health needs** • **Couple counselling** • **Access to and consistent use of condoms** • **Access to and need for frequent HIV testing** • **Early access to ART** • **STI treatment** • **Harm reduction for persons who drugs**

Pre-exposure prophylaxis assessment checklist for providers or equivalent

Item to Perform	Yes / No
HIV testing and counselling	
Symptoms of acute viral infection in last 6 weeks	
Behaviour risk assessment	
Substance use screening	
Mental health screening	
Partner information	
Education and understanding of PrEP	
Readiness and willingness to adhere to prescribed PrEP and follow up schedule	
STI screening and treatment (when possible)	
Serum creatinine and creatinine clearance > 60 mL/min	
Hepatitis B surface antigen	
Hepatitis C virus serology (when possible)	
Medication history	
Pregnancy test (women)	
Pregnancy and pregnancy intention (women)	
• **Is the client currently using any contraception?**	
• **If not, is she interested in using long-term hormonal contraception in addition to condoms?**	
• **Is the client trying to conceive?**	
• **Is the client pregnant or breastfeeding?**	

Summary of guidance for pre-exposure prophylaxis prescribing for providers or equivalent

<table>
<tr><th></th><th>Men who have sex with men</th><th>Transgender persons</th><th>Heterosexual women and men</th><th>Persons who inject drugs</th><th>Sero-discordant couples</th></tr>
<tr><td rowspan="2">Detecting substantial risk of acquiring HIV infection</td><td>HIV-positive sexual partner</td><td>HIV-positive sexual partner</td><td>HIV-positive sexual partner or partner of unknown HIV status</td><td rowspan="2">HIV-positive injecting partner Unknown status of injecting partner
Sharing injection equipment</td><td rowspan="2">HIV-positive partner with detectable viral load, not known to have an undetectable viral load, or not on treatment</td></tr>
<tr><td colspan="3">STI within prior 12 months
More than one sexual partner
History of inconsistent or no condom use
Commercial sex work
Use of PEP within prior 12 months</td></tr>
<tr><td>Clinically eligible</td><td colspan="5">Documented negative HIV test result before prescribing PrEP
No signs/symptoms of acute HIV infection
Normal renal function
No contraindicated medications</td></tr>
<tr><td>Prescription</td><td colspan="5">Daily, continuing, oral doses of TDF/3TC 300mg/300mg, ≤90 day supply (Event-driven PrEP in certain cases)</td></tr>
</table>

Testing and other services	**Follow-up visits at least every 3 months to provide the following:** HIV test, medication adherence counselling, behavioral risk reduction counselling, side effect assessment, STI symptom testing and treatment **Every 6 months assess renal function** For women, pregnancy testing and contraceptive counselling every 3-6 months

STI: sexually transmitted infection

Adapted from: Centers for Disease Control and Prevention: US Public Health Service: Pre-exposure prophylaxis for the prevention of HIV infection in the United States—2017 Update: a clinical practice guideline. https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2017.pdf.Published March 2018.

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Acknowledgements

We would like to acknowledge the input of the HIV Expert Group of Pakistan (Drs. Naseem Salahuddin, Samreen Sarfaraz, Shehla Baqi, Muneeba Ahsan, Azzizullah Khan Dhiloo, Syed Faisal Mahmood, Kiren Habib, Iffat Khanum, Nosheen Nasir, Farheen Ali, Asma Nasim, Sunil Dodani, Sobia Qazi, Faisal Sultan, Aun Raza, Ashraf Ali Khan, Salma Abbas, Naseem Akhtar, Amjad Mahboob, Samina Jonejo, Fatima Mir, Sonia Qureshi, Ejaz Khan and Muhammad Khalid), WHO Pakistan, UNAIDS Pakistan, WHO Headquarters Geneva, UNAIDS Regional Office for Asia and the Pacific & the World Health Organization, and Dr. Rupa R. Patel.